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TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF ANTISECRETORY MEDICINES

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF ANTACIDES

Purpose of the topic.

Acid-dependent diseases occupy a leading place in the structure of morbidity. In particular, an average of 8.2% of the population in Western Europe suffer from peptic ulcer (UB) of the stomach and duodenum (duodenum) in the countries of Western Europe, from 7 to 10% in the USA, 11% in Japan, and 25% in India. Symptoms of gastroesophageal reflux disease (GERD) are found in half of the adult population of the globe, and endoscopic signs - in 2-10% of the examined individuals.

Along with the "classic" acid-dependent diseases caused by excessive production of hydrochloric acid in the stomach, mediated and symptomatic disorders of the gastrointestinal tract are widespread. Complaints of dyspeptic (dyspeptic) phenomena are reported by 30–40% of the population of industrialized countries. For example, in the USA, heartburn occurs daily 25 million adults, and more than 50 million people experience it twice a week. Dyspeptic symptoms account for 5% of visits to general practitioners and 40 50% of visits to gastroenterologists

Chronic gastritis is a common disease of the digestive system, which in different countries of the world affects about 20-30% of the entire adult population.

Among all diseases of the stomach, chronic gastritis accounts for 80-85%. More often than not, doctors in their practice encounter chronic Helicobacter pylori gastritis, which occupies about 90% of all chronic gastritis. This gastritis is associated not only with Helicobacter pylori infection, but also genetically linked to peptic ulcer disease.

The prevalence of peptic ulcer disease among the adult population is, in different countries of the world, from 5 to 15%. Duodenal ulcers are 4 times more common than stomach ulcers. Given that peptic ulcer disease is a serious social problem in modern medicine, due to the high incidence, significant prevalence, often prolonged course and frequent relapses with a temporary, and sometimes persistent lo Academician V.Kh. Vasilenko's lung ulcer is often called a "mysterious" disease. It would be said that it is so mysterious, because volumes and thousands of articles have been written that reveal the etiology and pathogenesis, clinical options and treatment features, diagnostic algorithms are postulated.

Despite all the obvious achievements in the study of peptic ulcer, many questions remain, thanks to which interest in this problem does not subside. All this applies equally to the pediatric aspects of the disease, the most studied of which will be presented in this section.

Definition

Peptic ulcer as an independent nosological unit gained self-sufficiency thanks to the work of J. Crewell in the beginning of the XIX century. However, to this day there is no single universally accepted definition of this disease.

In the International Classification of Diseases of the X revision, peptic ulcer as a nosological form is absent, and only a stomach ulcer and a duodenal ulcer are distinguished.

The domestic medical school, which has always advocated a nosological approach to pathology, considers peptic ulcer disease as a disease with very complex etiopathogenetic relationships and defines it as a "chronic recurrent disease characterized by the formation of a peptic ulcer in the stomach or duodenum"

A stomach and duodenal ulcer is a wound, ulceration, i.e. deep defect in the wall of the duodenum or stomach. An ulcer can reach the deeper layers (it can penetrate into the muscle layer and even deeper) of the wall of the duodenum and stomach, it is often complicated by bleeding, as well as perforation of the walls of the duodenum and stomach, which is fraught with serious consequences.

In most cases, peptic ulcer disease occurs against the background of existing gastritis (gastroduodenitis), which, like peptic ulcer disease, develops as a result of exposure to the bacterium Helicobacter pylori (Helicobacter pylori, Helicobacteriosis).

If a person develops gastritis, cracks form on the surface of the mucous membrane of his stomach (the so-called erosion). If appropriate treatment has not been carried out, they deepen and get to the muscle layer of the stomach, after which they turn into ulcers.

The main symptom of peptic ulcer is the same as with gastritis - pain in the epigastric region on the left side. With peptic ulcer, they differ in frequency - they can fade and reappear (the so-called recidivism, or an exacerbation of peptic ulcer). In most cases, the appearance of symptoms of peptic ulcer depends on the time of year: more often it worsens in the fall and spring. This is its difference from gastritis, which is not seasonal in nature, and the occurrence of discomfort in the stomach with it is associated mainly with the quality of food consumed and the diet. At the same time, it is possible to find out more clearly whether the patient is sick with gastritis or peptic ulcer, and a diagnosis can be made only after the procedure of FGDS - *fibrogastroduodenoscopy*.

Causes of peptic ulcer

The main role in the appearance of peptic ulcer is played by Helicobacter pylori bacteria, as well as long-term administration (30 days) in a standard dosage of non-specific anti-inflammatory drugs (for example, aspirin), cytostatics, and corticosteroids (prednisone). They cause damage to the mucous membrane of the duodenum and stomach, reduce the protective factors of the mucous membrane and increase the factors of aggression (increase the contents of working capacity, the relevance of studying this topic is undeniable. hydrochloric acid, violate gastric motility.

Risk factors represent only the background, which paves the way for the development of all kinds of diseases. These factors have a negative effect on the course of the disease, often leading to relapse.

Factors that can be affected (modifying):

Disrupted nutrition

Drinking alcohol, smoking

Neuropsychiatric factors Motility of the stomach and gastric secretion are in conjunction with the state of the nervous system. 50-60% of patients have neurosis and depression.

Factors that cannot be influenced (non-modifying):

Gender and age of the patient

Genetic predisposition

Among all patients diagnosed with peptic ulcer, the ratio of male to female is 4 to 1. There are versions that the female body is protected against the appearance of ulcers by sex hormones. The ratio is leveled in women who have reached menopause. The appearance of peptic ulcer of the duodenum is characteristic of young age, and stomach ulcers are characteristic of the older generation

The main symptoms and signs of the duodenum and stomach ulcers

The main signs of the disease are pain and dyspeptic syndrome (sour belching, heartburn, vomiting and nausea).

Pain appears in the upper abdomen, in the navel. The pains are bursting, paroxysmal, baking, characterized by the so-called hungry pains (occurring on an empty stomach) or those that appear 2–3 hours after a meal (characteristic of patients with a duodenal ulcer) subside after eating. In patients with a diagnosis of "gastric ulcer" pain occurs 30 minutes to 1 hour after a meal. Patients often complain of pain at night.

Due to the fact that the contents of the stomach are thrown into the esophagus, heartburn appears, which is characterized by a burning sensation behind the sternum. May occur after eating.

Vomiting and nausea occur due to an increase in vagus tonus, increased hypersecretion of hydrochloric acid and gastric motility. Vomiting occurs when pain is most pronounced. After vomiting, a feeling of relief comes, the pains noticeably decrease or disappear altogether.

A large number of patients suffer from constipation.

If the disease lasts a sufficiently long time, emotional lability, asthenia (insomnia, malaise, weakness) develops. Body weight may decrease, due to the restriction in food intake, which the patient sets, fearing the appearance of pain.

Over the past ten years, the symptoms of peptic ulcer have changed. A large number of atypical and malosymptomatic ulcer varieties arose. Localization of pain is often characteristic of the right hypochondrium, in the projection of the gall bladder, pain can appear in the lumbar region, they resemble renal pathology (urolithiasis, pyelonephritis), behind the sternum, in the region of the heart, as in heart diseases (myocardial infarction, angina pectoris). In some cases, the disease can manifest itself without pain, only heartburn. In 10 cases out of 100, the disease does not show clinical symptoms, they appear only when complications arise.

The reason for immediately contacting a doctor - a gastroenterologist or therapist - to undergo an examination in order to prevent complications and the appearance of concomitant diseases is: the appearance of severe weakness, diarrhea, frequent cases of vomiting, the presence of blood impurities in the feces.

CLINICAL PHARMACOLOGY OF DRUGS FOR THE TREATMENT OF STOMACH AND DUODENAL ULCER

The treatment of peptic ulcer of the stomach and duodenum still remains an urgent problem of gastroenterology, which is due to the widespread prevalence of the disease.

The process of ulceration can be considered as a violation of the equilibrium between aggressive and protective factors

In this case, there is not only a violation of the ratio of the main components of gastric juice,but also a change in the phases of gastric secretion. As a rule, in patients with ulcer, basal secretion is most disturbed, the maximum increase is observed from 0 to 4 hours. Gastric secretion phases

1. The basal

2. Stimulated

2.1. Cephalic (cerebral, neuroreflex)

2.2. Gastric (neurohumoral)

2.3. Intestinal

One of the leading places in the complex of therapeutic measures (surgical, therapeutic, prophylactic) belongs to pharmacotherapy of ulcer disease, including the use of basic antiulcer drugs in combination with radiation-induced anti-Helicobacter pylori therapy (AChT), as well as auxiliary agents.

Classification of drugs for the treatment of peptic ulcer

I. Basic funds (mainly affecting aggression factors)

1. Antacid preparations

2. Antisecretory drugs

2.1. H2-histamine blockers (H2-GB)

2.2. Proton Pump Inhibitors (PPIs)

2.3. Selective M1 anticholinergics (M1-HB)

2.4. Preparations of different groups

II. Auxiliary means (mainly affecting protection factors)

1. Gastroprotectors

2. Tissue-specific regeneration stimulants

III. Anti-Helicobacter Therapy

1. Antibiotics

2. Synthetic antimicrobial agents

3. Antisecretory drugs

The main goals of peptic ulcer pharmacotherapy

• Relief of symptoms of exacerbation of the disease (optimally for up to 3-4 days).

• Achievement of rapid healing of a peptic ulcer (preferably within 14-28 days).

• Prevention of relapse of the disease (with the help of AHT, which reduces the frequency of relapse throughout the year by 10-15 times).

It is generally accepted that gastric and duodenal ulcers are scarred in 100% of cases if the intragastric pH can be maintained at a level above 3.0 for about 18 hours a day. For the healing of a peptic ulcer with reflux esophagitis, a pH value of> 4.0 is critical. HP eradication is successful with intragastric pH values> 5.0 (the worst conditions for bacteria and the best for the effect of antibiotics are created).

The treatment of ulceration of the stomach and duodenum is basically the same, but with regard to media gastric ulcers, oncological alertness should always be present, since ulcers of this localization are most often malignant. Therapy for ulcer includes antacid and antisecretory drugs (table. 7.2), the main points of application of which are presented in figure 7.2. The greater the severity of the course of ulcer, the more powerful antisecretory drugs should be prescribed, since there is a direct relationship between the degree of suppression of secretion and the rate of scarring of ulcers.

Criteria for the effectiveness of antiulcer therapy

• Endoscopic criteria (frequency and rate of scarring).

• The presence of pain and its severity.

• The need for additional antiulcer drugs (for example, the frequency of antacid use).

MAIN DRUGS FOR THE TREATMENT OF ULCER DISEASE

Antacids:

Resorbable (absorbed):

• Sodium bicarbonate (NaHCO3).

• Calcium carbonate precipitated (CaCO3) - Calcimax.

Non-absorbable (non-absorbable):

Monopreparations:

• Algeldrat (aluminum hydroxide, Al (OH) 3) - Rochelle, Aluminum hydroxide.

• Rivopharm.

• Carbaldrate (sodium salt of dihydroxyaluminium carbonate) - Alyugastrin, Compensan.

• Magaldrate (magnesium hydroxide aluminate) - Magalfil, Magaldrat.

• Simaldrate (aluminum-magnesium trismetasilicate (in the form of a hydrate)) - Gelusil.

• Diamond (aluminum hydrated silicate) - Megalac diamond.

• Hydrotalcite (aluminum magnesium carbonate) - Rutacid, Tisacid.

• Aluminum phosphate (Al2 (PO3) 3) - Phosphalugel, Alfogel.

• Magnesium oxide (MgO).

• Magnesium hydroxide (Mg (OH) 2) - magnesia.

• Magnesium carbonate basic (Mg (OH) 2 • 4MgCO3 • H2O).

Combined:

1. Aluminum hydroxide + magnesium hydroxide:

• Maalox (aluminum hydroxide, magnesium hydroxide).

• Almagel (aluminum hydroxide, magnesium hydroxide, D-sorbitol).

• Almagel-A (aluminum hydroxide, magnesium hydroxide, D-sorbitol, benzoca-in).

• Digin (aluminum hydroxide, magnesium hydroxide, dimethicone, sodium carboxymethyl cellulose).

• Alprogel (aluminum hydroxide, magnesium hydroxide, simethicone).

• Anacid compositum (aluminum hydroxide, magnesium hydroxide, oxetacaine).

2. Aluminum hydroxide + magnesium hydroxide + magnesium trisilicate:

• Gestide (aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, simeti-con).

3. Aluminum hydroxide + magnesium hydroxide + magnesium carbonate.

• Gastal (aluminum hydroxide, magnesium hydroxide, magnesium carbonate).

4. Aluminum hydroxide + magnesium hydroxide + calcium carbonate:

• Di Gel (aluminum hydroxide, magnesium hydroxide, calcium carbonate).

5. Aluminum hydroxide + aluminum oxide + magnesium oxide + magnesium carbonate:

• Regla PX (aluminum hydroxide, aluminum oxide, magnesium oxide, magnesium carbonate).

6. Aluminum hydroxide + magnesium hydrochloride:

• Alumag (aluminum hydroxide, magnesium hydrochloride).

7. Magnesium carbonate + calcium carbonate:

• Rennie (basic magnesium carbonate, precipitated calcium carbonate).

8. Magnesium carbonate + calcium carbonate + sodium bicarbonate:

• Calmagin (basic magnesium carbonate, precipitated calcium carbonate, sodium bicarbonate).

Mixed:

• Alcide (bismuth subnitrate, sodium carbonate, sodium bicarbonate, aluminum hydroxide).

• Alcid-B (basic bismuth nitrate, basic sodium carbonate, aluminum hydroxide, licorice, chamomile, buckthorn bark extracts, coriander and fennel fruits).

• Vicalin (basic bismuth nitrate, basic magnesium carbonate, sodium hydrogen carbonate, calamus rhizome, buckthorn bark, rutin, kellin).

• Vicair (Rother) (basic bismuth nitrate, basic magnesium carbonate, sodium bicarbonate, calamus rhizome, buckthorn bark).

The first pharmacological agents that began to be used to treat acid-dependent diseases several centuries ago were antacids. They remained the main drugs for the treatment of these diseases almost until the middle of the 20th century, but then they were largely “crowded out” by drugs of new pharmacological groups, primarily H2 histamine receptor blockers and proton pump inhibitors. However, even today, antacids continue to be widely used drugs. This is evidenced by the number of drugs of this group located on the pharmaceutical market (more than 30 trade names are registered in Ukraine), and their sales volumes. For example, in 2003 the volume of pharmacy sales of antacids in the United States amounted to $ 25.2 million in wholesale prices and increased by 14% compared to 2002. In the United States, only for the prevention of gastrointestinal side effects of drugs approximately 6 million people use antacids to treat arthritis

The advantages of antacids over drugs of other pharmacological groups used to treat acid-dependent diseases are the rapid relief of pain and dyspepsia. Modern antacids also have a number of other favorable properties, for example, adsorbing and cytoprotective, the ability to correct intestinal motility, improve the quality of ulcer scarring, etc.

Currently, antacids are used mainly in the following situations:

• to relieve symptoms of gastroduodenal ulcers, reflux esophagitis with self-medication;

• as means of differential diagnosis ex juvantibus between cardiac and noncardial chest pains;

• as means of differential diagnosis of ex juvantibus epigastric ulcer and biliary pain;

• to stop the symptoms of ulcer, GERD, chronic pancreatitis in the first days of exacerbations before the appointment of a standardized treatment;

• as a medicine taken by patients on demand for heartburn, peptic ulcer pain, peptic ulcer dyspepsia, etc.

Antacids are very effective as agents for the treatment of peptic ulcer disease and, depending on the severity of the lesions, can be used in different patients both as monotherapy and as part of complex therapy. Researchers give a special place to antacids in pediatric practice, considering them as means of basic therapy and prevention of acid-dependent gastrointestinal pathology in children.

The pharmacological properties of a number of modern antacids make it possible to consider them the drugs of choice for the treatment and prevention of reflux gastritis and to be successfully used in GERD and acid-dependent diseases that occur with impaired intestinal motility. However, in order to achieve favorable treatment outcomes, it is necessary to choose the antacid drug correctly, taking into account its pharmacological properties and characteristics of a particular patient.

The antacid effect, which is the main one for the preparations of this group, can be considered either as acid-neutralizing (if 1 antacid molecule neutralizes 1 HCl molecule), or as acid-absorbing (if 1 antacid molecule neutralizes more than 1 HCl molecule). In this case, all drugs This group only neutralizes the already isolated HCl, without affecting its secretion.

Acid-neutralizing activity (KNA) of antacids is expressed in milliequivalents (meq), which is equivalent to the amount of 1N hydrochloric acid, which is titrated to pH 3.5 with a certain dose of the drug for a specified time (usually 10-15 minutes). KNA of antacids is considered low if it is less than 200 meq / day; medium, if its indicator lies in the range of 200-400 meq / day, and high with a KNA of more than 400 meq / day. It should be noted that an increase in the acid-neutralizing effect of more than 600 meq / day does not increase the antacid effect.

Optimal for antacids is KNA ~ 200 meq / day, which allows scarring to reach 75% of ulcers after 4 weeks of use of the drug. With an increase in KPA in the range of 200-600 meq / day, a healing increase of only 10% occurs, and a subsequent increase in KPA is even accompanied by a decrease in the scarring rate. In the table. 7.4 presents a comparative characteristic of KNA of some active substances that are part of antacids, and in table. 7.5 - various commercial preparations based on them.

The therapeutic effect of antacids is due to their cationic composition

Thus, under the influence of antacids, an increase in the pH in the stomach occurs, accompanied by a decrease in the formation of a number of proteolytic enzymes and a decrease in the action of aggressive factors. Moreover, alkalization of the gastric contents increases the tone of the lower esophageal sphincter, which may be important, for example, with gastroesophageal reflux.

The rate of onset of the antacid effect is determined by the rate of dissolution of the drug. So, sodium bicarbonate and magnesium hydroxide dissolve in the stomach quite easily, providing a rapid development of the buffering effect. Aluminum hydroxide and calcium carbonate dissolve slowly, therefore, a pronounced neutralization of gastric acid begins in about 10 minutes. Suspensions tend to dissolve faster than tablets or powders.

The duration of antacid action depends on how long the drug stays in the stomach. When taken on an empty stomach, a rapid evacuation of antacids occurs and their duration does not exceed 20-40 minutes. If the stomach contains food, the evacuation from it slows down significantly, therefore, the antacid drug taken after a meal stays in the stomach longer. Thus, an antacid taken 1 hour after a meal retains its acid-neutralizing effect for approximately 3 hours. Sodium bicarbonate and magnesium hydroxide have the shortest duration of neutralizing

action, and aluminum hydroxide and calcium carbonate - the greatest. Antacids containing a combination of aluminum and magnesium are characterized by an average duration of action.

Adsorbing effect. This effect is most pronounced in Al-containing combined antacids and is practically absent in resorbable preparations. Adsorption of pepsinogen and pepsin, bile acids, lysolecithin, toxins, bacteria leads to a decrease in the proteolytic activity of gastric juice and a decrease in the damaging effect of a number of other aggression factors.

Improving the protective properties of the mucous membrane (gastroprotective effect). It does not depend on the acid-neutralizing ability of antacids and is most characteristic of Bi- and Mg-containing preparations. Under their influence, there is a slight increase in the synthesis of cytoprotective and vasoactive prostaglandins, as well as the binding of the epithelial growth factor to its fixation in the area of the ulcer defect. As a result, this stimulates the proliferation and normal differentiation of cells, the development of vascular collaterals and tissue regeneration, which, of course, affects the quality of the forming scar at the site of the ulcer defect. Al-, Bi- and Mg-containing drugs can increase the formation of mucus and fucoglycoproteins, which further increases the resistance of the gastric mucosa to the action of aggression factors.

Enveloping and / or astringent (for Bi preparations) action. It is characterized by a decrease in the contact of aggressive factors of the gastric environment with the wall of the organ and is accompanied by an increase in the protection of the mucous membrane from the action of aggressive factors, and an increase in its resistance.

Low anti-inflammatory effect. To a greater extent inherent in Bi- and Mg-containing antacids and can somewhat reduce the severity of inflammatory processes in the mucous membrane.

Ideal Antacid Requirements

• High acid neutralizing and adsorbing activity.

• Retention of intragastric pH in the range of 3.0-5.0.

• Quick onset and lasting effect.

• Lack of secondary hypersecretion.

• Lack of gas formation.

• Lack of systemic side effects and CBS disturbances associated with cation absorption.

• Good organoleptic properties.

• Stability during long-term storage.

• Acceptable price.

General indications for the use of antacids: ulcer of the stomach and duodenum, reflux esophagitis, hiatal hernia. These drugs can be successfully used for the treatment of peptic ulcer in order to consolidate remission, treat its mild forms and relieve episodically occurring symptoms if eradication of HP has been performed.

The modern tactics of using this group of drugs gives unconditional preference to combined antacids, especially drugs with an average KHA and a sufficient duration of action, among which the most successful combination is aluminum hydroxide / magnesium hydroxide and magaldrate. Resorbable drugs retain very limited use only as a means of quick one-time relief of pain and heartburn, as they have a wide range of side effects. Doses of sodium bicarbonate and calcium carbonate in this case are 0.25-1.0 g.

Mixed antacids differ from combined preparations by the additional introduction of bismuth salts and plant extracts into the formulation. The bismuth subnitrate or basic nitrate that is part of them has an astringent and antibacterial effect; antiseptic and anti-inflammatory effect is inherent in chamomile and fennel; calamus rhizome powder improves digestion; Licorice has a gastroprotective effect; buckthorn bark powder gives a laxative effect; rutin and kellin provide anti-inflammatory effect; in addition, kellin has an antispasmodic effect. Currently, drugs in this group have largely lost ground to combined antacids. However, sometimes they are used in combination with tablet forms of combined antacids. Average doses are 2 tablets 4 times a day and at night.

In the treatment of ulcer, antacids are well combined with other antisecretory drugs, which can significantly accelerate the duplication of pain and dyspeptic disorders. With rational therapy with drugs of this group, after 2-3 days there is a significant decrease in pain, heartburn, normal gastrointestinal motility.

When using antacids, it should be borne in mind that: - drugs should be taken during the termination of the buffering action of food at the maximum gastric secretion (approximately 1 hour after eating);

- it is necessary to replenish the antacid equivalent after evacuation of the gastric contents (3 hours after eating). It should be borne in mind that the neutralizing effect of antacids taken after meals is longer than when taken before meals;

- obligatory intake of the drug before bedtime: to suppress nighttime secretion during an exacerbation of ulcer, it is necessary to take an antacid every 1-2 hours (from 2 to 4 weeks), followed by intake in the inter-digestive period;

- the frequency of taking the drug is more important than the dose;

- it is necessary to additionally take into account the individual "profile" of pain, timed administration of drugs at the time they occur;

- gelled antacids, as a rule, are superior to tablet formulations of drugs in terms of KNA and duration of action.

Depending on the location of the ulcer, standard treatment regimens may undergo some changes.

With pronounced signs of hyperacidity (painful heartburn, belching acidic, high level of basal secretion), it is recommended to take an additional 5 ml of antacid 20-30 minutes before meals.

The feasibility of prescribing antacids with low and normal acidity is doubtful, although their use is sometimes recommended 10-15 minutes before or during meals.

The main disadvantage of most recommended regimens is the development of side effects in patients with antacids. Most often, they occur in the form of dyspeptic disorders. In this case, for correction, you can try to use the multidirectional effect on the stool of Mg-containing (cause diarrhea) or Al-containing (cause constipation) antacids. Another disadvantage of these drugs is the need for their frequent use (more than 4 times a day), which reduces the patient's adherence to treatment. You should also not prescribe drugs containing aluminum hydroxide and magnesium, long-term courses, as in this case, the risk of developing gastrointestinal tract evacuation disorders and encephalopathy is significantly increased.

Despite the rather high efficiency of modern combined antacids and the evidence that has appeared in recent years that in monotherapy their effectiveness for treating ulcer is 70-75%, it is still advisable to consider this class of drugs as additional antiulcer drugs. Antisecretory drugs

Means that block cholinergic receptors:

- M - anticholinergic blockers of non-selective action (non-selective) - atro-pin sulfate, metacin.

- Means that block mainly M1 - cholinergic receptors (selective) - gastrocepin = pirenzepine, telenzepine;

- Ganglion blockers - pyrene, benzohexonium;

H2 blocking histamine receptors:

1st generation - cimetidine (histodine, whiteness, tagomet, acyloc); 2nd generation - rapitidine (ranisan, acyloc E, zantac, ranigast); 3rd generation - famotidine (ul-famid, pepsid); 4th generation - nizatidine (axide); 5th generation - roxacidin.

Inhibitors of the proton ("proton") pump:

1st generation - omeprazole = gastrosol, vine, omizac; 2nd generation - lapsop split; 3rd generation - pantoprazole; 4th generation - rabeprazole = soars; 5th generation - nexium; 6th generation - tenatoprazole. Atropine and atropine-like drugs are contraindicated in glaucoma, prostate adenoma, heart failure. Their use is unhealthy in case of cardia insufficiency and gastroesophageal reflux, which are often associated with peptic ulcer, since in such cases the reverse reflux of acidic gastric contents from the stomach to the esophagus may increase. In addition, in recent years, it was found that the antiulcer activity of traditional (non-selective) anticholinergics is insufficient. So, for example, the antisecretory effect of platifillin turned out to be weak, while atropine did not last long. Therefore, atropine, platifillin and metacin have become less commonly used in the treatment of peptic ulcer in recent years. At the same time, the drug pirenzepine (gastrocepin), which also blocks cholinergic receptors, but significantly different in its mechanisms of action from atropine and other cholinolytics, has found widespread use in clinical practice.

Pirenzepine is a selective cholinolytic drug that selectively blocks predominantly M1 cholinergic receptors of the gastric mucosa and does not affect therapeutic doses of the choline receptors of the salivary and bronchial glands, cardiovascular system, eye tissues, and smooth muscles. Despite its structural similarity to tricyclic antidepressants, pirenzepine does not cause undesirable reactions from the central nervous system, since, having predominantly hydrophilic properties, it does not penetrate the blood-brain barrier.

Pharmacodynamics

The leading mechanism of the antiulcer action of pirenzepine is the suppression of hydrochloric acid secretion. With oral administration, the maximum antisecretory effect is observed after 2 hours and lasts, depending on the dose taken, from 5 to 12 hours. Nocturnal secretion of hydrochloric acid is inhibited by 30-50%, basal - by 40-60%, and secretion stimulated by pentagastrin - by 30-40%. Pirenzepine suppresses the basal and stimulated production of pepsin, but does not affect the secretion of gastrin and a number of other gastrointestinal peptides (somatostatin, neurotensin, secretin).

Pirenzepine somewhat slows the evacuation from the stomach, but, unlike non-selective anticholinergic blockers, when taken orally in moderate therapeutic doses, it does not reduce the tone of the lower esophageal sphincter. With intravenous administration of the drug, sphincter tone and esophageal motility decrease.

The effectiveness of pirenzepine in the treatment of peptic ulcer was initially explained by its antisecretory activity. However, subsequent work showed that the drug has a cytoprotective effect, that is, the ability to increase the protective properties of the gastric mucosa. This effect is to a certain extent associated with the ability to expand the blood vessels of the stomach and enhance the formation of mucus.

Pharmacokinetics

Gastrin receptor antagonists: proglumide (milid) - a derivative (derivative) of glutamic acid.

2. Antimicrobial agents: imidazole groups (metronidazole), penicillins (amoxicillin) tetracycline (tetracycline, doxycycline), macrolides (clarithromycin, erythromycin), nitrofurans (furazoli-don).

3. Gastrocytoprotectors

a. Preparations that create mechanical protection of the mucous membrane (su-kralfat (Venter); bismuth citrate base, de-nol, smecta)

b. Drugs that increase the protective function of the mucous barrier and the stability of the mucous membrane to the action of damaging factors of the prostaglandins and their synthetic derivatives: misoprostone (cytotek, siteitek), a synthetic analogue of PgE1.

4. Reporters: methyluracil, pentoxyl, anabolic steroids (retabolil, methandrostenolone), potassium orotate, ATP preparations, biogenic stimulants (salt-coseryl, Kalanchoe juice, apilak, propolis, rosehip oil, sea-buckthorn oil, eta-den, sodium oxyferrycororbone, gastof, gastof)

SELECTIVE CHOLINOLITICS

The use of anticholinergics as antiulcer drugs is explained by their influence on the main pathogenesis links of this disease. Holinolitics reduce acid production, inhibit gastrin release, reduce pepsin production, prolong the effect of antacids, enhance the buffering properties of food, and reduce the motor activity of the stomach and duodenum.

At the same time, the use of drugs such as atropine, platifillin and metacin in the treatment of peptic ulcer is limited due to the systemic nature of their anticholinergic action and, as a consequence, the high frequency of undesirable reactions. The latter include dry mouth, disturbance of accommodation, tachycardia, constipation, urinary retention, dizziness, headache, and insomnia.

The bioavailability when taken on an empty stomach is an average of 25%. Food reduces it to 10-20%. The maximum concentration of the drug in serum develops 2-3 hours after oral administration and 20-30 minutes after intramuscular injection. Only about 10% of the drug is metabolized in the liver. Excretion is carried out mainly through the intestines and to a lesser extent through the kidneys. The elimination half-life is 11 hours.

Clinical efficacy and indications for use

Over the past years, many works have been published that testify to the rather high efficiency of pirenzepine in the treatment of exacerbations of gastric ulcer and duodenal ulcer. In particular, the ability of the drug to quickly stop pain and dyspeptic disorders was noted. Pirenzepine had no hepatotoxic and nephrotoxic effects and was effective in patients with so-called "hepatogenic" ulcers, usually resistant to the treatment, in patients with chronic renal failure, in the elderly. There are reports of successful use of the drug in the treatment of erosive and ulcerative lesions of the gastric mucosa caused by taking non-steroidal anti-inflammatory drugs.

In general, the use of pirenzepine at a dose of 100-150 mg per day allows the healing of duodenal ulcers within 4 weeks in 70-78% of patients. The drug can be used to prevent the occurrence of "stress" ulcers, as well as for preventive therapy.

Adverse reactions

Pirenzepine is generally well tolerated. Dry mouth, accommodation disorders are sometimes noted, less often - constipation, tachycardia, headaches. Moreover, the frequency of their occurrence clearly correlates with the dose. So, when prescribing medium therapeutic doses (100 mg per day), dry mouth occurs in 7–13% of patients, and accommodation disturbance occurs in 1–4% of patients. At higher doses (150 mg per day), the frequency of these adverse reactions increases to 13–16% and 5–6%, respectively. In most cases, adverse reactions are mild and do not require discontinuation of the drug.

Pirenzepine usually does not cause an increase in intraocular pressure, impaired urination and adverse reactions from the cardiovascular system. However, with glaucoma, prostate adenoma and a tendency to tachycardia, the drug should be prescribed with caution.

Drug interactions

Pirenzepine reduces the stimulating effect of alcohol and caffeine on gastric secretion. The simultaneous administration of pirenzepine and H2 blockers leads to potentiation of antisecretory action, which can be used in patients with Zollinger-Ellison syndrome.

Dosage and Administration

With exacerbation of peptic ulcer - 50 mg 2 times a day (morning and evening) half an hour before meals. The duration of the course is usually 4-6 weeks. With maintenance therapy, 50 mg per day.

Intravenously or intramuscularly - with very persistent pain (for example, in patients with Zollinger-Ellison syndrome) - 10 mg 2-3 times a day. Intravenous administration is performed slowly in a jet or (better) droplet fashion.

Release Forms

25 and 50 mg tablets; ampoules of 10 mg / 2 ml.

H2-HISTAMINE RECEPTOR BLOCKERS

H2 blockers, which have been used in clinical practice since the mid-70s, are currently among the most common antiulcer drugs. Several generations of these drugs are known. After cimetidine, ranitidine, famotidine were synthesized sequentially, and later, nizatidine and roxatidine.

Pharmacodynamics

The main effect of H2-blockers is antisecretory: due to the competitive blocking of H2-histamine receptors in the mucous membrane of the stomach, they inhibit the production of hydrochloric acid. This is due to their high antiulcer activity. New generations of drugs are superior to cimetidine in the degree of suppression of nighttime and total daily secretion of hydrochloric acid, as well as in the duration of the antisecretory effect.

In addition to inhibiting the secretion of hydrochloric acid, H2-blockers also have a number of other effects. They suppress basal and stimulated production of pepsin, increase the production of gastric mucus and bicarbonates, enhance the synthesis of prostaglandins in the wall of the stomach, and improve microcirculation in the mucus. In recent years, it has been shown that H2-blockers inhibit mast cell degranulation, reduce the histamine content in the periulcerous zone and increase the number of DNA-synthesizing epithelial cells, thereby stimulating reparative processes.

H2-histamine blockers (H2-GB) competitively inhibit the action of histamine on the H2-histamine receptors of the lining and main cells, suppressing basal and stimulated secretion In this case, there is a decrease in the production of HC1 and pepsinogen without a concomitant decrease in the formation of mucus and bicarbonates. Gastrin production is slightly suppressed, severe suppression is possible only with high doses and long-term treatment. Under the influence of some H2-GB (ranitidine, famotidine), the formation of prostaglandin (Pg) E2 in the mucous membrane of the stomach and duodenum increases, which mediates their cytoprotective and indirect reparative effect. In addition, the ability of ranitidine to increase the tone of the lower esophageal sphincter has been shown, which is especially important for eliminating heartburn.

Representatives of all three generations of H2-GB have a direct antioxidant effect both due to the blockade of the formation of hypochlorous acid and hydroxyl radical, and due to an increase in the activity of superoxide dismutase, the most important antioxidant enzyme. Perhaps these effects,

combined with a pronounced antisecretory effect, can help to reduce damage to the gastrointestinal mucosa in peptic ulcer disease.

A special place is occupied by ranitidine-bismuth citrate (pyloride), which is a complex consisting of ranitidine, trivalent bismuth and citrate in a weight ratio of 81:64:55. In the stomach, the drug dissociates into individual components: ranitidine blocks the H2-histamine receptors of the gastric lining cells, bismuth citrate has an astringent and gastroprotective effect on the gastric mucosa and a bactericidal effect against Helicobacter pylori. The drug found predominant use in anti-Helicobacter therapy regimens.

When taken orally, drugs have a fairly high bioavailability, independent of food intake. Maximum blood concentrations are established after about 1-3 hours. An important indicator of the effectiveness of the drug is its IC50 concentration in the blood, at which stimulated acid production decreases by 50%. So, for famotidine it is almost 1.5 orders of magnitude lower than for cimetidine.

Comparison of the effects of different regimens and doses of drugs (in equivalent doses) showed the absence of significant differences in their clinical efficacy. On average, the healing frequency of peptic ulcers over a 4-6-week period with an H2-GB value of about 2 times exceeds this indicator with a placebo, with a mediastral efficacy somewhat lower. In the treatment of ulcer in most patients, it is sufficient to take H2-GB once a day (at night).In patients with severe pain, the dose can be divided into two doses (morning-evening).

Similar efficacy of H2-GB is also shown in relation to NSAID-induced ulcers. In standard doses, these drugs can prevent ulceration in the duodenum, however, for successful prevention of gastric ulcers, as a rule, doubling the dose of the drug is required (for example, famotidine up to 80 mg / day). At the same time, H2-GB are more effective than antacids and gastroprotectors (sucralfate, misoprostol), but are noticeably inferior to proton pump inhibitors.

Conditions that are accompanied by more pronounced hyperacidity (reflux esophagitis, Zollinger-Ellison syndrome) require an increase in either the dose or the frequency of administration of the drugs (see table 7.13). So, in patients with reflux esophagitis, frequent use of H2-GB is close in effectiveness to the action of proton pump inhibitors (PPIs) and is comparable to cisapride monotherapy (for mild esophagitis). H2-GB can reliably reduce heartburn, although the endoscopic signs of esophagitis subside in only 60% of patients even after 12 weeks of therapy.

Long-term antisecretory therapy of H2-GB with this pathology, although it leads to an improvement in well-being and healing of esophageal erosion, however, in the future, after 6-12 months, regardless of the original drug used, relapse occurs in 36-82% of patients in the absence of maintenance therapy . After discontinuation of antisecretory therapy, the symptoms may resume within the first day, and erosion in the esophagus appears within 10-30 days, which requires long-term maintenance therapy.

With Zollinger-Ellison syndrome, a 3-4-fold intake of drugs should provide acid production at a level of 10 meq / h (pH about 4.0) However, even in this case, the effectiveness of therapy ranges from 50-70%, which may require the replacement of H2-GB with PPI.

A special area of application of H2-GB in ulcer is maintenance therapy, in which these drugs can sometimes be more preferable than, for example, PPIs (since they do not cause severe hypergastrinemia). So, a single half-dose dose of H2-GB overnight from the average therapeutic dose has been successfully used to prevent recurrence of ulcer, reduce the risk of repeated bleeding and stop the symptoms of hyperacidity. In this case, during the year, exacerbation symptoms develop only in 20% of patients compared with 60-70% of patients not receiving treatment. It is possible to increase the effectiveness of anti-relapse treatment by conducting anti-Helicobacter therapy.

Although the clinical efficacy of H2-GB is quite high, there is a group of patients (11-25% of all patients with ulcer) resistant to this group of drugs. Among the main causes of refractory

- high maximum gastric secretion;

- insufficient drug suppression of gastric secretion (especially at night);

- certain structural features of the ulcer itself (large sizes, linear shapes, location near the pyloric canal);

- male gender (especially elderly people with a long ulcerative anamnesis);

- smoking;

- prolonged or uncontrolled use of non-steroidal anti-inflammatory drugs (NSAIDs);

- HP infection;

- low adherence to treatment.

In this case, an increase in the dose (or the duration of treatment) and the transition to PPI can give some effect.

The frequency and severity of side effects caused by H2-GB is generally small: with cimetidine, it is 3.2%, ranitidine - 2.7%, famotidine - 1.3%.

Due to the significant antisecretory effect, H2-GB can affect the pH-dependent absorption of drugs by changing their ionization. So, cimetidine reduces the absorption of ketoconazole, antipyrine, chlorpromazine and iron preparations. With the simultaneous administration of other drugs along with H2-GB, it is recommended that they be taken 1-2 hours before taking H2-GB.

The absorption of H2-GBs themselves is reduced to 30% when taken together with aluminum-containing antacids or sucralfate, which makes it reasonable to use antacids 2 hours after H2-GB. However, with such a regimen of administration, the effectiveness of sucralfate may slightly decrease.

H2-GB are a widely prescribed group of drugs that are used in many areas of gastroenterology due to their high safety and favorable price / effectiveness ratio. Famotidine, which has a number of advantages compared with other drugs in this group, can be called one of the best H2-GB:

• The highest activity.

• Enough long action.

• The minimum number of side effects and the greatest safety during prolonged use.

• Lack of interaction with the cytochrome P-450 system.

• Availability of dosage forms for oral and parenteral use.

• Relatively low cost.

In addition, a number of pharmacokinetic and pharmacodynamic interactions with other drugs are inherent in drugs of this group means. They are mainly due to the ability of some H2-GBs to inhibit the P-450 cytochrome system in the liver or by reducing the active secretion of drugs by the kidneys, which leads to an increase in the concentration of drugs in the blood. The main drug interactions of H2-GB are presented in table. 7.15.

Pharmacokinetics

When administered, H2 blockers are well absorbed in the proximal sections of the small intestine, reaching peak blood concentrations after 30-60 minutes. The bioavailability of cimetidine is 60-80%,

ranitidine - 50-60%, famotidine - 30-50%, nizatidina - 70%, roxatidine - 90-100%. Excretion of drugs is carried out through the kidneys, and 50-90% of the dose taken is unchanged. The half-life of cimetidine, ranitidine and nizatidine is 2 hours, famotidine - 3.5 hours, roxatidine - 6 hours.

H2-GB is partially metabolized in the liver and in a significant amount (up to 50-60%) is excreted by the kidneys unchanged (especially after intravenous administration) both by filtration and by the mechanism of active tubular secretion, which requires dose adjustment in cases of impaired renal function .

Clinical efficacy and indications for use

15 years of experience with H2 blockers have convincingly proven their high effectiveness. After their introduction into clinical practice, the number of surgical interventions for peptic ulcer in many countries decreased by 6-8 times.

When using H2-blockers for 2 weeks, pain in the epigastric region and dyspeptic disorders disappear in 56-58% of patients with exacerbation of stomach ulcers and 12 duodenal ulcers. After 4 weeks of treatment, scarring of duodenal ulcers is achieved in 75-83% of patients, after 6 weeks in 90-95% of patients. Gastric ulcers heal somewhat more slowly (as with other drugs): the frequency of scarring after 6 weeks is 60-65%, after 8 weeks - 85-90%.

Comparative multicenter randomized trials showed that the effectiveness of double and single doses of cimetidine, ranitidine, famotidine, nizatidine is approximately the same. Comparing the separate generations of H2-blockers, it should be noted that, although ranitidine and famotidine are superior to cimetidine in antisecretory activity, no convincing evidence of their higher clinical efficacy has been obtained. The main advantage of the latter is better patient tolerance. Nizatidine and roxatidine do not have any particular advantages over ranitidine and famotidine and therefore are not widely used.

For the treatment of ulcerative lesions of the stomach and duodenum in patients with Zollinger-Ellison syndrome, H2 blockers are prescribed in very high doses (4-10 times higher than the average therapeutic ones), and in case of ulcerative bleeding parenterally.

H2-blockers are used for anti-relapse therapy, for the treatment and prevention of erosive and ulcerative lesions of the stomach and duodenum, caused by the use of non-steroidal anti-inflammatory drugs, as well as “stress” ulcers.

Adverse reactions

Characteristic mainly for cimetidine:

• antiandrogenic effect observed with prolonged use (especially in high doses) is manifested by an increase in prolactin levels in the blood, the occurrence of galactorrhea and amenorrhea, a decrease in the number of spermatozoa, and the progression of gynecomastia and impotence;

• hepatotoxicity: impaired hepatic blood flow, increased levels blood transaminases, in rare cases, acute hepatitis;

• penetrating the blood-brain barrier, the drug causes cerebral disorders (especially in the elderly): headaches, anxiety, fatigue, fever (due to the effect of the drug on hypothalamic thermoregulation centers), depression, hallucinations, confusion, sometimes to whom;

• hematotoxicity: neutropenia, thrombocytopenia;

• cardiotoxicity: sinus node weakness syndrome, rhythm disturbances;

• nephrotoxicity: increased serum creatinine.

Next-generation H2 blockers - ranitidine, famotidine, nizatidine and roxatidine - are much better tolerated. They do not have antiandrogenic and hepatotoxic effects, do not cross the blood-brain barrier and do not cause neuropsychiatric disorders. When using them, only dyspeptic disorders (constipation, diarrhea, flatulence) and allergic reactions (mainly in the form of urticaria), which are relatively rare (1-2%), can be noted.

With prolonged use of H2 blockers (more than 8 weeks), especially in high doses, one should bear in mind the potential possibility of developing hypergastrinemia with subsequent hyperplasia of enterochromaffin cells in the gastric mucosa.

With the abrupt cancellation of H2 blockers, especially cimetidine, the development of a "rebound syndrome" is possible, accompanied by secondary hypersecretory reactions. Drug interactions

Cimetidine is one of the most potent inhibitors of the microsomal cytochrome P-450 system in the liver. Therefore, it slows down the metabolism and increases the concentration in the blood of a number of drugs: theophylline, diazepam, propranolol, phenobarbital, indirect anticoagulants and others. Weak inhibition of cytochrome P-450 by ranitidine has no clinical significance. Other H2 blockers do not have such an effect at all.

H2 blockers can reduce the absorption of ketoconazole, which depends on the presence of hydrochloric acid in the stomach.

Dosage and dosage forms

Cimetidine (altamet, histodil, neutronorm, primamet, tagamet) with ulcer exacerbation is usually prescribed 200 mg 3 times a day before meals and 400 mg at night (1000 mg per day). In renal failure, the dose is reduced to 400-800 mg per day. The maintenance dose is 400 mg at night. With ulcerative bleeding, intramuscularly or intravenously, 200 mg 8-10 times a day. Available in tablets of 200 and 400 mg, ampoules of 200 mg / 2 ml.

Ranitidine (zantac, raniberl, ranisan, histak, ulcodin) is used in a therapeutic dose of 150 mg 2 times a day (morning and evening) or 300 mg at night. The maintenance dose is 150 mg at night. In chronic renal failure, the therapeutic dose is reduced to 150 mg, the maintenance dose is reduced to 75 mg per day. With bleeding , intramuscularly or intravenously, 50 mg every 6-8 hours. Available in tablets of 150 and 300 mg, ampoules of 50 mg / 2 ml.

Famotidine (gastrosidine, quamatel, lecedil, ulfamide) is prescribed 20 mg 2 times a day or 40 mg at bedtime. The maintenance dose is 20 mg at night. In chronic renal failure, the therapeutic dose is reduced to 20 mg per day or the intervals between doses are increased (up to 36-48 hours). Intravenously - 20 mg every 12 hours (per 5-10 ml of isotonic sodium chloride solution). Available in tablets of 20 and 40 mg, ampoules of 20 mg.

Nizatidine (axide) - 150 mg 2 times a day or 300 mg at night. The maintenance dose is 150 mg per day. In chronic renal failure - 150 mg per day or every other day. With bleeding - intravenously drip for a long time at a rate of 10 mg / hour or 100 mg for 15 minutes. 3 times a day. Available in capsules of 150 and 300 mg, bottles of 100 mg / 4 ml.

Roxatidine (Roxane) - 75 mg 2 times a day or 150 mg at night, with maintenance therapy - 75 mg per day. With chronic renal failure - 75 mg 1 time per day or every other day. Available in tablets of 150 mg.

PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs) are central to antiulcer drugs. This is due, firstly, to the fact that they are significantly superior to other drugs in antisecretory activity (and therefore in clinical efficacy). Secondly, IDUs create a favorable environment for the anti-helicobacter effect of antibacterial

agents, and therefore they are included as an integral component in most eradication schemes of the pyloric helicobacter. • Omeprazole (Lo-sec).

Proton pump inhibitors

• Pantoprazole (Control).

• Rabeprazole (Pariet).

• Lansoprazole (Lanzap).

• Esomeprazole (Nexium). Combined:

• Pilobact (omeprazole + clarithromycin + tinidazole).

• Zegeride (omeprazole + sodium bicarbonate).

Pharmacodynamics

Inhibition of the proton (acid) pump is achieved due to inhibition of the H + K ± ATPase of parietal cells. The antisecretory effect in this case is realized not by blocking any receptors (H2-histamine, M-cholinergic) involved in the regulation of gastric secretion, but by directly affecting the synthesis of hydrochloric acid. The functioning of the acid pump is the final stage of biochemical transformations within the parietal cell, the result of which is the production of hydrochloric acid. By acting on this stage, PPIs cause maximum inhibition of acid formation.

IDUs initially do not have biological activity. But, being chemically weak bases, they accumulate in the secretory tubules of parietal cells, where under the influence of hydrochloric acid they are converted to sulfenamide derivatives, which form covalent disulfide bonds with cysteine H + K ± ATPases, inhibiting this enzyme. To restore secretion, the parietal cell is forced to synthesize a new enzyme protein, which takes about 18 hours.

The high therapeutic efficacy of PPIs is due to their pronounced antisecretory activity, 2-10 times higher than that of H2 blockers. When taking the average therapeutic dose 1 time per day (regardless of the time of day), gastric acid excretion during the day is suppressed by 80-98%, while when taking H2-blockers - by 55-70%. Essentially, PPIs are currently the only drugs that can maintain an intragastric pH above 3 for more than 18 hours and thus satisfy the requirements formulated by Burget for ideal antiulcer drugs.

IITs do not directly affect the production of pepsin and gastric mucus, but - in accordance with the law of "feedback" - they increase (by 1.6–4 times) the level of gastrin in the serum, which quickly normalizes after discontinuation of treatment.

Pharmacokinetics

When ingested, the proton pump IDIs, falling into the acidic environment of the gastric juice, can prematurely turn into sulfenamides, which are poorly absorbed in the intestine. Therefore, they are used in capsules, resistant to the action of gastric juice. The bioavailability of omeprazole in such a dosage form is about 65%, pantoprazole is 77%, it is variable in lansoprazole. The drugs are rapidly metabolized in the liver, excreted through the kidneys (omeprazole, pantoprazole) and the gastrointestinal tract (lanoprazrazole). The half-life of omeprazole is 60 minutes, pantoprazole is 80-90 minutes, lansoprazole is 90-120 minutes. In diseases of the liver and kidneys, these values are not significantly changed. Sulfenamide is a charged molecule and therefore does not penetrate through cell membranes, remaining inside the secretory tubules of the parietal cell. Here, it irreversibly (with the exception of lansoprazole) covalently binds to the sulfhydryl groups of K + / H'-ATPase, which completely blocks its work

After ingestion of drugs, their antisecretory effect develops within about 1 hour and reaches a maximum after 2 hours. The duration of the antisecretory effect is determined by the rate of renewal of proton pumps - approximately half of them are updated in 30-48 hours. the receptor effect is not maximal, since not all K + / H'-ATPase molecules are in an active state. With a course prescription, the effect increases over 4 days, stabilizing by the 5th day (HC1 production is thus suppressed by more than 95%), i.e., the phenomenon of functional cumulation develops (accumulation of the effect of the drug, and not the actual substances).

Accordingly, the restoration of the enzyme after discontinuation of the drug also occurs after 4-5 days, which avoids the development of the "return" phenomenon. Thus, proton pump inhibitors provide an active, powerful and long-lasting suppression of acid production.

Since an acidic environment is necessary for the formation of the active form of PPI, the optimal effectiveness of the drug is observed when it is taken 30 minutes before meals. A less permanent effect is observed when taken on an empty stomach at night and when combined with other antisecretory drugs. Therefore, the appointment of drugs is recommended in the morning, before meals, 1 time per day.

Since PPIs are characterized by a relatively slow onset of action (not earlier than after 30-60 minutes), they are not suitable for “on demand” therapy (for relief of pain, heartburn), with the possible exception of rabeprazole, the inhibitory effect of which is already beginning to manifest itself after 5 minutes For such therapy, it is advisable to use modern antacids or soluble forms of H2-GB (the effect manifests itself within 1-6 minutes).

An attempt to create an IPP with a fast onset of action was the creation of a combination of omeprazole (20-40 mg) with sodium bicarbonate (1100 mg) - the preparation zegeride. The rapid development of the effect in this case is ensured by sodium hydrogen carbonate, and maintenance by omeprazole.

The pharmacokinetics of PPIs have similar features.Absorption of drugs (in the vast majority being optically active) occurs in the small intestine, after which they enter the liver, where they are metabolized by isoenzymes of the P-450 cytochrome system (CYP2C19 and CYP3A4) with the formation of inactive metabolites (effect of the "first pass"). In the human population, there are three groups of people with different IPP metabolism due to mutations in the gene encoding CYP2C19: 1) homozygotes with an intensive metabolism, 2) heterozygotes with an intermediate metabolism, and 3) gozozygotes with a low metabolic rate. So, the half-life of the drug in the 1st group is about 1 hour, and in the third - 2-10 hours.

According to metabolism, esomeprazole is significantly different from other PPIs, which is a product of stereoselective synthesis and is an S-isomer of omeprazole

As a result, esomeprazole has an almost 3 times lower (compared with omeprazole and R-isomer) clearance, which determines its higher bioavailability, since it is less exposed to the “first pass” effect. In addition, compared with omeprazole, esomeprazole more pronouncedly reduces acid production.

PPIs are excreted mainly with urine (up to 80%) in the form of inactive metabolites, which does not require a significant dose adjustment in case of impaired renal function. But in case of impaired liver function, the clearance of drugs can decrease sharply (which requires the appointment of half doses of drugs at the beginning of treatment with their subsequent increase).

This group of drugs is characterized by pharmacokinetic and pharmacodynamic interactions with a number of drugs. For long-term maintenance (anti-relapse) therapy, omeprazole (20 mg 3 times a week or daily) and lan-soprazole (30 mg each) are currently allowed for 4 (up to 6-8) weeks. At the same time, a significantly higher efficiency of daily intake of drugs was proved in comparison with a more convenient reception for patients only 2 days a week.

Proton pump inhibitors are used during anti-Helicobacter therapy (see below). At the same time, they provide not only moderate growth pressure of HP (due to a decrease in the activity of the urease of the microorganism), but also significantly potentiate the effectiveness of antibacterial agents. Especially for anti-Helicobacter therapy, a combined set of saw-bacterium has been created, which includes omeprazole capsules (20 mg), clarithromycin tablets (250 mg) and tinidazole (500 mg). 1 blister from this set contains the necessary daily doses of drugs and is taken in 2 doses per day, the course is calculated for 7 days.

The incidence and severity of side effects caused by PPI are generally small (up to 3-5%), especially with short courses of treatment (up to 3 months).

All PPIs reduce basal and stimulated gastric secretion regardless of the nature of the stimulus. Their clinical efficacy is the highest among antiulcer drugs.

Comparison of different regimens and preparations (in equivalent doses) showed the absence of significant differences in their clinical efficacy (esomeprazole may be somewhat more effective due to less variable metabolism, providing a more standard clinical response). Peptic ulcers scar in 2 weeks in 60-65% of patients, in 4 weeks in 96% of patients, mediastric ulcers in 4 weeks in 69%, in 8 - 89-93%. PPIs are effective and economically more beneficial with resistance to H2-GB antisecretory therapy - for example, scarring of stomach and duodenal ulcers with ranitidine-resistant ulcers on the background of omeprazole (40 mg / day) occurs in 94% of cases. PPIs (in standard doses) are also superior to H2-GB and prostaglandin preparations in the prevention and treatment of NSAID-induced ulcers. Clinical efficacy and indications for use

Multicenter and meta-analytical studies have confirmed the higher efficacy of IIT in the treatment of peptic ulcer exacerbations compared with H2 blockers. So, within 2 weeks, clinical remission (the disappearance of pain and dyspeptic disorders) is achieved in 72% of patients with duodenal ulcers and 66% with stomach ulcers. In 69% of patients, a peptic ulcer of the duodenum is scarred at the same time. After 4 weeks, healing of duodenal ulcers is already observed in 93-100% of patients. Gastric ulcers heal after 4 and 8 weeks, on average, in 73% and 91% of patients, respectively.

Gastroduodenal ulcers resistant to therapy with H2 blockers serve as a special indication for the use of PPI. This resistance occurs in 5-15% of patients receiving H2 blockers. With a 4-week application of IIT, duodenal ulcers heal in 87% and gastric ulcers in 80% of these patients, after 8 weeks in 98 and 94% of patients, respectively.

In case of difficult to heal ulcers, which are often localized in the stomach, an increase in the effect is noted with a double increase in the dose. The frequency of scarring after 4 weeks rises to 80%, and after 8 weeks to 96%.

PPIs are also used for anti-relapse treatment of peptic ulcer, for the treatment of peptic ulcer lesions caused by NSAIDs. In gastroduodenal ulcers in patients with Zollinger-Ellison syndrome, PPIs are prescribed in doses exceeding the average therapeutic by 3-4 times.

As already indicated, IDUs are part of many anti-helicobacter therapy regimens.

Adverse reactions

The safety profile of PPI with short (up to 3 months) courses of therapy is very high. Most often, headache (2-3%), fatigue (2%), dizziness (1%), diarrhea (2%), constipation (1% of patients) are noted. In rare cases, allergic reactions in the form of a skin rash or bronchospasm. With intravenous administration of omeprazole, isolated cases of visual and hearing impairment are described.

With prolonged (especially for several years) continuous administration of high-dose PPI (40 mg of omeprazole, 80 mg of pantoprazole, 60 mg of lansoprazole), hypergastrinemia occurs, atrophic gastritis progresses, sometimes - nodular hyperplasia of enterochromaffin cells of the gastric mucosa.

The need for long-term use of such doses is usually present only in patients with Zollinger-Ellison syndrome and in severe erosive-ulcerative esophagitis

It should be taken into account that with the use of IPP, reversible hypergastrinemia develops, due to the physiological response of G cells to an increase in intragastric pH.

It is most pronounced with prolonged (especially for several years) continuous intake of PPI (especially rabeprazole). It is believed that the hypergastrinemia caused by these drugs does not have significant clinical significance. However, one cannot ignore that against the background of this condition, the phenomena of atrophic gastritis can develop or progress, nodular hyperplasia of endocrine cells (ECL cells) of the gastric mucosa producing histamine may form, or the histological purity of the mucous membrane can change (gastrin has a noticeable mitogenic effect). In case of discontinuation of treatment, the level of gastrin in the blood serum returns to the initial level after 2-3 weeks. If prolonged or continuous therapy for PPI is necessary (without the possibility of replacing it with H2-GB) to reduce the severity of hypergastrinemia, synthetic analogues of prostaglandins (misoprostol) can be added to the scheme.

It also seems to be important to decrease the gastric motor-evacuation function of the stomach after IPP therapy (due to hypomotilinemia), which can be of great importance for patients with GERD.

PPIs are contraindicated in case of malignant neoplasms in the gastrointestinal tract, pregnancy (especially in the first trimester), and breastfeeding.

Dosage and dosage forms

Omeprazole (elk, omeprol, omez) is usually given orally at a dose of 20 mg once a day in the morning on an empty stomach. With ulcers that are difficult to heal, as well as with anti-helicobacter therapy, 20 mg 2 times a day. With maintenance therapy, the dose is reduced to 10 mg per day. In case of ulcerative bleeding, in case of "stressful" ulcers, 42.6 mg of omeprazole sodium (corresponding to 40 mg of omeprazole) is drip intravenously in 100 ml of 0.9% sodium chloride solution or 5% glucose solution. Available in capsules of 10 and 20 mg, in bottles of 42.6 mg of omep-razol sodium.

Pantoprazole - by mouth, 40 mg once daily before breakfast. With anti-gel-cobacter therapy, 80 mg per day. 45.1 mg of pantoprazole sodium (corresponding to 40 mg of pantoprazole) are dripped intravenously in an isotonic sodium chloride solution. Available in capsules of 40 mg, vials of 45.1 mg of pantoprazole sodium.

Lansoprazole (lanzap) - inside 30 mg once a day (morning or evening). With anti-helicobacter therapy - 60 mg per day. Available in capsules of 30 mg.

Drug interactions

Omeprazole and lansoprazole moderately inhibit cytochrome P-450 in the liver and, as a result, slow down the elimination of certain medications - diazepam, warfarin, phenothoin. At the same time, the metabolism of caffeine, theophylline, propranolol, quinidine is not disturbed. Pantoprazole has virtually no effect on cytochrome P-450. The antisecretory effect of drugs of this group is based on their ability to block M-cholinergic receptors (see Scheme 7.1). Non-selective M-cholinoblockers (M-HB) block M1-cholinergic receptors (M1-XP) in the intramural ganglia of the stomach and M3-XP on the lining and gastrin-producing cells of the mucous membrane, which leads to a decrease in basal and stimulated secretion to 50 % In addition, the blockade of M3-XP significantly affects the motility of the gastrointestinal tract - the tone, amplitude and frequency of peristaltic contractions decrease, the sphincters relax.

Side effects of non-selective M-CB are caused by blockade of M1-3 receptors in various organs and are similar to those of atropine, however, their severity is less. Preparations of this group are

contraindicated in case of glaucoma, prostate adenoma, pyloric stenosis, they are prescribed with caution in case of reflux esophagitis.

Of the selective M1-HB, pirenzepine, which blocks M1-X / P in the intramural ganglia of the stomach, as well as on the lining and gastrin-producing cells, has found clinical use. This drug has a fairly pronounced antisecretory activity, reducing basal secretion by 50-60% (when administered intravenously to 80-90%) and superior in clinical effect to both antacids and non-selective anticholinergic blockers, but inferior to H2-GB and PPI. The drug does not have a noticeable effect on the motor activity of the stomach, cardiac activity, the eye, does not penetrate the blood-brain barrier.

Pirenzepine is currently rarely used to treat moderate to mild peptic ulcer. At the same time, it can be combined with H2-GB, giving an additive effect. The drug is usually prescribed 50 mg 30 minutes before breakfast and dinner, the course of treatment is 3-4 weeks. It is also possible to take the drug prophylactically, primarily to prevent stress ulcers (50-100 mg 1-2 times a day) for up to 6 months. In an acute situation, intramuscular administration of 10 mg 2 times a day is allowed.

Side effects (given the lack of effect on M2 and M3 cholinergic receptors) are not pronounced and usually occur with prolonged use (most often dry mouth and dizziness).

Antisecretory drugs of different groups

Acetazolamide (diacarb) is a carbonic anhydrase inhibitor. As a result of the blockade of this enzyme, the formation of carbonic acid does not occur, which dissociates with the formation of a hydrogen proton and a bicarbonate ion (see. Scheme. 7.1). Moreover, basal secretion is reduced by more than 50% and stimulated by 60%. The effect persists after discontinuation of the drug for another 3-5 days. The antisecretory effect of the drug is manifested in large doses - 25 mg / kg 1-3 times a day. Due to the large number of side effects (paresthesia in the extremities, weakness, headaches due to electrolyte disturbances, and also a violation of CBS), diacarb is not currently used as an antisecretory agent.

Somatostatin (sandostatin, octreotide) is a synthetic analogue of somatostatin. It inhibits the secretion of hydrochloric acid, pepsinogen, gastrin and other entero-hormones, reduces blood flow in the gastrointestinal tract, and regulates the transport of water and electrolytes. In ulcer, it was used in the treatment of ulcerative bleeding and bleeding from varicose veins of the esophagus and stomach (25 μg per hour by continuous intravenous infusion for 5 days).

Prostaglandins. The antisecretory effect of prostaglandins E, A, I2 is realized through specific prostaglandin receptors (EP1-EP4) and manifests itself only in large doses, in smaller doses they have a gastroprotective effect, regulating microcirculation in the mucosa, secretion of mucus and bicarbonates (see below). Misoprostol (Saitotek), an agonist of EP2 / EP3 receptors, which is methylprostaglandin E1, has a therapeutic effect in gastroduodenal ulcers at a dose of 800 μg per day (in 2-4 doses) for 4 to 8 weeks. After a single dose of the drug, a decrease in the secretion of hydrochloric acid occurs after about 30 minutes, the maximum effect develops after 60-90 minutes.

A similar effect is exerted by a synthetic derivative of prostaglandin E2 - enprostil, an EP1 / EP3 receptor agonist, which showed a dose comparable to H2-GB at a dose of 70 μg (in 2 doses or overnight). In addition, prostaglandins are able to potentiate the antisecretory effect of H2-GB.

An unambiguous judgment on the antisecretory potential of this group of drugs has not yet been formed, however, a direct comparative study of misoprostol and omeprazole revealed the advantage of IPP in antisecretory effect. The use of these drugs is also hindered by tolerance problems and high cost.

AUXILIARY TREATMENT FOR ULCER DISEASES

Gastroprotectors

Gastroprotectors can be divided into two main groups: drugs whose action is associated with mechanical protection of the mucous membrane (film-forming) and affecting the physiological mechanisms of protection of the mucous membrane (prostaglandins).

Film-forming gastroprotectors:

• Sucralfat (Venter).

• Preparations of colloidal bismuth.

Non-film-forming gastroprotectors:

• Carbenoxolone (Biogastron).

• Ekabet sodium (Ekabet).

• Prostaglandins:

• Misoprostol (Saitotek).

• Enprostil.

Sucralfate is a complex of aluminum hydroxide and sucrose sulfate. Under the influence of hydrochloric acid in the stomach, the drug hydrolyzes and acquires a negative charge, forming a polyanion of sucralfate, which is accompanied by its transformation into a viscous sticky mass, which creates a protective film on the surface of the mucous membrane. Through electrostatic interactions with positively charged inflammatory exudate proteins at low pH (<4.0), sucralfate is fixed on the affected areas of the mucous membrane of the digestive tract (including on the surface of ulcerative defects). Sufficiently slightly neutralizing hydrochloric acid, sucralfate at the same time creates a protective film that isolates and protects the affected parts of the mucous membrane from aggressive factors. In addition, the drug has an adsorbing effect, increases the secretion of prostaglandins, mucus and bicarbonates in the mucous membrane of the stomach and duodenum. The pepsin activity in this case decreases by a third.

The drug is prescribed 1 tablet before each meal (3 times a day 1 hour before meals) and 1 tablet immediately before bedtime. The duration of treatment is an average of 4-6 weeks, up to a maximum of 12 weeks. Sucralfate is significantly inferior to proton pump inhibitors in peptic ulcer efficacy and now occupies a modest place in the treatment of this disease. Of the side effects of the drug, constipation is most often noted.

Among bismuth preparations, colloidal bismuth subcitrate (CVC), which has an antibacterial and gastroprotective effect proper and is slightly different in effect from other bismuth preparations, has found the greatest use. In an acidic medium, PBC forms precipitates in the form of glycoprotein-bismuth complexes, which are stored on the gastric mucosa for a long time. At the same time, the proteolytic activity of pepsin decreases, the secretion of bicarbonate and prostaglandins increases, the level of the epidermal growth factor increases, which increases the resistance of the mucous membrane to the action of aggressive factors and its reparative capabilities.

The bactericidal action of PBC is important. Thus, under the action of bismuth ions, HP loses its ability to adhere, vacuolization and fragmentation of the cell wall and the suppression of bacterial enzyme systems occur, i.e., a bactericidal effect is achieved. This effect is not insignificant (only in the range of 14–40%), but it is not susceptible to the development of resistance during CVC monotherapy, it is sharply potentiated with the simultaneous administration of bismuth preparations with antibiotics. The drug is given in the anti-Helicobacter therapy section.

The drug is well tolerated, due to its extremely low absorption from the gastrointestinal tract (less than 1%). Diarrhea, headache, dizziness rarely develop, cases of bismuth encephalopathy are described.

Carbenoxolone (biogastron) is obtained from licorice root. Its mechanism of action is not precisely established, but it is believed that due to its similarity with mineralocorticoid hormones, it enhances the secretion of mucus, which is a mucosal protective factor. It stimulates the formation of collagen in the ulcer and its epithelialization processes, activates the synthesis of prostaglandins. Assign 50-100 mg 3 times a day after meals for 4-8 weeks. The use of the drug is limited due to the large number of side effects. Like mineral corticoids, the drug retains sodium and water, enhances the excretion of potassium. Perhaps the development of edema, increased blood pressure.

A new word in the creation of mucosal cytoprotectors was the appearance of the sodium salt of 12-sulfodehydroabietic acid (ecobet sodium). Its mechanism of action is associated with the ability to stimulate the restoration of epithelial cells, increase the cytoprotective properties of the mucosa and inhibit 5-lipoxygenase and, accordingly, the formation of leukotriene B4.

In addition to the ability to activate the synthesis of mucopolysaccharides in the gastrointestinal mucosa and antisecretory activity (comparable to cimetidine), this drug interferes with the adhesion of IR, significantly increasing the percentage of eradication compared to the same scheme without mucoprotective support. Average doses of the drug are 1.5 g twice a day for 4-8 weeks.

The cytoprotective effect of prostaglandins E, A, I2 is realized due to binding to specific receptors (EP1-EP4) and is due to the following factors:

- optimization of blood flow in the gastrointestinal mucosa, a decrease in vascular permeability;

- increased secretion of mucus, fucoglycoproteins and bicarbonate, which leads to an increase in the protective properties of the mucosa

The gastroprotective effect after oral administration of drugs develops very quickly, but, unfortunately, is short-lived (up to 2 hours). Preparations of prostaglandins in cytoprotective doses (they are almost an order of magnitude smaller than antisecretory ones), unfortunately, do not give a reliable anti-ulcer effect, therefore they are prescribed in antisecretory doses in order to obtain a gastroprotective effect. Misoprostol has proven itself best as a protective anti-ulcerogenic agent when taking NSAIDs.

Side effects include diarrhea, abdominal pain, in women - menstrual irregularities, during pregnancy it may be interrupted.

Tissue-specific regeneration stimulants

Nonsteroidal Anabolics:

• Methyluracil (Metacil).

• Pentoxyl. Steroid Anabolics:

• Nandrolone decanoan (Retabolil).

In the treatment of peptic ulcer, drugs that stimulate regeneration processes in the gastrointestinal mucosa are sometimes used. The main effect of these drugs is the activation of mitotic activity and protein-synthetic processes, mainly in debilitated debilitated patients (the state after chemotherapy, exposure to ionizing radiation, etc.).

Of the non-steroidal anabolics, the limited use in the treatment of ulcer has found use of pyrimidine derivatives - methyluracil and pentoxyl. They are inhibitors of the uridine phosphatase enzyme, which breaks down the uridine monophosphate necessary for the synthesis of thymidine

monophosphate, which is a limiting substrate in DNA synthesis. Thus, mitotic activity of cells in rapidly renewable tissues (primarily epithelial) is stimulated, and processes of protein synthesis are activated. Average doses of methyluracil are 500 mg 4 times a day for 30-40 days, pentoxyl 200-300 mg 3-4 times a day for 24-30 days.

Steroid anabolics, interacting with specific nuclear receptors, cause a change in the activity of a number of genes, which leads to an increase in the formation of mRNA in the nucleus, and subsequently to a powerful stimulation of protein synthesis and an increase in the mitotic activity of cells. Most often in gastroenterology retabolil is used (intramuscularly 1 ml of 5% solution once every 3-4 weeks). For a full manifestation of the effect of the drug, a diet balanced in terms of protein, mineral and vitamin composition is necessary. The use of steroidal anabolics is limited by a large number of their side effects, among which are the manifestations of androgenization (especially dangerous for women), cholestasis, hormonal imbalance in men.

The activity of stimulants of regeneration of animals (solcoseryl) and plant (sea buckthorn, rosehip oil, aloe extract, etc.) origin remains the subject of discussion, and the clinical and economic feasibility of use is very doubtful.

In general, the question of the need for the use of reparants in ulcer disease cannot be considered resolved. Most of them have remained from the time when the main antisecretory agents had insufficient effectiveness. The final answer about the advisability of prescribing this group of drugs for ulcer can be obtained only when conducting studies in accordance with the standards of good clinical practice.

ANTIHELICOBACTER THERAPY

The great importance attached to the infection of Helicobacterpylori (HP) is due to the formation of Helicobacter pylori gastritis under the influence of this microorganism in the gastric mucosa, which is an important factor in the pathogenesis of ulcer, low grade malignant stomach lymphoma (maltoma), and gastric cancer.

Accordingly, the eradication of HP leads to the disappearance of inflammatory infiltrate in the gastric mucosa, a significant decrease in the frequency of relapses of ulcer, histological remission of gastric maltoma, and probably to a decrease in the risk of gastric cancer. In the absence of an inflammatory process, the mucous membrane is able to successfully withstand the effects of various factors of aggression.

The basis of anti-Helicobacter therapy is the use of antibacterial agents with the addition of antisecretory drugs. The additional inclusion of antisecretory drugs in AHT allows you to:

- increase the anti-Helicobacter activity of antibacterial agents;

- reduce the dose of antibiotics;

- reduce the duration of the course of treatment to 7-10 days;

- reduce the frequency of side effects and improve tolerability of the treatment regimen;

- reduce the cost of treatment.

In addition, the fact of a direct anti-Helicobacter pylori effect in IPP was established and the presence of a similar mechanism in H2-GB is assumed.

It makes sense to start IPP therapy somewhat earlier than using antibiotics, which can increase the effectiveness of antibacterial drugs (by increasing the pH of the gastric contents). An exception is rabeprazole, the maximum effect of which occurs very quickly

The ulcer associated with IR is an indication for anti-Helicobacter therapy (AHT) both in the period of exacerbation and in the period of remission of the disease. The basis of treatment is the use of combination (three-component) therapy, capable of eliminating IR in at least 80% of cases, effective for a course duration of no more than 7-14 days and not causing the cessation of anti-Helicobacter pylori treatment due to the development of side effects (permissible interruption cases treatment no more than 5%). Triple therapy for 14 days can increase the effectiveness of eradication compared to the 7-day regimen by about 12%. Moreover, the combination in a triple regimen of clarithromycin with amoxicillin is preferable to clarithromycin with metronidazole or amoxicillin with metronidazole. At the same time, if the resistance of HP to clarithromycin in a population of a particular region exceeds 15% or the patient has recently received this antibiotic, then a triple regimen should not be prescribed. It is advisable to start treatment with quadrotherapy (PPI + bismuth preparations + nitroimidazole + tetracycline) (Table 7.20). Quadrotherapy may also be preferred if the patient is intolerant of β-lactams.

The Maastricht agreement emphasizes that with uncomplicated ulcer of the duodenum, there is no need to continue antisecretory therapy after a successful course of eradication therapy. However, it is generally accepted in our country that AChT does not replace the basic treatment with anti-ulcer drugs, as it is not able to fully relieve pain, dyspeptic disorders and does not heal a ulcer in a short time, especially when it comes to large ulcers the stomach.

If the three-component therapy is ineffective (PPI + amoxicillin + metronidazole), you can repeat the eradication course with the replacement of nitroimidazole with clarithromycin or go to the triple combination with bismuth preparations or use the four-component treatment regimen.

If in this case as well, success cannot be achieved, a determination should be made of the sensitivity of the HP strain to all antibacterial agents included in AXT. So, in Europe by 2005 the average level of resistance of NR to metronidazole was 19-42% (Eastern Europe 37.9%), clarithromycin - 9.8% (4.4% in the north of Europe, 8.7% in the center, in the south - 24%, Eastern Europe - 9.5%, Moscow - 13-17%), tetracycline - 1.9%, amoxicillin - 0.9%, ciprofloxacin - 3.9%, combinations of metronidazole and clarithromycin - 6.1%

A constantly increasing level of resistance makes us look for new regimens and combinations of drugs that are highly effective at low or medium cost costs

It should be borne in mind that the effectiveness of eradication therapy is influenced by factors such as smoking and coffee consumption (decreased efficiency).

The appearance of a microorganism in the patient’s body a year after treatment should be considered as a relapse of the infection, and not reinfection, which requires the selection of a more effective anti-Helicobacter pylori regimen.

It should be emphasized that successful eradication of HP reduces both direct and indirect costs in the treatment of ulcer, including the elimination of the need for expensive maintenance treatment with antisecretory drugs, reducing the risk of repeated exacerbations, complications and surgical intervention.

In HP-positive patients with non-ulcer dyspepsia, anti-helicobacter therapy provides a small but statistically significant decrease in symptoms, but in patients with gastroesophageal reflux disease, HP eradication does not affect the severity of the disease and the frequency of relapses.

The purpose of the lesson:

To learn:

1. Classification of drugs used to treat peptic ulcer and hyperacid gastritis.

2. The role of genetic factors in the effectiveness of drug therapy.

Basic agents (mainly affecting aggression factors)

1. Antacid preparations.

a. Resorbable (absorbed):

Sodium bicarbonate (NaHCO3).

Calcium carbonate precipitated (CaCO3) - Calcimax

b. Non-absorbable (non-absorbable):

Monopreparations:

Algeldrat (aluminum hydroxide, Al (OH) 3) - Rochelle, Aluminum hydroxide.

• Rivopharm.

• Carbaldrate (sodium salt of dihydroxyaluminium carbonate) - Alyugastrin, Compensan.

• Magaldrate (magnesium hydroxide aluminate) - Magalfil, Magaldrat.

• Simaldrate (aluminum-magnesium trismetasilicate (in the form of a hydrate)) - Gelusil.

• Diamond (aluminum hydrated silicate) - Megalac diamond.

• Hydrotalcite (aluminum magnesium carbonate) - Rutacid, Tisacid.

• Aluminum phosphate (Al2 (PO3) 3) - Phosphalugel, Alfogel.

• Magnesium oxide (MgO).

• Magnesium hydroxide (Mg (OH) 2) - magnesia.

• Magnesium carbonate basic (Mg (OH) 2 • 4MgCO3 • H2O).

Combined:

1. Aluminum hydroxide + magnesium hydroxide:

Maalox (aluminum hydroxide, magnesium hydroxide).

• Almagel (aluminum hydroxide, magnesium hydroxide, D-sorbitol).

• Almagel-A (aluminum hydroxide, magnesium hydroxide, D-sorbitol, benzoca-in).

• Digin (aluminum hydroxide, magnesium hydroxide, dimethicone, sodium carboxymethyl cellulose).

• Alprogel (aluminum hydroxide, magnesium hydroxide, simethicone).

• Anacid compositum (aluminum hydroxide, magnesium hydroxide, oxetacaine).

2. Aluminum hydroxide + magnesium hydroxide + magnesium trisilicate:

• Gestide (aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, simeti-con).

3. Aluminum hydroxide + magnesium hydroxide + magnesium carbonate.

• Gastal (aluminum hydroxide, magnesium hydroxide, magnesium carbonate).

4. Aluminum hydroxide + magnesium hydroxide + calcium carbonate:

• Di Gel (aluminum hydroxide, magnesium hydroxide, calcium carbonate).

5. Aluminum hydroxide + aluminum oxide + magnesium oxide + magnesium carbonate:

• Regla PX (aluminum hydroxide, aluminum oxide, magnesium oxide, magnesium carbonate).

6. Aluminum hydroxide + magnesium hydrochloride:

• Alumag (aluminum hydroxide, magnesium hydrochloride).

7. Magnesium carbonate + calcium carbonate:

• Rennie (basic magnesium carbonate, precipitated calcium carbonate).

8. Magnesium carbonate + calcium carbonate + sodium bicarbonate:

Calmagin (basic magnesium carbonate, precipitated calcium carbonate, sodium bicarbonate).

Mixed:

• Alcide (bismuth subnitrate, sodium carbonate, sodium bicarbonate, aluminum hydroxide).

• Alcid-B (basic bismuth nitrate, basic sodium carbonate, aluminum hydroxide, licorice, chamomile, buckthorn bark extracts, coriander and fennel fruits).

• Vicalin (basic bismuth nitrate, basic magnesium carbonate, sodium hydrogen carbonate, calamus rhizome, buckthorn bark, rutin, kellin).

• Vicair (Rother) (basic bismuth nitrate, basic magnesium carbonate, sodium bicarbonate, calamus rhizome, buckthorn bark).

Ideal Antacid Requirements

I. Antisecretory drugs

1. Means that block cholinergic receptors:

M - anticholinergic blockers of non-selective action (non-selective) - atropine sulfate, metacin.

 Means that block mainly M1 - cholinergic receptors (selective) - gastrocepin = pirenzepine, telenzepine;

Ganglion blockers - pyrene, benzohexonium;

2. Means that block H2 histamine receptors:

1st generation - cimetidine (histodine, whiteness, tagomet, acylc);

2nd generation - rapitidine (ranisan, acyloc E, zantac, ranigast);

3rd generation - famotidine (ulfamide, pepsid);

4th generation - nizatidine (axide);

5th generation - roxacidin.

3. Inhibitors of the proton ("proton") pump:

1st generation - omeprazole = gastrosol, vine, omizac;

2nd generation - lapsoprazole;

3rd generation - pantoprazole;

4th generation - rabeprazole = soars;

5th generation - nexium;

6th generation - tenatoprazole.

4. Antagonists of gastrin receptors: proglumide (mild) - derivative (derivative) of glutamic acid.

II. Antimicrobial drugs:

1. Derivatives of imidazole (metronidazole),

2. Penicillins (amoxicillin)

3. Tetracyclines (tetracycline, doxycycline),

4. Macrolides (clarithromycin, erythromycin),

5. Nitrofurans (furazolidone).

III. Gastrocytoprotectors

a. Preparations that create mechanical protection of the mucous membrane (su-kralfat (Venter); bismuth citrate base, de-nol, smecta)

b. Drugs that increase the protective function of the mucous barrier and the stability of the mucous membrane to the action of damaging factors of the prostaglandins and their synthetic derivatives: misoprostone (cytotek, siteitek), a synthetic analogue of PgE1.

IV. Repairs:

1. anabolic steroids (retabolil, methandrostenolone),

2. non-steroidal anabolics: potassium orotate, methyluracil, pentoxyl,

3. ATP preparations,

4. biogenic stimulants (solcoseryl, Kalanchoe juice, Apilak, propolis, rosehip oil, sea buckthorn oil, etaden, sodium oxyferricorbon, gastopharm).

Know:

1. Etiology, pathogenesis, clinic, complications, acid-dependent gastrointestinal diseases

2. Research methods for gastroesophageal reflux disease, peptic ulcer, gastritis

3. The main etiological factors and pathogenetic mechanisms that are the object of drug exposure in gastroesophagal reflux disease, peptic ulcer, hyperacid gastritis

 M-anticholinergics. Mechanisms of action. Pharmacodynamics, pharmacokinetics. Undesirable effects.

 Features of the use of H2-histamine blockers. Mechanisms of action. Undesirable effects. Contraindications to the appointment. The phenomenon of "rebound"

 Features of the use of proton pump blockers. Mechanisms of action. Undesirable effects. Contraindications to the appointment.

 Features of the use of antacids. Mechanisms of action. Undesirable effects. Contraindications

4. Pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics, the interaction of the above drugs

5. The principles of complex therapy - peptic ulcer, gastroesophageal-reflux disease

3. Be able to:

a) select the necessary drugs for a particular patient with the indicated pathology, select criteria for therapeutic efficacy and safety;

b) prescribe combination therapy;

The list of practical works:

Homework.

1. To study the main tasks and directions of the choice of drugs for acid-dependent gastrointestinal diseases

The task for self-checking the initial level.

1. Etiology, pathogenesis, classification of peptic ulcer, GERD.

2. List the main groups of antisecretory and antacid drugs.

3. Formulate the significance of the leading pharmacokinetic characteristics (T1 / 2el,%, association with plasma proteins, \ / d l / kg) in an individual selection of the above drugs.

4. Highlight the clinical and laboratory-functional criteria for therapeutic efficacy of antisecretory and antacid drugs.

Task number 1.

A young woman in a pharmacy filed prescriptions for tetracycline, almagel, calcium gluconate for the treatment of acute bronchitis and bronchitis and gastritis in a 10-year-old child.

Rate these appointments. Your recommendations.

Task number 2

A patient with peptic ulcer of the duodenum with prescriptions for vicalin and almagel turned to the pharmacy. From the anamnesis it is known that a patient with fibro-gastroscopy shows Helicobacter pylori.

Tactics of treatment. Your recommendations.

Task number 3.

A patient with exacerbation of a duodenal ulcer (“hungry” and night pains, heartburn) turned to the pharmacy. From the anamnesis, you have established that he takes indomethacin for joint disease.

Your recommendations for treatment tactics.

Task number 4.

A lactating woman contacted the pharmacy so that she would be released omeprazole and metronidazole for the complex treatment of exacerbation of duodenal ulcer.

What is the tactic of a pharmacist? Your recommendations.

Task number 5.

Patient T., 24 years old, with complaints of heartburn, nightly and hungry pains in the epi-gastric region during endoscopic examination revealed an ulcer along the posterior wall of the duodenal bulb. Within a week, the patient received the therapy prescribed by the attending physician: clarithromycin 1 g, amoxicillin 2 g, omeprazole 40 mg / day. By the end of the seventh day, heartburn and pain persisted, but decreased in intensity and duration.

How can you increase the effectiveness of first-line therapy? What is the doctor's next tactic?

Task number 6.

Patient M., 52 years old, complains of aching pains in the epigastric region and left hypochondrium, which occur 10-20 minutes after ingestion of greasy, fried, spicy foods; aching pains in the thigh bones. According to FGS - antral gastritis. Found H. Pylori. According to radiography, there are signs of osteoporosis of the femur.

Formulate a diagnosis. Justify the choice of pharmacotherapy in this patient. Specify methods for monitoring the effectiveness and safety of the prescribed combination therapy.

Task number 7.

Patient P., 23 years old, was admitted to the hospital with complaints of heartburn, aching pain in the epigastric region on an empty stomach, stopped by taking soda. In FGS, a peptic ulcer (0.7 cm) along the anterior wall of the duodenal bulb. pH-metry: acid-forming function of the stomach of medium intensity with low alkaline reserves, cholinergic type of reception.

Formulate a diagnosis. Choose the most optimal drug for the treatment of the patient, determine the dosage and administration regimen. Explain the mechanism of action. Indicate the possible side effects of the selected drug.

Task number 8.

A 26-year-old patient was admitted to the therapeutic department with a diagnosis of exacerbation of duodenal ulcer with severe pain and dyspeptic syndrome. In complex therapy, the patient is prescribed atropine 0.1% solution of 0.5 ml subcutaneously 2 times a day. After a week, the pain syndrome and burns decreased significantly, while there was dryness in the mouth, nose, and vision deteriorated a little.

Assess the pharmacodynamics of atropine. What are the further tactics of using this drug?

Task number 9.

A patient, 32 years old, was admitted for treatment with a diagnosis of peptic ulcer with localization of an ulcer in the duodenal bulb. A functional study of the gastric contents revealed an increase in gastric secretion (basal and stimulated), a high level of acidity. With endoscopy, the presence of a chronic ulcer with a bleeding vessel.

Determine the effective drugs for the treatment of this disease, their dose, time and frequency of administration, duration of treatment.

Task number 10.

A 43-year-old patient is undergoing treatment in the gastroenterological department for exacerbation of duodenal ulcer. The study found a moderate increase in the acidity of the gastric contents, the presence of H. pylori. Make a selection of the drug or drugs that cause scarring of the duodenal ulcer, indicate their effective dose, time and frequency of doses, duration of treatment.

Task number 11.

A 42-year-old patient with gastrointestinal bleeding was delivered to the surgical department. An endoscopic examination revealed an acute stomach ulcer. History: rheumatoid arthritis. The pharmacotherapy of arthritis was carried out. What drug caused the development of a stomach ulcer and bleeding.

Task number 12.

The doctor prescribed an antacid for a man who suffers from duodenal ulcer. Against the background of taking the remedy, nausea and abdominal pain appeared. The examination revealed a violation of acid-base balance in the direction of alkalosis.

What drug could cause this disorder?

Task number 13.

Patient 21 years old, was admitted with complaints of heartburn, pain in the epigastric region on an empty stomach. EGDFS revealed an ulcer along the anterior wall of the duodenal bulb. Rn-measurement of gastric juice: acid-forming function of medium intensity with low alkaline reserves, cholinergic type of reception.

Task number 14.

Prescribe the most effective drug.

1. A patient came to your pharmacy about the first signs of an exacerbation of duodenal ulcer ("hungry" epigastric pain, heartburn). Your recommendations in this case. Prescribe prescriptions for your suggested medicines.

2. A patient with peptic ulcer of the duodenum with prescriptions for vicalin and almagel turned to your pharmacy. From the anamnesis you found out that he had the presence of Helicobacter pylori with fibrogastroduodenoscopy. Your opinion on treatment tactics. Your recommendations. Write out prescriptions for missing drugs.

3. The patient who went to the pharmacy complains of sharp pains in the stomach, which occurred suddenly after physical exertion, nausea, vomiting of "coffee grounds", dizziness, general weakness. The patient is pale, covered with cold, sticky sweat. What could be causing this condition? What is the tactic of a pharmacist?

4. Patient Z., 27 years old, complains of severe pressing pain in the epigastrium, closer to the median line, which regularly occurs between 24 and 3 o'clock in the morning, decreases after taking soda. Slight pain occurs in the same place after 1.5 - 2 hours after eating. The pain is accompanied by heartburn. These symptoms disturb the patient for approximately 15 days. Objectively: severe pain in the epigastrium during palpation. Your alleged diagnosis. Recommendations regarding treatment tactics. Write out the recipes.

TESTS

1. Indicate a central action drug - a dopamine receptor blocker used for nausea and vomiting accompanying gastrointestinal diseases, after surgery, for migraines, and also for vomiting provoked by cytotoxic drugs and radiotherapy.

A. Metoclopramide.

B. Famotidine.

C. Pancreatin.

D. Gastrocepin.

E. Dandelion root.

2. Indicate the group of drugs that inhibit the secretory function of the stomach.

A. H +, K + -ATP-inhibitors of the first and second generation ..

B. Blockers of H2 – histamine receptors of the first, second, third generations.

C. M1 anticholinergics.

D. Means that weaken the irritation of the afferent endings of the vagus nerve - antacids, adsorbents, enveloping, astringents, local anesthetics.

E. * All of the above groups.

3. Preparations for the etiological treatment of gastric ulcer.

A. Famotidine + Almagel.

B. Pantoprazole + Eglonil.

C. De-nol + metronidazole.

D. Gastrocepin + Elenium.

E. Omeprazole + misoprostol.

9. The child was diagnosed with peptic ulcer of the duodenum, fresh ulcer with increased acid-forming function of the stomach, in the phase of exacerbation. Helicobacter pylori detected. What is the minimum period of time for antichelicobacter therapy?

A. 3 days.

B. 7 days.

C. 14 days

D. 12 days.

E. 10 days.

10. Medicines used for gastric ulcer in order to improve the regenerative processes of the gastric mucosa and duodenal ulcer.

A. Famotidine + Almagel.

B. Pantoprazole + Eglonil.

C. De-nol + metronidazole.

D. Gastrocepin + Elenium.

E. Oxyferriscarbon + Vitamin U.

11 For the eradication of Helicobacter pylori, the combination therapy of chronic gastritis should include:

A. Gastrocepin.

B. Clarithromycin.

S. Almagel.

D. Ceftriaxone.

E. Furosemide

12. A patient came to the pharmacy with prescriptions for omeprazole 20 mg 1 time / day, clarithromycin 0.5 g 2 times / day. This treatment regimen was most likely prescribed for:

A. Chronic pancreatitis.

B. * Chronic gastritis type B.

C. Chronic hepatitis.

D. Chronic gastritis type A.

E. Chronic cholecystitis.

13. What is the most rational scheme for the use of almagel for exacerbation of duodenal ulcer? The drug should be used:

A. During meals and at bedtime.

B. Throughout the day with pain and at bedtime.

C. Just before each meal and at bedtime.

D. 1 and 3 hours after each meal and at bedtime

E. Immediately after each meal and at bedtime.

14. The patient, 38 years old, six months ago, during treatment in the clinic for duodenal ulcer, revealed an increase in cholesterol to 8.0 mmol / L. After a hypocholesterolemic diet for 6 months and morning exercises, cholesterol decreased in the range of 7.4 - 7.8 mmol / l. From the anamnesis it is known that the patient's father died of coronary heart disease at the age of 45 years. Objectively: height 175 cm, body weight - 78 kg, pulse - 80 beats. in 1 min, blood pressure - 130/80 mm RT. Art. No changes on the part of internal organs were revealed. What drug treatment should be prescribed to the patient for the primary prevention of coronary heart disease?

A. Lovastatin.

B. Nicotinic acid.

C. Lipostable.

D. Gemfibrozil.

E. Cholestyramine.

15. A man, 20 years old, complains of baking pressing pain in the epigastric region, heartburn, belching sour. Objectively: the condition is satisfactory. On palpation, pain in the epigastric region is determined. FGDS with morphology of the biopsy pathology from the mucous membrane did not reveal. What drug is most effective?

A. Gastrocepin.

B. Almagel.

C. Omeprazole.

D. De-nol.

E. Metoclopramide.

16. A man, 27 years old, 12 years old, suffers from peptic ulcer of the duodenum. Real deterioration is observed for 2 weeks. What pathogenetically substantiated treatment regimen is appropriate for this patient?

A. Trichopolum, omeprazole, clarithromycin.

V. Atropin, vikalin, festival.

C. No-spa, omeprazole, phosphalugel.

D. De-nol, platyphyllin, essentials.

E. Trichopol, but-shpa.

17. A boy, 14 years old, for 2 months worried about bouts of pain in the stomach, which appear 2-3 hours after eating and at night. An endoscopic examination on the anterior wall of the duodenal bulb revealed a defect in the mucous membrane of a round shape with a diameter of 6-8 mm, limited by a high hyperemic roller. The edges of the defect are edematous, the bottom is covered with a gray coating. The response to H. pulori is positive. What drug is most appropriate for monotherapy at the first stage of treatment?

A. Gastrocepin.

B. Cimetidine.

C. De-nol.

D. Gastroparm.

E. Almagel.

18. A pregnant woman suffers from heartburn due to toxicosis. Which remedy is optimal in this case?

A. Almagel

B. Sodium bicarbonate

C. Bismuth subnitrate

D. Omeprazole

E. Ranitidine

19. A 37-year-old man is diagnosed with chronic gastritis with increased secretory function. What drug is appropriate for this patient?

A. Pepsin

B. Pancreatin

C. Desopimon

D. Contrycal

E. Gastrocepin

20. A 35-year-old patient after a two-week pharmacotherapy of a stomach ulcer went to the doctor with complaints of trembling hands, increased muscle tone, stiffness of movements. Which of the following drugs could cause such a complication?

A. Sucralfate

B. Metoclopramide

C. Omeprazole

D. Bismuth subcitrate

E. Pirenzepine

21. In a patient undergoing a course of treatment for gastric ulcer, a concomitant disease is glaucoma. In this regard, what group of drugs is it not recommended to include in antiulcer therapy?

A. Antacids

B. M-anticholinergics

C. Histamine receptor blockers

D. Antispasmodics of myotropic action

E. Proton pump inhibitors

22. Patient with peptic ulcer prescribed famotidine. The acidity of the gastrointestinal juice significantly decreased. What mechanism underlies the action of this drug?

A. Blockade of ganglioreceptors

B. Blockade of H1-histamine receptors

C. Blockade of M1 cholinergic receptors

D. Inhibition of H + K + ATPase activity

E. Blockade of H2-histamine receptors

23. Systemic antacids include:

A. Magnesium hydroxide

B. Aluminum hydroxide

C. Sodium bicarbonate

D. Almagel NEO

E. Maalox

24. Individual dosing of M-anticholinergics is carried out according to the appearance of the patient:

A. Mydriasis

B. Small tachycardia

C. Signs of intestinal atony

D. Dry mouth

E. Paralysis of accommodation

25. Choose a drug that is not considered a proton pump inhibitor:

A. Omeprazole

B. Lansoprazole

C. Rabeprazole

D. Misoprostol

E. Esomeprazole

26. Choose a drug that has anti-helicobacter and gastroprotective effects:

A. Carbenoxolone

B. Misoprostol

S. de nol

D. Sucralfate

E. Arbaprostil

27. Indicate the group of drugs that inhibit the secretory function of the stomach.

A. H +, K + -ATP-inhibitors of the first and second generation ..

B. Blockers of H2 – histamine receptors of the first, second, third generations.

C. M1 anticholinergics.

D. Means that weaken the irritation of the afferent endings of the vagus nerve - antacids, adsorbents, enveloping, astringents, local anesthetics.

E. * All of the above groups.

28. For diarrhea caused by an infectious process, appoint:

A. Furazolidone.

B. Intetrix.

C. Tetracycline antibiotics.

D. Linex.

E. * All listed.

29. The drug for replacement therapy for pancreatitis.

A. Bromocriptine.

B. Tserukal.

C. Pancreatin.

D. Gastrocepin.

E. De-nol.

30. Preparations for the etiological treatment of gastric ulcer.

A. Famotidine + Almagel.

B. Pantoprazole + Eglonil.

C. De-nol + metronidazole.

D. Gastrocepin + Elenium.

E. Omeprazole + misoprostol.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.

2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF HEPATOPROTECTORS

Purpose of the topic.

Diseases occupy a leading place among diseases of the digestive system. According to WHO, there are more than 2 billion people with liver disease in the world, which is 100 times higher than the prevalence of HIV infection. Every year, from 500 thousand to 1 million people suffering from liver pathology are registered in the CIS countries. In Ukraine over the past 10 years, the prevalence of liver disease has increased by 20.1%.

Diseases of the liver and gall bladder and pancreas represent a large section of the pathology encountered by doctors of many specialties (infectious disease specialists, therapists, surgeons). In the liver, the main transformations of drugs undergo metabolism, their inactivation, the appearance of biological activity and even toxicity to the body. On the other hand, drugs themselves are capable of causing liver damage (toxic hepatitis, chronic active and cholestatic hepatitis). The formation and secretion of bile, dysfunction of the gallbladder can accompany the disease of the hepatic parenchyma, as well as cause secondary damage to it. In case of gallbladder disease, acute conditions (hepatic colic) occur, when it is necessary to provide urgent help to the patient. The need to know the main groups of drugs that improve the function of liver cells, as well as affecting the processes of bile secretion, the ability to use them in a particular patient, depending on the nature and course of the pathological process, determine the importance of this topic.

Despite the recent successes in the treatment of chronic liver diseases, in clinical practice there are frequent situations where the appointment of etiotropic therapy for one reason or another is impossible, and, at the same time, a decrease in the activity of the inflammatory process is required. Traditionally, for this purpose, drugs belonging to the group of hepatoprotectors are used, which are supposed to increase the resistance of the liver to pathological influences, enhance its neutralizing function by activating various enzyme systems (including the cytochrome P450 system and other microsomal enzymes), as well as contributing to the restoration of its function in various injuries, thereby contributing to a slowdown in the progression of the disease.

Given the absence of a direct effect on the etiology of the disease, the principal direction of action of the drugs of the hepatoprotective group is the effect on the pathogenetic mechanisms underlying liver diseases and, as a result, the slowdown of disease progression. These mechanisms are complex and diverse, depending on the etiology of the disease (viral, autoimmune, toxic, etc.), however, all of them are characterized by cellular damage, accompanied by an inflammatory reaction, cytolysis and, ultimately, the development and progression of fibrosis. Typical liver disease syndromes and the underlying mechanisms are presented here.

Motivational characteristic of the topic.

The unjustified prescription of a large number of drugs, self-medication, environmental environmental stress lead to increased risk of toxic effects of exogenous chemicals on the human body. First of all, this refers to the liver, the “target” organ, which plays a leading role in the biotransformation of xenobiotics, which can affect the liver and cause specific dose-dependent changes in terms of its function and morphological structure. In recent years, there has been an increase in the incidence of the liver of viral etiology, which is more dangerous for its complications.

Thus, one of the important and, at the same time, quite complex problems of modern pharmacology and hepatology is the search and implementation of new hepatoprotective agents. On the other hand, studying these issues in a course of clinical pharmacology is of great practical interest to future therapists, specialists in the field of family medicine, surgeons, infectious disease specialists, etc.

PATHOLOGY OF THE HEPATOBILIARY SYSTEM

The liver is involved in many pathological processes, and its damage causes serious metabolic disorders, immune response, detoxification and antimicrobial protection. The liver refers to organs capable of regeneration after damage due to cell cooperation, the presence of molecular mechanisms of the acute phase reaction and the synthesis of a number of protective substances. Most often, liver damage is realized through chemical and immunological mechanisms.

Chemical damage

A fairly large number of substances are known - detergents, reagents of oxidative phosphorylation and free breathing, carcinogens, drugs, etc. Natural substances and xenobiotics, including drugs, can cause chemical damage to the liver. It is known that the liver is a target for the manifestation of the toxicity of a number of drugs, since it is in this organ that xenobiotics are metabolized. Hepatocytes function in conditions of high concentrations of reactive and toxic forms of drugs. The latter may be toxic in their native form or become such in the process of their metabolism. In the process of neutralizing xenobiotics, two phases are described: 1) metabolism, that is, the introduction of polar groups using the cytochrome P450-hydroxylase system; 2) conjugation of molecules with water-soluble ligands. Both processes serve to eliminate the foreign components of their internal environment. Conjugation processes most often catalyze UDF-glucuronyltransferase, glutathione-S-transferase. Glucuronidation is the main form of conjugation in the detoxification of substances. Sulfation, as a rule, provides a reduction in toxicity and accelerated clearance of xenobiotics. Glutathione-S-transferase reaction is important for unstable electrophilic molecules. Microsomal glutathione S-transferase is closely associated with the cytochrome P450 system, which serves to quickly inactivate active metabolites formed during the metabolism of xenobiotics. The metabolism of drugs is localized not only in hepatocytes, but also in sinusoidal endothelial cells capable of xenobiotic transformations. A number of drugs exhibit selective toxicity to these cells compared to hepatocytes. This selectivity is associated with weaker protective mechanisms of sinusoidal endothelial cells to the action of xenobiotics.

Currently, there are 5 main mechanisms leading to cell death: 1) damage to the plasma membrane and cytoskeletal disorders; 2) mitochondrial dysfunction; 3) loss of intracellular ionic homeostasis; 4) activation of enzymes degradation of substances; 5) oxidative stress resulting discrepancies of prooxidant and antioxidant resources of the cell.

Immune mechanisms of hepatotoxicity

Several main mechanisms of liver damage are distinguished by molecular mechanisms related to immune responses: the functioning of killer lymphocytes and cell cooperations, the formation of neoantigens and autoantibodies, the action of mediators (cytokines, nitric oxide), and the activation of the complement system.

1. Immunoallergic hepatotoxicity

Electrophilic metabolites can covalently bind to proteins to form haptens. Oxidative damage to proteins as a result of the formation or translocation of disulfide bonds, as well as the oxidation of radicals of amino acid residues, leads to the formation of new antigenic determinants. An immune response is possible against haptens and neoantigens. Autoantibodies are detected in immunoallergic hepatitis caused by a number of drugs. Modified proteins have 2 effects: 1) how antigens initiate the formation of circulating antibodies; 2) trigger lymphocytotoxicity cytotoxicity.

2. Cytotoxic lymphocytes

The cytotoxicity of lymphocytes occupies a prominent place in the pathogenesis of various liver diseases. There are at least two main mechanisms for the manifestation of cytotoxicity of lymphocytes. First, T-lymphocytes are able to find antigens of target cells and activate when

interacting with them. In this case, cytotoxic agents are released that cause cytolysis of target cells. Secondly, it has been suggested that lymphocyte-mediated cell death is a process independent of the presence of calcium ions. It is assumed that endonuclease hydrolysis is preceded by a change in the permeability of the plasma membrane of target cells during intercellular interaction.

3. Cytokines

The formation of cytokines is an important element in maintaining the homeostasis of the body. However, if there is overproduction of cytokines, liver damage is possible. Most cytokines are formed in the liver by various stimuli. g-IFN is produced by hepatocytes during viral infection. TNF-a is synthesized by Kupffer cells under the action of a whole gamut of hepatotropic damaging agents. The pro-inflammatory cytokines TNF-a, IL-1, and IL-6 are secreted by Kupffer cells for hepatitis. This effect is associated with the synthesis of acute phase proteins and increased adhesion of neutrophils in sinusoids. These same cytokines underlie the action of many bacterial toxins. It is believed that TNF-a and IL-1 determine the mechanisms of necrosis and disorders of transport systems, IL-6 stimulates the synthesis of acute phase proteins, IL-8 serves as a potential chemoattractant for neutrophils. g-IFN and lipopolysaccharides through the induction of NO synthase enhance the production of nitric oxide toxic to intracellular pathogenic factors (mycobacteria, Leishmania) and liver tumor cells.

4. The complement system

The complement system consists of a cascade of plasma proteins. Many of them are synthesized in the liver. The activation of the system occurs when the C1 component is bound to the immune complex. It is accompanied by an increase in phagocytosis of opsonized microorganisms (C3b), activation of Kupffer cells and neutrophils, etc. The process serves to form an attacking membrane complex on the cell surface (C5b-C9). This mechanism is implemented in the liver with endotoxemia, ischemia-reperfusion, the action of free radicals oxygen and immune responses.

5. Cellular cooperatives

Kupffer cells have been shown to play an important role in the development of liver damage. The following sequence of events can be described: an increase in the concentration of endotoxin received through the portal vein — activation of Kupffer cells and release of chemoattractants, including interleukins, leukotriene B4, the C5 component of the compliment — receipt of neutrophils from the circulation — activated neutrophils with adhesion molecule receptors adhere to sinusoidal endothelium, and the adhesion molecule promotes the migration of leukocytes into the liver parenchyma - activated neutrophils produce free radical forms isloroda that cause various types of damage, such as the activation of membrane peroxidation - liver macrophages produce toxic mediators and induce platelet aggregation, which leads to mikrotrombozov - develops local hypoxia - lobular necrotic lesions appear.

The cytotoxicity of a number of humoral factors is associated with the features of sinusoidal endothelial cells. Unlike other types of endothelium, the sinusoidal endothelium is fenestrated and does not have a basement membrane. In hepatic venous-occlusive diseases, after bone marrow transplantation and some other conditions, damage to endothelial cells is the initial stage of a T-lymphocyte-mediated immune response. The narrowing of small intrahepatic veins with the development of microthrombosis leads to impaired blood outflow and the development of liver ischemia with secondary damage to hepatocytes. Some drugs (dacarbazine) and the chemical components of many plants exhibit selective toxicity to sinusoidal cells, initiating the development of veno-occlusive liver disease.

The basic principles of the treatment of liver diseases

In accordance with modern principles of the treatment of liver diseases, the complex therapy program for such a pathology includes two main areas. The first is etiotropic therapy aimed at

suppressing the pathological pathogen, its elimination and reorganization of the body. In clinical practice, etiotropic therapy is used only for viral hepatitis with a parenteral infection mechanism. The second direction corresponds to pathogenetic therapy, with the goal of adequate pharmacological correction of universal, multifactorial, and different-time links of pathogenesis. It should be noted that the universalism of the main links in the pathogenesis of various liver lesions makes it possible to use a fairly close pathogenetic therapy for all the polyetiology of this pathology, which can be based on drugs with a targeted effect on liver cells. When using pathogenetic treatment, the similarity of clinical manifestations in a variety of liver diseases allows the use of the same means. Currently, about 1000 drugs used in liver therapy are presented on the pharmaceutical market.

For the pharmacological correction of various diseases of the organs of the hepatobiliary system, depending on the etiological factors, the characteristics of the pathogenesis and clinical manifestations, drugs are used that can conditionally be divided into the following groups:

1) agents affecting the processes of tissue metabolism (vitamins, amino acids and protein hydrolysates, peptides, steroid and non-steroid anabolics, adaptogens);

2) agents that increase the detoxification function of the liver and other organs (adsorbents, antidotes);

3) choleretic drugs;

4) antiviral and antimicrobial agents;

5) immunomodulators;

6) anti-inflammatory drugs (steroidal and non-steroidal);

7) inhibitors and inducers of microsomal systems that metabolize xenobiotics;

8) hepatoprotectors.

9) antioxidants.

In general, the range of drugs used in the complex treatment of diseases of the liver and biliary tract, has more than 1000 items. However, among such a variety of drugs, a relatively small group of hepatoprotectors is shown to have a selective effect on the liver. Their action is aimed at restoring homeostasis in the liver, increasing the organ's resistance to the action of pathogenic factors, normalizing functional activity and stimulating reparative and regenerative processes in the liver. The basic requirements for an ideal hepatoprotector were formulated by R. Preisig:

• • sufficiently complete absorption;

• • the presence of the effect of the "first passage" through the liver;

• • pronounced ability to bind or prevent the formation of highly active damaging compounds;

• • the ability to reduce excess inflammation;

• • suppression of fibrogenesis;

• • stimulation of liver regeneration;

• • natural metabolism in liver pathology;

• • extensive enterohepatic circulation;

• • lack of toxicity.

Unfortunately, to date, none of the hepatoprotectors used in medical practice fully satisfies these requirements, although in recent years the arsenal of modern hepatoprotective agents has expanded both due to the advent of synthetic drugs and new natural remedies . In general, at present, the predominant use is for herbal remedies (up to 54%), while phospholipid preparations account for 16%, and for other drugs, including synthetic ones, organopharmaceuticals, and amino acid preparations, 30 % of the total number of "true" hepatoprotective drugs.

Unfortunately, the exact mechanisms of action of the representatives of the hepatoprotective group have not been sufficiently studied, and, in most cases, are only presumptive, which makes it difficult to determine the indications for their use. In addition, reliable scientific data with a high level of evidence (large-scale, multicenter, randomized, placebo-controlled studies and their meta-analyzes / systematic reviews), which would confirm the positive effect of these drugs on the human body, are often lacking. As a result, the use of most of the drugs of this group in wide clinical practice is controversial.

Classification of hepatoprotectors:

1. Preparations containing natural or semisynthetic milk thistle flavonoids: hepabene, legalon, karsil, hepatofalk plant, silibor.

2. Preparations containing natural or semi-synthetic flavonoids of other plants: hofitol, catergen (cyanidanol), LIV-52 (hepatal).

3. Organic preparations of animal origin: sirepar, hepatosan.

4. Preparations containing essential phospholipids

essentiale, phosphogliv, essliver, eplier.

5. Preparations of different groups: bemitil, ademetionin (heptral), lipoic acid (thioctacid), hepamerz (ornithine), ursodeoxycholic acid (ursofalk), non-steroidal anabolics (methyluracil, pentoxyl, sodium nucleate).

6. Amino acids or their derivatives (ornithine aspartate)

7. Vitamins-antioxidants and vitamin-like compounds (vitamin C and E, lipoic acid),

Actually, the methods of "evidence-based medicine" have confirmed to one degree or another the clinical effectiveness of a very small number of drugs marketed as hepatoprotectors. These include drugs containing phospholipids (essentials, energetic), amino acid preparations (ornithine aspartate, ademethionine), ursodeoxycholic acid.

The mechanisms of action of various hepatoprotectors

Essential phospholipids

- antioxidant

- Replenishment of lipid membranes

Adenosylmethionine

- antioxidant

- Synthesis of hepatocyte structural proteins

- Sulfurization of toxic FAs (anticholestatic)

Silymarin

- antioxidant

- Synthesis of hepatocyte structural proteins

- Blocking some poisons (antitoxic)

UDHK (URSOFALK®)

- Cytoprotective (displacement of toxic hydrophobic FAs)

- Choleretic (increased synthesis and excretion of FA)

- Immunomodulating (decreased synthesis of pro-inflammatory cytokines)

- Anti-apoptotic (blockade of the caspase mitochondrial destruction cycle)

- antioxidant

1. Preparations containing natural or semisynthetic milk thistle flavonoids All of these preparations contain extract (or a mixture of flavonoids) of milk thistle, the main component of which is silymarin. Silymarin itself is a mixture of 3 basic isomeric compounds - silibinin, silikristin and silidianin (in legalon, for example, their ratio is 3: 1: 1). All isomers have a phenylchromanone structure (flavolignans). Silibinin is the main component not only in content, but also in clinical effect.

The main effects of silymarin (silibinin) are: membrane-protective, antioxidant and metabolic.

Silibinin stabilizes the membranes of liver cells. At the same time, the membrane resistance increases and the loss of cell constituents decreases.

In addition, silibinin blocks PDE, which contributes to the delayed decomposition of cAMP, and therefore, stimulates a decrease in the concentration of intracellular calcium in hepatocytes and reduces the calcium-dependent activation of phospho-lipases.

Antioxidant and metabolic properties of silibinin are also important for membrane stabilization.

Silibinin is able to block the corresponding communication sites of a number of toxic substances and their transport systems.

This is the mechanism of action of silibinin in case of poisoning with one of the toxins. pale toadstool - alpha amantine. Especially for the protection of the liver in this case, an easily soluble form for intravenous administration (dihydro rosuccinate sodium salt (legalon-strength)) was developed.

Silibinin is able to bind radicals due to its phenolic structure and interrupt LPO processes. At the same time, it inhibits both the formation of malondialdehyde and increased oxygen uptake.

Silibinin contributes to a significant increase in the content of reduced glutathione in the liver, thereby increasing the organ's protection against oxidative stress, supporting its normal detoxification function.

The metabolic effect of silibinin is to stimulate protein synthesis and accelerate the regeneration of damaged hepatocytes.

Silibinin stimulates RNA polymerase I in the cell nucleus and activates transcription and the rate of RNA synthesis, and, consequently, protein in liver cells.

Silibinin does not affect the rate of reduction and transcription in altered cells, which excludes the possibility of tumor-proliferating action. With liver cirrhosis, a slowdown in organ fibrosis occurs under the influence of the drug.

Studies that demonstrate the immunomodulatory activity of silymarin derivatives in patients with alcoholic cirrhosis of the liver are also of interest.

Long-term therapy with legalone (about 6 months) helps to reduce initially elevated CD8 + lymphocytes and increases the blasttransformation of lymphocytes. The level of gamma globulins decreases. Silymarin derivatives can be used in patients with liver diseases with clinical and biochemical signs of activity. Caution should be observed in patients with cholestasis, since there is evidence that under the influence of drugs, cholestasis may increase. The duration of the course should not exceed 4 weeks, after which, if necessary, continue treatment, it is advisable to change the drug, for example, prescribe a drug of essential phospholipids.

Karsil and legalon are used for acute and chronic hepatitis, cirrhosis of the liver, toxic and metabolic lesions of the liver, including xenobiotics.

LEGALON (Legalonum)

Synonyms: Silibinin, Hepadestal, Silymarin, Flavobion, Karsil, Api-repar, Darling, Durikol, Laragon, Silarin, Silgen, Silibankol, Silybin, Silibor, Silimarol, Somatron, etc.

It is a total preparation containing silymarin, silibinin, and milk thistle fruit extract.

Pharmachologic effect. Hepatotropic (affecting the liver) drug. The active substance of legalon is silymarin - a compound that can stabilize the membranes of liver cells and thereby protect the liver from various harmful effects, as well as accelerate reparative processes (tissue repair processes) in the liver at the cellular level.

With the use of legalon, the general condition of the patient improves as a result of the activation of detoxifying (detoxifying) liver function, discomfort that occurs during digestion is reduced, appetite is increased, body weight is increased.

Indications for use. It is used legally for acute (toxic) hepatitis (inflammation of the liver tissue), for maintenance therapy for chronic liver diseases and liver cirrhosis.

Dosage and administration. For the treatment of severe liver damage first, legalon-140 is prescribed, 1 capsule 3 times a day, then 1 capsule 2 times a day. In less severe cases and for maintenance therapy, legalon-70 is prescribed for 1-2 tablets 3 times a day, then 1 tablet 3 times a day. In severe cases, legalon-70 is prescribed, starting with 2 tablets 3 times a day.

Dragees and capsules are taken orally, without chewing, with a small amount of liquid.

A suspension (suspension of solid particles in a liquid) is prescribed at the beginning of treatment and in severe cases 4 times a day, 1 scoop (10 ml each containing about 100 mg of silymarin); for maintenance therapy - 1 scoop 2 times a day (about 200 mg of silymarin in total). In severe cases, children are prescribed 1 scoop 3 times a day, then 1/2 scoop 3 times a day.

Side effect. The drug is usually well tolerated; in some cases, a laxative effect is observed.

Release form. Legalon-70 tablets - 20 each; 100 and 400 tablets in a package; le-galon-140 - 20 and 100 capsules per pack; legalonsuspension - 450 ml per pack.

Storage conditions. Ordinary.

A feature of the hepatofalk plant preparation is that, along with the extract of milk thistle, it includes extracts from celandine of large and Javanese turmeric.

Due to this, along with hepatoprotective, the drug has a choleretic, antispasmodic and anti-inflammatory effect, reduces the saturation of bile with cholesterol, and has antibacterial properties.

It is used for acute and chronic hepatitis, fatty hepatosis, liver cirrhosis.

Close in properties is the hepabene preparation, which consists of extracts of milk thistle and smoky pharmacy. The latter has an antispasmodic effect. The drug is used for chronic hepatitis and cirrhosis of the liver, fatty degeneration of the organ, toxic-metabolic lesions of the organ, including xenobiotics.

The main active ingredient from the family of medicinal thistle flavonoids - silibinin - is part of various drugs: Sibektan, Legalon, Siramin and others. The differences between these drugs are in quantitative ratios of flavonoids, as well as combinations of milk thistle with other drugs, usually with choleretic or antiseptic effect.

The drug Sibektan contains in its composition a dry extract from tansy, fruits of the milk thistle, St. John's wort and birch.

St. John's wort grass contains tannins of the catechins group (tannins, flavonoids, essential oils), which have an astringent and anti-inflammatory effect on the mucous membrane of the gastrointestinal tract.

Tansy flowers also contain various flavonoids, essential oils and organic acids, which have a choleretic effect (increase the co-operative activity of the gallbladder).

The birch leaf extract also has an antiseptic, mild gallstone and distinct diuretic effect.

Sibektan is successfully used in the treatment of chronic cholecystitis, hypotonic dyskinesia of the gallbladder. It is prescribed for hepatitis and cirrhosis of the liver in order to prevent the progression of the process.

Given the presence of substances with a sufficiently pronounced cholekinetic activity in the composition of the drug that can enhance the motor function of the gallbladder, Sibektan should be prescribed with caution in gallstone illnesses.

Preparations of spotted milk thistle flavonoids are prescribed primarily orally, half an hour before a meal. They are quickly and completely absorbed from the gastrointestinal tract. Plasma protein binding is weak. Excreted mainly with bile, to a lesser extent - with urine; the half-life is about 6 hours. They are actively included in the enterohepatic circulation, which seems to be an advantageous pharmacokinetic parameter.

The duration of treatment is from 25 days to 1.5 months. Repeated courses are possible.

Numerous studies have found that milk thistle preparations belong to the category of low toxic substances and in therapeutic doses do not have a damaging effect on the main organs and systems of the animal and human body.

When prescribing, the possibility of developing allergic reactions to plant components should be considered.

2. Preparations containing natural or semi-synthetic flavonoids of other plants

Cyanidanol-3 (catergen) is tetra-hydroxy-5,7,3-4-flavanol-3. It is a semisynthetic flavonoid derivative of plant origin and is very close in chemical structure to quercetin and rutin, as well as to silibinin.

It is believed that the mechanism of hepatoprotective action is due to the binding of toxic free radicals and stabilization of cell membranes and lysosomes (which is also characteristic of other flavonoids).

In addition, under the influence of catergen, ATP biosynthesis in the liver is stimulated, thereby facilitating the flow of biochemical reactions associated with energy expenditure and phosphorylation in the liver.

Catergen has a membrane-stabilizing effect, reducing the permeability of cell membranes for low molecular weight water-soluble compounds transported by free and exchange diffusion.

The clinical use of catergen in the treatment of acute and chronic liver diseases of various etiologies indicates the effectiveness of the drug not only in reducing cholestasis, but also in reducing the activity of transaminases. It is used for acute and chronic hepatitis, liver cirrhosis, including alcoholic liver damage. When catergen is used in patients with chronic parenchymal liver diseases, the effect of the drug may be insufficient. The drug is used for a long time (course duration of about 3 months).

Hofitol is a preparation, one ampoule of which contains 0.1 g of a purified extract of artichoke leaves in an isotonic solution. The main hepatoprotective and choleretic effect is due to the presence in the extract of the phenolic cinnarine compound in combination with phenolic acids (coffee, chlorogenic, etc.). In addition, it contains carotene, vitamins C, B1, B2, inulin. Affects the functional activity of liver cells, stimulates the production of enzymes; this explains the effect of the drug on lipid, fat metabolism, increased antitoxic function of the liver. Hofitol lowers blood cholesterol in the initial hypercholesterolemia, has a choleretic effect due to moderate choleretic and weak cholekinetic effect. Used for toxic hepatitis, cirrhosis. The drug is low toxic.

LIV-52 (Liv-52)

A complex preparation made from juices and decoctions of a number of plants.

Pharmachologic effect. Prevents and eliminates violations liver function, stimulates the growth of the body, improves appetite, contains a number of medicinal plants widely used in traditional Indian medicine. Liv-52 is believed to protect the liver parenchyma from toxic agents. It acts as a therapeutic or prophylactic agent. Enhances intracellular metabolism and stimulates regeneration. At the same time, there is evidence that the use of the drug in acute liver pathology can aggravate the severity of cytolytic and mesenchymal inflammatory syndromes. Due to this, the drug may be recommended at a time when the severity of the inflammatory syndrome in the liver is minimal and the phenomena of synthetic organ failure prevail.

Indications for use. impaired liver function in chronic viral and toxic hepatitis (inflammation of the liver tissue), cirrhosis, chronic hepatitis, impaired liver function in children and other liver diseases. The drug also improves appetite, digestion, promotes the passage of gases from the intestines.

Dosage and administration. Inside, adults take 2-3 tablets, children 1-2 tablets 3-4 times a day.

Side effect. Dyspeptic disorders (digestive disorders) are possible.

Contraindications Acute infectious hepatitis.

Release form. Tablets in a package of 100 pieces.

HEPALIV (Hepaliv)

Pharmachologic effect. Combined drug of plant origin. It has a hepatoprotective (protecting liver tissue) effect. Promotes the regeneration (restoration) of hepatocytes (liver cells), accelerates metabolic (metabolic) processes in the liver, normalizes its function in various injuries. Increases the resistance of the liver to pathological effects. It has a lipotropic effect (selectively interacts with fats).

Improves digestion and assimilation of food, increases appetite, helps to increase body weight. Stimulates hematopoiesis (hematopoiesis).

Indications for use. Fatty hepatosis (non-inflammatory liver disease); viral hepatitis (inflammation of the liver tissue) A; viral hepatitis B; toxic hepatitis (inflammation of the liver tissue caused by toxins) of various origins; chronic active hepatitis; cirrhosis of the liver; hypoproteinemia (low blood protein); hepatic encephalopathy (headaches due to liver disease); toxicosis of pregnant women; jaundice; anorexia (lack of appetite); weight loss and growth retardation in children; the period of convalescence (recovery) after a serious illness, injuries and burns. For the prevention of liver damage with alcohol, drugs and chemicals. Digestive disorders, diabetes mellitus, infectious diseases, coronary heart disease (as part of combination therapy as an adjuvant).

Dosage and administration. Children are prescribed 1-2 tablets 3-4 times a day. Adults are prescribed 2-3 tablets 3-4 times a day. With cirrhosis and infectious hepatitis, the dose can be increased 3 times.

Side effect. In rare cases, allergic reactions to the components of the drug.

Contraindications Hypersensitivity to the components of the drug.

The drug is prescribed with caution in patients with acute inflammatory diseases of the stomach and intestines.

Release form. Tablets in a package of 100 pieces. Composition 1 tablet: Capparisshinoza- 65 mg, Cichoriuminthybus- 65 mg, Solanumnigrum- 32 mg, Cassiaocci-dentalis- 16 mg, Termihaliaarjuna- 32 mg, Achilleamillefolium- 16 mg, Tamarixgallica- 16 mg, Mandurbrasma- 33 mg.

Storage conditions. In a dry, dark place.

VALILIV (Valiliv)

Pharmachologic effect. A herbal preparation similar in effect to Liv-52. Contains juices and decoctions of 15 plants.

Indications for use. To improve liver function in infectious and toxic hepatitis, chronic hepatitis (inflammatory diseases of the liver tissue) and other liver diseases.

Dosage and administration. Assign inside adults 2-3 tablets 3 times a day, children 1-2 tablets 3 times a day.

Release form. Tablets in a package of 100 pieces.

Storage conditions. In a cool, dark place.

Tykveol is a complex of biologically active substances obtained from pumpkin seeds. The therapeutic effect of the drug is due to its biologically active substances

The hepatoprotective effect of pumpkin is determined by its membrane-stabilizing properties and is manifested in slowing down the development of damage to the membranes of hepatocytes and accelerating their recovery. In addition, the drug reduces inflammation, slows the development of connective tissue and accelerates the regeneration of the parenchyma of the damaged liver. Tykveol has a choleretic effect, normalizes the chemical composition of bile, reduces the risk of developing cholelithiasis and has a beneficial effect on its course. However, it should be noted that convincing evidence of the high effectiveness of the drug has not yet been obtained. Tykveol is used for chronic liver diseases of various etiologies: chronic liver lesions of various etiologies (hepatitis, cirrhosis), cholecystocholangitis and biliary dyskinesia, in the postoperative period of cholecystectomy, for the prevention of cholelithiasis.

3. Organic preparations of animal origin

Sirepar is a hydrolyzate of cattle liver extract containing 10 mg of cyanocobalamin in 1 ml. The reparative effect of the drug is obviously associated with the presence in its composition of amino acids, low molecular weight metabolites, and, possibly, fragments of growth factors of the liver. The drug promotes the regeneration of the liver parenchyma, has a detoxifying effect.

Sirepar should not be prescribed to patients with active forms of liver diseases, since in this case the phenomena of cytolytic, mesenchymal-inflammatory and immunopathological syndromes may increase. It is prescribed for chronic hepatitis and cirrhosis of the liver, toxic and medicinal infections of the liver parenchyma. Before treatment, a determination of sensitivity to the drug is mandatory.

The use of isolated hepatocytes obtained by freeze-drying of liver cells of donor animals (hepatosan) has become a new direction in the treatment of liver diseases. The mechanism of action of the drug has 2 phases: intestinal, in which the drug has a detoxifying effect due to sorption of toxic products in the intestine and metabolic (hepatoprotective), during which hepatocytes are destroyed, and their degradation products are absorbed and act as protectors at the level of liver c The drug is able to limit the phenomena of cytolysis, enhance the protein-synthetic ability of the liver. The use of hepatosan in the complex treatment of active, decompensated liver cirrhosis with the phenomena of hepatic cell failure has a detoxifying effect and helps to accelerate reparative processes.

4. Preparations containing essential phospholipids

Remembering that for all liver diseases, damage to the membranes of hepatocytes is noted, the appointment of therapy, which has a restoring and regenerating effect on the structure and functions of cell membranes and provides inhibition of the process of cell destruction, is pathogenetically justified. Means of this orientation of action are drugs containing essential phospholipids (EFL).

The substance EFL is a highly purified extract from soybeans and contains mainly phosphatidylcholine (FC) molecules with a high concentration of polyunsaturated fatty acids. The main active ingredient in EFL is 1,2 - dilinoleoil - phosphatidylcholine, the synthesis of which is impossible by the human body. The presence of two essential (necessary) fatty acids makes this special form of phospholipids superior to endogenous phospholipids.

The membrane stabilizing and hepatoprotective effect of EFL is achieved by directly incorporating EFL molecules into the phospholipid structure of damaged liver cells, replacing defects, and restoring the barrier function of the lipid bilayer of membranes. Unsaturated fatty acids of phospholipids increase the activity and fluidity of membranes, reduce the density of phospholipid structures, and normalize permeability. Exogenous EFLs promote the activation of phospholipid-dependent enzymes and transport proteins located in the membrane, which, in turn, has a supporting effect on metabolic processes in liver cells, and contributes to an increase in its detoxification and excretory potential.

The hepatoprotective effect of EFL, obviously, is also based on the inhibition of lipid peroxidation (lipid peroxidation) processes, which are considered as one of the leading pathogenetic mechanisms of the development of liver lesions. However, obviously, one should not overestimate the intrinsic antioxidant properties of EFL, since they themselves can be involved in lipoperoxidation processes.

The prototype of compounds containing the substance EFL is an essentialia drug, which includes essential phospholipids, unsaturated fatty acids and vitamins. Not so long ago, Essential N appeared on the market, which will contain only a highly refined EFL substance. In clinical practice, essentials are used in 3 main areas: for liver diseases and its toxic lesions; with pathology of internal organs complicated by liver damage; as a method of "medical cover" when using drugs that cause liver damage (tetracycline, rifampicin, paracetamol, indomethacin, etc.). In hepatology, essentials are prescribed for chronic hepatitis, liver cirrhosis, fatty degeneration, and hepatic coma. It is also used for radiation syndrome and toxicosis of pregnant women, for the prevention of relapse of gallstone disease, for preoperative preparation and postoperative treatment of patients, especially in cases of surgical interventions on the liver and biliary tract. At the same time, the use of essentials for active

hepatitis requires a certain caution, because in some cases it can contribute to increased cholestasis and inflammatory activity. Usually, the effectiveness of esential is estimated to be quite high, however, there are a number of reports of the lack of convincing ells, restoring functional activity of hepatocytes data in favor of the expressed clinical activity of essentials in acute and chronic liver lesions. Essliver is similar in composition and properties to the essence. Essliver preparation contains, in addition to the substance of essential phospholipids, therapeutic doses of vitamins (B1, B2, B6, B12, tocopherol and nicotinamide), which provides the drug with a wide range of therapeutic properties. The action of the components of the drug is aimed at restoring hemostasis in the liver, increasing the resistance of the organ to the action of pathogenic factors, normalizing the functional activity of the liver, stimulating reparative and regenerative processes. The drug is used for acute and chronic hepatitis, cirrhosis, alcohol, drug intoxication and other forms of poisoning, radiation syndrome, psoriasis.

Eplir is a fraction of polar lipids of silt lake sediment containing phospholipids, sulfolipids, and tetraterpenoid pigments. It is a rather active antioxidant (it inhibits the formation of primary and secondary lipid peroxidation products, protects endogenous antioxidant systems of the liver from depletion), supplies native phospholipids to damaged hepatocyte membranes, prevents their fatty degeneration, improves bioenergetics and glycogen synthesis. Thiols in the composition of the eplir may become precursors in the synthesis of glutathione. Eplir improves the excretory function of the liver, stimulates the neutralization of bilirubin by conjugation with glucuronic acid. Under the influence of the drug, the activation of stellate reticuloendotheliocytes in the liver is reduced. Eplir affects the indicators of the cytolytic syndrome, cholestasis, reduces the effects of protein and fatty degeneration. Under the influence of the drug, the state of health improves faster, however, asthenovegetative disorders respond less effectively to therapy. Eplir is used mainly for chronic hepatitis.

Of particular interest is the drug phosphogliv, consisting of 0.1 g of phosphatidylcholine and 0.05 g of the trisodium salt of glycyrrhizic acid. Due to EFL, which is part of the preparation, the normalization of subjective symptoms of liver diseases, their clinical manifestations and laboratory parameters improves or accelerates. The severity of inflammatory reactions, necrosis of liver cells, their fatty infiltration is reduced. Glycyrrhizic acid has an immunostimulating effect, causing the stimulation of phagocytosis and increased activity of EKK cells, the induction of gamma interferon. In addition, it has an antiviral effect, blocking the penetration of viruses into cells, and exhibits antioxidant properties. It is used for acute hepatitis, with relief of alcohol withdrawal syndrome, in the pre- and postoperative period of cholecystectomy. However, it should be noted that an improvement in the liver condition and a decrease in symptoms of intoxication are not observed in all patients. In addition, the use of the drug requires very careful monitoring of patients with autoimmune aggression.

5. Preparations of different groups

The mechanism of action of bemitil is to activate the synthesis of RNA, and then proteins in various cells. Under the influence of the drug, protein synthesis is enhanced - enzymatic, structural, proteins related to the immune system. The increased formation of mitochondrial enzymes and structural mitochondrial proteins provides an increase in energy production and maintains a high degree of conjugation of oxidation with phosphorylation. Maintaining a high level of ATP synthesis with oxygen deficiency contributes to the pronounced antihypoxic and anti-ischemic activity of bemitil. The drug enhances the synthesis of antioxidant enzymes and has a fairly pronounced antioxidant activity. Additional component to the mechanism the hepatoprotective effect of the drug introduces its immunomodulating effect, which consists in the normalization of the humoral and, mainly, cellular parts of the immune system.

The use of bemitil in the complex rehabilitation therapy of hepatitis and cirrhosis leads to an acceleration of both clinical recovery and restoration of physical performance of convalescents. A positive effect of the drug on the indicators of cytolytic and mesenchymal-inflammatory syndromes

was also noted. An important feature of the drug is its pronounced effect on the protein-synthetic and glucostatic functions of the liver.

BILIGNIN (Biligninum)

Modified lignin derived from plant wood.

Pharmachologic effect. When ingested, binds bile acids in the intestine, reduces their reverse absorption and promotes their excretion with feces.

Indications for use. Liver diseases (cholestatic hepatitis, biliary cirrhosis, extrahepatic partial violations of the outflow of bile) and other diseases associated with metabolic disorders and increased levels of bile acids and cholesterol in the blood.

Dosage and administration. Inside, 5-10 g (1-2 teaspoons) 3 times a day 30-40 minutes before meals, washed down with water. The course of treatment is from 7 days to 3 months; if necessary, repeat the treatment.

Side effect. Possible dyspeptic symptoms (digestive disorders), passing with a decrease in dose.

Contraindications In patients with a complete violation of bile secretion.

Release form. Powder 75 g per pack.

Storage conditions. In a dry place at room temperature.

VIGERATIN (Vigeratinum)

Pharmachologic effect. It gives hepatitis protective (protecting liver) and antianemic (preventing hemoglobin in the blood decrease) effect.

Indications for use. Chronic hepatitis (inflammation of the liver tissue), pancreatitis (inflammation of the pancreas) and gastritis (inflammation of the stomach) with reduced secretory function.

Dosage and administration. Inside, before meals, 2-3 tablets 3 times a day for 3-4 weeks. The course of treatment can be extended up to 1.5 months.

Side effect. Heartburn, dry mouth, nausea.

Contraindications Hyperacid gastritis (inflammation of the stomach due to a persistent increase in acidity), peptic ulcer of the stomach and duodenum with increased acidity of gastric juice.

Release form. Coated tablets in a package of 50 pieces. 1 tablet contains lyophilized liver extract (dehydrated by freezing in vacuum) 0.167 g and pancreatin 3 units.

Storage conditions. In a dry place at a temperature not exceeding +20 ° C.

HEPASTERIL-A (Hepasteril-A)

Pharmachologic effect. Solution for parenteral (bypassing the gastrointestinal tract) application. It has hepatoprotective (protecting liver tissue) and detoxifying (neutralizing) effect. Energy value - 200 yusal / l.

Indications for use. Hepatic coma (unconsciousness due to a serious liver disease), precoma (a condition preceding a coma), acute and chronic hepatitis (inflammation of the liver tissue), cirrhosis, hepatic encephalopathy (headaches due to liver disease), condition after applying a portal-caval anastamosis (creating a surgical connection between the venous system of the liver and the inferior vena cava), an increase in the level of ammonia in the blood after massive tissue damage.

Dosage and administration. Doses are selected individually taking into account the initial concentration of ammonia and adjusted depending on the dynamics of the patient's condition. Usually start with an intravenous drip of 500 ml of the solution at a rate of 40 drops per minute. The introduction of the drug can be repeated every 12 hours.

The appointment of the drug is possible only with preserved filtration (excretory) kidney function. In the process of using the drug, it is necessary to monitor the level of potassium in the blood.

Side effect. Allergic reactions.

Contraindications Acute and chronic liver failure, hypersensitivity to the drug.

Release form. 500 ml infusion solution in a vial. 1 liter of solution contains: aspartic acid - 10.0 mmol, malic acid (in the form of malate) - 14.7 g (27 mmol), arginine - 28.9 g, sorbitol - 50.0 g, riboflavin (vit. Vg) - 0.012 g, pyridoxine hydrochloride (vit. Wb) - 0.08 g, nicotinamide (vit. PP) - 0.1 g, panthenol - 0.02 g, sodium - 37 mmol, potassium - 40 mmol, chlorine - 40 mmol.

Storage conditions. In a cool place.

HEPASTERIL-B (Hepasteril-B)

Pharmachologic effect. Hepasteril-B has detoxification (neutralizing) and hepatoprotective (protecting liver tissue) properties. The energy value of the solution is 400 kcal / l.

Indications for use. Hepatitis (inflammation of the liver tissue) acute and chronic, impaired liver function.

Dosage and administration. Intravenously administered dropwise. The daily dose of the drug is 500-1000 ml, average

the rate of introduction of the solution is 40 drops per minute, which corresponds to 1.7 ml / kg of body weight per hour or 120 ml per hour (for a patient weighing 70 kg). The maximum daily dose of levulose (one of the components of the drug) is 1.5 g / kg of body weight. Improvement of drug tolerance can be achieved by slower administration of the solution.

Side effect. Allergic reactions.

Contraindications Severe renal dysfunction, hypersensitivity to fructose and other components of the drug.

Release form. Solution for infusion in 500 ml vials. 1 liter of solution contains: sodium - 50.6 mmol, potassium - 20.0 mmol, anion bicarbonate - 13.6 mmol, chlorine -67.0 mmol, phosphorylcholine-3.0 g, malic acid 1.34 g, methionine -0.75 g, riboflavin (vit.B2) - 0.012 g, pyridoxine hydrochloride (vit.Вб) - 0.08 g, nicotinamide (vit.PP) -0.1 g, panthenol 0.02 g, biotin - 0.001 g, levulose - 100.0 g.

Storage conditions. In a cool place.

JUVAL (Juval)

The combined preparation containing choline acetylmethioninate, di-hydroxydibityl ester, cyancobalamin, sorbitol (70%), orthosiphon stamineus, aubergin.

Pharmachologic effect. It has hepatitis protective (protecting liver tissue), choleretic and antispastic (preventing the development of spasms) action.

Indications for use. Mild liver failure dyspepsia (digestive upsets) due to hepatosis or acute hepatitis (non-inflammatory and inflammatory diseases of the liver tissue), dyskinesia (impaired mobility) of

the biliary tract, hyposecretory anorexia (lack of appetite due to decreased secretion / secretion / gastric juice), constipation.

Dosage and administration. Adults are prescribed 1-2 tablespoons of syrup (10-20 ml), children - 1 teaspoon (5 ml) before meals.

Release form. Syrup in 200 ml vials. 100 ml of syrup contains: choline acetylmethioninate - 4 g, dihydroxydibitilester - 3 g, cyancobalamine (vit. Vp) - 3000 μg, sorbitol (70%) - 20 g, orthosiphon stamineus - 1.5 g, aubergine - 1.8 g

Storage conditions. List B. In a cool, dark place.

ZIKSORIN (Zixorin)

Synonyms: Flumecinol, Sinclite.

Pharmachologic effect. Hepatoprotective (protecting liver tissue) agent. Induces oxidase enzymatic activity of liver microsomes; enhances the formation of glucuronides, promotes the excretion of endogenous and exogenous metabolites (metabolic products) from the body, increases the excretion of bile. The drug acts relatively selectively on microsomal enzymes; it does not have other pronounced pharmacological effects.

Indications for use. It is used for functional hyperbilirubinemia (increased bilirubin in the blood), for patients with chronic diffuse liver diseases, for jaundice due to enzymes (diseases associated with the absence or impairment of liver enzymes) and benign intrahepatic cholestasis (bile congestion), for food allergies accompanied by jaundice, and also for the prevention and treatment of jaundice in newborns. There is evidence of the effectiveness of zixorin in the treatment of skin diseases (psoriasis, atonic dermatitis) and with chemotherapy for tuberculosis patients.

Dosage and administration. Prescribe zixorin to adults (during or after meals) for chronic diseases, 0.4-0.6 g (4-6 capsules) once a week or 0.1 g 3 times a day. The course of treatment is 2 weeks. After a 2-4 week break, it is possible to repeat the course using the same dose or reduced depending on the patient's condition.

With jaundice, newborns are given from the 2nd day of life at 10 mg / kg per day for 3-5 days. For the prevention of jaundice, newborns pregnant give 1-3 g before the expected birth of 0.4 g (4 capsules) once.

With atopic dermatitis in children, zixorin is prescribed at 2 mg / kg in 1-2 doses.

It should be borne in mind that in connection with the induction (activation) of liver enzymes, zixorin can accelerate the metabolism (decomposition) of other drugs used simultaneously.

Side effect. When using the drug, nausea, individual intolerance are possible.

Release form. Capsules of 0.1 g in a package of 25 pieces.

Storage conditions. In the dark place.

ADEMETIONINE (Ademetionine)

S-adenosyl-L-methionine Synonyms: Heptral. Pharmachologic effect. Ademethionine, which is the active substance of the drug, is a substance that is part of all tissues and body fluids. Its molecule is involved in transmethylation reactions (transfer of the methyl group in the metabolic reactions of the body) as a donor of the methyl group, and is also a predecessor thiol compounds (cysteine, taurine, glutathione, CoA, etc.).

Ademethionine also has an antidepressant (relieving depression) effect, which manifests itself gradually, starting from the end of the first week of treatment. In patients with hypochondriacal depression (depressed state due to fear of the disease), a regression (reverse development) of the symptoms of the disease is observed. plays a central role in the biochemical reactions of transmethylation (biosynthesis of phospholipids), transfusion (synthesis and turnover of glutathione and taurine, conjugation of bile acids with an increase in their hydrophilicity, detoxification of bile acids and many xenobiotics) and aminopropylation (synthesis of polyamines such as putrescin, spermidine , which play an important role in the formation of ribosome structure and regeneration processes), where it serves either as a group donor or as a modulator of a number of enzymes. With the use of ademetionine, the elimination of free radicals and other toxic metabolites from hepatocytes increases. The experiment shows the antifibrotic activity of ademetionine. The drug also has antineurotoxic and antidepressant effects. Ademethionine is quite effective in liver pathology, accompanied by hepatic encephalopathy. However, it should be noted that the hepatoprotective effect reaches its maximum severity only if the drug is administered parenterally. Ademethionine has a predominant effect on the manifestations of toxemia and to a much lesser extent affects the indicators of cytolysis and cholestasis.

The drug has hepatoprotective (protective liver tissue) activity. With prolonged use, an improvement in liver function indicators is noted.

In patients with alcoholic cirrhosis, an increase in the level of glutamine in the liver, an increase in the level of cysteine and taurine in the blood plasma and a decrease in the level of methionine in the blood serum are observed, which indicates the normalization of metabolic (metabolic) reactions in the body.

Indications for use. Intrahepatic cholestasis (stagnation of bile) with precirrotic and cirrhotic conditions; depressive syndromes, including secondary ones.

Dosage and administration. Intensive care: 5-10 ml of solution (0.4-0.8 g) per day intramuscularly or intravenously during the first two or three weeks of treatment. Maintenance therapy: 2-4 tablets per day. Tablets are recommended to be taken between meals.

The lyophilized (dried by freezing in vacuum) dry substance is dissolved in a special solvent applied immediately before use. Intravenously should be administered very slowly.

Given the tonic effect of ademetionine, it is not recommended to take it before bedtime. The appointment of ademetionine in children is possible only according to strict indications, which is associated with insufficient clinical observations.

Ademethionine tablet should be removed from the packaging immediately before use. The tablets are coated with a special membrane that dissolves only in the intestine, due to which ademethionine is released only in the duodenum.

If the color of the tablet or lyophilized substance is different from white, you should refrain from using them.

When prescribing ademetionine tablets to patients with cirrhosis and associated hyperazotemia (excessive nitrogen content in the blood), it is necessary to observe a doctor and systematically monitor the level of nitrogen in the blood.

Side effect. Possible discomfort in the epi-gastria (area of the abdomen, located immediately below the convergence of the costal arches and sternum) associated with the fact that the active substance of the drug has an acid reaction.

Contraindications Hypersensitivity to the drug; the first 6 months pregnancy.

Release form. Enteric-coated tablets containing 0.76 g of 1,4-butanedisulfonate ademethionine (corresponding to 0.4 g of ademethionine). Lyophilized dry matter for injection in vials containing 0.76 g of ademethionine 1,4-butanedisulfonate (corresponding to 0.4 g of ademethionine), complete with a solvent (L-lysine caustic soda buffer solution) in 5 ml ampoules.

Storage conditions. In a dry, cool, dark place.

L-Ornithine-L-Aspartate (Hepa-Merz) is a fairly new drug for the treatment of liver diseases that regulates the metabolism in the liver cells. In the intestine, the drug dissociates into its constituent components - the amino acids ornithine and aspartate, which are involved in further biochemical processes:

1. Ornithine is included in the urea cycle as a substrate (at the stage of citrulline synthesis);

2. Ornithine is a stimulant of carbamoylphosphate synthetase I (the first enzyme in the urea cycle);

3. aspartate is also included in the urea cycle (at the stage of synthesis of arginine succinate);

4. Aspartate serves as a substrate for the synthesis of glutamine, participating in the binding of ammonia in perivenous hepatocytes, the brain and other tissues.

Thus, ornithine aspartate enhances the metabolism of ammonia, both in the liver and in the brain. A positive effect of hepamerza on hyperammonemia and the dynamics of encephalopathy in patients with cirrhosis of the liver was revealed. It contributes to the normalization of the body's CBS, the production of insulin and somatotropic hormone. It is used for fatty degeneration, hepatitis, cirrhosis, and liver damage due to alcoholism and drug addiction, for the treatment of brain disorders resulting from liver dysfunction. The duration of the course of treatment is determined by the dynamics of the concentration of ammonia in the blood and the condition of the patient. The course of treatment can be repeated every 2-3 months.

Ursodeoxycholic acid (UDCA) - hydrophilic, non-toxic, tertiary bile acid. Its content in the natural pool of human bile acids is only 4%. UDCA administration leads to a decrease in the enterohepatic circulation of hydrophobic bile acids with a hepatotoxic effect, thereby preventing their toxic effect on the membranes of hepatocytes and on the epithelium of the bile ducts, inhibits the production of immunoglobulins, normalizes HLA-DR antigens on the surface of cell membranes, which reduces their auto-immunity, reduces cholestasis-mediated immunosuppression. A certain effect is also given to the positive choleretic effect of UDCA, which, due to an increase in the passage of bile, also leads to increased excretion of toxic substances from the liver. UDCA has an antioxidant effect, reducing the oxidative activation of Kupffer cells by hydrophobic bile acids. Currently, the appointment of UDCA is considered justified for liver diseases accompanied or caused by cholestasis, regardless of the etiology. There is a consensus on the dosage of UDCA, which consists in the fact that the daily doses of the drug effective for cholestasis do not differ from the doses used to dissolve gallstones and amount to 8-15 mg / kg of the patient's body weight. Use the drug for acute and chronic hepatitis (including autoimmune), toxic (including alcoholic) liver damage, non-alcoholic steatohepatitis, primary biliary cirrhosis (before the formation of severe cirrhic liver transformation), hepatopathy of pregnant women.

Alpha-lipoic acid (lipamide, thioctacid) is a coenzyme involved in the oxidative decarboxylation of pyruvic acid and alpha-keto acids, plays an important role in the bioenergy of liver cells, is involved in the regulation of carbohydrate, protein, lipid metabolism, and renders lipotropic effect. She participates as a coenzyme in multi-enzyme complexes of mitochondria:

• in pyruvic acid dehydrogenase, which provides the conversion of PVA to acetyl-CoA (the formation of NAD) through the respiration-ATP chain;

• in the ketoglutarate alpha-dehydrogenase, an enzyme in the citrate cycle that catalyzes the conversion of alpha-ketoglutarate to succinyl-CoA (the formation of NAD through the respiration-ATP chain);

• in the dehydrogenase of branched chain amino acids.

According to experimental data, lipoic acid has an immunomodulating effect, restoring the immune response in immunosuppressed mice. The drug also showed antioxidant activity. The additional administration of alpha-lipoic acid has a good effect in the pathology associated with the occurrence of oxidative stress (reperfusion organ injuries, diabetes, cataracts, radiation injuries). Alpha-lipoic acid is used for viral hepatitis A, fatty hepatosis, chronic hepatitis, alcoholic lesions and cirrhosis.

Nonsteroidal anabolics (methyluracil, pentoxyl, potassium orotate, sodium nucleinate, riboxin).

The value of this group of drugs is currently insignificant due to their relatively low efficiency, however, they sometimes still continue to be used for various liver pathologies due to low toxicity and low cost.

Riboxin is a purine derivative. Penetrating through the cell membrane, phosphorylates, turning into inosinic acid, which is a common precursor of adenyl and guanyl nucleotides. Due to this, riboxin provides:

• creating the basis for the formation of basic macroergs during oxidative and substrate phosphorylation (the course of energy-dependent reactions and synthesis reactions improves, tissue respiration is activated, utilization of lactate and pyruvate is optimized);

• formation of a pool of purine nucleosides, which is used in the synthesis of RNA and DNA (the processes of regeneration and adaptive synthesis are accelerated);

In the treatment of liver diseases with riboxin, the effect of the drug is manifested in a decrease in metabolic and antitoxic functions, in accelerating the regeneration of liver tissue. The drug is used in acute and chronic hepatitis, cirrhosis.

Potassium orotate is the single biochemical precursor of all pyrimidine nucleic acid bases. Unlike riboxin, it does not contain a ribose residue and requires the use of a pentose phosphate cycle to form orotidine 5-phosphate, which directly goes on the synthesis of pyrimidine nucleotides. At the same time, however, a significant amount of ATP energy is consumed (which can be compensated by the simultaneous administration of riboxin). Potassium orotate facilitates the creation of a pyrimidine nucleotide stock necessary for the operational syntheses of RNA (and, consequently, protein) and DNA reduplication. With liver pathology, the drug has the greatest effect on the protein-synthetic function, contributes to the speedy restoration of the participation of the organ in pigment metabolism, and the duration of the icteric period is reduced. The detoxifying effect of the drug, however, is often insufficient. Virtually no effect on cholestasis. Assign mainly in acute viral hepatitis.

Methyluracil and pentoxyl are analogues of pyrimidine nucleotides, but they are practically not included in the exchange as precursors in the synthesis of nucleotides. The action of these drugs is realized thanks to the blockade of the enzyme uridine phosphatase, as a result of which the destruction of d-thymidine monophosphate, which limits the synthesis of DNA, is reduced. As a result, mitogenesis is stimulated in sensitive cells. Activation of the synthesis of RNA and protein is secondary and less pronounced than, for example, with the introduction of riboxin and potassium orotate. In case of liver pathology, the inclusion of methyluracil and pentoxyl in the therapy accelerates the restoration of the protein-synthetic function of the liver, reduces intoxication symptoms and dyspeptic phenomena. The duration of the icteric period is reduced and the participation of the liver in pigment metabolism improves. The indicators of nonspecific resistance of the body increase. In terms of severity of the hepatoprotective effect, methyluracil is superior to

pentoxyl. They use drugs for acute viral hepatitis, before and after cholecystectomy (1.0 по3 r / day r10 days before and after surgery).

Sodium nucleinate is the sodium salt of nucleic acids obtained by hydrolysis of yeast and further purification. It contains both purine and pyrimidine nucleotides, which can be used in various nucleic synthesis in the body, activates protein synthesis. Like methyluracil, it stimulates granulocytopoiesis and nonspecific resistance of the body. It is mainly used for acute hepatitis. The drug has low toxicity and very rarely causes side effects (allergic in nature). Used for acute viral hepatitis.

Thus, the use of hepatoprotectors for liver lesions of various etiologies is justified in terms of the pathogenesis mechanisms of this pathology. An important factor is the absence of pronounced toxicity in the drugs of this group and a small number of side effects, even with severe damage to the liver parenchyma. Alcoholic liver damage

Alcohol abuse has a higher risk of developing liver damage due to increased formation of acetaldehyde.

10 15% of ethanol is metabolized in the microsomes of the smooth endoplasmic reticulum by the microsomal ethanol oxidizing system (MEOS). The cytochrome P450 2E1 included in the system is involved in the metabolism of not only alcohol, but also a number of drugs, including paracetamol (acetaminophen). With an increased load on MEOS, it exhibits the properties of self-induction, which largely determines the increase in alcohol tolerance at a certain stage of chronic alcohol abuse. The increased work of MEOS leads to increased formation of toxic drug metabolites, which can cause liver damage when even therapeutic doses of drugs are used.

2. The mechanisms of alcoholic liver damage

1. The toxic effect of acetaldehyde. Acetaldehyde, which is formed in the liver under the influence of both ADH and MEOS, accounts for a significant part of the toxic effects of ethanol. The main of these effects are given below:

increased lipid peroxidation;

violation of the electron transport chain in mitochondria;

suppression of DNA repair;

impaired microtubule function;

formation of complexes with proteins;

stimulation of superoxide production by neutrophils

complement activation;

stimulation of collagen synthesis.

One of the most important hepatotoxic effects of acetaldehyde, which is manifested as a result of increased lipid peroxidation and the formation of stable complex compounds with proteins, is a dysfunction of the most important structural component of cell furniture phospholipids. This leads to increased membrane permeability, disruption of transmembrane transport, the functioning of cell receptors and membrane-bound enzymes.

The formation of acetaldehyde-protein complexes disrupts the polymerization of tubulin of microtubules, which manifests itself in a pathomorphological phenomenon that bears the name of alcoholic hyaline or Mallory bodies. Due to the fact that micro-tubules are involved in intracellular transport and secretion of proteins, impaired function leads to the retention of proteins and water with the formation of balloon dystrophy of hepatocytes.

In experimental models, it was shown that suppression of DNA repair in chronic use of ethanol leads to increased apoptosis of programmed cell death.

2. Violation of lipid metabolism. Oxidation of ethanol leads to an increased consumption of coenzyme NAD and an increase in the ratio of NADH: NAD. The latter leads to a shift to the right of the synthesis reaction of glycero-3-phosphate:

The consequence of increased glycerol-3-phosphate synthesis is increased fatty acid esterification and triglyceride synthesis, which serves as the initial stage in the development of hyperlipidemia and fatty liver dystrophy. Along with this, an increase in the concentration of NADH is accompanied by a decrease in the rate of oxidation of fatty acids, which also contributes to their deposition in the liver.

3. Dysfunction of mitochondria. Chronic use of alcohol reduces the activity of mitochondrial enzymes and the separation of oxidation and phosphorylation in the electron transport chain, which, in turn, leads to a decrease in ATP synthesis. The direct culprits of these violations are acetaldehyde and fatty acids. The development of microvesicular steatosis of the liver, one of the most serious complications of ABP, is associated with damage to mitochondrial DNA by peroxide products Alcoholic liver damage

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7) inhibitors and inducers of microsomal systems that metabolize xenobiotics;

8) hepatoprotective agents:

plant polyphenols;

synthetic drugs;

phospholipid and liposome preparations;

organizational preparations;

9) antioxidants.

In general, the assortment of drugs used in the complex treatment of liver and biliary tract diseases has more than 1000 items. However, among such a variety of drugs, relatively small group that have a selective effect on the liver is distinguished. These are hepatoprotectors. Their action is aimed at restoring liver homeostasis, increasing the organ's resistance to the action of pathogenic factors, normalizing functional activity and stimulating reparative and regenerative processes in the liver.

Traditionally, the group of hepatoprotective agents includes herbal polyphenolic preparations (Karsil, Legalon, Leprotek, Lyvolek, Silibor, Valiviv, Hepaliv, LIV 52, Hepabene, Hepatofalk plant, Cynarin, etc.), Essential phospholipid preparations (Essential) and organ preparations (Vitohepat , cire-steam, trophopar, simepar).

In recent years, the arsenal of modern hepatoprotective agents has expanded due to the appearance of synthetic drugs (antral, thiotriazolin, ziksorin) and new phospholipid and liposomal agents (phospholip, lipin, lipofen, lipopharm).

An analysis of the pharmaceutical market for hepatoprotective drugs, based on data from the Le-kinform regional drug information center, indicates that phospholipid preparations account for 16%, while herbal products account for 54%, while other drugs including synthetic, organ drugs and amino acid preparations - 30% of the total number of “true” hepatoprotective drugs (see chart).

Remembering that for all liver diseases, damage to the membranes of hepatocytes is pathogenetically justified, the appointment of therapy has a restoring and regenerating effect on the structure and functions of cell membranes and inhibits the process of cell destruction. Means of this orientation of action are phospholipid preparations.

Essential phospholipids - substances of natural origin - are the main elements in the structure of the cell membrane and cellular organelles. They have a metabolic and hepatoprotective effect; regulate lipid and carbohydrate metabolism. As a rule, they are used as part of complex therapy for the following diseases: hepatitis, drug and alcohol-induced liver damage, poisoning, fatty liver, liver cirrhosis, liver failure, hepatic coma, hepatobiliary surgery, hyperlipoproteinemia, diseases organs of the cardiovascular system (coronary heart disease, impaired cerebral and peripheral circulation, atherosclerosis, diabetic angiopathy), digestive diseases (chronic pancreatitis, ulcerative disease of the stomach and duodenum), toxicosis of pregnancy, radiation sickness, psoriasis, atopic dermatitis, eczema, etc.

Active-active substance:

It is known that phospholipids, contained in a sufficiently large amount in some food products (eggs, liver, meat, soybeans, etc.), cannot be considered as therapeutic food sources of phospholipids, since they contain other components (cholesterol, la, esters, etc.). To ensure a therapeutic effect in medicine, a specially developed medicinal substance EFL is used, which is purified from oils and undesirable impurities, the active principle of which is polyunsaturated phosphaditylcholine (FC). This is a significant difference between the drug substance EFL and phospholipids contained in living organisms, where saturated or monounsaturated fatty acids predominate (the proportion of polyunsaturated PF in them does not exceed 1.3%). It is the polyunsaturated form of PL that provides a number of pharmacotherapeutic effects.

Groups of essential phospholipids:

- Essential phospholipids are represented by two groups of compounds: phosphadiacyl-glycerols (phosphatidylethanolamine, phosphatidylcholine (lecithin), phosphatidylserine) and

- sphingomyelins.

Phosphatidylcholine is a phospholipid that is a universal building block for cell membranes.

Phosphatidylcholine is one of the most important nutrients for maintaining an active liver.

The functions of essential fossfolipids:

1) Restorative and hepatoprotective:

Phospholipids "integrate" into damaged membranes of the liver cells, "patching" the defects formed in them and restoring the normal functioning of hepatocytes. As a result, the liver continues to actively perform its many functions, improves lipid and protein metabolism, decreases fatty infiltration of hepatocytes and accelerates their regeneration.

2) Antifibrotic:

As a result of the restoration of the integrity of the membranes, the development of fibrosis (the formation of connective tissue) is stopped.

3) Antioxidant:

Phospholipids containing polyunsaturated fatty acids in their composition easily establish bonds with free radicals and thereby become a kind of trap for them.

4) Transport:

Phospholipids are involved in the processes of molecular transport, cell division and differentiation, realizing the activity of various enzyme systems.

In addition, phospholipids increase the bioavailability of the nutrients with which it is administered together.

Dosage Forms:

Capsules Solution for injection (lyophilisate for solution).

Essential phospholipids, phosphatidylcholine

Properties / Action:

Phospholipids are the main structural component of all cell membranes.

Essential phospholipids (EPL substance) are complex substances of natural origin, which are diglycerin esters of holinophosphoric acid (phosphatidylcholine) and unsaturated fatty acids

(linoleic, linolenic, oleic).

Essential phospholipid preparations have membranotropic properties; metabolic and hepatoprotective action; regulate lipid and carbohydrate metabolism.

Essential phospholipids are the main elements in the structure of the cell membrane and cellular organelles (mitochondria). An important role in the mechanism of hepatoprotective action belongs to the substitution effect.

Essential phospholipids improve the functional state of the liver. In case of impaired liver metabolism, Essential phospholipids provide the intake of high-energy phospholipids ready for assimilation, which ideally combine with endogenous phospholipids in chemical structure. They mainly penetrate the liver cells, invading their membranes.

Under the influence of essential phospholipids, clinical and biochemical parameters characteristic of fatty degeneration of the liver, chronic hepatitis of various etiologies, and cirrhosis are improved. With these diseases, the detoxification function of the liver is impaired, and the resistance of hepatocytes to toxic effects and the function of the antioxidant system of the body are also reduced. The use of essential phospholipids leads to the normalization of the structural and functional integrity of the hepatocyte cell membranes and allows the normal metabolism of the cell to be restored. Treatment with essential phospholipids leads to a significant improvement in biochemical parameters, such as serum ALT, AST, as well as a decrease in necrosis and inflammation. Positive dynamics of the indicators (reduction of intralobular necrosis, portal inflammation, general improvement in well-being) compared with the initial level was observed in patients taking Essential phospholipid preparations for one year.

The activity spectrum of Essential phospholipids in chronic degenerative liver diseases (CDLD) can be represented as follows:

• restoration and preservation of the integrity of hepatocyte membranes;

• activation of membrane phospholipid-dependent enzymes;

• improvement of lipid metabolism during the synthesis of lipoproteins in the liver;

• activation of RNA synthesis, normalization of protein metabolism;

• increase in glycogen content in the liver;

• increase in detoxification excretory potential (detoxification function of the liver);

• the conversion of neutral fats and cholesterol into easily metabolizable forms;

• reduction in the level of energy expenditure of the liver;

• reduction and disappearance of fatty infiltration of hepatocytes;

• antifibrotic effects (reducing the risk of connective tissue development: fibrosis and cirrhosis);

• stabilization of the physico-chemical properties of bile.

The biopotential of essential phospholipids is realized not only in the digestive system. There are many reasons to believe that essential phospholipids:

• modify the course of metabolic processes;

• reduce atherosclerotic lesions of blood vessels (normalize the content of lipoproteins, reduce the increased level of lipids in the blood, provide mobilization of cholesterol and its removal from the walls of the arteries with atherosclerosis);

• have a positive effect on lipid peroxidation in patients with coronary heart disease;

reduce the severity of clinical manifestations in diabetes;

• improve rheological properties of blood.

The good tolerance of Essential phospholipids allows us to consider them as a sufficiently powerful tool to increase the body's resistance, which allows you to significantly expand the indications for their use.

Pharmacokinetics:

Essential phospholipids are well absorbed in the small intestine, including in the form of biologically active products of their hydrolysis by digestive enzymes that are transported through the intestinal wall into the lymphatic channel. Partial resynthesis of phosphatidylcholine from hydrolysis products occurs in the liver.

Indications:

Essential phospholipids are usually used as part of complex therapy:

- hepatitis (acute and chronic), toxic hepatitis, drug and alcohol-related liver damage (alcoholic hepatitis), poisoning;

- fatty liver disease - fatty hepatosis - of various origins (diabetes mellitus, chronic infections);

- impaired liver function in somatic diseases;

- cirrhosis of the liver;

- liver cell necrosis, liver failure, hepatic coma and pre-coma (injection);

- pre- and postoperative treatment, especially during operations in the hepatobiliary area, for example, cholecystectomy (injection);

- hyperlipoproteinemia, hypercholesterolemia, hypertriglyceridemia;

- diseases of the organs of the cardiovascular system: coronary heart disease, angina pectoris, condition after myocardial infarction and stroke, cerebral and peripheral circulatory disorders, hypertension, vascular atherosclerosis, diabetic angiopathy, prophylaxis of thromboembolism before surgery, prevention fat embolism treatment (injection);

- diseases of the digestive system (chronic pancreatitis, peptic ulcer of the stomach and duodenum, etc.);

Беременности pregnancy toxicosis (edema, proteinuria and hypertensive disorders);

- radiation sickness (radiation syndrome);

- psoriasis, atopic dermatitis, diffuse neurodermatitis, eczema;

-prevention of premature aging.

Dosage and administration:

Treatment with Essential phospholipid preparations often begins with the combined use of an injection solution and capsules (parenterally and orally).

The solution for intravenous injection is administered slowly in 1-4 ampoules of 5 ml (Essential N) or 1-2 vials of 2.5 g (Phosphogliv) per day; course duration 10 to 30 days. At the same time, preparations of Essential phospholipids can be prescribed by mouth. The contents of the ampoules (Essential H) are previously diluted with glucose solution or with the patient's own blood; mixing with electrolyte solutions (sodium chloride) is prohibited, mixed injections are avoided. The contents of the vial (Phosphogliv) are diluted in 10 ml of pyrogen-free water (water for injection).

As the patient's condition improves, treatment can only be continued oral forms of preparations of Essential phospholipids (capsules).

Inside, preparations of Essential phospholipids are taken 1 to 2 capsules 2-3 times a day before or during meals. Capsules should be swallowed whole with a little water.

In acute hepatitis, treatment with Essential phospholipid preparations is continued for 1-3 months, with chronic liver lesions, regardless of causative factors, treatment is continued for at least 6 months. The course of treatment, if necessary, can be continued or repeated.

Treatment of psoriasis with Essential phospholipid preparations should be started with a two-week intake of 2 capsules 3 times a day (Essential Forte N), then 10 intravenous infusions of 1 ampoule of 5 ml (Essentiale N) are given daily and PUVA therapy begins. After infusions, you should resume taking the capsules and continue it for 2 months. In the presence of contraindications for PUVA therapy, it is possible to confine oneself only to the oral administration of Essential phospholipids, including in combination with generally accepted methods of treating psoriasis.

Overdose:

Currently, there are no data on cases of overdose of drugs of Essential phospholipids.

Contraindications:

individual intolerance (including a history of hypersensitivity).

If benzyl alcohol (Essential H) is included in the injection, it should not be used to treat newborns and premature babies.

Use during pregnancy and lactation:

Perhaps the use of Essential phospholipids during pregnancy, if indicated.

Data on the use of essential phospholipids during lactation (breastfeeding) are not available.

Side effects:

Essential phospholipid preparations are usually well tolerated, including with prolonged use.

In rare cases, discomfort in the epigastric region, nausea, diarrhea, allergic reactions (skin rash) are possible.

Drug Interactions:

Drug interaction Essential phospholipids not described.

Currently, more than 50 years of positive experience in the study and therapeutic use of drugs containing essential phospholipids ("EFL"), in particular, Essential, have been accumulated in the world.

The substance EFL is a highly purified extract from soybeans and contains mainly phosphatidylcholine (FC) molecules with a high concentration of polyunsaturated fatty acids. The main active ingredient in EFL is 1,2 - dilinoleoil - phosphatidylcholine, the synthesis of which is not possible by the human body. The presence of two essential (necessary) fatty acids makes this special form of phospholipids superior to endogenous phospholipids

The membrane-stabilizing and hepatoprotective effect of EFL is achieved by directly incorporating EFL molecules into the phospholipid structure of damaged liver cells, replacing defects and restoring the barrier function of the lipid bilayer of membranes. Unsaturated fatty acids of phospholipids promote an increase in membrane activity and fluidity, prevent membrane as a result of which the density of phospholipid structures decreases, permeability normalizes Exogenous phospholipids promote the activation of phospholipid-dependent enzymes located in the membrane. This, in turn, has a supporting effect on metabolic processes in the liver cells, contributes to an increase in its detoxification and excretory potential

The hepatoprotective effect of EFL is obviously also based on the inhibition of lipid peroxidation (lipid peroxidation) processes, which are considered as one of the leading pathogenetic mechanisms for the development of liver lesions. Restoring the "packaging" of polyunsaturated fatty acids in the hepatocyte membrane, essential phospholipids reduce oxygen access to them, thereby reducing the rate of nucleation of free radicals

The prototype of compounds containing the substance EFL, is "Essential". This is a multicomponent preparation, which includes essential phospholipids, unsaturated fatty acids: linoleic, oleic, linolenic, and vitamins B1, B2, B6, B12, PP, E.

In clinical practice, Essential is used in 3 main areas: for diseases of the liver and its toxic lesions; with pathology of internal organs complicated by liver damage; as a method of "medical cover" when using drugs that cause liver damage (tetracycline, rifampicin, paracetamol, indomethacin, etc.). In hepatology, Essential is prescribed for chronic hepatitis, cirrhosis, fatty degeneration, hepatic coma. It is also used for radiation syndrome and toxicosis of pregnant women, for the prevention of relapse of gallstone disease, for preoperative preparation and postoperative treatment of patients, especially in cases of surgical interventions on the liver and biliary tract

Until recently, Essentiale remained the only representative of the group of phospholipid preparations. However, clear progress has been noted in the field of creating, studying and introducing into clinical practice this class of drugs, not only abroad, but also in Ukraine. Convincing proof of this is the appearance on the domestic market of pharmaceutical products of such drugs as Phospholip, Essel forte, Lipin, as well as clinical trials of new drugs Lipofen, Lioliv, Eplir ". The active substances of the Phospholip preparation are essential phospholipids: phosphatidylcholine (FC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS), linoleic acid, contained in soybean lecithin. The drug is a protector of the cellular structures of hepatocytes and phospholipid-mediated enzyme systems. Phospholip normalizes protein and fat metabolism, has a lipotropic effect. This explains the effectiveness of the drug in fatty liver disease, in complex therapy

for the treatment of chronic hepatitis, alcoholic hepatitis, liver cirrhosis and other liver lesions of various etiologies (immune genesis, toxic and drug liver damage, radiation sickness, pregnancy toxicosis)

The State Scientific Center of Medicines (Kharkov) has developed the combined drug “Lipofen”, which includes essential phospholipids, vitamins B1, B6, E and flacumin. Lipofen has a hepatoprotective effect, the mechanism of which is due to the inhibition of the processes of lipid peroxidation of hepatocytes, normalization of indicators antioxidant protection, membrane stabilizing activity. According to the data, the severity of the antioxidant effect of Lipofen significantly exceeds both Essentiale and individual phospholipids, which is due to the synergistic action of the powerful antioxidant flacumin and phosphatidylcholine in the combined preparation. Lipofen approved Pharmacological Committee of Ukraine and recommended for clinical trials as a pathogenetic agent for chronic, including alcoholic, liver diseases

Eplir is a new original hepatoprotective drug of phospholipid nature, created at the departments of pharmacology and drug technology of the Siberian Medical University. Eplir is a fraction of polar lipids of a lake silt sediment containing biologically active substances PF, PE, sulfolipids, carotenoids, xanthophylls, and bile acids. In experiments on models of acute and chronic toxic liver damage, Eplir prevented the development of structural metabolic disorders in the liver, protected the organ parenchyma from the development of cytolysis and necrosis

The hepatoprotective effect of Eplir is ensured by the antioxidant properties of phospholipids, a decrease in the formation of detergent lysophosphatides and the inclusion of PF in the composition of cell membranes.

A group of scientists from the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine created an original drug of natural origin for parenteral use - Lipin, which is a lyophilized egg phosphatidylcholine in liposomal form. Lipin is approved for medical use and industrial production. The drug is used as a suspension in physiological saline with the formation of small single-layer liposomes. Therefore, it can be considered both as a phospholipid and as a liposomal preparation. Lipin has antihypoxic, antioxidant, detoxifying, cardioprotective, anti-inflammatory and hepatoprotective effects. High clinical efficacy, almost complete absence of contraindications for use, low toxicity made it possible to recommend this drug for use in the practice of phthisiatric, pulmonological, pulmonary, cardiological and resuscitation departments, as well as in gastroenterology for the correction of impaired liver and gastrointestinal organs

The results of a preclinical study of lipin as a hepatoprotective drug in various models of liver damage (acute dystrophy, chronic hepatitis, subhepatic cholestasis, drug hepatitis) showed that administration of it to experimental animals is accompanied by inhibition of lipid peroxidation in the blood and tissues, increased enzyme activity antiradical protection of the body, improvement of exocrine liver function, membrane-stabilizing effect, increase of nonspecific immunity. Positive changes were manifested to a greater extent with acute liver dystrophy and subhepatic cholestasis

Tests of lipin in the clinic of gastroenterological diseases confirmed its pharmacotherapeutic viability in acute and chronic active hepatitis, chronic stoneless cholecystitis, cirrhosis of the liver, ulcerative colitis.

The effectiveness of the use of lipin in gastroenterology and hepatology is explained not only by a unique range of pharmacological effects, but also by the proven hepatospecificity of the pharmacokinetics of liposomes. This is evidenced by the fact that 97% of phosphatidylcholine liposomes introduced into the body are found in hepatocytes, and only 3% in non-parenchymal cells

Until recently, the organ-specificity of liposomes with respect to liver cells was practically not used to create drugs targeted action. The use of liposomes as drug transport systems and the inclusion of compounds with hepatoprotective activity in them has demonstrated the promise of this area and has made it possible to propose a new liposome hepatoprotector “Lioliv” for clinical studies. The Lioliv

belongs to the class of metal-liposomal preparations and is a composition of membrane phospholipid (Lipin) and a coordination compound of aluminum with mefenamic acid (Antral). Pharmacological studies of the lyoliv were performed at the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine in collaboration with specialists from the Department of Pharmacology of the Ukrainian Pharmaceutical Academy (Kharkov).

According to the results of the preclinical study, it was found that lyol administration in the parenteral and enteric routes of administration in acute, subacute, and chronic toxic liver damage weakens the effect of hepatotoxins, activates reparative processes in hepatocytes, and promotes the practical normalization of the structural and functional state of the liver in adults, young and immature experimental animals of different species. The hepatoprotective effect is due to inhibition of lipid peroxidation processes, support of endogenous antioxidant systems of the body, stabilization of the structure of the liver and hepatocyte membranes, activation of reparative reactions in the liver and level of adaptation, as well as a function of nonspecific detoxification. Along with the hepatoprotective effect, liolivum shows a pronounced prolonged anti-inflammatory effect

Comprehensively affecting different links in the pathogenesis of toxic hepatitis (peroxidation of membrane lipids, cholestasis, cytolysis, inflammation), lyo-liv provides a high protective effect and can compete with traditional hepatoprotective agents (essentials, silybor) in the treatment and prevention of various hepatopathies .

The clinic suggests the use of lyol for mono- and combination therapy of acute and chronic dystrophic and hepatitis liver conditions (toxic, alcoholic, drug hepatitis, fatty steatosis), and liver cirrhosis.

Thus, the above analysis of the current state of the market of phospholipid preparations allows us to conclude that the creation and study of compounds with the ability to normalize the structure and functions of the membranes of liver cells should be considered the most promising direction in the treatment of hepatological patients.

USE OF PHOSPHOLIPID MEMBRANE PROTECTORS IN THE TREATMENT OF CARDIOVASCULAR DISEASES

In the human body, phospholipids directly or indirectly participate in metabolic processes. Their biological significance lies in the fact that they are structural elements of biological membranes.

The composition and spatial orientation of fatty acids in phospholipids are crucial in the formation of such characteristics of cell structures as membrane fluidity, membrane permeability, receptor and enzymatic activity of membrane-bound proteins.

A change in these characteristics underlies a number of diseases of the cardiovascular system and associated pathological conditions.

Mechanisms of action and pharmacological effects of essential phospholipids used in cardiology.

Essential. phospholipids promote enhanced emulsification of fat particles in the intestinal lumen, which contributes to their optimal absorption, and further to more effective action of endogenous lipoprotein-idlipases. Due to the increased activity of specific enzymes responsible for cholesterol esterification, essential phospholipids stimulate its reverse transport, which partially underlies the anti-atherogenic effect of the latter. Phospholipids are an important component of the outer shell of lipoprotsidny particles. Therefore, exogenous essential phospholipids, integrating into the membrane of circulating lipoproteins, can significantly modify their transport role.

In particular, when included in antiatherogenic lipoproteins of high density, essential phospholipids help to remove more cholesterol from blood plasma. The anti-atherogenic effect of essential phospholipids also manifests itself in their positive effect on the rheological properties of blood - a

decrease in platelet aggregation activity and an increase in the fluidity of the phospholipid layer of erythrocyte membranes.

The purpose of the lesson:

To learn:

Pharmacokinetics, pharmacodynamics, indications for use, pharmacotoxic dynamics: drugs:

1. Preparations containing natural or semisynthetic milk thistle flavonoids: hepatene, legalon, karsil, hepatofalk plant, silibor.

2. Preparations containing natural or semi-synthetic flavonoids of other plants: hofitol, catergen (cyanidanol), LIV-52 (hepatal).

3. Organic preparations of animal origin: sirepar, hepatosan.

4. Preparations containing essential phospholipids: essentiale, phosphogliv, essliver, eplir.

5. Preparations of different groups: bemitil, ademetionin (heptral), lipoic acid (thioctacid), hepamerz (ornithine), ursodeoxycholic acid (ursofalk), non-steroidal anabolics (methyluracil, pentoxyl, sodium nucleinate).

The mechanisms of action of various hepatoprotectors

Essential phospholipids

- antioxidant

- Replenishment of lipid membranes

Adenosylmethionine

- antioxidant

- Synthesis of hepatocyte structural proteins

- Sulfurization of toxic FAs (anticholestatic)

Silymarin

- antioxidant

- Synthesis of hepatocyte structural proteins

- Blocking some poisons (antitoxic)

UDHK (URSOFALK®)

- Cytoprotective (displacement of toxic hydrophobic FAs)

- Choleretic (increased synthesis and excretion of FA)

- Immunomodulating (decreased synthesis of pro-inflammatory cytokines)

- Anti-apoptotic (blockade of the caspase mitochondrial destruction cycle)

- antioxidant

To Know:

1. Research methods for chronic hapatitis, cirrhosis

2. Etiology, pathogenesis, clinic, chronic hapatitis, cirrhosis

3. At any state using hepatoprotectors, membrane protectors

3. Be able to:

a) select the necessary drugs for a particular patient with the indicated pathology, select criteria for therapeutic efficacy and safety;

b) prescribe combination therapy;

The list of practical works:

Homework.

1. To study the main tasks and directions of the choice of medicines

chronic hapatitis, cirrhosis of the liver

The task for self-checking the initial level.

1. Etiology, pathogenesis, classification of chronic hapatitis, cirrhosis

2. List the main groups of hepatoprotectors, membrane protectors

3. Formulate the significance of the leading pharmacokinetic characteristics (T1 / 2el,%, association with plasma proteins, \ / d l / kg) in an individual selection of the above drugs.

4. Highlight the clinical and laboratory-functional criteria for the therapeutic effectiveness of the use of hepatoprotectors, membrane protectors

5. List the clinical and laboratory safety criteria for the use of drugs in the analyzed clinical syndromes.

Control of the intermediate level of knowledge.

1. After acute viral hepatitis, a 46-year-old patient retains pain and heaviness in the right hypochondrium, an increase in liver size, an increase in serum ALT and AST levels, as markers of the presence of hepatocyte cytolysis syndrome.

TESTS

1. The patient, 20 years old, who is examined and treated in the gastroenterological department, is diagnosed with autoimmune hepatitis. What group of drugs is included in the basic therapy of this disease?

A. Glucocorticoids and cytostatics.

B. Anabolic steroid drugs.

C. Antibacterial drugs.

D. Hepatoprotective drugs.

E. Vitamins.

2. The patient has small-node cirrhosis of the liver. Over the past 2 years, shortness of breath, edema in the lower extremities, ascites appeared. The patient took hepatoprotectors and glucocorticoids. Which combination of drugs is most appropriate to prescribe?

A. Veroshpiron + ascorutin.

B. Nerabol + furasemide.

C. Lidocaine + hypothiazide.

D. Albumin + ascorutin.

E. Veroshpiron + furosemide.

3. The patient, 36 years old, complains of general weakness, irritability, heaviness in the right hypochondrium, subfebrile condition. 4 years ago she had viral hepatitis. These complaints grew over the course of 3 months. Objectively: the liver 3 cm protrudes from under the edge of the costal arch. Laboratory: total bilir-bin - 64.5 mmol / l: direct - 22.7 mmol / l. Gamma globulins - 31%, AST - 1.42 mmol / h • l, ALT - 1.96 mmol / h • l. Signs of active virus replication were detected (HBeAg - positive reaction). Which drug is most effective for etiotropic treatment?

A. Essential Forte.

B. Alpha interferon.

C. Levamisole.

D. Prednisone.

E. Carsil.

4. The patient has small-node cirrhosis of the liver. Over the past 2 months, shortness of breath, edema in the lower extremities, ascites appeared. The patient took hepatoprotectors and glucocorticoids. What combination of drugs is most appropriate to add to treatment?

A. Aldactone + ascorutin.

B. Nerobol + furosemide.

C. Lidocaine + hypothiazide.

D. Albumin + ascorutin.

E. Spironolactone + furosemide.

5. A patient, 56 years old, showed moderate ictericity of the skin and sclera, an increase in the size of the liver and spleen. Three years ago, he was treated for hepatitis B. In the blood: HBsAg, HBeAg (+). High concentration of HBV DNA. Which of the following is the most effective for basic therapy?

A. Karsil ..

B. Vitohepat.

C. Prednisolone.

D. α-interferon.

E. Essential Forte.

7. For liver diseases with the inclusion of autoimmune and inflammatory reactions in the pathogenesis, as well as in the presence of cholestasis in a patient, the drugs of choice are:

A. Sirepar, tropofar

V. Essential, energetic

S. Ursofalk, ursosan

D. Lipoic acid, espa lipon

E. Silymarin, silibinin

8. The patient, 36 years old, complains of general weakness, irritability, heaviness in the right hypochondrium, subfebrile condition. 4 years ago suffered a viral hepatitis. Complaints significantly progressively increased over 3 months. Objectively: the 3 cm liver protrudes from under the edge of the costal arch. Laboratory: total bilirubin - 64.5 mmol / l: direct - 22.7 mmol / l. Γ-globulin - 31%, AcAT - 1.42 mmol / h • l, ALT - 1.96 mmol / h • l. Signs of active virus replication were detected (HBeAg - positive reaction). Which of the drugs is most effective for etropic treatment?

A. Essential Forte.

B. Carsil.

C. Levamisole.

D. Prednisone.

E. α-interferon.

9. The patient has small-node cirrhosis of the liver. Over the past 2 years, shortness of breath, edema in the lower extremities, ascites appeared. The patient took hepatoprotectors and glucocorticoids. What drug combination is most appropriate?

A. Aldocton + ascorutin.

B. Nerabol + furasemide.

C. Lidocaine + hypothiazide.

D. Albumin + ascorutin.

E. Aldocton + furasemide.

10. A 40-year-old man has autoimmune hepatitis. The examination revealed in the blood: bilirubin - 42 μmol / l, AlAt - 2.3 μmol / (hour • l), AsAt - 1.8 μmol / (hour • l). Which of the following is most effective for the treatment of this patient?

A. Antibacterial agents.

B. Hepatoprotectors.

C. Glococorticoids, cytostatics.

D. Antiviral drugs.

E. Hemosorption, vitamin therapy.

11. A 60-year-old patient who has been suffering from angina pectoris along with coronolytics for a long time, the doctor prescribed acetylsalicylic acid to reduce platelet aggregation. What is the mechanism of antiplatelet function of acetylsalicylic acid?

A. Reduces the activity of phosphodiesterase.ose the drug necessary for the patient to stabilize membrane permeability:

B. Reduces cyclooxygenase activity.

C. Increases platelet adenylate cyclase activity.

D. Increases the synthesis of prostacyclin.

E. It exhibits a membrane stabilizing effect.

12. A patient, 20 years old, who is examined and treated in the gastroenterological department, is diagnosed with autoimmune hepatitis. What group of drugs is included in the basic therapy of this disease?

A. * Glucocorticoids and cytostatics.

B. Anabolic steroid drugs.

C. Antibacterial drugs.

D. Hepatoprotective drugs.

E. Vitamins.

13. The patient has small-node cirrhosis of the liver. Over the past 2 years, shortness of breath, edema in the lower extremities, ascites appeared. The patient took hepatoprotectors and glucocorticoids. Which combination of drugs is most appropriate to prescribe?

A. Nerabol + furasemide.

B. Lidocaine + hypothiazide.

C. Albumin + ascorutin.

D. Veroshpiron + furosemide.

E. Veroshpiron + ascorutin.

14. A patient with hepatitis C, an alcohol abuser, developed cirrhosis of the liver. The drug of choice is:

A. Essential.

B. Sirepar.

C. Methionine.

D. Heptral.

E. Nicotinic acid.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF MEDICINES FOR THE HYPOACID STATES AND FOR INTESTINAL DYSBACTERIOSIS

Purpose of the topic:

Chronic gastritis (CG) affects more than 40-50% of the adult population of the globe. The prevalence of the disease largely depends on the place and living conditions of people.

CG is a disease with a chronic recurrent course, which is based on inflammatory and dystrophic, dysregenerative lesions of the gastric mucosa, accompanied by a violation of its secretory, motor-evacuation and incretory functions.

CG is a clinical-morphological concept, but the final diagnosis becomes valid only after histological confirmation

Type A gastritis is an autoimmune atrophic fundal gastritis, which is several times less common than type B gastritis (in 20-30% of patients). It is accompanied by progressive atrophy of the glands, achlorhydria, hypergastrinemia, the formation of antiparietal antibodies and the development of B12-deficient anemia. In this gastritis, antibodies to the internal factor are detected in the gastric juice. A low level of IgA and IgG, a frequent absence of release of AB0 antigens, and a low level of normal anti-tissue antibodies were found. Accelerated death of epithelial cells due to the penetration of activated lymphocytes through the basement membrane of the glands is noted. Type A CG is detected in immediate relatives, in individuals with a hereditarily determined immune background. Sometimes it is combined with autoimmune thyroiditis, hypothyroidism, vitiligo.

It is usually diffuse. It develops in persons of an elderly and mature age. More often due to malnutrition, less often - toxic effects (alcohol, drugs, occupational hazards).

Intestinal dysbiosis

Dysbacteriosis is a quantitative (decrease in the content of beneficial and increase of pathogenic microflora) and qualitative (change in the biological properties of the intestinal flora, weakening of the performance of useful functions and increased toxicity) change in the intestinal microflora.

According to modern epidemiological studies, intestinal dysbiosis to one degree or another affects 90% of the world's population. This is primarily due to poor nutrition, stress, decreased immunological reactivity of the body, environmental and physico-chemical environmental factors, unjustified and uncontrolled use of drugs that affect the microflora of the body. It was found that after acute intestinal infection in the absence of adequate therapy, dysbiotic changes in the intestine persist for at least 2-3 years.

Especially often intestinal dysbiosis is observed in children of the first year of life (70–80%) and newborns (80–100%). At the age over 1 year, dysbacteriosis is found in 60–70% of children, in healthy children over 3 years old - in 30–50% of cases. However, most children do not have any clinical manifestations of the disease.

Motivational characteristic of the topic.

Gastritis is a term used to refer to inflammatory and dystrophic changes in the gastric mucosa (coolant), which are different in origin, course, and clinical manifestations.

There are two main forms of gastritis - acute and chronic.

As a rule, alcohol gastritis is considered separately.

Description of morphological changes are supplemented by a description of endoscopic categories of gastritis:

• erythematous / exudative gastritis (superficial gastritis);

• flat erosion;

• elevated erosion;

• hemorrhagic gastritis;

• hyperplastic gastritis;

• gastritis, accompanied by DGR (reflux gastritis).

The diagnosis of chronic hepatitis C should be formed on the basis of an assessment of all 4 signs of the disease: the localization of the pathological process (Fig. 1), histological changes, macroscopic changes in the mucosa revealed by endoscopy, etiological factorsIt should be noted that these classifications do not contain such important clinical and functional signs of the disease as an assessment of the secretory function of the stomach (normal, increased or decreased secretion of hydrochloric acid), the stage of the disease (exacerbation, remission) and the presence of complications (erosion, bleeding, malignancy) .

Working classification of chronic gastritis

By type of gastritis:

1. Neatrophic (superficial) gastritis.

2. Atrophic gastritis (autoimmune atrophic and multifocal atrophic).

3. Special forms of gastritis (reactive, radiation, lymphocytic, granulomatous, eosinophilic, giant hypertrophic, etc.).

By localization:

1. The antrum of the stomach.

2. The body of the stomach.

According to the endoscopic picture:

1. Superficial.

2. Erosive.

3. Atrophic.

4. Hemorrhagic.

5. Hyperplasia of the mucosa.

6. The presence of GDR, etc.

According to morphology:

1. The degree of inflammation.

2. The activity of inflammation.

3. The presence of atrophy of the gastric glands.

4. The presence and type of intestinal metaplasia.

5. The degree of contamination of the mucous membrane Nr.

According to the functional basis:

1. Normal secretion.

2. Increased secretion.

3. Secretory insufficiency (moderate or severe).

According to clinical signs:

1. The phase of exacerbation.

2. The phase of remission.

Complications:

1. Bleeding.

2. Malignancy.

Clinical diagnosis is based on medical history, identification of clinical signs, determination of the type of chronic gastritis, assessment of the prevalence of morphological signs of the disease, infection, the presence and severity of gastric dysfunction.

Etiology and pathogenesis

The occurrence and progression of chronic hepatitis is due to the combined effect on the coolant of many factors. The pathogenesis of chronic gastritis for each form and type of disease has its own characteristics.

There are two groups of etiological factors of chronic hepatitis - exogenous and endogenous.

Exogenous factors contributing to the onset of chronic hepatitis C:

• HP infection;

• nutritional factors;

• alcohol abuse;

• smoking;

• long-term use of drugs that irritate the coolant;

• exposure to coolant chemical agents;

• exposure to radiation;

• other bacteria (except HP);

• mushrooms;

• parasites.

Endogenous factors contributing to the onset of chronic hepatitis C:

• genetic factors;

• duodenogastric reflux;

• autoimmune factors;

• endogenous intoxication;

• hypoxemia;

• chronic infection;

• metabolic disorders;

• endocrine dysfunctions;

• hypovitaminosis;

• reflex effects on the stomach from other affected organs.

Nonsteroidal anti-inflammatory drugs

NSAIDs with prolonged use cause severe lesions of the coolant, mainly the antrum and duodenum (hemorrhage, erosion, ulcers). Side effects of NSAIDs are associated with their ability to inhibit the key enzyme of arachidonic acid metabolism - cyclooxygenase (COX), which leads to inhibition of prostaglandin synthesis. Prostaglandins, in turn, determine the most important physiological reactions of the body, including speed of reparative processes in the coolant and duodenum.

There are two COX isoenzymes - COX1 (provides synthesis of prostaglandins) and COX2 (its activity increases only with inflammation).

The modern classification of NSAIDs is precisely based on the degree of selectivity of drugs to various forms of COX. It is advisable to use NSAIDs with maximum selectivity for COX2 (celecoxib, rofecoxib).

In fig. 2 shows the pH-gram of the body of the stomach with GDR.

Autoimmune mechanisms

The formation of autoimmune atrophic CG is based on the formation of antibodies to parietal (parietal) cells of the fundus of the stomach. As a result of this formation, the following occurs:

• decrease in the production of hydrochloric acid and pepsin (hypochlorhydria, achlorhydria and achilia);

• atrophy of the coolant, mainly the fundus;

• a decrease in the production of Castle's internal factor and the development of B12-deficient anemia;

• an increase in gastrin production by G-cells of the antrum.

Clinical picture

The clinical manifestations of chronic gastritis are conditionally characterized by both local and general disorders.

Local disorders are characterized by symptoms:

• Dyspepsia (heaviness and a feeling of pressure, fullness in the epigastric region, appearing or intensifying during eating or shortly after eating, belching, regurgitation, nausea, an unpleasant aftertaste in the mouth, burning in the epigastrium, often heartburn, which indicates a violation of

evacuation from the stomach and throwing gastric contents into the esophagus). These manifestations more often occur with certain forms of antral CG, which lead to impaired evacuation from the stomach, increased intragastric pressure, increased gastroesophageal reflux and exacerbation of all of these symptoms. • In case of chronic hepatitis C, the disorders of the body are reduced mainly to severity in the epigastric region that occurs during or shortly after eating.

• Patients with bacterial (Helicobacter pylori-associated) chronic hepatitis C, which for a long time proceeds with an increase in the secretory function of the stomach, may show signs of intestinal dyspepsia in the form of defecation disorders (constipation, weakness, unstable stools, rumbling, bloating).

• In patients with eosinophilic (allergic) chronic hepatitis C - chronic diarrhea, intolerance to certain foods, drugs, abdominal pain, nausea, vomiting, weight loss, eosinophilia.

General disorders can manifest themselves in the following syndromes:

• Asthenoneurotic syndrome (weakness, irritability, disorders of the cardiovascular system - cardialgia, arrhythmias, arterial instability with a tendency to hypotension).

• In atrophic forms of chronic hepatitis C in the stage of secretory insufficiency, a symptom complex similar to dumping syndrome may develop (sudden weakness, unstable stool, hiccups, pallor, sweating, drowsiness, which occur shortly after eating, fast satiety).

• Patients with chronic hepatitis C of the body and the development of B12-deficient anemia develop weakness, increased fatigue, drowsiness, a decrease in vitality and a loss of interest in life; there are pains and burning in the mouth, tongue, symmetrical paresthesia in the lower and upper limbs.

• Patients with antral, Helicobacter pylori-associated chronic hepatitis C in the stage of secretory hyperfunction may develop a “ulcer-like” symptom complex, often indicating a pre-ulcerated state.

Diagnostics

In the case of type A CG, non-ulcer gastric dyspepsia syndrome predominates: unpleasant taste in the mouth, poor appetite, nausea, belching with bitterness, bloating, diarrhea. The pain has a diffuse character, appears in the epigastrium immediately after eating. On palpation of the abdomen - moderate diffuse soreness in the subrenal region. Diffuse atrophic fundal gastritis is associated with B12-deficient anemia. At the same time, there is a decrease in the content of Pepsiogen 1 and clinical signs do not correlate with histological changes.

As a rule, pains are observed after or shortly after eating (a sign of irritation of the stomach), are dull, aching. Its duration is not long. The localization of pain is different, but more often in the epigastric region, a little to the right.

Sometimes after eating, a feeling of pressure in the epigastrium, overflow of the stomach. With erosive and antral gastritis - ulcerative pain. With gastroptosis, pain intensifies in a standing position, while walking and decreases while lying down.

Endoscopic diagnosis with biopsy. The nature and localization of coolant changes is being clarified.

Laboratory diagnostics. Clinical analysis of blood, biochemical analysis of blood, clinical analysis of urine, clinical analysis of feces, analysis of feces for occult blood, morphological studies, determination of pepsin and pepsinogen in the blood, immunological studies.

X-ray examination. There are ulceration of the coolant, ulcers, cardia failure, hiatal hernia, cancer, polyposis, DGR, giant hypertrophic gastritis, chronic obstruction of the duodenum.

Intragastric pH-metry - determination of the state of secretion and diagnosis of functional disorders. With non-atrophic chronic hepatitis C and reflux gastritis, the secretory function is normal or

increased, with atrophic chronic hypertrophy, giant hypertrophic gastritis, secretory function is reduced. In fig. 3, an example of a pH gram of two stomach sections of a patient with chronic hepatitis C with increased acidity is presented.

Normal acid production is characterized by the following numbers:

on an empty stomach, the pH in the cavity of the body of the stomach is 1.5–2.0, after the introduction of the stimulant — pentagastrin or histamine — 1.1–1.2.

Electrogastroenterography - a study of the motor evacuation function of the gastrointestinal tract in order to determine GDR.

Floor manometry of the upper gastrointestinal tract. - Pressure in WPC is normal 80–130 mm of water. Art., with reflux gastritis rises to 200–240 mm of water. Art.

Ultrasound examination (ultrasound). An ultrasound of the liver, pancreas and gall bladder is performed to identify concomitant diseases of the gastrointestinal tract (GIT). In recent years, ultrasound makes it possible to determine the presence of damage to the wall of the stomach.

Means used for decreased secretory function of the stomach – replacement therapy

The main components of gastric juice are hydrochloric acid (produced by parietal cells), pepsinogen (produced by the main cells), and mucin (produced by additional cells). With hypoacid and anacid gastritis, the secretion of hydrochloric acid (achlorhydria) may be reduced or, accordingly, completely absent, and there may also be a decrease in the secretion of hydrochloric acid and pepsin (achilia). Achilia can be observed with stomach cancer, pernicious anemia.

In case of insufficiency of secretion of gastric juice to improve food digestion, it is prescribed as replacement therapy: abomin, natural gastric juice, pepsin, diluted hydrochloric acid.

Their therapeutic effect is due to a change in the reaction of the environment in the stomach, which leads to a weakening of the peristalsis of the antrum, closure of the pylorus, a longer delay in food in the stomach, the release of gastrin, and stimulates its own acid and pepsin formation.

In addition, hydrochloric acid stimulates secretion of the duodenal mucosa of secretin, cholecystokinin, motilin and other hormones that promote the separation of pancreatic juice, bile, normalizes motility, improving the intestinal phase of digestion, and prevents the development of secondary pancreatitis.

Gastric juice is prescribed in combination with drugs that affect the motility of the output section of the stomach (motilak or motilium).

Natural gastric juice (Succus gastricus naturalis) contains all the enzymes secreted by the glands of the stomach; its pH varies from 0.8 to 1.2. The drug is obtained from healthy dogs (with imaginary feeding) or horses. Apply with insufficiency of secretory function of the stomach, achilia, dyspepsia, hypo-and anacid gastritis. Prescribe the drug one tablespoon during or immediately after a meal.

Pepsinum (Pepsinum) - a proteolytic enzyme obtained from the mucous membrane of the stomach of pigs and calves. Pepsin breaks down proteins into peptides. It is active only at pH = 1.5 - 4.0, therefore, its use in chronic hypoacid gastritis is carried out together with hydrochloric acid. Pepsin in powder is prescribed before meals 3-4 times a day, 0.3-0.5 per meal with powder or in a 1-3% solution of hydrochloric acid.

Acidin-pepsin (betacid) is available in tablets of 0.25 and 0.5 g, each of which contains one part of pepsin and four parts of acidin, the latter, by hydrolysis, releases free hydrochloric acid. The drug is used for the same indications as pepsin and natural gastric juice. The Acidin-Pepsin tablet is

dissolved in 1/3 cup of water. Prescribe the drug 3-4 times a day during or after meals. The course of treatment is 30-45 days.

Domperidone - Motilium, the central blocker of dopamine receptors - a dopamine antagonist with antiemetic properties. Domperidone penetrates poorly through the BBB. The use of domperidone is rarely accompanied by extrapyramidal side effects, especially in adults, but domperidone stimulates the release of prolactin from the pituitary gland. Antiemetic effect, possibly due to a combination of peripheral (gastrokinetic) action and antagonism to dopamine receptors in the trigger zone of chemoreceptorsAnimal studies and low drug concentrations found in the brain indicate a central effect of domperidone on dopamine receptors.

When used internally, domperidone increases the duration of antral and duodenal contractions, increases pressure in the esophagus and accelerates gastric emptying in healthy people.

Domperidone has no effect on gastric secretion.

Pharmacokinetics

Suction

After ingestion on an empty stomach, domperidone is rapidly absorbed from the digestive tract. Cmax in the blood plasma is reached within about 30-60 minutes. The low absolute bioavailability of domperidone when administered orally (approximately 15%) is due to extensive primary metabolism in the intestinal wall and liver.

Although in healthy people, the bioavailability of domperidone is increased when taken after meals, patients with gastrointestinal complaints should take domperidone 15-30 minutes before meals. Hypoacidity of gastric juice reduces the absorption of domperidone.

When taking the drug after meals, it takes longer to reach Cmax, and the AUC increases slightly.

Distribution

When administered, domperidone does not cumulate and does not induce its own metabolism. After taking domperidone for 2 weeks at a dose of 30 mg / day, Cmax in blood plasma 90 minutes after the last dose was 21 ng / ml and was almost the same as after the first dose (18 ng / ml).

Binding to plasma proteins - 91-93%.

Metabolism

The drug is metabolized in the liver by hydroxylation and N-dealkylation. In vitro metabolism studies using diagnostic inhibitors, it was found that CYP3A4 is the main isoenzyme of the cytochrome 450 system involved in the N-dealkylation of domperidone, while CYP3A4, CYP1A2 and CYP2E1 are involved in the aromatic hydroxylation of domperidone.

Breeding

Excretion with urine and feces is 31% and 66% of the oral dose, respectively.

It is excreted unchanged with feces (10%) and urine (approximately 1%).

T1 / 2 from blood plasma after taking a single dose in healthy volunteers is 7-9 hours.

Pharmacokinetics in special clinical cases

In patients with severe renal failure, severe T1 / 2 domperidone increases. In such patients (serum creatinine> 6 mg / 100 ml, i.e.> 0.6 mmol / L), T1 / 2 of domperidone increased from 7.4 to 20.8 hours, but the drug concentration in plasma was lower than in healthy volunteers.

Dosage

It is recommended that you take Motilium tablets before meals, if you take them after meals, the absorption of domperidone may slow down.

Adults and adolescents over 12 years of age are prescribed 1-2 tablets. 3 or 4 times / day, the maximum daily dose is 80 mg.

Children are prescribed 1 tab. 3-4 times / day. In the absence of the desired effect, the indicated dose can be doubled. The maximum daily dose is 80 mg.

Motilium tablets are indicated only for adults and children weighing more than 35 kg; in pediatric practice, a suspension should be used Motilium.

In renal failure, a single dose adjustment is not required. With a second appointment, the frequency of administration should be reduced to 1 or 2 times / day, depending on the severity of the failure, and the need to reduce the dose may also occur. With prolonged therapy, patients should be monitored regularly.

Overdose

Overdose symptoms are most common in infants and children. Signs of an overdose are agitation, altered consciousness, convulsions, disorientation, drowsiness, and extrapyramidal reactions.

Treatment: there is no specific antidote for domperidone. In case of an overdose, gastric lavage and the use of activated carbon are recommended. It is recommended to closely monitor the patient's condition and conduct maintenance therapy. Anticholinergics, drugs used to treat parkinsonism, or antihistamines may be effective in the event of extrapyramidal reactions.

Drug interaction

Anticholinergic drugs can neutralize the effects of Motilium.

The oral bioavailability of Motilium is reduced after previous administration of cimetidine or sodium bicarbonate. Do not take antacid and antisecretory drugs at the same time as domperidone, because they reduce its bioavailability after oral administration.

The main role in the metabolism of domperidone is played by the isoenzyme CYP3A4. The results of in vitro studies and clinical experience show that the simultaneous use of drugs that significantly inhibit this isoenzyme can cause an increase in plasma concentrations of domperidone. Potential CYP3A4 inhibitors include: azole antifungal drugs such as fluconazole *, itraconazole, ketoconazole * and voriconazole *; macrolide antibiotics, e.g. clarithromycin * and erythromycin *; HIV protease inhibitors, for example, amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir and saquinavir; calcium antagonists such as diltiazem and verapamil; amiodarone *; aprepitant; nefazodone; telithromycin. (Drugs marked with an asterisk also extend the QTc interval).

In a number of studies of the pharmacokinetic and pharmacodynamic interactions of domperidone with oral ketoconazole and oral erythromycin in healthy volunteers, it was shown that these drugs significantly inhibit the primary metabolism of domperidone by CYP3A4 isoenzyme.

Side effects are given with a distribution of frequencies and organ systems. The frequency of side effects was classified as follows: very often (> 1/10), often (> 1/100, <1/10) and infrequently (> 1/1000, <1/100), rarely (> 1/10 000, <1/1000) and very rarely (<1/10 000, including isolated cases).

From the digestive system: rarely - gastrointestinal disorders; very rarely - transient intestinal cramps, impaired liver function tests.

From the nervous system: very rarely - extrapyramidal syndrome, cramps, drowsiness, headache. Extrapyramidal phenomena very rarely occur in children and in isolated cases in adults, they are completely reversible and disappear immediately after stopping the drug.

Mental disorders: very rarely - agitation, nervousness. Side effects such as cramps, drowsiness, and agitation are very rare and ound mainly in children and newborns.

On the part of the immune system: very rarely - anaphylactic reactions, including anaphylactic shock, angioedema, allergic reactions, urticaria.

From the endocrine system: rarely - an increase in plasma prolactin levels due to the fact that the pituitary gland is outside the blood-brain barrier, in rare cases, this hyperprolactinemia can stimulate the appearance of neuro-endocrine phenomena, such as galactorrhea, gynecomastia and amenorrhea.

From the skin: very rarely - itching, rash.

Indications

A complex of dyspeptic symptoms, often associated with

delayed gastric emptying, gastroesophageal reflux, eso phagitis:

- a feeling of fullness in the epigastrium, early satiety, a feeling of bloating, pain in the upper abdomen;

- belching, flatulence;

- nausea, vomiting;

- heartburn, belching with or without gastric contents.

Nausea and vomiting of a functional, organic, infectious origin caused by radiotherapy, drug therapy or a dietary disorder. A specific indication is nausea and vomiting caused by dopamine agonists if used for Parkinson's disease (such as le-water and bromocriptine).

Contraindications

- prolactin-secreting pituitary tumor (prolactinoma);

- the simultaneous administration of oral forms of ketoconazole, erythromycin, or other potent inhibitors of the CYP3A4 isoenzyme, causing a prolongation of the QTc interval, such as fluconazole, voriconazole, clarithromycin, amiodarone and telithromycin;

- gastrointestinal bleeding, obstruction or perforation of the gastrointestinal tract, in which stimulation of the motor function of the stomach can be dangerous;

- body weight less than 35 kg;

- established intolerance to the drug and its components.

With caution, the drug should be prescribed for renal and liver failure, as well as for children.

special instructions

With the combined use of the drug Motilium with antacid or antisecretory drugs, the latter should be taken after meals, and not before meals, i.e. they should not be taken simultaneously with Motilium.

Film-coated tablets contain lactose, so they should not be used in patients with lactose intolerance, galactosemia and impaired glucose and galactose absorption.

Given the high degree of domperidone metabolism in the liver, Motilium should be prescribed with caution in liver failure.

Since a very small percentage of the drug is excreted by the kidneys unchanged, a single dose correction in patients with renal failure is not required. However, when re-prescribed, the frequency of administration should be reduced to 1 or 2 times / day, depending on the severity of the failure, and it may also be necessary to reduce the dose.

With prolonged therapy, patients should be regularly monitored. Glucocorticoid hormones are prescribed in the initial and progressive stages of the disease with preserved secretory function of the stomach in case of a serious violation of the immune processes (short courses, average doses not exceeding 30 mg of prednisolone per day, provided that immune tests are performed). The lack of effect makes a repeated course of such therapy impractical.

At the stage of stabilization of the process, in the absence of clinical manifestations, patients do not need treatment.

In the case of the development of B12-deficient anemia, vitamin B12 is treated.

Often, the observed decrease in pancreatic excretory function is compensated by replacement therapy (pancreatin, creon, panzinorm, etc.).

The drug Limontar - a mixture of citric and succinic acids with calcium stearate - enhances the acid-forming function of the stomach, it is prescribed 0.25 g per 0.5 cup of water and taken on an empty stomach.

Assign panangin, aspartame, potassium chloride, as they help to restore the electrolyte barrier and reduce the back diffusion of hydrogen ions. Brewer's yeast is effective at 0.5 cups 3 times a day before meals for 2-3 weeks.

To enhance mucus formation, astringents and enveloping preparations are used: bismuth salts (bismuth nitrate, aluminum bismuth, bismuth carbon) 1 g 4 times a day before meals for 2-3 weeks. Plantain preparations (plantaglucid, which has an anti-inflammatory effect) are widely used, 0.5 g 4 times a day on an empty stomach.

Anticholinergics are prescribed only for persistent pain, severe motor evacuation disorders. The solution of atropine is taken orally at 8-10 drops 3 times a day, metacin is administered orally at 5 mg 3 times a day for 7-10 days or in injections of 1 ml of a 0.1% solution. Often used platyphyllin in combination with papaverine, no-shpu, halidor, motilak, stopping pain and eliminating dysmotorics.

To stimulate secretion, caffeine and aminophylline are prescribed, which increase the content of cAMP and thus potentiate the action of histamine. Other drugs from the group of methylxanthines (theophylline, theobromine) also inhibit phosphodiesterase and activate the formation of hydrochloric acid.

Etymizole helps maintain the level of Ca in the membranes of the mucous membrane of the stomach, which causes its trophic effect on the cells, the drug is prescribed 100 mg 3 times a day 1 hour before meals for 1 month. To improve microcirculation, prodectin, chimes, teonikol are used.

Stimulation of protein synthesis is achieved by the use of anabolic steroids, which are indicated for chronic hepatitis C, which occurs with loss of body weight. Nerobol is prescribed at a dose of 10 mg 2 times a day for a week, possibly in combination with protein preparations such as aminosol, hepasol, polyamine, administered intravenously.

Among enzyme preparations for the correction of reduced gastric secretion, Abomin deserves attention, which is obtained from the mucous membrane of the stomach of young calves and lambs.

Abomin contains the amount of proteolytic enzymes - mainly chymosin, or rennin (~ 70%) and pepsin (~ 30%).

The advantages of the drug Abomin are: the ability to use as a "starting" drug for mild digestive disorders.

The usual scheme for the use of Abomin: inside, 1 tablet 3 times a day with meals for 1-2 months. With insufficient effectiveness, a single dose can be increased to 2-3 tablets per reception, and the course of treatment is extended to 3 months.

INTESTINAL DYSBACTERIOSIS

Dysbacteriosis is a quantitative (decrease in the content of beneficial and increase of pathogenic microflora) and qualitative (change in the biological properties of the intestinal flora, weakening of the performance of useful functions and increased toxicity) change in the intestinal microflora.

Dysbacteriosis or dysbiosis is a violation of the microecology of the surface or mucous membrane of the body, which has contact with the external environment. Normally, the microbiological composition of the flora of the human body is in constant dynamic equilibrium with the environment - eubiosis. When disturbances occur in the body or in the external environment, an imbalance occurs, which leads to a reduction in the number of microorganisms alone and to an increase in the colonies of certain microflora representatives: bacteria, fungi, viruses, protozoa, or their complex. Such disturbances can be temporary, when the disturbed balance of microflora is independently restored (dysbacterial reactions), and persistent (dysbiosis), in which a return to the microflora balance is possible only during certain events.

Most often, the term "dysbacteriosis" means an imbalance in the intestinal microflora, although microflora dysbiosis can also occur on the surface of the skin, nails, conjunctiva of the eyes, on the mucous membrane of the genitals, nose and paranasal sinuses, in the oral cavity.

The microflora inhabiting the intestine is subdivided into obligate (obligatory normal) and optional (or optional). The obligate flora includes the main anaerobic bacteria, which make up 90-99% of the entire flora: bifidobacteria, which live mainly in the large intestine, and associated aerobic flora: “useful” E. coli (0.5%), lactobacilli (inhabit the oral cavity, stomach, small intestine), eubacteria, entero-cocci (0.5% -8.5%). The composition of the optional (conditionally pathogenic) flora may vary, but normally it should represent no more than 1% of the total micro-flora. It includes micrococci, streptococci, Proteus, Klebsiella, yeast. The weight of intestinal microflora is from 1 to 3 kg. Up to 20% of human food is used to maintain the vital activity of obligate intestinal microflora.

Dysbiosis or dysbiosis alone is not a disease, although its presence is characterized by clinical manifestations of varying severity. The International Classification of Human Diseases (ICD-10) does not include the concept of “dysbiosis” or “dysbiosis” as an independent disease. Dysbacteriosis may be a direct result of any disease, may occur as a result of ongoing therapeutic measures. Also, dysbiosis can lead to the occurrence of certain diseases.

It is believed that chronic dysbiosis can play a role in the development of diseases such as functional and inflammatory diseases of the gastrointestinal tract, oral cavity, nasopharynx, chronic fatigue syndrome, obesity, cancer, inflammatory joint diseases, autoimmune diseases, allergies, vitamin B deficiency, skin diseases, cardiovascular diseases and many others.

According to statistics on gastroenterological diseases in outpatient practice, dysbacteriosis in Russia is detected in 89% of the adult population and in more than 25% of children under the age of one year, as well as in 75% of children under one year who are breast-fed.

The role of obligate microflora of the human intestine Normal

the intestinal microflora carries a large number of useful and necessary functions for the normal functioning of the human body:

The main composition and functions of normal intestinal microflora

The human digestive tract is the habitat of a large number of microorganisms, the quantitative and qualitative composition of which differs in different sections of the gastrointestinal tract.

The greatest number of microflora is observed in the large intestine, where three groups of microorganisms are normally found:

• bifidobacteria and bacteroids (main group),

• lactic acid bacteria and E. coli strains (concomitant group),

• staphylococci, mushrooms,

• Proteus (residual group).

Normally, the composition of microflora in an adult is quite stable and is characterized by certain ratios between its individual representatives.

Temporary disturbances of microflora can occur depending on the characteristics of nutrition, human conditions.

The microflora of the digestive tract refers to factors of nonspecific defense of the body.

The main functions of intestinal microflora are normal

• Reduces the content of factors that can cause atherosclerosis.

• Provides good blood supply to the mucous membranes of the gastrointestinal tract.

• Detoxification (inactivation of enterokinase, alkaline phosphatase). Provides detoxification from pesticides, amines, heavy metal salts, many medicines, nitrates, which are spoiled with food.

• Provides protection against pathogenic microbial colonization.

• Regulates intestinal motor function.

• Enzymatic (hydrolysis of metabolic products of proteins, lipids, carbohydrates).

• Synthetic (synthesis of vitamins, antibiotic and other biologically active substances).

• Digestive (increase the physiological activity of the digestive tract). Synthesizes digestive enzymes, provides parietal digestion, utilization of digestion products and bile acids

• Prevents the development of internal allergenic factors, protects the body from the penetration of allergens into the blood.

• Antianemic (promotes absorption of iron).

• Antirachitic (promotes absorption of calcium, and vitamin D).

• Immune, produces and forms factors of local and general immunity. (activation of the immune system, synthesis of immunoglobulins, interferon).

• Participates in the synthesis of amino acids, proteins, and vitamins (K, group B).

• Intermicrobial antagonism.

Factors leading to disruption of the normal intestinal microflora are many and varied.

The main factors for the development of dysbiosis

Exogenous:

• industrial poisons;

• violation of sanitary standards in everyday life and at work;

• ionizing radiation;

• climatic and geographical factors;

• surgical interventions on the organs of the gastrointestinal tract.

Endogenous:

• immune disorders;

• stressful conditions;

• non-infectious diseases of the gastrointestinal tract (pathology of the intestine and gall bladder, gastric ulcer, etc.);

•infectious diseases;

•diabetes;

• rheumatic diseases;

• starvation;

• poor nutrition;

• old and senile age;

• irrational medication.

In addition to the above, in children, dysbacteriosis development factors can also be:

• anatomical disorders;

• food allergy;

• errors in nutrition;

• antibiotic therapy (including rational).

Antibiotics. One of the most common causes of dysbiosis is taking antibiotics. Antibiotics, killing pathogenic flora, at the same time destroy and useful microorganisms. At the same time, many components of the disease-causing flora can be resistant to antibiotics, and begin to multiply actively with the death of beneficial microorganisms, which restrained their growth before treatment. Keep in mind that industrial foods such as meat of artificially grown fish (salmon, trout) or poultry (chicken) contain antibiotics that affect the composition of the intestinal microflora.

Anti-inflammatory drugs. Abuse of non-specific anti-inflammatory drugs (NSAIDs), such as aspirin or indomethacin, can lead to a decrease in the population of obligate microflora and cause chronic diarrhea.

Other medicines. Corticosteroids, immunosuppressants, and anticancer drugs can cause an imbalance in the intestinal microflora.

Food abuse. The growth of mushrooms and yeast flora may be caused by a diet of abused refined carbohydrates and sugars. A diet with an excess of starch, flour products and sugars (including in fruits and fruit juices) most often leads to the growth of Candida yeast. The use of lemonades containing phosphoric acid leads to a decrease in the population of obligate microflora. In beer, in canned meat and fish products, in meat and fish products in vacuum packaging, nitrosamines are found, which are toxic and carcinogenic substances. In the human body, nitrosamines are metabolic products of opportunistic and pathogenic intestinal microflora, and their regular intake with food can reduce the population of beneficial obligate flora.

Inadequate fluid intake. The reduced volume of fluid intake (less than 2 liters per day) leads to an imbalance in the microflora of the small intestine.

Changes in hormonal levels. Pregnancy, taking hormonal drugs or drugs that stimulate the production of hormones can cause dysbiosis. Chronic stress leads to hormonal imbalance and, as a result, to dysbiosis. Constant and excessive consumption of tea and coffee physiologically simulates chronic stress, which leads to hormonal imbalance in the body.

Ecology. A humid climate, the presence of mold or fungi in houses, toxic substances in the decoration materials and the atmosphere of the room can also lead to dysbiosis

The clinical manifestations of dysbacteriosis are diverse and are largely determined by the degree of violation of the normal intestinal biocenosis. In some patients, any manifestations of dysbiosis may be absent, however, most often there are the following characteristic complaints:

• unstable stools (constipation, diarrhea or alternating constipation and diarrhea);

• bloating and rumbling of the abdomen;

• pain in the lower abdomen, decreasing after the discharge of gases;

• nausea, belching, bitterness in the mouth.

In addition, as a result of a long-lasting dysbiosis, a number of pathological conditions arise a second time, namely:

• asthenoneurotic syndrome (due to hypovitaminosis and intoxication);

• anemia;

• hypoproteinemia;

• osteomalacia;

• weight loss;

• hypovitaminosis (mainly fat-soluble vitamins).

In young children with the development of dysbiosis, regurgitation, vomiting, a decrease in the rate of increase in body weight, anxiety, and sleep disturbance are observed. The stool can be plentiful, liquid or gruel, frothy, greenish with an acidic or putrid odor. Abdominal pains are paroxysmal, appear 2–3 hours after eating and are accompanied by bloating, urges to defecate.

Clinically distinguish three degrees of severity of violations of the microbial landscape of the intestine.

Stage dysbiosis

1 degree -

compensated (latent dysbiosis) - is characterized by a change in the quantitative composition of aerobic microorganisms with a normal ratio of bifidobacteria and lactobacilli. Clinical signs are absent.

2 degree -

subcompensated (or localized) dysbiosis - manifests itself along with a decrease in the qualitative and quantitative composition of Escherichia, a moderate decrease in the content of bifidobacteria with a simultaneous increase in opportunistic microorganisms. At the same time, a moderately pronounced inflammatory process (enteritis, colitis) takes place in the intestine.

3 degree -

widespread dysbiosis - characterized by significant changes in the qualitative and quantitative composition of normal microflora. Clinically manifested by intestinal dysfunction of varying severity.

4 degree -

generalized (decompensated dysbiosis) - along with a significant increase in the content of E. coli, it is characterized by an almost complete absence of bifidobacteria and a sharp decrease in lactic acid bacteria. Clinically manifested by severe intestinal dysfunction, bacteremia, septic complications, degenerative changes in the internal organs Manifestations of dysbiosis

1. Dysbacteriosis of the small intestine is characterized by diarrhea and the formation of a syndrome of impaired intestinal absorption (diarrhea or frequent stools, indigestion, bloating, intestinal colic).

2. Dysbacteriosis of the colon may not have clinical manifestations, or may be characterized by constipation.

Common but non-specific manifestations of dysbiosis may include: milk protein intolerance, chronic fatigue, muscle and joint pain, allergies, thrush and other yeast infections, decreased sex drive, overweight, craving for sweets and alcohol, skin diseases, nail fungus hyperactivity in children, depression in adults.

Correction of dysbiosis

Correction of intestinal microecology disorders has the following goals:

1. Elimination of excess growth of opportunistic flora.

3. Restoring the normal balance of microbial flora.

4. Improving intestinal digestion and absorption.

5. Restoring impaired intestinal motility.

6. Correction of the resulting nutrient deficiency.

At the early (compensated) stages of the development of dysbiosis, microflora disturbances can be corrected with the help of correctly selected diets. Eating certain foods will help to remove toxic products of the conditionally pathogenic flora from the body, improve the promotion of digested food along the gastrointestinal tract, replenish the number of useful obligate microorganisms and create nutritional conditions and micro-ecology for their optimal development.

At the decompensated stages of the development of dysbiosis, when a doctor's intervention and the likely prescription of drugs are required, a therapeutic diet will also play a significant role in the successful restoration of the intestinal microflora.

Food products used in the correction of dysbiosis can be divided into several groups:

- Prebiotics - products containing components that stimulate the growth of beneficial obligate microflora.

- Probiotics - products containing live microorganisms (lactic acid bifidobacteria or lactobacilli, sometimes yeast), which belong to the obligate microflora of the intestines of a healthy person.

- Sources of natural sorbents - products containing a sorbing substance that can bind and remove toxic products from the body.

- Sources of dietary fiber - products containing substances that serve to form a formed food lump and improve the movement of food through the intestines. At the same time, dietary fiber has a sorption effect: they bind and remove toxic substances and digestion products. Dietary fiber also serves as a biological substrate for the nutrition of beneficial obligate intestinal microflora.

- Sources of substances that reduce inflammation and restore (heal) the intestinal mucosa.

An equally important component of nutrition correction for dysbiosis is the exclusion or reduction of food intake, which can inhibit the growth of beneficial obligate microflora and stimulate the growth of individual colonies of opportunistic microorganisms. Also excluded are products that irritate the intestinal mucosa.

When drawing up a therapeutic nutrition plan, one should focus on the expected type of imbalance in the intestinal microflora: dysbiosis (microbial contamination) of the small intestine or dysbiosis of the large intestine.

With dysbacteriosis of the small intestine, an increase of 10-30 times the number of colonies of eubaceria, streptococci, enterococci, and yeast is noted. Perhaps the appearance of bacteria of the genus Akinetobacter and herpes viruses. At the same time, the number of lactobacilli and other anaerobic bacteria, actinomycetes, Klebsiella and other microorganisms decreases from 2 to 30 times. Dysbacteriosis of the small intestine results in digestive disorders, diarrhea or frequent stools, malabsorption of fat-soluble vitamins and assimilation of B vitamins. With excessive use of flour, starch products and sugars, excessive growth of acidophilic flora can occur, which is accompanied by active fermentation. As a result of fermentation of carbohydrates in the small intestine, an excess amount of gases is formed, which leads to bloating, winds, sounds of “rumbling” and transfusion of fluid in the stomach. Gas fullness can lead to cramping, poor blood supply to the intestinal wall, and pain.

With dysbiosis of the large intestine, the population of bifidobacteria decreases and colonies of staphylococci, protea, yeast, enterococci and Pseudomonas aeruginosa grow. At the compensated stage of dysbiosis (before the onset of colon diseases), no symptoms may be observed, or dysbiosis may manifest as chronic constipation. With an excess of protein or fatty foods, or with a deficiency of digestive enzymes responsible for the digestion of proteins, putrefactive phenomena occur in the lower intestine, accompanied by an increase in the population of putrefactive bacteria. With putrefactive dyspepsia, the stool and exhaust gases become fetid. Chronic putrefactive dysbiosis can be associated with the occurrence of cancer of the rectum and breast.

The basic principles of the treatment of intestinal dysbiosis

The treatment of intestinal dysbiosis is complex. It is aimed at eliminating the cause of dysbiosis, elimination of pathogenic and conditionally pathogenic microorganisms and the restoration of normal colon microflora. The latter is achieved using drugs called “probiotics”. Outpatient treatment

is possible only with a latent (compensated) form of intestinal dysbiosis. You should not start it yourself - it is necessary to conduct a microbiological examination of feces and be sure to consult a doctor.

Non-drug treatment of intestinal dysbiosis

Based on rational diet therapy. Diet therapy for intestinal dysbiosis should be complete, chemically, mechanically and thermally sparing and aimed at:

• providing good nutrition;

• improvement of the functional state of the intestine and other organs of the digestive system;

• stimulation of regeneration processes and increase immunity.

With dysbiosis, lean boiled meat, fish, cereals (buckwheat, oatmeal, rice), low-fat cottage cheese, white stale bread, fruits and vegetables in large quantities (as products containing dietary fiber) are indicated.

In case of diarrhea, it is recommended that patients with dysbiosis temporarily exclude black bread, whole milk, raw vegetables and fruits, and fatty and spicy seasonings. It is rational to use mucous rice and oat soups, cereals, jelly, sautéed pecans made from boiled vegetables, jelly and juices from carrots, black currants, quinces, pomegranates.

In case of constipation, the diet of patients with dysbiosis should include foods rich in dietary fiber and have a laxative effect - bread with bran, vegetable vinaigrettes, buckwheat porridge, kefir, raw vegetables and juices, sour fruits, highly mineralized mineral waters.

With severe flatulence, the use of legumes, cabbage, foods with a high glucose content is limited - honey, jam, sweets, grapes. It is recommended to increase the content of boiled meat and fish in the diet.

In children, it is advisable to use traditional fermented milk products and special adapted fermented milk mixtures that are close to human milk in chemical composition - “ASU-1”, “ASU-2”, acidophilic “Malyut-ka”, “Bifilin”. For older children, non-adapted lactic acid mixtures are intended - Acidolact, Biolokt, Narine, Bifilin-M, Lactobacterin, Tonus, Vita, Biokefir, Bifidokefir, Beef Dock, yoghurts.

Drug treatment of intestinal dysbiosis

In compensated dysbiosis, to normalize microflora and suppress the growth of pathogenic and conditionally pathogenic microbes, pro-biotics are used that contain components or waste products of more than 20 types of microorganisms.

Probiotics (eubiotics) - freeze-dried live weakened strains of normal intestinal microflora, which, after ingestion, colonize the intestines. Bacteria that live in the intestines produce acetic and lactic acids, creating an acidic medium in it that inhibits putrefactive and gas-forming microorganisms (clostridia, protea, bacteroids); produce anti-bacterial substances that inhibit the division of various opportunistic bacteria and pathogens of intestinal infections (salmonella, shigella, etc.).

Probiotics are prescribed not as replacement therapy, but as agents providing conditions for the restoration of normal microflora.

The suppression of rotting and fermentation processes by eubiotics eliminates flatulence, normalizes digestion and absorption in the intestine. Restoring normal microflora in turn promotes immunization organism, increases its resistance to infection.

Eubiotics are used both for treatment and for the prevention of dysbacteriosis, especially in children.

For the prevention and treatment of dysbiosis, along with probiotics, functional food products are used. This is a special form of probiotics, which is food products, which include substances of natural origin, intended for daily use and that have a regulatory effect on the physiological functions and biochemical reactions of the human body.

In our country, functional food products include lactic acid products containing bifidobacteria and lactobacilli - “Biokefir”, “Beef-life”, “Narine”, “Gerolact”, “Streptosan”, “Yogurt”, the above products for children.

Regular use of products containing lactic acid, bifi-dobacteria, dietary fiber and natural antioxidants helps maintain health, softens the effects of adverse environmental factors, and helps to increase life expectancy.

Probiotics

The term “probiotic” was first used by R. Parker in 1974 to refer to live microorganisms that were introduced into animal feed to stimulate growth and resistance to stress. This definition, no doubt, was also applicable to the human body.

By definition of most authors, probiotics are living microorganisms or products fermented by them, which contribute to the preservation or restoration of the normal composition of the intestinal microflora.

Most experts and researchers attribute eubiotics (representatives of normal intestinal microflora and other body cavities) to probiotics of the bacterium: bifidobacteria and lactic acid microorganisms of the genus Lactobacillus. They are called classic probiotics.

At the same time, there is sufficient evidence that indicates the presence of probiotic properties in lactic acid bacilli and cocci, as well as other microorganisms - Bacillus, E. coli, Citrobacter, yeast and fungi.

Probiotics include drugs and biologically active food supplements containing live microorganisms, which, when administered in adequate doses, have a beneficial effect on human health by changing the properties of normal microflora. The use of probiotics is also called "bacterial therapy."

The mechanisms of positive action of probiotics:

- Suppression of pathogenic and excessive conditionally pathogenic flora due to the production of antibacterial substances and competition for nutrient substrates and for adhesion sites on intestinal mucosa epithelial cells.

- Stimulation of the reproduction of indigenous flora as a result of the production of growth-promoting factors.

- Effect on the enzymatic activity of intestinal microorganisms.

- Stimulation of the immune system of a macroorganism.

- Antiallergic effect.

- Anticarcinogenic effect.

- Reduction of Helicobacter pylori infection.

Requirements for probiotics:

The probiotic should have a positive effect on the human body, confirmed by laboratory studies and clinical observations.

The probiotic must be non-pathogenic and non-toxic with prolonged use.

The probiotic should contain viable cells, preferably in large numbers.

The probiotic should have colonization potential - the ability to survive and to survive in the intestinal microenvironment (resistance to low pH in the stomach, resistance to organic acids).

The probiotic must be stable and viable for long-term storage of bacteria.

Classifications of probiotics

Depending on the purpose:

Heteroprobiotics.

Assigned regardless of the species of the host, from which strains of probiotic bacteria were originally isolated.

Homobiotics.

They are assigned only to representatives of that animal species and to the person from whose biomaterial the corresponding strains were isolated.

Autoprobiotics.

Strains of normal microflora, isolated from a particular individual duum and designed to correct its microecology.

Depending on the composition:

Monocomponent - bifidumbacterin, lactobacterin, colibacterin.

Multicomponent - Bifilong (2 types of bifidobacteria bifidum et longum), Bifinorm (3 types of bacteria bifidum, longum, adolescentis), Acylact (3 different strains of Lactobacillusacidophilus - 100 AIII, NK1, K3, III24), Acipole (Lactobacillus acidophilus), Bifidin (Bifidumbacterium adolescentis, Escherichia coli), Linex (Lactobacillus acidophilus, B. bifidum, Enterococcus faecium SF68), Bifiform (B. longum and Enterococcus faecium SF68), Polybacterin.

Combined - Kipacid (Lactobacillus acidophilus and complex immunoglobulin), Bifilis (Bifidumbacterium bifidum and lysozyme), Bioflor (E. Coli M-17, extracts of soy, vegetables, propolis).

Recombinant or genetically engineered probiotics - based on genetically engineered strains of microorganisms, their structural components and metabolites with specified characteristics.

Depending on the time of creation and improvement, several generations of probiotics are distinguished:

I generation.

Microcomponent preparations consisting of one strain of microorganisms - typical inhabitants of the intestine (bifidobacteria, lactobacilli).

I generation.

Self-eliminating antagonists (Bactisubtil, Enterol). For all types of dysbiosis, it is possible to use Enterol 250 mg 2 times a day between meals for 10-15 days.

III generation.

Multicomponent preparations (symbiotics), consisting of several (from 2 to 30) strains of bacteria (Bifilong) or of several types of bacteria (Li-Nex, Bificol).

IV generation.

Combined drugs (synbiotics), consisting of a strain of bacteria and ingredients that promote their growth, reproduction and metabolic activity (Bifilis, Kipatsid).

V generation.

Multicomponent combined preparations consisting of several types of bacteria and ingredients that promote their growth, reproduction and metabolic activity (Bifiform).

In the correction of intestinal microbiocenosis disorders, the purpose of which is to suppress the excess conditionally pathogenic flora, the principle is the division of probiotics into:

Preparations containing live bacteria belonging to representatives of normal symbionts (bifidobacteria, lactobacilli, Escherichia coli).

Self-eliminating antagonists containing microorganisms and fungi that normally do not live in the human intestines (Bacillus subtilis, B. licheniformis, Saccharomyces boulardii).

"Seeding" of useful microflora must be carried out strictly individually. Otherwise, the formation of iatrogenic intestinal dysbacteriosis, which often occurs as a result of improper therapy, is possible.

When choosing drugs, the relationship of microbes in the natural intestinal biocenosis should be taken into account. Bifidobacteria provide the conditions for the growth and metabolic activity of lactobacilli. Lactobacilli contribute to the growth of bifidoflora, as well as the growth and development of full-fledged E. coli. Therefore, it is not recommended to immediately begin treatment with colibacterin and other probiotics containing E. coli when reducing coliflora by 1-2 orders of magnitude, since normal E. coli can be restored during treatment with bifidobacteria and lactopreparations.

Significant is the route of administration of probiotics. In people with high rates of acid production in the stomach, due to the high asepticity of the gastric juice for bacteria, a rectal route of administration is indicated, or before oral administration in such cases, it is necessary to give whole mineral waters or antacids. Inside, bacterium-containing drugs are prescribed 20-30 minutes before meals, before use, diluted with boiled water directly in the bottle, then transferred to a glass.

Prebiotics. The term “prebiotics” is used to refer to substances (drugs, food, or biologically active food supplements) that are mostly not absorbed in the human intestines, but beneficially affect the host’s body by stimulating growth and activating the metabolism of beneficial representatives of its intestinal microflora. Prebiotics stimulate the growth and development of normal microflora. Thus, prebiotics are probiotic stimulants.

Prebiotics can be combined with probiotics, functional nutrition products or for dysbiosis, or used as monotherapy.

Prebitotic medicines include: Hilak-forte, lactulose (Dufalac, Normase, Lactusan), Lactofiltrum.

Positive effects of prebiotics:

Mucolytic effect.

Reparative action.

Maintaining optimal pH values.

Increased fecal volume.

Improved intestinal motility.

Reduced gas production.

Stimulation of the synthesis of B vitamins and vitamin K.

Antibacterial effect mediated by non-specific factors resistance.

Bifidogenic activity.

Recovery of disturbed normal microflora.

Prebiotics stimulate the reproduction and functional activity of the "native" for the patient's own normal intestinal microflora.

The following food components and medications have prebiotic effects:

-Oligosaccharides (lactulose, fructooligosaccharides, galactooligosaccharides).

Dietary fiber.

Plant microbial extracts (yeast, carrot, potato, corn, rice, pumpkin, garlic).

Algae extracts.

Monosaccharides, alcohols (xylitol, raffinose, sorbitol, xylobiosis).

Polysaccharides (pectins, dextrin, inulin, chitosan).

Amino acids (valine, arginine, glutamic acid).

Antioxidants (vitamins A, C, E, selenium, ubiquinone, glutathione, carotenoids).

Unsaturated fatty acids (eicosopentaenoic acid).

Enzymes (microbial beta-galactosidases, saccharomycete proteases).

Pectins.

Symbiotics and synbiotics

In addition to pre- and probiotics, in the literature you can find such terms as symbiotics and synbiotics.

Synbiotics are a combination of several probiotic types of bacteria (for example, Bificol, Bifilin). Their action is based on the synergism of probiotics and prebiotics, due to which not only the introduced microorganisms are most effective - probiotics in the gastrointestinal tract of the host, but are stimulated its own microflora. Dietary fibers, enzymes, trace elements, herbal supplements may also be included in synbiotics.

Symbiotics are complex preparations, including pre- and probiotics (Biovestin, Biovestin-Lacto, Bifilis, Euflorins (Euflorin-L and Euflorin-B), Bifiform, Bifido-tank, Laminolact).

Groups of probiotics Supplements parapharmaceuticals

1 Monoprobiotics

Bifid-containing Bifidumbacterin Bifidumbacterin forte ProbiforBi-phidogen Eugalan Bifidumbacterin 1000 Liquid bifidum bacteria Biosorb bifidum Soya lactum Soya bifidum

Lactobacillus Lactobacterin Biobactone Gastrofarm Biobactone NarineVaitadofilius

Colibacterin

II Polyprobiotic

Bifid-containing Bifilong Lactic-containing Acylact Bifido and lactic-containing Bifacid Bifido and colic-containing Bificol Linex Omniflora

III Probiotics - self-eliminating antagonists - bacillary - saccharomycete-containing Sporobacterin Baktisporin Biosporin Baktisubtil Shlonivin V Enterol Lactofiber Lactospore Enrich Pro-Bionics

IV Combined probiotics (synbiotic)

Bifid-containing: Bifilis Lactic-containing: Acipol in tab

Coliform: Bioflor Bifid-containing: Bifiform Laminolact Bifistim Acipol in a cap Kipatsid Bifiform Baby Bifid- and lactic and inulin (prebiotic) Bifiform Nompleks

V Metabolic probiotics Hilak-forte

The composition of monoprobiotics includes only one strain of different bifidobacteria, lactobacilli and Escherichia - permanent representatives of intestinal microflora:

B. bifidum - Bifidumbacterin, Probifor, Bifidumbacterin forte

(in Bifidumbacterin Fort and Probifor, live bifidobacteria are immobilized on a sorbent, which helps to increase their activity).

L. acidophilus - Biobactone

L. planfarum - Lactobacterin

L. fermentum - Lactobacterin

L. bulgaricus - Holofarm

E. coli M-17 - Colibacterin

Monoprobiotics, with the exception of adsorbed on charcoal, are used for dysbacterioses of the first degree, with substitution and prophylactic purposes for 2 weeks.

Multicomponent probiotics are drugs based on symbiotic communities that dominate the microecology of indigenous microorganisms, which allows their composition to be brought closer to the natural intestinal microbiocenosis to achieve a complex effect.

The features of the biological effect of multicomponent probiotics include:

• summation of the beneficial properties inherent in individual strains and an increase in their biological activity;

• the possibility of selective colonization of the intestine with useful microorganisms of the species that is most appropriate for the microbiocenosis of a particular individual individual, which does not include the need for mandatory microbiological analyzes.

Multicomponent probiotics include:

Bifikol - B. bifidum, E. coli M 17

Bifacid - B. bifidum, L. acidophilus

Acylact - 3 strains of L. acidophilus

Bifilong - B.bifidum, B.longum

Linex - Lactobacillus, Streptocccus faecium, B.infantis

The multicomponent composition consists mainly of parapharmaceuticals, which have a pronounced clinical and microbiological associated effect in various diseases in children: “Bifiform Baby” (a new complex for children from the first days of life), “Bifiform Baby” (Denmark), “Polybacterin” , Bifidum-bacterin Multi 1,11, III, Primadofilus and others.

Polyprobiotics are used to correct intestinal dysbiosis of the I and II degree with a course of 7-14 days.

Bacillary probiotics belong to the group of self-eliminating antagonists.

The composition of the preparations includes transient bacilli - B.subtilis (Sporobacterin, Biosporin, Baktisporin) B.cereus ("Bactisubtil", "Flonivin B").

Features of the probiotic action of bacillary probiotics:

• high antagonistic activity to pathogenic and conditionally pathogenic flora;

• pronounced enzymatic activity in the breakdown of proteins, fats and carbohydrates

• immunomodulatory effect (It stimulates the formation of endogenous interferon, activates phagocytosis, etc.);

• antihistamine effect.

Bacillary probiotics do not contain lactose (lactose-free drugs), which explains the feasibility of their use in lactase deficiency.

Indications for the use of bacillary probiotics:

• acute invasive intestinal infections;

• decontamination of opportunistic flora and Candida albicans with dysbacteriosis of the II and III degree of various origins;

• allergic diseases;

• fermentopathy;

• urogenital infections;

• bacterial vaginosis.

Bacillary probiotics are prescribed for children older than 1 year. The course is 7-10 days.

Combined probiotics - a group of drugs containing strains of bacteria of indigenous flora and probiotic additives (metabolites, microflora growth stimulants, vitamins, etc.).

Requirements for Combined Probiotics:

• the content of viable cells of normal flora (preferably in the range from 106 to 109 CFU / g);

• the presence in the preparation of useful substances that help optimize the biological activity of microflora.

Combined probiotics include:

bifid-containing - "Bifiform", "Bifilis";

lactic-containing - “Acipol”, “Kipatsid”;

colic-containing - "Bioflor".

The combination of probiotics also includes streptococci.

Types of apatogenic streptococci that are part of the combined probiotics:

• Streptococcus thermophilus

Baby Beefiform

Symbioflex

Symbioflos

ABS Dofilus

• Enterococcus f aecium

Bifiform

Kio Dofiluss

Premium Acidophilus

Ventrux Acido

Bioflorin

• Aerococcus viridans

A-bacterin

As prebiotic substances, lysozyme, pantothenic acid, B vitamins, yeast extract, lactose, proteins, amino acids, minerals, pectins, lactulose, dietary fiber, saccharin, gum are added to the preparation.

The combined probiotic with a proven clinical and microbiological effect is BIFFORM.

Bifiform contains beneficial microflora and a special nutrient medium for its reproduction.

The composition of the combined probiotic Bifiform® includes:

A representative of the genus Bifidum is Bifidobacterium longum.

B.longum - anaerobes colonizing the colon. Their properties:

• the most viable of bifidobacteria;

Normally present in all age groups;

• the most pronounced immunomodulatory effect;

• antagonism to pathogenic and conditionally pathogenic flora;

• produce lactic and acetic acid.

Lactulose is a prebiotic whose clinical effect is mediated through the following effects:

• bifidogenic (a source of carbohydrates and energy for bifidobacteria);

• suppression of toxic metabolites;

• inhibition of secondary bile acids

• increased absorption of minerals and trace elements;

• prokinetic effect due to increased osmotic pressure in the large intestine;

• creation of optimal conditions for the persistence of living cultures introduced into the macroorganism.

Due to the complex composition, the effects of combined probiotics are diverse:

• antagonistic activity, “antibiotic-like effect”;

• metabolic and enzymatic ability;

• immunomodulatory effect;

• antitoxic effect;

• inhibition of bile acids;

• regulation of colon motility.

Indications for the use of combined probiotics include a large number of various diseases, accompanied by intestinal dysbiosis, grade II:

• acute intestinal infections and post-infectious diarrhea;

• chronic colitis and enterocolitis;

• disaccharidase deficiency;

• antibiotic-induced diarrhea;

• nematodoses;

• DZhVP, cholepathy;

• motor impairment

• allergic diseases.

Metabolic probiotics include drugs based on a set of microbial metabolites - representatives of normal microflora. These include Hilak-forte, which includes microbial metabolites of lactobacilli, Escherichia coli and fecal streptococcus: lactose, amino acids, lactic acid, short-chain fatty acids.

Metabolic probiotics, contributing to the normalization of intestinal microflora, eliminate atrophic processes in the intestinal mucosa in inflammatory and allergic diseases, and stimulate the production of lgA.

PROBIOTIC APPLICATION TACTICS

To date, in clinical studies it has been established that different strains of probiotics and their components have an immunomodulating effect of varying severity. The use of fermented milk products or probiotics containing lactobacilli stimulates the production of IFN g by peripheral blood mononuclear cells, which in turn enhances the capture of antigens in Peyer's plaques, as a result of

which IgA-synthesizing cells are induced and IgA production is increased. Oral bacteriotherapy of L. rhamnosus GG (ATCC 53103) in children with atopic dermatitis and intolerance to cow's milk led to an increase in the production of anti-inflammatory cytokine IL-10 and a weakening of the clinical manifestations of the disease. At the same time, the high level of proinflammatory cytokine, TNF a, characteristic of these patients, decreased. It is believed that probiotics have not only a local, but also a systemic anti-inflammatory effect. Evidence of their systemic anti-inflammatory activity is a decrease in the concentration of inflammatory cytokines (IL-12, TNF) and an increase in the level of regulatory cytokine TGF b. This universal mechanism of action of probiotics allows them to be used to treat both local and systemic inflammatory processes.

Experimental studies have shown that probiotics cause proliferation of lymphocytes (Darroch C. J., 1994), increase the resistance of experimental animals to influenza viruses and cytomegaloviruses (Malin M., 1996; Norton I. M., 1994). In vitro studies indicate that GG lactobacilli reduce the production of TNF-a by activated macrophage-activated lipopolysaccharides in mice and do not affect IL-10 synthesis (Repa J. A., 2003). The revealed ability of bifidumbacterin forte to reduce serum IFN and increase IFN induction in leukocytes (a- and g-IFN) in children with chronic gastrointestinal tract pathology suggests the enhancing effect of probiotics on direct killing of viruses and intracellular bacteria and on the activation of protection against many pathogens of infections through immunity mediators.

The choice of drugs and the tactics of using probiotics in children's practice is carried out taking into account the age of patients, the nature of nutrition, premorbid background, the underlying disease, taking into account microbiological analyzes of feces. In this case, the severity and depth of intestinal dysbiosis (compensated, subcompensated, decompensated), its degree - I, II, III, are taken into account.

***The purpose of the lesson*:**

To learn:

1. Classification of drugs used to treat hypoacid gastritis and dysbiosis.

I. Classification of hyperacid drugs

1. Drugs that enhance gastric secretion

2. Drugs for replacement therapy: abomin, natural gastric juice (Succus gastricus naturalis), acidin-pepsin (betacid) pepsin (Pepsinum), diluted hydrochloric acid

3. Drugs affecting gastric motility - Central dopamine receptor blocker dopamine antagonist with antiemetic properties. Metaclopramide, Domperidone - Motilium or Mochi-varnish,

II. Classification of drugs with dysbiosis

1. Probiotics - products containing living microorganisms (lactic acid bifidobacteria or lactobacilli, sometimes yeast), which relate to the obligate intestinal microflora of a healthy person.

2. Requirements for probiotics

The probiotic should have a positive effect on the human body, confirmed by laboratory tests and clinical observations.

The probiotic should be non-pathogenic and non-toxic with prolonged use.

The probiotic should contain viable cells, preferably in large numbers.

The probiotic should have colonization potential - the ability to survive and live in the intestinal microenvironment (resistance to low pH in the stomach, resistance to organic acids).

The probiotic must be stable and preserve the viability of bacteria for a long shelf life.

3. Classifications of probiotics

Depending on the purpose:

Heteroprobiotics.

Assigned regardless of the species of the host, from which strains of probiotic bacteria were originally isolated.

Homobiotics.

They are assigned only to representatives of that animal species and to the person from whose biomaterial the corresponding strains were isolated.

Autoprobiotics.

Strains of normal microflora, isolated from a particular individual duum and designed to correct its microecology.

Depending on the composition:

Monocomponent - bifidumbacterin, lactobacterin, colibacterin.

Multicomponent - Bifilong (2 types of bifidobacteria bifidum et longum), Bifinorm (3 types of bacteria bifidum, longum, adolescentis), Acylact (3 different strains of Lactobacillusacidophilus - 100 AIII, NK1, K3, III24), Acipole (Lactobacillus acidophilus), Bifidin (Bifidumbacterium adolescentis, Escherichia coli), Linex (Lactobacillus acidophilus, B. bifidum, Enterococcus faecium SF68), Bifiform (B. longum and Enterococcus faecium SF68), Polybacterin.

Combined - Kipacid (Lactobacillus acidophilus and complex immunoglobulin), Bifilis (Bifidumbacterium bifidum and lysozyme), Bioflor (E. Coli M-17, extracts of soy, vegetables, propolis).

Recombinant or genetically engineered probiotics - based on genetically engineered strains of microorganisms, their structural components and metabolites with specified characteristics.

Depending on the time of creation and improvement, several generations of probiotics are distinguished:

I generation.

Microcomponents consisting of one strain microorganisms - typical inhabitants of the intestine (bifidobacteria, lactobacilli).

II generation.

Self-eliminating antagonists (Bactisubtil, Enterol). For all types of dysbiosis, it is possible to use Enterol 250 mg 2 times a day between meals for 10-15 days.

III generation.

Multicomponent preparations (symbiotics), consisting of several (from 2 to 30) strains of bacteria (Bifilong) or of several types of bacteria (Li-Nex, Bificol).

IV generation.

Combined drugs (synbiotics), consisting of a strain of bacteria and ingredients that promote their growth, reproduction and metabolic activity (Bifilis, Kipatsid).

V generation.

Multicomponent combined preparations consisting of several types of bacteria and ingredients that promote their growth, reproduction and metabolic activity (Bifiform).

In the correction of intestinal microbiocenosis disorders, the purpose of which is to suppress the excess conditionally pathogenic flora, the principle is the division of probiotics into:

Preparations containing live bacteria belonging to representatives of normal symbionts (bifidobacteria, lactobacilli, E. coli).

Self-eliminating antagonists containing microorganisms and fungi that normally do not live in the human intestines (Bacillus subtilis, B. licheniformis, Saccharomyces boulardii).

Probiotic Groups

1 Monoprobiotics

Lactobacillus Lactobacterin Biobactone Gastrofarm Biobactone NarineVaitadofilius

Colis-containing colibacterin

Bifid-containing Bifidumbacterin Bifidumbacterin forte Probi-forBifidogen Eugalan Bifidumbacterin 1000 Liquid bifidumbacterium Biosorb bifidum Soya lactum Soya bifidum

II Polyprobiotic

Bifid-containing Bifilong Lacto-containing Acylact Bifido and lacto-containing Bifacid Bifido and colic-containing Bificol Linex Omniflora

III Probiotics - self-eliminating antagonists - bacillary - saccharomycete-containing Sporobacterin Baktisporin Biosporin Bak-tisubtil Shlonivin V Enterol Lactofiber Lactospore Enrich Pro-Bio-Nyx

IV Combined probiotics (synbiotic)

Bifid-containing: Bifilis Lacto-containing: Acipol in tab

Colic: Bioflor Bifid-containing: Bifiform Laminolact Bifistim Acipol in the mouth Kipatsid Bifiform Kid Bifid and lact-containing and inulin (prebiotic) Bifiform Nompleks

V Metabolic probiotics Hilak-forte

4. Prebiotics - products containing components that stimulate the growth of useful obligate microflora.

Hilak-forte, lactulose (Dufalac, Normase, Lactusan), Lactofiltrum.

5. Positive effects of prebiotics:

Mucolytic effect.

Reparative action.

Maintaining optimal pH values.

Increased fecal volume.

Improved intestinal motility.

Reduced gas production.

Stimulation of the synthesis of B vitamins and vitamin K.

Antibacterial effect mediated by non-specific resistance factors.

Bifidogenic activity.

Recovery of disturbed normal microflora.

Prebiotics stimulate the reproduction and functional activity of the "native" for the patient's own normal intestinal microflora.

6. Food components and drugs with prebiotic effects

a. Oligosaccharides (lactulose, fructooligosaccharides, galactooligosaccharides).

b. Alimentary fiber.

c. Plant microbial extracts (yeast, carrot, potato, corn, rice, pumpkin, garlic).

d. Algae extracts.

e. Monosaccharides, alcohols (xylitol, raffinose, sorbitol, xylobiosis).

f. Polysaccharides (pectins, dextrin, inulin, chitosan).

g. Amino acids (valine, arginine, glutamic acid).

h. Antioxidants (vitamins A, C, E, selenium, ubiquinone, glutathione, carotenoids).

i. Unsaturated fatty acids (eicosopentaenoic acid).

j. Enzymes (microbial beta-galactosidases, saccharomycete proteases).

k. Pectins.

7. Synbiotics - a combination of several probiotic types of bacteria (for example, Bifikol, Bifilin). Their action is based on the synergism of probiotics and prebiotics, due to which not only the introduced microorganisms - probiotics in the gastrointestinal tract of the host are most effective, but their own microflora is stimulated. Dietary fiber, enzymes, trace elements, and herbal supplements may also be included in synbiotics.

8. Symbiotics are complex preparations, including pre- and probiotics (Biovestin, Biovestin-Lacto, Bifilis, Euflorins (Euflorin-L and Euflorin-B), Bifiform, Bifido-tank, Laminolact).

9. Sources of natural sorbents - products containing a sorbing substance that can bind and remove toxic products from the body.

Know:

6. Etiology, pathogenesis, clinic, complications, hypoacid gastritis, dysbacteriosis

7. Research methods for hypoacid gastritis, dysbiosis

8. The main etiological factors and pathogenetic mechanisms that are the object of drug exposure

9. Pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics, the interaction of the above drugs

10. The principles of complex therapy - hypoacid gastritis, dysbiosis

3. Be able to:

a) select the necessary drugs for a particular patient with the indicated pathology, select criteria for therapeutic efficacy and safety;

b) prescribe combination therapy;

The list of practical works:

Homework.

1. To study the main tasks and directions of the choice of medicines for acid-dependent diseases of the gastrointestinal tract and dysbiosis

The task for self-checking the initial level.

1. Etiology, pathogenesis, classification of hypoacid gastritis, dysbiosis.

2. List the main groups of drugs for hypoacid gastritis, dysbacteriosis

3. Formulate the significance of the leading pharmacokinetic characteristics (T1 / 2el,%, connection with plasma proteins, \ / d l / kg) in an individual selection of the above-mentioned drugs.

8. Highlight the clinical and laboratory-functional criteria for therapeutic efficacy of drugs.

9. List the clinical and laboratory safety criteria for the use of drugs in the analyzed clinical syndromes.

Situational Tasks

Task number 1.

At the pharmacy, having bored with ailments of chronic gastritis type A in the course of chronic pancreatitis.

Your recommendation of an excellent therapy in this wrap-up. Vidpovid obgruntuy-those.

Task number 2.

The pharmacist received a certificate of prescription for tetracycline hydrochloride and al-magel A.

Your recommendations for the sum total of the valuation of the value of the concerns.

Go ahead.

Task number 3.

A 48-year-old patient, an engineer, by the nature of his work often happens on mission, turned to the clinic for an exacerbation of chronic gastritis. Pain in the epigastric region after eating was disturbed, decreased appetite, belching with the smell of food eaten. When examining gastric juice, a decrease in the secretory function of the stomach was revealed, with fibrogastroscopy - signs of a moderate atrophic process in the gastric mucosa. The doctor prescribed a diluted hydrochloric acid with pepsin in combination with pancreatin. After 2 weeks, the patient's condition improved significantly; from complaints, a feeling of heaviness remained in the epigastric region after eating. In the future, the patient is recommended, against the background of a diet, to continue taking only diluted hydrochloric acid during meals.

Explain the purpose of prescribing these drugs at the 1st stage of treatment of the patient. Explain the further tactics of the attending physician in relation to this patient.

Task number 4.

A child, 10 years old, delivered an ambulance to the hospital for acute poisoning with vinegar essence. The doctor injected subcutaneously with 0.1 ml of a 1% solution of apo-morphine hydrochloride, made a gastric lavage with a 0.5% tannin solution and injected 10 g of activated charcoal into the stomach through a tube. However, the patient's condition soon deteriorated sharply, symptoms of peritonitis and progressive acidosis appeared.

Task number 5

Khvora Zh., 40 Rokiv, turned into a district polikliniku with skargs on an unstylish chair, flatulence, pain in the stomach of an undetermined character of average intensity. 10 days ago, she independently took antibiotics to a wide range of motors with a drive of GRZ. Vishcheznacheni skargi appeared on the sixth day to receive the antibiotics. In the anamnesis: non-repeated stasis of antibiotics, psychological stresses, state intestines. With severe feces: the main thing is the change in the number of intestinal sticks, the lactobacillus bacterium.

Signify forward diagnosis. Assign the recommended group of drugs for likuvannya. Bring likarsky hobbies, whip recipes.

Task number 6

Patient I., 51 years old, was admitted to the department with complaints of intestinal dysfunction, weakness, shortness of breath with little physical exertion. The examination revealed: pallor of the skin, glossitis, a decrease in the level of hemoglobin to 60 g / l, a color indicator of 1.2, the concentration of serum iron in the normal range, megaloblastic type of hemopoiesis in the bone marrow puncture.

Your preliminary diagnosis. Indicate the possible causes of the development of this type of anemia. Give an example of the most appropriate pharmacotherapy and note methods for evaluating its effectiveness.

Describe the tactics of the doctor and make your own corrections to it.

TESTS

1. Indicate a centrally acting drug - a dopamine receptor blocker used for nausea and vomiting accompanying gastrointestinal tract diseases, after surgery, for migraines, and also for vomiting provoked by cytotoxic drugs and radiotherapy.

A. * Metoclopramide.

B. Famotidine.

C. Pancreatin.

D. Gastrocepin.

E. Dandelion root.

2. A man, 20 years old, complains of baking pressing pain in the epigastric region, heartburn, belching sour. Objectively: the condition is satisfactory. On palpation, pain in the epigastric region is determined. FGDS with morphology of the biopsy pathology from the mucous membrane did not reveal. What drug is most effective?

A. Gastrocepin.

B. Almagel.

C. De-nol.

D. Omeprazole.

E. Motilium.

3. The patient, 60 years old, during the examination revealed chronic autoimmune gastritis with secretory insufficiency. What drug is most appropriate for this patient?

A. Ranitidine.

B. Gastric juice.

S. De-nol.

D. Almagel.

E. Venter.

4. A patient with hypoacid gastritis applied to the pharmacy. What drugs can you offer him for replacement therapy

A. Ranitidine.

B. Betacid.

S. De-nol.

D. Almagel.

E. Venter.

5. For the prevention of dysbiosis in the treatment of antibiotics, it is necessary to mean:

A. Nystatin

B. Linex.

C. Flucanazole.

D. Essential.

E. Venter.

6. Indicate the central action drug - a blocker of pre-family receptors used for nausea and vomiting accompanying gastrointestinal diseases, after operations, for migraines, and also for vomiting provoked by cytotoxic drugs and radiotherapy.

A. Metoclopramide.

B. Famotidine.

C. Pancreatin.

D. Gastrocepin.

E. Dandelion root.

7. For laxatives containing anthraglycosides, the following undesirable effects are characteristic with prolonged use.

A. Addiction. Colitis followed by atrophy of the mucosa and muscle membranes.

B. Atony of the intestine and the formation of chronic habitual constipation.

C. Hepatotoxicity, hypokalemia.

D. Staining of sweat, urine, milk: in an acidic environment - in yellow, in alkaline - in red.

E. All of the above effects.

8. A drug from the group of anticholinesterase, which penetrates poorly through the blood-brain barrier, enhancing motility and secretion of the gastrointestinal tract.

A. Bromocriptine.

B. Proserin.

C. Pancreatin.

D. Gastrocepin.

E. Galantamine

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF CHOLERETICS AND CHOLECINETICS

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE

ENZYME AND ANTI-ENZYMIC DRUGS

Purpose of the topic

Chronic cholecystitis is a chronic inflammation of the mucous membrane of the gallbladder.

More often women are sick, especially those suffering from fullness. A certain role in the occurrence of the disease is played by a hereditary predisposition, excessive nutrition, metabolic disorders, circulatory disorders of the gallbladder wall, a sedentary lifestyle.

Chronic inflammatory process in the gallbladder and biliary tract is often secondary, developing against the background of dyscholia and dyskinesia. Chronic cholecystitis is much less common - a consequence of acute cholecystitis.

The infectious process in the gallbladder is usually bacterial, less often viral. Of the bacteria, the causative agents are often representatives of autoflora - E. coli, staphylococci, enterococci, Proteus, which more often enter the gallbladder and intestines (ascending pathway), less often - by the lymphogenous and hematogenous route.

There are calculous (predominant) and non-calculous (very rare) forms of chronic cholecystitis.

Chronic stoneless cholecystitis is a widespread disease affecting people of different ages. Disease more often occurs in women than in men, the ratio, according to various authors, is 1: 3, 1: 4

Motivational characteristic

Chronic stoneless cholecystitis is an inflammatory disease of the mucous membrane of the gallbladder, accompanied by pain, dyspeptic syndromes and general manifestations. The disease is polyetiologic. In its development, several main causative factors can be distinguished: infection, the presence in the bile of agents irritating the mucous membrane of the gallbladder, food allergy.

Currently, the infectious factor is not considered leading. Pathogenic staphylococci, streptococci, Escherichia coli and others are often the cause of the development of acute cholecystitis. However, in some cases, especially if a low-virulent microflora takes place in the gallbladder, especially in combination with stagnation of bile, the development of infectious forms of chronic cholecystitis is possible. The development of infection in the biliary tract contributes to a decrease in immunity, the presence of foci of chronic infection, the period after the transferred viral hepatitis.

One of the main causes of chronic cholecystitis is irritation of the mucous membrane by various agents. Such agents most often include fat frying products, chemical food additives, the evil use of fatty foods, which leads to a constant excessive intake of bile acids, especially deoxycholates, which irritate the mucous membrane of the gallbladder. Disorders of diet, rare or very frequent meals, the irregularity of its meals, as well as a violation of the motility of the gallbladder, especially hypotonic-hypokinetic dyskinesia are important.

CLINIC (SYMPTOMS) OF CHRONIC STONE-FREE CHOLECY STITIS

The clinic of chronic stoneless cholecystitis is mainly characterized by the presence of pain, dyspeptic syndromes and general manifestations.

The pain is localized in the right hypochondrium, sometimes in the epigastric region, closer to its right side. It can be of varying degrees of severity, but basically it is dull, aching, radiating to the right half of the chest, to the right collarbone, neck to the right, right shoulder, shoulder blade. The pain intensifies after eating, especially after eating fats and fried foods. The intensification of pain after eating is associated with an increase in pressure in the cavity of the gallbladder, as a result of the release of cholecystokinin-pancreosimine under the influence of fats, an increase in the tone of the gallbladder. The development of pain is facilitated by the presence of bends and constrictions in the neck of the gallbladder, as well as swelling of the mucous membrane of the neck of the gallbladder. As a result of such changes, the secretion of cystic bile is disrupted, and if the effect of cholecystokinin-pancreosimine is imposed, which causes a contraction of the gallbladder, then the pain can be quite severe.

In some cases, pain may be absent or appear only after errors in nutrition - intake of fried, fatty foods, plentiful food. In these cases, dyspeptic syndrome predominates in the clinic of the disease. Patients complain of a feeling of heaviness in the right hypochondrium, epigastric region, bloating, nausea, a bitter taste in the mouth, and stool disorders. The development of dyspeptic phenomena is associated with impaired bile secretion and changes in the biochemical composition of bile. The secretion of bile during the inter-digestive period can cause biliary reflux, nausea, and a bitter aftertaste in the mouth. Reduced bile acids in the bile lead to digestion, especially hydrolysis and absorption of fats. Also bile acids stimulate intestinal motility, their deficiency can cause hypotonic constipation, and excess causes cholera diarrhea.

The appetite in patients is basically preserved, and sometimes in the remission stage it is increased, and only with a pronounced exacerbation can its decline be observed, which quickly passes.

Of the common manifestations, weakness, headache, periodic chills, fever to subfebrile numbers, pain in the joints, in the heart, tachycardia are possible.

Depending on the severity of the clinical manifestations of the disease, the functional state of the liver, pancreas, the functional state of the gallbladder, mild, moderate and severe forms of chronic cholecystitis are distinguished.

For mild cholecystitis, rare and short-term exacerbations are characteristic for 2-3 days, mainly provoked by errors in nutrition and easily amenable to dietetic correction. Under the influence of the diet, the clinical manifestations of the disease pass after a few days. The general condition of patients is not disturbed, body temperature is normal, appetite is preserved. During the examination, there are

no significant violations of the functional state of the gallbladder, liver, pancreas. With duodenal sounding, the microscopic data of bile without any significant changes.

Chronic cholecystitis of moderate severity occurs with the presence of clear periods of remission and exacerbations. Exacerbations last 2-3 weeks, with the presence of pain, positive cystic symptoms, severe dyspeptic syndrome. They are usually caused by the intake of fatty, fried foods, plentiful food. In some cases, exacerbations can be triggered by an infection of the upper respiratory tract, etc. During an exacerbation, patients have decreased appetite, some weight loss, intoxication phenomena (general weakness, headache), and joint pain can bother.

Some patients, in addition to pain in the right hypochondrium, may complain of heaviness and dull pain in the epigastric region, left hypochondrium, upper abdomen. Pain, as a rule, radiates to the right half of the chest, sometimes to the region of the heart.

In chronic stoneless cholecystitis of moderate severity, a marked dyspeptic syndrome is noted. Patients are not afraid of nausea, worse after eating, especially fats, heaviness in the epigastric region, flatulence, and stool disorders. Changes in stool can be of a different nature. Some patients have constipation, which can sometimes be replaced by relaxation of the stool. Such changes in stool are usually associated with a sharp contraction of the gallbladder, overflowing with bile, and a single entry into the intestinal lumen of a large amount of concentrated bile. In some patients, the stool is unformed, mushy, lightish. These changes in stool are associated with a significant violation of bile secretion, as well as the digestion of fats (a decrease in exocrine pancreatic function is not ruled out).

When examining patients with chronic stoneless cholecystitis of moderate severity, one can detect a number of positive cystic symptoms (Kera, Ortner, right-sided phrenicus, Boas, etc.). When x-ray examination of the gallbladder, there is a decrease in its concentration and motor-evacuation functions. Microscopic examination of portions of bile reveals an increased amount of mucus, leukocytes, leukocytoid cells, epithelium, as well as sedimentary elements - cholesterol crystals, bilirubinate Ca, soap, bile salts, in some cases microliths. With a bacteriological study of bile, microflora can be detected.

During exacerbation in patients, changes in some functional liver samples can be detected. Most often, moderate hypoalbuminemia, a slight increase in the activity of transaminases, mainly AJIT, a moderate increase in the thymol test, and alkaline phosphatase activity are most often noted. Changes in biochemical liver samples during remission pass. During the period of remission in patients, a mild dyspeptic syndrome may persist in the form of a tendency to constipation, diarrhea, often after eating, severity in the upper abdomen, flatulence may disturb. Dyspeptic changes have a clear dependence on the nature of nutrition. Abundant food, intake of coarse fiber, fatty and fried foods enhance dyspepsia and can cause pain, up to an exacerbation of the disease.

Chronic stoneless cholecystitis of a severe form is characterized by a continuously recurrent course, the absence of clear and prolonged remissions. The disease is not limited to the gall bladder. The clinic of chronic cholecystitis joins the clinic of chronic hepatitis, pancreatitis. Patients complain of decreased appetite, a constant feeling of nausea, heaviness and pain in the upper abdomen. Sometimes the pain is girdle-like. Due to frequent pain and severe dyspeptic syndrome, patients are forced to stay on a strict diet, which ultimately leads to weight loss, the development of asthenic syndrome. In some cases, the disease is accompanied by prolonged subfebrile condition and is in the nature of chronic sepsis. With an X-ray examination, gallbladder function is severely impaired. On cholecystograms, a decrease in the intensity of the shadow of the gallbladder is noted, which indicates a decrease in its concentration function. The contractile and evacuation functions are also impaired, there may be signs of periprocess, thickening of the wall of the bladder. If in patients with chronic stoneless cholecystitis of moderate severity, violations of some liver functions are detected during an exacerbation of the disease, then in severe cases it reveals chronic hepatitis, and sometimes chronic cholangitis. At the same time, an increase in the size of the liver, changes in its functional state are noted: a decrease in the level of serum albumin, an increase in globulin fractions, an

increase in the concentration of total bilirubin, mainly due to direct bilirubin, an increase in the activity of transaminases, alkaline phosphatase, lactate dehydrogenase, and thymol test.

Ultrasound examination of the abdominal organs shows an increase in liver size, hepatitis, expansion of the intrahepatic bile ducts, and an enlarged, stagnant gallbladder.

When examining the pancreas, the phenomena of chronic pancreatitis with reduced exocrine pancreatic function are found. Patients often complain of severe dyspeptic syndrome, nausea, weight loss. They reveal coprological changes characteristic of exocrine pancreatic insufficiency: an increase in the mass of feces (polyfecalia), steatorrhea, and in severe cases, the presence of creatorrhea and amylorrhea.

In the severe course of chronic stoneless cholecystitis, cardiovascular system disorders are frequent: vegetative-vascular dystonia, myocardial dystrophy, aggravation of the course of chronic coronary insufficiency with corresponding changes in the ECG.

In some cases, the clinic of chronic stoneless cholecystitis can be atypical. The most common among atypical forms is dyspeptic form, which is not characterized by pain, and dyspeptic syndrome comes to the fore in the clinical picture of the disease: severity in the epigastric region, flatulence, nausea, stool disorders. In adolescence and young adulthood, chronic cholecystitis is sometimes clinically reminiscent of latent rheumatism. Patients are concerned about general weakness, increased fatigue, joint pain, prolonged subfebrile condition. With auscultation, you can listen to weakened heart sounds, systolic murmur at the apex.

In middle-aged and elderly people, the cardiac form of chronic cholecystitis resembles angina pectoris or chronic coronary insufficiency. Patients complain of pain in the heart, palpitations. On the ECG, you can detect a decrease in the voltage of the teeth, segment S-T. However, at the same time, an atypical course of angina pectoris and a low treatment efficiency are noted.

Atypical forms include lumbar and pyloroduodenal forms of chronic cholecystitis. The lumbar form is characterized by pain in the spinal column, more often at the level of TIX — TXII. It reminds me of pain in spon-dilesis, osteochondrosis. Abdominal symptoms are absent. In such cases, an X-ray examination of the spinal column is necessary.

With a gastroduodenal form, the clinic of chronic cholecystitis resembles a clinic of peptic ulcer or gastroduodenitis with increased acid-forming function of the stomach. Patients complain of hungry, sometimes nightly pain.

Treatment

Cholagogue - medicines that enhance bile formation or promote the secretion of bile into the duodenum.

Bile (bilis - lat., Fel - eng.) - a secret produced by hepatocytes. The production of bile occurs in the body continuously. Bile produced in the liver is secreted into the extrahepatic bile ducts, which collect it into the common bile duct. Excess bile accumulates in the gallbladder, where it is concentrated 4-10 times as a result of absorption of water by the mucous membrane of the gallbladder. In the process of digestion, bile from the gallbladder is secreted into the duodenum, where it is involved in the processes of digestion and absorption of lipids. The flow of bile into the intestines is regulated by neuro-reflex mechanisms. Of the humoral factors in the process of bile secretion, cholecystokinin (pancreosimin), which is produced by the mucous membrane of the duodenum when the gastric contents enter it, is of greatest importance and stimulates the contraction and emptying of the gallbladder. As you move through the intestines, the main part of bile is absorbed through its walls along with nutrients, the rest (about a third) is removed with feces.

The main components of bile are bile acids (FA) - 67%, about 50% - primary FAs: cholic, chenodeoxycholic (1: 1), the remaining 50% - secondary and tertiary FAs: deoxycholic, lithocholic, ursodeoxycholic, sulfolitocholic. Bile also includes phospholipids (22%), proteins (immunoglobulins - 4.5%), cholesterol (4%), bilirubin (0.3%).

By their chemical structure, FAs are derivatives of cholanic acid and represent the main end product of cholesterol metabolism. Most FAs are conjugated to glycine and taurine, which makes them stable at low pH values. Bile acids facilitate the emulsification and absorption of fats, inhibit cholesterol synthesis by the feedback mechanism, the absorption of fat-soluble vitamins (A, D, E, K) depends on their presence In addition, bile acids increase the activity of pancreatic enzymes.

Violations of the formation or outflow of bile into the duodenum can be of a different nature: liver disease, biliary dyskinesia, increased lithogenicity of bile, etc. When choosing a rational choleretic agent, the pharmacodynamics of choleretic drugs must be taken into account.

Depending on the leading mechanism of action, choleretic drugs are divided into two subgroups: agents that enhance the formation of bile and bile acids (Choleretica, Cholesecretis), and agents that facilitate its secretion from the gallbladder into the duodenum (Cholagoga, or Cholekinetica). This division is rather arbitrary, because most choleretic drugs simultaneously enhances the secretion of bile, and facilitates its entry into the intestines.

The mechanism of action of choleretics is due to reflexes from the intestinal mucosa (especially when using preparations containing bile, bile acids, essential oils), as well as their effect on liver exosecretion. They increase the amount of secreted bile and the content of cholates in it, increase the osmotic gradient between bile and blood, which increases the filtration of water and electrolytes into the bile capillaries, accelerates the flow of bile through the bile ducts, and reduces the chance of cholesterol precipitation, i.e. - Prevent the formation of gallstones, enhance the digestive and motor activity of the small intestine.

Drugs that promote the secretion of bile can act by stimulating the contraction of the gallbladder (cholekinetics), or by relaxing the muscles of the biliary tract and the sphincter of Oddi (cholespasmolytic).

Clinical classification of choleretic drugs

I. Drugs stimulating bile formation - choleretics

A. Increasing the secretion of bile and the formation of bile acids (true choleretics):

1) preparations containing bile acids: Allochol, Cholenzyme, Vigeratin, dehydrocholic acid (Hologon *) and sodium salt of dehydrocholic acid (Deholin *), Lyobil * and others;

2) synthetic preparations: hydroxymethylnicotinamide (Nicodine), osal mid (Oxafenamide), cyclovalone (Cyqualone), gimecromon (Odeston, Holonerton *, Cholestil *);

3) herbal preparations: sandwort immortelle flowers, corn stigmas, tansy (Tanacekhol), rose hips (Ho-losas), Berberina bisulfate, birch buds, blue cornflower flowers, DO-shitsa grass, tallow oil, turpentine oil, peppermint oil, leaves of scumpia (Flacumin), Far Eastern lily of the valley grass (Convaflavin), turmeric root (Febichol *), buckthorn, etc.

B. Drugs that increase the secretion of bile due to the aqueous component (hydrocholeretics): mineral waters, sodium salicylate, valerian preparations.

II. Biliary stimulants

A. Cholekinetics - increase the tone of the gallbladder and reduce the tone of the biliary tract: cholecystokinin *, magnesium sulfate, pituitrin *, cholesterin *, barberry preparations, sorbitol, mannitol, xylitol.

B. Cholespasmolytics - cause relaxation of the biliary tract: atropine, platifillin, metocinium iodide (Metacin), belladonna extract, papaverine, dro-taverine (No-shpa), mebeverin (Duspatalin), aminophylline (Eufillin), Olimin-tin.

I.A.1) Preparations containing bile acids and bile are drugs containing either bile acids themselves or combined drugs in the composition which, in addition to lyophilized bile of animals, can include extracts of medicinal plants, extract of liver tissue, pancreatic tissue and mucous membranes of the small intestine of cattle, activated charcoal.

Bile acids, absorbed into the blood, stimulate the bile-forming function of hepatocytes, the non-absorbed part performs a replacement function. In this group, preparations that are bile acids increase the volume of bile to a greater extent, and preparations containing animal bile increase the content of cholates (salts of bile acids) to a greater extent.

I.A.2) Synthetic choleretics have a pronounced choleretic effect, but do not significantly alter the excretion of hololates and phospholipids into the bile. After entering the hepatocytes from the blood, these drugs are secreted into the bile and dissociate, forming organic anions. A high concentration of anions creates an osmotic gradient between bile and blood and causes the osmotic filtration of water and electrolytes into bile capillaries. In addition to the choleretic, synthetic choleretics have a number of other effects: antispasmodic effect (oxaphenamide, gimekromon), lipid-lowering (oxaphenamide), antibacterial (hydroxymethylnicotinamide), anti-inflammatory (cyclovalon), and also suppress the processes of decay and fermentation (hydrocystic) .

I.A.3) The effect of herbal preparations is associated with the influence of the complex of components that make up their composition, including such as essential oils, resins, flavones, phytosterols, phytoncides, some vitamins and other substances. Drugs of this group increase the functional ability of the liver, increase the secretion of bile, increase the content of cholates in the bile (for example, Helichrysum, Rosehip, Holagol), and reduce the viscosity of bile. Along with increased secretion of bile, most phytopreparations of this group increase the tone of the gallbladder while relaxing the smooth muscles of the bile ducts and sphincters of Oddi and Lutkens. Cholagogue phytopreparations also have a significant effect on other functions of the body - they normalize and stimulate the secretion of the glands of the stomach, pancreas, increase the enzymatic activity of the gastric juice, and increase intestinal motility during its atony. They also have antimicrobial (e.g. immortelle, tansy, mint), anti-inflammatory (olimetin, Holagol, rosehip), diuretic, antimicrobial action.

As medicinal preparations from plants, in addition to extracts and tinctures, infusions and decoctions from herbs are prepared. Usually take phytopreparations 30 minutes before meals, 3 times a day.

I.B. Hydrocholetics. This group includes mineral waters - Essen Tuki No. 17 (highly mineralized) and No. 4 (slightly mineralized), Jer-Muk, Izhevskaya, Naftusya, Smirnovskaya, Slavyanovskaya and others.

Mineral waters increase the amount of secreted bile, making it less viscous. The mechanism of action of choleretic drugs of this group is due to the fact that, being absorbed in the digestive tract, they are secreted by hepatocytes in the primary bile, creating increased osmotic pressure in the bile capillaries and contributing to an increase in the aqueous phase. In addition, the reverse absorption of water and electrolytes in the gallbladder and biliary tract is reduced, which significantly reduces the viscosity of bile.

The effect of mineral waters depends on the content of sulfate anions (SO42) bound to magnesium cations (Mg2 +) and sodium (Na +), which have a choleretic effect. Mineral salts also contribute to the increase in colloidal stability of bile and its fluidity. For example, Ca2 + ions, forming a complex with bile acids, reduce the likelihood of a poorly soluble precipitate.

Mineral water is usually consumed in a warm form 20-30 minutes before a meal.

Salicylates (sodium salicylate) and valerian preparations are also referred to hydrocholetics.

II.A. To cholekinetics include drugs that increase the tone and motor function of the gallbladder, reduce the tone of the common bile duct.

The cholekinetic effect is associated with irritation of the receptors of the intestinal mucosa. This leads to a reflex increase in the release of endogenous cholecystokinin. Cholecystokinin is a polypeptide produced by the cells of the mucous membrane of the duodenum. The main physiological functions of cholecystokinin are to stimulate the contraction of the gallbladder and the secretion of digestive enzymes by the pancreas. Cholecystokinin enters the bloodstream, is captured by the liver cells and secreted into the bile capillaries, while providing a direct activating effect on the smooth muscles of the gallbladder and relaxing the sphincter of Oddi. As a result, bile enters the duodenum and its stagnation is eliminated.

The choleretic effect is exerted by magnesium sulfate when taken orally. A solution of magnesium sulfate (20–25%) is administered orally on an empty stomach, and is also administered through a probe (with duodenal sounding). In addition, magnesium sulfate also has an antispasmodic effect.

Polyhydric alcohols (sorbitol, mannitol, xylitol) have both cholenetic and choleretic effects. They favorably affect the function of the liver, contribute to the normalization of carbohydrate, lipid and other types of metabolism, stimulate the secretion of bile, cause the release of cholecystokinin, and relax the sphincter of Oddi. Polyhydric alcohols are used in duodenal sounding.

Olive and sunflower oil, plants containing bitterness (including dandelion, yarrow, wormwood, etc.), essential oils (juniper, cumin, coriander, etc.), extract and juice of cranberry, cranberry and other

II.B. Cholespasmolytics include drugs with a different mechanism of action. The main effect of their use is the weakening of spastic phenomena in the biliary tract. m-anticholinergics (atropine, platifillin), blocking m-cholinergic receptors, have a non-selective antispasmodic effect in relation to various parts of the gastrointestinal tract, including in relation to the biliary tract.

Papaverine, drotaverine, aminophylline - have a direct (myotropic) effect on the tone of smooth muscles.

Other drugs also have cholespasmolytic effects. However, they are rarely used as choleretic drugs. So, nitrates relax the sphincter of Oddi, the lower esophageal sphincter, reduce the tone of the biliary tract and esophagus. Nitrates are not suitable for long-term therapy, as have pronounced systemic side effects. Glucagon may temporarily decrease the tone of the sphincter of Oddi. But both nitrates and glucagon have a short-term effect.

Indications for the appointment of choleretics are chronic inflammatory diseases of the liver and biliary tract, including chronic cholecystitis and cholangitis, they are used in biliary dyskinesia, in the treatment of constipation. If necessary, choleretics are combined with antibiotics, analgesics and antispasmodics, with laxatives.

Unlike other choleretic drugs, preparations containing bile acids and bile are substitution therapy for endogenous bile acid deficiency.

Cholekinetics cause an increase in the tone of the gallbladder and relaxation of the sphincter of Oddi, therefore they are prescribed mainly for the hypotonic form of biliary dyskinesia. Indications for

their use are atony of the gallbladder with stagnation of bile with dyskinesia, chronic cholecystitis, chronic hepatitis, with anacid and severe hypoacid conditions. They are also used in duodenal sounding.

Cholespasmolytics are prescribed for the hyperkinetic form of biliary dyskinesia and for gallstone disease. They are used for the relief of pain of moderate intensity, often accompanying pathology of the biliary tract.

Choleretics are contraindicated in acute hepatitis, cholangitis, cholecystitis, pancreatitis, gastric ulcer and duodenal ulcer in the acute stage, in gallstone disease with blockage of the excretory ducts, in obstructive jaundice, as well as in dystrophic lesions of the liver parenchyma.

Cholekinetics are contraindicated in acute liver diseases, in the presence of stones in the gall bladder, with exacerbation of hyperacid gastritis and peptic ulcer of the stomach and duodenum.

Criteria for assessing the effectiveness and safety of the use of drugs used in violation of bile secretion:

- Laboratory: determination of bile acids in the blood and gallbladder bile (with pathology, the amount of FA in the blood increases, and in bile it decreases, the ratio between their three main forms - cholic, hypodeoxycholic, deoxycholic - and glycine and taurine conjugates), analysis blood (an increase in blood FA leads to hemolysis, leukopenia, disrupts blood coagulation processes), determination of indirect and direct bilirubin, ALT, AST, bile pigments in the blood, etc.

- Paraclinic, including duodenal sounding, contrast cholecystography, ultrasound.

- Clinical: high concentrations of blood cholates cause bradycardia, arterial hypertension, skin itching, jaundice; symptoms of neurosis appear; pain in the right hypochondrium or epigastrium, an increase in the size of the liver.

The drugs used for increased lithogenicity of bile (in the absence of calculi) include Allochol, Cholenzym, hydroxymethylnicotin-mid (Nikodin), sorbitol, Olimetin. Means of this group have different mechanisms of action, since the lithogenicity of bile depends on many factors.

Cholelitolytic drugs A number of derivatives of deoxycholic acid, in particular ursodeoxycholic, isomeric chenodeoxycholic, can not only prevent the formation of cholesterol stones in the gallbladder, but also dissolve existing ones.

Cholesterol, which forms the basis of most gallstones, is normally in a dissolved state in the center of micelles, the outer layer of which is formed by bile acids (cholic, deoxycholic, chenodeoxycholic). Phospholipids that concentrate in the center of a micelle increase its ability to inhibit cholesterol crystallization. A decrease in the content of bile acids in bile or an imbalance between the concentration of phospholipids and cholesterol and a supersaturation of bile with cholesterol can cause bile to become lithogenic, i.e. capable of forming cholesterol stones. The change in the physicochemical properties of bile leads to precipitation of cholesterol crystals, which then form the core with the formation of cholesterol gallstones.

Both ursodeoxycholic and chenodeoxycholic acids alter the ratio of bile acids, reduce the secretion of lipids in bile and lower the cholesterol content in bile, reduce the cholesterol-cholesterol index (the ratio between acid and cholesterol content in bile), thereby reducing lithogenicity bile. They are prescribed as cholelitolytic agents in the presence of small cholesterol stones as an addition to surgical or shock-wave methods for treating cholelithiasis.

GENERAL MECHANISM OF ACTION AND BASIC PHARMACODYNAMIC EFFECTS

Choleretics

The action of choleretics is due to reflex reactions of the mucous membrane of the predominantly small intestine when exposed to bile, bile acids or essential oils, as well as the effect of these drugs on liver exosecretion. True choleretics can increase the secretion of bile and the content of cholates in it. Hydrocholetics do not increase the cholecholesterol coefficient. Cholagogue also contributes to an increase in the osmotic gradient between bile and blood, which enhances the filtration of water and electrolytes into the bile capillaries, accelerates the outflow of bile through the bile ducts, reduces the chance of cholesterol precipitation, and therefore prevents the formation of cholelithiasis, prevents ascending infections, and reduces the intensity of inflammation .

Choleretics also enhance the digestive and motor activity of the small intestine and promote better absorption of fat-soluble vitamins. In chronic cholangitis, choleretics improve the general condition, reduce itching of the skin, yellowness, and bilirubin level in the blood. The use of choleretics also helps to reduce pain, nausea, constipation, etc.

GENERAL INDICATIONS FOR PURPOSE

Indications for the appointment of choleretics: cholecystitis, cholangitis. Choleretics are often combined with laxatives, which eliminate constipation and reduce the absorption of toxic substances from the intestines. The combination of choleretics with myotropic antispasmodics can help promote small stones along the common bile duct and exit them into the intestines.

GENERAL CONTRAINDICATIONS

Acute hepatitis, acute and subacute dystrophy of the liver, obstructive jaundice.

FEATURES OF ACTION AND DOSAGE MODE OF VARIOUS MEDICINES

Drugs that increase the secretion of bile and the formation of bile acids (true choleretics)

Bile Acids

Allohol

Allochol is a combined preparation and contains dry animal bile (0.08 g), dry garlic extract (0.04 g), nettle extract (0.005 g), activated charcoal (0.025 g), filler (0.3 g) . The dry bile contained in the preparation causes an increase in the secretion of its own bile, while the content of bile acids in it increases. The effect of the drug is due to an increase not only in the secretory function of the liver, but also in the secretory and motor activity of the gastrointestinal tract, a decrease in the processes of rotting and fermentation in the intestine, and an increase in peristalsis of the colon. Take 1-2 tablets 3-4 times a day after meals for a month. The course of treatment can be repeated after 3 months.

Cholenzyme

This is a combined drug in the form of dragees. Contains dry animal bile (0.1 g), enzymes of the pancreas and intestines of animals (0.1 g each). The drug has choleretic activity and, due to the content of enzymes (trypsin and amylase) and bile, improves the digestion of proteins, fats, carbohydrates, which contributes to their more complete absorption in the small intestine. Improves the functional state of the gastrointestinal tract, normalizes the digestive process. The choleretic effect of cholenzyme * is low, it has a spaz-prayer effect. 2 tablets (0.5 g) are prescribed 3 times after a meal, the action lasts 1.5-2 hours, and the treatment lasts up to 4 weeks. Improves appetite and assimilation of food, reduces pain in the stomach and gall bladder.

Hologon (dehydrocholic acid)

The least toxic of all bile acids. The action begins in 10-20 minutes, the maximum occurs in 2 hours. The course duration is up to 4-8 weeks. Assign 0.2-0.4 g 3-4 times a day orally after meals with cholangitis, chronic cholecystitis.

Deholin

This is the sodium salt of dehydrocholic acid. It acts like a holo-gon. Available in ampoules of 5ml5i20% solution. The action lasts 2-3 hours. The maximum action is observed within 1 hour. There is an increase in diuresis, therefore, it can be used for cirrhosis of the liver with ascites. About 5-10 ml of a 5% solution is injected into a vein once a day, then 5-10 ml of a 20% solution for 2-3 days. Then take a break for 2-3 days. Sometimes decholine is prescribed with caution to remove small stones, 0.5 ml of a 0.1% solution of atropine (atropine sulfate) is preliminarily injected, then 5 ml of 20% decholine * are intravenously administered.

Bile (lyobil)

Lyobil is a lyophilized bovine bile. 0.2 g white coated tablets. They include acetylphthalylcellulose, which ensures the stability of the tablet in the acidic environment of the stomach and solubility in the alkaline environment of the intestine. The bile contained in the tablets promotes the formation and outflow of bile, enhances the secretion of pancreas, the breakdown and absorption of fats in the intestines, and the increase in intestinal motility. Applied as a choleretic agent for hepatitis, cholecystitis and other liver diseases, chronic colitis with reduced motility and habitual constipation. Also used in chronic pancreatitis with decreased secretory function of the pancreas. Assign inside adults to 1-3 tablets 3 times a day at the end of the meal. The course of treatment is 1-2 months. If necessary, repeat the treatment.

Cholecine is a complex compound of sodium choleinate and lecithin. Sodium cholena sodium is a mixture of the sodium salt of deoxycholic acid with the sodium salt of palmitic, oleic or stearic acid in a ratio of 8: 1, due to which the drug has a stabilizing effect on the colloidal state of bile and prevents the precipitation of its insoluble components. Cholecine can be used not only for chronic cholecystitis, but also for cholelithiasis, especially in the early stages.

The use of bile acid and bile preparations depends on the goals that we set. If there is a need to improve digestion processes, then they can be prescribed after meals. In cases where it is necessary to stimulate choleresis, it is advisable to use these drugs 30 minutes before meals. The course of treatment is 20-25 days.

A strong choleretic property was found in phenanthrene derivatives - in podocarpic acid, which is an integral part Resin Javanese trees. In terms of choleretic effect, it is superior to de-hydrocholic acid. A pronounced choleretic effect was found in the condensation product of vanillin and cyclohexanone. Vanillin is a structural fragment of one of the active ingredients of turmeric - curcumin, which gives a choleretic effect. Turmeric is part of hepatofalk, which has a hepatoprotective and choleretic effect.

Choleretic properties were found in caffeic acid, which is part of the active substance of artichoke - cynarin. Cinarin, in addition, has the property of normalizing lipid metabolism by enhancing the excretion of cholesterol with bile. Nicodene is referred to as choleretic drugs. In the body, it is broken down into foraldehyde, which has an antimicrobial effect, and nicotinic acid amide, which positively affects liver function. It is administered orally at 0.5-1 gZ — 4 times a day for 10-15 days. In the presence of infection in the biliary tract, the dose of nicodine can be increased to 8 g per day.

Some derivatives of butyric acid also have a choleretic effect. Phenobarbital has a significant effect on the bile-forming function of the liver. Its effect is due to the property of phenobarbital to increase the activity of liver enzymes associated with the biotransformation processes of a number of

lilophilic exo- and endogenous compounds. This effect, called enzymatic induction, increases the activity of microsomal enzyme systems, especially cytochrome P-450. Phenobarbital has a positive effect on the exchange of bilirubin, enhances its capture from the bloodstream, as well as conjugation with plutathione, increases excretion of exogenous substances with bile, accelerates the restoration of the enzymatic activity of hepatocytes and stimulates their mitotic activity. Phenobarbital has a versatile effect on bile formation and biliary excretion: enhances the synthesis of primary bile acids; their conjugation with taurine and glycine stimulates the conjugation of bilirubin. Due to these properties, it is indicated for some forms of intrahepatic cholestasis.

Of inorganic substances, selenium has a positive effect on choleresis. Under the influence of sodium selenite, there is an increase in the level of bilirubin, bile acids, cholesterol in the bile, and the cholocholesterol coefficient increases moderately. Selenium is a part of many preparations (multivitamin preparations with macro- and microelement additives).

In addition to chemical choleretics, in medicine, choleretic drugs of plant origin are widely used in the form of galenical and newgalenic preparations. Currently, there are more than 100 medicinal plants used as choleretic drugs. In most cases, these plants are included in the category of choleretic on the basis of one indicator - an increase in the amount of secreted bile. However, the question of which active principle determines choleretic activity has been little studied. Apparently, the choleretic properties of plants are primarily associated with the presence of essential oils, resins, flavones, phytosterols. The most popular and well-known choleretic herbs include immortelle sand. They use a sand coniferous sand in the form of a decoction and granules (10 and 2 g, respectively, for 250 ml of water, take half a glass in a warm form), liquid extract (1 teaspoon), and dry extract (1 g each). Flamin is prescribed at 0.05 g 2-3 times a day. The course of treatment is 2-3 weeks. In some patients, preparations of sandwort immortelle can enhance or cause acidism, therefore, with a combination of peptic ulcer, gastroduodenitis with high gastric secretion during exacerbation, they should not be prescribed.

As a choleretic agent, corn columns are used with stigmas collected during cob ripening. They are used in the form of a decoction, infusion (10 g per 200 ml of water, 1-2 tablespoons each) and a liquid extract (30-40 drops) 2-3 times a day before meals. In addition to the choleretic effect, corn stigmas have the property of increasing the prothrombin formation function of the liver due to the high content of vitamin K, increasing the number of platelets and enhancing blood coagulation.

Barberry is used in folk medicine for diseases of the digestive system, and for tuberculosis. Bark is used for cancer of the liver and stomach. The drug (25-30 drops per day) has a positive effect on dyskinesia of the gallbladder, chronic cholecystitis, as well as gallstone disease, not complicated by jaundice. Of the barberry alkaloids, berberine is used in the form of a berberine sulfate preparation (5-10 mg 3 times a day before meals). The drug also slows down cardiac activity and promotes uterine contractions.

Rosehip is used in the form of syrups, tablets, the drug Holosas (1 teaspoon 2-3 times a day). The drug is rich in vitamins, especially vitamin C. Common tansy gives a choleretic effect due to the resinous fraction (alcoholic extract - 1/2 teaspoon 3 times a day 30 minutes before meals).

Synthetic Choleretics

Hydroxymethyl nicotinamide (nicodine□)

Hydroxymethylnicotinamide is a derivative of nicotinic acid amide and formaldehyde. It has a choleretic (choleretic) effect, and also contributes to the secretion of bile (cholekinetic effect). In addition, it has a bacteriostatic and bactericidal effect, which is due to the fact that in the process of metabolism, the formaldehyde part of the drug molecule is cleaved. Another part of the molecule (nicotinamide) has the properties of vitamin PP, increases the secretory function of the liver parenchyma, enhancing the secretion of bile and facilitating its entry into the intestine. The drug is used in the complex treatment of impaired liver function, with cholecystitis, as well as urinary tract

infections and gastroenteritis. It is effective in the treatment of infections caused by E. coli. The drug is advisable to use with a combination of inflammatory diseases of the biliary tract with gastritis and colitis. To enhance the antibacterial effect used in conjunction with antibiotics.

Assign inside 0.5-1.0 g (1-2 tablets) 3-4 times a day before meals, 1/2 cup of water is recorded. The dose of hydroxymethylnicotinamide can be increased to 8 g / day in the treatment of diseases accompanied by a febrile state, as well as with co-administration with antibiotics if they are not effective enough. After lowering the body temperature to normal values, the daily dose of the drug is reduced to 4-3 g, and then give 1.0-0.5 g / day for 10-14 days. The course of treatment is repeated if necessary.

Osalmide (oxaphenamide, paraoxyphenyl salicylamide)

Osalmide enhances the formation (choleretic effect) and excretion (cholekinetic effect) of bile, has an antispasmodic effect, reducing the tone of the biliary tract. Helps normalize the composition of bile. It has the ability to lower blood cholesterol, which is more clearly manifested in hypercholesterolemia. It is prescribed for chronic cholecystitis, cholangitis, cholecystohepatitis, cholelithiasis and other diseases accompanied by impaired bile formation and bile secretion. The drug is also used to enhance bile secretion before duodenal sounding. Take orally in tablets of 0.25-0.5 g 3 times on average 15-20 days.

Cyclovalon (cyclovalon

The drug stimulates bile formation and has an anti-inflammatory effect. Assign inside in the first 2 days at 0.3 g (3 tablets) per day, then 0.4 g / day in 3-4 doses. The course of treatment is 3-4 weeks. If necessary, conduct repeated courses with a break for a month. The drug is usually well tolerated. In some cases, at the beginning of treatment, a feeling of pressure in the liver and gall bladder, the appearance or intensification of bitterness in the mouth may be noted. These phenomena pass independently and do not require additional treatment.

Gimekromon (oeston)

It stimulates the receptors of the intestinal mucosa and reflexively enhances the secretion and separation of bile. The drug boosts

the osmotic gradient between bile and blood, which leads to an increase in the filtration of electrolytes and water into the bile ducts, and a decrease in the content of cholates. Prevents crystallization of cholesterol and the development of cholelithiasis. It also has a selective myotropic antispasmodic effect on the bile ducts and their sphincters, but does not affect the motility of the gallbladder and ducts, smooth muscles of the intestine (does not weaken intestinal motility) and blood vessels (does not reduce blood pressure).

It is also indicated in the state after surgical interventions on the gallbladder and bile ducts. Decreased appetite, nausea, constipation, vomiting (against the background of bile hyposecretion).

Prescribe the drug inside 30 minutes before eating. Adults 200-400 mg (up to 800 mg) 3 times a day before meals for 2-3 weeks; children 200-600 mg / day for 1-3 doses. Of the adverse reactions, allergic reactions are noted, with prolonged use - diarrhea, flatulence, headache, abdominal pain, ulceration of the mucous membrane of the gastrointestinal tract.

Phenipentol

It increases the volume of secreted bile (choleretic effect), normalizes the amount of cholesterol and bile acids contained in it, and also contributes to the release of bile (cholekinetic effect). Its action is mediated through the excitation of receptors of the intestinal mucosa and reflex stimulation of bile secretion. An increase in the secretion of bile acids activates the pancreatic juice lipase and improves the emulsification of fats with the subsequent normalization of their absorption. It inhibits the

formation of gallstones and cholesterol stones mainly due to an increase in the osmotic filtration of water and electrolytes into the bile ducts. It also helps to facilitate the release of bile into the intestines.

Phenipentol® is indicated for fermentative, putrefactive dyspepsia, for chronic diseases of the gall bladder, liver and pancreas. The drug is prescribed orally 200 mg 3 times a day immediately before meals, drinking at least 200 ml of water. Among the side effects, discomfort in the epigastric region (feeling of fullness, overflow, pressure), nausea, heartburn, flatulence, allergic reactions are noted. Phenipentol® is contraindicated in case of hypersensitivity to it, acute hepatitis with obstruction of the biliary tract, acute cholecystitis, cholangitis, acute pancreatitis, empyema of the gallbladder. Use with caution during pregnancy and in childhood.

Herbal preparations

Barberry ordinary (Berberis vulgaris)

A dosage form in the form of alcohol tincture is used. Contains alkaloid berberine (isoquinoline derivative) from the roots and leaves of barberry

It enhances bile formation (choleretic effect) and facilitates the secretion of bile (cholekinetic effect). In addition, berberine has a wide range of pharmacological effects: it reduces blood pressure and heart rate, and causes uterine contractions. Previously used to treat leishmaniasis and malaria. The choleretic effect is also exerted by tincture from the leaves of the Amur barberry (Tinctura foliorum Berberis amurensis), which in addition to berberine also contains other alkaloids. Tincture is prepared at the rate of 1: 5 on 40% alcohol. Assign 15-20 drops 2-3 times a day.

Berberine bisulfate

It is a derivative of barberine in tablet form. It has choleretic and cholekinetic properties. It is used as a choleretic agent for chronic hepatitis, cholecystitis, cholelithiasis. Take orally at 0.005-0.01 g (1-2 tablets) 3 times a day before meals. The course of treatment is 2-4 weeks. Barberin preparations are contraindicated during pregnancy.

Immortelle sand

The flavonoids contained in the immortelle lead to increased secretion of bile, gastric and pancreatic juice, improve the composition of bile, help to slow the peristalsis of the stomach and intestines, increase urine output and increase the urge to urinate. Immortelle sand also has a bactericidal effect. It is indicated for gallstone disease, chronic cholecystitis and hepatitis, biliary dyskinesia. In practice, various dosage forms are used. They are represented by infusions, decoctions, as well as tablet forms. The broth is prepared at the rate of 6.0-12.0 g of dry matter per 200 ml of water. Assign 0.5 cups in a warm form 2-3 times a day for half an hour before meals. It does not give side effects even with prolonged use.

Flaming

Flamingin * is a tablet form of a dry concentrate of immortelle sand, containing the sum of flavonoids. Used for chronic cholecystitis, hepatocholecystitis, biliary dyskinesia. Adults are prescribed at 0.005 (1 tablet) 3 times a day 30 minutes before meals (with a small amount of warm water, since the drug is difficult to dissolve in cold water). The course of treatment is from 10 to 40 days, depending on the course of the disease. For use in pediatric practice, flam-on * granules are prepared for the preparation of a suspension. They are packed in glass jars with a capacity of 150 ml, containing 18.4 g of granules. The granules include flaming (0.18 g), pectin (1 g), citric acid (0.1 g), sorbic acid and sugar (up to 18.4 g). To prepare the dosage form, freshly boiled and cooled to room temperature (to the mark of 100 ml) water is added to the contents of the can, and shaken until a uniform suspension is formed. Give children in the following doses: from 1 month to 1 year - a

single 2.5 ml, daily - up to 7.5 ml; 1-3 years - single 5 ml, daily - 15 ml; 4-5 years - single 7.5 ml, daily - 22.5 ml; older than 5 years - a single 10 ml, daily - 30 ml. The course of treatment is 10-14 days.

Corn stigmas

Corn columns with stigmas are collected during the ripening cobs of corn. The composition of this plant raw material includes such active substances as sitosterol, stigmasterol, fatty and essential oils, saponins, vitamin K. Corn stigmas serve as a choleretic and diuretic, they are used for chronic cholecystitis, cholangitis, and for disorders of bile secretion. The drug enhances the secretion of bile, reduces its viscosity, reduces the content in bilirubin, reduces the tone of the sphincter of Oddi, and also increases the content of prothrombin in the blood and increases blood coagulation due to the presence of vitamin K.

Tansy ordinary

It is used in the form of an alcoholic extract from leaves and flowers. The action consists in enhancing the secretion of bile, increasing the tone of the gallbladder, reducing the viscosity of bile. It has an analgesic and antimicrobial effect.

It also has a pronounced anti-giardic effect. Apply 1 tablespoon 2-4 times for 15-20 days.

Tansy common flower extract (Tanaceholex)

Tanacechol is a preparation obtained from the flowers of common tansy (Tanacetum vulgare L.). It enhances the secretion and secretion of bile, has an antispasmodic effect on the gallbladder and bile ducts. It is used in adults as a choleretic and antispasmodic agent for chronic cholecystitis, biliary dyskinesia. Assign inside after meals at 0.05-0.1 g (1-2 tablets) 3-4 times a day. The course of treatment is 20-30 days. When using tanacechol * allergic reactions are possible.

Rosehip Fruit Extract (Holosas)

The drug is a concentrated aqueous extract from the fruits of brown rose hips. Apply 1 teaspoon 3 times a day. It increases the secretion of bile and the content of bile acids in it, reduces the tone of the common bile duct and sphincter of Oddi, and facilitates the exit of bile into the duodenum.

Artichoke leaf extract (hofitol)

It is an aqueous extract of fresh leaves of the field artichoke (Cynara scolymus). Plant materials contain ascorbic acid, carotene, vitamins B1 and B2, as well as other active substances. They contribute to the normalization of metabolism in the body. The drug has choleretic, hepatoprotective and diuretic properties, reduces blood urea, has a detoxifying effect on the liver and kidney parenchyma during antibiotic treatment, and promotes the release of toxins from the body (including nitro compounds, alkaloids, salts of heavy metals).

Drugs that increase bile secretion due to the aqueous component (hydrocholeretics)

1. Sodium salicylate.

2. Mineral waters.

Hydrocarbonate-chloride-sodium water “Essentuki” No. 4, 17, 20, “Izhevskaya”, “Slavyanovskaya”, “Smirnovskaya”, “Narzan”, “Naftusya” and others belong to mineral waters with hydrocholeretic effect. Artificial Karlovy Vary salt * and Morshyn laxative salt * also have similar effects. With the hypertonic-hyperkinetic form of dyskinesia, mineral waters of a low degree of mineralization are prescribed ("Slavyanovskaya",

"Smirnovskaya", "Essentuki" No. 4 and 20, "Narzan", etc.). Apply preheated to 40-45 ° C fractionally, 5-6 doses per day, or 45 minutes before meals, in an amount of 100-150 ml. In the hypotonic-hypokinetic form of dyskinesia, mineralized waters of a high degree of mineralization (Essentuki No. 17) are recommended in the form of cold or warmed up to 25 ° C, 200-250 ml 2-3 times a day 30-90 minutes before meals. It is better to start taking water with 50-100 ml, gradually increasing to a full volume. In case of gallstone disease, it is recommended to take “Naftusya” water, which has a weak choleretic effect, in the form heated to 40-45 ° C.

General mechanism of action and basic pharmacodynamic effects of cholekinetics

The action of this group of drugs is associated with an increase in the tone of the gallbladder, as well as a decrease in the tone of the bile ducts and sphincter of Oddi. It is believed that cholekinetics irritate the mucosal interoreceptors of the duodenum, in the specialized cells of which cholecystokinin (pancreosimin) is produced - a hormone whose molecule consists of 33 amino acid residues. The main effects of this hormone are a powerful increase in the motility of the gallbladder and a significant stimulation of pancreatic secretion of enzymes. Synchronized with the contraction of the gallbladder, the relaxation of the sphincter of Oddi promotes the flow of bile into the duodenum, and pancreatic enzymes stimulated by the endogenous or exogenous hormone are released there. This creates optimal conditions for the breakdown of food.

General indications

Preparations of this group are used during duodenal sounding, X-ray and ultrasound examinations, as well as in the complex treatment of cholecystitis, dyskinesia and other biliary tract diseases.

Features of the action and dosage regimen of various drugs

Magnesium sulfate

Magnesium sulfate irritates the nerve endings of the mucous membrane of the duodenum, has an antispasmodic and choleretic effect. Often used for duodenal sounding.

(50 ml of a 30% solution). As a therapeutic agent, a 25% solution is prescribed (1 tablespoon 3 times a day).

Polyols

Sorbitol (sorbitol), xylitol, mannitol (mannitol), militet have a cholekinetic effect, cause the gallbladder to contract and relax the sphincter of Oddi. Magnesium sulfate is superior in cholekinetic activity. Sorbitol stimulates the production of endogenous cholecystokinin, increases the bacterial synthesis of vitamins B1 and B2, enhances the absorption of vitamin B12. Recommended for duodenal sounding and X-ray examination as a stimulator of motor function of the gallbladder.

Some drugs with a pronounced effect of stimulating bile formation (choleretic effect) are also referred to cholekinetics. These are herbal preparations: barberry preparations (berberine bisulfate *) and synthetic preparations: hydroxymethylnicotinamide, osalmide, phenipentol®. Their description is presented in the section on choleretics.

CLINICAL-PHARMACOLOGICAL APPROACHES TO THE CHOICE AND APPLICATION OF CHOLESPASMOLITIC MEANS (SPASMOLITICIANS)

The main pharmacological effect of drugs of this group is spasmolytic. Relaxation of the tone of the biliary tract leads to the elimination of spasm, improvement of the outflow of bile, reduction or relief of pain. Medicines from this group are used for biliary dyskinesia, cholelithiasis, chronic cholecystitis, cholangitis. However, drugs belonging to this group have a different mechanism of action.

1. Anticholinergics (M-anticholinergics):

- herbal preparations: belladonna leaves;

- synthetic drugs: atropine (atropine sulfate), platifillin (platifillina hydrotartrate *), hyoscine butyl bromide, metocinium iodide, pyrene-zepine.

2. Non-selective myotropic antispasmodics:

- derivatives of isoquinoline (papaverine, drotaverine);

- Xanthine derivatives (theophylline, aminophylline).

3. Various (bencyclan, pinaveria bromide, trimebutin, mebeverin, adifenin, etc.).

CLINICAL PHARMACOLOGY OF ANTICHOLINERGIC MEANS

(M-CHOLIN BLOCKERS)

The main representative of this group is atropine and its alkaloids: homatropin-methylbromide, scopolamine, platyphyllin, metocinium iodide (metacin *) and others. Atropine is a derivative of troponin and is found in plants of the nightshade family: belladonna, bleached, and dope. Therefore, the anticholinergics used

for diseases of the biliary tract, include herbal preparations and synthetic drugs.

The mechanism of action and the main pharmacodynamic effects

Preparations of this group, due to blocking of M-cholinergic receptors and impaired transmission of impulses from postganglionic cholinergic neurons to the effector organs they innervate, have a wide range of pharmacological effects. On the part of the eyes, relaxation of the smooth muscle of the iris and ciliary body is caused. On the cardiovascular system, their effect is expressed in an increase in the frequency of cardiovascular contractions and an improvement in atrial ventricular conduction. Drugs of this group also have a bronchodilatory effect and reduce the secretory function of the bronchi. Reduce the tone of the bladder and uterus. Their action leads to a decrease in the secretory function of the glands of the digestive tract, and a decrease in the tone and peristalsis of the esophagus and stomach. They inhibit the production of mucin, reduce basal, nocturnal and, to a lesser extent, stimulated secretion, which leads to a decrease in the amount and decrease in the total acidity of gastric juice. The drugs have an antispasmodic property, facilitate the passage of bile through the bile ducts, but can increase the tone of the sphincters.

Indications

It is used for diseases of the gastrointestinal tract accompanied by spastic conditions, for example, with peptic ulcer of the stomach and duodenum with concomitant pylorospasm, hyperkinetic biliary dyskinesia, etc.

Side effects

Due to the wide spectrum of action, drugs in this group have a large number of side effects. The weakening of the cholinergic effect, which indirectly enhances the influence of the sympathetic nervous system, causes expansion of the pupils (mydriasis) and increased intraocular pressure due to relaxation of the circular muscles of the iris, as well as accommodation paralysis resulting from paralysis of the ciliary muscle of the eye. Hyperemia of the skin of the eyelids and photophobia are possible. Preparations of this group lead to the development of positive chrono- and inotropic effects, which causes an increase in cardiac output, an increase in blood pressure. There is difficulty urinating, intestinal atony. Side effects of anticholinergics include a sharp decrease in the activity of

the salivary and bronchial glands, drying of the bronchial wall and thickening of sputum. In case of an overdose, psychomotor agitation and acute urinary retention are possible.

Features of the action and dosage regimen of various drugs

Herbal preparations

Belladonna extract

International name: belladonna leaves (Belladonnae folia). It is used in the form of tinctures, rectal suppositories, as well as in the form of plant materials (powder) for the preparation of broth. It has all the characteristic effects described above, side effects and contraindications related to the action of non-selective M-anticholinergics.

Indications for use: peptic ulcer of the stomach and duodenum, cholelithiasis, smooth muscle spasm of the abdominal organs, biliary colic, renal colic, bradycardia, AV block, hemorrhoids, anal fissures.

Dosage and administration: by mouth, for adults, 5-10 drops of tincture 3-4 times a day; children 1-5 drops. The highest dose for adults: single - 0.5 ml (23 drops), daily - 1.5 ml (70 drops). Thick extract is taken in 0.01-0.02 g; the highest single dose - 0.05 g; daily - 0.15 g. Dry extract - 0.02-0.04 g; the highest single dose - 0.1 g, daily - 0.3 g. Rectally, 1 suppository 2-3 times a day; the maximum dose is 10 suppositories per day.

Special instructions: during the treatment period, care must be taken when driving vehicles and engaging in other potentially hazardous activities that require an increased concentration of attention, speed of psychomotor reactions.

Synthetic drugs

Atropine (atropine sulfate

It has a pronounced anticholinergic and antispasmodic effect. Penetrates through the blood-brain barrier. With intravenous administration, the maximum effect develops after 2 minutes, with oral administration - after 30 minutes. With plasma proteins, up to 50% binds. Metabolized in the liver. The half-life is 13-38 hours. Up to 50% of the drug is excreted by the kidneys in unchanged form. For oral administration, 5-8 drops of a 0.1% solution are prescribed 2-3 times a day before meals.

Platifillin (platifillina hydrotartrate)

It is an alkaloid of a romanbolic or broadleaf godson. Quickly absorbed in the gastrointestinal tract. It easily penetrates through histohematological barriers, cell and synaptic membranes. It has an inhibitory effect on vasomotor centers. Stronger than atropine, inhibits the cholinergic systems of the autonomic nerve nodes. When used in large doses, it is able to accumulate in the tissues of the central nervous system, but with the right dose selection it does not cumulate. Excreted by the urinary and digestive systems. With spasms of smooth muscles (relief of pain) subcutaneously 1-2 ml of 0.2% solution. For a course of treatment - inside before meals at 0.003-0.005 g (for children at 0.0002-0.003 g) 2-3 times a day for 15-20 days. Highest doses: single - 0.01 g, daily - 0.03 g.

Hyoscine butyl bromide

It is a quaternary ammonium derivative. It does not penetrate the histohematological barriers; therefore, it does not have an anticholinergic effect on the central nervous system.

It is used as part of the complex treatment of diseases of the gastrointestinal tract, accompanied by spastic conditions.

Metocinia iodide

Quaternary nitrogenous compound. Almost does not penetrate the histohematological barriers, to a lesser extent than atropine, increases the heart rate. It has an antispasmodic effect. Relieves spasm of the esophagus, stomach, intestines. In gastroenterology, it is used for hepatic and renal colic, peptic ulcer

stomach and duodenum, chronic gastritis. For the relief of pain, a parenteral solution of 0.5-2 ml of a 0.1% solution is used.

(intramuscularly, subcutaneously, intravenously). With the course of administration, it is taken orally before meals, 2-5 mg 2-3 times a day for 4 weeks. The highest single dose is 5 mg, daily - 15 mg.

Pirenzepine

Selective blocker of M1-cholinergic receptors. Due to the blockade of these receptors at the level of the intramural ganglia and inhibition of the vagotonic effect, it inhibits the secretion of hydrochloric acid and pepsinogen and only slightly blocks the M-cholinergic receptors of the salivary glands, heart, smooth muscles of the eye and other organs. Pirenzepine reduces basal gastric secretion by 50% when taken orally and by 80% when given intravenously. The antisecretory effect of the drug is more pronounced than the antispasmodic.

It is mainly used for acute and chronic ulcers of the stomach and duodenum, hyperacid conditions, combined with spastic pain. It is administered orally at 50 mg 30 minutes before meals for at least 4 weeks. In severe forms of peptic ulcer, 10 mg is prescribed intravenously 2-3 times a day.

CLINICAL PHARMACOLOGY OF NON-SELECTIVE

MYOTROPIC SPASMOLITICS

A common feature of the drugs of this group is their ability to eliminate spastic contractions (cramps) of smooth muscles, restoring the normal functioning of smooth muscle organs and suppressing pain.

Derivatives of isoquinoline

Their typical representatives are papaverine and drotaverine.

The mechanism of action and the main pharmacodynamic effects

These drugs have antispasmodic and hypotensive properties. The mechanism of their action is realized through the inhibition of phosphodiesterase and the accumulation of cyclic 3,5-AMP, as well as through

a decrease in the intracellular level of calcium ions, which leads to a decrease in tone and relaxation of the smooth muscles of blood vessels and internal organs.

Indications

Spasms of various genesis and localization, cholecystitis, cholangitis, renal and hepatic colic, pylorospasm, spastic colitis. As an additional treatment used for angina pectoris and endarteritis. Also used in gynecology (dysmenorrhea, strong labor pains).

Side effects

In large doses, drugs can reduce myocardial excitability and slow intracardiac conduction, leading to ventricular extrasystoles. May cause constipation, drowsiness, eosinophilia and increase the content of transaminases in the blood.

Contraindications

Hypersensitivity, AV block, glaucoma, impaired liver function, elderly and infants.

Features of the action and dosage regimen of various drugs

Papaverine (papaverine hydrochloride□)

Quickly and completely absorbed by any route of administration. It binds well to plasma proteins. Easily overcomes histohematological barriers. Metabolized in the liver. The elimination half-life is 0.5-2 hours. It is excreted by the kidneys in the form of metabolites. Apply orally at 0.04-0.06 g or subcutaneously, intramuscularly, but 1-2 ml 3-5 times a day. For relief of spasms, an intravenous slow injection of 1 ml of a 2% solution of papaverine (papaverine hydrochloride *) in 10-20 ml of isotonic sodium chloride solution is used.

Drotaverinum (drotaverine hydrochloride)

Fully and rapidly adsorbed from the gastrointestinal tract. The maximum plasma concentration is reached after 2 hours.

With plasma proteins binds to 95-98%. With parenteral administration, the elimination half-life is 2.4 hours. It is excreted mainly by the kidneys, a smaller part with feces. In its action, the drug is close to papaverine, but has a stronger and longer antispasmodic activity. Take inside 0.04-0.08 g (1-2 tablets) 2-3 times a day. If necessary, the same dose (2-4 ml of a 2% solution) is administered intramuscularly. With attacks of hepatic and renal colic and angina, 2-4 ml of a 2% solution is injected slowly.

Xanthine derivatives

Theophylline and aminophylline (aminophylline *) are typical representatives of this group of drugs. Their mechanism of action is associated with the blocking of phosphodiesterase, stabilization of cyclic 3,5-AMP, a decrease in the concentration of intracellular calcium, as well as with blockade of purine (adenosine) P1 receptors. They have a wide range of actions, the main ones are antispasmodic, bronchodilator, anti-asthma, vasodilating, cardiotonic, diuretic. In diseases of the hepatobiliary tract are used as auxiliary drugs.

CLINICAL PHARMACOLOGY OF DRUGS RELATING TO THE “DIFFERENT” GROUP

Bicyclan

It has vasodilating, antispasmodic, as well as moderate local anesthetic and sedative properties. Reduces the tone and motor activity of smooth muscles of internal organs. Virtually no effect on blood pressure. When taken quickly and completely absorbed from the gastrointestinal tract. The maximum concentration in blood plasma after a single dose is achieved after 2-3 hours. It is metabolized in the liver. The elimination half-life is 6–8 hours. It is excreted mainly by the kidneys in the form of inactive metabolites. Its use may be accompanied by dizziness, headache, sleep disturbance, weakness, tremors, agitation, tachycardia and dyspeptic disorders. Assign inside 100-200 mg 1-2 times a day for 3-4 weeks. Maintenance dose - 100 mg 2 times a day. The maximum daily dose is 400 mg.

Pinaveria bromide

An antispasmodic with myotropic and slight M-anticholinergic action. Selectively blocks calcium channels located in the smooth muscles of internal organs (mainly the intestines and biliary tract), reduces the secretion of gastric juice, accelerates the evacuation function of the stomach. When taken orally, less than 10% is absorbed. The maximum concentration in the blood serum is observed after 1

h. About 97% is bound to plasma proteins. Metabolized mainly in the liver. It is excreted mainly with feces, a small part - with urine. It is used for cholecystitis, cholangitis, gastritis.

Trimebutin

The mechanism of antispasmodic action is realized through the enkephalinergic system of the intestine, which helps to regulate peristalsis. It has a stimulating effect in hypokinetic states of smooth musculature of the intestine and antispasmodic in case of hyperkinetic.

Apply inside 100-200 mg 3 times a day. With intramuscular or intravenous administration, a single dose is 50 mg.

Mebeverin

An antispasmodic of myotropic action, has a direct effect on the smooth muscle of the mainly small intestine. Eliminates spasm without affecting normal intestinal motility. It does not have anticholinergic action. When taken orally, it undergoes presystem hydrolysis and is not found in blood plasma.

Metabolized in the liver. It is excreted mainly by the kidneys in the form of metabolites, in small quantities - with bile.

It is indicated for spasm of the organs of the gastrointestinal tract, for intestinal and hepatic colic, for irritable bowel syndrome.

Side effects are allergic reactions and dizziness. Take orally 20 minutes before meals, without chewing and drinking with water, 200 mg 2 times a day.

Adifenin

It has anticholinergic, myotropic, antispasmodic action. Blocks peripheral M-cholinergic receptors. It relaxes the smooth muscles of internal organs and blood vessels, and also causes local anesthesia. It is used for spasms of smooth muscles of the gastrointestinal tract, bile ducts, bronchi.

Contraindications and side effects are the same as for M-anticholinergics. The dose of the drug should be selected individually, usually 0.05-0.1 g 2-4 times a day. The course of treatment is 3-4 weeks.

The advantages of antispasmodic drugs are that they do not directly interfere with the mechanisms of pain, and, therefore, do not complicate the diagnosis of acute surgical pathology.

3. Mineral waters of low mineralization (Essentuki No. 4, 20, Narzan, Smirnovskaya, Slavyanskaya) in warm (hot) form, without gas, 5-6 times a day, 100-150 ml .

ENZYME AND ANTI-ENZYME PREPARATIONS

Enzyme preparations: classification, principles of action and indications for use. The use of antienzyme preparations.

Enzymatic agents are medicines containing enzymes — high molecular weight thermolabile proteins that play the role in the body of biological catalysts in metabolic reactions.

Enzyme classification

1. Peptidases: acidin-pepsin, pepsidil, natural gastric juice.

2. Proteases: crystalline trypsin, chymotrypsin, chymopsin.

3. Nucleases: ribonuclease, deoxyribonuclease.

4. Fibrinolytic enzymes: streptoliasis, alt plaza (actilis), fibrinolysin.

5. Hyaluronidases: lidase, ronidase, collagenase.

6. Polyenzyme agents: pancreatin, festal, wobenzym, panzinorm, me-zim forte.

7. Other enzyme agents: asparaginase, penicillinase, cytochrome C.

Crystalline trypsin breaks peptide bonds in a protein molecule, splitting protein breakdown products, necrotic tissue, and fibrin filaments. Living tissue contains trypsin enzyme inhibitors. After intramuscular administration, the action develops in 25-30 minutes. The drug has an expectorant, anti-inflammatory effect, improves microcirculation, indirectly has an antimicrobial and immunomodulating effect.

Indications for use: inflammatory diseases of the respiratory tract (as a sputum thinner), thrombophlebitis, osteomyelitis, sinusitis, otitis media, burns, pressure sores.

Side effects: pain when injected into the muscle, hyperemia, allergies, tachycardia.

A similar effect is observed in chymotrypsin, ribonuclease, deoxyribonuclease.

Lidase The composition of the drug includes hyaluronidase, which depolymerizes hyaluronic acid, reducing its viscosity, causing an increase in tissue permeability. However, it should be borne in mind that the effect of the drug is reversible. Pharmacokinetics: onset of action in 1-2 hours, half-life - 20-24 hours. I- Indications for use: joint contractures, scars after burns and operations, hematomas.

Side effects: allergic reactions.

A special place is occupied by the enzyme agents of systemic therapy: Voben-zim, phlogenzyme.

Wobenzym contains papain, bromelain, lipase, amylase, trypsin, chymotrypsin, therefore it has anti-inflammatory, decongestant, fibrinolytic, immunomodulatory, secondary analgesic effects, improves microcirculation, rheological properties of the blood, blood supply, tissue oxygenation, exhibits anti-lipid antipyrine action, affects the risk factors for reinfarction.

Indications for use: sinusitis, bronchitis, pneumonia, pancreatitis, ulcerative colitis, Crohn’s disease, multiple sclerosis, thrombophlebitis, inflammatory processes after surgery, gynecological and urological diseases, injuries. Side effects: allergic reactions, changes in the consistency and smell of feces.

Phlogenzyme contains trypsin, bromelain, and reutoside. Main effects: anti-inflammatory, decongestant, helps to reduce pain, reduces blood viscosity, prevents blood clots, improves microcirculation.

Indications for use: acute inflammatory processes, exacerbation of chronic inflammatory diseases, burns, injuries, postoperative inflammation and edema, rheumatic myositis, tendonitis, inflammatory-dystrophic joint diseases in the acute phase.

Side effects: allergic reactions, a feeling of fullness of the stomach, flatulence.

Digestive enzyme preparations - Enzyme preparations are a group of pharmacological agents that help improve the digestion process and include digestive enzymes (enzymes) in their composition.

Examples of enzyme preparations are:

pancreatin: Westal, gastenorm forte, gastenorm forte 10000, creon, creon 10000, creon 25000, creon 40,000, mezim 20,000, mezim forte, mezim forte 10,000, mikrazim, pangrol 10000, pangrol 25000, panzikam, panzim forte, panzinorm forte-N, panzinorm 10,000, panzinorm forte 20,000, pancreasim,

pancrealipase 8000, Kirchner pancreal, pancreatin-concentrate, pancreatin-lect, pancreatin, pancreatin tablets (soluble in the intestines), pancrelipase, pancreas-norm, pancital, fenital n, enzistal-p, hermital

biofestal, digestal, digestal forte, normoenzyme, normoenzyme forte, panolez, ferestal, festal, enzistal, pancreoflat, combicin, chymopsin, enzyme.

1. Insufficiency of abdominal digestion due to:

• pancreatogenic exocrine insufficiency in:

• chronic pancreatitis, pancreatic stones

• subtotal pancreatectomy

• pancreatic cancer

• fistula of the pancreas

• cystic fibrosis

• kwashiorkor

• decrease in enterokinase activity and inactivation of pancreatic enzymes in the intestine with:

• Zollinger-Ellison syndrome

• duodenal ulcer

• duodenitis

• dysbiosis of the small intestine

• impaired transit of intestinal contents and impaired mixing of enzymes with food chyme with:

• duodeno- and gastrostasis

• intestinal pseudo-obstruction

• irritable bowel syndrome

• conditions after vagotomy and drainage operations

• reducing the concentration of enzymes as a result of dilution with:

• postgastroectomy syndrome

• dysbiosis of the small intestine

• a condition after cholecystectomy

• disorders in the production of cholecystokinin, pancreosimine, secretin • deficiency of bile acids in the small intestine, congenital or with:

• biliary obstruction

•severe hepatitis

• primary biliary cirrhosis

• pathology of the terminal small intestine

• dysbiosis of the small intestine

• treatment with cholesterol

• gastrogen deficiency in:

• gastric resection, gastrectomy

• atrophic gastritis

2. Violation of parietal digestion with:

• deficiency of disaccharidases (congenital, acquired lactase or other disaccharidase deficiency)

• violation of the intracellular transport of food components as a result of the death of enterocytes (Crohn's disease, celiac enteropathy, sarcoidosis, radiation, ischemic and other enteritis)

3. Violation of the outflow of lymph from the intestines (obstruction of the lymphatic ducts) with:

• lymphangectasia

• lymphoma

• intestinal tuberculosis

• carcinoid

4. Combined violations with:

• diabetes

• giardiasis

•hyperthyroidism

• hypogammaglobulinemia

• amyloidosis

• AIDS

Almost all of the above conditions, to one degree or another, are indications for the appointment of enzyme therapy.

Despite the variety of causes of digestive upsets, the most severe disorders cause pancreatic diseases, which are accompanied by primary pancreatic insufficiency. It occurs in diseases of the pancreas, combined with insufficiency of its exocrine function (chronic pancreatitis, pancreatic fibrosis, etc.).

In clinical practice, secondary or relative pancreatic insufficiency is more common, usually caused by ingestion of non-ordinary food, its excessive amount or temporary pancreatic functioning disorders. Pancreatic insufficiency limits the absorption of food and can lead to disruption of absorption processes.

Enzyme replacement therapy is the main focus in the treatment of patients with impaired digestion syndrome, especially when it is impossible to eliminate the causes of its development. Currently, in clinical practice there is a large number of enzyme preparations that differ in a combination of components, enzyme activity, production method and release forms.

In clinical practice, the choice and dosage of enzyme preparations are determined by the following main factors:

1. the composition and amount of active digestive enzymes that ensure the breakdown of nutrients

2. form of release of the drug

- ensuring the stability of enzymes to the action of hydrochloric acid
- providing rapid release of enzymes in the duodenum
- providing the release of enzymes in the range of 5-7 units. pH

3. good tolerance and lack of adverse reactions

4. long shelf life

The composition of enzyme preparations

In case of digestive disorders, various drugs containing enzymes are used. Depending on the composition, enzyme preparations can be divided into several groups:

1. Extracts of the gastric mucosa, the main active substance of which is pepsin (abomin, acidinpepsin).

2. Pancreatic enzymes represented by amylase, lipase and trypsin (pancreatin, pancytrate, mesim forte, creon).

3. Combined enzymes containing pancreatin in combination with bile components, hemicellulose and other additional components (digestal, festal, panzinorm-forte, enzistal).

4. Plant enzymes represented by papain, fungal amylase, protease, lipase, and other enzymes (pepphys, oraza)

5. Combined enzymes containing pancreatin in combination with plant enzymes, vitamins (Wobenzym).

6. Disaccharidases (tilactase).

The first group of enzymes is mainly aimed at correcting secretory dysfunction of the stomach. The pepsin, cathepsin, peptidase contained in their composition break down almost all natural proteins. These drugs are used mainly for atrophic gastritis, they should not be prescribed for diseases that occur against a background of normal or increased acid formation. Drugs, including pancreatic enzymes, are used to correct digestive disorders, as well as to regulate the functions of the sub-gastric gland. Traditionally, complex preparations containing the main enzymes of the pancreas of domestic animals (primarily lipase, trypsin, chymotrypsin and amylase) are used for this. These enzymes provide a sufficient spectrum of digestive activity and contribute to stopping the clinical signs of exocrine pancreatic insufficiency, which include a decrease in appetite, nausea, rumbling in the abdomen, flatulence, steato-, creato- and amylorrhea.

The drugs differ in the activity of the components, which should be taken into account when selecting them for a particular patient. The amylase complex decomposes starch and pectins into simple sugars - sucrose and maltose. Amylase breaks down mainly extracellular polysaccharides (starch, glycogen) and practically does not participate in the hydrolysis of plant fiber.

Proteases in enzyme preparations are predominantly chitotrypsin and trypsin. The latter, along with proteolytic activity, is able to inactivate cholecystokinin-releasing factor, resulting in a decrease in blood cholecystokinin and pancreatic secretion by the feedback principle.

In addition, trypsin is an important factor in regulating bowel motility. This is a result of interaction with the RAP-2 receptor enterocytes. Lipase is involved in the hydrolysis of neutral fat in the small intestine.

Combined drugs along with pancreatin contain bile acids, hemicellulase, simethicone, plant choleretic (turmeric), etc.

The introduction of bile acids into the preparation significantly changes its effect on the function of the digestive glands and the motility of the gastrointestinal tract. Preparations containing bile acids increase pancreatic secretion and choleresis, stimulate intestinal and gall bladder motility. Bile acids increase the osmotic pressure of intestinal contents. Under conditions of microbial contamination of the intestine, their deconjugation occurs, which in some cases promotes the activation of cAMP enterocytes with the subsequent development of osmotic and secretory diarrhea.

Combined preparations containing components of bile and hemicellululase create optimal conditions for the rapid and complete breakdown of proteins, fats and carbohydrates in the duodenum and jejunum. The drugs are prescribed for insufficient exocrine pancreatic function, in combination with pathology of the liver, biliary system, with impaired chewing function, a sedentary lifestyle, short-term errors in food

The presence of combined preparations, in addition to pancreatic enzymes, components of bile, pepsin and amino acid hydrochlorides (panzinorm) ensures the normalization of digestion in patients with hypoacid or anacid gastritis. In these patients, as a rule, the functions of the pancreas, bile formation and bile secretion suffer.

Hemicellulase, which is part of some drugs (festal), promotes the breakdown of plant fiber in the lumen of the small intestine, normalization of intestinal microflora.

Many enzyme preparations contain simethicone or dimethicone, which reduce the surface tension of gas bubbles, as a result of which they disintegrate and are absorbed by the walls of the stomach or intestines.

Plant-based enzyme preparations contain papa-in or fungal amylase, protease, lipase (pepphys, oraza). Papain and proteases hydrolyze proteins, fungal amylase - carbohydrates, lipase, respectively - fats.

In addition to the above three groups, there are small groups of combined enzymatic preparations of plant origin in combination with pancreatin, vitamins (Wobenzym) and disaccharidases (tilactase).

The form of release of the drug is an important factor determining the effectiveness of treatment. Most enzyme preparations are available as dragees or tablets in enteric coatings, which protects the enzymes from being released in the stomach and destroyed by hydrochloric acid of gastric juice. The size of most tablets or dragees is 5 mm or more. Nevertheless, it is known that solid particles, the diameter of which is not more than 2 mm, can be evacuated from the stomach simultaneously with food. Larger particles, in particular enzyme preparations in tablets or dragees, are evacuated during the inter-digestive period when the food chyme is absent in the duodenum. As a result, drugs do not mix with food and are not actively involved in digestion.

To ensure fast and homogeneous mixing of enzymes with a food chyme, a new generation of enzyme preparations was created in the form of microtablets (pancytrate) and microspheres (creon, lycrease), the diameter of which does not exceed 2 mm. The preparations are coated with enteric (enteric) membranes and are enclosed in gelatin capsules. When ingested, gelatin capsules dissolve quickly, microtablets mix with food and gradually enter the duodenum. At a pH of the duodenal contents above 5.5, the membranes dissolve and the enzymes begin to act on a large surface. In this case, the physiological processes of digestion are practically reproduced, when pancreatic juice is secreted in portions in response to periodic intake of food from the stomach.

Brief pharmacological characteristics

Acidin-pepsin is a drug containing a proteolytic enzyme. Pigs are obtained from the gastric mucosa. Tablets of 0.5 and 0.25 g contain 1 part pepsin, 4 parts acidin (betaine hydrochloride). They are prescribed for hypo- and anacid gastritis, 0.5 g 3-4 times a day with meals. Do tablets dissolve in? glasses of water.

Wobenzym is a combined preparation containing highly active enzymes of plant and animal origin. In addition to pancreatin, it contains papain (from the Carica Papaya plant), bromelain (from ordinary pineapple) and rutoside (vitamin P group). It occupies a special place in the series of enzyme preparations, since Along with pronounced enzymatic properties, it has anti-inflammatory, decongestant, fibrinolytic and secondary analgesic effects. The range of applications is very wide. It is used for pancreatitis, ulcerative colitis, Crohn's disease, injuries, autoimmune oncological, urological, gynecological diseases. The dose is set individually and ranges from 5 to 10 tablets 3 times a day.

Digestal - contains pancreatin, cattle bile extract and hemicellulase. The drug is prescribed for 1-2 tablets 3 times a day during or after meals. Creon is a drug in the gelatin capsule of which contains a large amount of pancreatin in granules resistant to hydrochloric acid. The drug is characterized by rapid (within 4-5 minutes) dissolution of gelatin capsules in the stomach, the release and uniform distribution of granules resistant to gallstone juice throughout the chyme. Granules freely pass through the pyloric sphincter simultaneously with the chyme into the duodenum, completely protect pancreatin enzymes during passage through the acidic environment of the stomach, and are characterized by the rapid release of enzymes when the drug enters the duodenum.

Lycrease is an enzyme preparation based on an extract obtained by grinding, degreasing and drying a fresh or frozen pig’s pancreas. Capsules contain microspheres with a diameter of 1-1.2 mm, containing pancreatin, are stable and not destroyed in the environment of the stomach with a pH below 5.5. For dyspeptic disorders, 1-3 caps. / Day is prescribed. For chronic pancreatitis, 3-6 caps. / Day.

Mezim-forte - is often prescribed for the correction of short-term and minor pancreatic dysfunctions. Mezim-forte tablets are coated with a special glaze coating that protects the components of the drug from the aggressive effects of the acidic environment of the stomach. It is applied 1-3 tablets 3 times a day before meals.

Merkenzyme - a combined drug that contains 400 mg of pan-creatine, 75 units. bromelain and 30 mg bovine bile. Bromelaines are a concentrated mixture of proteolytic enzymes extracted from fresh fruits of pineapple and its branches. The drug is two-layer. The outer layer is bromelain, which is released in the stomach and exhibits a proteolytic effect. The inner layer is resistant to hydrochloric acid of the stomach, enters the small intestine, where pancreatin and bile are released. Bromelaines remain effective over a wide pH range (3-8), and therefore, the drug can be prescribed regardless of the amount of hydrochloric acid in the stomach. Merkenzyme is prescribed 1-2 tablets 3 times a day after meals.

Nygedase is a tablet preparation of 0.02 g each containing a lipolytic enzyme. Obtained from damask blackberry seeds. Nygedase causes hydrolytic breakdown of fats of plant and animal origin. The drug is active in conditions of high and normal acidity of the gastric juice and is half active in conditions of low acidity of the gastric juice. The drug is prescribed orally 1-2 tablets 3 times a day 10-30 minutes before meals. Due to the lack of proteolytic and amylolytic enzymes in the preparation, it is advisable to combine the use of nigedase with the administration of pancreatin.

Oraza is an acid-resistant complex of proteolytic and amylolytic enzymes (from the culture of the fungus Aspergillus oryzae), consisting of amylase, maltase, protease, lipase. The drug does not break down in the stomach, it dissolves in the intestines (at alkaline pH). 0.5-1 teaspoon of granules is

prescribed 3 times a day during or immediately after meals. One teaspoon contains 2 g of granules, which corresponds to 0.2 g of oraza.

Panzinorm - a drug consisting of an extract of the gastric mucosa, an extract of bile, pancreatin, amino acids. The extract of the gastric mucosa contains pepsin and cathepsin with high proteolytic activity, as well as peptides that promote the release of gastrin, the subsequent stimulation of the gastric glands and the release of hydrochloric acid. Panzinorm is a two-layer drug. The outer layer contains pepsin, cathepsin, amino acids. This layer dissolves in the stomach. The inner layer is acid-resistant, soluble in the intestine, contains pancreatin and bile extract. Panzinorm has a substitutional and digestive stimulating effect. The drug is taken in 1-2 tablets during meals 3-4 times a day.

Pancreatin is an enzymatic agent from cattle pancreas, contains lipase, protease, amylase. Release form: dragees. Assign 1-3 tablets before meals.

Indications for use: replacement therapy, achilia, insufficient pancreatic function, anacid gastritis, dyspepsia, enterocolitis.

Side effects: exacerbation of gout.

The daily dose of pancreatin is 5-10 g. Pancreatin is taken 1 g 3-6 times a day before meals.

Pancurmen is a combined preparation, in 1 tablet of which contains pancreatin and turmeric extract (choleretic agent). Take 1-2 tablets before meals 3 times a day.

Pancytrate is a new generation drug with a high content of pancreatin. Has pharmacodynamics similar to creon. Gelatin capsules contain microtablets in a special enteric coating resistant to gastric juice, which guarantees the release of all enzymes in the intestine. It is prescribed 1 capsule 3 times a day. Pepphiz - contains plant enzymes (papain, diastase) and simethicone. Unlike other enzyme preparations, pepfiz is available in the form of effervescent soluble tablets with an orange flavor, which, when dissolved in water, release sodium and potassium citrate. They neutralize hydrochloric acid in the stomach and reduce heartburn. The drug is used in case of a hangover syndrome, overeating, heavy drinking of beer, coffee, kvass, gas-containing drinks, foods rich in carbohydrates, a sharp change in the nature of nutrition. Apply 1 tablet 2-3 times a day after meals.

Solisim, a lipolytic enzyme obtained from Perucillium solitum, hydrolyzes plant and animal fats, which leads to the relief of steatorrhea, normalization of the content of total lipids and lipase activity of blood serum. The drug is taken in 2 tablets (40,000 LU) 3 times a day during or immediately after a meal. Tilactase is a digestive enzyme that is a lactase that is located in the brush border of the jejunum mucosa and proximal ileum. Breaks down lactose into simple sugars. Assign inside of 250-500 mg before consuming milk or dairy products. The drug can be added to foods containing lactose.

Festal, enzystal, panzistal - combined enzyme preparations containing the main components of the pancreas, bile and hemicellulase. Apply 1-3 dragees with meals 3 times a day.

Festal contains three digestive enzymes (lipase, amylase, protease), in addition, bile acids, which improve the digestion of fats, stimulate the biliary and biliary functions of the liver, increase the permeability of cell membranes. Hemicellulose, also present in the preparation, improves the motor function of the stomach and intestines, binds toxic waste products of intestinal bacteria. Festal should be recognized as one of the most successful enzymatic combination drugs that improve digestion. They take the festival for 1-3 tablets during or immediately after a meal. The number of doses of the drug depends on the number of meals. Similar combinations are found in enzistal, digestal, mesim fort, etc. There are also drugs with improved pharmacokinetics (creon, Kirchner pancreal, panzinorm). In medical practice, digestive enzymes are used in individuals with insufficient gastric secretion, with insufficient pancreatic function, with digestive disorders, atrophic gastritis, chronic colitis, and eating disorders. Digestive enzymes are contraindicated for individuals with increased

gastric secretion (with increased acidity), as they can aggravate the disorders associated with increased aggressiveness of the gastric juice.

Clinical features of application

One of the important factors determining the success of treatment is the correct choice of the enzyme preparation, its dose and duration of treatment. When choosing a drug, the nature of the disease and the mechanisms underlying the digestive disorder are taken into account. The choice of the dose of the enzyme preparation is determined by the severity of the underlying disease and the degree of functional disorders of the damaged organ. So, the use of medium-active pancreatic enzymes is advisable in "borderline" conditions, when there are minor violations of the pancreas, accompanying various diseases of the upper digestive tract or occurring with errors in food, overeating, alcohol excesses.

In this case, patients present subjective complaints of a certain indisposition, occasionally occurring nausea, heaviness in the abdomen after eating. Similar symptoms occur when you overeat, take unusual, "unfamiliar" food. This is especially common in people who are on holiday away from their usual places of residence. A new diet, a new mineral composition of water and products cause digestive disorders. After 20-30 minutes after eating, short-term aching or pressing pain in the umbilical region can sometimes occur. In addition, there may be a short-term disorder of the stool in the form of its softening (the so-called "travelers diarrhea"), flutulence appears. However, with an objective clinical and laboratory examination, any pronounced changes, as a rule, are not determined.

The appointment of large doses or highly active enzymes is advisable for replacement therapy in patients with chronic pancreatitis. In this case, the dose of enzymes depends on the degree of exocrine insufficiency, as well as individual eating habits and the patient's desire to follow a diet. With mild steatorrhea, not accompanied by diarrhea and weight loss, digestion correction is achieved by a low-fat diet or 10,000 pansitrate. It is extremely important to consider that the dose of enzyme preparations depends on the degree of pancreatic insufficiency and on the content of lipase in the preparation. When enzymes enter the small intestine, their activity drops sharply and, already behind the Treitz ligament, only 22% trypsin and 8% lipase remain active. Consequently, even with moderate pancreatic insufficiency, lipase deficiency occurs.

With steatorrhea, more than 15 g of fat per day, as well as in the presence of diarrhea and weight loss, as a rule, the diet does not give a significant effect. Such patients are shown the appointment of capsules of pancitrate or creon containing 25,000 lipases at each meal. In this case, you can expand the diet to include predominantly vegetable fats up to 60-70 g / day. Nevertheless, in some patients, symptoms of digestive disorders persist even when using high doses of enzymes. A further increase in dose, in most cases, does not improve treatment outcomes.

The main reasons for the ineffectiveness of enzyme therapy are:

• inactivation of enzymes in the duodenum as a result of acidification of its contents;

• concomitant diseases of the small intestine (helminthic invasions, intestinal dysbiosis, etc.);

• duodenostasis;

• non-compliance by patients with the recommended treatment regimen;

• use of enzymes that have lost their activity.

The activity of enzyme preparations to a large extent depends on factors such as intraduodenal pH and small intestine motility, which provide optimal duration of contact of the enzymes with food chemicals. With a decrease in pH in the duodenum less than 4, irreversible inactivation of lipase occurs, less than 3.5 - trypsin. At pH less than 5, precipitation of bile salts is observed, which is

accompanied by impaired emulsification of fats, a decrease in the number of micelles of bile and fatty acids, and a decrease in their absorption.

The main causes of duodenal acidification are increased secretion of hydrochloric acid, decreased secretion of bicarbonates. In these cases, together with enzyme preparations, H2 histamine receptor blockers (ranitidine, famotidine) or proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, rabeprazole) are used to increase the intraduodenal pH. Doses of drugs and duration of treatment are determined individually depending on the leading mechanism of this violation. Small bowel motility disorders are also accompanied by impaired mixing of enzyme preparations with the food chyme, which reduces their effectiveness. The use of microtableted and microspherical preparations (pancytrate, creon, lycrease), as well as the additional use of agents that normalize intestinal motility (antispasmodics, prokinetics), can significantly improve treatment results

With dysbiosis of the small intestine, the effectiveness of enzyme therapy can be increased by prescribing eubiotics for decontamination of the small intestine.

The choice of combined enzyme preparations is important when combining diseases of the biliary system and liver with digestive disorders. Nevertheless, it must be remembered that the use of drugs with bile acids can increase intoxication in severe chronic hepatitis and cirrhosis. In case of chronic diarrhea syndrome, in conditions of secondary malabsorption of bile acids in the intestine, their additional administration can increase diarrhea. In patients with duodenogastric reflux, the use of enzyme preparations containing bile acids (festal, digestal, panzystal, etc.) in their composition are not advisable, since under these conditions bile acids enhance the damaging effect of reflux on the gastric mucosa. At present, it has been established that with exacerbation of chronic pancreatitis, substitution therapy with enzymes promotes reverse inhibition of gland secretion, and reduces hypertension in the ducts, as a result of which an analgesic effect is noted.

It is important to consider that in chronic pancreatitis, enzyme preparations should not lower the pH of the stomach, stimulate pancreatic secretion and increase diarrhea. The drugs of choice in such cases are those that do not contain bile and extracts of the gastric mucosa (pancreatin, somilase, solisim, triferment, creon, pancytrate, etc.). In hyperacid conditions, it is pathogenetically unreasonable to include dosage forms containing gastric juice components (panzinorm) in complex therapy. The use of panzinorm for hyperacid gastritis, peptic ulcer increases the activity of proteolytic enzymes, increases the acidity of the stomach, which clinically can manifest such a debilitating symptom as heartburn.

Correction of creatorrhea requires lower doses of drugs, since the secretion of pancreatic proteases remains preserved for a long time even with pronounced structural changes in the pancreas. In addition, in oral enzyme preparations, lipase activity, and then protease, is primarily reduced. Enzyme preparations for CP with exocrine insufficiency are prescribed for a very long time, often for life. Their doses can be reduced by following a strict diet with a restriction of fat and protein and should increase with the expansion of the diet.

The effectiveness of treatment with enzyme preparations is evaluated clinically and by laboratory diagnostic methods. In this case, the most informative coprological examination of feces and tests based on the determination of the excretion of fat with feces. The studies are carried out according to the Van de Chamber method (quantitative determination of fats in feces), infrared spectrophotometry, radioisotope and other methods.

Currently, to assess exocrine pancreatic insufficiency, an elastase test has become widespread. Unlike existing non-invasive tests, an elastase test allows you to identify endocrine pancreatic insufficiency in the early stages of the disease. Elastase in feces most reliably reflects exocrine pancreatic insufficiency, because unlike other enzymes, it does not inactivate during transit through the intestines. A standard elastase coprological test contains monoclonal antibodies to human pancreatic elastase.

Tolerance and side effects

Side effects when using enzyme preparations are extremely rare (less than 1%) and are most often dose-dependent in nature.

In the urine of patients using high doses of pancreatic enzymes, elevated uric acid levels may be observed. Hyperuricosuria contributes to the precipitation of uric acid in the tubular apparatus of the kidney, forms the conditions for the development of urolithiasis. In patients with cystic fibrosis, for a long time using high doses of pancreatic enzymes, the development of interstitial fibrosis is possible. With celiac disease, against the background of atrophy of the mucous membrane of the small intestine in the blood of patients, the exchange of purine bases changes dramatically with the accumulation of high concentrations of uric acid and an increase in its excretion. With caution, enzyme preparations are used in patients with gout. In some cases, patients taking enzymes may be disturbing diarrhea, constipation, discomfort in the stomach, nausea, irritation of the perianal region. The main contraindications for the administration of enzyme preparations containing bile components are acute and chronic pancreatitis, acute and severe chronic liver diseases, diarrhea, inflammatory bowel diseases, an allergic reaction in the history of pork or beef.

Thus, therapy with enzyme preparations should be carried out differentially, taking into account the mechanism of the development of the disease, which is the basis of digestive disorders. The presence of highly active microtableted and microgranular drugs at the doctor's disposal can significantly increase the effectiveness of enzyme treatment.

ANTI-ENZYME PREPARATIONS (ENZYME INHIBITORS).

Medicines used to suppress enzyme activity are called enzyme inhibitors.

Classification

1. Proteinase inhibitors: contracal.

2. Inhibitors of fibrinolysis: amino-caproic acid.

3. Anticholinesterase drugs: proserin, physostigmine salicylate, galantamine hydrobromide, etc.

4. MAO inhibitors: nialamide.

5. Inhibitors of carbonic anhydrase: diacarb.

6. Xanthine oxidase inhibitors: allopurinol.

7. Inhibitors of acetaldehydrogenase: cyamide, teturam (disulfiram), etc.

Kontrikal - an antienzyme drug that inhibits the activity of trypsin, kallikrein, plasmin. Pharmacokinetics: with intravenous administration, the action develops in 10-15 minutes.

Indications for use: acute pancreatitis, pancreatic necrosis in combination with heparin in the acute period of myocardial infarction. Contraindications: with caution in persons prone to allergic reactions. Side effects: allergic reactions.

The purpose of the lesson:

To learn:

I. Classification of choleretics and cholekinetics

I. Drugs stimulating bile formation - choleretics

A. Increasing the secretion of bile and the formation of bile acids (true choleretics):

1) preparations containing bile acids: Allochol, Cholenzym, Vigeratin, dehydrocholic acid (Hologon *) and sodium salt of dehydrocholic acid (Deholin *), Lyobil *, etc .;

2) synthetic drugs: hydroxymethylnicotinamide (Nicodine), osalmide (Oxafenamide), cyclovalone (Cycalvalon), gimekromon (Odeston, Holonerton *, Cholestil *);

3) herbal preparations: flowers of the immortelle sand-dog, corn stigmas, tansy (Tanacehol), rose hips (Holosas), Berberine bisulfate, buds of birch, blue cornflower flowers, oregano grass, sweet oil, turpentine oil, peppermint oil, scumpia leaves (Flacumin), Far Eastern lily of the valley grass (Convaflavin), turmeric root (Febichol *), buckthorn, etc.

. Drugs that increase bile secretion due to the aqueous component (hydrocholeretics): mineral waters, sodium salicylate, valerian preparations.

II. Biliary stimulants

a) Cholekinetics - increase the tone of the gallbladder and reduce the tone of the biliary tract: cholecystokinin *, magnesium sulfate, pituitrin *, cholesterin *, barberry preparations, sorbitol, mannitol, xylitol.

b) Cholespasmolytics - cause relaxation of the bile ducts: atropine, platifillin, metocinium iodide (Metacin), ex-tract of belladonna, papaverine, drotaverin (No-shpa), mebeverin (Duspatalin), aminophylline (Eufillin), Olimetin.

II. To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of enzyme and antiferment drugs

III. Classification of enzyme and antienzyme preparations

1. Peptidases: acidin-pepsin, pepsidil, natural gastric juice.

2. Proteases: crystalline trypsin, chymotrypsin, chymopsin.

3. Nucleases: ribonuclease, deoxyribonuclease.

4. Fibrinolytic enzymes: streptoliasis, alta plaza (actilose), fibrinolysin.

5. Hyaluronidases: lidase, ronidase, collagenase.

6. Polyenzyme agents: pancreatin, festal, wobenzym, panzi-norm, mezim forte.

7. Other enzyme drugs

1) Drugs used mainly in purulent-necrotic processes, trypsin, chymotrypsin, chymopsin, terrylitin, deoxyribonuclease, collagenase, profesim, etc .;

Drugs used to improve the digestion of pepsin, gastric juice, abomin, oraza, pancreatin, panzinorm, festal, mezim forte, etc .;

3) Fibrinolytic drugs fibrinolysin, streptokinase, strepto-decase, urokinase, alteplase;

4) Various enzyme preparations of lidase, cytochrome C, penicillinase, ac paraginase.

Enzyme inhibitors.

1) Inhibitors of proteinases kontrikal, gordoks;

2) Inhibitors of fibrinolysis, aminocaproic acid;

3) Anticholinesterase drugs proserin, physostigmine, galantamine;

4) MAO inhibitors iprazide, nialamide;

5) Diacarb carbonic anhydrase inhibitors;

6) Xanthine oxidase inhibitors allopurinol;

7) Inhibitors of acetaldehyde oxidase cyamide, teturam.

8) ACE inhibitors - captopril, enalapril

9) Aminocaproic acid and aminomethylbenzoic acid fibrinolysis inhibitors (amben)

a) Animal origin

pepsin, trypsin, chymotrypsin

b) Microbial origin

terrilitin, hygrolithin, streptokinase

c) Plant origin

d) papain, bromelain.

other ribonuclease or deoxyribonuclease, lidase, ronidase

Know:

1. Etiology, pathogenesis, clinical features, complications, cholecystitis, pancretitis

2. Research methods for cholecystitis, pancretitis

3. The main etiological factors and pathogenetic mechanisms that are the object of drug exposure

4. Pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics, the interaction of the above drugs

5. The principles of complex therapy - hypoacid gastritis, dysbiosis

3. Be able to:

a) select the necessary drugs for a particular patient with the indicated pathology, select criteria for therapeutic efficacy and safety;

b) prescribe combination therapy;

Control questions of the studied topic.

1. What processes improvement do you expect when using enzyme drugs?

2. What are the pharmacodynamics of enzyme inhibitors? Choose and justify the methods of administration.

3. What is the risk of possible undesirable consequences of the use of enzyme preparations and enzyme inhibitors?

4. What are the features of the use of fibrinolytic therapy in acute thrombosis?

5. What is common in the use of contracal and streptokinase?

6. What are the main features of the action of lipase?

7. What enzyme preparations are important in the treatment of purulent-necrotic processes?

8. On what criteria is the choice of enzyme preparations based?

9. How are proteolytic drugs classified? What are the features of their application?

10. What enzyme and antiferment drugs are used in emergency conditions?

Enumeration of practical work.

Homework.

1. Write down recipes for enzyme and antiferment drugs (one from each group). Indicate the point of application of the action, the spectrum of diseases (syndromes) indicated for their purpose.

2. Indicate and explain possible effective and undesirable combinations of drugs.

Independent practical work in class.

1. To supervise a thematic patient in the ward.

2. To study the working history of the disease (data from laboratory and instrumental studies, conclusions of consultants) and the list of medical appointments.

3. Write a protocol of independent work on the selection and selection of a primary drug for the patient to be supervised and the rationale for the appointment of combined drug therapy.

4. In a subjective and objective study of the patient, highlight the signs characterizing the violation of enzymatic processes. Write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient.

6. Based on the theoretical data of pharmacodynamics and own observations, choose a drug for the patient under supervision.

7. Choose the optimal dosage regimen for the drug taking into account the pharmacokinetics, pathogenesis of the disease, route of administration, age, body weight.

8. To highlight the clinical and instrumental criteria for assessing the effectiveness and safety of the applied drugs, to evaluate.

9. Justify the need for combination drug therapy and suggest possible options for a safe combination of drugs.

10. Make a forecast of side effects of drugs prescribed to the patient, and outline a plan for identifying them in the early stages.

11. Justify the duration of the main and supporting therapy.

12. To make a plan for urgent medical care in acute myocardial infarction, pancreatic necrosis, DIC, pulmonary artery thrombosis, hypertonic crisis.

The list of practical works:

Homework.

1. To study the main tasks and directions of the choice of medicines for cholecystitis, pancretitis

The task for self-checking the initial level.

1. Etiology, pathogenesis, classification of cholecystitis, pancretitis.

2. In case of cholelithiasis, a conservative method of treatment is possible. Explain its pathogenetic mechanisms, name the corresponding drugs.

3. What unites the following drugs: allochol, lyobil, cholenzyme?

4. Specify the features of the action of cholenzyme.

5. What are the most important choleretics of plant origin.

6. List the main groups of drugs for cholecystitis, pancreatitis

7. Formulate the significance of the leading pharmacokinetic characteristics (T1 / 2el,%, association with plasma proteins, \ / d l / kg) in an individual selection of the above-mentioned drugs.

8. Highlight the clinical and laboratory-functional criteria for the therapeutic efficacy of drugs.

9. List the clinical and laboratory safety criteria for the use of drugs in the analyzed clinical syndromes.

Control of the intermediate level of knowledge.

1. The choice of cholekinetic drugs depends on the clinical and pathogenetic features of biliary dyskinesia. Justify the choice of cholekinetics in each variant of the course of the disease.

2. For some types of biliary dyskinesia, the need for combined use of choleretic drugs. What is this option for dyskinesia? Make a combination treatment plan. Can polypharmacy be avoided?

3. Make a plan for urgent relief for hepatic colic. What drug can not be used in this case, explain the reason.

The solution of situational problems.

4. Patient A., 34 years old, was admitted to the hospital with complaints of paroxysmal pain in the left hypochondrium, which appear after a diet violation. The pain is girdle-like, accompanied by nausea, vomiting, diarrhea gives way to constipation, general weakness is noted. On palpation of the abdomen, pain in the left hypochondrium is noted. Attacks are accompanied by an increase in blood amylase and urine diastase, leukocytosis and an increase in ESR. Which disease is most likely described by the clinical picture? Your recommendations regarding the examination and treatment tactics of this patient. Write out the recipes.

5. Patient A., 34 years old, was admitted to the hospital with complaints of paroxysmal pain in the left hypochondrium, which appear after a diet violation. The pain of the sieve is girdling, accompanied by nausea, vomiting, diarrhea, followed by constipation, and general weakness is noted. On palpation of the abdomen, pain in the left hypochondrium is noted. Attacks are accompanied by an increase in blood amylase and urine diastase, leukocytosis and an increase in ESR. What disease most likely corresponds to the described clinical picture? Your recommendations regarding the examination and treatment tactics of this patient. Write out the recipes.

6. Patient D., 42 years old, complains of a feeling of heaviness and pain in the epigastrium, in the left hypochondrium, nausea, belching with air, a mushy stool up to 3-4 times a day. These complaints occur 20-30 minutes after a meal, especially with symptoms of alcohol and diet errors. Objectively: low nutrition, the tongue at the root is covered with a white coating, the abdomen is swollen, painful on palpation in the epigastric region. Blood amylase - 56 mg / (p mL), fecal elastase - 120 μg / g. Ultrasound: the pancreas is enlarged, the contour is fuzzy, the structure is heterogeneous, echogenicity is unevenly increased.

Formulate a preliminary diagnosis. What is the focus pharmacotherapy in this case. Indicate the mechanism of action of the proposed drugs, as well as criteria for their effectiveness.

8. The patient, 38 years old, weighing 65 kg, was admitted to the therapeutic department in connection with the exacerbation of chronic cholecystic pancreatitis. The patient is tormented by epigastric pain, repeated vomiting with bile, severe weakness, dizziness. Objectively: pale, cold, clammy sweat. Respiration is frequent, shallow. AKD - 100/50 mm RT. Art .. Heart rate - 92 in 1 min. The abdomen is painful in the upper half, there are no symptoms of peritoneal irritation, peristalsis is preserved. The doctor on duty prescribed treatment with anticholinergics, antispasmodics, non-narcotic analgesics (all drugs are administered parenterally), in addition, 200 ml of 4% sodium bicarbonate solution is administered intravenously. Contrary to the expectation of the doctor after the measures taken, the patient's condition worsened. Intensified nausea, vomiting, weakness, dizziness, AKD - 90/50 mm RT. Art., heart rate 106 in 1 min.

Explain the reason for the deterioration. What did the doctor on duty not take into account? Treatment tactics

9. With a decrease in the function of the liver cells, many pharmacokinetic processes change.

Explain the clinical effects of propranolol, which has presystemic elimination, in a patient with cirrhosis. Explain the pharmacokinetic features of the use of theophylline, phenobarbital, clindamycin, which have low hepatic clearance.

10. A patient with portal cirrhosis of the liver developed a right-sided lower lobar pneumonia. The use of penicillin at a dose of 1 million 6 times a day had no effect and on the third day the doctor decided to start treatment with erythromycin phosphate at a dose of 0.2 g 2 times a day intravenously. Give an assessment of the situation.

11. Choose a drug for the treatment of severe staphylococcal pneumonia in a patient with chronic hepatitis: benzylpenicillin sodium salt in a daily dose of 20 million; benzylpenicillin sodium salt in a daily dose of 40 million; doxycycline; rifampicin; cefazolin. Explain your actions.

12. A 20-year-old patient, a student, suffered Botkin's disease a year ago and complains of paroxysmal pain in the right hypochondrium. Objectively: sharply expressed pain during palpation of the gallbladder. With cholecystography, an increase in the gallbladder and a slowdown in evacuation were noted. Ultrasound of the abdominal organs showed that the gallbladder was emptied by 20% of the initial volume after a test breakfast.

What is your diagnosis? Variant of the disease. What drugs affecting the function of the gallbladder are indicated for the patient?

13. A 56-year-old patient with excess body weight consulted a general practitioner at the polyclinic complaining of pain in the epigastrium and right hypochondrium, aggravated after fried foods, belching, and dry mouth in the morning. Objectively: the heart, lungs - without features. The abdomen is moderately swollen, soft on palpation. Ortner's symptom is negative. Positive symptom Kera, phrenicus - a symptom. No swelling.

What is your preliminary diagnosis? What is the most important examination to appoint a patient and for what purpose. Outline a treatment plan and explain its steps.

14. A 23-year-old patient with chronic stoneless cholecystitis made cholecystography with a definition of function. Hypomotor hypokinetic dyskinesia of the gallbladder was revealed. Prescribe a treatment.

15. A 59-year-old woman with acute pain syndrome was admitted to the surgical department amid an exacerbation of pancreatitis. What kind of analgesic should be prescribed for the relief of an attack?

16. A 55-year-old patient complains of dull pain in the right hypochondrium, bitterness in the mouth. From the age of 35 he suffers from chronic cholecystitis. A year ago, during the ultrasound examination in the gall bladder, single stones were found - 4-5 mm. What cholekinetic drug is contraindicated in a patient?

17. A patient of 53 years, over the past 15 years, has suffered from chronic cholecystitis. Currently, in connection with an exacerbation of the course of the disease (bitterness in the mouth, nausea, dull pain in the right hypochondrium), a control ultrasound examination of the gallbladder has been performed. Identified a single calculus up to 6 mm in size. Refuses surgical treatment. Which drug is adequate for the patient?

18. A patient with burns of 3-4 degrees of lower legs was delivered to the burn center. To clean the wounds from dead tissue and mucus for local treatment, the doctor prescribed an enzyme preparation. Which one?

19. A patient with signs of acute pancreatitis was admitted to the surgical department of the hospital: vomiting, diarrhea, severe girdle pain in the abdomen, weakness., Hypotension, with signs of dehydration. In the study of urine revealed an increased activity of the enzyme - alpha-amylase. Assign therapy to this patient, taking into account the fact that it is necessary to reduce the activity of pancreatic enzymes.

20. What enzyme preparations are used to completely remove decayed pulp from the canals?

21. Due to the poor bioavailability of bone tissue, electrophoretic methods of administering drugs are widely used to stimulate reparative processes in it during periodontitis. Justify the feasibility and feasibility of introducing enzymes in this way. Which enzyme is most appropriate to introduce electrophoretically?

22. A patient with a clinical picture of acute myocardial infarction was admitted to the cardiac resuscitation department. The period of development of the disease is 3-4 hours. Is it possible to carry out fibrinolytic therapy? If yes, then choose a drug, draw up an administration schedule and justify the dosage. What is this "reperfusion" syndrome? What measures should be envisaged to reduce unwanted effects during fibrinolytic therapy?

TESTS

1. The patient, 20 years old, who is examined and treated in the gastroenterological department, is diagnosed with autoimmune hepatitis. What group of drugs is included in the basic therapy of this disease?

A. Glucocorticoids and cytostatics.

B. Anabolic steroid drugs.

C. Antibacterial drugs.

D. Hepatoprotective drugs.

E. Vitamins.

2. The drug for replacement therapy for pancreatitis.

A. Bromocriptine.

B. Tserukal.

C. Pancreatin.

D. Gastrocepin.

E. De-nol.

3. The patient has small-node cirrhosis of the liver. Over the past 2 years, shortness of breath, edema in the lower extremities, ascites appeared. The patient took hepatoprotectors and glucocorticoids. Which combination of drugs is most appropriate to prescribe?

A. Veroshpiron + ascorutin.

B. Nerabol + furasemide.

C. Lidocaine + hypothiazide.

D. Albumin + ascorutin.

E. Veroshpiron + furosemide.

4. The drug for pancreatonerosis:

A. Pancreatin.

B. Contrikal.

C. Panzinorm.

D. Festal.

E. Betaine.

5. A patient with acute pancreatitis appeared in the surgical department of the hospital: vomiting, diarrhea, severe girdle pain in the abdomen, weakness, hypotension, and dehydration. What drug with antiferment activity is indicated for the patient?

A. Adrenaline

B. Analgin

C. Atropine sulfate

D. Countered

E. Sodium bicarbonate

7. A 58-year-old patient was diagnosed with acute pancreatitis. Contrikal has been prescribed among other drugs. Why in acute pancreatitis is prescribed contracal?

A. Inhibits the activity of hyaluronidase

B. Relaxes the sphincter of Oddi, increases secretion

C. Inhibits trypsin activity

D. Increases trypsinogen secretion

E. Inhibits the secretion of bile

8. The patient, 36 years old, complains of general weakness, irritability, heaviness in the right hypochondrium, subfebrile condition. 4 years ago she had viral hepatitis. These complaints grew over the course of 3 months. Objectively: the liver 3 cm protrudes from under the edge of the costal arch. Laboratory: total bilir-bin - 64.5 mmol / l: direct - 22.7 mmol / l. Gamma globulins - 31%, AST

- 1.42 mmol / h • l, ALT - 1.96 mmol / h • l. Signs of active virus replication were detected (HBeAg - positive reaction). Which drug is most effective for etiotropic treatment?

F. Essential Forte.

A. Alpha interferon.

B. Levamisole.

C. Prednisone.

D. Carsil.

9. The patient has small-node cirrhosis of the liver. Over the past 2 months, shortness of breath, edema in the lower extremities, ascites appeared. The patient took hepatoprotectors and glucocorticoids. What combination of drugs is most appropriate to add to treatment?

F. Aldactone + ascorutin.

A. Nerobol + furosemide.

B. Lidocaine + hypothiazide.

C. Albumin + ascorutin.

D. Spironolactone + furosemide.

10. For laxatives containing anthraglycosides, the following undesirable effects are characteristic with prolonged use.

A. Addiction. Colitis followed by atrophy of the mucosa and muscle membranes.

B. Atony of the intestine and the formation of chronic habitual constipation.

C. Hepatotoxicity, hypokalemia.

D. Staining of sweat, urine, milk: in an acidic environment - in yellow, in alkaline - in red.

E. All of the above effects.

11. Indicate a central action drug that reduces appetite (anorexigenic), used in alimentary obesity.

A. Bromocriptine.

B. Deoxypeganine.

C. Pancreatin.

D. Metoclopramide.

E. Peritol.

12. Indicate the central drug used for anorexia nervosa.

A. Bromocriptine.

B. Deoxypeganine.

C. Pancreatin.

D. Gastrocepin.

E. Peritol.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF INSULIN DRUGS AND ORAL ANTIDIABETIC DRUGS

PHARMACOTHERAPY OF DIABETIC COM

Purpose of the topic

The World Health Organization reports that now in the world 6% of the population is sick with diabetes, this is approximately 284.7 million people, it is less common in children, determining average values within 0.3%. Forecasts for the future are disappointing, according to experts, the number of patients will grow steadily, and by 2030 they will already be 438.4 million. Every year, the number of patients with diabetes increases by approximately 6-10%. Thus, it can be argued that approximately every 15 years the number of patients with diabetes mellitus doubles.

Predisposition to diabetes

The main cause of diabetes is considered a genetic predisposition. If at least one of the parents has diabetes, the child automatically falls into the “risk group”. In such a situation, no precautionary measures will save the disease, but you can recognize its development in a timely manner and immediately choose the right tactic to prevent it from moving to a more difficult stage.

This problem, of course, is one of the most urgent, because diabetes firmly takes its place in the "top three" - diseases that are most often the cause of human death. Only cancer and atherosclerosis are not inferior to it. Doctors sound the alarm and urge all people to be more attentive to their health in order to prevent the disease, or have time to start fighting it at an early stage.

Motivational characteristic of the topic.

With diabetes, a chronic increase in blood sugar level develops, which determines a condition such as hyperglycemia, which occurs due to insufficient secretion of insulin or because of a decrease in the sensitivity of body cells to it.

ETIOLOGY AND PATHOGENESIS OF DIABETES MELLITUS

Type 1 diabetes mellitus (insulin-dependent) is a polyetiological disease. Factors that cause its development often act in combination on a genetically predisposed organism. Several genes take part in the implementation of the action, and only a certain combination of them leads to a tendency to diabetes. The connection between the development of diabetes and HLA - DR3 antigens has been proven; DR4; Dw3; Dw4; B8; B18, Bw15; DQB10302; DQA10301, in the presence of which the risk of developing diabetes increases by 7 to 14 times (the greater the number of antigens, the higher the risk of developing diabetes).

According to modern concepts, IDDM is considered as an autoimmune disease. Against the background of a genetic predisposition, various diabetogenic environmental factors act on b-cells - viruses (Coxsackie, retroviruses, mumps, hepatitis A), toxins, nutritional factors (excessive amounts of nitrates and nitrites in food, etc.), drugs (cimetidine, glucocorticoids, indomethacin, etc.), which lead to the destruction of β-cells. The resulting antigens act on the multinuclear phagocytic system, including it in the immune and inflammatory processes, modulate the immune response through T and B lymphocytes (B lymphocytes produce antibodies, and T lymphocytes produce a growth factor - interleukin IL, g-interferon, tumor necrosis factor). As a result, the production of autoantibodies to b-cells in macrophages is enhanced, which leads to their destruction and the continuation of the autoimmune reaction. When type 1 diabetes lasts up to 5-6 years, b-cells in Langerhans islets disappear almost completely. Clinic of diabetes manifests itself in the destruction of more than 2/3 of b-cells.

The rationale for this theory is:

a) the development of the disease is associated with a system of HLA antigens;

c) there is a close relationship between diabetes and other autoimmune diseases

c) antibodies to b-cells are detected in the blood of patients with diabetes;

e) during histological examination, islet infiltration occurs ymphocytes (mononuclear cells)

f) insulin is observed in the islets.

Due to the action of diabetogenic factors, an increase in free radical oxidation is also observed. Under the influence of free radicals (O2-, NO -), the proteins of the membrane of β-cells denature and autoantigens become, which enhances the autoimmune reaction.

In the pathogenesis of type 2 diabetes, insulin resistance is important.

The reasons for it may be: the presence of antibodies to insulin, an increase in the level of contrainsular hormones, free fatty acids (FFA), ketone bodies.

Insulin resistance distinguish between hepatic and peripheral. When treating with insulin after 3-6 months, there is a restoration of sensitivity to insulin in the liver and, as a result, a decrease in glucose production by the liver, but glucose utilization in peripheral tissues remains reduced.

Type 2 diabetes is also a polyetiological disease, however, the causes of its occurrence and pathogenesis are different from type 1 diabetes.

1. Genetic factor (heredity).

The presence of the above HLA antigens creates a predisposition to the development of diabetes.

2. Decreased insulin sensitivity of the liver and peripheral tissues. This can be congenital or acquired (an increase in the level of contra-hormonal hormones in Itsenko-Cushing's disease, acromegaly, chronic stress, etc.) defects that lead to the development of peripheral insulin resistance. Factors that contribute to the development of insulin resistance are obesity, arterial hypertension, hyperlipidemia, hyperuricemia, a sedentary lifestyle, increased levels of hormones: glucocorticoids, growth hormone, catecholamines, thyroxine, etc.

3. Violation of insulin secretion. At the initial stages, hyperinsulinemia is noted, but subsequently hypoinsulinemia is observed. A decrease in the sensitivity of β cells to glucose leads to impaired insulin secretion (phase 1). In combination with insulin resistance at the periphery (to endo- and exogenous insulin), this leads to constant post-mortem hyperglycemia, which, ultimately, leads to depletion of β-cells.

4. Obesity. Normally, about 50,000 insulin receptors are found on lipocytes. With obesity, not only the sensitivity of the receptors to insulin decreases, but also their number. In the initial stages of hyperinsulinemia, an increase in the absorption of glucose by adipose tissue is observed, which leads to an increase in obesity. However, over time, the number and sensitivity of receptors on adipocytes decreases and, as a result, glucose uptake decreases and hyperglycemia increases.

5. Hyperproduction of contra-hormonal hormones - impaired insulin secretion and hyperglycemia occur according to the mechanisms of action inherent in individual hormones (glucocorticoids increase gluconeogenesis, glycolysis in the liver, reduce glucose permeability through tissue membranes, etc.).

6. A decrease in muscle glycogen synthetase activity is accompanied by an increase in the amount of free glucose in the blood. This leads to hyperinsulinemia and β-cell depletion.

7. Enhanced amylin formation (discovered in 1989, formed in secretory granules together with insulin as a result of intracellular granular degradation).

When diabetes is observed:

deposition of amyloid in the islets of Langerhans as a result of the action of antibodies to amylin;

hyperinsulinemia leads to an increase in the formation of aniline, dysfunction of β-cells and a decrease in insulin production.

Amylin is an antagonist of insulin in the muscles: it reduces glucose uptake, reduces glycogen synthesis, enhances gluconeogenesis, glycogenolysis, glucagon synthesis, and promotes the development of insulin resistance.

8. Toxicity of hyperglycemia. Due to chronic hyperlycemia, β-cell function (insulin secretion) is reduced. With normoglycemia, the synthesis of insulin improves, which explains the phenomenon of the "honeymoon" (improvement of the course and decrease in the dose of insulin in the debut of type 1 diabetes). As a consequence of hyperglycemia:

a) there is resistance to insulin receptors. A decrease in glycemia is accompanied by a decrease in hyperinsulinemia and an increase in the sensitivity of receptors to insulin;

b) the level of glycosylated proteins increases, which leads to tissue damage and an increase in their immunogenicity.

9. The toxicity of hyperinsulinemia. Hyperinsulinemia enhances the proliferation of smooth muscles, increases the synthesis of cholesterol, LDL, reduces the activity of Na-dependent ATPase. These actions contribute to the development of atherosclerosis.

10. Autoimmune factors. Hyperglycemia, hyperinsulinemia change the immunogenicity of tissues, leading to damage and trigger autoimmune processes.

Several factors act simultaneously, which often reinforce each other. The result is:

• Peripheral insulin resistance

• Impaired β-cell function

• Increased glucose formation in the liver

• metabolic disorders in patients with diabetes

The main role in the pathogenesis of diabetes and its complications belongs to the violation of carbohydrate metabolism. Due to insulin deficiency, the permeability of the membranes in the muscles and adipose tissue for glucose and its intracellular metabolism decreases, and glucose production in the liver also increases. The hyperglycemia present in diabetes leads to increased glycosylation of the proteins of cell membranes, primarily blood vessels. Due to an increase in the level of glycosylated hemoglobin (HbA1c) and a decrease in diphosphate in red blood cells, tissue hypoxia occurs at the periphery. Violation of the membrane of capillaries, red blood cells, platelets leads to a violation of hemostasis and blood rheology. Of great importance is the increase in the polyol path of glucose metabolism. If in healthy individuals about 2% of glucose is metabolized in the pentose cycle, then in patients with diabetes this indicator can increase to 6% or more.

An increase in the activity of aldose reductase and sorbitol glucose metabolism leads to an increase in secretion of STH.

Diabetes Risk Factors

An important manifestation of a carbohydrate metabolism disorder in patients with diabetes is glucosuria. In healthy individuals, glucose is practically absent in the urine, since it is reabsorbed from the primary urine in the renal tubules. This process is provided by the enzymes hexokinase and phosphatase. Hyperglycemia leads to increased activity of enzymes, but only to a certain limit (8.9 mmol / l). For insulin deficiency, glucose reabsorption is reduced and glucosuria can occur even with relatively low hyperglycemia, i.e. there is a mismatch between the degree of hyperglycemia and the expressiveness of glucosuria.

Hyperglycemia, due to an increase in the osmotic pressure of the blood and its effect on the central nervous system, also leads to tissue dehydration. Due to tissue dehydration, cellular metabolism is disturbed, thirst (polydipsia) occurs, and diuresis (polyuria) increases. One of the causes of polyuria is also an increase in the osmosis of urine due to glucosuria, and during decompensation and excretion of urinary protein and fat metabolism products (ketone bodies, etc.).

Violation of fat metabolism is a consequence of insulin deficiency and metabolic disorders of carbohydrates, as well as the action of contrainsular hormones. Inhibition of lipogenesis leads to hyperlipidemia and dyslipidemia. An increase in the content of NEFA in the blood of patients with diabetes is a compensatory reaction to a violation of carbohydrate metabolism. Hyperlipidemia is one of the factors of fatty liver. The intake of fat in the liver depleted in glycogen is a manifestation of its adaptation in energy metabolism: due to exhaustion of glycogen as a source of energy, another easily utilized substrate is formed from fat in it - ketone bodies. Thus, fatty liver and ketosis are the result of insulin deficiency. The development of fatty infiltration is promoted, in addition to glycogen depletion of the liver, a diet rich in fats and a lack of lipotropic food factors, excess production of STH and other factors.

A manifestation of decompensation of fat metabolism is ketosis. As a result of hyperketonemia and ketonuria, a violation of the water-salt metabolism occurs, the enzyme systems of the brain are suppressed, followed by the development of the coty.

Violation of fat metabolism is also manifested by hypercholesterolemia - a consequence of increased formation of cholesterol in the liver and a decrease in its breakdown. Its degree depends on the compensation of diabetes and during decompensation, the level of cholesterol can increase to 40 mmol / L.

One of the manifestations of dyslipidemia is an increase in the number of lipids of low and very low density (LDL and VLDL), which are viscoaterogenous. This creates the conditions for the development of atherosclerosis in patients with diabetes. An active role in this is also played by the enhancement of lipid peroxidation (LP), which leads to a violation of the structure and function of cell membranes.

Changes in protein metabolism are mainly manifested by impaired synthesis and increased protein breakdown. With glycogen deficiency, glucose is formed from non-carbohydrate substances: glycerin, lactic acid, amino acids, citric, oxalic, acetic, and ketoglutaric acids. This process is called gluconeogenesis. As a result of disturbed protein metabolism, dysproteinemia occurs (the amount of albumin decreases, the amount of a2-, b- and g-globulins increases), the formation of ammonia, urea and other protein breakdown products increases, which, when decompensated, leads to hyperazotemia and hyperazoturia (ketonuria).

Clinical classification of diabetes mellitus (A.S. Efimov, 1998)

I. Clinical forms:

1. Primary: essential, genetic (with or without obesity)

2. Secondary (symptomatic): pituitary, steroid, tyrogenic, adrenal, pancreatic (inflammation, tumors or removal of the pancreas). bronze (with hemochromatosis).

3. Diabetes of pregnant women (gestational).

4. Violation of tolerance to carbohydrates (latent).

5. Risk factors (prediabetes).

II. Types of diabetes over time:

I type - insulin-dependent

Type II - non-insulin independent

III. Severity: mild, moderate, severe.

IV. Compensation status: compensated, subcompensated, decompensated.

The presence of angiopathies (I - II - III stages) and neuropathies:

1. Microangiopathy - retinopathy, nephropathy, angiopathy (capillaropathy) of the lower extremities or other localization.

2. Macroangiopathy - damage to the vessels of the heart, brain, lower extremities or other localization.

3. Universal micro -, macroangiopathy.

4. Neuropathy (peripheral, autonomic, visceral, encephalopathy).

V. Damage to other organs and systems: hepatopathy, dermopathy, enteropathy, cataract, osteoarthropathy and others.

VI. Acute complications of diabetes:

1. Ketoneemic (ketoacidotic) coma

2. Hyperosmolar coma

3. Hyperlactacidemic coma

4. Hypoglycemic coma.

Clinical characteristics of certain types of diabetes

DIAGNOSTIC OF DIABETES

1. Determination of fasting glycemia and its repeated determination during the day is the main (key) method for diagnosing diabetes.

The diagnosis of diabetes can be made if:

With a two-time determination, fasting glycemia is more than 6.1 mmol / l (110 mg%);

With an arbitrary determination of glycemia in excess of 11.0 mmol / L during the day

A complement to this is the determination of glucosuria per day or fractionally in separate portions.

Indications for a standard glucose tolerance test
1. Temporary carbohydrate metabolism disorders:

• pregnant glucosuria
• hyperglycemia after eating up to 9.9 mmol / l;
• reactive hypoglycemia.
2. The presence of risk factors for diabetes:
• hereditary predisposition;
• overweight;
• pathological pregnancy and childbirth: miscarriages, polyhydramnios, stillbirth, toxicosis of pregnant women, weight of newborns more than 4 kg;
• lesions of peripheral vessels, arterial hypertension;
• chronic infection;
• Dermopathy, retinopathy, and neuropathy of an unexplained cause;
• hyperlipidemia, hyperuricemia.
Standard glucose tolerance test conditions
1. The test is not performed for various intercurrent diseases, injuries of the liver and kidneys.
2. Investigated within three days before the test is on a normal diet (at least 150 g of carbohydrates) and performs the usual physical work.
3. At least 3 days before the test, medicines that affect the test results (corticosteroids, estrogens, saluretics, salicylates), as well as hypoglycemic drugs should be canceled.
4. The test is carried out after night fasting 10-14 hours. Drinking water is allowed.
5. A blood sample for fasting sugar is taken from the examinee, after which he takes 75 g of glucose dissolved in 250-500 ml of water for 5-10 minutes. The second blood sample is taken after 60 minutes, and then after 1 hour. (According to the recommendations of the WHO Expert Committee on diabetes, the main diagnostic criterion for interpreting the oral glucose tolerance test is the glucose level on an empty stomach and after 2 hours. After exercise).
Determination of glycosylated hemoglobin level (HbA1c)
In healthy individuals, the amount of HbA1c is 4-6% of the total amount of hemoglobin. In patients with diabetes, its amount increases significantly depending on the level of hyperglycemia. Allows you to identify the early stages of diabetes (preclinical), since it is possible to diagnose hyperglycemia in the last month. The level of HbA1c> 6.5% approximately corresponds to fasting glycemia> 6.1 mmol / L, and more than 7.5% - glycemia> 7.0 mmol / L.
DIABETES CLINIC
In its development, diabetes usually goes through 3 stages, which are more clearly distinguished in patients with type 2 diabetes.
1. Prediabetes is a condition (the period of a patient’s life) that precedes the disease. Laboratory indicators do not go beyond the norm. Patients often have risk factors for diabetes mellitus:
• the presence of diabetes in relatives (in the presence of diabetes in both relatives, the risk of developing it in children rises to 50%)
• obesity (the risk increases with increasing degree of obesity)
• hyper and dyslipoproteinemia
• the birth of a child with a large (more than 4 kg) body weight - both for the child and the mother (the risk increases with increasing weight)
• in women, glucosuria during pregnancy; miscarriages and stillbirths
• viral diseases
• acute and chronic stress
• atherosclerosis, hypertension
• acute and chronic intoxication
• acute and chronic diseases of the liver and pancreas
• iatrogenic factors (thiazide diuretics, glucocorticoids, etc.)
2. Impaired glucose tolerance (latent diabetes) - a condition in which there is no clinic of diabetes, fasting normoglycemia and aglycosuria. Violation is detected during STG. In patients during this period, the so-called "small symptoms" of diabetes can manifest themselves:
• chronic gingivitis, stomatitis, periodontal disease, tooth loss
• chronic pustular skin diseases, furunculosis

• itching of the skin, genitals
• violation of trophism of the skin, skin injuries, nonhealing for a long time
• unmotivated sexual weakness, menstrual irregularities
• polyneuritis
• cataract

3. Explicit (manifest) diabetes mellitus - a condition when clinical symptoms become manifest, changes in laboratory parameters, primarily hyperglycemia and glucosuria. Clinical symptoms of diabetes, primarily complaints of patients due to the disease itself, its degree of compensation and complications.

In patients observed:
• polydipsia, thirst, dry mouth;
• polyuria, frequent urination, which leads to dehydration:
• muscle weakness, increased fatigue;
• weight loss (type 1 diabetes), weight gain (type 2 diabetes);
• loss of appetite (polyphagy is possible at first)
• leg pain, paresthesia, loss of sensation;
• itching (local - perineum, scalp or generalized);
• impaired vision, impaired sexual function;
• chronic pustular or fungal skin lesions

Depending on the clinic and laboratory parameters, 3 degrees of severity of diabetes are distinguished: mild, moderate and severe

Criteria for the severity of diabetes

By the degree of compensation of metabolic processes, diabetes can be compensated, subcompensated and decompensated.

Compensation is understood as a satisfactory general condition of the patient, preserved performance, absence of complications, normoglycemia, aglycosuria and normal biochemical parameters, achieved under the influence of treatment.

They consider diabetes mellitus to be subcompensated when the patient's condition is satisfactory, but the performance is reduced, complications are not pronounced, against the background of treatment, glycemia is 8-10 mmol / l, glucosuria 20-30 g / l, metabolic disturbances are insignificant, ketoacidosis is absent.

Decompensated diabetes is an expressive clinic of the disease, the patient’s condition is moderate or severe, complications are expressive, hyperglycemia and glucosuria are high, significant metabolic disturbances, ketoacidosis, ketonuria.

Insulin (from lat. Insula - islet) is a protein-peptide hormone produced by β-cells of the pancreatic islets of Langerhans. Under physiological conditions, in β-cells, insulin is formed from preproinsulin, a single-chain protein precursor consisting of 110 amino acid residues. After transferring a rough endoplasmic reticulum through the membrane, a signal peptide of 24 amino acids is cleaved from preproinsulin and proinsulin is formed. The long chain of proinsulin in the Golgi apparatus is packed into granules, where four main amino acid residues are cleaved by hydrolysis to form insulin and the C-terminal peptide (physiological function of the C-peptide is unknown).

The insulin molecule consists of two polypeptide chains. One of them contains 21 amino acid residues (chain A), the second - 30 amino acid residues (chain B). The chains are connected by two disulfide bridges. The third disulfide bridge is formed inside chain A. The total molecular weight of the insulin molecule is about 5700. The amino acid sequence of insulin is considered conservative. Most species have one insulin gene encoding one protein. The exception is rats and mice (each have two insulin genes), they form two insulin, which differ in two amino acid residues of the B chain.

The primary structure of insulin in different species, including and in different mammals, it is somewhat different. The closest to the structure of human insulin is pork insulin, which differs from the human one in one amino acid (in its chain B, instead of the amino acid residue, threonine, the alanine residue is contained). Bovine insulin differs from human insulin in three amino acid residues.

Historical reference. In 1921, Frederick G. Bunting and Charles G. Best, working in the laboratory of John J. R. MacLeod at the University of Toronto, isolated pancreatic extract (as it turned out later,

containing amorphous insulin), which lowered glucose in blood in dogs with experimental diabetes mellitus. In 1922, pancreatic extract was administered to the first patient - 14-year-old Leonard Thompson, a patient with diabetes, and thereby saved his life. In 1923, James B. Collip developed a method for purifying the extract secreted from the pancreas, which subsequently made it possible to obtain active extracts from the pancreas of pigs and cattle that produce reproducible results. In 1923, Bunting and Macle-od were awarded the Nobel Prize in Physiology or Medicine for the discovery of insulin. In 1926, J. Abel and V. Du Vigno received insulin in crystalline form. In 1939, insulin was first approved by the FDA (Food and Drug Administration). Frederick Sanger completely deciphered the amino acid sequence of insulin (1949–1954). In 1958, Sanger was awarded the Nobel Prize for his work on decoding the structure of proteins, especially insulin. In 1963, artificial insulin was synthesized. The first recombinant human insulin was approved by the FDA in 1982. The ultra-short-acting insulin analogue (insulin lispro) was approved by the FDA in 1996.

Mechanism of action. In the implementation of the effects of insulin, the leading role is played by its interaction with specific receptors localized on the plasma membrane of the cell, and the formation of the insulin-receptor complex. In combination with the insulin receptor, insulin enters the cell, where it affects the phosphorylation of cellular proteins and triggers numerous intracellular reactions.

Pharmacological effects of insulin. Insulin has an effect on almost all organs and tissues. However, its main targets are the liver, muscle and adipose tissue.

Endogenous insulin is the most important regulator of carbohydrate metabolism; exogenous insulin is a specific sugar-lowering agent. The effect of insulin on carbohydrate metabolism is due to the fact that it enhances the transport of glucose through the cell membrane and its utilization by tissues, and contributes to the conversion of glucose into glycogen in the liver. Insulin, in addition, inhibits endogenous glucose production by inhibiting glycogenolysis (breaking down glycogen to glucose) and gluconeogenesis (synthesis of glucose from non-carbohydrate sources - for example, amino acids, fatty acids). In addition to hypoglycemic, insulin has a number of other effects.

The effect of insulin on fat metabolism is manifested in the inhibition of lipolysis, which leads to a decrease in the flow of free fatty acids into the bloodstream. In-sulin prevents the formation of ketone bodies in the body. Insulin enhances the synthesis of fatty acids and their subsequent esterification.

Insulin is involved in protein metabolism: it increases the transport of amino acids through the cell membrane, stimulates the synthesis of peptides, reduces the consumption of protein tissues, inhibits the conversion of amino acids to keto acids The action of insulin is accompanied by the activation or inhibition of a number of enzymes: glycogen synthetase, pyruvate dehydrogenase, hexokinase are stimulated, lipases are inhibited (and hydrolyzing lipids of adipose tissue, and lipoprotein in lipase, which reduces the “haze” of blood serum after eating fat-rich foods).

In the physiological regulation of the biosynthesis and secretion of insulin by the pancreas, the main role is played by the concentration of glucose in the blood: with an increase in its content, insulin secretion increases, with a decrease it slows down. In addition to glucose, insulin secretion is influenced by electrolytes (especially Ca2 + ions), amino acids (including leucine and arginine), glucagon, somatostatin.

Pharmacokinetics Insulin preparations are administered subcutaneous, intramuscularly or iv (iv only short-acting insulins are administered and only in diabetic precoma and coma). You can not enter in / in a suspension of insulin. The temperature of the injected insulin should correspond to room temperature, as cold insulin is absorbed more slowly. The most optimal way for continuous insulin therapy in clinical practice is sc administration.

The completeness of absorption and the onset of the effect of insulin depend on the place of administration (usually insulin is injected into the abdomen, thighs, buttocks, upper arms), dose (volume of injected insulin), the concentration of insulin in the drug, etc.

The rate of absorption of insulin into the blood from the injection site depends on a number of factors - such as insulin, injection site, local blood flow rate, local muscle activity, the amount of insulin administered (it is recommended to administer no more than 12-16 units of the drug in one place). Most quickly, insulin enters the blood from the subcutaneous tissue of the anterior abdominal wall, slower from the shoulder, front of the thigh and even slower from the subscapular region and

buttocks. This is due to the degree of vascularization of the subcutaneous fatty tissue of these areas. The profile of insulin action is subject to significant fluctuations in both different people and the same person.

In the blood, insulin binds to alpha and beta globulins, normally 5–25%, but binding may increase during treatment due to the appearance of serum antibodies (production of antibodies to exogenous insulin leads to insulin resistance; when using modern highly purified insulin resistance is rare). T1 / 2 from the blood is less than 10 min. Most of the insulin entering the bloodstream undergoes proteolytic breakdown in the liver and kidneys. It is quickly excreted from the body by the kidneys (60%) and the liver (40%); less than 1.5% is excreted unchanged in urine.

The insulin preparations currently used differ in a number of ways, including by source of origin, duration of action, pH of the solution (acidic and neutral), the presence of preservatives (phenol, cresol, phenol-cresol, methylparaben), insulin concentration - 40, 80, 100, 200, 500 IU / ml.

Classification. Insulin is usually classified by origin (bovine, porcine, human, as well as analogues of human insulin) and duration of action.

Depending on the sources of production, animal insulin is distinguished (mainly porcine insulin preparations), semi-synthetic human insulin preparations (obtained from porcine insulin by enzymatic transformation), human-made insulin preparations (recombinant DNA obtained by genetic engineering).

Insulin activity is determined by the biological method (by the ability to lower blood glucose in rabbits) or by the physicochemical method (by electrophoresis on paper or by chromatography on paper). For one unit of action, or international unit, take the activity of 0.04082 mg of crystalline insulin. The human pancreas contains up to 8 mg of insulin (approximately 200 units).

CLASSIFICATION OF INSULIN DRUGS

1) by origin;

2) by the speed of the onset of effects and their duration;

3) according to the method of purification and degree of purity of the preparations.

I. By origin distinguish:

a) natural (biosynthetic), natural, insulin preparations made from the pancreas of cattle, for example, insulin GPP tape, ultralente MS and more often pigs (e.g. actrapid, insulrap SPP, monotard MS, semelent and other);

b) synthetic or, more precisely, species-specific, human insulin. These drugs are obtained using genetic engineering methods by DNA recombinant technology, and therefore they are most often called DNA recombinant insulin preparations (actrapid NM, homofan, isofan NM, humulin, ultratard NM, monotard NM, etc.).

II. According to the method of purification and purity of the drugs are distinguished:

a) crystallized (poorly purified), but not chromatographed - these are the majority of the so-called "traditional" insulin preparations produced

previously in our country (insulin for injection), but discontinued;

b) crystallized and filtered through gels ("molecular sieve") - the so-called single or mono-peak insulins (actrapid, insulrap, etc.);

c) crystallized and purified by means of a "molecular sieve" and ion exchange chromatography — the so-called monocomponent insulins (ac-trapid MS, semilent MS, monotard MS, ultra-MS).

Crystallized, but non-chromatographed insulins are, as a rule, naturally occurring insulin preparations. They contain various impurities in the form of molecules of proinsulin, glucagon, C-peptide (binding A and B chain of proinsulin), somatostatin and other proteins. In these preparations, the proinsulin content is more than 10,000 particles per million.

Highly purified insulin preparations (by filtration through gels), called monopic, since only one peak is visible on the chromatogram, contains less than 3000 impurities (from 50 to 3000), and even more improved ones are monocomponent - less than 10 particles per a million particles of insulin. Monocomponent preparations are becoming increasingly important.

III. The speed of the onset of effects and their duration distinguish:

a) short-acting drugs (actrapid, actrapid MS, actrapid NM, insulrap, homeopath 40, insuman rapid, etc.). The onset of action of these drugs is in 15-30 minutes, the duration of action is 6-8 hours;

b) drugs of average duration of action (the onset of action after 1-2 hours, the total duration of the effect is 12-16 hours); - semilent MS; - hu-mulin N, humulin tape, homophane; - tape, tape MS, monotard MS (2-4 hours and 20-24 hours, respectively);

• Iletin I NPH, Iletin II NPH;

• insulong SPP, insulin tape GPP, SPP, etc.

c) drugs of medium duration mixed with short-acting insulin: (onset of action 30 minutes; duration - from 10 to 24 hours);

• Actrafan NM;

• Humulin M-1; M-2; M-3; M-4 (duration of action up to 12-16 hours);

• insuman comb. 15/85; 25/75; 50/50 (valid for 10-16 hours).

g) long-acting drugs:

• ultra tape, ultra tape MS, ultra tape NM (up to 28 hours);

• insulin superlente SPP (up to 28 hours);

• humulin ultralente, ultratard NM (up to 24-28 hours).

The duration of action of insulin preparations is divided into short and ultrashort preparations - they mimic the normal physiological secretion of insulin by the pancreas in response to stimulation drugs of medium duration and drugs of long action - imitate basal (background) secretion of insulin, as well as combination drugs (combine both actions).

Currently, human insulin (Humulin - human) is produced in a semi-synthetic way from porcine insulin or in a biosynthetic method using specially grown bacteria or yeast (genetically engineered), which became available to patients only in the last 20 years.

The following groups are distinguished:

Ultra-short-acting insulins (the hypoglycemic effect develops 10–20 min after sc administration, the peak of action is achieved on average in 1-3 hours, the duration of action is 3-5 hours):

- insulin lispro (Humalog);

- insulin aspart (NovoRapid Penfill, NovoRapid Flexpen);

- insulin glulisin (Apidra).

Short-acting insulins (onset of action usually after 30-60 minutes; maximum action after 2-4 hours; duration of action up to 6-8 hours):

- soluble insulin [human genetic engineering] (Actrapid HM, Gensulin R, Rinsulin R, Humulin Regular);

- soluble insulin [human semisynthetic] (Biogulin R, Hu-modar R);

- soluble insulin [pork monocomponent] (Actrapid MS, Mono-Dar, Monosuinsulin MK).

Sustained-release insulin preparations - include drugs of medium duration and long-acting drugs.

Medium-duration insulins (beginning after 1.5–2 hours; peak after 3–12 hours; duration 8–12 hours):

- insulin-isophan [human genetic engineering] (Biosulin N, Gansulin N, Gensulin N, Insuman Bazal GT, Insuran NPH, Protafan NM, Rinsulin NPH, Hu-mulin NPH);

- insulin-isophan [human semi-synthetic] (Biogulin N, Humodar B);

- insulin-isophan [pork monocomponent] (Monodar B, Protafan MS);

- insulin-zinc suspension compound (Monotard MS).

Long-acting insulins (onset after 4–8 hours; peak after 8–18 hours; total duration 20–30 hours):

- insulin glargine (Lantus);

- insulin detemir (Levemir Penfill, Levemir Flexpen).

Combined-action insulin preparations (biphasic drugs) (hypoglycemic effect begins 30 minutes after sc administration, reaches a maximum after 2–8 hours and lasts up to 18–20 hours):

- biphasic insulin [human semisynthetic] (Biogulin 70/30, Hu-modar K25);

- two-phase insulin [human genetic engineering] (Gansulin30R, Gene-sulin M 30, Insuman Comb 25 GT, Mikstard 30 NM, Humulin M3);

- insulin aspart two-phase (NovoMix 30 Penfill, NovoMix 30 Flek-sPen).

Ultra-short-acting insulins are analogues of human insulin. It is known that endogenous insulin in the β-cells of the pancreas, as well as hormone molecules in the produced short-acting insulin solutions, are polymerized and are hexamers. With subcutaneous administration, the hexameric forms are absorbed slowly and it is impossible to create a peak in the concentration of the hormone in the blood, similar to that of a healthy person after eating. The first short-acting insulin analogue, which is absorbed from the subcutaneous tissue 3 times faster than human insulin, was lyspro insulin. Insulin lys-pro is a derivative of human insulin obtained by rearrangement of two amino acid residues in an insulin molecule (lysine and proline at positions 28 and 29 of the B chain). Modification of the insulin molecule disrupts the formation of hexamers and ensures the rapid entry of the drug into the blood. Almost immediately after sc administration of lyspro insulin molecules in the form of hexamers in tissues quickly dissociate into monomers and enter the bloodstream. Another insulin analogue, insulin aspart, was created by replacing proline at position B28 with negatively charged aspartic acid. Like Lyspro insulin, after sc administration, it also rapidly breaks down into monomers. In insulin glulisine, the replacement of the amino acid asparagine of human insulin at position B3 with lysine and lysine at position B29 with glutamic acid also promotes faster absorption. Ultra-short-acting insulin analogs can be administered immediately before or after meals.

Short-acting insulins (also called soluble) are solutions in a buffer with neutral pH values (6.6–8.0). They are intended for subcutaneous, less often - intramuscular administration. If necessary, they are also administered intravenously. They have a quick and relatively short hypoglycemic effect. The effect after subcutaneous injection occurs in 15-20 minutes, reaches a maximum after 2 hours; the total duration of the action is about 6 hours. They are used mainly in the hospital during the establishment of the dose of insulin necessary for the patient, and also when a quick (urgent) effect is required - with diabetic coma and precom. With an intravenous administration, T1 / 2 is 5 min; therefore, with a diabetic ketoacidotic coma, insulin is administered intravenously. Short-acting insulin preparations are also used as anabolic agents and are prescribed, as a rule, in small doses (4-8 units 1-2 times a day).

Medium-duration insulins are worse than soluble, they are slowly absorbed from subcutaneous tissue, as a result of which they have a longer effect. The long-term effect of these drugs is achieved by the presence of a special prolongator - protamine (isofan, protafan, basal) or zinc. Slowing down the absorption of insulin in preparations containing insulin zinc compound suspension is due to the presence of zinc crystals. NPH-insulin (neutral Hagedorn protamine, or isophane) is a suspension consisting of insulin and protamine (protamine is a protein isolated from fish milk) in a stoichiometric ratio.

Long-acting insulins include insulin glargine - an analogue of human insulin obtained by DNA recombinant technology - the first insulin preparation that does not have a pronounced peak of action. Insulin glargine is obtained by two modifications in the insulin molecule: substitution at position 21 of the A chain (asparagine) for glycine and the addition of two arginine residues to the C-terminus of the B chain. The drug is a clear solution with a pH of 4. Acidic pH stabilizes insulin hexamers and provides long-term and predictable absorption of the drug from subcutaneous tissue. However, due to the acidic pH, insulin glargine cannot be combined with short-acting insulins that have a neutral pH. A single injection of insulin glargine provides 24-hour peak-free glycemic control. Most insulin preparations have the so-called. "Peak" action, observed when the concentration of insulin in the blood reaches a maximum. Insulin glargine does not have a pronounced peak, as it is released into the bloodstream at a relatively constant rate.

Long-acting insulin preparations are available in various dosage forms that have a hypoglycemic effect of different durations (from 10 to 36 hours). The prolonged effect reduces the number of daily injections. They are usually produced in the form of suspensions administered only subcutaneously or intramuscularly. In diabetic coma and pre-coma, prolonged drugs are not used.

Combined insulin preparations are suspensions consisting of neutral soluble insulin of short action and insulin-on-isophan (medium duration of action) in certain proportions. Such a combination of insulins of different durations of action in one drug allows you to save the patient from two injections with separate use of drugs.

These are combined preparations, representing a mixture of short-acting insulins and medium-acting durations. Their feature is a two-peak action, in particular, the first peak due to short-acting insulin, the second - medium-acting insulin. Ready-made stable mixtures are available in cans (penfillas) for syringe pens, but you can choose the proportion of the mixture yourself for maximum adaptation to the needs of the patient. The numbers in insulin names mean concentration.

Humulin MZ (France)

Mikstard 10-50 NM Penfill (Denmark)

Insuman Comb (France / Germany)

The leading manufacturers of modern insulin preparations: Eli Lilly (USA), Novo Nordisk (Denmark), Aventis (Hochst Marion Roussel) (France / Germany).

For the convenience of patients with diabetes mellitus, in addition to insulin in vials, syringe pens are issued, into which cans are filled and changed after use (insulin names have the syllable “pen”), and ready-made syringes in the form of disposable pens (they are thrown out after use) . The needles in the syringe pens are much thinner and have double laser sharpening, which makes injections almost painless. In penfillas there is thermostable insulin (stalen for 30 days), so the patient can carry it in his pocket. Penfills free patients from the need to carry syringes and sterilizers with them, which significantly improves the quality of life.

Many research laboratories are conducting studies to develop insulin preparations for non-parenteral administration. In particular, in 1998 a message appeared about the inhalation form of insulin

("diabetic inhalation system"). Also, since 1999, oral insulin preparations - hexilinsulin - have been used in the experiment.

ACTRAPID, obtained from beta cells of pig pancreatic islets, is produced as an official preparation in 10 ml bottles, most often with an activity of 40 PIECES in 1 ml. It is administered parenterally, most often under the skin. This drug (like all drugs of the insulin subgroup of quick short-acting) has a quick sugar-lowering effect. The effect develops after 15-20 minutes, and the peak of action is noted after 2-4 hours. The total duration of the hypoglycemic effect is 6-8 hours in adults, and in children up to 8-10 hours.

Advantages of short-acting insulin drugs (actrapid):

1) act quickly;

2) give a physiological peak concentration in the blood;

3) act briefly.

4) The main disadvantage is the short duration of action, which requires repeated injections.

Indications.

The main indication for the use of insulin is type 1 diabetes mellitus, but under certain conditions it is also prescribed for type 2 diabetes mellitus, including with resistance to oral hypoglycemic agents, with severe concomitant diseases, in preparation for surgical interventions, diabetic coma, and diabetes in pregnant women. Insulin short actions are used not only in diabetes mellitus, but also in some other pathological processes, for example, with general exhaustion (as an anabolic agent), furunculosis, thyrotoxicosis, with diseases of the stomach (atony, gastroptosis), chronic hepatitis, initial forms of liver cirrhosis, and also with some mental illnesses (the introduction of large doses of insulin - the so-called hypoglycemic coma); it is sometimes used as a component of "polarizing" solutions used to treat acute cardiac insufficiency.

Indications for the use of short-acting insulin preparations:

Treatment of patients with insulin-dependent diabetes mellitus. The drug is administered under the skin.

In the most severe forms of non-insulin-dependent diabetes mellitus in adults.

For diabetic (hyperglycemic) coma. In this case, the drugs are administered both under the skin and in a vein.

Very rarely, drugs are used as an anabolic in children with poor nutrition. In this case, the drug is administered under the skin to increase appetite. According to this indication, drugs are used in patients with a general decline in nutrition, exhaustion, furunculosis, thyrotoxicosis, vomiting, chronic hepatitis

Drugs can be part of a polarizing mixture (potassium, glucose and insulin) to maintain myocardial function in cardiac arrhythmias (when the phenomenon of hypocalysis is detected, for example, during intoxication with cardiac glycosides).

In a psychiatric clinic, drugs were previously used for shock therapy in patients with schizophrenia (by achieving hypoglycemic coma). Now this evidence is practically absent, since there are a lot of good psychotropic drugs.

Drugs are indicated for patients with non-insulin-dependent diabetes mellitus during pregnancy, since hypoglycemic agents do not have teratogenic effects

Persons with non-insulin-dependent diabetes mellitus during cavity and other major surgical interventions, with infectious diseases

Dosing of insulin is an extremely difficult issue, as an individual selection of doses is needed.

One of the most primitive ways of calculating the dose of insulin is to enter 1 unit of insulin per gram of sugar in the patient's urine. The first insulin injections and the selection of the optimal dose are preferably performed in a hospital. At the same time, they try not to select an abstract dose, but a specific one. The patient is prescribed the whole diet for a week in advance.

Insulin is the main specific treatment for diabetes. Treatment of diabetes is carried out according to specially developed schemes using insulin preparations of different durations of action. The choice of the drug depends on the severity and characteristics of the course of the disease, the general condition of the patient and the speed of onset and duration of the hypoglycemic effect of the drug.

All insulin preparations are used subject to mandatory dietary regimen with a limitation of the energy value of food (from 1700 to 3000 kcal).

When determining the dose of insulin are guided by the level of glycemia on an empty stomach and during the day, as well as the level of glucosuria during the day. The final dose selection is carried out under the control of a decrease in hyperglycemia, glucosuria, as well as the general condition of the patient.

In addition to insulin preparations of short and fast action, sustained-release insulin is secreted. The presence in these preparations of the main proteins - protamine and globin, zinc, as well as salt buffer changes the rate of onset of the hypoglycemic effect, the time of maximum action, that is, the peak of action and the total duration of action. As a result of such a mixture, a suspension is obtained, which is slowly absorbed, maintaining a low dose of the drug in the blood for a long time. Now there are a lot of long-acting insulin preparations (see classification). All these drugs are administered only subcutaneously.

Advantages of prolonged insulin preparations:

1) drugs are administered only two or once a day;

2) the drugs have a high pH, which makes their injections less painful and insulin acts faster.

Disadvantages:

1) the absence of a physiological peak, from which it follows that these drugs can not be administered to patients with severe diabetes mellitus and should be used in relatively mild and moderate forms;

2) drugs should not be injected into a vein (to avoid embolism).

Contraindications

Insulin is contraindicated in diseases and conditions that occur with hypoglycemia (e.g. insulinoma), in acute diseases of the liver, pancreas, kidneys, gastric and duodenal ulcers, decompensated heart defects, in acute coronary insufficiency and some other diseases.

Use during pregnancy.

The main drug treatment for diabetes during pregnancy is insulin therapy, which is carried out under close supervision. In type 1 diabetes, insulin treatment is continued. With type 2 diabetes, oral hypoglycemic agents are canceled and diet therapy is carried out.

Gestational diabetes mellitus (pregnancy diabetes) is a violation of carbohydrate metabolism that first occurred during pregnancy. Gestational diabetes mellitus is accompanied by an increased risk of perinatal mortality, the incidence of congenital malformations, as well as the risk of diabetes progressing 5-10 years after birth. Treatment of gestational diabetes begins with diet therapy. With the ineffectiveness of diet therapy, insulin is used.

For patients with previous or gestational diabetes mellitus, it is important to maintain adequate regulation of metabolic processes throughout pregnancy. The need for insulin can decrease in the first trimester of pregnancy and increase in the second – third trimesters. During childbirth and immediately after them, the need for insulin can decrease dramatically (the risk of developing hypoglycemia increases). Under these conditions, careful monitoring of blood glucose is essential.

Insulin does not cross the placental barrier. However, maternal IgG antibodies to insulin pass through the placenta and are likely to cause fetal hyperglycemia by neutralizing the insulin secreted in it. On the other hand, undesired dissociation of insulin – antibody complexes can lead to hyperinsulinemia and hypoglycemia in the fetus or newborn. It has been shown that the transition from bovine / swine insulin preparations for monocomponent preparations is accompanied by a decrease in antibody titer. In this regard, during pregnancy, it is recommended to use only human insulin preparations.

Insulin analogs (like other recently developed drugs) are prescribed with caution during pregnancy, although there is no reliable data on adverse effects. In accordance with the generally accepted recommendations of the FDA (Food and Drug Administration), determining the possibility of using drugs during pregnancy, insulin preparations by their effects on the fetus belong to category B (animal reproduction studies did not reveal any adverse effects on the fetus, but adequate and strictly controlled studies in pregnant women women), or to category C (animal reproduction studies have shown adverse effects on the fetus, and adequate and strictly controlled studies in pregnant women have not been conducted, however the potential benefits associated with the use of drugs in pregnant women may justify its use, despite the possible risk). So, insulin lyspro belongs to class B, and insulin aspart and insulin glargine belongs to class C.

Complications of insulin therapy. Hypoglycemia. The introduction of too high doses, as well as the lack of carbohydrates with food, can cause an undesirable hypoglycemic state, hypoglycemic coma may develop with loss of consciousness, convulsions and depression of cardiac activity. Hypoglycemia can also develop due to the action of additional factors that increase insulin sensitivity (eg, adrenal insufficiency, hypopituitarism) or increase glucose uptake by tissues (physical activity).

Early symptoms of hypoglycemia, which are largely associated with activation of the sympathetic nervous system (adrenergic symptoms), include tachycardia, cold sweat, trembling, with activation of the parasympathetic system - severe hunger, nausea, and a tingling sensation in the lips and tongue . At the first signs of hypoglycemia, urgent measures are necessary: the patient should drink sweet tea or eat a few pieces of sugar. With a hypoglycemic coma, a 40% glucose solution in an amount of 20–40 ml or more is injected into a vein until the patient comes out of a coma (usually not more than 100 ml). Hypoglycemia can also be relieved by intramuscular or subcutaneous administration of glucagon.

Weight gain

with insulin therapy is associated with the elimination of glucosuria, an increase in the real calorie content of food, increased appetite and stimulation of lipogenesis under the action of insulin. Subject to the principles of good nutrition, this side effect can be avoided.

The use of modern highly purified hormone preparations (especially genetically engineered preparations of human insulin) relatively rarely leads to the development of insulin resistance and allergy phenomena, however, such cases are not excluded. The development of an acute allergic reaction requires immediate desensitizing therapy and drug replacement. When a reaction to bovine / swine insulin preparations develops, they should be replaced with human insulin preparations. Local

and systemic reactions (itching, local or systemic rash, the formation of subcutaneous nodules at the injection site) are associated with insufficient purification of insulin from impurities or with the use of bovine or porcine insulin that differ in amino acid sequence from human.

The most common allergic reactions are skin, mediated by IgE antibodies. Occasionally, systemic allergic reactions are observed, as well as insulin resistance mediated by IgG antibodies.

Visual impairment. Transient refractive errors occur at the very beginning of insulin therapy and pass independently after 2-3 weeks.

Swelling. In the first weeks of therapy, transient edema of the legs also occurs due to fluid retention in the body, the so-called insulin edema.

Local reactions include lipodystrophy at the site of repeated injections (a rare complication). Allocate lipoatrophy (the disappearance of deposits of subcutaneous fat) and lipohypertrophy (increased deposition of subcutaneous fat). These two states have a different nature. Lipoatrophy - an immunological reaction, mainly due to the introduction of poorly purified preparations of insulin of animal origin, at the present time practically does not occur. Lipohypertrophy also develops when highly purified preparations of human insulin are used and can occur if the technique of administration is impaired (cold product, alcohol gets under the skin), and also due to the anabolic local action of the drug itself. Lipohypertrophy creates a cosmetic defect, which is a problem for patients. In addition, due to this defect, the absorption of the drug is impaired. To prevent the development of lipohypertrophy, it is recommended to constantly change the injection site within the same area, leaving a distance between two punctures of at least 1 cm.

Local reactions such as pain at the injection site may be noted.

Interaction.

Insulin preparations can be combined with each other.

Many drugs can cause hypo- or hyperglycemia, or change the reaction of a patient with diabetes to treatment. The interaction possible with the simultaneous use of insulin with other drugs should be taken into account. Alpha-blockers and beta-adrenergic agonists increase the secretion of endogenous insulin and enhance the effect of the drug. The hypoglycemic effect of insulin is enhanced by oral hypoglycemic agents, salicylates, MAO inhibitors (including furazolidone, procarbazine, selegiline), ACE inhibitors, bromocriptine, octreotide, sulfanilamides, anabolic steroids (especially oxandrolone, and andandienone and increase tissue resistance to glucagon, which leads to hypoglycemia, especially in the case of insulin resistance; it may be necessary to reduce the dose of insulin), analogues of somatostatin, guanethidine, diz Osamide, clofibrate, ketoconazole, lithium preparations, mebendazole, pentamidine, pyridoxine, propoxyphene, phenylbutazone, fluoxetine, theophylline, fenfluramine, lithium preparations, calcium preparations, tetracyclines. Chloroquine, quinidine, quinine reduce insulin degradation and can increase blood insulin concentration and increase the risk of hypoglycemia.

Carbonic anhydrase inhibitors (especially acetazolamide), stimulating pan-creative β-cells, promote the release of insulin and increase the sensitivity of insulin receptors and tissues; although the simultaneous use of these drugs with insulin can increase the hypoglycemic effect, the effect can be unpredictable.

A number of drugs cause hyperglycemia in healthy people and exacerbate the course of the disease in patients with diabetes mellitus. The hypoglycemic effect of insulin is weakened by: antiretroviral drugs, asparaginase, oral hormonal contraceptives, glucocorticoids, diuretics (thiazide, ethacrynic acid), heparin, H2 receptor antagonists, sulfinpyrazone, tricyclic antidepressants, calcinitinazide, simonitazinaztinazitonitazu, dobitazinitazitonitazitonu, doben clonidine, BKK, diazoxide, morphine, phenytoin, growth hormone, thyroid hormones, phenothiazine derivatives, nicotine, ethanol.

Glucocorticoids and epinephrine exert on peripheral tissues effect opposite to insulin. So, prolonged use of systemic glucocorticoids can cause hyperglycemia, up to diabetes mellitus (steroid diabetes), which can be observed in about 14% of patients taking systemic corticosteroids for several weeks or with prolonged use of topical corticosteroids. Some drugs inhibit insulin secretion directly (phenytoin, clonidine, diltiazem) or by decreasing potassium reserves (diuretics). Thyroid hormones accelerate the metabolism of insulin.

Beta-blockers, oral hypoglycemic agents, glucocorticoids, ethanol, salicylates affect the action of insulin most significantly and often.

Ethanol inhibits gluconeogenesis in the liver. This effect is observed in all people. In this regard, it should be borne in mind that the abuse of alcoholic beverages on the background of insulin therapy can lead to the development of a severe hypoglycemic state. Small amounts of alcohol taken with food usually do not cause problems.

Beta-blockers can inhibit insulin secretion, alter carbohydrate metabolism and increase peripheral insulin resistance, leading to hyperglycemia. However, they can also inhibit the action of catecholamines on gluconeogenesis and glycogenolysis, which is associated with a risk of severe hypoglycemic reactions in patients with diabetes mellitus. Moreover, any of the beta-blockers can mask the adrenergic symptoms caused by a decrease in blood glucose (including tremors, palpitations), thereby disrupting the patient's timely recognition of hypoglycemia. Selective beta1-blockers (including acebutolol, atenolol, betaxolol, bisoprolol, metoprolol) exhibit these effects to a lesser extent.

NSAIDs and salicylates in high doses inhibit the synthesis of prostaglandin E (which inhibits the secretion of endogenous insulin) and thus enhance basal insulin secretion, increase the sensitivity of pancreatic β-cells to glucose; hypoglycemic effect with simultaneous use may require dose adjustment of NSAIDs or salicylates and / or insulin, especially with prolonged sharing.

Currently, a significant number of insulin preparations are produced, including obtained from the pancreas of animals and synthesized by genetic engineering. The drugs of choice for insulin therapy are genetically engineered highly purified human insulins with minimal antigenicity (immunogenic activity), as well as analogues of human insulin.

Insulin preparations are available in glass bottles, hermetically sealed with rubber stoppers with aluminum break-in, in special so-called insulin syringes or syringe pens. When using a syringe pen, the preparations are in special cartridge bottles (penfillas).

Intranasal forms of insulin and insulin preparations for oral administration are being developed. With a combination of insulin with a detergent and administration in the form of an aerosol to the nasal mucosa, the effective plasma level is reached as quickly as with an intravenous bolus. Insulin preparations for intranasal and oral administration are under development or are undergoing clinical trials.

GENERAL METHODS FOR THE SELECTION OF DOSES OF INSULIN FOR PATIENTS WITH DIABETES MELLITUS

The dose of the drug is calculated on the basis that 1 unit of insulin injected subcutaneously promotes the absorption of 4 g of glucose with compensated diabetes mellitus and 3 g of glucose in decompensated diabetes mellitus. Considering that the goal of insulin therapy is not only to maintain normal blood sugar levels, but also to normalize carbohydrate and fat metabolism, normalize body weight, and also prevent diabetic complications, there are several ways to select a daily dose of insulin. They are calculated depending on the course and duration of the disease, as well as on the initial indicators of sugar in the blood and urine. Let's consider some schemes.

The choice of insulin dose depending on the nature and course of diabetes

• Newly diagnosed diabetes: the daily dose of insulin is 0.5 units per 1 kg of body weight.

• The first year of diabetes without clinical manifestations of the disease: 0.3–0.4 units per 1 kg of body weight.

• Long-term current diabetes mellitus: 0.6–0.7 units per 1 kg of body weight.

In any case, the daily dose of insulin should not exceed 1 IU per 1 kg of body weight, otherwise, as a result of an overdose of insulin, the patient may develop hypoglycemic seizures and develop a coma. In these cases, it is necessary to choose a special way to reduce the dose of insulin. It is better to do this in a hospital, where there is the possibility of providing immediate medical care to remove the patient from a coma and remove other acute complications.

Choice of insulin dose depending on blood sugar (glycemia)

If the blood sugar level is above 8.3 mmol / L, then for every 0.22 mmol / L of glucose in the blood, 1 UNIT of simple insulin is required, which is administered every 6-8 hours.

For example, blood sugar levels rose to 9 mmol / L. This means that he exceeded the maximum threshold at which it is necessary to additionally administer inulin by 0.7 mmol / L, which is three times more than 0.22 mmol / L. Therefore, the patient needs 3 units of simple insulin every 6–8 hours.

The choice of insulin dose depending on the level of sugar in the urine (glucosuria)

It is necessary to control the daily loss of glucose in the urine. If the diabetes compensates well and 100 g of glucose goes out with urine, then, based on the fact that 1 U of insulin helps the absorption of 4 g of glucose, 25 g (0.25 U) of insulin must be administered. And with decompensated diabetes (when 1 unit of insulin helps to absorb 3 g of glucose), the patient needs 33 g of insulin, that is, 0.33 units.

The choice of insulin dose depending on several indicators for patients with complicated diabetes

This technique is used only in a hospital, when diabetes occurs with complications or cannot be compensated for by conventional methods. To determine the dosage of insulin administered, it is carefully monitored how insulin works throughout the day. Therefore, studies are carried out very often. On an empty stomach they determine the level of sugar in the blood, then examine the daily loss of sugar in the urine, as well as the level of hemoglobin bound in glucose. In addition to these indicators, it is necessary to determine the blood sugar level 6 times a day every 4 hours. Sugar samples are usually taken at 8 o'clock in the morning, then at 12 o'clock, at 16, 20, 24 hours and at 4 o'clock the next morning. Even more often - 5 times a day - they check the sugar in the urine. The first urine sample is taken from 9 a.m. to 12 a.m., the second one is taken from 12 a.m. to 6 p.m., the third urine sample is taken and examined for sugar from 18 a.m. to 10 p.m., the fourth one is taken from 22 a.m. to 6 a.m., and the fifth is taken from 6 a.m. to 9 a.m. in the morning. All this allows you to determine whether the injected insulin or not enough, that is, it helps to adjust the dose of insulin so that the sugar level remains stable throughout the day. Even triple determination of the level of sugar in the urine allows you to understand the effect of the injected insulin and choose the right dosage. When determining the level of sugar in urine three times, the first portion is taken from 8 to 14 hours. The amount of sugar in this portion reflects the effect of the morning dose of insulin. The second portion of urine is taken from 14 to 19 hours, and the amount of sugar in it indicates the effectiveness of the dose of insulin administered before lunch. And finally, the third portion of urine is taken from 19 to 8 in the morning.

Devices for the administration of insulin. Syringe pens and other devices

Each device is used for a specific purpose, but in home insulin therapy only insulin syringes and syringe pens are used, with which patients with diabetes can successfully correct their blood sugar levels.

They are used for uncomplicated diabetes.

In very serious cases, and only in a hospital, a special device is used - a biostator. It allows not only to quickly determine the level of sugar in the blood, to calculate and adjust the rate of insulin administration, but also injects glucose and insulin. In fact, it is a simulator of the pancreas.

Biostator is used in the following cases:

• with newly diagnosed diabetes;

• with labile diabetes;

• to remove the patient from the state of ketoacidosis and diabetic coma;

• during childbirth and surgery.

If diabetes is complicated, then insulin is administered in the hospital by microdosing. Using these devices, short and long-acting insulins can be administered subcutaneously and intravenously at a given speed. Microdosers are equipped with a device for controlling blood sugar. They are used to stabilize the course of diabetes and the selection of a dose of insulin in the following cases:

• with newly diagnosed diabetes;

• in severe diabetes mellitus;

• with labile diabetes;

• with frequent hypoglycemia;

• in the presence of acetone in the urine;

• in case of chronic overdose of insulin;

• in the presence of addiction to insulin.

Microdosers allow you to gradually increase the dose of insulin under the control of blood sugar and urine levels until a stable effect of lowering blood sugar to a normal level is obtained. After this, the patient may switch to the use of syringe pens or insulin syringes.

The needle in the syringe is built-in, so the dosage of insulin can be carried out quite accurately. However, it must be borne in mind that the syringe must be sterilized after each injection and stored in a protective case. Subject to these simple hygiene rules, a plastic syringe can be used repeatedly until the needle is dull.

Most patients with diabetes prefer to use syringe pens that are equipped with an insulin can (penfill) and a sterile needle. They work like ink pens. In the syringe pen, the needles are disposable, and the penfills change as you use insulin. To administer a specific dose of insulin, a button is used, under the influence of which the necessary amount of the drug enters the needle. Dignity the syringe pens also mean that the injections are completely painless. Among the most popular devices are Novopen-1, Plivapen-1, Optipen-1 syringe pens, which are used for short-acting insulins, as well as Novopen-2, Plivapen-2, Optipen-2 syringe pens intended for extended insulin actions.

Rules for insulin administration

Patients with diabetes mellitus and parents of sick children have to master the technique of administering insulin. This is not particularly difficult, but you need to know the rules for the injection, as well as the place where you can enter insulin.

So, the injection zone of subcutaneous insulin: the front wall of the abdomen, under the lo-patches, the outer side of the thigh, buttocks, shoulder. Since even during the day several injections have to be made, the injection sites of insulin need to be alternated, moreover, according to a certain pattern. If the previous injection was made in the front wall of the abdomen, then the next injection should be done in the same zone, but 2-3 cm higher, then move the place of insulin administration 23 cm lower, then to the left and, finally, to the right of the previous injection. After this, insulin can be injected into the thigh, where the injection sites can also be changed. Then - to another area, etc. Then, by the time the insulin is injected again into the front wall of the abdomen, the traces of injections will have time to heal.

Different zones respond slightly to insulin. So, from the front wall of the abdomen, insulin is absorbed most quickly, and most slowly - from the front surface of the thigh. Therefore, it is recommended to do injections in certain places at the same hours. For example, if you injected insulin in the thigh in the morning and under the shoulder blades in the evening, then the next day follow the same pattern: in the thigh in the morning and under the shoulder blades in the evening. Then the effectiveness of insulin during the day will be approximately the same.

Different types of insulin are better absorbed in certain areas. So, short-acting inulin is recommended most often to be introduced into the front wall of the abdomen. Long-acting insulin is usually injected into the buttocks, front wall of the thigh, under the shoulder blades or in the shoulder.

Injection of insulin into the shoulder should be done very carefully and in the most extreme cases, when other places are too punctured and there is a risk of complication. The fact is that there are muscles in the shoulder very close to the skin, and accidentally insulin can get there. In the muscle, it is absorbed into the blood much faster than subcutaneously, as a result, the action of insulin will manifest itself faster.

How to do an insulin injection

Subcutaneously, insulin is injected to a depth of 0.5 cm. In this case, it is necessary to fall with a needle into the subcutaneous layer between the muscles and skin. In order not to get into the muscle, you need to know the technique and sequence of the injection.

1. With the thumb and forefinger of one hand, slightly stretch the skin at the injection site so that a fold forms on the skin. But do not squeeze the skin strongly with your fingers.

2. Take the syringe with your other hand as you usually hold a pencil.

3. Holding the syringe vertically, with one movement of the hand, insert the needle along its entire length into the base of the fold.

4. Press on the piston or press the button, introducing insulin into the subcutaneous tissue, and count to ten.

5. Remove the needle from the skin.

Needles are 12 and 8 mm long. Depending on the patient's complexion, the size of the needle is chosen. Thin people are advised to use a shorter needle (8 mm), the rest - a standard needle (12 mm). After injection on a small bruise may appear at the injection site, which will quickly pass.

Rules for insulin storage

To maintain the activity of insulin, it must be kept in a refrigerator at a temperature of 2-8 ° C, and heated to body temperature before use. Be sure to pay attention to the shelf life of the insulin preparation, which is written on the ampoule, since it has a limited time. If the insulin preparation is a suspension, that is, a mixture, then it looks cloudy, therefore it must be thoroughly mixed, rolling the ampoule between the palms. Thus, the insulin solution will become homogeneous, and it can be administered under the skin. If flakes appeared in insulin, he changed the color or bite-bodies, which means that he is already damaged and can not be used in any case. Insulin can deteriorate both at too high a temperature, and at too low, as well as under direct sunlight.

Possible complications of insulin therapy

If certain safety measures and rules are not followed, then insulin treatment, like any other types of treatment, can cause various complications. The difficulty of insulin therapy lies in the correct selection of the dosage of insulin and the choice of treatment regimen, therefore, for a patient with diabetes mellitus, it is necessary to carefully monitor the entire treatment process. It seems complicated only at the beginning, and then people usually get used to and cope with all the difficulties perfectly. Since diabetes is a lifelong diagnosis, they learn to use a syringe like all other people - with a knife and a fork. However, unlike other people, patients with diabetes cannot afford even a little relaxation and “rest” from treatment. Otherwise, it threatens with complications, although such can arise not only due to the pain of the patients themselves, but also due to circumstances beyond their control. Moreover, you need to know about them in order to be able to prevent complications in time, which will be discussed.

Lipodystrophy

This complication develops at the injection site as a result of a violation of the formation and decay of adipose tissue, that is, at the injection site there are seals (when adipose tissue increases) or depressions (when adipose tissue decreases and subcutaneous fat disappears). Accordingly, this is called the hypertrophic and atrophic type of lipodystrophy.

Lipodystrophy develops gradually as a result of prolonged and constant trauma to small peripheral nerves with a syringe needle. This is its most common reason.

Another reason for the complication is the use of insufficiently pure insulin. Usually this complication of insulin therapy occurs after several months or even years of insulin administration. Complication is not dangerous for the patient, although it leads to impaired absorption of insulin, and also brings a certain discomfort to the person. Firstly, these are cosmetic skin defects, and secondly, soreness in places of complications, which intensifies when the weather changes.

Treatment of atrophic type lipodystrophy involves the use of porcine insulin along with novocaine, which helps restore trophic function of nerves. The hypertrophic type of lipodystrophy is treated with the help of physiotherapy: phonophoresis with hydrocortisone ointment.

Using preventive measures, you can protect yourself from this complication.

Prevention of lipodystrophy

• Alternating injection sites.

• The introduction of only insulin heated to body temperature.

• After treatment with alcohol, the injection site must be thoroughly wiped with a sterile cloth or wait for the alcohol to completely dry.

• Slowly and deeply inject insulin under the skin.

• Use only sharp needles.

Allergic reactions

This complication is due to the presence of foreign proteins in insulin. There are local allergic reactions that occur in and around injection sites in the form of redness of the skin, thickening, swelling, burning and itching. General allergic reactions, which manifest themselves in the form of urticaria, Quincke's edema, bronchospasm, gastrointestinal disorders, joint pain, enlarged lymph nodes and even anaphylactic shock, are much more dangerous.

Life-threatening allergic reactions are treated in the hospital by the administration of the hormone prednisone, the remaining allergic reactions are treated with antihistamines, as well as the administration of the hydrocortisone hormone together with insulin. However, in most cases, allergies can be eliminated by transferring the patient from swine insulin to human.

Chronic overdose of insulin

Chronic overdose of insulin occurs when the need for insulin becomes too high, that is, exceeds 1-1.5 units per 1 kg of body weight per day. In this case, the patient's condition worsens greatly. If such a painful patient reduces the dose of insulin, he will feel much better. This is the most characteristic sign of an overdose of insulin.

Other manifestations of complications:

• severe diabetes;

• high fasting blood sugar;

• sharp fluctuations in blood sugar during the day;

• large loss of sugar in the urine;

• frequent fluctuation of hypo- and hyperglycemia;

• tendency to ketoacidosis;

• increased appetite and weight gain.

Complications are treated by adjusting the doses of insulin and selecting the correct dosage regimen.

Hypoglycemic conditions and coma

The reasons for this complication lie in the incorrect selection of the dose of insulin, which was too high, as well as inadequate intake of carbohydrates. Hypoglycemia develops 2-3 hours after the administration of short-acting insulin and during the period of maximum prolonged-action insulin activity. This is a very dangerous complication, because the concentration of glucose in the blood can decrease very sharply, and the patient may have a hypoglycemic coma.

The development of hypoglycemic complications quite often leads to prolonged intensive insulin therapy, accompanied by increased physical exertion.

If you allow a drop in blood sugar below 4 mmol / l, then in response to this, a sharp rise in sugar may occur, that is, a state of hyperglycemia.

Prevention of this complication is to reduce the dose of insulin, the effect of which occurs at a time when the blood sugar drops below 4 mmol / L.

Insulin resistance

This complication is caused by addiction to certain doses of insulin: over time, they no longer give the desired effect and require them increase. Insulin resistance can be either temporary or prolonged.

If the need for insulin reaches more than 100-200 UNITS per day, but the patient has no attacks of ketoacidosis and there are no other endocrine diseases, then we can talk about the development of insulin resistance.

The reasons for the development of temporary insulin resistance include: obesity, high blood lipids, dehydration, stress, acute and chronic infectious diseases, lack of physical activity. Therefore, you can get rid of this type of complication by excluding the listed reasons.

Long-term, or immunological, insulin resistance develops due to the development of antibodies to injected insulin, a decrease in the number and sensitivity of insulin receptors, as well as impaired liver function. The treatment consists in replacing porcine insulin with human, as well as in the use of hydrocortisone or prednisone hormones and normalizing liver function, including through diet.

SUGAR DIABETES SELF-CONTROL

To avoid complications and maintain good health, everyone with diabetes should learn how to self-control. This is the only way to live with diabetes, feeling like a normal person.

It is impossible to choose the scheme of insulin administration and its dosage for a lifetime. The amount of insulin and the time of its administration have to be constantly adjusted, because the indicators of blood sugar depend on many factors that cannot be foreseen and excluded. These are unplanned physical activities, emotions, errors in diet, infections, stress. The life of any person consists of these circumstances, but for a patient with diabetes they can be dangerous, since their physiological parameters, on which their health depends, change too much. Therefore, a patient with diabetes should be constantly aware of these changes, observing his condition and monitoring laboratory parameters. Self-monitoring is necessary for all patients with diabetes mellitus, both insulin-dependent and non-insulin-dependent. The only difference is that with NIDDM, blood sugar control is performed much less frequently than with IDDM, but constantly, and with a deterioration in well-being, monitoring of blood sugar levels becomes more frequent.

Patient self-monitoring

• Before and after eating, blood sugar levels must be determined.

• Compare these indicators with physical activity and other unusual (emotional, stressful, painful) situations.

• Conduct a thorough analysis of their subjective feelings.

• Evaluate data received.

• Timely adjust the dosage of insulin and other therapeutic drugs, as well as the diet.

To quickly and clearly control your blood sugar and urine indicators, there are special devices - test strips and glucometers. They allow you to quickly and painlessly do a sugar test for yourself and immediately see its result.

Measuring blood sugar and urine using test strips and a glucometer

A test strip is a strip with a reagent applied - a substance that reacts to blood depending on the level of sugar in it. With a special device in the form of a pen (lancet), you need to pierce the skin on the fingertip and place a drop of blood on the test strip where the reagent is applied (colored part). This sensitive substance immediately changes color depending on the level of sugar in a drop of blood.

There are two ways to determine your blood sugar.

• Compare the color on the test strip with a color scale that indicates which color corresponds to the level of sugar in the blood.

• Using a glucometer - a device into which a test strip is inserted and in which an automatic assessment of the blood sugar level takes place. The patient can only read the result of the study on the digital display of the device.

Although using the device, research is carried out more quickly and conveniently, but with a certain skill, the visual method for determining blood sugar in blood is equally accurate. A minimal calculation error exists in both cases, but it does not play a role in determining the treatment regimen and dosage of insulin.

Measurement of sugar in the urine is carried out with special test strips in the same way. The test strip is immersed in the urine, and the test field changes color depending on the concentration of sugar in the urine. The most accurate are test strips with a double test field. They are recommended to be used, although analysis of sugar in the urine gives less information about the course of diabetes than the study of blood sugar levels.

Ketonuria urine test

A patient with diabetes must check the presence of ketone bodies (acetone) in the urine if he has a steady increase in blood sugar and its high concentration in the urine, that is, when several test results in a row show high numbers: above 14 mmol / l in the blood and 3% - in the urine. Indications for such a study are also deterioration of health (nausea and vomiting) and concomitant diseases with increased body temperature.

A urine test for ketone bodies is necessary in order to prevent an attack of ketonuria and prevent a diabetic coma. For this study, there are special test strips that are immersed in the urine and change their color depending on the concentration of ketone bodies in the urine. The very presence of ketone bodies in the urine indicates a serious metabolic disorder and requires immediate treatment.

Body weight control

It is necessary to control body weight so as not to miss the first signs of obesity and related developments of diabetic complications and other concomitant diseases. To control body weight, a special test has been developed that identifies an indicator of overweight. It is called the body mass index (BMI) or Ket-le index and is measured in kg / m2. Therefore, people with diabetes should regularly measure body weight and height. Based on these data, the Ketle index is calculated.

Calculation of the Ketle index: BMI = weight (kg) / (height (m2)).

The normal Quetelet index for men is 20–25, and for women is 19–24.

Keeping a diary of self-control

The patient writes the data of all these studies into his self-control diary, marking the date of the studies. In addition, he notes in the diary subjective and other objective data on general well-being. Namely, every three days it is recommended to measure blood pressure, and if the patient suffers from hypertension, then the pressure is measured every day. Body mass index is not necessary to calculate every three days, but weight should be measured, especially for people prone to overweight. The diary should be kept carefully so that, based on the notes, it can be easily concluded that the course of diabetes or its stable condition.

Keeping a self-monitoring diary allows the patient to manage his disease himself, correct small changes in time and live with diabetes without feeling any particular inconvenience.

Your well-being and health are in your own hands and depend on your desire and willingness to help yourself.

If a person keeps an excellent diary of self-control and, taking into account the results obtained, makes or does not make changes in his treatment, then his diabetes will be invisible to him. You can check how the patient copes with this task and controls his health with the help of another study, which is performed in the laboratory. This is a glycated hemoglobin assay.

The glycated hemoglobin HbA indicator indicates the general course of diabetes mellitus with all rises and drops in blood sugar, if any. Moreover, it gives an average value of blood sugar for 1.5–2 months and thereby indicates how well a person manages his disease. Depending on this indicator, one can judge how the patient adapted to life with diabetes.

• If HbA does not exceed 6% - there is no diabetes mellitus or the patient has perfectly adapted.

• HbA from 6 to 8% - the patient is well or satisfactorily adapted to the disease.

• HbA from 8 to 10% - the patient is unsatisfactory or poorly adapted to diabetes.

• HbA more than 10% - the patient is very poorly adapted to life with diabetes.

It is recommended to check the glycated hemoglobin index 1-2 times every three months for patients with an insulin-dependent type of diabetes mellitus and 1-2 times a year for patients with an insulin-independent type of diabetes mellitus.

TREATMENT OF DIABETES COMPLICATIONS

The fight against complications of diabetes primarily consists in their prophylaxis, that is, constant compensation for diabetes. Even with complications that have already begun, normalization of blood sugar levels allows you to reverse the process, that is, not only stop their development, but also minimize the disease.

Angiopathy treatment

The main treatment is persistent and long-term compensation for diabetes mellitus. Therefore, the patient is advised to strictly follow the diet, eat several times a day and a little, to exclude easily digestible carbohydrates from his diet. In addition to the diet, the patient should have moderate physical activity, which helps the absorption of sugar and improves the functioning of the cardiovascular system.

Drug treatment is prescribed by a doctor. Typically, these are angioprotectors, anticoagulants and antiplatelet agents, which help to normalize blood circulation and strengthen blood vessels. In addition, physiotherapy methods are used - hyperbaric oxygenation, acupuncture, laser irradiation, magnetotherapy.

Treatment of retinopathy (retinal vascular pathology)

In this case, the main effort of the patient himself should be aimed at compensating for diabetes. For therapeutic purposes, the patient is prescribed angioprotectors and anticoagulants to stabilize the vascular wall and improve blood circulation, and also use absorbable therapy, introducing drugs such as trypsin and lidase. If there is a risk of retinal detachment, then physiotherapeutic procedures are carried out, primarily photocoagulation.

Nephropathy treatment

The patient is recommended to adhere to a low-protein diet and take vitamins. It is necessary to monitor blood pressure and use drugs that reduce blood pressure, as well as anti-hypoxia drugs.

If nephropathy occurs with the development of renal failure, the patient is recommended to include alkaline mineral waters, natural berry and fruit juices in the diet.

In the hospital, special therapy is carried out to detoxify the body, that is, the elimination of toxic substances. In the case of severe nephropathy, I use blood purification using hemodialysis.

Polyneuropathy treatment

First of all, the patient is faced with the task of fully compensating for diabetes mellitus. Only in this case, the treatment of complications with medications and other means will give a positive result. In order to treat polyneuropathy, drugs are used that improve the functions of blood vessels and nerve fibers (i.e., angioprotectors, anticoagulants, antiplatelet agents, vitamins, lipoic acid). To improve the conductivity of nerve impulses along nerve fibers, the drug Prozerin is used.

Physiotherapeutic methods of treating complications include the following procedures: electrophoresis, balneotherapy, treatment with paraffin, ozokerite, massage and acupuncture. They help improve the condition of nerve fibers, as well as anesthetize and restore sensitivity in tissues.

ORAL DRUGS FOR THE TREATMENT OF DIABETES.

A person with type 2 diabetes has two problems that can increase sugar levels:

1. The production of small amounts of insulin, so glucose does not enter the cells. Such a problem today is the most common.

2. The resistance of cells to insulin. They do not perceive glucose. This problem occurs, but is not as widespread as the first.

If this process is not controlled, then cell deficiency may develop, which is unsafe. A person has to do constant injections of in-sulin. If this does not help, then it is necessary to be treated by combining insulin and sa-antipyretic tablets or taking them as a separate therapy

Sulfonylurea drugs increase the secretion of endogenous (intrinsic) insulin, their mechanism of action is different, but the effect is approximately equal. The figure shows the main active ingredients for INN of sugar-lowering drugs of sulfonylurea derivatives

Sugar-lowering S With derivatives of sulfonylureas

DERIVATIVES OF SULPHYL UREA I GENERATION:

Carbutamide (INN) - tab. Cn B Bukarban (Hungary);

Chlorpronamide (INN) - tab. Cn B (Poland, Russia).

Sulfonylurea Derivatives 2 Generations:

Glibenclamide (INN) - the first drug of the 2nd generation, on the market since 1969; tab. Cn B. There are 21 trade names for Glibenclamide in the pharmaceutical market, including Gilemal (Hungary), Glibenk-Lamid (Russia, Germany, etc.), Daonil (Germany, India), Maninil (Germany), etc.

Glyclazide (INN) - tab. Cn B. (Switzerland, India),

Glidiab (Russia),

Diabeton (France) and others.

Glipizide (INN) - tab. Cn B.

Minidiab (Italy),

Glibenez (France).

Glycvidone (INN) - tab. Cn B.

Glurenorm (Austria).

Glidifen (does not yet have an INN) - tab. Cn B (Russia).

Since 1995, the GENERATION OF PRO-DERIVED SULPHYL UREA 3 PRODUCT has been launched on the world pharmaceutical market:

Glimeniride (INN) - tab. Cn B. Amaril (Germany). By the strength of the sugar-reducing effect, it is stronger than the sulfonylurea derivatives of the 2nd generation, it is taken 1 time per day.

BIGUANIDES. These include 2 active substances, including:

Buformin (INN) - Dragee, Sp. B. Silubin Retard (Germany),

Metformin (INN) - inhibits the formation of glucose from non-carbonaceous products in the liver, slows down the absorption of carbohydrates in the intestines (appeared on the US pharmaceutical market in 1994), tab. Cn B (Poland, Croatia, Denmark),

Gliformin (Russia),

Glucophagus (France),

Siofor (Germany) and others.

ALFA-GLUCOSIDASE INHIBITORS are classified as

Acarbose (INN), manufactured in Germany under the trade name Gluco-Bai,

Miglitol (INN) -

Diastabol (Germany).

The mechanism of their action is to slow down the breakdown of carbohydrates entering the body into simple sugars (glucose, fructose, lactose). Taking these drugs does not replace insulin therapy, but is an additional treatment for type 2 diabetes. It is prescribed for patients when the use of a diet does not lead to normalization of blood glucose levels.

A similar effect to the sulfonylurea preparations of the 2nd generation, but belonging to the class of chemicals of the CARBAMOYLBEN-ZOIC ACID DERIVATIVES, PREANDIAL GLYC-MII REGULATORS MANIFEST:

Repaglinide (INN) - tab. Cn B NovoNorm (Denmark);

Nateglinide (INN) - tab., Starlix (Switzerland).

These drugs protect the beta cells of the pancreatic islets from excessive depletion, they are characterized by a quick corrective action to reduce the level of postprandial glycemia.

Among the new drugs - insulin sensitizers - GLITASONES ILITIAZOLIDINDEONE. This new group of substances gives a good effect of increasing glucose uptake into peripheral tissues and improves metabolism without increasing the need for insulin. However, the drugs have some adverse side effects. These drugs include:

Rosiglitazone (INN) tab., Avandia (France);

Pioglitazone (INN) tab., Aktos (USA).

COMBINED ORAL ORAL SUGAR-REDUCING AGENTS allow you to offer the patient drugs with optimal effect due to different mechanisms of action. In addition, as a rule, in combinations it is possible to reduce the dose of individual components, thus weakening side effects:

Glibomet - contains glibenclamide and metformin, tab. (Italy).

SUGAR-REDUCING MEANS OF VEGETABLE ORIGIN

Arfazetii - contains blueberry shoots, cusps of common bean fruit, Manchurian aralia root or rhizome with roots of a zamanicha, rosehips, horsetail, St. John's wort, chamomile flowers (Russia, Ukraine).

In diabetes mellitus, the following plant raw materials can be used: Aralia, Manchurian root, Aralia tincture, Psoralei, stone fruit, etc.

In recent years, a new drug appeared on the pharmaceutical market - Glucagon, an insulin antagonist, a protein-peptide hormone involved in the regulation of carbohydrate metabolism. It is used for severe hypoglycemic conditions that occur in patients with diabetes mellitus after insulin injections or oral medications.

Glucagon (INN) is a lyophilized powder in a vial. with solvent for injection. Cn B. Gluka, Gene HypoKit (Denmark).

Classification of antidiabetic oral drugs.

Oral sugar-lowering drugs can be divided into several types. Each of the presented species has its own principle of action on human organs:

1. The drug sulfinyl urea. These hypoglycemic tablets stimulate the pancreas to produce more insulin. First-generation drugs are now practically not used, since they did not possess power and the duration of their action was short. Now they use mani-nil, minidiab, amaryl. These pills can lower your sugar content by a few percent, which is very significant in the position of the patient.

2. Biguanides. These diabetes tablets have been given the ability to improve insulin's ability to move glucose into cells. They block the secretion of sugar by the liver. There are contra-indications for the use of biguanides. They cannot be prescribed to people who have heart or kidney disease.

3. Thiazolidinediones. Considered oral hypoglycemic drugs can increase the performance of insulin in muscle tissue. The effect of drugs begins 7 days after the first dose. It is necessary to control the liver when using these drugs.

4. Alpha glucosidase inhibitors. They block those particles that allow starch to be absorbed, well contribute to slowing down the growth of sugar. Side effects include diarrhea and bloating. It should be emphasized that there may not be a side effect. All individually.

5. Tablets Starlix and Novonorm. Stimulate the pancreas, as a result of which a large amount of insulin is released. It all depends on how much glucose is in the blood.

6. There are drugs that can signal the liver about a large amount of sugar, increase insulin secretion. They control the increase in sugar levels, but do not affect the patient's weight. They can be taken alone or in combination with other medicines.

7. Combined treatment. There are drugs that contain several drugs in one shell. However, this kind of therapy is always allowed strictly after passing a series of tests to patients, which, in turn, are assigned exclusively by the attending physician.A new type of drugs that act on the hormones of the alimentary canal (increatins) have appeared along with existing drugs. They respond to food intake and are able to increase insulin levels, that is, contribute to the following processes:

Significantly increase the insulin content and inhibit the production of glucagon by the pancreas.

Significantly increase insulin levels, thereby helping to utilize glucose to peripheral tissues.

Control the release of glucose by the liver with a combination of high insulin and low glucagon.

The use of oral hypoglycemic agents

1. Derivatives of sulfonylureas

Despite the presence of type 2 hyperinsulinemia in patients with diabetes mellitus (at least at the beginning of the disease), it is not enough to overcome the existing insulin resistance of own insulin, and it is necessary to increase the concentration of this hormone in the blood. An increase in blood insulin level under the influence of sulfonylurea derivatives (PSM) ensures the utilization of glucose by insulin-dependent tissues and the suppression of glucose production by the liver. Sulfonylurea preparations are prescribed starting from the minimum doses, gradually (with an interval of 1-2 weeks) assessing the effect and increasing the dose as necessary. In each case, the dose of drugs should be selected individually, bearing in mind the high risk of hypoglycemic conditions in senile people.

2. Biguanides

The effect of biguanides on the level of glycemia can be assessed as antihyperglycemic, and not hypoglycemic. Drugs Lower Elevated Glucose Levels blood (especially on an empty stomach) to normal values, but not to low.

Metformin is practically the only oral hypoglycemic agent, the treatment of which can lead not to increase, but even to reduce the body weight of patients, therefore, the indication for the use of metformin is not an opportunity to achieve compensation of the disease in people with type 2 diabetes mellitus (primarily with obesity) on the background of only diet therapy.

Metformin is prescribed starting with a small dose (usually 500 mg), during or immediately after an evening meal (despite the fact that the rate of absorption is slowed down, this can reduce side effects), then the dose is gradually increased to 850 mg 2-3 times per day.

3. Meglitinides (prandial glycemic regulators)

Meglitinides stimulate insulin secretion by binding to their own specific sites on pancreatic β-cells. They are rapidly absorbed. The onset of action occurs in 5-10 minutes, which allows the patient to take these medicines immediately before eating. The peak concentration in blood plasma is reached after 40-60 minutes, which regulates the level of postprandial glycemia. Drugs are inactivated just as quickly, therefore, insulin levels return to the original 3 hours after ingestion, which simulates the normal secretion of insulin during meals and reduces the likelihood of hypoglycemia in between meals. Thus, these drugs allow the patient more flexible approach to the issue of compliance with the diet. In case of skipping carbohydrate intake (for example, at lunch), drug intake is also skipped. If the use of meglitinides improves postprandial glycemia, and fasting glycemia remains elevated, they can be successfully combined with metformin or prolonged insulin before bedtime.

4. Thiazolidinediones

Drugs of this class can be used as monotherapy, as well as in combination with PSM, insulin or metformin. It is advisable to combine thiazolidinediones with metformin due to the fact that the action of biguanides is mainly aimed at suppressing gluconeogenesis, and the action of thiazolidinediones is aimed at increasing peripheral glucose utilization. They practically do not cause hypoglycemia, but, like biguanides, they are able to increase the frequency of hypoglycemia in combination with secretogogs.

5. Inhibitors of α-glucosidases

The effectiveness of monotherapy with these drugs is not large enough and manifests itself mainly in patients with newly diagnosed type 2 diabetes. Hypoglycemia does not develop with the use of α-glucosidase inhibitors, however, it should be noted that if hypoglycemia develops for other reasons (overdose of PSM), the absorption of carbohydrates taken orally taken for its correction is slowed down. Patients should be informed that in this situation they should take drugs or products containing glucose: grape juice, tableted glucose. Regular sugar is ineffective.

6. Combined medicines

Currently, ready-made combinations of PSM and metformin, thiazolidinediones and metformin are used.

7. Insulin therapy

Taking into account current knowledge about the development of complications of type 2 diabetes mellitus, the use of insulin should be started if other methods of treatment do not allow maintaining the level of glycated hemoglobin HbA1c less than 8%.

Absolute indications for the transfer of type 2 diabetes mellitus patients to insulin monotherapy include:

- diabetic ketoacidosis and coma;

- pregnancy and lactation;

- diabetic nephropathy at the stage of chronic renal failure with a creatinine level of 250 μmol / l or more;

- decompensation of diabetes mellitus against the background of serious infections and acute diseases (myocardial infarction, cerebral stroke);

- the need for surgical interventions using anesthesia.

CLINICAL PHARMACOLOGY OF SULPHONYL UREA DRUGS

Pharmacodynamics Sulfonylurea preparations have the ability to stimulate insulin secretion by pancreatic β-cells (but only when the cells have retained the ability to produce insulin) - This property is due to their interaction with specific receptors on the cell surface, which, like insulin receptors, cause the closure of potassium channels and depolarization of cell membranes. In the presence of glucose, the stimulating effect of sulfonylurea derivatives is more pronounced due to the fact that these drugs use the same β-cell activation mechanism as glucose. The difference between the individual drugs in this group is mainly related to pharmacokinetics.

Doses of sulfonylurea derivatives are selected individually by titration (the interval between the administration of the next titrated dose should be 1-2 weeks).

Pharmacokinetics Sulfonylurea preparations are well absorbed from the digestive tract, and the main differences in the pharmacokinetics of these drugs are determined by the features of their elimination.

NLR. The most serious NLR when taking sulfonyl-urea preparations is hypoglycemia, which occurs with inadequate dose selection or diet errors. Unlike hypoglycemia in the treatment with insulin, hypoglycemia with an overdose of sulfonylureas is more prolonged

due to the longer duration of the sugar-lowering effect of these drugs. Even after normal blood glucose concentration is restored, hypoglycemia can recur over the next 12-72 hours.

Drugs in this group can also cause dyspeptic syndrome (loss of appetite, abdominal pain, nausea, vomiting, diarrhea), which develops during the first months of treatment and usually does not require discontinuation of the drug. Allergic reactions, hematopoietic disorders - pancytopenia1, and toxic damage to the liver and kidneys are considered more serious NLR. In addition, drugs in this group can cause weight gain.

The interaction of sulfonylurea preparations: there is an increase in hypoglycemic effect when combined with salicylates, butadion, anti-TB drugs, chloramphenicol, tetracycline antibiotics, MAO inhibitors and BAB. A weakening of the hypoglycemic effect is observed when a combination of PSSP with oral contraceptives, chlorpromazine, sympathomimetics, glucocorticoids, thyroid hormones, drugs containing nicotinic acid.

Resistance to sulfonylureas. In the absence of a sa-lowering effect in sulfonylurea preparations, even when administered at the highest possible dose, it is necessary to ascertain the presence in the patient of primary resistance, which is observed in 5% of patients with type II diabetes. As a rule, the presence of primary resistance means the inability of β-cells of the pancreas to perform their functions, and such patients are indicated for the appointment of insulin preparations. Secondary resistance develops after several years of treatment, every year 5-10% of patients have to deal with this phenomenon. The cause of secondary resistance usually also lies in the progression of the disease, and this condition also requires the administration of insulin preparations. In other cases, the ineffectiveness of these drugs may be caused by exacerbation of concomitant diseases, and usually after a course of insulin therapy, the sensitivity of β-cells to sulfonylurea preparations is restored.

Glibenclamide (maninyl) is the most widely used PRSP in the world. There are two forms of the drug:

1 Decrease in the number of all blood cells - anemia, leukopenia and thrombocytopenia.

- usual - 5 mg tablets with bioavailability of up to 70% and a half-life of 10-12 hours;

- microionized - 1.75 and 3.5 mg tablets with bioavailability close to 100% and a half-life of slightly less than 10 hours.

The daily dose of glibenclamide in the usual form is from 2.5 to 20 mg. In the Russian Federation, glibenclamide is usually prescribed 3 times a day, but because of the long duration of action of this drug, it is considered more optimal to prescribe glibenclamide 1 or 2 times a day (in the latter case, the morning dose is equal to the evening or their ratio is 2: 1) . Take glibenclamide 30 minutes before a meal.

The effectiveness of the ionized form of glibenclamide is 50-75% of the usual form when using the same doses. Microionized glibenclamide begins to be actively absorbed after 5 minutes after administration, and the interval between taking the drug and food can be reduced. The maximum concentration of the drug in the blood is also noted earlier, coinciding with the peak of post-prandial glycemia. The action of this form of glibenclamide lasts about 24 hours, which allows to stimulate the secretion of insulin during the day and reduces the risk of hypoglycemia.

Glipizide - also represented by two forms with different kinetics: traditional and retarded GITS1 form (glibenesis retard).

The drug is prescribed in a dose of 2.5 to 20 mg per day, divided into two doses. Glipizide in the form of a gastrointestinal therapeutic system is taken 1 time per day. The difference in this form lies in the structure of the tablet, the core of which consists of two layers surrounded by a semipermeable membrane for water. In one of the layers of the core contains drugs, in the other - neutral substances with high osmotic activity. Water, penetrating into the dosage form, accumulates in the osmotic layer, which, expanding, gradually “squeezes” the active substance out through the smallest holes in the surface of the tablet, made using a laser. This ensures uniform release of the drug during the day

and reduces the risk of hypoglycemia. The drug in retarded form begins to act 2-3 hours after administration, the maximum is reached after 6-12 hours. Equilibrium

GITS is a gastrointestinal therapeutic system.

the concentration of the drug in plasma is reached on the 50th day of treatment. Eating food practically does not affect the kinetics and pharmacodynamics of this drug.

Gliclazide (Diabeton MV) is slightly inferior in effectiveness to glibenk-lamide, but along with stimulation of pancreatic β-cells it is able to improve microcirculation and rheological properties of blood. The drug stimulates mainly the early phase of insulin secretion. Gliclazide is taken 2 times a day. There is a form with modified properties - MV diabetone *, which has almost 100% bioavailability, prescribed once a day (the effective dose when taking this form of the drug is 2 times less than with conventional glycazide).

Glimepiride (amaryl) interacts with a receptor other than the sulfonylurea receptor, while the release of insulin when it is used is 2.5-3 times faster than with glibenclamide the mechanism of β-cell stimulation is the same in both drugs). In addition, increased secretion of insulin occurs exclusively after ingestion (in the presence of glucose), due to which hypoglycemia almost does not occur with glimepiride. The drug is produced in tablets of 1, 2, 3, 4 and 6 mg, which creates additional convenience in use; in addition, it can be prescribed only 1 time per day.

Glycvidone is almost completely (95%) excreted in feces, which allows the use of this drug in chronic renal failure. Glycvidone is the only PSSP that can be prescribed to patients with severe diabetic nephropathy.

CLINICAL PHARMACOLOGY OF BIGUANIDS

Pharmacodynamics Biguanides are used to treat mild or moderate forms of type II diabetes in patients with increased body weight. They do not affect the release of insulin, but in the presence of the latter increase the utilization of glucose by tissues. Biguanides reduce the production of glucose from glycogen in the liver and slow down the absorption of carbohydrates in the intestine. All this allows you to combine biguanides with sulfonylurea preparations.

Biguanides reduce lipogenesis and the concentration of triglycerides in the blood, but increase lipolysis, the concentration of free fatty acids and glycerol.

Pharmacokinetics The drugs of this group are characterized by a short duration of action, excreted mainly by the kidneys The bioavailability of the most commonly used drug of this group - metformin - is 50-60%. When it is prescribed in a dose exceeding 3 g, a further increase in the hypoglycemic effect is not observed. Metformin is taken simultaneously with food.

NLR. Biguanides increase anaerobic glycolysis, the production of lactate and pyruvate in the blood and can cause lactate acidosis. Along with impaired absorption of glucose in the small intestine, they reduce the absorption of amino acids, bile acids, water, vitamin B12, folic acid. The use of biguanides in patients consuming fructose in the diet is unacceptable because of the high likelihood of developing lactic acidosis. The least risk of lactic acidosis is observed with the use of metformin.

In the treatment with biguanides, photosensitization, nausea, a metallic taste in the mouth, and vomiting may appear. In addition, the use of these drugs can cause an increase in the activity of liver enzymes (alkaline phosphatase) and the development of cholestasis. However, these phenomena disappear on their own within 5-6 weeks after drug withdrawal. NLR also includes leukopenia and agranulocytosis.

Interactions. Salicylates and sulfonylurea preparations potentiate the action of biguanides.

CLINICAL PHARMACOLOGY OF ORAL ORAL DRUG-REDUCING DRUGS OF OTHER PHARMACOLOGICAL GROUPS

A-glucosidase inhibitors

This group of PSSPs includes pseudotetrasaccharides (acarbose), which competitively interact with digestive enzymes (sucrose, maltase, dextrase), slowing down the fermentation and absorption of di-, oligo- and polysaccharides, which helps to reduce the level of postprandial hyperglycemia. Acarbose is most effective in patients with isolated post-prandial hyperglycemia and a normal fasting blood glucose concentration.

Flatulence and diarrhea (activation of the intestinal microflora against the background of a high content of carbohydrates in feces) are referred to the NLR of these drugs.

Acarbose alone does not cause hypoglycemia, but can potentiate the sugar-lowering effect of other PSSPs.

Prandial Glycemic Regulators

Prandial glycemic regulators are represented by repaglinide (another drug of this group is nateglinide). Like sulfonylurea derivatives, these drugs stimulate insulin secretion by pancreatic β-cells, but they use a receptor different from the sulfonylurea receptor. In this case, cell stimulation is possible only in the presence of glucose (at a glucose concentration> 5 mmol / L), and the effectiveness of repaglinide is several times higher than the effectiveness of sulfonylurea preparations.

Repaglinide is rapidly absorbed from the gastrointestinal tract, the onset of action is noted already 5-10 minutes after administration, which allows it to be combined with food. Peak plasma concentration is reached after 40-60 minutes, and the duration of action does not exceed 3 hours. Thus, the kinetics of repaglinide allow you to effectively control postprandial hyperglycemia, with a minimal risk of developing hypoglycemic conditions. Repaglinide is excreted by 90% with bile, which allows prescribing the drug to patients with impaired renal function.

Repaglinide is prescribed in a dose of 0.5 to 4 mg before meals (2-4 times a day). If the patient is not going to eat, the next dose should be canceled.

Thiazolidinediones

The action of thiazolidinediones (pioglitazone, rosiglitazone) is to increase the sensitivity of tissues to insulin. However, unlike biguanides, the agents of the thiazolidinedione series affect the transcription of genes responsible for the transmission of the effects of insulin in cells, and, therefore, it takes several months to realize their effects. Drugs in this group do not cause hypoglycemia, so they can be safely combined with insulin and PSSP.

Pioglitazone is prescribed 1 time per day, regardless of food intake, during the treatment it is necessary to control the activity of liver enzymes.

Dipeptidyl Peptidase-4 Inhibitors

Vildagliptin is a new inhibitor of dipeptidyl peptidase-4, which improves glycemic control by correcting impaired function of pancreatic β-cells, thereby enhancing insulin secretion and decreasing glucagon secretion. The drug is not bio-transformed with the participation of cytochrome P-450, and no drug interactions with the most commonly prescribed drugs have been detected.

KETACACIDOSIS DIABETIC

Diabetic ketoacidosis (DKA) is an emergency condition that develops as a result of absolute (usually) or relative (rarely) insulin deficiency, characterized by hyperglycemia, metabolic acidosis,

and electrolyte disturbances. The extreme manifestation of diabetic ketoacidosis is ketoacidotic coma. Statistics: 46 cases per 10,000 patients, suffering from diabetes. The prevailing age is up to 30 years.

Risk factors

• Late diagnosis of diabetes.

• Inadequate insulin therapy.

• Concomitant acute illnesses and injuries.

• Prior dehydration.

• Pregnancy complicated by early toxicosis.

Key Points

• It is necessary to remember about the mandatory control of glycemia in patients receiving insulin and having any complaints or in the presence of objective symptoms.

• It is necessary to identify concomitant acute diseases (for example, infectious) that contribute to an increase in the concentration of glucose in the blood.

Ketoacidosis should be treated in a hospital setting. In outpatient treatment of a patient with glycemia (but without ketoacidosis), it is necessary to make sure that:

- the patient receives insulin, and the glucose level in the blood begins to decrease;

- the patient can take care of himself and is able to seek help in case of deterioration of health.

DIABETIC COMES. Pharmacological correction.

Diabetic coma is a condition that develops as a result of a lack of insulin in the body in patients with diabetes mellitus. Insulin deficiency leads to an increase in the concentration of glucose in the blood and "hunger" of peripheral insulin-dependent tissues that are unable to utilize glucose without the participation of insulin.

In response to the “hunger” of the body, the synthesis of glucose (gluconeogenesis) and ketone bodies from acetyl-CoA begins in the liver - ketosis develops, and with insufficient utilization of ketone bodies and aggravation of acidosis - ketoacidosis. The accumulation of under-oxidized metabolic products, in particular lactate, leads to the development of lactic acidosis. In some cases, gross metabolic disturbances against the background of diabetes mellitus decompensation lead to the development of hyperosmolar coma.

A diabetic coma can last for a very long time - the most prolonged case in history of a patient being in this condition is more than four decades.

Diabetic ketoacidotic coma is the result of absolute or relative insulin deficiency and a sharp decrease in glucose utilization by body tissues. Most often, it develops in patients with diabetes, characterized, as a rule, by a severe labile course.

The content of glucagon in blood serum in diabetic ketoacidosis is increased and there is a close relationship between an increase in blood glucose-gon levels and an increase in the concentration of glucose and keto acids. Contrinsular hormones, in particular glucagon, increase gluconeogenesis, glycogenolysis, lipolysis and production of ketone bodies in the liver.

Lipolysis is increased so much that the concentration of triglycerides, phospholipids, cholesterol and NEFA often increases by 50%. Massive absorption of lipids into the liver is accompanied by its fatty

infiltration and increase in size. Fatty acids are the source of energy primarily for the muscles, and ketone bodies - for the brain. Lipolysis and proteolysis are stimulated by glucocorticoids, catecholamines, STH and glucagon.

Fatty acids are metabolized in the liver to acetyl-CoA, which is fully oxidized to CO2 and H2O to the Krebs cycle or used for synthesis fatty acids in the processes of lipogenesis. Under normal conditions, only a small portion of it is converted to acetoacetyl-CoA, acetoacetic acid, and b-hydroxybutyric acid. Acetoacetic acid, in turn, turns into acetone. In diabetes, and especially with ketoacidotic coma, an increased breakdown of fats and an increase in their intake in the liver lead to the formation of an excess of acetyl-CoA and enhanced ketogenesis.

An amino acid imbalance also develops, since the concentration of ketogenic amino acids (leucine, isoleucine, valine) increases in the blood plasma with a relative decrease in the level of glucogenic amino acids (glycine, serine, alanine, glutamine), which are spent on gluconeogenesis.

Diabetic ketoacidosis begins with insulin deficiency. An increase in glucose concentration resulting from this, together with an increase in protein catabolism and lipolysis, leads to dehydrating diuresis, depletion of electrolytes, severe hyperglycemia, and severe acidosis. Correction of this condition requires replacement therapy with insulin, electrolytes and fluid

Massive intake of ketogenic substrates (lipids and amino acids) into the liver contribute to an increase in ketogenesis during diabetes decompensation. The progressive accumulation of ketonic acids in the blood causes the depletion of its alkaline reserves, as a result of which the blood pH decreases and metabolic acidosis develops, i.e. ketoacidosis.

The pathogenesis of impaired consciousness and other neuropsychiatric symptoms of diabetic coma is not fully understood. These disorders are usually associated with the following factors:

1) the toxic effect on the brain of excess ketone bodies;

2) cerebrospinal fluid acidosis (possibly intracellular acidosis in the central nervous system);

3) dehydration of brain cells;

4) hyperosmolarity of the intracellular space in the central nervous system;

5) central nervous system hypoxia due to a decrease in 2,3-diphosphoglycerophosphate;

6) a decrease in the content of GABA in the central nervous system.

Hyperosmolar (non-ketonemic) diabetic coma is more common in individuals suffering from mild or moderate severity of diabetes, receiving only diet therapy or sugar-lowering oral medications. Various infections (pneumonia, pyelitis, cis-tit, etc.), acute pancreatitis, burns, myocardial infarction, cooling, inability to quench thirst (in lonely elderly patients bedridden) contribute to the development of hyperosmolar coma.

The absence of ketoacidosis in hyperosmolar coma is due to the fact that, on the one hand, with this pathology, residual insulin secretion is detected, which is insufficient to eliminate hyperglycemia, but quite sufficient to inhibit lipolysis, and on the other, peripheral tissue insulin sensitivity is different from that of ketoacidosis.

The starting point of water-electrolyte disturbances in this type of coma is hyperglycemia, accompanied by an increase in osmotic pressure in the vascular bed. To preserve the isoosmolarity of the media, the compensatory movement of fluid from the cells and extracellular space into the vascular bed begins. At the same time, glucosuria develops and, as a consequence, polyuria develops, since the high osmotic pressure of primary urine prevents the reverse absorption of water in the renal

tubules. This so-called osmotic diuresis leads to a massive loss of not only water, but also electrolytes, primarily ions of Na +, K +, CI +, HCO3.

The restoration of isosmolarity between the three spaces does not occur due to a decrease in hyperosmolarity in the vascular bed, but due to cell dehydration and increased intracellular osmotic pressure.

Compared with ketoacidosis, in hyperosmolar coma, there is an increased tendency to various blood coagulation disorders, especially to disseminated intravascular coagulation (DIC), arterial and venous thromboses.

Lactic acidosis coma is much less common in diabetes than ketoacidosis and hyperosmolar coma. Lactic acidosis can be combined with ketoacidosis or hyperosmolar coma. Sometimes it develops while taking biguanides (phenformin and adebit) in patients with cardiac and renal insufficiency, diseases of the liver, lungs, as well as in shock, blood loss, sepsis.

It is known that the liver is able to metabolize about 3400 mmol of lactic acid per day. But under the conditions listed above, accompanied by significant tissue hypoxia, the formation of lactic acid prevails over the processes of its utilization. Parenteral administration of fluids containing fructose, sorbitol or xylitol also contributes to the development of lactic acidosis.

The general treatment regimen for diabetic coma includes:

• elimination of insulin deficiency and normalization of carbohydrate metabolism;

• optimally fast rehydration of the body;

• restoration of normal extra- and intracellular electrolyte composition;

• restoration of glucose (glycogen) reserves in the body;

• restoration of normal acid-base balance (COR);

• diagnosis and treatment of diseases or pathological conditions that caused a diabetic coma;

• a set of therapeutic measures aimed at restoring and maintaining the functions of internal organs (heart, kidneys, lungs, etc.).

Hypoglycemic (insulin) coma develops in patients with diabetes with the introduction of an excessive dose of insulin or sulfonamides (especially in combination with salicylates, alcohol) due to insufficient intake of carbohydrates with food or in the presence of insulinoma.

Hypoglycemic coma, of course, is determined by neuroglycopenia (a decrease in glucose in the brain). The pathogenesis of hypoglycemic hypoxia is based on energy starvation of neurons, disorganization of redox processes in neurons, i.e. acute substrate hypoxia of the brain

It is brain cells that are most sensitive to hypoglycemia, since they receive energy due to aerobic oxidation of glucose and are not capable of:

1) accumulate glucose in significant quantities;

2) synthesize glucose;

3) metabolize substrates other than glucose and ketone bodies. Moreover, the latter satisfy the energy needs of the brain to an insignificant degree;

4) glucose is extracted in insufficient quantities from extracellular fluid; insulin does not facilitate the flow of glucose from the extracellular fluid into neurons.

Hypoglycemic coma associated with an overdose of insulin requires correction with glucose, and to prevent it and provide detailed instructions to the patient about the time of administration of the drug relative to the intake of food.

Pharmacotherapy of pathologies of carbohydrate metabolism.

Pharmacotherapy of hypoglycemic conditions usually involves enteral or parenteral (intravenous) administration of glucose. In the latter case, it should be remembered that the isotonic plasma glucose solution is its 5% solution, this must be taken into account in order to avoid damage to cells by insufficient or excessive osmolarity during prolonged intravenous infusions, although slow infusion of more concentrated drugs is also acceptable for a short time.

Another approach for hypoglycemia (if only it is not the result of prolonged starvation) is the appointment of drugs that enhance glycogen lysis (adenylate cyclase stimulants such as beta-adrenoreceptor stimulants or phosphodiesterase blockers that destroy cAMP like caffeine and other representatives of this group).

REGULATION OF KETOGENESIS

For the synthesis of large quantities of β-hydroxybutyric and acetoacetic acids, it is necessary to supply the liver with the appropriate amount of free fatty acids and start their oxidation. The stimulus for lipolysis is insulin deficiency, the oxidation of fatty acids is triggered by glucagon. A direct signal to the beginning of oxidation is a decrease in the concentration of malonyl-CoA.

When collecting the patient's history, it is necessary to question:

- the presence of diabetes;

- previous episodes of diabetic ketoacidosis;

- currently taken drugs and any changes or errors when taking them;

- recent illnesses;

- the presence of polyuria, polydipsia and weakness.

Diabetic ketoacidosis

• Hyperglycemia (> 14 mmol / L).

• Metabolic acidosis (pH <7.35 or bicarbonate concentration <15 mmol / L).

• Increase in anionic difference.

• Ketoneemia.

• The presence of ketone bodies in the urine.

Hyperosmolar non-ketoacidotic condition

• The concentration of glucose in the blood is higher (often> 33 mmol / l).

• Lack of acidosis.

• Maximum ketonuria (+) when analyzing urine using indicator strips.

• Higher sodium concentration (often> 150 mmol / L). Keep in mind:

- up to 25% of cases of DKA are noted in patients with newly identified diabetes mellitus.

Evidence needs to be sought:

- dehydration;

- infections (e.g., lobar pneumonia, urinary tract infections);

- concomitant diseases (for example, myocardial infarction, pancreatitis).

Acidosis is suspected in any patient with hyperventilation of the lungs.

Causes of Diabetic Ketoacidosis

• Infection.

• Improper treatment.

• Newly diagnosed diabetes mellitus.

• Other diseases (pancreatitis, myocardial infarction, gastrointestinal bleeding, heart failure).

• Use of drugs or alcohol.

Often, the etiology of DKA remains unknown.

The most common causes of ketoacidosis

• Newly diagnosed diabetes.

• Discontinuation of insulin therapy (regardless of cause).

• Acute infectious disease.

• A sudden (acute) severe illness (such as myocardial infarction).

• Patients receiving continuous infusion of simple insulin through a needle located subcutaneously in the abdominal wall or thigh (portable infusion pump technique) have a significant predisposition to the occurrence of ketoacidosis, since there is no deposition of insulin in the subcutaneous fat.

Clinical picture

• Impairment of consciousness.

• Thirst.

• Polyuria.

• Nausea.

• Pain in the stomach and chest.

• Tachycardia.

• Deep noisy breathing (Kussmaul breathing).

• Smell of acetone from the mouth.

The clinical picture of a ketoacidotic coma is determined by its stage

Stage I (ketoacidotic precoma).

• Consciousness is not impaired.

• Polydipsia and polyuria.

• Moderate dehydration (dry skin and mucous membranes) without impaired hemodynamics.

• General weakness and weight loss.

• Impairment of appetite, drowsiness.

Stage II (beginning ketoacidotic coma).

• Sopor.

• Kussmaul type breath with the smell of acetone in exhaled air.

• Severe dehydration with impaired hemodynamics (arterial hypotension and tachycardia).

• Abdominal syndrome (pseudoperitonitis).

• Muscle tension of the anterior abdominal wall.

• Symptoms of peritoneal irritation.

• Repeated vomiting in the form of "coffee grounds" is caused by diapedetic hemorrhages and the paretic state of the vessels of the gastric mucosa.

Stage III (complete ketoacidotic coma).

• Consciousness is absent.

• Hypoili areflexia.

• Pronounced dehydration with collapse.

RESEARCH

• Quickly measure glucose concentration using special test strips or in capillary blood.

• Take a urine sample and examine it for:

- ketone bodies;

- leukocytes or nitrites: if a pathology is detected, a urine sample is sent for bacteriological examination.

Determine:

- glucose concentration;

- the concentration of urea, creatinine and electrolytes;

- pH and bicarbonate in arterial or venous blood;

- identify ketone bodies;

- count the formed elements of the blood;

- cardiospecific enzymes;

- concentration of amylase;

- concentration of magnesium and phosphates;

- conduct a bacteriological blood test.

Do:

- electrocardiography in 12 leads at once and in dynamics;

- chest x-ray;

- often measure the concentration of electrolytes and glucose to achieve their normal values.

Laboratory research

• Increasing the concentration of glucose in the blood to 17-40 mmol / l.

• An increase in the content of ketone bodies in the blood and urine (sodium nitroprusside reacting with acetoacetate is usually used to determine the content of ketone bodies).

• Glucosuria.

• Hyponatremia.

• Hyperamylasemia.

• Hypercholesterolemia.

• Increased blood urea.

• Serum bicarbonate <10 mEq / L, blood pH lowered.

• Hypokalemia (at the initial stage hyperkalemia is possible).

• Reduction of pCO2.

• Increased osmolarity of blood plasma (> 300 mosm / kg).

• Increase in anionic difference.

Diseases Affecting Results

With concomitant lactic acidosis, a lot of β-hydroxybutyrate is formed, so the content of acetoacetate is not so high. In this case, the reaction with nitroprusside, which determines only the concentration of acetoacetate, can be weakly positive even with severe acidosis.

Special studies

• ECG (especially with suspected myocardial infarction). As a rule, sinus tachycardia is detected.

• Chest x-ray to rule out respiratory tract infection.

DIFFERENTIAL DIAGNOSTICS

• Hypoglycemia.

• Hyperosmolar coma.

• Lactic acidosis.

• Uraemic coma on the background of diabetes.

• Intoxication, trauma, cerebrovascular accident, cardiac pathology.

• Alcoholic ketoacidosis (without hyperglycemia).

MODE

• Hospitalization in the intensive care unit.

• Bed rest.

• The goals of intensive care are the acceleration of glucose utilization by insulin-dependent tissues, the relief of ketonemia and acidosis, and the correction of water-electrolyte balance disturbances.

DRUG EXPOSURE

• Soluble insulin (human genetic engineering) intravenously at an initial dose of 0.1 U / kg followed by infusion of 0.1 U / kg per hour (approximately 5-10 U / h).

• Correction of dehydration:

1) 1000 ml of 0.9% sodium chloride solution for 30 minutes intravenously;

2) then 1000 ml of 0.9% sodium chloride solution for 1 h;

3) then a 0.9% sodium chloride solution at a rate of 500 ml / h (approximately 7 ml / kg per hour) for 4 hours (or until the dehydration is stopped), then infusion is continued at a rate of 250 ml / h (3.5 ml / kg per hour) by monitoring blood glucose.

The volume of solution administered per hour should not exceed an hourly diuresis of more than 500-1000 ml. The total amount of fluid introduced in the first 12 hours should not exceed 10% of body weight!

4. With a decrease in glucose concentration to 14 mmol / L, infusion of a 5-10% glucose solution (+ 3-4 IU ICD for every 20 g of glucose) begins: compensation for the loss of mineral substances and electrolytes.

5. When the concentration of potassium in the blood serum is less than 5.5 mmol / l - potassium preparations (for example, potassium chloride at a rate of 20 mmol / h): at a pH of arterial blood below 7.1 - sodium bicarbonate 3-4 ml / kg body weight.

6. Phosphates - 40-60 mmol with a speed of 10-20 mmol / h.

OBSERVATION

• Monitoring the mental state, vital functions, diuresis every 30-60 minutes until the condition improves, then every 2-4 hours for a day.

• The blood glucose level is determined every hour until a concentration of 14 mmol / l is reached, then every 2-6 hours.

• Level K +, HCO-, Na +, base deficiency - every 2 hours.

• The content of phosphates, Ca2 +, Mg2 + - every 4-6 hours

In patients with dehydration or in a coma, establish:

- central venous catheter;

- urinary catheter for monitoring the amount of urine excreted.

Foreign standards for the treatment of diabetic ketoacidotic coma

• If necessary, carry out resuscitation measures and seek help from other specialists.

• Intravenous infusion first with 0.9% saline at a rate of:

1) 1 liter for 30 minutes;

2) 1 liter for 1 hour;

3) 1 liter for 2 hours;

4) 1 liter for 4 hours

• Intravenous insulin infusion.

• Substitution therapy with potassium preparations after the onset of insulin

notherapy.

• If there are signs of infection, broad-spectrum antibiotics are prescribed (for example, amoxiclav * at a dose of 1.2 g every 8 hours).

• Patients with a hyperosmolar non-ketoacidotic state are prescribed heparin at a dose of 5000 units subcutaneously every 12 hours.

• The concentration of electrolytes and glucose in capillary blood is monitored first hourly, then every 2 hours until the condition stabilizes.

Infusions can be carried out if necessary at a slower rate if none of the following is found:

- shock;

- oliguria during the first 4 hours after admission;

- renal failure (urea concentration> 21 mmol / L or creatinine> 350 μmol / L).

Intravenous Insulin Therapy

To 50 ml of 0.9% sodium chloride solution add 50 IU of soluble insulin (actrapid). Infusion is carried out using a scale

It may be necessary to change the regimen of insulin therapy depending on the nature of the patient's response.

• Monitor vital signs, electrolyte concentration, and diuresis.

• The insulin infusion continues:

1) to a decrease in glucose concentration of less than 10 mmol / l;

2) until the disappearance of ketonemia (concentration of β-hydroxybutyrate less than 0.5 mmol / l).

As soon as stabilization occurs and the patient begins to eat, insulin preparations begin to be administered subcutaneously.

• After the first subcutaneous dose of insulin is administered, the infusion is stopped after an hour if the patient is in a satisfactory condition.

• The patient is sent to an endocrinologist or diabetologist and is provided with information about diabetes. It is necessary to monitor the possible development of cerebral edema in patients under the

age of 30 years, especially in those of them whose sodium concentration did not increase during rehydration.

If the glucose concentration is less than 10 mmol / l, but ketonemia persists, continue the infusion of insulin with 5 or 10% glucose solution to maintain its concentration in the blood within 5-10 mmol / l

• Half of the patients have a relapse of DKA.

HYPEROSMOLAR HYPERGLYCEMIC NECO-ACIDOTIC COMA

Diabetic hyperosmolar coma is a special type of diabetic coma that occurs with extremely high hyperglycemia in the absence of ketoacidosis.

Clinical picture

• The concentration of glucose in the blood is usually more than 50 mmol / l.

• Lack of ketoacidosis or slight ketoaciduria.

• An increase in body temperature (often occurs in this condition).

Risk factors

1. Taking medications that increase the concentration of glucose in blood.

2. Surgery and comparable stressful situations.

3. Acute diseases.

- Infections.

- Diabetic gangrene.

- Urethritis.

- Sepsis.

- Burns.

- Gastrointestinal bleeding.

- Acute brain damage (paralysis).

- Myocardial infarction.

- Pancreatitis.

4. Chronic diseases.

- kidney disease.

- Heart disease.

- Arterial hypertension.

- cerebral infarction.

- Alcoholism.

- Dehydration due to insufficient fluid intake due to mental illness.

Pathogenesis

• Insulin deficiency causes hyperglycemia, followed by glucosuria, osmotic diuresis and polyuria, enhancing previous dehydration.

• Hypovolemia develops with increased secretion of aldosterone, contributing to sodium retention, hypokalemia and increased blood osmolarity.

• Hyperosmolarity of the blood leads to a violation of hemodynamics (arterial hypotension), oliguria and anuria.

• Increased tendency to thrombosis with the possible development of ICE.

• Dehydration of the brain leads to the appearance of neurological symptoms (convulsions, nystagmus, hemiparesis).

• The absence of ketoacidosis is explained by partially preserved production of endogenous insulin, sufficient to block lipolysis and ketogenesis, but not enough to reduce hyperglycemia.

The clinical picture is determined by dehydration.

Diagnostics

• Hyperglycemia (44-55 mmol / L or more) and glucosuria.

• Hypernatremia.

• Hypokalemia.

• Hyperchloremia.

• Hyperazotemia.

• Increased plasma osmolarity above 360 mosm / kg.

• The reaction to acetone and urine is negative.

Treatment

Extremely important:

- early diagnosis of hyperosmolar hyperglycemic non-ketoacidotic coma;

- adequate rehydration;

- correction of hyperglycemia with short-acting insulin preparations;

- restoration of electrolyte balance;

- treatment of background diseases (e.g. infections). During the first 2 hours

•0.45% solution of sodium chloride 2 l intravenously with the addition (with a decrease in serum potassium level) of 8-5 ml of a 10% solution of potassium chloride.

• Soluble insulin (human genetic engineering) 20 IU intravenously, then 5-8 IU every hour intravenously or intramuscularly. When the concentration of glucose in the blood plasma drops to 200-300 mg% (11-12 mmol / l), 5% glucose solution is injected to prevent hypoglycemia.

Follow-up treatment

• Continued administration of a 0.45% sodium chloride solution at a rate of 1 l / h until normalization of CVP or osmolarity of blood.

• Continued infusion of potassium chloride with severe hypokalemia.

• Continued administration of insulin at a dose of 5-8 U / h intramuscularly or intravenously until blood glucose levels normalize.

Successful treatment requires a good laboratory base, experience with insulin therapy and the correction of water-electrolyte disturbances.

After emergency treatment, diet and oral medications are necessary.

Complications

Cerebral edema with excessive administration of 0.45% sodium chloride solution.

The purpose of the lesson:

To learn:

I. Diabetes mellitus - etiology, pathogenesis, clinical features, diagnosis

II. Classification of insulin preparations:

1) by origin;

2) by the speed of the onset of effects and their duration;

3) according to the method of purification and degree of purity of the preparations.

I. By origin distinguish:

a) natural (biosynthetic), natural, insulin preparations made from the pancreas of cattle, for example, insulin GPP tape, ultralente MS and more often pigs (e.g. actrapid, insulrap SPP, monotard MS, semelent and other);

b) synthetic or, more precisely, species-specific, human insulin. These drugs are obtained using genetic engineering methods by DNA recombinant technology, and therefore they are most often called DNA recombinant insulin preparations (actrapid NM, homofan, isofan NM, humulin, ultratard NM, monotard NM, etc.).

II. According to the method of purification and purity of the drugs are distinguished:

a) crystallized (poorly purified), but not chromatographed — these are most of the so-called “traditional” insulin preparations — insulin for injection, but discontinued;

b) crystallized and filtered through gels ("molecular sieve") - the so-called single or mono-peak insulins (actrapid, insulrap, etc.);

c) crystallized and purified by means of a "molecular sieve" and ion exchange chromatography — the so-called monocomponent insulins (ac-trapid MS, semilent MS, monotard MS, ultra-MS).

III. The speed of the onset of effects and their duration distinguish:

a) short-acting drugs (actrapid, actrapid MS, actrapid NM, insulrap, homeopath 40, insuman rapid, etc.). The onset of action of these drugs is in 15-30 minutes, the duration of action is 6-8 hours;

b) drugs of average duration of action (the onset of action after 1-2 hours, the total duration of the effect is 12-16 hours); - semilent MS; - hu-mulin N, humulin tape, homophane; - tape, tape MS, monotard MS (2-4 hours and 20-24 hours, respectively);

• Iletin I NPH, Iletin II NPH;

• insulong SPP, insulin tape GPP, SPP, etc.

c) drugs of medium duration mixed with short-acting insulin: (onset of action 30 minutes; duration - from 10 to 24 hours);

• Actrafan NM;

• Humulin M-1; M-2; M-3; M-4 (duration of action up to 12-16 hours);

• insuman comb. 15/85; 25/75; 50/50 (valid for 10-16 hours).

d) long-acting drugs:

• ultra tape, ultra tape MS, ultra tape NM (up to 28 hours);

• insulin superlente SPP (up to 28 hours);

• humulin ultralente, ultratard NM (up to 24-28 hours).

According to the duration of action, the following groups are distinguished:

Ultra-short-acting insulins (the hypoglycemic effect develops 10–20 min after sc administration, the peak of action is achieved on average in 1-3 hours, the duration of action is 3-5 hours):

- insulin lispro (Humalog);

- insulin aspart (NovoRapid Penfill, NovoRapid Flexpen);

- insulin glulisin (Apidra).

Short-acting insulins (onset of action usually after 30-60 minutes; maximum action after 2-4 hours; duration of action up to 6-8 hours):

- soluble insulin [human genetic engineering] (Actrapid HM, Gene-Sulin P, Rinsulin P, Humulin Regular);

- soluble insulin [human semisynthetic] (Biogulin R, Humo Dar R);

- soluble insulin [pork monocomponent] (Actrapid MS, Monodar, Monosuinsulin MK).

Sustained-release insulin preparations - include drugs of medium duration and long-acting drugs.

Medium-duration insulins (beginning after 1.5–2 hours; peak after 3–12 hours; duration 8–12 hours):

- insulin-isophan [human genetic engineering] (Biosulin N, Gansulin N, Gensulin N, Insuman Bazal GT, Insuran NPH, Protafan NM, Rinsulin NPH, Hu-mulin NPH);

- insulin-isophan [human semi-synthetic] (Biogulin N, Humodar B);

- insulin-isophan [pork monocomponent] (Monodar B, Protafan MS);

- insulin-zinc suspension compound (Monotard MS).

Long-acting insulins (onset after 4–8 hours; peak after 8–18 hours; total duration 20–30 hours):

- insulin glargine (Lantus);

- insulin detemir (Levemir Penfill, Levemir Flexpen).

Combined-action insulin preparations (biphasic drugs) (the hypoglycemic effect begins 30 minutes after sc administration, reaches a maximum in 2–8 hours and lasts up to 18–20 hours):

- biphasic insulin [human semisynthetic] (Biogulin 70/30, Hu-modar K25);

- two-phase insulin [human genetic engineering] (Gansulin30R, Gene-sulin M 30, Insuman Comb 25 GT, Mikstard 30 NM, Humulin M3);

- insulin aspart two-phase (NovoMix 30 Penfill, NovoMix 30 Flek-sPen).

III. Classification of oral hypoglycemic drugs

1. Prizvodnye sulfonylurea:

I generation: Carbutamide (INN) - tab. Cn B Bukarban (Hungary); Chloro-pronamide (INN) - tab. Cn B (Poland, Russia).

2 generations: Glibenclamide (INN) in the amount of 21 trade names, including Gilemal (Hungary), Glibenclamide (Russia, Germany, etc.), Daonil (Germany, India), Maninil (Germany), etc.

Glyclazide (INN) - tab. Cn B. (Switzerland, India), Glidiab (Russia), Dia-concrete (France), etc.

Glipizide (INN) - tab. Cn B. Minidiab (Italy), Glibenez (France).

Glycvidone (INN) - tab. Cn B. Glurenorm (Austria). Glidifen

3 generations: Glimeniride (INN) —tab. Cn B. Amaril (Germany).

2. Biguanides:

Buformin (INN) - Dragee, Sp. B. Silubin Retard (Germany),

Metformin (INN) tab. Cn B (Poland, Croatia, Denmark), Gliformin (Russia), Glyukofag (France), Siofor (Germany), etc.

3. Alpha glucosidase inhibitors:

Acarbose (INN), Gluco-bye, and Miglitol (INN) - Diastabol (Germany).

4. derivatives of carbamoylbenzoic acid, exhibit prandial glycemic regulators

Repaglinide (INN) - tab. Cn B NovoNorm, Nateglinide (INN) - tab., Starlix

5. Insulin sensitizers, - glitazones or thiazolidinediones.

Rosiglitazone (INN) - tab., Avandia (France);

Pioglitazone (INN) - tab., Aktos (USA).

6. Combined oral hypoglycemic agents, Glibomet

contains glibenclamide and metformin, tab. (Italy).

7. Herbal hypoglycemic agents

Arfazetii - contains blueberry shoots, cusps of common bean fruit, Manchurian aralia root or rhizome with roots of a zamanicha, rosehips, horsetail, St. John's wort, chamomile flowers (Russia, Ukraine).

In diabetes mellitus, the following plant raw materials can be used: Aralia, Manchurian root, Aralia tincture, Psoralei, stone fruit, etc.

8. Insulin antagonist - Glucagon - lyophilized powder in a vial. with solvent for injection. Cn B. Gluka, Gene HypoKit (Denmark).

IV. Coma for diabetes - pharmacology, correction

1. Hypoglycemic coma

2. Hyperglycemic coma

Ketoacidotic,

Hyperosmolar (non-ketonemic) diabetic,

Lactic acidosis coma

V. Diabetic coma treatment regimen

• elimination of insulin deficiency and normalization of carbohydrate metabolism;

• optimally fast rehydration of the body;

• restoration of normal extra- and intracellular electrolyte composition;

• restoration of glucose (glycogen) reserves in the body;

• restoration of normal acid-base balance (COR);

• diagnosis and treatment of diseases or pathological conditions that caused a diabetic coma;

• a set of therapeutic measures aimed at restoring and maintaining the functions of internal organs (heart, kidneys, lungs, etc.).

Know:

1. Etiology, pathogenesis, clinic, complications, diabetes

2. Research methods for diabetes

3. The main etiological factors and pathogenetic mechanisms that are the subject of drug exposure

4. Pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics, interaction of the above drugs

5. The principles of complex therapy - diabetic com

Be able to:

a) select the necessary drugs for a particular patient with the indicated pathology, select criteria for therapeutic efficacy and safety;

b) prescribe combination therapy;

The list of practical works:

Homework.

1. To study the main tasks and directions of the choice of medicines for cholecystitis, pancretitis

Control of the intermediate level of knowledge.

1. The choice of sugar-lowering drugs in type 1 diabetes

2. The choice of sugar-lowering drugs in type 2 diabetes

3. The choice of sugar-lowering drugs for diabetes mellitus of the second type, with pregnancy,

4. The choice of sugar-lowering drugs for diabetes and coronary heart disease,

5. The choice of hypoglycemic drugs in diabetes and obesity

6. Make an urgent care plan for a diabetic coma of hyo- and hyperglycemic

The decision of situational problems

Task number 1.
Partient Ch., 63 rokiv, the guard є on chukrovia diabetes. By stretching the remaining rock, I take the Butamid preparation 1 g 2 times a day. With the drive of a cold catarrh, Ioma bouillon is prescribed aspirin 0.5 g 2 times a day, biseptol-480 1 table. 2 times a day and tetracycline, 1 tablet 2 times a day. In the evening, the camp of condolences was significantly lost, in New Mali there are all signs of hymn.
What is the reason for this apparition? Who can you recommend a given vipad?
Task number 2.

Patient K., 32 rokiv, guards є on chukrovia diabetes. Independently introduced sob 25 OD insulina, which is why she has a vinikla rizka weakness. Hvora went to the pharmacy, she rang for help. In the pharmacy, she won the hospitality, with the test of the area from a non-wining court.

What is the reason for the camp? Can I help Yaku need nadati ailment?
Task number 3.
Patient D., 42 rock, guard on hyperthyroidism. I will stretch the therapy for two times: merkazolil 0.01 g 2 times a day, propranolol 60 mg per day, tincture valeriani 20 drops 3-4 times a day. Insider likuvannya changed: psycho-motional lability, dratlivost, tachikardiya, pitlivist.
Can you help me on the basis of this effectiveness about the effectiveness of anti-thyroid therapy merkazolil? Go ahead.
Task number 4.
Patient M., 52 rokiv, having bent his iz zakargami on the ground for weakness, sprague, often sechovipuskannya, overborg shkiri. When thoroughly honored, I respect obesity (100 kg weight with a height of 167 cm), glucose in blood - 7.8 mmol / l, in section - 1% zucru, re-action on acetone is negative.
Yaki tsukroznizhuyuchi likarski sobbi need to recommend in this video pad? Sviy vibir obgruntuyte.
Task number 5.
Patient K., 63 years old, suffers from non-insulin-dependent diabetes mellitus for 8 years of moderate severity. Constantly uses glibenclamide. In the last three months, furunculosis has been identified. Currently, she has been admitted to the therapeutic department with complaints of cough with scanty mucopurulent sputum, fever up to 37.60 ° C, chills, pain in the right half of the chest with a deep breath. During examination: vesicular breathing, moist fine-bubbling rales, weakening of percussion sound are weakened to the right below the angle of the patches. There radiographically: focal shadows of small caliber. A decrease in renal excretory function was also revealed: creatinine clearance of 25 ml / min.
Formulate a preliminary diagnosis. What additional screening methods would you recommend? Make a differentiated choice of priority antimicrobial pharmacotherapy with an indication of the dosage regimen of the selected drug. Specify methods for monitoring the effectiveness of treatment.
Task number 6.
The patient, 13 years old, fell ill acutely: there was a thirst, polyuria, general weakness. For 2 weeks he lost 4 kg. Objectively: general condition satisfactory, no acetone breath. The level of glucose in the blood is 32 mmol / l, in the urine - 6%, acetone (+).

What diagnosis do you make? What is the treatment tactic?
Task number 7.
The child's mother, 6 years old, notes that over the past 2 weeks the child constantly goes to the toilet several times, drinks a lot of water, has lost weight, and periodically complains of abdominal pain. Objectively: the skin is pale, dry, peeling on the soles, blush on the cheeks. Lips and tongue bright red, dry. Internal organs without features. Smell of acetone from the mouth. Glycemia - 12 mmol / L.
What diagnosis do you make? What therapy is appropriate in the near future?
Task number 8.
A 44-year-old patient was hospitalized in the endocrinology department with newly diagnosed, untreated diabetes mellitus. A clinical diagnosis is made: diabetes mellitus, first detected. Glycemic profile 'nato-schak - 21 mmol / l; in 1500 - 23.5 mmol / l; 2000-19.8 mmol / L. Glucose in the daily amount of urine is 22 mmol / l.
What is the insulin drug that should be prescribed to the patient. Calculate the starting dose, frequency and time of injection. Indicate further steps in the treatment of hypoglycemic drugs, criteria for evaluating the effectiveness and safety of therapy.
Task number 9.
Patient, 49 years old, height 160 cm, body weight 92 kg. Diagnosis: diabetes mellitus, type II, moderate, decompensated. Obesity II degree. Takes maninil I table. 3 times a day. Glycemic profile: on an empty stomach - 10.2 mmol / l; 1200--9.8 mmol / L; 1500-7.9 mmol / l; 2000-- 8.5 mmol / L.
Choose a compensating dose of oral sugar-lowering drugs.
A patient, 68 years old, height 172 cm, body weight 105 kg. He suffers from diabetes for 10 years. Takes ITSS-40 ED in the morning before breakfast. Diagnosis: diabetes mellitus, type I, moderate, decompensated. Obesity II degree. Glycemic profile: on an empty stomach - 6.8 mmol / l; 1200 - 10.5 mmol / l; 1,500 - 12.6 mmol / l; 2000 - 10.5 mmol / L. Choose a compensating dose of sugar-lowering drugs
Task number 10.
A man, 52 years old, has been ill with diabetes for 18 years. A year ago, he suffered cystitis. Takes maninil 0.005 g 3 times a day. Objectively: height - 176 cm, body weight - 82 kg. Fluctuations in fasting glycemia - 10.3-12.4 mmol / L. Proteinuria was detected - 0.033 g / l.
What is the treatment tactic for preventing the progression of diabetic nephropathy?
Task number 11.
A patient with diabetes needs to remove the root of the tooth. However, the patient complains of weakness, nausea, thirst, dry mouth. Similar phenomena have been taking place already on the 2nd day. During the inspection, attention is drawn to: dry skin, decreased tkrgor, dry tongue. Isorta has a specific odor of acetone.
Assess the patient's condition. Plan a patient examination plan. Prescribe pathogenetic therapy, aimed primarily at preventing the development of coma. Give recommendations for the rational preparation of the patient for surgery.
Task number 12.
At the dentist's appointment, the patient developed the following symptoms: a sharp excitement, which turned into an unconscious state. The skin is pale, covered with cold sweat, turgor is normal. The tongue is wet. The patient suffers from diabetes for a long time, receives inulin therapy.
Your diagnosis. Prescribe urgent therapy to this patient.

TESTS

1. The patient, 13 years old, fell ill acutely: there was a thirst, polyuria, general weakness. For 2 weeks he lost 4 kg. Objectively: the general condition is satisfactory, there is no smell of acetone from the mouth. The level of glucose in the blood is 32 mmol / l, in the urine - 6%, acetone (+). What is the treatment tactic?
A. The sulfonylurea preparation.
B. Insulin prolonged.
C. Biguanides.
D. Short acting insulin.

E. Diet.
2. The child's mother, 6 years old, notes that for the last 2 weeks the child constantly goes to the toilet several times, drinks a lot of water, lost weight, periodically complains of abdominal pain. Objectively: the skin is pale, dry, peeling on the soles, blush on the cheeks. Lips and tongue bright red, dry. Internal organs without features. Smell of acetone from the mouth. Glycemia - 12 mmol / L. Which therapy is feasible in the near future?
A. Biguanides.
B. Diet therapy.
C. Medium duration insulin.
D. Simple insulin.
E. Long-acting insulin.
3. A patient with diabetes was prescribed insulin. What is one of the mechanisms of action of this drug?
A. Inhibition of amino acid transport.
B. Activation of gluconeogenesis.
C. Inhibition of glycogenolysis.
D. Inhibition of triglyceride synthesis.
E. Inhibition of glucose utilization.
4. A patient with diabetes was prescribed insulin. What is the mode of administration of this drug?
A. 40 minutes after eating.
B. Before going to bed.
C. 30 minutes before meals.
D. with food.
E. 1.5 hours before meals.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
CLINICAL-PHARMACEUTICAL PRINCIPLES OF SELECTION OF DRUGSS APPLICABLE FOR THE TREATMENT OF THE THYROID GLAND DISEASES

Purpose of the topic

Diseases of the thyroid gland are among the most common disorders of the endocrine system; in women they are 10 times more common than in men.
Currently, various diseases of the thyroid gland affects 10-12% of the world's population. According to some reports, the prevalence of thyroid diseases is even higher than is known today. This is due to the frequent asymptomatic or subclinical course of many of its diseases. Thus, thyroid hormone preparations are among the thirteen of the most commonly prescribed drugs in the United States. In the UK, more than 1% of the country's population receives these hormones.
Motivational characteristic of the topic.
The thyroid gland is the largest endocrine gland of the human body, which has only intracretory function. Its mass in an adult is about 15-20 g. The thyroid gland consists of two lobes and an isthmus located on the front surface of the trachea and along its sides (Fig. 1). Sometimes an additional pyramidal lobe departs from the isthmus. The thyroid gland develops from a protrusion of the middle of the bottom of the primary pharynx. Her bookmark occurs at 15 weeks of fetal development, by 18-20 weeks she begins to produce thyroid hormones. In cases of thyroid embryogenesis, various anomalies of its location may develop. These include cysts of the thyroid-ovarian duct, lingual thyroid gland, as well as median and lateral remains of thyroid tissue.
The thyroid gland consists of two different types of cells: follicular and parafollicular (C-cells). The follicular cells producing thyroxin (T4) and tri-odtironin (T3) form numerous follicles in the iron, each of which consists of a central cavity filled with a colloid, the main component of which is thyroglobulin protein, surrounded by one layer of cuboid-like epithelial cells (Fig. 2). Parafollicular cells (C-cells) produce the protein hormone calcitonin.
T4 and T3 are synthesized from the amino acid tyrosine. In addition, there is a biologically inactive reversible triiodothyronine (pT3), which is formed by the deiodination of the inner T4 ring .
A necessary structural component of thyroid hormones is iodine. This trace element is almost completely absorbed in the intestine, from where it enters the blood plasma in ionized form. The transfer of iodine into the thyrocyte is energy-dependent and is carried out in conjunction with the reverse transportation of sodium by the sodium iodide symporter (NIS). In cells, the iodine ion is oxidized, after which it undergoes organization, joining the residues of the tyrosine amino acid molecules that are present in the thyroglobulin synthesized by follicular cells. After this, thyroglobulin changes its structure so that tyrosyl residues come closer to each other, facilitating the

condensation reaction between them. The iodination of tyrosyl residues and the condensation reaction occur with the participation of thyroid peroxidase (TPO), localized in the microsomal fraction of follicular cells. Next, thyroglobulin containing bound iodothyronines is transported through the apical membrane and deposited in the colloidal cavity of the follicle, after which it is reintroduced into thyrocytes, moves to their basement membrane, releases iodothyronines, which are released into the blood. Once in the blood, T4 and T3 are distributed throughout the body mainly in plasma protein bound (thyroxin-binding globulin, prealbumin (transthyretin), albumin). The half-life in blood for T4 is 7-9 days, for T3 2 days.

Free iodothyronines penetrate relatively easily through the cell membrane. The intracellular effects of thyroid hormones are closely related to the processes of their metabolism (primarily with the mechanisms of deiodination). The most important of these transformations is the conversion of T4 to more active T3. Since T3, rather than T4, directly interacts with thyroid hormone receptors, the latter is usually considered as a prohormone, and T3 as a true hormone. T3, acting on specific nuclear receptors that are present in most cells, leads to a change in the expression of various genes, which is manifested by the physiological effects of thyroid hormones, the main of which is the regulation and maintenance of basic metabolism. Only 5-10% of T3 circulating in the blood is synthesized directly by the thyroid gland; most of it is formed as a result of T4 deiodination in peripheral tissues. The conversion (conversion) of T4 to T3 is catalyzed by various deiodinases with tissue specificity.

The function of the thyroid gland is regulated by the adenohypophysis by the principle of negative feedback. The thyroid stimulating hormone (TSH) of the pituitary gland stimulates the production of thyroid hormones, which suppress the production of TSH (Fig. 4).

The effects of thyroid hormones are diverse. They provide maintenance of the main metabolism in most cells, regulating their metabolic activity, as well as proliferation and apoptosis. A normal level of thyroid hormones is necessary for the functioning of all body systems, and in cases of thyroid dysfunction, pathological changes are polysystemic in nature. Thyroid hormones are necessary for the formation of the nervous and other systems of the fetus and newborn. Thyroxine deficiency during this period leads to significant neurological disorders.

Hormones produced by the thyroid follicle epithelium are called thyroid. They include thyroxine and triiodothyronine. In addition to thyroid hormones, the hormone calcitonin is also produced in the gland, which lowers the calcium content in the blood by depositing it in the bones. Recently, calcitonin has been shown to inhibit the secretory activity of many digestive and endocrine glands.

The role of thyroxine and triiodothyronine hormones:

- provide the main body metabolism, increase oxygen consumption by tissues;
- prevent the deposition of fat, reduce overall weight;
- provide physical and mental development.

With a lack of these hormones in children, cretinism develops, in adults - myxedema. Hyperthyroidism is called bazedovoy disease.

In general, the effect of thyroid hormones is traditionally described as calorigenic: under their action, an increase in the main metabolism occurs due to an increase in oxygen consumption and an increase in the heat production of tissues.

METHODS FOR EXAMINING PATIENTS WITH DISEASES OF THE THYROID GLAND

Physical methods

Clinical diagnosis of thyroid disease involves the identification of symptoms of thyrotoxicosis, hypothyroidism, as well as changes in the structure of the thyroid gland, which can occur against the background of its normal, reduced and increased function. In the diagnosis of thyroid diseases, an important place is occupied by these palpations. In the vast majority of people, the thyroid is normally quite palpable. Palpation can be difficult in obese patients and in men with severe neck muscles. Feeling of the thyroid gland is carried out during the swallowing of saliva, when the larynx together with the thyroid gland first rises and then falls down. At this moment, the thyroid gland rolls through the fingers and feels like a soft-elastic roller. During palpation, the doctor can face the patient’s face (palpation is done with two thumbs) or be in the back (the patient is sitting) and palpate the thyroid gland with two index and middle fingers (Fig. 5).

It should be borne in mind that thyroid palpation is not an accurate method for assessing the size and structure of the thyroid gland - the probability of an erroneous conclusion reaches 30% or more. Nevertheless, indications for the use of more accurate methods for assessing thyroid function, such as ultrasound, are precisely the results of palpation. Currently, the most common classification proposed by WHO for estimating the size of endemic goiter in epidemiological studies

This classification proceeds from the fact that the sizes of the thyroid lobes normally correspond to the size of the distal phalanx of the patient's thumb. If, according to palpation, the proportion of the thyroid gland exceeds this size, but the gland itself is not visible during examination, they say goiter I degree. If the gland is visible during examination, they talk about goiter of the II degree (visible goiter). The advantages of this classification are its simplicity and accessibility, as well as the ability to compare data on the prevalence of goiter in different regions. It should be borne in mind that this classification was created primarily for the epidemiological assessment of the prevalence of endemic goiter.

Laboratory methods

The main method for evaluating thyroid function is to determine the level of TSH. Without determining the level of TSH according to modern concepts, the assessment of the thyroid function in most cases is incorrect. If an increased level of TSH is detected, the study is supplemented by a determination of the level of T4, with a decreased level of TSH - T4 and T3 (Figure 6). The often practiced appointment of three hormone tests at once (TSH, T4 and T3) for the diagnosis of thyroid diseases (or monitoring the effectiveness of their treatment) is clearly excessive and significantly increases the cost of the examination.

The production of TSH by the pituitary and T4 of the thyroid gland is in a negative logarithmic relationship. In other words, with a minimal change in the level of thyroid hormone production, a multiple opposite change in the level of TSH occurs. This pattern underlies the isolation of the so-called subclinical thyroid dysfunction, which means an isolated change in TSH levels at a normal level of thyroid hormones.

Subclinical hypothyroidism (minimal thyroid insufficiency) is an isolated increase in TSH level at a normal level of T4, and subclinical thyrotoxicosis is a decrease in TSH level at a normal level of T4 and T3. In the latter case, that is, when a decreased level of TSH is detected, as indicated, it is necessary to determine both thyroid hormones (T4 and T3), since it is possible that a decrease in TSH is accompanied by a normal level of T4, but increased T3 (T3-thyrotoxicosis), which is more common with multinodular toxic goiter in elderly patients. It is important to note that the fact of the presence or absence of clinical symptoms for the diagnosis of subclinical thyroid dysfunction does not matter: these phenomena have exclusively laboratory diagnostic criteria. By explicit or manifest hypothyroidism is meant a situation where, along with an increased level of TSH, a decrease in the level of T4 is determined, and by explicit or manifest thyrotoxicosis is a situation where, along with a reduced level of TSH, the blood concentration of T4 and T3 is increased

Modern methods of hormonal research make it possible to determine the common fractions of T4 and T3 (free hormone + bound) and the individual level of free T4 and T3. The definition of the latter with rare exceptions (patients in the intensive care unit) has a significantly greater diagnostic value. Firstly, this is due to the fact that it is free thyroid hormones that have biological activity, and secondly, fluctuations in the level of binding proteins that occur in a number of diseases and conditions are not reflected in their concentration.

Determination of thyroglobulin level is used to monitor patients who received complex therapy (thyroidectomy + 131I therapy) according to highly differentiated thyroid cancer. In patients who underwent complete ablation of thyroid tissue, the appearance (increase) in the level of thyroglobulin in the blood may indicate a relapse of the tumor.

For the diagnosis of autoimmune thyroid diseases, the level of various autoantibodies is used. Classical antibodies include antibodies to thyroglobulin (AT-TG) and antibodies to thyroid peroxidase (AT-TPO). These antibodies are a surrogate marker for any autoimmune thyroid pathology, that is, determining their level does not allow to differentiate numerous autoimmune thyroid diseases. They are determined in approximately 70-90% of patients with autoimmune thyroiditis, in 75% of patients with Graves' disease, and no less than 10% of healthy people without

impaired thyroid function. A more specific study is the determination of antibodies to the TSH receptor (AT-rTTG), which are determined in most cases of Graves disease.
Determination of calcitonin level is used to diagnose medullary thyroid cancer (cancer originating from C cells), and its basal level and its dynamics after administration of stimulants such as pentagastrin and calcium gluconate can be estimated.
Determination of urinary iodine excretion is used as part of epidemiological studies to assess the severity of iodine deficiency in a particular area. In clinical practice, that is, for the diagnosis of any disease, this study is not used. An exception is iodine-induced thyroid disease, in which, to confirm the fact that an excess of iodine enters the body, the level of ioduria can be estimated, which in this case will be significantly increased.
Instrumental methods
Instrumental methods for examining patients with thyroid disease include ultrasound, scintigraphy, puncture biopsy, computed tomography and magnetic resonance imaging, as well as a number of other methods. The simplest, most informative, safe and non-invasive method for thyroid research is ultrasound, which allows you to accurately determine the size of the lobes, the presence and size of nodular formations, and features of the echostructure Ultrasonic monitoring significantly increases the information content of thyroid puncture biopsy.
Features of the echostructure of both the thyroid gland itself and the nodular formations found in it in combination with data from other research methods can have important diagnostic value, however, ultrasound itself does not allow us to establish the morphological structure of the revealed changes. An important question that can be answered by ultrasound is the estimation of thyroid volume. To calculate the volume of the thyroid gland share, its largest dimensions are determined in three projections. The product of the obtained results is multiplied by the elliptic coefficient (0.479)
In adult women, the thyroid volume normally does not exceed 18 ml, in adult men - 25 ml. Thus, goiter or pathological enlargement of the thyroid gland should be considered an excess of its volume in women more than 18 ml, and in men - more than 25 ml according to ultrasound Unified approaches to assessing thyroid volume in children are currently lacking. The easiest way is to use approximate age standards; in epidemiological studies, as a rule, the use of standards is adopted, which takes into account the surface area of the child's body.
If a hormonal study evaluates the function of the thyroid gland, and palpation and ultrasound - its structure, then thyroid scintigraphy allows you to get its morphofunctional characteristic, in particular, to evaluate two main parameters: capture of the radiopharmaceutical and its distribution in the thyroid gland. Actually, to assess the size, identify structural changes (the presence of nodes) and thyroid function, scintigraphy is uninformative. For thyroid scintigraphy, the technetium 99mTc-pertechnetate (99mTc) isotope is most often used, which is a monovalent anion, like iodide, which is actively captured by the thyroid gland, but unlike iodine, it is not subject to organization. A short half-life of 99 tTc (6 h), along with a slight absorption of the thyroid isotope, significantly reduces the radiation dose. 99tTc is administered intravenously and is tested almost immediately after administration of the isotope. The main indications for scintigraphy with 99mTc are:
• differential diagnosis of various pathogenetic variants of thyrotoxicosis: true thyroid hyperfunction (Graves' disease, thyroid functional autonomy) and destructive thyrotoxicosis (postpartum thyroiditis, genital thyroiditis, amiodarone-induced thyrotoxicosis type 2). In the first case, scintigraphy will determine an increase in capture of 99 tTs (Fig. 9 a), and in the second case, its decrease or complete absence);
• diagnosis of compensated (against euthyroidism) and decompensated (with thyrotoxicosis) functional thyroid autonomy. According to this indication, the study is most often carried out with nodular and multinodular goiter.
When diagnosing thyroid functional autonomy, several scintigraphic characteristics of nodular formations are distinguished. A “hot” or autonomously functioning node is diagnosed in cases where the thyroid gland, which is determined by ultrasound as a node, accumulates more isotope than normal tissue. The accumulation of the isotope in the tissue surrounding the node can be either reduced or completely suppressed; in this case, only a hyperfunctioning node is visualized. Warm nodes have the same level of isotope accumulation as the surrounding tissue. “Cold” nodes are

defined as defects in the accumulation of the isotope on the scintigram (Fig. 9 g). Functionally, they have normal or reduced activity. Thyroid scintigraphy does not allow us to draw a conclusion about the morphology of nodular formations: a fine-needle biopsy is most valuable in this regard. “Cold” nodes turn out to be malignant tumors in about 5-8% of cases, “hot” nodes are extremely rare.

Along with 99tTc, two iodine isotopes are used for thyroid scintigraphy: 131I and 123I. Due to the relatively large radiation dose and a relatively long half-life, the use of 131I is limited to situations when, based on the indicators of its capture and elimination from the thyroid gland, the treatment dose of the same isotope is calculated (therapy of 131I toxic goiter and thyroid cancer). In addition, it can be used to visualize the functioning, not having lost the ability to capture iodine, metastases of highly differentiated thyroid cancer. For this purpose, it is much more convenient to use 123I, since scintigraphy in this case can be carried out after a short period of time after the introduction of the isotope.

Since, unlike 99tTc, iodine isotopes undergo organization, they are indispensable for the etiological diagnosis of congenital hypothyroidism associated with defects in the organization of iodine. In addition, iodine isotopes can be used to visualize ectopic thyroid tissue.

A fine-needle aspiration biopsy (TAB) of the thyroid gland is indicated for all palpable nodular formations, as well as for formations exceeding (according to ultrasound data) 1 cm in diameter. With smaller nodular formations, the TAB can be indicated if there are ultrasound suspected thyroid cancer signs. The main purpose of TAB is the differential diagnosis of diseases that occur with nodular goiter. Conducting a TAB under ultrasound control significantly increases the information content of the study, especially in the case of cystic and small-diameter nodules. It should be noted that TAB is followed by a cytological rather than histological examination, that is, the study of disparate groups of cells, and not a cut of the thyroid gland.

Of the additional research methods in the diagnosis of thyroid disease, MRI and CT can be used. Indications for them are limited to rather rare cases when it is necessary to visualize a large sternal goiter, compressing the organs of the mediastinum. In this case, MRI is significantly more informative. In addition, it can be used to diagnose and evaluate the effectiveness of the treatment of endocrine ophthalmopathy. Among the instrumental methods of research, the radiography of the neck organs (trachea, esophagus) and the chest cavity with contrasting food-water barium did not lose their significance. This study is indicated for suspected tracheal displacement with significant goiter.

CLASSIFICATION OF THYROID GLAND DISEASES

Before discussing the classification, it is necessary to consider a number of terminological issues. The term thyrotoxicosis refers to a clinical syndrome caused by an excess of thyroid hormones in the body, while pathogenetically it is divided into three options:

♦ Hyperthyroidism - hyperproduction of thyroid thyroid hormones (Graves disease, multinodular toxic goiter)

♦ Destructive (thyreolytic) thyrotoxicosis, which is a typical pathological reaction of the thyroid gland to a number of external and internal factors, which consists in the massive destruction of thyroid follicles with the release of their contents (thyroid hormones) into the bloodstream. With this option, thyroid hyperfunction is absent. Diseases occurring with destructive thyrotoxicosis, for example, subacute and postpartum thyroiditis, are accompanied by significantly less pronounced thyrotoxicosis than those caused by thyroid hyperfunction (Graves' disease). In addition, they usually have a good prognosis.

♦ Drug thyrotoxicosis associated with an overdose of thyroid hormone preparations.

Etiology of hyperthyroidism

• Diffuse toxic goiter (Graves disease) is the most common cause of hyperthyroidism.

• Nodular toxic goiter (thyrotoxic adenoma, Plummer's disease) is observed less often than Graves disease, and usually in older people.

• Subacute thyroiditis (de Querven's thyroiditis) can cause transient thyrotoxicosis (in the absence of hyperthyroidism).

• Artificial hyperthyroidism may be the result of uncontrolled intake of thyroid hormones.

Rare causes of hyperthyroidism

• Pituitary tumors with excessive TSH secretion (for example, Tru-ell-Junet syndrome or acromegaloid hyperthyroidism with hyperostosis, a combination of diffuse hyperostosis of the cranial vault, acromegaly, and signs of hyperthyroidism caused by increased secretion of somatotropic hormone T hormone A).
• Ovarian teratomas producing thyroid hormones (ovarian nasal struma).
• Hyperproduction of hormones by the thyroid gland after excessive introduction of iodine into the body ("iodine-bazedov" syndrome).
Etiological classification of thyrotoxicosis
• Due to hyperthyroidism:
- excess production of TSH (rarely);
- pathological stimulation of the thyroid gland;
- antibodies to TSH receptors in diffuse toxic goiter;
- Chorionic gonadotropin in trophoblast tumors;
- functional autonomy of the thyroid gland;
- toxic adenoma;
- multinodular toxic goiter.
• Due to other reasons:
- violations of storage of T4 and T3;
- subacute granulomatous thyroiditis;
- subacute lymphocytic thyroiditis;
- ectopic source of T4 and T3;
- ectopic thyroid gland;
- T4 and T3-secreting ovarian teratoma;
- metastases of functionally active thyroid cancer;
- latent source of T4 and T3;
- overdose or abuse of thyroid hormones;
- foods containing animal thyroid tissue.
The most common cause of thyrotoxicosis is diffuse toxic goiter. This autoimmune disease is characterized by the presence of thyroid-stimulating antibodies. When it occurs, Graves' ophthalmopathy (the main symptom of exophthalmos) and pretibial myxedema, which does not happen with thyrotoxicosis of another etiology. Other causes of thyrotoxicosis: iodine-containing drugs (amiodarone, radiopaque substances), thyroid adenomas, subacute granulomatous thyroiditis, subacute lymphocytic thyroiditis, postpartum thyroiditis (a type of lymphocytic), abuse of thyroid hormone preparations. Secondary (caused by increased TSH) thyrotoxicosis is extremely rare.
Special notes
• In the elderly, the only manifestations of thyrotoxicosis may be cardiovascular disorders, more often arrhythmias and heart failure.
• In severe neurosis, thyrotoxicosis should be excluded.
Goiter (struma), as indicated, is understood to mean an increase in thyroid volume above established standards (18 ml for women, 25 ml for men). According to the macroscopic characteristic, it is divided into diffuse (enlarged entire thyroid gland), nodular, multinodular (two or more nodular formations) and mixed (a combination of the total enlarged thyroid gland with the presence of one or more nodular formations). According to the functional state of the thyroid gland, goiter is euthyroid, toxic and proceeding with a decrease in thyroid function.
The first group includes a lot of autoimmune thyroid diseases. In terms of their general population prevalence, they occupy first place among other autoimmune human pathologies. Benign hyperplastic thyroid processes are even more common, which include various forms of colloidal proliferating goiter.
Most often, goiter formation is promoted by various goitrogenic factors, the most common of which is the deficiency of iodine intake in the body and thyroid gland. Here, a unique feature of thyroid pathology as a whole should be noted: the spectrum, prevalence and prognosis of most thyroid diseases will largely depend on how much iodine (insufficient, normal, excess) a patient lives in the region.

Infectious thyroidopathies, with the exception of subacute thyroiditis, the etiology of which is not fully understood, are relatively rare, as are the infectious diseases of all endocrine glands as a whole. Separate categories of thyroid diseases include tumors, which differ significantly in morphology and prognosis, and congenital (hereditary) diseases, for some of which the immediate cause of development is already known to date.

Graves disease - Bazedov's disease

Graves' disease (BG, Bazedov's disease, diffuse toxic goiter) is a systemic autoimmune disease that develops as a result of the production of antibodies to the thyroid stimulating hormone receptor (TSH), which is clinically manifested by thyroid disease with the development of thyrotoxicosis syndrome in combination with extrathyroid pathology : endocrine ophthalmopathy, pretibial myxedema, acropathy (table. 5). The disease was first described in 1825 by Caleb Parry, in 1835 by Robert Graves, and in 1840 by Karl von Bazedov

As a result of impaired immunological tolerance, autoreactive lymphocytes (CD4 + and CD8 + T-lymphocytes, B-lymphocytes) with the participation of adhesive molecules (ICAM-1, ICAM-2, E-selectin, VCAM-1, LFA-1, LFA-3, CD44) infiltrate the thyroid parenchyma, where a number of antigens are recognized, which are presented by dendritic cells, macrophages and B-lymphocytes. Subsequently, cytokines and signaling molecules initiate antigen-specific stimulation of B-lymphocytes, as a result of which the production of specific immunoglobulins against various components of thyrocytes begins. In the pathogenesis of BG, the main importance is attached to the formation of stimulating antibodies to the TSH receptor (AT-rTTG) (Fig. 10).

Etiology

BG is a multifactorial disease in which the genetic characteristics of the immune response are realized against the background of environmental factors. Along with an ethnically associated genetic predisposition (carriage of the HLA-B8, -DR3 and -DQA1 * 0501 haplotypes in Europeans), psychosocial and environmental factors are of particular importance in the pathogenesis of HD. Emotional stressors and exogenous factors, such as smoking, can contribute to the realization of a genetic predisposition to GB. Smoking increases the risk of developing HD by 1.9 times, and the development of endocrine ophthalmopathy with existing HD by 7.7 times. BG in some cases is combined with other autoimmune endocrine diseases (type 1 diabetes mellitus, primary hypocorticism); this combination is commonly referred to as type II autoimmune polyglandular syndrome

Unlike most other autoimmune diseases, in case of GB or Basedova's disease, it is not destruction but stimulation of the target organ. In this case, autoantibodies are produced to a fragment of the TSH receptor, which is located on the membrane of thyrocytes. As a result of interaction with an antibody, this receptor becomes active, triggering a postreceptor cascade for the synthesis of thyroid hormones (thyrotoxicosis) and, in addition, stimulating hypertrophy of thyrocytes (an increase in thyroid gland). For reasons that are not completely understood, T lymphocytes sensitized to thyroid antigens infiltrate and cause immune inflammation in several other structures, such as retrobulbar cellulose (endocrine ophthalmopathy), cellulose of the anterior surface of the lower leg (pretibial myxedema).

Pathogenesis

Clinically, the most significant syndrome that develops in HD due to hyperstimulation of the thyroid gland with antibodies to the TSH receptor is thyrotoxicosis. The pathogenesis of changes on the part of organs and systems developing with thyrotoxicosis consists in a significant increase in the level of basic metabolism, which over time leads to degenerative changes. The most sensitive structures for thyrotoxicosis, in which the density of thyroid hormone receptors are highest, are the cardiovascular (especially atrial myocardium) and nervous system.

• Thyroid hormones increase tissue oxygen consumption, increasing heat production and energy metabolism.

• Increases tissue sensitivity to catecholamines and sympathetic stimulation.

• The conversion of androgens to estrogens in tissues increases and the content of circulating globulin that binds sex hormones increases, which increases the ratio of estrogens and androgens. These hormonal changes can cause gynecomastia in men.

• The rapid destruction of cortisol under the influence of thyroid hormones determines the clinical picture of hypocorticism (reversible adrenal insufficiency).

RISK FACTORS

• A burdened family history.
• Female.
• Autoimmune diseases.

Epidemiology

In regions with normal iodine consumption, BG is the most frequent disease in the nosological structure of thyrotoxicosis syndrome (if you do not take into account diseases that occur with transient thyrotoxicosis, such as postpartum thyroiditis, etc.). In regions of varying severity of iodine deficiency, functional autonomy of the thyroid gland prevails in prevalence in the population with BG. The prevalence of thyrotoxicosis in the region with normal iodine intake reaches 2% among women; the incidence of new HD cases is 3 per 1000 women per year. Women are sick 8-10 times more often, in most cases between 30 and 50 years. The incidence of GB is the same among representatives of the European and Asian races, but lower among the Negroid races. In children and the elderly, the disease is quite rare.

CLINICAL PICTURE

For BG, in most cases, a relatively short anamnesis is characteristic: the first symptoms usually appear 4-6 months before going to the doctor and making a diagnosis. As a rule, key complaints are associated with changes in the cardiovascular system, the so-called catabolic syndrome and endocrine ophthalmopathy

The main symptom of the cardiovascular system is tachycardia and quite pronounced sensations of palpitations. Thyrotoxicosis is accompanied by dilatation of resistive arterioles and decentralization of blood circulation. On the one hand, this leads to the fact that patients can feel palpitations not only in the chest, but also in the head, arms, and stomach. On the other hand, the hyperkinetic state of the heart (high heart rate) in combination with the decentralization of blood circulation leads to an increase in pulse pressure (the difference between systolic and diastolic blood pressure). Heart rate at rest with sinus owl tachycardia due to thyrotoxicosis can reach 120-130 beats per minute.

With long-existing thyrotoxicosis, especially in elderly patients, pronounced dystrophic changes in the myocardium develop, often manifested in supraventricular rhythm disturbances, which is called atrial fibrillation (blinking). This complication of thyrotoxicosis rarely develops in patients younger than 50 years old. Further progression of myocardial dystrophy leads to the development of changes in the myocardium of the ventricles and congestive heart failure.

As a rule, catabolic syndrome is manifested, manifested by progressive weight loss (sometimes by 10-15 kg or more, especially in individuals with initial excess weight) against the background of increasing weakness and increased appetite. The skin of patients is hot, sometimes there is severe hyperhidrosis. The feeling of heat is characteristic, patients do not freeze at a sufficiently low temperature in the room. In some patients (especially in old age), evening subfebrile condition may be detected.

Changes in the nervous system are characterized by mental lability: episodes of aggressiveness, agitation, chaotic unproductive activity are replaced by tearfulness, asthenia (irritable weakness). Many patients are uncritical of their condition and try to maintain an active lifestyle against the background of a rather severe somatic state. Long-existing thyrotoxicosis is accompanied by persistent changes in the psyche and personality of the patient. A frequent but non-specific symptom of thyrotoxicosis is a small tremor: a small tremor of the fingers of the outstretched arms is detected in most patients. In severe thyretoxicosis, tremor can be detected throughout the body and even impede the patient's speech.

Thyrotoxicosis is characterized by muscle weakness and a decrease in muscle volume, especially the proximal muscles of the arms and legs. Sufficiently expressed myopathy sometimes develops. A very rare complication (possibly a manifestation of GB) is thyrotoxic hypokalemic periodic paralysis, which is manifested by periodically occurring sharp bouts of muscle weakness. In a laboratory study, hypokalemia, an increase in the level of CPK are detected. It is more common among representatives of the Asian race.

Intensification of bone resorption leads to the development of the syndrome of osteopenia, and thyrotoxicosis itself is considered as one of the most important risk factors for osteoporosis. Frequent complaints of patients are hair loss, brittle nails.

Changes in the gastrointestinal tract develop quite rarely. In elderly patients, in some cases there may be diarrhea. With prolonged severe thyrotoxicosis, dystrophic changes in the liver (thyrotoxic hepatosis) can develop.

Menstrual irregularities are rare. In contrast to hypothyroidism, moderate thyrotoxicosis may not be accompanied by a decrease in fertility and does not exclude the possibility of pregnancy. Antibodies to the TSH receptor penetrate the placenta, and therefore, children born (1%) to women with HD (sometimes years after radical treatment) may develop transient neonatal thyrotoxicosis. In men, thyrotoxicosis is often accompanied by erectile dysfunction.

In severe thyrotoxicosis, a number of patients have expressed symptoms of thyrogen (relative) adrenal insufficiency, which must be differentiated from true. Hyperpigmentation of the skin, exposed parts of the body (Jellinek symptom), arterial hypotension are added to the symptoms already listed. In most cases, in case of BG, an increase in thyroid size occurs, which, as a rule, has a diffuse character. Often, iron is increased significantly. In some cases, systolic murmur can be heard over the thyroid gland. Nevertheless, goiter is not an obligate symptom of HD, since it is absent in at least 25-30% of patients.

Of key importance in the diagnosis of BG are changes in the eyes, which are discussed in Section 3.5 and are a kind of “visiting card” of BG, i.e. their detection in a patient with thyrotoxicosis almost unambiguously testifies specifically to HD, and not to another disease.

Very often, due to the presence of severe ophthalmopathy in combination with the symptoms of thyrotoxicosis, the diagnosis of GB is already evident upon examination of the patient .

Another rare (less than 1% of cases) associated with HD is pretibial myxedema. The pathogenesis of damage to the tissue of the pretibial region is probably similar to that of EOP (see clause 3.5). The skin of the anterior surface of the lower leg becomes edematous, thickened, purplish-red in color (“orange peel”), often accompanied by erythema and itching.

The clinical picture of thyrotoxicosis may have deviations from the classical version. So, if in young BG there is a detailed clinical picture, in elderly patients its course is often oligo or even monosymptomatic (heart rhythm disturbance, subfebrile condition). With the so-called "apathetic" version of the course of BG, which occurs in elderly patients, clinical manifestations include loss of appetite, depression, and lack of exercise.

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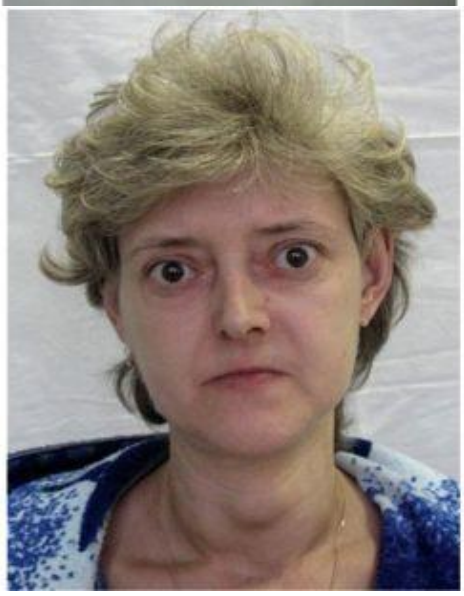

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A A very rare complication of HD (extremely rare other diseases that occur with thyrotoxicosis) is thyrotoxic crisis, the pathogenesis of which is not entirely clear, because A crisis can develop without a prohibitive increase in the level of thyroid hormones in the blood. The cause of thyrotoxic crisis may be associated with acute acute infectious diseases, surgical intervention or therapy with radioactive iodine against the background of severe thyrotoxicosis, cancellation of thyrostatic therapy, administration of a contrasting iodine-containing drug to the patient. Clinical manifestations of thyrotoxic crisis include a sharp increase in symptoms of thyrotoxicosis, hyperthermia, confusion, nausea, vomiting, and sometimes diarrhea. Sinus tachycardia of over 120 beats / min is recorded. Atrial fibrillation, high pulse pressure, followed by severe hypotension, are often noted. The clinical picture may be dominated by heart failure, respiratory distress syndrome. The manifestations of relative adrenal insufficiency in the form of hyperpigmentation of the skin are often expressed. The skin can be icteric due to the development of toxic hepatosis. In a laboratory study, leukocytosis (even in the absence of a concomitant infection), moderate hypercalcemia, an increase in the level of alkaline phosphatase can be detected. Mortality in thyrotoxic crisis reaches 30-50%.

Diagnostics

The diagnostic criteria for BG include:

1. Laboratory-confirmed thyrotoxicosis (TSH ↓, T4 and / or T3 ↑).
2. Endocrine ophthalmopathy (60-80% of cases).
3. Diffuse increase in thyroid volume (60-70%).
4. Diffuse capture enhancement 99mTc according to thyroid scintigraphy.

5. Elevated levels of antibodies to the TSH receptor.
At the first stage of the diagnosis of hypertension, it is necessary to confirm that the patient's clinical symptoms (tachycardia, weight loss, tremor) are due to thyrotoxicosis syndrome. To this end, a hormonal study is performed that detects a decrease or even complete suppression of TSH levels and an increase in T4 and / or T3 levels. Further diagnosis is aimed at differentiating BG from other diseases occurring with thyrotoxicosis. In the presence of a clinically pronounced EOP, the diagnosis of GB is almost obvious
In some cases, in the absence of an explicit image intensifier tube, it makes sense to carry out its active search using instrumental methods (ultrasound and MRI orbits).
LABORATORY AND INSTRUMENTAL RESEARCH
Hormonal study:
- increased levels of T4 (and T3) in serum;
- a decrease in serum TSH levels.
Thyroid scintigraphy is used for differential diagnosis. With diffuse toxic goiter, a uniformly increased accumulation of the isotope is observed. With multinodular toxic goiter, isotope capture is also increased, but its distribution is uneven. Subacute granulomatous thyroiditis and drug thyrotoxicosis are characterized by low absorption of the isotope.
Hyperthyroidism, or thyrotoxicosis, develops with excessive formation of thyroid hormones (T3 and T4). Currently, there are three forms of thyrotoxicosis:
- diffuse toxic goiter (Graves disease, bazedova disease);
- toxic nodular goiter;
- Autonomous thyroid adenoma.
In patients with thyrotoxicosis who did not receive antithyroid treatment, the blood levels of T4, cT4, triglycerides are increased, and the concentration of TSH is reduced. In these patients, the TRH test is negative, which indicates a sharp inhibition of thyrotropic function and the absence of thyrotropin reserves in this disease.
An increase in T4 blood concentration in 80% of cases indicates a diagnosis of overt thyrotoxicosis. In 15% of cases of apparent thyrotoxicosis, high levels of T3 (T3 toxicosis) are observed. In this regard, the joint determination of T4 and T3 allows you to diagnose explicit thyrotoxicosis in 95% of cases. The remaining 5% is determined by the concentration of thyroxin-binding globulin (TSH), but the best tests for the diagnosis of thyrotoxicosis are the determination of cT4 and cT3, which
with a joint determination, they can diagnose up to 100% of cases of apparent thyrotoxicosis and identify subclinical forms of the disease without an additional definition of TSH.
ESTIMATION OF THE HORMONAL THYROID STATUS
A decrease in the level or complete absence of TSH is the most significant indicator of primary hyperthyroidism. The determination of cT4 is most informative in patients with suspected abnormalities of binding proteins and allows us to evaluate the true thyroxine content in the body. The joint determination of TSH and CT4 is of great importance for the selection of adequate treatment for detected thyroid dysfunctions
In assessing the functional state of the thyroid gland, of interest are the calculated indices: the integral thyroid index (ITI) and the peripheral conversion index (IPC). ITI is the ratio of the thyroid hormones themselves to their pituitary regulator:
Normally, it is 7.04-27.21.
An increase in this index is the earliest sign of hyperthyroidism, whereas a decrease in ITI even reflects the initial stages of hypothyroidism. IPC, an indicator of the tissue conversion of thyroxine into its biologically more active metabolite triiodothyronine, is calculated by the formula:
The normal IPC is 1.37-4.43.
The clinic often calculates the coefficient of effectiveness of thyroxine (CAT) T4 / TSH, with which differentiate eu-, hypo- and hyperthyroid states. The coefficient value from 0.86 to 1.13 indicates an euthyroid state, above 1.13 - about hyperthyroidism, below 0.86 - about hypothyroidism.
DIFFERENTIAL DIAGNOSTICS
A. Exophthalmos and pretibial myxedema are found only with diffuse toxic goiter, with other diseases that cause thyrotoxicosis, they do not exist.

B. Palpation of the thyroid gland. A diffusely enlarged, painless thyroid gland with thyrotoxicosis almost certainly indicates diffuse toxic goiter.
B. History. Recent pregnancy, iodine, and neck pain are indicative of diffuse toxic goiter.
G. Thyroid uptake of radioactive iodine. This study makes it possible to distinguish diffuse toxic goiter and multinodular toxic goiter (absorption increased) from subacute thyroiditis and thyrotoxicosis caused by taking iodine preparations or thyroid hormones (absorption is reduced). Thyroid scintigraphy is not used for the differential diagnosis of thyrotoxicosis.
Differential diagnosis of HD and diseases with similar symptoms occurring with normal thyroid function (atrial fibrillation in the presence of atherosclerotic cardiosclerosis) is simple due to the availability of hormonal studies that evaluate thyroid function. The main difficulties arise in the differential diagnosis of GB and other diseases that occur with thyrotoxicosis. In this regard, as indicated, the presence of endocrine ophthalmopathy, which does not occur in other diseases, can be of great help in the diagnosis of GB.
With subacute thyroiditis, as well as other diseases that occur with destructive thyrotoxicosis (postpartum, silent and cytokinin-induced thyroiditis, type 2 amiodarone-induced thyrotoxicosis), thyroid scintigraphy determines a decrease or even complete absence of capture of the radiopharmaceutical.
In addition, subacute thyroiditis is characterized by a bright clinical picture (pain syndrome) and an increase in ESR. Functional autonomy of the thyroid gland, clinically most often represented by multinodular toxic goiter, manifests itself in old age (most often after 50-60 years); thyroid scintigraphy reveals “hot” nodes, there are no signs of an autoimmune pathology (AT-TPO, AT-TG, AT-rTTG).
Certain difficulties may arise in the diagnosis of HD in pregnant women. Normally, during pregnancy, which is accompanied by thyroid hyperstimulation mainly due to chorionic gonadotropin, in many women (about 30%) there is a decrease in TSH levels below normal, and in some (2%), along with this, there is a slight increase in the level of free T4. The differentiation of this situation (transient gestational hyperthyroidism) from BG allows the absence of EOP and most typical symptoms of thyrotoxicosis, as well as the gradual normalization of altered parameters according to dynamic observation. It should be noted that during pregnancy in all women, the level of total T4 significantly exceeds the norm, which is associated with an increase in TSH under the influence of an excess of estrogen. In this regard, to assess thyroid function during pregnancy, the level of free T4 and TSH should be used. Artificial (patient taking large doses of thyroid hormone preparations) thyrotoxicosis from BG is distinguished by a decrease in the accumulation of radiopharmaceuticals according to scintigraphy and the absence of an increase in thyroglobulin level characteristic of most diseases accompanied by hyperfunction of the thyroid gland.
Treatment
There are three methods of treating HD (conservative treatment with thyrostatic drugs, surgical treatment and 131I therapy), while none of them is etiotropic. In different countries, the proportion of using these treatments is traditionally different. Thus, in European countries and in the Russian Federation, conservative therapy with thyreostatics is the most accepted as the primary method of treatment; in the USA, the vast majority of patients receive 131I therapy.
BASIC RULES FOR TREATING HYPERTHYROIDISIS
1. Initial treatment with radioactive iodine. Patients with mild hyperthyroidism and a satisfactory general condition can be immediately prescribed radioactive iodine in combination with a β-blocker. Other patients should first be led to an euthyroid state by prescribing a short course of thyreostatic drugs.
2. Long-term treatment with thyreostatics (12-18 months) is prescribed to pregnant women and children with a small thyroid gland.
3. With a large thyroid gland, surgical treatment is performed.
MEDICINAL TREATMENT OF HYPERTHYROIDISM
1. Symptomatic treatment.
- β-blockers:
- propranolol 40 mg 3 times a day;

- metoprolol 50 mg 2 times a day;
- sotalol 80 mg 2 times a day (especially with atrial fibrillation).

2. Initial preventive treatment.

Conservative therapy is carried out with the help of thiomochevin preparations, which include thiamazole (mercazolil, tyrosol, metizol) and propylthiouracil (PTU, propitsil). The mechanism of action of both drugs is that they actively accumulate in the thyroid gland and block the synthesis of thyroid hormones due to the inhibition of thyroid peroxidase, which carries out the addition of iodine to tyrosine residues in thyroglobulin. There is quite conflicting evidence that tiamazole in parallel has a certain immunomodulating effect, which in some cases promotes remission of the disease.

Thyrostatic therapy can be prescribed either in terms of preparing the patient for other methods of treatment (surgery), which are carried out against the background of euthyroidism, or as a course of thyrostatic therapy lasting 12-18 months. It should be emphasized that while taking thyreostatic drugs, a gradual euthyroid state can be achieved in almost all patients: cases of resistance to thyreostatics are casuistry.

Long-term (12-18 months) conservative therapy makes sense to plan far from all patients. First of all, we are talking about patients with a moderate increase in thyroid volume (up to 35-40 ml); with large goiter, after the abolition of thyreostatics, thyrotoxicosis will inevitably develop. In addition, conservative therapy should not be planned in patients with severe complications of thyrotoxicosis (atrial fibrillation, severe osteoporosis, etc.). The appointment of repeated courses of treatment with the development of a relapse of thyrotoxicosis after 12-18 months of thyrostatic therapy is practically unpromising and unsafe for the patient.

If the patient is scheduled to undergo a course of thyrostatic therapy, thionamides at the beginning are prescribed in relatively large doses: 30-40 mg of tiamazole (for 1-2 doses) or vocational schools - 300-400 mg (for 3 doses). Against the background of such therapy, after 4-6 weeks, in 80-90% of patients with moderate thyrotoxicosis, it is possible to achieve an euthyroid state, the first sign of which is the normalization of the level of free T4 and T3. TSH levels may remain low for a long time. For the period until euthyroidism is achieved, and often for a longer period, it is advisable for most patients to use beta-blockers (propranolol - 120-180 mg / day, atenolol - 50-100 mg / day), which many quickly stop cardiovascular symptoms of thyroid toxicosis. After normalization of the level of free T4, the dose of thyreostatics is reduced to a maintenance dose (5-15 mg of tiamazole per day). In the future, two options for thyrostatic therapy are possible. The first option (“block” scheme) implies the appointment of a small (5-10 mg / day of tiamazole) alone thyreostatic drug. In the second variant (“block and replace” scheme), levothyroxine (L-T4), which prevents the development of drug-induced hypothyroidism in the patient, is administered in conjunction with a relatively higher dose of thyreostatic (10-20 mg of tiamazole). The criterion for the adequacy of therapy is persistent maintaining a normal level of T4 and TSH (the latter may return to normal within a few months from the start of treatment).

Maintenance therapy lasts from 12 to 18 months. During the entire treatment, the patient must determine the level of leukocytes and platelets. A rare but formidable complication of thionamides (both thiamazole and PTU) is agranulocytosis, very rarely isolated thrombocytopenia. After the course of treatment, the drugs are canceled; most often relapse develops during the first year after discontinuation of therapy. The likelihood of relapse even among patients with a small initial increase in the thyroid gland is quite high and reaches 70-75%. In the event of a recurrence of thyrotoxicosis, as well as if the patient does not initially meet the criteria for making long-term thyrostatic therapy appropriate, he is shown radical treatment: surgery or 131I therapy.

The mechanism of action and pharmacological effects

Thyreostatics is a group of drugs that are used to inhibit the synthesis of thyroid hormones (T4 and T3) in endogenous thyrotoxicosis syndrome. Thionamide drugs have a common ability to block thyroid peroxidase, a key enzyme for the synthesis of thyroid hormones. Propylthiouracil also inhibits the peripheral conversion of T4 to biologically more active T3 by inhibiting type 1 selenodeiodinase in peripheral tissues.

Pharmacokinetics

Thionamides are well and quickly absorbed from the digestive tract. The therapeutic concentration of propylthiouracil in the blood is reached already 20-30 minutes after ingestion. Thyrostatics are mainly metabolized in the liver, where they undergo glucuronidation.

Indications for use

Thyrotoxicosis due to overproduction of thyroid hormones.

Principles of choice in various clinical situations

At present, with Graves disease, it is recommended to use lower doses (15-20 mg of tiamazole) in order to avoid side effects. The effectiveness of the low dose regimen is confirmed by the results of the European Multicenter Study (European multicenter study).

As a supportive treatment, two modes of exposure are used: low doses of thyreostatics ("block" scheme) or higher doses in combination with levothyroxine sodium ("block and replace" scheme).

In patients with multinodular toxic goiter, thyreostatics are indicated only as preparation for surgery or radioiodine therapy.

Contraindications

Hypersensitivity to thionamides.

Undesirable drug reactions and safety control methods

The most formidable complication of thionamide use is agranulocytosis. It is recommended in the first 3 months of treatment to examine the number of leukocytes and the leukocyte formula of peripheral blood every 7-10 days, and in the future every 3-4 weeks. With a decrease in the level of leukocytes less than 3x109 / l, treatment with thyreostatics is interrupted.

The use of thionamides is associated with the possibility of thrombocytopenia and an increased risk of spontaneous bleeding, so it is necessary to control prothrombin time, especially before surgical procedures.

Skin rashes of various origins that occur during treatment should not be automatically considered an allergic reaction to thyreostatic drugs. It can only be confirmed with a skin test.

Thionamide Reaction

Thionamides can enhance the effect of anticoagulants. They increase the risk of side effects of β-blockers, cardiac glycosides, and disrupt the clearance of theophylline. The simultaneous administration of drugs that can cause agranulocytosis (NSAIDs, clozapine, sulfasalazine, etc.) should be avoided.

Special Use

Thionamides at risk of use during pregnancy are class D, therefore, in pregnant and lactating women, they can still be used under strict medical supervision as an alternative to surgical treatment. Propylthiouracil is preferred. Pregnancy is an absolute contraindication for the "block and replace" scheme, since thyreostatics (but not sodium levothyroxine) easily pass through the placenta and can cause severe hypothyroidism in the fetus.

- A thyreostatic drug (usually carbimazole□) should be prescribed as part of monotherapy or, preferably, in combination with a β-blocker.

1 week after the start of treatment, it is necessary to check the content of white blood cells in the blood, and subsequently this procedure should be repeated at each visit to the doctor. The patient should be informed about the possible development of agra-nulocytosis (the patient should be aware of the need to consult a doctor if there is a fever or sore throat).

Ongoing preventive treatment

• Carried out if the patient refuses surgical treatment or the use of radioactive iodine.

• A combination of thyreostatic carbimazole (20 mg / day) and sodium levothyroxine (50-100 μg / day) or only sodium levothyroxine should be used.

ADVERSE EFFECTS OF THYROOSTATIC DRUGS

1. Agranulocytosis (due to thyreostatics).

- The first signs are fever and tonsillitis.
- Develops within 3 months after the start of treatment.
- The most common in elderly patients.
- The highest risk of developing agranulocytosis in patients who used the same thyrostatic drug in the past.

- Treatment consists in the immediate abolition of drug treatment.
- β-blocker (iodide) + surgical treatment or treatment with radioactive iodine - an alternative treatment.
2. Leukopenia.
3. Skin rashes.
4. Damage to the joints.
5. Permanent remission is rarely achieved.

RADIOACTIVE IODINE TREATMENT DISADVANTAGES

• Often, persistent hypothyroidism develops, in which it is necessary to observe the patient throughout his life.
• Transient radiation thyroiditis.
• Eye manifestations may become more pronounced.

Disadvantages of surgical treatment

• Persistent hypothyroidism, as a result of which there is a need for monitoring the patient throughout his life.
• Recurrent paresis (especially in those patients whose professional activity is associated with constant tension of the vocal cords).
• Removal of the parathyroid glands leads to the development of hypoparathyroidism.

Thyrotoxic crisis

Thyrotoxic crisis is a rare, but life-threatening syndrome, manifested by a sharp increase in the severity of thyrotoxicosis symptoms in patients with diffuse or diffuse-nodular toxic goiter.

Thyrotoxic crisis often develops in patients not treated for thyrotoxicosis. Risk factors include surgery and acute infectious diseases.

Clinical manifestations - tachycardia (more than 150 minutes, anxiety, weakness, fever), arrhythmias, heart failure.

EMERGENCY ASSISTANCE NEEDED

To prevent death (its frequency according to various sources is from 10 to 75%) with thyrotoxic crisis, early diagnosis and adequate intensive care are necessary. Treatment is carried out in the intensive care unit. Treatment includes the administration of antithyroid drugs, saline solutions, glucocorticoids, antiarrhythmic and cardiotonic drugs.

The thyroid gland belongs to the pituitary-dependent glands, the insufficiency of which is divided into primary and secondary. Primary hypothyroidism means a deficiency of thyroid hormones in the body due to pathology (destruction, removal) of the thyroid gland, and secondary hypothyroidism means a deficiency of thyroid hormones due to a decrease (absence) of trophic and secretory effects of TSH on the thyroid gland (hypothalamic-pituitary thyroidism).

The goal of surgical treatment, as well as 131I therapy, is to remove almost the entire thyroid gland, on the one hand, ensuring the development of postoperative hypothyroidism (which is fairly easily compensated), and on the other, eliminating any possibility of a thyrotoxicosis relapse. For this purpose, a thyroidectomy or an extremely subtotal thyroid resection (with a thyroid residue of no more than 2 ml), which from a functional point of view is identical to thyroidectomy (in both cases, hypothyroidism is recommended), is recommended.

In most countries of the world, the majority of patients with HD, as well as with other forms of toxic goiter, receive radioactive 131I as the main method of radical treatment. This is due to the fact that the method is effective, non-invasive, relatively inexpensive, devoid of the complications that can develop during thyroid surgery. The only contraindications to 131I treatment are pregnancy and breastfeeding. In significant amounts, 131I accumulates only in the thyroid gland; after getting into it, it begins to decay with the release of beta particles, which have a path length of about 1-1.5 mm, which provides local radiation destruction of thyrocytes. A significant advantage is that the treatment of 131I can be carried out without prior preparation with thyreostatics. In HD, when the goal of the treatment is to destroy the thyroid gland, therapeutic activity, taking into account the thyroid gland volume, maximum capture, and half-life of 131I from the thyroid gland, is calculated based on the estimated absorbed dose of 200-300 Gray. With an empirical approach, a patient without preliminary

dosimetric studies with small goiter is prescribed about 10 mCi, with a larger goiter, 15-30 mCi. Hypothyroidism usually develops within 4-6 months after the introduction of 131I.

The general treatment regimen for HD is shown in Fig. 13. This approach to the treatment of this disease is most accepted in Europe and the Russian Federation. Along with the listed factors, the choice of a treatment option for HD can be determined by both individual characteristics of the patient (very large goiter, concomitant pathology, pregnancy planning), and social factors.

A feature of the treatment of HD during pregnancy is that thyreostatics (preference is given to vocational schools, which penetrate the placenta worse) is given in the minimum necessary dose (only according to the “block” scheme), which is necessary to maintain the level of free T4 at the upper border norms or slightly above it. Usually, as the duration of pregnancy increases, the need for thyreostatics decreases and most women do not take the drug at all after 25-30 weeks. Nevertheless, most of them after the birth (usually after 3-6 months) develop a relapse of the disease.

Treatment of thyrotoxic crisis involves intensive measures with the appointment of large doses of thyreostatics. Preference is given to vocational schools in a dose of 200-300 mg every 6 hours, if it is impossible to independently take the patient through a nasogastric tube. In addition, β-blockers (propranolol: 160-480 mg per day per os or iv in the dose of 2-5 mg / hour), glucocorticoids (hydrocortisone: 50-100 mg every 4 hours, or prednisone (60 mg / days), detoxification therapy (saline, 10% glucose solution) under the control of hemodynamics.An effective method of treating thyrotoxic crisis is plasmapheresis.

Prognosis In the absence of treatment, it is unfavorable and is determined by the gradual development of atrial fibrillation, heart failure, exhaustion (marantic thyrotoxicosis). In case of normalization of thyroid function, the prognosis of thyrotoxic cardiomyopathy is favorable - in most patients cardiomegaly regresses and the sinus rhythm is restored. The probability of relapse of thyrotoxicosis after a 12-18-month course of thyrostatic therapy is 70-75% of patients.

ENDOCRINE OPHTHALMopathy

Endocrine ophthalmopathy (EOP, Graves ophthalmopathy, autoimmune ophthalmopathy) is an autoimmune disease pathogenetically associated with Graves disease, characterized by edema and lymphocytic infiltration, and subsequently fibrotic changes in the retrobulbar muscle and the eye.

In 95% of cases, EOP is combined with Graves' disease and is an integral component of this systemic autoimmune disease (its "calling card"), while EOP can manifest before thyrotoxicosis. In approximately 5% of cases, EOP is combined with autoimmune thyroiditis, and in the remaining 5% it is an isolated disease, i.e. the only component of the autoimmune process that develops in HD. For an incomprehensible reason, in 5-10% of cases, the image intensifier is one-sided .

Etiology

According to one fairly common theory, due to an autoimmune process that develops in HD, the preadipocytes of retrobulbar cellulose are differentiated into adipocytes expressing a TSH receptor for an incomprehensible reason. Following this, the cell is infiltrated with TSH receptor-sensitized T-lymphocytes, which initiate the development of immune inflammation. In response to the effects of pro-inflammatory cytokines, adipocytes of retrobulbar cellulose begin to produce acid glycosaminoglycans in excess. The latter have pronounced hydrophilic properties, which contributes to the development of edema and an increase in the volume of retrobulbar fiber. In the future, the intensity of inflammatory changes decreases, and fibrotic changes of varying severity develop.

Pathogenesis

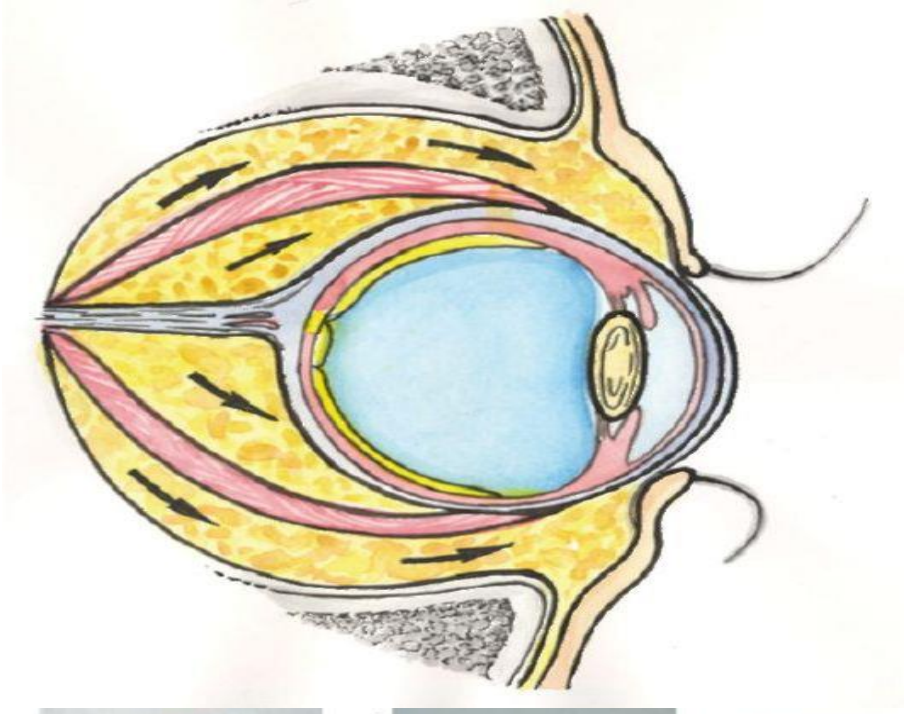
In the development of image intensifiers, two main phases are distinguished (Fig. 14). In the first phase of active inflammation, inflammatory changes in retrobulbar fiber occur. These changes are accompanied by an increase in its volume, which leads to the development of exophthalmos, and in severe cases, to compression of the optic nerve (optic neuropathy) .

Inflammatory changes in the oculomotor muscles develop non-uniformly, which leads to the fact that at a certain angle of view (when looking up or to the side) the patient develops diplopia. With severe changes in the oculomotor muscles, persistent strabismus with permanent diplopia can develop. A dangerous complication of severe EOP is pronounced exophthalmos, which leads to the impossibility of completely closing the eyes, with subsequent changes in the cornea, up to its ulceration.

In the second inactive phase of the image intensifier, the inflammatory process gradually subsides in the structures of the orbit. In the case of mild EOP, the process ends in complete remission, in severe EOP, fibrotic changes develop, leading to persistent exophthalmos, persistent retraction of the upper eyelid, strabismus with diplopia, as well as secondary changes on the part of the eyeball, such as cataracts. The use of anti-inflammatory drugs, such as glucocorticoids, in the inactive phase of the image intensifier tube is ineffective. Risk factors for the development and progression of EOPs are smoking and thyroid dysfunction (both hypothyroidism and thyrotoxicosis).

Clinical manifestations

With EOP, several groups of symptoms can develop. It should be noted right away that the so-called ocular symptoms of thyrotoxicosis, , are not fully manifestations of an EOP, but can develop with thyrotoxicosis of any genesis. Their pathogenesis is associated with a violation of the autonomic innervation of the eyeball. These symptoms were given great importance in the past, when a direct assessment of thyroid function using hormonal research was very difficult. In the future, it became apparent that many eye symptoms, such as small tremor of the eyelids of closed eyes, can occur in the absence of thyrotoxicosis in healthy people.



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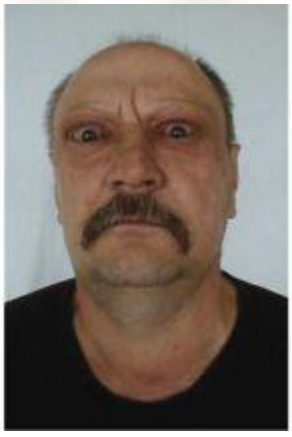

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In fact, two groups of symptoms are characteristic of an EOP: the first are associated with a change in the soft tissues of the orbit, and the second are associated with a change in the oculomotor muscles. As a result of changes in retrobulbar and partially periorbital tissues, exophthalmos develops with the accompanying retraction of the upper eyelid .

The first symptoms of an image intensifier are often the sensation of “sand” in the eyes, lacrimation and photophobia. The main muscle symptoms are double vision when looking in one direction or up, inability to divert eyes to one side, and in severe cases, squint

The severity of ophthalmopathy is usually classified according to the international classification NOSPECS (table. 8). Most often, the image intensifier tube has a fairly easy flow that does not require active therapeutic measures; Severe image intensifiers with the development of changes that threaten eyesight account for no more than 1-1.5% of cases.

Diagnostics

Concomitant BG, but much less often autoimmune thyroiditis, is of primary, but not absolute importance. In this case, the presence of a characteristic bilateral process in the patient practically verifies the diagnosis. Less often it is necessary to carry out an ultrasound of the orbits, which allows you to identify a characteristic thickening of the oculomotor muscles (Fig. 17).

In some cases, this study is carried out with the aim of actively diagnosing a clinically unexpressed image intensifier tube, the detection of which allows us to establish the diagnosis of BG in cases where the latter is difficult to differentiate from other diseases that occur with thyrotoxicosis. For this purpose, an MRI scan can be performed, which is a more expensive but more informative study. An important indication for her is the identification of a patient with unilateral exophthalmos (especially in the absence of inflammatory changes and other eye symptoms) in order to exclude retrobulbar tumor.

Differential diagnosis

EOPs must be differentiated from retrobulbar tumors (especially with unilateral exophthalmos), infiltrative diseases of the orbit, myasthenia gravis, optic neuropathy of a different genesis.

Treatment

When choosing treatment tactics, one should proceed from the fact that the inflammatory process in EOP is prone to spontaneous remission, in other words, the active phase of EOP, sooner or later, always ends. Approaches to the treatment of EOPs, as indicated, are determined by the severity of the disease and its activity

In most cases of EOP, no active therapy is required in general. An important condition for the remission of EOP is the persistent maintenance of euthyroidism. In the case of moderate and severe EOP, the most commonly used method is pulse therapy with methylprednisolone (1 g IV, daily, for 5 days. Another treatment method is X-ray therapy in the orbit area, which is often combined with glucocorticoid therapy. In severe EOP, especially with the development of neuropathy of the optic nerve, surgery may be indicated for decompression of the orbits.

Forecast

In the overwhelming majority of cases, it is favorable: a self-voluntary or anti-inflammatory therapy-induced remission develops. In approximately 1-2% of cases, the image intensifier is characterized by a severe course, which ends with pronounced residual phenomena in the inactive phase.

Hypothyroidism

Hypothyroidism is a clinical syndrome that develops due to a deficiency of thyroid hormones. According to the pathogenesis, hypothyroidism can be primary (due to the pathology of the thyroid gland itself) and secondary (due to TSH deficiency) (Table 3.11), and more than 99% of cases occur in primary acquired hypothyroidism. The prevalence of hypothyroidism in the general population is about 2%, and in some age groups (elderly women) it can reach 6-8%.

It is one of the most common endocrine diseases . The main cause of persistent primary hypothyroidism is chronic autoimmune thyroiditis (AIT), followed by iatrogenic hypothyroidism, which develops as a result of thyroid surgery or radioactive 131I therapy.

Etiology

Of the greatest clinical importance is hypothyroidism, which developed as a result of chronic autoimmune thyroiditis (AIT) and iatrogenic hypothyroidism (postoperative, in the outcome of therapy with radioactive 131I). Iatrogenic hypothyroidism accounts for at least 1/3 of all cases of hypothyroidism. In these diseases, hypothyroidism in most cases is persistent irreversible. Along with this, for many thyroid diseases (destructive thyroiditis), as well as when exposed to a number of substances (large doses of iodine, thyreostatics), transient hypothyroidism can develop, which self-limits either during the natural course of these diseases, or upon termination of exposure to the factor that caused it (cancellation of thyreostatics). In some cases, the genesis of primary hypothyroidism remains unclear (idiopathic hypothyroidism).

Acquired Hypothyroidism

One of the causes of primary hypothyroidism can be severe iodine deficiency. Mild and moderate iodine deficiency cannot lead to hypothyroidism in adults under normal conditions.

In newborns, due to moderate, and sometimes even slight iodine deficiency, due to the combination of low iodine content in the thyroid gland and a high level of thyroid hormone metabolism, transient neonatal hyperthyrotropinemia may develop (see section 3.6.2). Pregnant women with iodine deficiency may develop relative gestational hypothyroxinemia. However, the last two phenomena should not be fully identified with hypothyroidism syndrome.

The reason for the relatively rare secondary hypothyroidism, as a rule, is various destructive processes in the hypothalamic-pituitary region. Most often, we are talking about macroadenomas of the pituitary gland and suprasellar structures, as well as surgical interventions for these diseases.

Pathogenesis

With a deficiency of thyroid hormones, changes in all develop without the exception of organs and systems. Since the main function of thyroid hormones is to maintain the main metabolism (cellular respiration), when they are deficient, there is a decrease in oxygen consumption by tissues, as well as a decrease in energy expenditure and utilization of energy substrates. For the same reason, with hypothyroidism, there is a decrease in the production of a number of energy-dependent cellular enzymes that ensure their normal functioning. The universal change that is found in severe hypothyroidism is mucinous edema (myxedema), most pronounced in connective tissue structures. Myxedema develops due to excessive accumulation in the interstitial tissues of hyaluronic acid and other glycosaminoglycans, which, due to their hydrophilicity, retain excess water

Epidemiology

The epidemiology of hypothyroidism is largely determined by the fact that AIT is its most common cause. Firstly, AIT, like most other thyroid diseases, is 10 or more times more common in women. Secondly, this disease is characterized by a long course and leads to hypothyroidism after many years and decades from its onset. In this regard, hypothyroidism is the most common among women over the age of 50-60. If the prevalence of hypothyroidism in the general population is about 1%, among women of childbearing age - 2%, then among women older than 60 this indicator in some populations can reach 10-12% or more.

Clinical manifestations

The clinical picture of hypothyroidism is determined by its etiology, the age of the patient, and the rate of development of thyroid hormone deficiency.

The main problems in the clinical diagnosis of hypothyroidism are:

• lack of specific (occurring only in hypothyroidism) symptoms;

• high prevalence of symptoms similar to hypothyroidism in the general population, which are associated with other chronic somatic and mental illnesses. In approximately 15% of adults with normal thyroid function, up to several symptoms characteristic of hypothyroidism can be detected;

• the absence of a direct relationship between the degree of deficiency of thyroid hormones and the severity of clinical manifestations (in some cases, the symptoms may be completely absent with obvious hypothyroidism, in others they are significantly pronounced even with subclinical hypothyroidism).

As indicated, the clinical picture of hypothyroidism as a whole is characterized by polysystemicity, but complaints and symptoms from a single system dominate in individual patients, and therefore the patient is often diagnosed with a mask disease (Fig. 18).

With severe and long-lasting hypothyroidism, a rather characteristic “myxedematous” appearance is formed in the patient, which is characterized by general and periorbital edema. The face is puffy, pale jaundice, the gaze is alienated, the facial expressions are poor (masked face) .

In addition, there is a thinning and tarnishing of the hair, their increased out-fall. In general, patients are lethargic, slowed down or even inhibited. For severe hypothyroidism, speech retardation is very characteristic; sometimes it seems that the patient has something in his mouth (tongue is plaited). Swelling of the laryngeal mucosa is manifested by a low or even hoarse timbre of the voice. The patient may stumble on the utterance of individual words, after which, with some effort, wear them out more clearly. Classically, with hypothyroidism, swelling of the tongue is described, on which

tooth prints can be seen. Swelling of the mucous membrane of the Eustachian tube may occur with some hearing loss. A common complaint is dry skin.
Among the changes on the part of the nervous system, one should point to a decrease in memory and intelligence, drowsiness, and depression. In children older than 3 years and in adults, changes in the nervous system are not irreversible and completely stop against the background of replacement therapy. In contrast, congenital hypothyroidism in the absence of replacement therapy leads to irreversible neuropsychic and physical disorders. Peripheral nervous system rarely changes, although in some patients myxedema causes the development of tunnel syndromes (carpal tunnel syndrome).
A general decrease in the level of basal metabolism is manifested by a certain tendency of patients with hypothyroidism to gain weight, while hypothyroidism itself never leads to the development of severe obesity. With extremely severe hypothyroidism, hypothermia can develop. Patients often complain of chilliness (they freeze all the time). In the genesis of this symptom, along with a decrease in basal metabolism, centralization of blood circulation, characteristic of hypothyroidism, is important.
The most frequent changes in the cardiovascular system are a tendency to bradycardia, mild diastolic arterial hypertension and the formation of an effusion in the pericardial cavity. Most patients with hypothyroidism develop atherogenic dyslipidemia.
On the part of the digestive system, constipation is a common symptom. In addition, biliary dyskinesia, hepatomegaly may develop; a slight decrease in appetite is characteristic. With severe hypothyroidism, hypochromic anemia can develop. In some cases, hypothyroidism in the outcome of AIT is combined with another autoimmune disease - B12-deficient anemia.
Very often, especially in women, changes in the reproductive system come to the fore. With hypothyroidism, various disorders of the menstrual cycle can occur: from amenorrhea to dysfunctional uterine bleeding. Both men and women experience a decrease in libido. Secondary hyperprolactinemia is of some importance in the pathogenesis of changes in the reproductive system. Expressed hypothyroidism is almost always accompanied by infertility, but a less pronounced deficiency of thyroid hormones in some women (about 2% among all pregnant women) may not prevent pregnancy, which in this case accompanied by a high risk of her interruption or childbirth with impaired development of the nervous system.
With prolonged hypothyroidism, hyperstimulation of the pituitary thyrotrophs can result in the formation of a secondary adenoma. After hypothyroidism is compensated against the background of replacement therapy as a result of a decrease in the volume of the pituitary gland, the formation of an "empty" Turkish saddle can occur
The most severe, but currently extremely rare complication of hypothyroidism is hypothyroid (myxedema) coma. Hypothyroid coma, as a rule, develops in elderly patients with a long undiagnosed hypothyroidism, severe concomitant diseases with a low social status and lack of care. Intercurrent diseases (usually infectious), cooling, injuries, and the use of drugs that depress the central nervous system provoke the development of hypothyroid coma. Clinically, hypothyroid coma is manifested by hypothermia, hypoventilation with hypercapnia, hypervolemia, hyponatremia, bradycardia, arterial hypotension, acute urinary retention, dynamic intestinal obstruction, hypoglycemia, heart failure, progressive inhibition of the central nervous system. Mortality in myxedema coma reaches 80%.
Diagnostics
Diagnosis of hypothyroidism, that is, evidence of a decrease in thyroid function, is quite simple. It involves determining the level of TSH and T4, while the detection of an isolated increase in TSH indicates subclinical hypothyroidism, while a simultaneous increase in TSH and a decrease in T4 indicates clear or manifest hypothyroidism. A much larger problem is the determination of the indications for this study, since the non-specificity of the clinical picture of hypothyroidism is determined by the fact that even "clear symptoms" may not be confirmed by hormone testing, along with this, in some cases, hypothyroidism, even accompanied by a significant increase in the level TSH and a decrease in T4, sometimes asymptomatic. If we talk about subclinical hypothyroidism, then in the vast majority of cases it does not have any manifestations that would allow him to be suspected. When comparing these facts, a logical question arises about the appropriateness of

screening determination of thyroid function in order to diagnose hypothyroidism, which is supported by many recommendations. Risk groups for the development of hypothyroidism, that is, in fact, indications for evaluating thyroid function, regardless of the presence or absence of any symptoms, are presented in table. thirteen.

Thyroid hormones are extremely important for the laying and formation of the central nervous system, both in the period of intrauterine development and in the postnatal period.

Treatment

Manifest hypothyroidism (TSH ↑, T4 ↓) is an absolute indication for prescribing replacement therapy with levothyroxine (L-T4), regardless of any additional factors (age, concomitant pathology). Only the option of starting treatment can differ (the initial dose and the rate of its increase). The question of the advisability of treating subclinical hypothyroidism (TSH ↑, T4 - normal) remains controversial. An absolute indication for replacement therapy for subclinical hypothyroidism is its detection in a pregnant woman, or planning for pregnancy in the near future.

THYROID HORMONE PREPARATIONS

Currently, thyroid hormones obtained synthetically are widely used.

Classification

• Levothyroxine preparations.
• Lyotironin preparations.
• Combined.

The mechanism of action and pharmacological effects

Under the influence of thyroid hormones, oxygen consumption increases in almost all body tissues, the main metabolism rises and the heat production increases. Thyroid hormones have a positive inotropic and chronotropic effect on the myocardium, increase the expression of catecholamine receptors and increase myocardial oxygen demand. Under the influence of thyroid hormones, the processes of gluconeogenesis and glycogenolysis are activated, erythropoiesis is stimulated, cortisol metabolism is accelerated, the activity of the respiratory center is activated.

Pharmacokinetics

Thyroid hormones are well absorbed in the digestive tract. Absorption decreases when mixed with food, so the entire dose is recommended to be taken in the morning on an empty stomach, at least 30 minutes before the first meal.

Tissue peripheral conversion of T4 to T3 takes place in tissues by cleavage of the iodine atom from the external tyrosyl ring of T4, therefore, when prescribing mono-therapy with sodium levothyroxine in an adequate dose, the body's need for thyroid hormones is fully provided. With the appointment of levothyroxine sodium, the concentration of T3 in the blood plasma increases gradually, over several weeks. Some pharmacokinetic parameters of thyroid hormones are presented in table. The excretion of thyroid hormones is carried out mainly by the kidneys.

Indications for use

• Substitution therapy for hypothyroidism.
• Suppressive therapy.

Principles of choice in various clinical situations

With manifest hypothyroidism in adults, the calculated dose of sodium levothyroxine is 1.6-1.8 μg / kg. In subclinical hypothyroidism, the dose of sodium levothyroxine is approximately 1 μg per kilogram of body weight. The level of TSH during treatment should be within normal values (0.5-3.5 mU / L).

Suppressive therapy i.e. a supraphysiological dose of levothyroxine sodium (2.2–2.8 μg / kg), which suppresses a TSH level of at least 0.5–0.1 mU / L, is prescribed for patients operated on for highly differentiated thyroid cancer.

Contraindications

• Uncompensated thyrotoxicosis.
• Untreated adrenal insufficiency.
• Acute myocardial infarction.

Relative contraindications

• Heart rhythm disturbances.

• Unstable angina pectoris.
• Myocarditis.

Undesirable drug reactions and safety control methods

With an overdose or too rapid increase in dose, symptoms of thyrotoxicosis are observed. In patients with coronary artery disease, the appointment of thyroid hormones, especially lyiotironin, can cause a decrease in tolerance to physical exertion and an increase in angina attacks. Long-term suppressive therapy with thyroid hormones can lead to a decrease in the mineral density of bone tissue, especially in menopausal women.

In primary hypothyroidism and endemic goiter, treatment is carried out under the control of TSH concentration, and in case of secondary hypothyroidism - under the control of the level of free T4.

Special Use

Thyroid hormones at risk of use during pregnancy are class A, so their use in pregnant women, if indicated, is absolutely safe. Minimum amounts of thyroid hormones are excreted in breast milk, which is not an obstacle to their use in lactating women.

The need for levothyroxine sodium in children is significantly higher than in adults. The initial dose of levothyroxine sodium in congenital hypothyroidism is 10-15 mcg / kg per day.

In young patients without concomitant pathology, L-T4 can be immediately prescribed in a complete replacement dose, which is initially calculated based on the patient's weight (1.6 μg / kg body weight). For women, the dose of L-T4 averages 100 mcg, for men - 150 mcg per day. The drug is taken once a day, in the morning 30 minutes before breakfast. The control parameter by which the quality of hypothyroidism compensation is evaluated is the level of TSH. If the outcome was significantly increased, then its normalization can last up to 4-6 months (the first control study is usually done after 2-3 months). After compensation for hypothyroidism is achieved (normal TSH level), this parameter is evaluated at intervals of one year.

Compensated hypothyroidism is not a contraindication for pregnancy planning (with its onset, the dose of L-T4 should be increased at about 2.3 μg / kg body weight).

The principles of substitution therapy for secondary hypothyroidism are similar, except that the quality of its compensation is assessed at the T4 level. Treatment of hypothyroid coma involves intensive measures, including the administration of thyroid hormone, glucocorticoids, and the correction of hemodynamic and electrolyte disorders.

Forecast

The quality of life of patients with compensated hypothyroidism, as a rule, does not significantly suffer: the patient has no restrictions, except for the need for daily intake of L-T4.

THYROIDITIS

The term "thyroiditis" unites a heterogeneous group of inflammatory thyroid diseases. The most common are various variants of autoimmune thyroiditis.

Autoimmune thyroiditis

Autoimmune thyroiditis (AIT) is a heterogeneous group of inflammatory thyroid diseases of autoimmune etiology, the basis of the pathogenesis of which is the destruction of follicles and follicular thyroid cells of varying severity.

Chronic autoimmune thyroiditis

Chronic autoimmune thyroiditis (Hashimoto thyroiditis, lymphocytic thyroiditis) is a chronic inflammatory disease of the thyroid gland with autoimmune genesis, in which, as a result of chronically progressive lymphoid infiltration, a gradual destruction of the thyroid parenchyma occurs with a possible outcome in primary hypothyroidism6 . The disease was first described by the Japanese surgeon N. Hashimoto in 1912. He observed several cases of thyroid enlargement due to lymphoid infiltration (lymphomatous goiter), in connection with which the term Hashimoto's thyroiditis refers to the hypertrophic variant of AIT, although it is often spread to chronic AIT in general .

Etiology

The disease develops against the background of a genetically determined defect in the immune response, leading to T-lymphocytic aggression against own thyroid cells, ending in their destruction. Histologically, lymphocytic and plasmacytic infiltration, oncocytic transformation of thyrocytes (the

formation of Gürtle-Ashkenazi cells), and follicular destruction are determined histologically. AIT tends to manifest itself in the form of family forms. In patients with an increased frequency, haplotypes HLA-DR3, DR5, B8 are detected. In 50% of cases, relatives of patients with AIT show circulating antibodies to the thyroid gland. In addition, there is a combination of AIT in the same patient or within the same family with other autoimmune diseases pernicious anemia, autoimmune primary hypocorticism, chronic autoimmune hepatitis, type 1 diabetes, vitiligo, rheumatoid arthritis, etc.

Pathogenesis

The pathological significance for the body of AIT is practically limited to the fact that it is a risk factor for hypothyroidism. The fact of carriage of antibodies to the thyroid gland, which are markers of AIT, in the population many times exceeds the prevalence of hypothyroidism, indicates that in most cases the disease does not lead to the development of hypothyroidism, that is, the severity of thyroid parenchyma replacement with lymphoid and fibrous tissue does not exceeds a certain critical level. The difference in the rate of progression of the process in individual patients, as well as the reasons for the increase in the thyroid gland in some cases (hypertrophic form) and its significant decrease in others (atrophic form) remain incomprehensible.

The progression of AIT from the euthyroid phase to hypothyroidism. The euthyroid phase, as indicated, can last for many years or decades, or even throughout life. Further, in the case of progression of the process, namely, a gradual increase in thyroid lymphocytic in-filtration and destruction of its follicular epithelium, the number of cells producing thyroid hormones decreases. Under these conditions, in order to provide the body with a sufficient amount of thyroid hormones, the production of TSH increases, which hyperstimulates the thyroid gland. Due to this hyperstimulation for an indefinite time (sometimes tens of years), it is possible to maintain T4 production at a normal level. This is the phase of subclinical hypothyroidism (TSHT, T4 - normal). With further destruction of the thyroid gland, the number of functioning thyrocytes falls below a critical level, the concentration of T4 in the blood decreases and hypothyroidism manifests itself (a phase of overt hypothyroidism).

Epidemiology

The prevalence of AIT itself is difficult to assess, since in the euthyroid phase it has practically no exact diagnostic criteria. The prevalence in the general population of carriage of antibodies to thyroid peroxidase (AT-TPO) is about 10% and varies depending on its ethnic composition. The prevalence of both AT-TPO carriage and hypothyroidism in the outcome of AIT is about 10 times higher in women compared with men. AIT is the cause of approximately 70-80% of all cases of primary hypothyroidism, the prevalence of which leaves about 2% in the general population and reaches 10-12% among older women.

Clinical manifestations

In the euthyroid phase and the phase of subclinical hypothyroidism are absent. In separate, relatively rare cases, an increase in the volume of the thyroid gland (goiter), which quite rarely reaches significant degrees, comes to the fore in the euthyroid phase. With the development of hypothyroidism in the patient, the corresponding symptoms begin to increase

Diagnostics

The criteria, the combination of which allows you to establish a diagnosis of AIT, include:

• an increase in the level of circulating antibodies to the thyroid gland (the determination of AT-TPO is more informative);

• detection of typical ultrasound signs of AIT (thyroid hypoechogenicity);

• primary hypothyroidism (subclinical or manifest).

In the absence of at least one of the listed criteria, the diagnosis of AIT is probabilistic, since an increase in the level of AT-TPO or hypoechoicity of the thyroid gland according to ultrasound data does not yet indicate AIT and does not allow to establish this diagnosis. Thus, the diagnosis of AIT in the euthyroid phase (before the manifestation of hypothyroidism) is quite complicated. At the same time, there is usually no real practical need to establish a diagnosis of AIT in the euthyroidism phase, since treatment (L-T4 replacement therapy) is shown to the patient only in the hypothyroid phase.

Differential diagnosis
In regions of iodine deficiency, it may be necessary to differential diagnosis of simple endemic goiter and hypertrophic forms of AIT in the euthyroidism phase. It should be borne in mind that a moderate increase in the level of AT-TPO is also found in endemic goiter, in addition, the development of AIT against the background of a preexisting goiter (strumitis) is possible. In the hypothyroid phase of AIT, differential diagnosis between irreversible hypothyroidism in the outcome of chronic AIT and transient hypothyroidism, which is one of the phases of destructive variants of AIT (postpartum, silent, cytokinduced), may be needed. The conclusion about the persistent nature of hypothyroidism is made if, when trying to temporarily discontinue replacement therapy after about a year from its start, the patient has an increase in TSH level and a decrease in T4 level.
Treatment Specific treatment has not been developed, and today there are no effective and safe methods of influencing the autoimmune process developing in the thyroid gland, which could prevent the progression of AIT to hypothyroidism. With the development of hypothyroidism, levothyroxine replacement therapy is indicated.
The prognosis of AIT and carriage of AT-TPO should be considered as risk factors for the development of hypothyroidism in the future. The likelihood of hypothyroidism in a woman with elevated levels of AT-TPO and normal
In women who carry AT-TPO without impairing its function, the risk of hypothyroidism and the so-called relative gestational hypothyroxinemia is increased during pregnancy (see paragraph 3.9.3). In this regard, such women need to control thyroid function in the early stages of pregnancy, and, if necessary, at a later date.
Postpartum, painless, and cytokine-induced thyroiditis
These types of AIT are united by the phase nature of the changes occurring in the thyroid gland associated with autoimmune aggression: in the most typical course, the phase of destructive thyrotoxicosis is replaced by a phase of transient hypothyroidism, after which, in most cases, restoration of the thyroid function occurs. 17. The most studied and most common postpartum thyroiditis.
Etiology
It is similar to that in chronic AIT, since all variants of destructive AIT develop in carriers of AT-TPO, and in the thyroid gland lymphocytic infiltration and the formation of lymphoid follicles are detected. As the cause of postpartum thyroiditis, excessive reactivity of the immune system after natural gestational immunosuppression (the rebound phenomenon), which in susceptible individuals (carriers of AT-TPO) leads to destructive AIT, is considered. The provoking factors for painless ("silent") thyroiditis are unknown; this variant of destructive AIT, in fact, is a complete analogue of the postpartum one, but develops independently of pregnancy. The reason for the development of cytokine-induced thyroiditis is the appointment of interferon preparations for the patient for various diseases (hepatitis C, blood diseases), while there is no clear time relationship between the development of thyroiditis and the duration of treatment with interferons: thyroiditis can develop as at the beginning treatment, and after months.
Pathogenesis With all destructive AITs, the disease goes through several phases (Fig. 3.24). The thyrotoxic phase, apparently, is a consequence of an antibody-dependent complement attack on thyrocytes, which results in the release of ready-made thyroid hormones into the bloodstream. If thyroid deformation was quite pronounced, the second phase begins - hypothyroid, which usually lasts no more than a year. In the future, restoration of thyroid function most often occurs, although in some cases hypothyroidism remains persistent. In all three variants of the destructive AIT, the process can have a monophasic character (only thyrotoxic or only hypothyroid phase
Epidemiology
Postpartum thyroiditis develops in the postpartum period in 5–9% of all women, while it is strictly associated with carriage of AT-TPO. It develops in 50% of carriers of AT-TPO, while, as indicated, the prevalence of carriage of AT-TPO among women reaches 10%. Postpartum thyroid-id develops in 25% of women with type 1 diabetes.
The prevalence of painless (silent) thyroiditis is unknown. Like postpartum thyroiditis, it is associated with carriage of AT-TPO and, due to the benign course, most often remains undiagnosed.

Cytokine-induced thyroiditis, like the two discussed above, more often develops in women (4 times) and is associated with carriage of AT-TPO. The risk of its development in carriers of AT-TPO receiving interferon preparations is about 20%. There is no correlation between the onset time, duration, and the regimen of interferon therapy. With the development of cytokinduced thyroiditis, the abolition or change in the treatment regimen of interferons in the natural course of the disease, apparently, is not reflected.

Clinical manifestations

For all three destructive AITs, the symptoms of thyroid dysfunction are very moderate or absent. The thyroid gland is not enlarged if thyroiditis has not developed against the background of a preexisting goiter, painless on palpation. Endocrine ophthalmopathy never develops. Postpartum thyroiditis usually manifests with mild thyrotoxicosis at about 14 weeks after delivery. In most cases, non-specific symptoms in the form of fatigue, general weakness, some weight loss are associated with recent births. In some cases, thyrotoxicosis is significantly expressed and the situation requires differential diagnosis with Graves' disease. The hypothyroid phase develops at about 19 weeks after birth, while severe hypothyroidism, as a rule, is not discussed. In some cases, with the hypothyroid phase of postpartum thyroiditis is associated with postpartum depression.

Painless (silent) thyroiditis is diagnosed with mild, often subclinical thyrotoxicosis, which, in turn, is detected by non-targeted hormonal examination. The diagnosis of the hypothyroid phase of painless thyroiditis can be established retrospectively, with dynamic observation of patients with subclinical hypothyroidism, which ends with the normalization of thyroid function.

Cytokine-induced thyroiditis also, as a rule, is not accompanied by severe thyrotoxicosis or hypothyroidism and is most often diagnosed with a planned hormonal study, which is part of the observation algorithm for patients receiving interferon preparations.

Diagnostics

Diagnosis is based on anamnestic indications of recent birth (abortion) or the patient receiving interferon therapy. In these situations, thyroid dysfunction in the overwhelming majority is associated with postpartum and cytokine-induced thyroiditis, respectively. Painless thyroiditis should be suspected in patients with mild, often subclinical thyrotoxicosis who do not have clinical manifestations and endocrine ophthalmopathy. The thyrotoxic phase of all three thyroiditis is characterized by a decrease in the accumulation of the radiopharmaceutical according to thyroid scintigraphy. Ultrasound reveals a reduced echogenicity of the parenchyma that is nonspecific for all autoimmune diseases.

Treatment

In the thyrotoxic phase, the appointment of thyrostatics (tiamazole) is not shown, since there are no thyroid hyperfunctions with destructive thyrotoxicosis. With severe cardiovascular symptoms, β-blockers are prescribed. In the hypothyroid phase, levothyroxine replacement therapy is prescribed. After about a year, an attempt is made to cancel it: in case hypothyroidism was transient, the patient will continue to have euthyroidism, with persistent hypothyroidism, an increase in TSH level and a decrease in T4 will occur.

Forecast

In women with postpartum thyroiditis, the probability of recurrence after the next pregnancy is 70%. Approximately 25-30% of women who have undergone postpartum thyroiditis later develop a chronic variant of AIT with outcome in persistent hypothyroidism.

Subacute thyroiditis

Subacute thyroiditis (De Kerven’s thyroiditis, granulomatous thyroiditis) is an inflammatory thyroid disease, presumably of viral etiology, in which destructive thyrotoxicosis is combined with pain in the neck and symptoms of acute infectious disease.

Etiology

Presumably viral, because during the course of the disease, some of the patients show an increase in the level of antibodies to viruses

influenza, mumps, adenoviruses. In addition, subacute thyroiditis often develops after infections of the upper respiratory tract, influenza, mumps, measles. A genetic predisposition to the development

of the disease is proved. Among patients with subacute thyroiditis, carriers of the HLA-Bw35 antigen are found 30 times more often.

Pathogenesis

If you adhere to the viral theory of the pathogenesis of subacute thyroiditis, it is most likely that the introduction of the virus into the thyroid cell causes the destruction of the latter with the ingress of follicular contents into the bloodstream (destructive thyrotoxicosis). The tissue reaction to the introduction of the virus is histologically manifested by focal granulomatous infiltration by histiocytes and giant cells. At the end of the viral infection, thyroid function is restored, in some cases after a short hypothyroid phase.

Epidemiology Mostly people between the ages of 30 and 60 fall ill, with women being 5 or more times more likely than men; in children, the disease is casuistically rare. In the structure of diseases occurring with thyroid toxicosis, subacute thyroiditis occurs 10-20 times less often than Graves' disease. We can assume a slightly greater incidence, given the fact that subacute thyroiditis can have a very mild course that masquerades as another pathology (tonsillitis, SARS), followed by spontaneous remission.

Clinical manifestations The clinical picture is represented by three groups of symptoms: pain in the neck, thyrotoxicosis (mild or moderate) and symptoms of an acute infectious disease (intoxication, sweating, subfebrile condition). Typical for subacute thyroiditis is the rather sudden appearance of diffuse pain in the neck. Cervical movements, swallowing and various irritations of the thyroid gland are very unpleasant and painful. The pain often radiates to the back of the head, ears and lower jaw. On palpation, the thyroid gland is painful, dense, moderately enlarged; soreness can be local or diffuse depending on the degree of involvement of the gland in the inflammatory process. Variable intensity and passing (wandering) pain from the area of one lobe to another, as well as pronounced general phenomena: tachycardia, asthenization, weight loss, are characteristic.

An increase in temperature (subfebrile condition or mild fever) occurs in approximately 40% of patients. Often, pain in the neck is the only clinical manifestation of subacute thyroiditis, while thyrotoxic goats in the patient may be completely absent.

Diagnosis An increase in ESR is one of the most typical manifestations of subacute thyroiditis, while it can be increased significantly (more than 50-70 mm / hour). Leukocytosis characteristic of bacterial infections is absent, moderate lymphocytosis can be determined. As with other diseases occurring with destructive thyrotoxicosis, the level of thyroid hormones is increased moderately; subclinical thyrotoxicosis is often found, often the euthyroid course of the disease.

According to ultrasound, subacute thyroiditis is characterized by vague limited hypoechoic areas, less commonly diffuse hypoechoicity. Scintigraphy revealed a decrease in 99mTc uptake.

The results of treatment with prednisolone (ex juvantibus diagnosis), the initial stage of which is known as the Craill test, are of important diagnostic value. The latter is considered positive if, in the first 12-48 hours after the drug was prescribed at a dose of about 30 mg / day, the patient experiences a significant reduction or disappearance of pain in the neck, an improvement in overall well-being, and a noticeable tendency to a decrease in ESR.

Differential diagnosis

It is carried out with diseases in which thyrotoxicosis is caused by thyroid hyperfunction (Graves disease, multinodular toxic goiter); subacute thyroiditis is characterized by a decrease in 99mTc accumulation according to scintigraphy, the absence of endocrine ophthalmopathy. With very rare acute purulent thyroiditis, along with soreness in the neck, leukocytosis is detected, thyrotoxicosis is absent, ultrasound reveals a fluid cavity (abscess), with a puncture biopsy of which purulent contents are obtained. Crail's test is positive almost exclusively with subacute thyroiditis.

Treatment In the case of mild subacute thyroiditis, in which only some pain in the neck is determined and there is no intoxication, treatment may not be necessary at all, and the disease ends spontaneously. In case of mild pain, non-steroidal anti-inflammatory drugs can be prescribed (aspirin - 300-600 mg every 6 hours). In severe pain syndrome (most patients), prednisone in a daily dose of about 30 mg is prescribed with its gradual decrease and withdrawal over a period of 2-3 months, depending on the severity of the disease. In some cases, after the end of treatment, and sometimes, after several months, a relapse of the disease occurs (sometimes not one), the treatment of which is

similar. With transient hypothyroidism, which is quite rare in subacute thyroiditis, temporary replacement therapy with levothyroxine is indicated.
Prognosis In general, the disease is prone to spontaneous resolution, that is, when treatment is not prescribed for some reason, subacute thyroiditis is still gradually resolved, ending with a full recovery. In the vast majority of cases, subacute thyroiditis does not recur and ends in complete recovery.
Rare thyroiditis Rare thyroiditis includes acute purulent thyroiditis, Riedel's fibrosing thyroiditis, as well as specific thyroiditis (tuberculosis, syphilitic, fungal, actinomycosis and others). Most of them are casuistically rare.
Nodular and multinodular euthyroid goiter
Nodular goiter is a collective clinical concept that combines morphological volumetric thyroid masses detected by palpation and instrumental diagnostic methods (primarily ultrasound). The term "multinodular goiter" should be used when two or more nodular formations are detected in the thyroid gland. The clinical concept of "nodular (multinodular) goiter" combines the following most frequent nosological (morphological) forms:
- nodular colloidal to a varying degree proliferating goiter;
- follicular adenomas;
- malignant tumors of the thyroid gland
IODINE DEFICIENCY DISEASES
Iodine deficiency diseases (IDD) include all pathological conditions that develop in a population due to iodine deficiency, which can be prevented by normalizing iodine intake. This term emphasizes the fact that thyroid disease is far from the only and not the most serious consequence of iodine deficiency. The minimum physiological need for iodine varies depending on the age and physiological state of the body
Epidemiology of iodine deficiency diseases
Iodine deficiency is a natural environmental phenomenon, since fertile soil, as well as plant and animal foods contain very little of this trace element. In this regard, IDDs are a serious public health problem in many regions of the world. According to WHO, about 1570 million people (30% of the world's population) are at risk of developing IDD, including more than 500 million people living in regions with severe iodine deficiency and high prevalence of endemic goiter.
The main indicator of the intensity of iodine deficiency in a population is the level of urinary iodine excretion in a representative group of the population living in a particular region. A representative group is considered to be children of primary school age (7-12 years), while the survey itself is usually carried out directly in schools, which determines the randomness of selection and representativeness of the sample. After determining the level of iodine excretion in individual portions of urine, an integral indicator, the median of ioduria, is calculated. An indirect and less reliable indicator of the severity of iodine deficiency is the prevalence of an increase in the thyroid gland (goiter) in the same group of children.
Thanks to mass iodine prophylaxis, iodine deficiency was eliminated in Poland, Great Britain, Germany, the countries of Scandinavia, Great Britain, China, Turkmenistan, Armenia, and the countries of South America. Since the main method of iodine prophylaxis is iodization of table salt, the main criterion for eliminating iodine deficiency in a particular region is the number of households consuming iodized salt. The elimination of iodine deficiency can be said in a situation where their share exceeds 90%.
Iodine deficiency diseases of the thyroid gland
Diffuse euthyroid goiter
Etiology
The most common cause of thyroid enlargement (goiter) is iodine deficiency. Goiter, detected in regions of iodine deficiency, is designated by the term endemic, and in regions with normal iodine intake, it is sporadic. Rarely enough, endemic goiter is associated not with iodine deficiency, but with the action of other goiterogenic factors (flavonoids, thiocyanates). The etiology of sporadic goiter is poorly understood and, apparently, heterogeneous. In some cases, it is associated with congenital defects of the enzyme systems involved in the synthesis of thyroid hormones.

Pathogenesis

The most studied pathogenesis of iodine deficiency goiter. With a decrease in iodine content in thyroid cells, the content of iodized lipids, such as iodlactones, decreases in them

These compounds have a blocking effect on the production of local tissue growth factors (epidermal and insulin-like growth factor 1, fibroblast growth factor). As a result, with iodine deficiency, there is an intensification of the production of these substances by thyrocytes, the result of which is their hyperplasia. An additional effect on the increase in thyroid gland is indicated by stimulation of TSH, which increases slightly with a tendency to a decrease in the level of thyroid hormones in the blood.

A diffuse small-sized euthyroid goiter is far from always surely interpreted as an obvious pathology, or at least as a situation requiring aggressive treatment tactics. This is due to the fact that thyroid volume standards, especially in children, are the subject of debate.

Epidemiology

Prevalence depends on the severity of iodine deficiency. So, if in the regions of mild iodine deficiency the prevalence of euthyroid goiter is about 10% of the population, then with severe iodine deficiency it can reach 100%. In some regions, some zobogens (tapioca and cassava containing thiocyanates, which are used in food in a number of African countries) may be additional, but usually not decisive.

Clinical manifestations

As a rule, they are absent with the exception of relatively rare cases of a significant increase in the thyroid gland with compression syndrome. Sometimes patients complain of an unpleasant sensation in the neck, although, on the other hand, such complaints are rarely quite directly related to the thyroid pathology. Visible goiter can become a cosmetic problem, in connection with which the patient is referred to an endocrinologist.

Diagnostics

Patients in whom goiter was detected during thyroid palpation, an ultrasound of the thyroid gland is shown to assess its volume, as well as determining the level of TSH to exclude the violation of its function. Normally, thyroid volume in women does not exceed 18 ml, and in men, 25 ml. With diffuse euthyroid goiter, iron is increased due to both lobes, while the patient has a normal TSH level.

Differential diagnosis

Chronic AIT often proceeds with an increase in the volume of the thyroid gland (Hashi-moto goiter), while ultrasound can reveal a characteristic change in its echogenicity, serum AT-TPO are determined, and with hormonal examination, thyroid hypofunction. The latter is not a mandatory sign, but it is very valuable for diagnosis. Many diseases that occur with an increase in thyroid volume are accompanied by a violation of its function (Graves disease). In some cases, an increase in the thyroid gland is due to the use of goiter preparations (lithium preparations, amiodarone, thyreostatics).

Treatment

A small increase in the thyroid gland without impairing its function, especially in the elderly, does not always require therapy. More active treatment is indicated for young patients. In regions of iodine deficiency endemic at the first stage, the patient is usually prescribed iodine preparations in physiological doses (100-200 mcg per day), against the background of which a dynamic assessment of thyroid volume is carried out. Typically, within six months, the volume of the thyroid gland is significantly reduced or normalized. If this does not occur, the appointment of a suppressive therapy with levothyroxine (L-T4) preparations is discussed, possibly in combination with potassium iodide preparations. Its goal is to maintain a slightly reduced or low normal TSH level, in connection with which the drug is prescribed at a dose of 75-150 mcg per day

Against the background of such therapy, a decrease in thyroid volume occurs in most patients. After this, the transfer of the patient to monotherapy with potassium iodide preparations is discussed, since the desirability of long-term suppressive therapy with L-T4 is doubtful.

Forecast

Favorable, in most cases, these therapeutic measures can normalize the volume of the thyroid gland. In regions of mild iodine deficiency, diffuse euthyroid goiter, even if untreated, very rarely reaches

significant levels and leads to compression syndrome; some patients form nodules, and later functional thyroid autonomy may develop
Functional autonomy of the thyroid gland
Functional autonomy (FA) of the thyroid gland is the production of thyroid hormones independent of the regulatory effects of the pituitary gland in the absence of external stimulants.
Etiology
The cause of the development of FA is chronic thyroid hyperstimulation, which occurs in conditions of iodine deficiency of mild to moderate severity. The main etiological background of the development of FA is the microheterogeneity of thyrocytes, in which the proliferative potential differs significantly

The purpose of the lesson:
To learn:
I. Anatomy and physiology of the thyroid gland
II. Classification of thyroid disease
a) Hyperthyroidism - etiology, pathogenesis, clinical features, diagnosis, treatment Classification of drugs with hyperthyroidism
Antithyroid drugs - thioamides (mercazolyl, propylthiouracil), thiamazole (metizol, tyrosol), carby-mazole,
preparations containing iodine
a) monocomponent: potassium iodide (iodide);
b) radioactive iodine.
Mechanisms of action. Pharmacodynamics Undesirable effects. Application.
b) Thyroid hypofunction - etiology, pathogenesis, clinical features, diagnosis
Classification of drugs with hypothyroidism (replacement therapy)
Thyroid hormone preparations - levothyroxine, triiodothyronine hydrochloride (lyiotironin), thyroid-idin, and combination drugs (thyrocomb, thyro-tom).
a) monocomponent preparations: levothyroxine sodium (L-thyroxine, euthyroxin, eferox, thyroxine); lyothyronine (triiodothyronine T4);
b) combination preparations: levothyroxine sodium and lyothyronine (noviral, thyrotome, thyroidin), levothyroxine sodium and potassium iodide (iodine thyrox); levothyroxine sodium, lyothyronine and potassium iodide (thyrocomb); thyroidin.
Pharmacodynamics, mechanisms of action. Undesirable effects. Application
Be able to:
a) select the necessary drugs for a particular patient with the indicated pathology, select criteria for therapeutic efficacy and safety;
b) prescribe combination therapy;
1. To study scientifically based approaches to rational pharmacotherapy with thyroid hormone preparations and thyreostatics, as well as methods for monitoring their effectiveness and safety.
Know:
1) Etiology, pathogenesis, clinic, complications, Graves disease
2) Research Methods for Graves Disease
3) Etiology, pathogenesis, clinic, complications of Myxedema, cretinism
4) Research Methods of Myxedema, cretinism
5) The main etiological factors and pathogenetic mechanisms that are the object of drug exposure
6) Pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics, interaction of the above drugs
7) Diseases of Graves, Myxedema, cretinism
The student must know:
a) a unified algorithm for choosing pharmacotherapy for hypo- and hyperthyroidism, monitoring its effectiveness and safety;
b) the etiological classification of diseases of the thyroid gland leading to its hyper- and hypofunction;

c) the main pathogenetic mechanisms that are the object of drug exposure in the above types of pathology;
d) pharmacodynamic characteristics of the main groups of drugs used in
thyroid dysfunction:
thyroid hormone preparations
antithyroid drugs:
e) the pharmacodynamics of thyroid-stimulating drugs and conditions that alter the intake, distribution, metabolism and elimination of these drugs in the body;
e) the basic principles of thyreostatic and thyroid-stimulating therapy;
g) undesirable effects of thyreostatics and thyroid hormones, methods for their early detection and methods of prevention;
h) the principles of the combination of thyrotropic drugs;
i) criteria for the effectiveness and safety of their use.
3. The student must be able to:
a) select the necessary drugs for the patient with thyroid gland dysfunction, select its dose, regimen and route of administration;
b) identify criteria for evaluating the therapeutic efficacy and safety of thyreotropic drugs used;
c) provide urgent differentiated medication with:
thyrotoxic crisis; - hypothyroid coma.
The task for the self-test of the initial level:
1. List the mechanism of neurohumoral regulation of the synthesis of hormones of the thyroid gland.
2. Evaluate the molecular biochemical mechanisms of the influence of thyroid hormones on metabolic processes in the body.
3. What is the current classification of diffuse toxic goiter and the basic principles of pharmacotherapy, depending on the stage of the disease.
4. Light the pathogenesis of diffuse toxic goiter and other thyroid diseases with thyrotoxic manifestations.
5. List the main diseases of primary and secondary genesis, accompanied by a decrease in thyroid function.
6. Explain the pathogenesis of hypothyroidism (myxedema).
7. List the modern clinical and laboratory diagnostic methods used in diseases of the thyroid gland.
8. What are the main pathogenetic mechanisms of the development of thyrotoxic crisis, the general principles of its pharmacological correction.
9. What are the main pathogenetic mechanisms for the development of hypothyroid coma, the general principles of its medical correction.
10. What is the modern classification of drugs used for hypo- and hyper-function of the thyroid gland.
11. List known groups of drugs whose possible side effect is associated with an effect on the function of the thyroid gland.
The list of practical works:
Homework.
1. To study the main tasks and directions of the choice of medicines for Greves disease, Myxedema, cretinism
Control of the intermediate level of knowledge.
Drug Selection for Greves Disease
The choice of drugs for replacement therapy
The choice of thyreostatics during pregnancy,
Make an urgent care plan for thyrotoxic crisis
The decision of situational problems
Task number 1.
Patient D., 42 rock, guard страж on hyperthyroidism. I will stretch the therapy for two times: merkazolil 0.01 g 2 times a day, propranolol 60 mg per day, tincture valeriani 20 drops 3-4 times a day. Insider likuvannya changed: psycho-motional lability, dratlivost, tachikardiya, pitlivist.

Can you help me with the effectiveness of anti-thyroid therapy merkazolil? Go ahead.
1. Patient, 36 years old. Diagnosis: diffuse toxic goiter II-III art; thyrotok-sycosis of moderate severity, decompensated.
Which thyreostatic drugs should be prescribed to a patient? Choose a dose, multiplicity of doses, indicate criteria for the effectiveness of the application. Does the patient need thyroid hormones?
2. Patient, 32 years old. Diagnosis: diffuse toxic goiter III-IV century; thyrotok-sycosis, severe, decompensated. The patient was hospitalized in the endocrinological department in order to prepare for surgical treatment.
Make a combination drug therapy, determine the dose of drugs, the frequency of administration, criteria for the effectiveness of therapy, after which surgical treatment is possible.
3. Patient, 36 years old. Diagnosis: Hashimoto's autoimmune thioriditis, moderate hypothyroidism, decompensated.
Choose an adequate dose of thyroid hormone, indicate criteria for effectiveness.
4. Patient, 55 years old. Diagnosis: moderate secondary hypothyroidism, decompensated. Concomitant: coronary heart disease: stable angina pectoris II f.kl, extrasystolic arrhythmia, NK I art.
Choose an adequate dose of thyroid hormone, indicate the features of its selection, taking into account the concomitant disease. Justify the need and plan for combination therapy.
5. The patient is 35 years old. Subtotal resection of the thyroid gland due to diffuse toxic goiter was performed. The postoperative period of the feces without complications. 3 months later after surgery, the patient complained of an increase in weight of 4 kg, swelling of the face, drowsiness after dinner, heart attacks and sweating in the first half day. On the ECG, a decrease in the voltage of the teeth.
Give a clinical assessment of the patient's condition. Schedule an examination plan and justify drug therapy.
6. Patient, 36 years old. Diagnosis: diffuse toxic goiter II-III Art. thyrotoxic goats of moderate severity, decompensated.
Which thyreostatic drugs should be prescribed to a patient? Choose a dose, multiplicity of doses, indicate criteria for the effectiveness of the application. Does the patient need to prescribe thyroid hormones?
7. Sick. 32 years old. Diagnosis: diffuse toxic goiter III-IV century; thyrotok-sycosis, severe, decompensated. the patient was hospitalized in the endocrinological department in order to prepare for surgical treatment. Compose a combination drug therapy, determine the dose of drugs, the frequency of administration, criteria for the effectiveness of therapy, after which surgical treatment is possible.
8. Patient, 36 years old. Diagnosis: Hashimoto's autoimmune thyroiditis, moderate hypothyroidism, decompensated. Choose an adequate dose of thyroid hormone, indicate effectiveness criteria.
9. Patient, 55 years old. Diagnosis: moderate secondary hypothyroidism, decompensated. Related: coronary heart disease: stable angina pectoris II f. C., extrasystolic arrhythmia, IR I Art.
Choose an adequate dose of thyroid hormone, indicate the features of its selection, taking into account the concomitant disease. Justify the need and plan for combination therapy.
10. Patient 35 years old. Subtotal resection of the thyroid gland due to diffuse toxic goiter was performed. The postoperative period of the feces without complications. 3 months later after surgery, the patient complained of an increase in weight of 4 kg, swelling of the face, drowsiness after dinner, heart attacks and sweating in the first half day. On the ECG, a decrease in the voltage of the teeth.
Give a clinical assessment of the patient's condition. Schedule an examination plan and justify drug therapy.

TESTS

1. During an objective examination of a 38-year-old woman, there was detected pasposiness of the face, dry skin, and hair loss on the pubic and inguinal areas. Sick of increased nutrition. The isthmus of the thyroid gland is palpated, painless, mobile. Pulse - 56 rpm, rhythmic. HELL -100/60 mm RT. Art. The boundaries of relative dullness of the heart are moderately expanded. The activity of the heart is rhythmic, the tones are weakened. Predisposition to constipation. Daily diuresis 400-500 ml. Which of the following drugs should be prescribed?
A. Estrogen replacement drugs.

B. Cardiac products.
C. Cholesterol lowering drugs.
D. Iron preparations.
E. Thyroid hormones.
2. A woman, 47 years old, had a thyroid resection due to nodular euthyroid goiter. What treatment is most likely to help prevent relapse of nodular goiter?
A. Antistrumin.
V. Merkazolila.
C. thyrotropin.
D. Thyroid hormones.
E. Radioactive iodine.
3. In a woman, 46 years old, after subtotal resection of the thyroid gland, paresthesia appeared in the face, limbs, shortness of breath, pain behind the sternum. Heart rate - 89 rpm; BH - 20 rpm; BP - 150/100 mmHg. Art. What drugs should be prescribed to prevent a sharp deterioration?
A. Nitrates.
B. Antipsychotics.
C. Tranquilizers.
D. Calcium preparations.
E. β-Blockers.
4. A woman, 40 years old, daily consumes 50 μg of L-thyroxine in connection with primary hypothyroidism. What examination is appropriate to assess the effectiveness of the dose of the drug?
A. Determination of cholesterol.
B. Determination of the level of triiodothyronine.
C. Determination of thyroxine level.
D. Determination of thyroglobulin level.
E. Determination of thyrotropin level
5. A woman, 47 years old, had a thyroid resection due to nodular euthyroid goiter. What treatment is most likely to help prevent relapse of nodular goiter?
A. Antistrumin.
B. Thyroid hormones.
C. thyrotropin.
D. Merkazolil.
E. Radioactive iodine.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн, В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF ANTI-ALLERGIC DRUGS

Relevance of the topic.

A fifth of our planet suffers from various allergic diseases. The results of studies of the epidemiology of allergic diseases indicate not only their wide distribution, but also an increase in the frequency of the latter. Almost every doctor is faced with allergic manifestations in a patient, with cases of intolerance to drugs and food products, unusual reactions to chemicals of a domestic or professional environment, including clothing made from synthetic fabrics, cosmetics, and much more.

In most cases, when there is an acute manifestation of an allergic reaction, the pharmacist does not have the opportunity to consult an allergist professionally, and therefore he has to decide the whole complex of diagnostic, and most importantly therapeutic issues.

Motivational characteristic of the topic.

The concept of antiallergic drugs

When S. Pirquet coined the term “allergy” for the first time in 1906, he had a specific change in his ability to react to an antigen acquired by the body and attributed both hyper- and hyporeactivity to it. An example of the latter was immunity (immunodeficiencies). At present, allergy is understood only as the organism’s hyperreactivity to various environmental influences, to any substance, most often with antigenic properties (A.D. Ado, 1980). It has now been proven that only those reactions that are based on immunological mechanisms are classified as true, specific allergic reactions, since only with their participation a specific, selective increase in sensitivity to certain substances is possible. Thus, the common thing that unites immunity and allergy is the fundamental one-typeness of the

mechanisms involved in either form of the reaction - that is, in the immune and allergic, and their protective, beneficial character for the body (to limit the spread of individual antigen). What is the difference between the reactions of immunity and allergies? To answer this question, you need to remember the features of the course of an allergic reaction. Among these features, the following processes are most often encountered:
1) inflammation of a hyperergic nature;
2) edema;
3) bronchospasm;
4) skin itching;
5) cytotoxic and cytolytic effects;
6) shock.
What is common in these processes? Only one thing is common - the presence of a moment of damage, that is, all these clinical signs of an allergic reaction are an expression, the realization of damage caused by the immune mechanism. This is the line that distinguishes the immune response from an allergic one. There is no damage, and we call this reaction to the antigen immune, there is damage - and we classify the same reaction as allergic. Thus, an allergic reaction is both protection (limitation of hypertension) and damage at the same time, it is both beneficial and harmful to the body.
According to the simplest classification proposed in 1930 by R.A. Cooke, allergic reactions are of two types:
immediate hypersensitivity reactions (RGNT)
delayed-type hypersensitivity reactions (RGZT).
GNT reactions develop very quickly - a few minutes after the allergen enters the sensitized body and lasts for hours.
With HRT, the reaction develops after 8-12 hours and lasts several days and even weeks. The mechanism of development of HRT and GNT is one - the immune, but its options are different.
In the development of GNT, the reactions of humoral immunity (reactions of B-lymphocytes, plasmocytes) are of primary importance.
In this case, the interactions of the allergen and antibodies, especially those belonging to immunoglobulins of the IgE and IgG4 classes, on the surface (membrane) of mast cells that occupy a strategic position around blood vessels and basophils with the subsequent main role in the formation of immediate allergic reactions the opening of calcium channels, the aspiration of calcium ions into the cell and the release, release (release) of various biologically active substances from them, such as histamine, heparin, serotonin, bradykinin, leukotrienes (LTD4, LTS4, LTE4 or a slow-reacting substance of anaphylaxis), prostaglandins (Pg I-2 - prostacyclin, Pg D-2 and all others), platelet activation factor (platelet aggregation).
Due to the fact that antibodies of the IgE and IgG4 classes are called reagins (re + agere (lat.) - act, enter), this type of allergic damage reaction is called the reactin type of tissue damage or the anaphylactic type of GNT.
Anaphylactic shock, serum sickness, atopic bronchial asthma, hay fever, urticaria, and Quincke's edema include allergic reactions of an immediate type (GNT) in humans. As we see, these are life-threatening reactions, often leading to the death of the patient.
The development of delayed-type hypersensitivity (HRT) is characterized by tissue reactions and is associated with cellular immunity reactions, namely, the activity of T-lymphocytes, macrophages. Therefore, with HRT, the following allergy mediators were found:
- a factor inhibiting the migration of macrophages or lymphocytes;
- lymphokine, increasing the number of these cells in the focus of inflammation;
- factor activating macrophages;
- factor stimulating complement and other lymphokines.
The listed lymphokines provide tissue lymphocytic-monocytic reactions. With HRT, autoimmune diseases of the liver, kidneys, heart, joints, rejection of transplanted tissues, contact dermatitis and eczema, late reactions to microbial toxins (bacterial allergies), and mycoses occur.
Classification of antiallergic drugs

According to two types of allergic reactions, antiallergic drugs are divided into two groups:
A. Means used in non-slow type hypersensitivity reactions (GNT);
B. Drugs used in slow-type hypersensitivity reactions (HRT).
In turn, group A is divided into 4 subgroups, and group B is divided into 2 subgroups. With GNT, the following 4 subgroups of drugs are used:
1. Means that prevent the release of histamine and other biologically active substances from mast cells and basophils:
a) glucocorticoids (prednisone, dexamethasone);
b) beta-adrenergic agonists (adrenaline, isadrine, orciprenaline, salbutamol, berotek);
c) xanthines (aminophylline);
g) cromolin sodium (intal);
e) heparin;
e) M-anticholinergics (atropine, atrovent).
2. Means that interfere with the interaction of free histamine with tissue receptors (H1 - histamine blockers - diphenhydramine group: diphenhydramine, diprazine, diazolin, tavegil, etc.)
3. Drugs that reduce tissue damage (steroidal anti-inflammatory drugs - glucocorticoids);
4. Means that reduce (eliminate) the general manifestations of allergic reactions such as anaphylactic shock:
a) adrenergic agonists;
b) bronchodilators of myotropic action;
c) glucocorticoids.
These four groups are the means that primarily affect the anaphylactic version of GNT. To influence its cytotoxic version or the formation of the CEC of drugs there are very few.
With HRT, 2 groups of drugs are used:
1. Means that suppress immunogenesis, inhibit mainly cellular immunity (immunosuppressants):
a) glucocorticoids (prednisone, dexamethasone, triamcinolone, etc.);
b) cytostatics (cyclophosphamide, azathioprine, mercaptopurine);
c) anti-lymphocyte serum, anti-lymphocyte globulin and human anti-allergic immunoglobulin;
d) anti-rheumatic drugs of slow action (hingamine, penicillamine);
e) antibiotics (cyclosporin A).
2. Means that reduce tissue damage:
a) glucocorticoids (prednisone, dexamethasone, triamcinolone, etc.)
b) NSAIDs (voltaren, piroxicam, indomethacin, naproxen, etc.).
Tools used for GNT
1. Means that prevent the release of mast cells and biologically active substances from mast cells and basophils.
a) Adrenergic agonists and, to a greater extent, beta-adrenergic agonists, primarily adrenaline, orciprenaline, isadrine, salbutamol, as well as selective beta-2-adrenergic agonists such as fenoterol (berotek).
These drugs have common mechanisms of action. First of all, it should be said that in the anti-allergic action of beta-adrenergic agonists, the activation of the membrane enzyme adenylate cyclase and an increase in the level of cAMP in the mast cell and basophils are important.
This prevents the opening of calcium channels and the entry of calcium ions into the cell, the release of calcium from intracellular depots, which inhibits the increase in the concentration of free calcium in the cytoplasm of cells and the development of subsequent reactions (release of biologically active substances).
However, such alpha-, beta-adrenergic agonists as adrenaline, ephedrine have a double effect. In addition to the indicated pharmacological effect, these adrenergic agonists also reduce the systemic manifestations of an immediate allergic reaction (they reduce bronchospasm, increase vascular tone, and stimulate heart activity). In connection with the indicated pharmacological effects and depending on the clinical situation, adrenomimetics are used for the following indications:
1) Adrenaline, ephedrine for injection are indicated for the development of anaphylactic shock (intravenously, with cardiac arrest - intracardially); the effect with the introduction of ephedrine

occurs more slowly (30-40 minutes), but also more prolonged; adrenaline and ephedrine are also injected under the skin (0.3 ml) - to stop attacks of bronchial asthma of atopic origin. A recently created new dosage form of adrenaline (oil solution) with intramuscular injection lasts 16 hours, but aseptic abscesses are possible. A racemic mixture of L- and D-adrenaline in a 2.25% solution is used in aerosol (adnephrine preparation - 2-3 breaths 3-4 times a day).
2) Beta-adrenergic agonists, especially selective beta-2-adrenergic agonists (phenoterol) in the form of aerosols can be used both for stopping the bronchial asthma priest and for its prevention (before going out).
Due to the limited time action of these dosage forms of beta-adrenergic drugs (up to 5 hours), selective beta-2-adrenergic agonists with a duration of about 10 hours have been created in recent years. These are the so-called, prolonged beta-adrenergic agonists, or retarded beta-adrenergic agonists. They are available in tablet and inhaled dosage forms.
- formoterol (foradil), which lasts about 9 hours, 2 times a day; - bigolterol - action time of about 8-9 hours;
- salmeterol - action time about 12 hours.
The listed preparations of retarded beta-adrenergic agonists are mainly used according to one indication - prevention of night attacks of atopic bronchial asthma.
Xanthines are the next group of drugs that prevent the release of histamine and other mediators of immediate allergy from mast cells. The most typical representative is theophylline and its preparations, in particular, eu-phyllin. Theophylline itself, which has a pronounced anti-allergic effect and directly affects the tone of the smooth muscles of the bronchi (antispasmodic myotropic action), is water-insoluble. The latter significantly limits the possibility of its use only in the form of tablets and powders. In connection with the foregoing, a drug based on theophylline, which has good water solubility, was created. This drug is called aminophylline (Euphyllinum). It is a mixture of 80% theophylline and 20% ethylenediamine. It is the last substance that gives the properties of water solubility to aminophylline. It is released in powders, tablets at 0.15; there are dosage forms for parenteral administration: solutions in 10 ml ampoules of 2.4% concentration (intravenous), 1 ml ampoules - 24% concentration (intramuscularly).
The drug has:
1) a pronounced antiallergic effect;
2) direct antispasmodic effect (myotropic).
The antiallergic effect is associated both with the presence of a depressing effect on the release of biologically active substances from mast cells, and with other mechanisms characteristic of this drug. In addition to the fact that the drug eliminates spasm of the smooth muscles of the bronchi (direct bronchodilator effect), it
3) eliminates circulatory failure of the bronchi;
4) dilates the coronary vessels, which helps to improve blood supply to these organs;
5) stimulates myocardial contractile activity;
6) increases diuresis (optional diuretic);
7) reduces the pressure in the pulmonary artery system, which is very important in the development of pulmonary edema.
Eufillin is used in injectable form for the relief of asthma attacks and for the relief of asthmatic status, and in tablets it is used for the prevention of bronchial asthma attacks. In the anti-allergic effect of xanthines (theophylline, in tablets, powders), two more points matter. First, xanthines are antagonists of the adenosine, the mediator of the purinergic system, and this means that long-term administration of xanthines leads to an increase in the concentration of catecholamines in the blood and, therefore, contributes to their bronchodilating effect. The second one. Long-term administration of xanthines contributes to the induction of the formation of T-suppressors, cells that suppress the synthesis of reagin antibodies IgE and IgG4). According to some ideas, it is believed that allergy is a partial immunodeficiency in the content and functioning of T-suppressors. In addition, xanthines have been shown to improve the contractility of the "wasted" diaphragmatic muscle. A new qualitative leap in the development of basic therapy for patients with bronchial asthma occurred as a

result of the creation of prolonged theophylline preparations. These drugs are currently the main means of preventing nighttime attacks of bronchial asthma.

The rational use of drugs of this group requires compliance one condition - mandatory monitoring of theophylline concentration in the patient's blood. A constant concentration of this drug in the blood should be in the range of 10-20 μg / ml. The loading dose is 5.6 mg / kg, then every 6 hours 3 mg / kg.

Short-acting theophylline preparations are used when it is necessary to quickly achieve a high concentration of the drug in the blood.

With long-term treatment, longer-acting drugs are preferred. Already 3 generations of durant (prolonged) theophylline preparations have been created:

I generation - theophylline, diprofillin;

II generation - bamifillin (1200 mg / day) 1/3 in the morning +2/3 at night;

- theophylline retard;
- teotard (2 times);
- durofillin (2 times);
- theo-dur is the best drug;

III generation - Theonova;

- armophylline;
- unifil (1 time per day);
- eufilong and others.

The first domestic drug of theophylline of prolonged action, theopec, was also created (tablets 0.2, 2 times a day).

The following two drugs, Cromolin-Sodium (sodium chromoglycate) or Intal (Cromolyn-Sodium (Intalum), are available in capsules containing 0.02 metallic as well, which belong to the group of drugs that limit the release of biologically active substances from mast cells due to the membrane-stabilizing effect. It's a kind of powder. These capsules are not for use per os, but for placement in a special inhaler called a spinhaller. When placing the capsule in an inhaler, the patient crushes it and immediately takes 4 deep breaths, inhaling particles of intal powder. pronounced The membrane-stabilizing effect on the mast cells of the mucous membranes of the respiratory tract, severely limits the realization of the mast cell degranulation phenomenon, preventing their reaction to the allergen. administration of the drug.Therefore, intal is used only according to the following indications:

1) to reduce the frequency of asthma attacks;

2) to prevent asthma attacks, asthma attacks with asthmatic bronchitis, pneumosclerosis and other conditions with bronchospasm.

Mast cells by the content of some enzymes in them can be divided into 2 types:

1) containing tryptase and localized mainly in the mucous membranes;

2) containing tryptase and chymase and localized in the submucous and mesentery of the intestine.

It turned out that the membrane-stabilizing effect of intal is most pronounced only in relation to mast cells of the first type (containing only tryptase).

- optic feed (from the words optics and cromolyn sodium), which is used to treat patients with allergic diseases (lesions) of the eyes; a drug
- lomuzole - for stopping allergic lesions of the nose, by insufflation in the nasal passages;
- nalkrom - for the treatment of patients with food allergy phenomena

Sodium Nedocromil (tiled). Tyled is very active against the syndrome of bronchial hyperreactivity, that is, it has a pronounced broncho-dilating effect.

The drug has no side effects, it significantly reduces the need for patients to use beta-adrenergic agonists, which can lead to a worsening of the patient's condition.

- Ketotifen (zaditen) - Ketotifenum - is available in capsules and tablets of 0.001 for oral administration, as well as syrup (pediatrics), 1 ml of which contains 0.2 mg of the drug. This is one of the best drugs for chronic treatment of patients with bronchial asthma. He also, having a membrane-stabilizing effect, like Intal, reduces the reaction of mast cells to an allergen, limiting the release of biologically active substances (allergy mediators) from them. In addition, the drug directly blocks H1 - histamine receptors on the smooth muscles of the bronchi, which limits the reaction of the latter to histamine. In addition,

ketotifen also has sedative and potentiating effects. The last three pharmacological effects (H1-histamine-blocking, sedative, hypnotics) are inherent in diphenhydramine, and therefore ketotifen can be simplistically described as a drug with intal and diphenhydramine properties. As a rule, tablets and capsules of ketotifen are used for the chronic treatment of adult patients with bronchial asthma, and syrup is used for the treatment (prevention of seizures) of sick children with bronchial asthma. The effect is noted after 2 weeks.

The first subgroup of drugs also includes glucocorticoid hormones: cortisone, hydrocortisone - preparations of natural hormones, but there are also their synthetic analogues - prednisone, dexamethasone, beclomethasone, etc.

The mechanism of action of glucocorticoid hormones is multifaceted. The antiallergic and anti-inflammatory effects of glucocorticoids are associated with their stabilizing effect on the membrane (membrane-stabilizing), including mast cell lysosomes. This inhibits the interaction of mast cell Fc receptors with the IgE Fc region. The latter significantly reduces the output of various mediators from the cell (histamine, heparin, serotonin), which protects the tissue from destructive processes. In addition, glucocorticoids in the pathochemical stage of allergic reactions significantly inhibit the release of IL-2 through inhibition of IL-1 secretion by macrophages and a direct effect on the T cell.

The drugs inhibit the activity of phospholipase-A2, that is, they prevent the formation of metabolic products of arachidonic acid. In addition, glucocorticoids in rather high doses inhibit lymphopoiesis, the cooperation of Ti B cells, inhibit fibroblast proliferation and their function, and inhibit antibody formation and the formation of immune complexes.

Of glucocorticoids in atopic asthma, the use of beclomethasone or becotide becomes important. It is prescribed by inhalation, so it does not have a systemic effect, that is, it acts locally.

Heparin is also referred to the group of drugs that limit the release of mediators of allergic reactions from mast cells. In certain quantities, heparin is found in mast cells and its main biological role is that it binds histamine and serotonin. Given this fact, it is administered for this purpose in the treatment of patients with allergic diseases, in particular, patients with bronchial asthma. In addition, heparin disrupts the cooperation of T and B lymphocytes, inhibits the activity of the complement system, reduces the formation of anaphylotoxins that release histamine from mast cells, and prevents the interaction of antibodies with antigens, as well as the formation of CEC. As a rule, heparin in this case is prescribed in the form of inhalations.

Sometimes, M-cholinoblockers are used for the same purpose, which block M-cholinergic receptors on mast cells, reduce the activity of guanylate cyclase and the level of cGMP in them and prevent the opening of calcium channels, and therefore, the start of the entire cascade cytochemical process. Mostly used for bronchial asthma.

In this regard, the atrovent, which is available in the form of a patented aerosol inhaler, is beneficial. Due to the fact that this is a Quaternary amine - it is less absorbed, does not penetrate into the central nervous system, has less effect on the digestive tract.

Atrovent, adsorbed mainly on the surface of the bronchial mucosa, suppresses excessive secretion and bronchospasm. Children under 7 years of age are inhaled 3-4 times a day.

The second subgroup of drugs used in GNT reactions are drugs that interfere with the interaction of released histamine, that is, H1-histamine blockers (antihistamines).

In 1968, P. Gell, Coombs R., taking into account the peculiarities of the mechanisms of development of various allergic reactions, proposed a classification of the types of allergic reactions. So, from the pathogenetic position, there are 4 types of allergic reactions:

1) anaphylactic or reagin type of reaction, where the immune response mechanism is associated with the production of IgE and IgG4 (antibody-reagins);

2) the cytotoxic type of reactions in which the immune mechanism is associated with antibodies of the IgG and IgM classes that react with antigenic determinants of cell membranes;

3) Arthus phenomenon - immunocomplex type, tissue damage by immune complexes (IgG and IgM);

4) delayed hypersensitivity (sensitized lymphocytes).

H1-blockers are effective, only with the first type of allergic reactions - with reagin.

Histamine, this major mediator of various physiological and pathological processes in the body, was chemically synthesized in 1907. Subsequently, it was isolated from animal and human tissues

(Windaus A., Vogt W.). Even later, its functions were determined: gastric secretion, neurotransmitter function in the central nervous system, allergic reactions, inflammation, etc. After almost 20 years, in 1936, the first substances with antihistamine activity were created (Bovet D., Staub A.). And already in the 60s, the heterogeneity of the receptors in the body to histamine was proved and their three subtypes were distinguished: H1, H2 and H3, which differ in structure, localization and physiological effects that occur during their activation and blockade. From this time, an active period of synthesis and clinical testing of a variety of antihistamines begins.

Histamine, acting on the receptors of the respiratory system, eyes and skin, causes characteristic allergy symptoms, and antihistamines that selectively block the H1-type receptors are able to prevent and stop them.

Most antihistamines used have a number of specific pharmacological properties that characterize them as a separate group. These include the following effects: antipruritic, decongestant, antispastic, anticholinergic, antiserotonin, sedative and local anesthetizing, as well as the prevention of histamine-induced bronchospasm. Some of them are caused not by histamine blockade, but by structural features.

H-1-RECEPTORS

and effects of histamine

smooth muscles of the intestine;

- smooth muscle. bronchi;
- smooth muscle. urine. a bubble;
- capillaries, vessels;
- mucous membranes of the nose.
- reduction of intestinal muscles;
- reduction of the bronchi;
- reduction of the bladder;
- expansion of blood vessels, capillaries, decrease. HELL; increase penetration. blood vessels, edema, hyperemia, feeling of heat, itching;

rhinorrhea, swelling of the nose, sneezing.

H-2-RECEPTORS

and the effects of histamine.

- glands of the stomach;
--salivary glands;
- Musculature of the uterus.
- increased secretion

gastric juice;

- increased salivation;
- Decreased uterine tone.

Antihistamines block the action of histamine on H1 receptors by the mechanism of competitive inhibition, and their affinity for these receptors is significantly lower than that of histamine. Therefore, these drugs are not able to displace the histamine associated with the receptor, they only block unoccupied or released receptors. Accordingly, H1-blockers are most effective in preventing allergic reactions of an immediate type, and in case of a developed reaction they prevent the release of new portions of histamine.

By their chemical structure, most of them are fat-soluble amines, which have a similar structure. The core (R1) is represented by an aromatic and / or heterocyclic group and is bonded to an amino group via a nitrogen, oxygen or carbon (X) molecule. The nucleus determines the severity of antihistamine activity and some of the properties of the substance. Knowing its composition, one can predict the strength of the drug and its effects, for example, the ability to penetrate the blood-brain barrier.

There are several classifications of antihistamines

According to one of the most popular classifications, antihistamines are divided into first and second generation drugs by the time of creation. First-generation drugs are also commonly called sedatives (by the dominant side effect), in contrast to non-sedative second-generation drugs. At present, it is customary to isolate the third generation: it includes fundamentally new drugs - active metabolites,

which, in addition to the highest antihistamine activity, exhibit a lack of sedation and cardiotoxic effects characteristic of second-generation drugs (see table).

In addition, according to the chemical structure (depending on the X-bond), anti-histamine preparations are divided into several groups (ethanolamines, ethylene diamines, alkylamines, derivatives of alfacarbolin, quinuclidine, phenothiazine, piperazine and piperidine).

Three generations of antihistamines (brand names in parentheses)

I generation	II generation	III generation
• Diphenhydramine (diphenhydramine, benadryl, allergen) • Clemastine (tavegil) • Doxylamine (decaprine, donormil) • Diphenylpyraline • Bromodiphenhydramine • Dimenhydrinate (Dedalon, Dramamine) • Chloropyramine (suprastin) • Pyrilamine • Antazolin • mepiramin • Brompheniramine • Chloropheniramine • Dexchlorpheniramine • Pheniramine (Avil) • Mebhydrolin (diazolin) • Quifenadine (fencarol) • Sequifenadine (bicarfen) • Promethazine (fenergan, diprazine, pipolfen) • Trimeprazine (teralen) • Oxomazine • Alimemazine • Cyclizine • Hydroxyzine (atarax) • Meclizine (Bonin) • Cyproheptadine (peritol)	• Acrivastin (Semprex) • Astemizole (gismanal) • Dimetinden (fenistil) • Oxatomide (tinset) • Terfenadine (bronal, histadine) • Azelastine (allergodil) • Levocabastine (histimet) • Misolastine • Loratadine (clarithin) • Epinastine (alesion) • Ebastin (Kestin) • Bamipin (soventol	• Cetirizine (zyrtec) • Fexofenadine (telfast

First generation antihistamines (sedatives). All of them are well soluble in fats and, in addition to H1-histamine, also block cholinergic, muscarinic and serotonin receptors. Being competitive blockers, they reversibly bind to H1 receptors, which leads to the use of rather high doses. The following pharmacological properties are most characteristic of them.

• Sedative effect is determined by the fact that most first-generation antihistamines, easily dissolved in lipids, penetrate well through the blood-brain barrier and bind to the H1 receptors of the brain. Perhaps their sedative effect consists of blocking the central serotonin and acetylcholine receptors. The degree of manifestation of the sedative effect of the first generation varies in different drugs and in different patients from moderate to severe and increases when combined with alcohol and psychotropic drugs. Some of them are used as sleeping pills (doxylamine). Rarely, instead of sedation, psychomotor agitation occurs (more often in medium therapeutic doses in children and in high toxic doses in adults). Due to the sedative effect, most drugs cannot be used during work that requires attention. All first-generation drugs potentiate the effects of sedative and hypnotic drugs, narcotic and non-narcotic analgesics, monoamine oxidase inhibitors and alcohol.

• The anxiolytic effect inherent in hydroxyzine may be due to the suppression of activity in certain areas of the subcortical region of the central nervous system.

• Atropine-like reactions associated with the anticholinergic properties of drugs are most common for ethanolamines and ethylenediamines. Pro-are dry mouth and nasopharynx, urinary retention, constipation, tachycardia and visual impairment. These properties provide the effectiveness of the

discussed remedies for non-allergic rhinitis. At the same time, they can enhance obstruction in bronchial asthma (due to an increase in sputum viscosity), cause exacerbation of glaucoma and lead to infravesical obstruction in prostate adenoma, etc.

• The antiemetic and anti-pumping effect is also probably related to the central anticholinergic effect of the drugs. Some antihistamines (diphenhydramine, promethazine, cyclizine, meklizin) drugs reduce the stimulation of the vestibular receptors and inhibit the function of the labyrinth, and therefore can be used for movement diseases.

• A number of H1-histamine blockers reduce the symptoms of parkinsonism, which is due to the central inhibition of the effects of acetylcholine.

• The antitussive effect is most characteristic of diphenhydramine, it is realized due to the direct effect on the cough center in the medulla oblongata.

• The antiserotonin effect, which is primarily characteristic of cyproheptadine, determines its use in migraines.

• The α1-blocking effect with peripheral vasodilation, especially inherent in the antihistamine phenothiazine series, can lead to a transient decrease in blood pressure in sensitive individuals.

• Local anesthetic (cocaine-like) action is typical for most antihistamines (occurs due to a decrease in the permeability of membranes for sodium ions). Diphenhydramine and promethazine are stronger local anesthetics than novocaine. However, they have systemic quinidine-like effects, manifested by lengthening the refractory phase and the development of ventricular tachycardia.

• Tachyphylaxis: a decrease in antihistamine activity with prolonged use, confirming the need for alternation of drugs every 2-3 weeks.

• It should be noted that antihistamines of the first generation differ from the second generation in the short duration of exposure with a relatively rapid onset of clinical effect. Many of them are in parenteral form. All of the above, as well as low cost determine their broad.

Moreover, many of the qualities that were discussed, allowed to occupy a niche in the field of treatment of certain pathologies (migraine, sleep disturbances, extrapyramidal disorders, anxiety, motion sickness, etc.) that are not related to allergies by the "old" antihistamines. A lot of first-generation antihistamines are part of the combined preparations used for colds, as sedatives, sleeping pills and other components.

Some 1st generation drugs may also be effective in the following situations:

1. In acute respiratory viral infections (drugs with anticholinergic effects have a "drying" effect on the mucous membranes):

Pheniramine (Avil);

paracetamol + ascorbic acid (Fervex).

Promethazine (Pipolphen, Diprazin);

paracetamol + dextromethorphan (Coldrex Nite).

Chloropyramine (Suprastin).

chlorphenamine; + paracetamol + ascorbic acid (Antigrippin);

biclotimol + phenylephrine (Hexapneumine);

phenylpropanolamine (CONTAC 400);

phenylpropanolamine + acetylsalicylic acid (HL-cold).

o Diphenhydramine (Dimedrol).

2. To suppress cough:

Diphenhydramine (Dimedrol)

Promethazine (Pipolphen, Diprazin)

3. For the correction of sleep disorders (improve falling asleep, depth and quality of sleep, but the effect lasts no more than 7-8 days):

Diphenhydramine (Dimedrol);

paracetamol (Efferalgan Nightcare).

4. To stimulate appetite:

Cyproheptadine (Peritol);

Astemizole (Hismanal).

5. For the prevention of nausea and dizziness due to labyrinthitis or Meniere's disease, as well as to reduce the manifestations of motion sickness:
Diphenhydramine (Dimedrol)
Promethazine (Pipolphen, Diprazin)
6. For the treatment of pregnant vomiting:
Diphenhydramine (Dimedrol)
7. To potentiate the effects of analgesics and local anesthetics (premedication, a component of lytic mixtures):
Diphenhydramine (Dimedrol)
Promethazine (Pipolphen, Diprazin)
8. For the treatment of small cuts, burns, insect bites (the effectiveness of topical administration of drugs is not strictly proven, it is not recommended to use> 3 weeks due to the increased risk of local irritating effects):
Bamipin (Soventol).
The most commonly used are chloropyramine, diphenhydramine, clemastine, cypro-heptadine, promethazine, phencarol, and hydroxyzine.
H1 antagonists of the first generation have advantages in the following cases:
1. relief of acute allergic reactions (urticaria, Quincke's edema) when parenteral administration of drugs is required;
2. treatment of pruritic dermatoses (atopic dermatitis, eczema, chronic recurrent urticaria, etc.). Painful skin itching is often the cause of insomnia and a decrease in the quality of life. In these cases, the sedative effect of the first generation antihistamines is useful. A number of drugs produced in the form of a gel (dimetinden) are effective for stopping local allergic reactions;
3. premedication before diagnostic and surgical interventions to prevent the release of histamine of non-allergic origin;
4. symptomatic therapy of acute respiratory viral infections (local and oral)administration as part of combination drugs) eliminates itching in the nose, sneezing;
5. cholinergic urticaria.
Indications for the use of H1 antagonists of the first generation:
1. allergic diseases:
2. seasonal allergic rhinitis, conjunctivitis;
3. year-round allergic rhinitis, conjunctivitis;
4. acute urticaria and Quincke's edema;
5. chronic relapsing urticaria;
6. food allergy;
7. drug allergy;
8. insect allergy;
9. atopic dermatitis;
10. hypersensitivity of non-allergic genesis caused by histamine-liberalization or prophylactic use with the introduction of histamine liberators (reactions to radiopaque agents, to the administration of dextrans, medication, food, etc.);
11. prophylactic use with the introduction of histamine liberals;
12. insomnia;
13. vomiting of pregnant women;
14. vestibular disorders;
15. colds (ARVI).
Side effects
Classical H1 antagonists can have:
hypnotic effect associated with the penetration of drugs through the blood-brain barrier and blockade of H1 receptors in the central nervous system, which is facilitated by their lipophilicity, and other actions on the central nervous system: impaired coordination, lethargy, dizziness, decreased ability to concentrate.

antiemetic effect of AHLS (ethanolamines), which is associated both with the H! -Antagonistic effect, and partly with anticholinergic and sedative activity. This effect of AHL is used for medicinal purposes.

from the digestive system (increase or decrease in appetite, nausea, vomiting, diarrhea, discomfort in the epigastric region).

with prolonged use of classic H1 antagonists, a decrease in the therapeutic effectiveness of drugs (tachyphylaxis) often develops.

Some drugs have local anesthetic properties.

In rare cases, cardiotoxic effects are possible (QT interval prolongation).

Contraindications and Cautions

Contraindications to the use of antihistamines

1. generations, in addition to hypersensitivity to the drug, relative:
2. pregnancy;
3. breastfeeding;
4. work requiring high mental and motor activity, concentration of attention;
5. urinary retention.

Given the presence of an atropine-like effect, drugs of this group should not be prescribed to patients with bronchial asthma, glaucoma and prostate adenoma. Caution is required when prescribing antihistamines of the first generation for astheno-depressive conditions and cardiovascular diseases.

Interactions

I generation antihistamines potentiate the anticholinergic action of M-anticholinergics, synthetic anticonvulsants, antipsychotics, tricyclic antidepressants, MAO inhibitors, and drugs for treating parkinsonism.

Antihistamines increase the central depressive effect of hypnotics (general anesthetics), sedatives and hypnotics, tranquilizers, antipsychotics, central analgesics, alcohol.

Chloropyramine (suprastin) is one of the most widely used sedative antihistamines. It has significant antihistamine activity, peripheral anticholinergic and moderate antispasmodic effect. Effective in most cases for the treatment of seasonal and year-round allergic rhinoconjunctivitis, Quincke's edema, urticaria, atopic dermatitis, eczema, itching of various etiologies; in parenteral form - for the treatment of acute allergic conditions requiring emergency care. It provides a wide range of therapeutic doses used. It does not accumulate in the blood serum, therefore, does not cause an overdose with prolonged use. Suprastin is characterized by a rapid onset of effect and a short duration (including side) of action. In this case, chloropyramine can be combined with non-sedative H1 blockers in order to increase the duration of antiallergic action. Suprastin is currently one of the best-selling antihistamines in Russia. This is objectively associated with the proven high efficiency, controllability of its clinical effect, the presence of various dosage forms, including injectable ones, and low cost.

Diphenhydramine, the most famous in our country under the name of diphenhydramine, is one of the first synthesized H1-blockers. It has a fairly high antihistamine activity and reduces the severity of allergic and pseudo-allergic reactions. Due to the significant cholinolytic effect, it has an antitussive, antiemetic effect and at the same time causes dry mucous membranes and urinary retention. Due to its lipophilicity, diphenhydramine gives pronounced sedation and can be used as sleeping pills. It has a significant local anesthetic effect, as a result of which it is sometimes used as an alternative for intolerance to novocaine and lidocaine. Diphenhydramine is presented in various dosage forms, including for parenteral use, which has determined its widespread use in emergency therapy. However, a significant range of side effects, unpredictability of consequences and effects on the central nervous system require increased attention to its use and, if possible, the use of alternative agents.

Clemastine (tavegil) is a highly effective antihistamine drug similar in action to diphenhydramine. It has a high anticholinergic activity, but to a lesser extent penetrates the blood-brain barrier. It also exists in injectable form, which can be used as an additional remedy for anaphylactic shock and angioedema, for the prevention and treatment of allergic and pseudo-allergic reactions. However, hypersensitivity to clemastine and other antihistamines with a similar chemical structure is known.

Cyproheptadine (peritol), along with an antihistamine, has a significant antiserotonin effect. In this regard, it is mainly used for some forms of migraine, dumping syndrome, as a means of increasing appetite, with anorexia of various genesis. It is the drug of choice for cold urticaria.
Promethazine (pipolfen) - a pronounced effect on the central nervous system determined its use in Meniere's syndrome, chorea, encephalitis, sea and air sickness, as an antiemetic. In anesthesiology, promethazine is used as a component of lytic mixtures to potentiate anesthesia.
Quifenadine (phencarol) - has a lower antihistamine activity than diphenhydramine, but is also characterized by less penetration through the blood-brain barrier, which determines a lower severity of its sedative properties. In addition, fencarol not only blocks histamine H1 receptors, but also reduces the histamine content in tissues. It can be used in the development of tolerance to other sedative antihistamines.
Hydroxyzine (atarax) - despite the existing antihistamine activity, it is not used as an anti-allergic agent . It is used as anxiolytic, sedative, muscle relaxant and antipruritic.
Thus, first-generation antihistamines, which affect both H1 and other receptors (serotonin, central and peripheral cholinergic receptors, a-adrenergic receptors), have various effects, which determined their use in many conditions. But the severity of side effects does not allow us to consider them as drugs of first choice in the treatment of allergic diseases. The experience gained in their use has allowed the development of unidirectional drugs - the second generation of antihistamines.
Second generation antihistamines (non-sedative). Unlike the previous generation, they almost do not have sedative and anticholinergic effects, but differ in the selectivity of action on H1 receptors. However, for them, the cardiotoxic effect was noted to varying degrees.
The most common for them are the following properties.
• High specificity and high affinity for H1 receptors with no effect on choline and serotonin receptors.
• Rapid onset of clinical effect and duration of action. Prolongation can be achieved due to high protein binding, cumulation of the drug and its metabolites in the body, and delayed excretion.
• Minimal sedation when using drugs in therapeutic doses. It is explained by the weak passage of the blood-brain barrier due to the structural features of these agents. Some especially sensitive individuals may experience moderate sleepiness, which is rarely the cause of drug discontinuation.
• Lack of tachyphylaxis with prolonged use.
• The ability to block the potassium channels of the heart muscle, which is associated with lengthening of the QT interval and impaired heart rhythm. The risk of this side effect increases with the combination of antihistamines with antifungal (ketoconazole and intracozole), macrolides (erythromycin and clarithromycin), antidepressants (fluoxetine, sertraline and paroxetine), with the use of grapefruit juice, as well as in patients liver function.
• Lack of parenteral forms, however, some of them (azelastine, levocabastine, bamipine) are available as topical forms.
The benefits of 2nd generation antihistamines include a wider range of indications for use. However, the idea of the clinical effectiveness of 2nd generation antihistamines in the treatment of bronchial asthma and atopic dermatitis is based on a small number of uncontrolled studies. The action of the drug develops rather slowly (within 4-8 weeks), and the pharmacodynamic effects of the 2nd generation drugs are proved only mainly in vitro.
Below are the second generation antihistamines with the most characteristic properties.
Terfenadine is the first antihistamine drug that has no inhibitory effect on the central nervous system. Its creation in 1977 was the result of a study of both types of histamine receptors and the structural features and effects of existing H1 blockers, and marked the beginning of the development of a new generation of antihistamines. Currently, terfenadine is used less and less, due to its increased ability to cause fatal arrhythmias associated with lengthening the QT interval (torsade de pointes)
Astemizole is one of the longest acting drugs of the group (the half-life of its active metabolite is up to 20 days). It is characterized by irreversible binding to H1 receptors. Almost no sedative effect, does not interact with alcohol. Since astemizole has a delayed effect on the course of the disease, in the acute process its use is impractical, however, it can be justified in chronic allergic diseases. Since the drug has the property of cumulating in the body, the risk of developing serious cardiac

arrhythmias, sometimes fatal, increases. In connection with these dangerous side effects, the sale of astemizole in the USA and some other countries has been suspended.
Akrivastin (Semprex) is a drug with a high antihistamine activity with minimally pronounced sedative and anticholinergic effects. A feature of its pharmacokinetics is a low metabolic rate and the absence of cumulation. Acrivastin is preferred in cases where there is no need for continuous anti-allergic treatment due to the rapid achievement of the effect and short-term action, which allows the use of a flexible dosage regimen.
Dimethenden (fenistil) is the closest to the first generation antihistamines, however, it differs from them by a significantly less pronounced sedative and muscarinic effect, a higher antiallergic activity and duration of action.
Loratadine (claritin) is one of the second-generation best-selling drugs, which is understandable and logical. Its antihistamine activity is higher than that of astemizole and terfenadine, due to the greater binding strength to peripheral H1 receptors. The drug is deprived of a sedative effect and does not potentiate the effect of alcohol. In addition, loratadine practically does not interact with other drugs and does not have a cardiotoxic effect.
The following antihistamines relate to topical preparations and are intended to relieve local manifestations of allergy.
Levocabastine (histimet) is used in the form of eye drops for the treatment of histamine-dependent allergic conjunctivitis or as a spray for allergic rhinitis. When applied topically, it enters the systemic circulation in small quantities and does not have undesirable effects on the central nervous and cardiovascular systems.
Azelastine (allergodil) is a highly effective treatment for allergic rhinitis and conjunctivitis. Used in the form of a nasal spray and eye drops, azelastine is practically devoid of a systemic effect.
Another topical antihistamine, bamipin (soventol) in the form of a gel, is intended for use in allergic skin lesions accompanied by itching, insect bites, jellyfish burns, frostbite, sunburn, and mild thermal burns.
Third generation antihistamines (metabolites).
Their fundamental difference is that they are active metabolites of previous generation antihistamines. Their main feature is the inability to influence the QT interval. Currently, they are represented by two drugs - cetirizine and fexofenadine.
Cetirizine (zyrtec) is a highly selective peripheral H1 receptor antagonist. It is an active metabolite of hydroxyzine, which has a much less pronounced sedative effect. Cetirizine is almost not metabolized in the body, and its excretion rate depends on renal function. Its characteristic feature is the high ability to penetrate the skin and, accordingly, the effectiveness in skin manifestations of allergies. Cetirizine neither in the experiment nor in the clinic showed any arrhythmogenic effect on the heart, which predetermined the field of practical use of metabolite preparations and determined the creation of a new drug - fexofenadine.
Fexofenadine (telfast) is an active metabolite of terphe-nadine. Fexofenadine does not undergo transformations in the body and its kinetics do not change with impaired liver and kidney function. It does not enter into any drug interactions, does not have a sedative effect and does not affect psychomotor activity. In this regard, the drug is approved for use by persons whose activities require increased attention. The study of the effect of fexofenadine on the QT value showed both in the experiment and in the clinic that there is no cardiotropic effect when using high doses and with prolonged use. Along with maximum safety, this tool demonstrates the ability to stop symptoms in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria. Thus, pharmacokinetics, safety profile and high clinical efficacy make fexofenadine the most promising antihistamine currently.
So, in the doctor’s arsenal there is a sufficient amount of antihistamines with various properties. It should be remembered that they provide only symptomatic relief from allergies. In addition, depending on the specific situation, you can use both various drugs and their diverse forms. It is also important for the doctor to remember the safety of antihistamines.

Recently, 3rd generation antihistamines have been created with significant selectivity and no side effects from the central nervous system. The use of antihistamines of the 3rd generation is more justified during long-term therapy of allergic diseases:

• year-round allergic rhinitis;
• seasonal allergic rhinitis (conjunctivitis) with a duration of seasonal exacerbations> 2 weeks;
• chronic urticaria;
• atopic dermatitis;
• allergic contact dermatitis;
• early atopic syndrome in children.

The pharmacokinetic properties of antihistamines vary significantly. Modern antihistamines of the 3rd generation have a long duration of action (12-48 hours). Astemizole has a maximum half-life (about 10 days), which inhibits skin reactions to histamine and allergens for 6-8 weeks. Serious cardiotoxic side effects in the form of severe cardiac arrhythmias have been described for two 3rd generation antihistamines (terfenadine and astemizole).

Topical antihistamines, in particular, acelastine (allergo-dil) has a quick (within 20-30 minutes) symptomatic effect, improves mucociliary clearance, has no significant systemic side effects.

The most promising oral antihistamines are loratadine and cetirizine

Loratadine (claritin) is an antihistamine that does not have a sedative effect, significant drug interactions, and is recommended for use by patients of all age groups. The excellent safety profile of clarithin allowed the drug to be included in the list of over-the-counter drugs.

Cetirizine (zyrtec) is a basic antihistamine, especially in young children, when the inhalation route of medication is difficult. It has been shown that long-term administration of cetirizine in children with early atopic syndrome can reduce the risk of progression of atopic conditions in the future.

The second large group of drugs is those used in delayed-type hypersensitivity reactions.

With the development of HRT, contact dermatitis, autoimmune diseases, transplant rejection reaction, bacterial allergy, mycoses, many viral infections occur. During these processes, mainly reactions of cellular immunity develop and sensitization of T-lymphocytes is noted.

There are two groups of drugs used for this type of allergy: -

 drugs that suppress immunogenesis (immunosuppressants);
 means that reduce tissue damage.

The drugs of the first group, first of all, include anti-rheumatic drugs of slow action (hingamine, penicillamine):

a) Chingaminum (delagil) (Chingaminum; available in tablets of 0.25 each) - introduced into medicine as an antimalarial drug, but due to the fact that it was able to suppress the inflammatory reactions in which HRT is involved, it is used as a remedy for HRT. Mechanism of action: hingamine stabilizes cell and subcellular membranes, restricts the release of lysosomes from hydrolases that damage cells, thereby preventing the emergence of clones of sensitized cells in tissues, activation of complement systems, killers. As a result, the focus of inflammation is limited, that is, the drug has an anti-inflammatory effect. It is used for continuous recurrent rheumatism, RA, SLE and other diffuse diseases of the connective tissue. The effect develops slowly for 10-12 weeks, treatment is long, for 6-12 months.

Penicillamine is a metabolic product of penicillin containing a sulfhydryl group that can bind heavy metals (iron, copper) and eliminate oxygen free radicals. Apply with actively progressing RA. The effect occurs after 12 weeks, improvement after 5-6 months

b) Glucocorticoids (mainly prednisone) inhibit the response of cells to lymphokines, thereby limiting the clone of sensitized cells; reduce tissue infiltration by monocytes, stabilize cell membranes, reduce the number of T cells, reduce the cooperation of T and B cells and the formation of immunoglobulins. Used for diffuse diseases of the connective tissue - SLE, scleroderma, RA, etc.

c) Cytostatics (cyclophosphamide, azathioprine): Azathioprine (Azathioprinum; in tablets of 0.05). They inhibit cell division, especially lymphoid tissue, limit the formation of immunocompetent cells (T-sensitized lymphocytes) and the development of the above immunopathological mechanisms in RA, SLE, etc. Usually they are used only in especially severe cases, therefore they are used as reserve ones. When using cytostatics, serious complications are possible.

d) ALS and anti-lymphocyte globulin are biological preparations obtained by immunizing animals with appropriate antigens (T-lymphocytes, mononuclear cells). Use for the same indications as the previous group of funds.
d) Cyclosporin (Cyclosporin A, Sandimmune; an aqueous solution is produced - 100 mg in 1 ml; oral solution in 50 ml vials; soft capsules of 25, 50, 100 mg of active substance) - a cyclic polypeptide consisting of 11 amino acids; from the mushroom Tolypocladium inflatum gams. It has an immunosuppressive effect in the form of suppression of the secretion of interleukins and interferons and other lymphokines, activated T-lymphocytes. Suppresses the secretion of these mediators during activation of T-lymphocytes by antigen. Used in transplantology, for the treatment of skin diseases (psoriasis). Thus, the group of antiallergic drugs is a developing group of drugs that has significant practical value.
Most emergency conditions in allergology belong to type I allergic reactions, the manifestation of anaphylaxis.
ANAPHYLAXIS
This is an acute systemic reaction of a sensitized organism to repeated contact with an antigen, developing according to type I allergic reactions and manifesting itself as acute peripheral vasodilation.
An extreme manifestation of anaphylaxis is anaphylactic shock.
BASIC PROVISIONS
1. If anaphylactic reaction is suspected, epinephrine should be administered as soon as possible.
2. All patients who have previously experienced anaphylactic shock should have a syringe tube with epinephrine. Domestic allergists recommend that patients with reactions to stings of hymenoptera insects have syringes containing, in addition to epinephrine, systemic antihistamines [for example, chloropyramine (suprastin□), clemastine (tavegil□)] and systemic glucocorticoids (for example, dexamethasone, prednisone).
3. Offices where vaccination, allergy tests and allergen-specific immunotherapy or radiopaque studies are performed should be fully provided with the necessary tools for emergency medical care in the development of anaphylactic or anaphylactoid reactions.
ETIOLOGY
1. Allergens during allergen-specific immunotherapy.
2. Medicines and vaccines:
- antibiotics (e.g. penicillins);
- non-steroidal anti-inflammatory drugs;
- adrenocorticotropic hormone, insulin, etc.
3. Insect bites:
- wasps, bees, mosquitoes.
4. Food:
- nuts (e.g. peanuts), fish, shellfish, celery, kiwi, eggs, milk, etc.
5. X-ray contrast substances.
6. Natural rubber (latex):
- gloves, catheters, condoms, etc.
7. Exercise, chills, cold.
8. Patients often reveal atopy.
CLINICAL PICTURE
1. Primary symptoms:
- weakness, dizziness, trembling, shortness of breath is possible;
- erythema, burning of the skin;
- itching of the palate and external auditory canal;
- a feeling of an impending attack;
- nausea is possible.
2. Secondary symptoms:
- swelling of the skin, especially the eyelids and lips;
- urticaria;

- swelling of the larynx, hoarseness, shortness of breath;
- abdominal pain, nausea, vomiting, diarrhea;
- arterial hypotension, collapse;
- in severe cases, laryngospasm, loss of consciousness, involuntary urination and defecation, shock, respiratory arrest and cardiac activity are possible.

DIFFERENTIAL DIAGNOSTICS

1. An acute attack of bronchial asthma.
- Skin manifestations are absent.
- Blood pressure is normal or elevated.
2. Fainting.
- There are no signs of skin and respiratory system involvement.
- Bradycardia.
3. Hereditary angioedema.

“The urticaria rash is uncharacteristic.”

- The introduction of epinephrine is ineffective.

TREATMENT

1. Epinephrine:
- epinephrine (adrenaline) 0.1% solution (1 mg / ml) intramuscularly at a dose of 0.1 ml / 10 kg; injected deep into the thigh or shoulder;
- an injection of epinephrine can be repeated after 10-30 minutes;
- epinephrine (adrenaline) 0.01% solution (0.1 mg / ml) can be administered at a dose of 1-3 ml intravenously to an adult in deep shock or 0.1-0.5 ml to a child. Rarely prescribed outside the hospital.
2. Prerequisites:
- the patient should lie on a flat surface with raised legs;
- you should make sure that the patient is breathing. If possible, start inhalation of oxygen.
3. Intravenous use of glucocorticoids:
- methylprednisolone 80-125 mg for adults or 2 mg / kg for children. Hydrocortisone 250-500 mg for adults and 10 mg / kg for children or dexamethasone 8-24 mg are prescribed intravenously as alternatives;
- In addition, prednisolone is prescribed orally in an initial dose of 30-50 mg / day
4. Intravenous fluid administration:
- you should immediately start to administer Ringer's solution * or isotonic sodium chloride solution intravenously. Adults need to enter 500-1000 ml of liquid during the first hour.
5. Aminophylline:
- if symptoms of bronchial asthma appear, it is necessary to introduce amino-phyllin at a dose of 5 mg / kg (adults 4-6 ml, i.e. 200-300 mg) intravenously for 5-10 minutes when signs of bronchospasm appear.
6. Antihistamines:
- preparations for oral administration, for example, hydroxyzine (atarax):
- The dose for adults is 25-50 mg:
- in children, solutions of a drug substance with a concentration of 2 mg / ml are used, and depending on age, different volumes of solution are prescribed:

◊ up to 1 year - 2.5 ml;
◊ from 1 to 5 years - 5 ml;
◊ from 6 to 10 years - 10 ml;

- Domestic experts recommend intravenous administration of antihistamines.

ANAPHYLACTIC SHOCK

• T78.2 Anaphylactic shock, unspecified.
• T78.0 Anaphylactic shock caused by a pathological reaction to food.
• T80.5 Anaphylactic shock associated with serum administration.
• T88.6 Anaphylactic shock due to a pathological reaction to an adequately prescribed and correctly applied drug.

Definition
Anaphylactic shock is a life-threatening, rapidly developing condition, accompanied by a violation of hemodynamics,
leading to circulatory failure and hypoxia in all vital organs.
Anaphylactic shock develops after the patient contacts the allergen that is intolerable to him (foreign proteins during blood transfusion; medications; allergens introduced during seasonal immunotherapy; venom of echidroporous insects, etc.). Like all types of shock, anaphylactic shock has 4 degrees of severity.
A distinctive feature of anaphylactic shock is the possible development of skin manifestations in the form of urticaria, erythema, edema, as well as the development of bronchospasm before or simultaneously with the appearance of hemodynamic disorders. The remaining manifestations are similar to those for any other form of shock.
The standard of care for patients with anaphylactic shock, unspecified (prehospital stage)
1. Patient model.
• Age category: adults and children.
• Nosological form: anaphylactic shock, unspecified.
• Phase: acute condition.
• Stage: first appeal.
• Complications: regardless of complications.
• Terms of delivery: ambulance.
Diagnostics and treatment at the rate of 20 minutes
ATX - anatomical-therapeutic-chemical classification. ODD - estimated daily dose. EKD - equivalent course dose.
Before admission to the intensive care unit
1. Stop the introduction of the alleged medication - an allergen.
2. If possible, apply a tourniquet above the injection site or chop the injection site with a 0.1% solution of epinephrine or norepinephrine in a dose of 0.3-0.5 ml with 4-5 ml of physiological saline.
3. Perform venipuncture or venesection and begin intravenous administration of drugs:
- if necessary, by intravenous drip: dopamine (individual dose) from 300 to 700 μg / ml (max. 1500 μg / ml) with a gradual decrease, the duration of administration is determined by hemodynamic parameters;
- the introduction of glucocorticoids (hydrocortisone 250 mg intravenously, prednisone 90-120 mg intravenously, dexamethasone 8-32 mg, etc.);
- with arterial systolic pressure above 90 mm RT. Art. antihistamines [clemastine (tavegil) 2.0 ml] may be given;
- plasma-replacing drugs intravenously drip or stream;
- in case of bronchial obstructive syndrome - aminophylline (aminophylline) 2.4% 10 ml intravenously in physiological saline.
4. The administration of pressor amines (0.1% epinephrine solution (adrenaline *) subcutaneously at intervals of 5-10 minutes).
5. Oxygenation.
6. Correction of acid-base state (CBS).
7. Treatment of acute respiratory failure, transfer to mechanical ventilation and transportation of the patient to intensive care.
8. Symptomatic therapy.
If treatment is ineffective, continue treatment in the intensive care unit and intensive care unit
Terms of hospitalization
• The duration of hospitalization is from 1 to 10 days. Treatment Requirements
• Complete recovery or rehabilitation.
ACUTE TOXIC-ALLERGIC REACTIONS TO MEDICINES
Definition
Acute toxic-allergic reactions (OTAR) to medicines are

a systemic reaction of the body that occurs in response to the introduction of a therapeutic dose of the drug, which is based on both immune and non-immune development mechanisms and proceeds with the clinical picture of generalized multiforme exudative erythema (L51.8, 77090), bullous dermatosis (L13.8, 77080), toxic epidermal necrolysis (L53.0, 77100).
The main pathogenetic mechanism of OTAR is the development of non-specific generalized vasculitis (from serous to necrotic), which causes 4 degrees of severity of the disease.
Hospitalization: I and II severity - in the allergological, therapeutic and dermatological departments, III and IV severity - in intensive care units or intensive care units.
Survey
1. Mandatory laboratory tests (tab. 189):
- a clinical blood test, deployed daily, until the condition stabilizes, then as needed;
- coagulogram; with III-IV severity - in dynamics;
- biochemical analysis of blood (total protein and protein fractions, creatinine, bilirubin, ALT, AST, fibrinogen, CRP, glucose, electrolytes);
Clinical characteristics of acute toxic-allergic reactions to medicaments
- with III-IV severity, dynamic control of the level of total protein, creatinine, blood sugar, transaminases, electrolytes;
- glycemic profile;
- determination of blood type and Rh factor;
- Wassermann reaction (RW), HIV;
- general urine analysis daily until the condition stabilizes, if necessary, urine analysis according to Nechiporenko;
- crops from the skin and mucous membranes with III-IV severity, multiplicity according to indications;
- bacteriological examination of sputum;
- bacteriological examination of feces;
- Bacteriological examination of bronchodilution;
- CBS during mechanical ventilation.
2. Instrumental examination methods.
- Mandatory:
- electrocardiography;
- X-ray examination of the chest.
- Additional:
- esophagogastroduodenoscopy during stabilization and after epithelialization of the mucous membranes of the oral cavity;
- bronchoscopy according to indications;
- ultrasound examination of the abdominal cavity, thyroid gland with I-II severity upon admission, with III-IV severity with stabilization.
3. Consultations of specialists.
- Mandatory:
- allergist-immunologist;
- dentist;
- optometrist;
- ENT;
- a dermatologist.
- Additional:
- other specialists - according to indications.
4. Allergological examination.
- It is carried out with severity after recovery; with III-IV degree of severity - after 3-4 months. The scope of an allergological examination is determined by an allergist-immunologist.
5. Immunological examination.
- Mandatory:
- determination of the level of total IgE, IgA, IgM, IgG, subpopulations of lymphocytes;

- determination of specific IgE and IgG antibodies.
- Additional:
- determination of LE cells, anti-DNA, CEC, CRP, antistreptolysin O, acantholytic cells.

Care for patients with acute toxic-allergic reactions to severity III-IV copper coments

Treatment of OTAR patients with III-IV severity medications must be carried out in specially created sterile conditions in an open way (using sterile wards or aerotherapeutic units with the supply of heated sterile air) with an individual post. In the case of an exudative component, the skin must be dried and disinfected with solutions, without using ointment bases, as epithelialization solutions can gradually be replaced with creams and ointments.

Treatment of the mucous membranes of the eyes with a severity of III-IV severity should be carried out 6 times a day (three times massage with hydrocortisone ointment in combination with collargol *, three times instillation of dexamethasone eye drops).

Treatment of the oral cavity after each meal (rinsing with re-polyglucin *, freshly brewed tea, treating hydrogen with peroxide, disinfecting solutions); at the beginning of epithelization and the absence of contraindications, it is possible to use rosehip seed oil and sea buckthorn oil.

Description of therapeutic measures

1. Nonspecific hypoallergenic diet, with III-IV degree of severity - table rubbed or parenteral nutrition.

2. Glucocorticoids: parenteral administration, an individual dose of 4 to 32 mg of dexamethasone or betamethasone per day based on the minimum necessary, especially with III-IV severity, with a gradual decrease during stabilization until complete withdrawal.

3. Intensive transfusion therapy aimed at detoxification and elimination of a causative allergen-medication is indicated for all OTAR patients. The daily volume of transfusion exposure in patients with Otar III-IV degree of severity can reach 6000-8000 ml / day under the control of the central hemodynamics, diuresis, CBS:

- electrolyte solutions;
- plasma substituting solutions;
- saline solutions.

4. Substitution therapy with blood products:

- albumin;
- native plasma;
- immunoglobulins (sandoglobulin□, pentaglobin□, octagam *, etc.);
- transfusion of fresh donor blood in patients of III-IV degree of severity with the development of leukopenia and agranulocytosis.

5. Symptomatic treatment:

- antihistamines;
- anticoagulants;
- disaggregants;
- diuretic drugs;
- vasopressor amines (with hemodynamic impairment);
- analgesic drugs (strictly according to indications);
- protease inhibitors;
- cardiac glycosides;
- sedatives.

6. Additional methods of detoxification can be used with stable hemodynamics and adequate replacement therapy:

- therapeutic plasmapheresis;
- hemosorption;
- hemodialysis.

7. Antibacterial effects - broad-spectrum antibiotics, taking into account the pharmacological history and the results of bacteriological studies. It is strictly forbidden to use antibiotics of the penicillin series and their derivatives, if necessary, other antimicrobial and antifungal drugs are prescribed.

8. An additional method of immunocorrection is extracorporeal immunopharma-cotherapy.

9. Correction of dysbiosis (eubiotics in combination with enzyme preparations).
10. If necessary, mechanical ventilation, therapeutic bronchoscopy.
ALLERGIC HORSE
Allergic urticaria is an allergic gene disease characterized by the occurrence of urticarial elements on the skin. The main allergens are medicines, foodstuffs, hymenoptera insects, plant pollen, house dust. In this category of patients, urticaria is often combined with respiratory manifestations of allergies (allergic rhinitis, bronchial asthma For patients with allergic urticaria, there is a clear relationship between exposure to the allergen and the development of the exacerbation of the disease. acute and chronic (more than 6 weeks) urticaria. Rashes are characterized by severe itching and complete reversibility.
Standard of care for patients with angioedema and urticaria
1. Patient model.
• Age category: adults and children.
• Ideological form: urticaria; angioedema.
• Phase: acute condition.
• Stage: first appeal.
• Complications: regardless of complications.
• Terms of delivery: ambulance.
Diagnosis and treatment
Treatment of exacerbation of allergic urticaria
(standard)
Severe course
• Conducting elimination activities.
• Parenteral antihistamines of the first generation: clemastine (ta-vigil□) 0.1% 2 ml intramuscularly or intravenously in an isotonic solution of sodium chloride or chloropyramine (suprastin *) 2.5% for 5-7 days. With non-effectiveness - glucocorticoids of systemic action: dexamethasone 4-12 mg intramuscularly or intravenously, prednisone 30-90 mg intramuscularly, intravenously 2-3 days. Then antihistamines of the second generation - loratadine (clarithin *) 10 mg 1 time per day, astemizole (gismanal) □ 10 mg 1 time per day. Duration of admission is up to 1 month. It is possible to use antihistamines with a stabilizing effect on mast cell membranes: ketotifen (zaditen *) 0.001 g 2 times a day for 3 months.
The purpose of the lesson:
To learn: the basic principles of antiallergic therapy. Know the pharmacodynamics of the main antiallergic drugs, the pharmacotherapy of anaphylactic shock. To be able to choose a drug for a certain pathology and write a prescription for it.
I. To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of anti-allergic drugs
1. Classification of antiallergic drugs
A. Histamine and serotonin receptor blockers
a) oxatomide (tinset)
b) azelastine (allergodil)
c) loratadine
- clarithin, loratadine-KMP, loraderm-KMP, lorizan-KMP
g) terfenadine (treksil)
d) promethazine
- diprazine, pipolfen
e) diphenhydramine (diphenhydramine)
g) chloropyramine (suprastin)
h) mebhydrolin (diazolin)
i) clemastine (tavegil)
k) quifenadine (fencarol)
l) cyproheptadine (peritol)
m) dimenhydrinate (dedalon)

B. Membrane stabilizers and anti-mediators
a) cromoglic
- (cromolyn sodium, intal)
b) ketotifen (zaditen)
c) fenspiride (erespal)
B. Glucocorticosteroids
a) prednisone (depersolone)
b) budesonide
- apulent, pulmicort
c) hydrocortisone butyrate
- laticort, locoid
g) triamcinolone acetonide
- fluorocort, azmacort)
Treatment of exacerbation of allergic urticaria
(standard)
Severe course
• Conducting elimination activities.
• Parenteral antihistamines of the first generation: clemastine (ta-vigil□) 0.1% 2 ml intramuscularly or intravenously in an isotonic solution of sodium chloride or chloropyramine (suprastin *) 2.5% for 5-7 days. With non-effectiveness - glucocorticoids of systemic action: dexamethasone 4-12 mg intramuscularly or intravenously, prednisone 30-90 mg intramuscularly, intravenously 2-3 days. Then antihistamines of the second generation - loratadine (clarithin *) 10 mg 1 time per day, astemizole (gismanal) □ 10 mg 1 time per day. Duration of admission is up to 1 month. It is possible to use antihistamines with a stabilizing effect on mast cell membranes: ketotifen (zaditen *) 0.001 g 2 times a day for 3 months.

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I. To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of anti-allergic drugs
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B. Membrane stabilizers and anti-mediators
a) cromoglic
b) (cromolyn sodium, intal)
b) ketotifen (zaditen)
c) fenspiride (erespal)
B. Glucocorticosteroids

a) prednisone (depersolone)
b) budesonide
- apulent, pulmicort
c) hydrocortisone butyrate
- laticort, locoid
g) triamcinolone acetonide
- fluorocort, azmacort)
e) monetazone furoate (nasonex)
e) dexamethasone (fortecortin)
G. Selective Leukotriene D4 Receptor Antagonists Combined
a) zafirlukast (acolate)
b) montelukast sodium (singular)
c) clarinase
d) Coldrex Knight
Have an understanding of allergic diseases. Etiopathogenetic factors of their occurrence.
1. Modern approaches to the pharmacotherapy of allergic diseases
A. Drugs used primarily for immediate allergies
a) drugs that prevent the release of histamine and other allergy mediators
- glucocorticoids and ACTH
- cromoglicic acid (cromolyn sodium, intal);
b) antihistamines;
c) symptomatic agents (functional antagonists)
- adrenergic agonists - adrenaline, ephedrine, mesatone
- myotropic bronchodilators (antispasmodics) - aminophylline, papaverine
B. Drugs used for delayed-type allergies
a) drugs that suppress immunogenesis and inflammation
- glucocorticoids, cytostatics, NSAIDs
b) Antihistamine drugs
- diphenhydramine (diphenhydramine)
- chloropyramine (suprastin),
- promethazine (diprazine, pipolfen)
- mebhydroline (diazolin)
- clemastine (tavegil), chifenadine (fencarol).
c) drugs blocking the release of mast cell allergy mediators
- Cromolin sodium (intal)
- Ketotifen (zaditen)
g) Means that enhance the binding of histamine.
- histaglobin (histaglobulin).
e) immunosuppressive drugs
- azathioprine, methotrexate, cyclophosphamide or cyclophosphamide, cytostatic antibiotics)
B. Glucorticoid ointments for topical use in diseases of allergic genesis
- "Fluorocort", "Sinalar", "Lorinden" and others.
2. Requirements for antiallergic drugs
3. Pharmacology of antiallergic drugs of different groups, mechanism of action, features of use. Comparative characteristics of drugs. Indications for use. Undesirable effects.
4. Features of the clinical use of antiallergic drugs, depending on the characteristics of the course of the allergic process
-anaphylactic shock
- seasonal allergies
- food allergies
- chronic processes with a pronounced allergic and autoimmune component (bronchial asthma, dermatoses, etc.)

5. Urgent measures for anaphylactic shock. Sequence of actions, list of drugs. Measures aimed at preventing anaphylactic shock. Rules for performing intradermal tests for drug sensitivity.

Know

1. The main pathogenetic mechanisms of allergic reactions.
2. The main measures aimed at preventing allergic reactions
3. The tactics and scheme of drug therapy for allergic reactions

Be able to

1. Select and select the necessary drug for a specific patient
2. To highlight the criteria for therapeutic efficacy and safety of drugs used for
- anaphylactic shock
- seasonal allergies
- food allergies
- chronic processes with a pronounced allergic and autoimmune component (bronchial asthma, dermatoses, etc.)
3. Perform an intradermal test for drug sensitivity

The task for self-testing of the initial level of knowledge:

1. Classification of allergic reactions.
2. Etiology, pathogenesis and clinical manifestations of allergic reactions of an immediate type
3. Etiology, pathogenesis and clinical picture of delayed-type allergic reactions
4. Characterization of the basic functions of the immune system. Biological and physiological significance of the antigen-antibody reaction.
5. Features of the clinical picture of allergic reactions encountered in dentistry
6. Classification of antiallergic drugs
7. The tactics of using antiallergic drugs, depending on the type, severity and severity of the allergic reaction.
8. What are the clinical and laboratory criteria for therapeutic efficacy and safety of the use of drugs considered.
9. Formulate an emergency care plan for anaphylactic shock, Quincke's edema, and other acute allergic conditions.
10. Outline a set of measures aimed at preventing allergic reactions.

Control questions of the studied topic.

1. What indications and contraindications (absolute and relative) for the use of antiallergic drugs do you know?
2. What do you know the main groups of the most active and sufficiently studied anti-allergic drugs?
3. How are antiallergic drugs classified?
4. What are the effects of antiallergic drugs? What is their clinical significance?
5. What provisions should be followed when choosing anti-allergic drugs?
6. What clinical and laboratory indicators indicate the achievement of a therapeutic effect?
7. What are the features of the action of antiallergic drugs when combining them with drugs of other groups?
8. What measures should be taken to prevent allergic reactions?
9. What are the main stages of urgent care for allergic reactions of the immediate type?
10. What medical measures should be included in the provision of urgent care for bronchial obstruction syndrome caused by an allergen?
11. What medical measures should be included when providing urgent care for pulmonary edema?

Enumeration of practical work.

A homework.

1. Write down the prescriptions for drugs (tablets and / or ampoules) presented in the section "Purpose of the lesson", indicate the point of application of the action, the spectrum of diseases (syndromes) indicated for their purpose.
2. Indicate and explain possible effective and undesirable combinations of drugs.

B Independent practical work in class.

1. To supervise a thematic patient in the ward.

2. To study the medical history (data of laboratory and instrumental studies, examination by consultants, records of the attending physician) and the list of medical appointments.
3. When examining a patient, identify subjective, physical, laboratory and instrumental signs: anaphylactic shock, Quincke's edema, hay fever, acute allergic reaction.
4. Write a clinical diagnosis:
a) underlying disease; complications of the underlying disease;
b) concomitant diseases.
5. Determine the group of drugs necessary for the correction of existing violations.
6. Based on theoretical data and own observations, select a specific drug for the patient to be supervised.
7. Taking into account gender, age, body weight, route of administration and pharmacokinetics of this drug, select the optimal dosage regimen for the drug.
8. Select clinical criteria for evaluating the effectiveness and safety of the use of this drug.
9. Make a forecast of side effects of drugs prescribed to the patient and outline a plan for identifying them in the early stages.
10. Justify the duration of the main and supporting therapy.
11. Write a protocol of independent work on the selection and selection of a patient with antiallergic drugs to be supervised, to substantiate the importance of combined drug therapy.
Control of the intermediate level of knowledge.
The decision of situational problems
1. A woman, 30 years old, every year over the past 4 years in August, complains of nasal congestion, mucous discharge from it, cough, itching of the eyelids, lacrimation. After applying suprastin, these symptoms disappear. What type of allergic reaction does occur? What are the features of observation and clinical management of this patient?
2. A woman, 32 years old, suffering from bronchial asthma, is planned for the operation of cholecystectomy. What are the features of premedication of this patient? List the main drugs that will prevent an attack of bronchial asthma. What anti-allergic drugs will be preferred?
3. A 10-year-old boy with the use of ampicillin sharply developed drug allergy in the form of generalized urticaria, massive Quincke edema. The condition of the child is serious. What is your tactic? What is the sequence of actions of the doctor? What drugs should I start intensive therapy with?
4. The doctor prescribed the patient intramuscularly benzylpenicillin. In the list of appointments, he also assigned an intradermal test for sensitivity to pecillin and novocaine. The nurse asked the patient whether he had previously received penicillin and whether he had previously had allergic reactions to penicillin and novocaine. The patient replied that he had previously received penicillin and that he had been repeatedly given local anesthesia during surgical interventions and allergic reactions. The nurse made an independent decision and, without testing for sensitivity in penicillin and novocaine, was about to inject benzylpenicillin into the patient. What is the main mistake of a nurse? What can the first injection in a given patient lead to?
6. Patient P., 34 years old, with community-acquired pneumonia, 5 minutes after an intradermal test for penicillin, suddenly had a cough, shortness of breath, restlessness, dizziness, tinnitus, nausea, and abdominal pain. Objectively: the state is serious, consciousness is confused, convulsions, involuntary urination, pale skin, PE - 120 strokes per 1 minute, weak filling, AKD - 60/20 mm RT. Art., heart sounds are deaf.
Formulate a diagnosis. Make an intensive care plan, justify its choice.
7. The antihistamine used for motion sickness was advertised on TV. The father, about to fly on a business trip, asked the son, a medical student, to choose this drug from the list of antihistamines: 1) astemizole, 2) terfenadine, 3) loratadine, 4) cimetidine, 5) diphene-hydramine (diphenhydramine), 6) meclizine. Make a choice of means and justify the answer.
8. Woman V., 23 years old, after a bee sting suddenly had an asthma attack, skin itching, hoarseness, swelling of the lips. Objectively: the condition is serious, consciousness is not impaired, BH - 30 in 1 minute, state of emergency - 102 strokes in 1 minute, AKD - 100/60 mm RT. Art., heart sounds are muffled, dry wheezing in the lungs.

What is the intended diagnosis in this case? What is the treatment tactic for this patient? Justify the answer.

TESTS

3. To conduct conduction anesthesia, a 35-year-old man was given 2 ml of a 1% lidocaine solution without a burdened history. After a few minutes, the patient developed profuse sweating, general weakness, visual impairment, severe pallor, nausea, and difficulty breathing. Pulse of weak filling and voltage, heart rate - 118 in 1 min, blood pressure - 60/20 mm RT. Art., BH - 28 in 1 min. Which drug is most effective in treating this patient?
A. Atropine sulfate.
B. Norepinephrine hydrotartrate.
C. Prednisone.
D. Adrenaline hydrochloride.
E. Dimerol or suprastin.
4. The patient, 60 years old, was taken to the intensive care unit and intensive care with a diagnosis of wasp sting, anaphylactic shock. Which of the following drugs is the first and most effective for emergency care for anaphylactic shock?
A. Suprastin.
B. Prednisone.
C. Calcium chloride.
D. Diphenhydramine.
E. Ephedrine hydrochloride.
3. A 12-year-old girl who has been ill for 6 years with bronchial asthma has an asthma attack. What medicines should be prescribed in the first place?
A. Mucolytics.
B. Antibiotics.
C. Inhaled β2 agonists.
D. Corticosteroids.
E. Antihistamines.
4. A child, 12 years old, has been suffering from atopic dermatitis since infancy. Which group of drugs is the least acceptable for the treatment of this disease?
A. Hyposensitizing.
B. Non-steroidal anti-inflammatory.
C. Immunomodulators.
D. Sedatives.
E. Antihistamines.
5. A 10-year-old boy with the use of ampicillin sharply developed a copper-stone allergy in the form of generalized urticaria, massive Quincke edema. The condition of the child is serious. What drugs should I start intensive therapy with?
A. Sedative.
B. Calcium gluconate.
C. Corticosteroids.
D. Antihistamines.
E. Diuretics.
6. The patient has anaphylactic shock. What is the drug of choice.
A. Fenoterol
B. Adrenaline
C. Ephedrine
D. Mesaton
E. Norepinephrine
7. After vaccination, the doctor prescribed an antihistamine to prevent the allergic reaction in the trolley bus driver. Name him.
A. Diphenhydramine.

B. Tavegil.
C. Diprazine.
D. Suprastin.
E. Diazolin.
8. For the treatment of urticaria in order to eliminate itchy rashes on the skin, the patient is prescribed diphenhydramine. What mechanism ensures its effectiveness in this case?
A. Inhibition of histamine release
B. Inhibition of histamine synthesis
C. Independent histamine antagonism
D. Acceleration of the destruction of histamine
E. Competitive blockade of H1 receptors
9. To prevent an attack of bronchial asthma, the doctor prescribed cromolyn sodium to the patient. Which of the following mechanisms is typical for this tool?
A. Blockade of histamine receptors
B. Decrease in concentration of immunoglobulins
C. The binding of free histamine
D. Stabilization of mast cell membranes
E. Inactivation of histamine
10 What drug should be prescribed to a patient who has insomnia due to an allergic rash with redness, swelling, severe itching?
A. Sodium hydroxybutyrate
B. Phenobarbital
C. Nitrazepam
D. Chloral Hydrate
E. Diphenhydramine
11 A 45-year-old woman suffers from seasonal allergic rhinitis associated with ragweed bloom. Which of the following medications can be used to prevent this disease?
A. Tavegil
B. Diazolin
C. Fenkarol
D. Ketotifen
E. Diphenhydramine
12. An antihistamine used for motion sickness was advertised on TV. Father, about to fly on a business trip, asked his son, a medical student, to choose this drug from the list of antihistamines:
1) astemizole,
2) terfenadine,
3) loratadine,
4) cimetidine,
5) meclizine.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison’s principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE IMMUNOTROPIC MEDICINES

Relevance of the topic.

At present, the way of life of the majority of Earth's inhabitants has radically changed: chronic stress, physical inactivity and overeating are characteristic of the population of developed countries, while malnutrition and a lack of protein components of the diet are for residents of developing countries. Climate change and environmental pollution also affect the health of the inhabitants of the planet, as a result of which our contemporaries have mutations in the genome more often than their ancestors. This leads to a violation of homeostasis, a decrease in the resistance of the body. Many people develop chronic pathological conditions, including secondary immunodeficiency, which is accompanied by a high risk of developing infectious and oncological diseases, and allergic pathology. In this regard, there is an increasing interest in pharmacological drugs that affect the immune system.

The main goal of clinical immunopharmacology is the choice of immunopharmacological agents adequate to the clinical condition of the patient, in doses that correspond to his individual characteristics, for a proper period of time to ensure recovery or a long-term recovery of diseases, as well as to improve the quality of life.

Motivational characteristic of the topic.

Immunity is a state of security or immunity of an organism to agents bearing signs of foreignness. The immune system is able to recognize millions of diverse substances, revealing subtle differences even between closely related molecules.

The functions of the immune system are to protect the body from biological aggression by recognizing the antigen and the immune response to it, in addition, the system has an immune memory, preserving information about previous antigenic effects.
There are several groups of immunopharmacological agents.
• Immunostimulants.
• Immunomodulators.
• Immunosuppressants.
• Antiallergic drugs.
Immunostimulants are drugs that have a stimulating effect on the immune system.
Immunomodulators are drugs that lead to the physiological relationship of all parts of the immune system.
Immunosuppressants are drugs that have an inhibitory effect on the immune system activated by a pathological process.
Antiallergic drugs are drugs that affect a hyperactive or hypersensitized immune system.
In fig. a simplified diagram of the human immune response is presented and application points for various drugs affecting this process are indicated.
The optimal functioning of the system is ensured by subtle mechanisms of cell interaction, both in direct contact and with the participation of soluble intermediaries. The effector components of the immune system are:
- cells (lymphocytes, macrophages, NK cells (natural killer cells, "Natural killer cells"), mast cells, basophils, dendritic cells, eosinophils) (cellular immunity);
- humoral factors (antibodies, antimicrobial peptides, complement system) (humoral immunity).
The regulation of the immune system is carried out through intercellular contacts and with the help of cytokines.
Humoral defense factors
1. Complement is a system of protein molecules that carry out the lysis and opsonization of infectious agents, which is involved in the immunoregulation and elimination of circulating immune complexes
(CEC).
2. Antibodies (immunoglobulins) are proteins that bind to an antigen and mediate the effector functions of the immune system. Antibodies that bind antigen can form CECs.
3. Endogenous antimicrobial peptides (defensins, cathelicidins) - effector molecules that cause the lysis of microorganisms.
Cytokines and their functions:
- interleukins;
- interferons;
- tumor necrotic factor;
- factor inhibiting migration.
Functions:
- regulation of innate immunity
- regulation of the activation, growth and differentiation of B- and T-lymphocytes - regulation of immune inflammation
- stimulation of hematopoiesis
The immune system among all life-support systems of the body is one of the most significant, performing extremely important functions to protect the body from various foreign substances. These substances include:
- infectious factors dangerous to the body (bacteria, viruses, fungi, protozoa);
- Modified cells (e.g., tumor cells) that arose in the body;
- components of transplanted organs and tissues;
- allergens.
Impaired function of the immune system leads to various diseases - from recurrent infections and allergic pathologies to rheumatoid arthritis and malignant neoplasms. In this regard, it seems

important for a doctor of any specialty to be able to recognize and diagnose possible violations of the immune response and correct them in a timely manner

Immunodeficiency is a quantitative or functional insufficiency of the main components of the immune system.

International Classification of Diseases

- immunodeficiency with a predominance of antibody defects;
- combined immunodeficiency states;
- immunodeficiency in combination with other significant defects;
- defects in the complement system.

Clinical signs of immunodeficiency may include:

- frequent bacterial, viral, mycotic infections;
- various lesions of the skin and visible mucous membranes (rash, warts, genital warts, acne, etc.);
- weight loss;
- overweight;
- intestinal dysfunction (diarrhea, rumbling, bloating, intestinal dysbiosis, etc.);
- the presence of chronic inflammatory diseases (chronic bronchitis, tonsillitis, cholecystitis, prostatitis, cystitis, urethritis, nephritis, sinusitis).

Immune deficiency can develop as a result of genetic defects or under the influence of any damaging factors. According to this principle, primary and secondary immunodeficiencies are distinguished. In addition, the modern classification of immunodeficiencies is based on the predominant lesion of a particular immunity.

PRIMARY IMMUNO DEFICIENCIES

Primary immunodeficiencies (often congenital) - rare diseases

The occurrence of primary immunodeficiencies may be due to:

1. With a lack of cellular immunity:
2. With violations of humoral immunity:
3. With combined insufficiency of humoral and cellular immunity:

• Wiskott-Aldrich syndrome (mutation of the X-chromosome protein gene);
• X-linked severe combined immunodeficiency;
• Hood syndrome (spindle cell thymoma);

4. With metabolic disorders:

• enteropathic acrodermatitis (congenital malabsorption of zinc);

5. With phagocyte deficiency:

• lack of phagocytes due to impaired adhesion;
• Chediak-Higashi syndrome;

6. With insufficiency of the complement system:

• hereditary angioedema.

SECONDARY IMMUNO DEFICIENCIES

Secondary immunodeficiencies are quantitative and qualitative deviations from physiological functions in the immune system, reducing the supervision of structural and functional homeostasis of the body, clinically manifested by exacerbation and chronicity of diseases. Immunodeficiencies are a risk factor for the occurrence of infectious, oncological, autoimmune, allergic and other diseases. Medicines, whose arsenal is growing steadily, can also cause secondary immunodeficiency. This is due to the fact that they have a modifying effect on immunogenesis, including suppression and hyperstimulation. This effect is regarded as immunotoxic and is a kind of adverse side reactions.

Classification of secondary immunodeficiencies (main groups)

1. Combined immunodeficiencies.
2. T cell deficits.
3. Mostly B-cell deficiencies.
4. Defects of natural killers.
5. Deficits of macrophages and granulocytes.
6. Deficits of the complement system.
7. Deficits of the platelet system.

The occurrence of secondary immunodeficiencies may be associated with many factors.
1. With chronic relapsing infectious diseases (AIDS).
2. With secondary immunodeficiency disorders of homeostasis:
- with diabetes;
- dialysis or renal failure;
- nephrotic syndrome;
- cirrhosis of the liver (hepatic cell failure);
- prolonged as well as severe intestinal dysbiosis.
3. With secondary immunodeficiencies in eating disorders:
- with a chronic deficiency in the intake of proteins, vitamins (B6, A, BC) and micro-elements (iron, zinc);
- reaction of the thymus gland (thymus) during fasting;
- An increase in diseases and mortality from infection during fasting (malnutrition).
4. With secondary immunodeficiencies in autoimmune diseases:
- with systemic lupus erythematosus;
- rheumatoid arthritis.
5. With secondary immunodeficiencies due to environmental influences:
- with a mechanical injury;
- burn injury;
- ionizing radiation (x-rays and γ-radiation);
- ultraviolet radiation;
- toxic chemical compounds;
- chronic intoxications (alcoholism, smoking, drug addiction).
6. With secondary immunodeficiencies caused by unreasonably long-term use of drugs that affect immunity (hormonal drugs, immunomodulators, cytostatics) and self-medication.
7. With secondary immunodeficiencies associated with other conditions and diseases:
- with intestinal lymphangiectasia;
- asplenia or hyposplenism;
- allogeneic blood transfusion;
- pregnancy;
- aging;
- stress.
One of the most important tasks of a doctor examining patients with secondary immunodeficiency is to identify possible causes that contributed to the development of this pathological condition. This determines the choice of etiotropic therapy as the most effective treatment for any pathological condition. And the appointment of immunomodulators serves only as an additional component of the complex effect.
Characterization of secondary immunodeficiencies
Progress in experimental and clinical immunology has contributed to the development of many laboratory diagnostic methods for immune system disorders. A full assessment of changes in the immune status allows you to establish a diagnosis, choose the appropriate treatment and carry out dynamic monitoring during it. The following is a list of laboratory diagnostic methods for studying the immune system, as well as approaches to assessing immunograms and choosing immunotherapy.
LABORATORY METHODS FOR STUDYING AN IMMUNE SYSTEM
Exploratory survey
• General blood analysis.
• Determination of serum IgM, IgG content. IgA, IgD and IgE.
The study of the function of T-lymphocytes
The study of the function of b-lymphocytes
Complement research
The study of the functions of phagocytosis

Immunotherapy is a method of treating and / or preventing the development of a human disease with the help of medicinal and non-pharmacological agents aimed at enhancing, suppressing and replacing the functions of the immune system.
Immunostimulants - medications that mainly enhance the immune response to normal, activate immune responses or their individual links, both damaged and intact.
Immunosuppressants are drugs that suppress the immune response.
In accordance with the recommendations of WHO / IUIS / IAACI (World Health Organization, International Immunological Societies), the forms of treatment and prevention in clinical immunology are identified:
· Immunostimulation.
· Immunosuppression.
· Substitution therapy.
· ASIT.
Modern immunotherapy has several ways of exposure:
I. The use of immunomodulators.
II. Substitution therapy - the introduction into the body of immunity factors in the case of genetically or phenotypically caused by their insufficiency (the introduction of immunoglobulins, cytokines, etc.).
III.Introduction of highly specific preparations of exogenous therapeutic antibodies.
IV. Antibacterial and antiviral therapy.
V. Immunization with a given antigen:
Allergen-specific immunotherapy.
VI. System adaptation - a set of measures aimed at adapting the body to the environment (physiotherapy, hardening, diet, vitamin therapy, etc.).
VII. Efferent methods of exposure: hemosorption, plasma, cytopheresis, etc.
Viii. Physical methods: laser, ultraviolet and infrared irradiation of lymphoid organs and blood.
IX. Immune and genetic engineering: transplantation of organs, tissues and cells of the immune system, bone marrow, stem, dendritic and embryonic cells, gene therapy.
X. Immunosuppressive therapy.
The main mechanisms of action of immunotropic drugs:
1. Stimulation of the differentiation of immunocompetent cells due to the effect on the hematopoiesis system.
2. Interaction of immunotropic drugs with receptors of immunocompetent cells.
3. Stimulation or inhibition of the synthesis of cytokines.
4. Formation of specific active and passive immunity.
5. Replacement therapy.
6. Combined immunocorrecting effect and direct effect on antigen (antiviral effect).
Indications for immunotherapy:
1. Primary and acquired immunodeficiencies.
2. Allergic diseases.
3. Autoimmune diseases.
4. Oncological diseases.
5. Infectious diseases.
6. Conditions after allotransplantation.
7. Diseases accompanied by a violation of regeneration.
8.Others.
The main principles of immunotherapy:
1. Immunotherapy is prescribed on the basis of identified violations in the links of the immune system (data of immunological and allergological history, clinical and laboratory results of the examination, taking into account the accompanying somatic diseases).
2. The type of immunotherapy is selected taking into account the nature of the microflora (bacterial, viral, fungal) and the characteristics of the nosological forms of the patient, his age, stage of the

process. So, for example, the selection of immuno-correction depends on what stage the patient has acute, subacute, chronic course, etc.
3. In those cases where only changes in individual laboratory parameters are detected, but there are no clinical signs of immune deficiency, administration of immunomodulators should be abstained.
4. Immunotherapy usually complements the basic treatment. Relatively rarely, an immunocorrective drug is prescribed as monotherapy, as in primary immunodeficiency. For example, the appointment of a patient with a chronic infectious disease, the use of adequate immunocorrection together with etiotropic anti-infective drugs leads to a much better effect than the appointment of the same drugs separately.
5. Accounting, registration and analysis of the possible and identified side effects of immunotherapy.
6. Evaluation of long-term results of treatment.
Currently there is no single universally recognized classification of immunotropic drugs. Therefore, in this methodological manual only one of the many options is given and methods for pharmacological immunocorrection and vaccination will be mainly considered. Other methods of influencing the human immune system are described in detail on elective classes of the department and other training cycles of a medical university.
Pharmacological immunocorrection.
Classification of immunocorrective agents:
I. Immunomodulators
1. Drugs of endogenous origin.
· Immunoregulatory peptides obtained from the central organs of the immune system (thymus, bone marrow).
· Cytokines (interferons, colony stimulating factors, interleukins, monokines).
· Immunoglobulins (specific and non-specific).
2. Preparations of exogenous origin.
· Microbial preparations based on viruses, bacteria, fungi
· Synthetic (analogues of endogenous immunomodulators, directional synthesis immunomodulators, known drugs with the properties of immunomodulators): lycopid, immunofan, polyoxidonium, sodium nucleinate, etc.
· Others: interferonogens, adaptogens, multivitamin preparations, preparations containing zinc, selenium, etc. and other trace elements.
II. Immunosuppressants
· Antimetabolites
· Alkylating compounds
· Antibiotics
· Glucocorticoids
· Cyclosporins
· Antibodies and their constructs
N.B. Any immunotropic drug that selectively acts on the corresponding component of the immune system (phagocytosis, cellular or humoral immunity) will, to one degree or another, affect other components of the immune system.
Given this position, nevertheless, it is possible to identify the leading directions of the pharmacological action of the main immunomodulating drugs, which belong to different groups according to the presented classification.
Immunomodulatory drugs
The experience of using immunotropic drugs in medicine totals several decades, and to date, the final views on generally recognized international recommendations for the use of most of them have not been formulated. In this regard, it is necessary to be guided by the basic principles of the use of immunotherapy.
1. Immunomodulators of thymic origin.
These drugs are divided by origin into 2 groups:
1. Preparations of natural origin (T-activin, thymalin, timothy-mulin).
2. Synthetic origin (thymogen, immunofan).

They are mainly used for severe, recurrent, torpid-like treatment of infectious (usually viral, such as herpes virus, papillovirus infections) and oncological diseases. Their main target in the body are T-lymphocytes and a cellular immune response. With initially lower indices of the T-cell immunity link, preparations of this series increase the number of T-cells and their functional activity. In this case, the immunoregulatory index is normalized (CD4 / CD8 ratio), the ability of T cells to give a proliferative response to T mitogens and the production of the corresponding cytokines increase. At the same time, the functional activity of innate immunity factors increases: neutrophils, monocytes / macrophages and NK cells.

2. Immunomodulators of bone marrow origin.

The main target of exposure is B-lymphocytes. These drugs with immunodeficiencies restore T and B immunity, stimulating antibody synthesis, differentiation of bone marrow cells into mature B-lymphocytes. Their action is based on the biological effects of bone marrow myelopeptides (MP). TakMP-1 restores the balance of activity of T-helper and T-suppressors, MP-2 has an antitumor effect, MP-3 stimulates the activity of the phagocytic link, MP-4 stimulates the process of differentiation of hematopoietic cells. Representatives of this group of drugs are myelopid and seramil.

3. Cytokines

· Interferons (IFN). These are biologically active proteins with predominantly antiviral, immunostimulating and antiproliferative effects (Table 1), although the spectrum of their biological activity has not been definitively determined. The structure and biological properties of IFN are divided into IFN-α, IFN-β, IFN-γ.

IFN drugs are used primarily for viral infections from acute and chronic viral hepatitis, herpetic lesions to acute respiratory viral infections. Interferon therapy is actively used in the complex treatment of oncological diseases.

· Interleukins.

In clinical practice, two recombinant drugs have found the most active use: betaleukin ironcoleukin.

Betaleikin is a dosage form of recombinant IL-1β person. The drug stimulates blood formation, immunity and early post-radiation recovery. In addition, the drug accelerates the restoration of bone marrow hematopoiesis, especially granulopoiesis, after the damaging effects of cytostatics and ionizing radiation. The immunomodulatory effect of the drug is realized by increasing the functional activity of neutrophilic granulocytes, inducing differentiation of immunocompetent cell precursors, enhancing lymphocyte proliferation, activating cytokine production and increasing antibody formation.

Roncoleukin is a recombinant human IL-2. The drug stimulates the proliferation of T-lymphocytes, activates cytotoxic killers, which leads to an increase in antiviral and antitumor defense reactions. Indirect activation of B-lymphocytes, monocytes, and macrophages determines its antibacterial and antifungal activity.

Examples of patterns of use of group drugs:

Roncoleukin - a solution for sc or iv administration in ampoules of 250 and 500 mcg. The drug is administered sc or iv in the drip 1 time / day. in doses up to 2 mg.

The course of treatment for septic conditions of various etiologies (with post-traumatic, surgical, obstetric, gynecological, burn, wound and other types of sepsis): 1-3 p / c or iv injection of 0.5-1 mg with interruptions of 1 -3 days.

· Colony-stimulating factors

Human granulocyte colony stimulating factor

(G-CSF) is a glycoprotein that regulates the formation of functionally active neutrophils and their release into the blood from the bone marrow. G-CSF significantly increases the number of neutrophils in peripheral blood already in the first 24 hours after administration. Preparations based on G-CSF: filgrastim, lenograstim, neupogen, grastim, granostim, leukostim, granocyte.

The main indications for use:

1. Neutropenia, in patients receiving intensive myelosuppressive cytotoxic chemotherapy for malignant diseases, with myelo-ablative therapy followed by allogeneic or autologous bone marrow transplantation;

2. Mobilization of peripheral blood stem cells;
3. Severe congenital, periodic or idiopathic neutropenia in children and adults with a history of severe or recurring infections, in patients with advanced stage of HIV - infection
tion to reduce the risk of bacterial infections when it is impossible to use other methods of treatment.
· Other cytokines.
The registered pharmaceutical preparations of this group are
py in our country there. Two new domestic recombinant preparations of TNF-α (alnorin) and TNF-β (befnorin) are expected to enter the market. Also, a combination drugrefont - based on veVNO-α and thymosin - is undergoing clinical trials. The drug has a direct (tumor cell apoptosis) antitumor effect. According to the spectrum of the cytotoxic and cytostatic effects on tumor cells, the drug corresponds to TNF-α of the person, however, it has 10–100 times less general toxicity.
4. Immunostimulants of microbial origin.
The action of this group of drugs is directed mainly to phagocytic cells. As a result, the functional properties of phagocytes are enhanced: phagocytosis and intracellular killing of absorbed bacteria increase. In addition, an increase in the humoral and cellular immune response is noted: the synthesis of IgA, IgG, IgM increases, the activity of NK cells increases, the production of cytokines INF-α, INF-γ, IL-2, TNF-α is increased.
Natural lysates include bacterial lysates (bronchomunal, IRS-19, immudon, ribomunil). The preparations of this group are proteoglycan complexes identical to the surface antigens of bacteria, most often causing infections of the ENT and respiratory tract.
The main indications for the appointment of bacterial lysates:
1. Prevention and treatment of recurrent infections of the ENT organs (otitis media, rhinitis, sinusitis, pharyngitis, laryngitis, tonsillitis), respiratory tract in patients older than 6 months;
2. Prevention of recurrent infections in patients at risk (often and for a long time, before the start of the autumn-winter season, especially in environmentally unfavorable regions, patients with chronic diseases of the ENT organs, chronic bronchitis, bronchial asthma, including children over 6 months old and an elderly person age).
3. Comprehensive therapy of conditions accompanied by secondary immunodeficiencies, including chronic infections of the upper and lower respiratory tract; in acute and chronic purulent-inflammatory diseases of the skin and soft tissues (including purulent septic postoperative complications); herpetic infection, human papillomavirus infection, chronic viral hepatitis B and C, psoriasis, pulmonary tuberculosis.
Examples of patterns of use of group drugs:
Likopid tablets 1 and 10 mg for sublingual use. Adult In chronic infections of the upper and lower respiratory tract Likopid is prescribed sublingually for 1-2mg 1 time / day for 10 days.
5. Synthetic exogenous immunomodulators
· Nucleic acids.
The main pharmacological action of nucleic acids is
stimulation of leukopoiesis, regeneration and repair processes, functional activity of almost all cells of the immune system. Preparations of this group stimulate the functional activity of neutrophils and monocytes / macrophages, increase anti-infection resistance to infection by pathogenic microorganisms, probably due to the activation of phagocytosis, increase the functional activity of T-helper and T-killers, and increase the proliferation of B cells and antibody synthesis. Nucleic acid preparations possess antioxidant effect, which is manifested in their ability to remove free radicals from the body. Due to these properties, nucleic acid preparations can reduce the damaging effects on the body of radio and chemotherapy. An example of such preparations is sodium nucleinate.
· Herbal preparations.
Currently, for the stimulation of immunity, herbal preparations are widely used as immunostimulants: immunal, echinacea, tonsilgon, etc.
It is believed that drugs of this kind are more appropriate to be attributed to adaptogens such as ginseng root, eleutherococcus, pantocrine, etc. Drugs of this group to one degree or another have an immunostimulating effect, in the form of stimulation of phagocytosis, an increase in the synthesis of

INF, but they can not be attributed to drugs, possessing a selective effect on the human immune system and evidence-based medicine speaks very carefully about their use.

· Chemically pure immunomodulators.

A diverse group of drugs, whose representatives have a multidirectional effect on the human immune system.

This section presents data on the pharmacological activity of the latest generation of immunomodulators: galavit, groprinosin, polyoxidonium.

For example: A low molecular weight immunomodulator galavitoblasts an immunomodulatory and anti-inflammatory effect. Its main pharmacological effects are associated with effects on the functional activity of macrophages. Their functional state is normalized, cytokine production and antigen presentation are restored. Galavit also stimulates the functional activity of neutrophils, natural killers. The consequence of this is an increase in the nonspecific resistance of the body to infections.

Indications for use: Acute and chronic inflammatory diseases of the gastrointestinal tract, accompanied by intoxication and / or diarrhea (peptic ulcer of the stomach and duodenum, etc.), diseases of the urogenital tract (genital herpes, chlamydia, etc.), purulent septic processes in the pre- and postoperative period, for the prevention of surgical complications, chronic and often recurring furunculosis, chronic inflammatory diseases that arose against the background of secondary immunological deficiency, with cancer aniyah.

Groprinosin (inosine pranobex) is an immunostimulating drug with antiviral activity. The immunostimulating effect is due to the influence on the function of T-lymphocytes (activation of the synthesis of cytokines), an increase in the phagocytic activity of macrophages. The antiviral effect is associated with impaired replication of both DNA and RNA viruses, expressed by interferonogenic activity. Indications for use: viral infections, especially in combination with immunosuppressive conditions (herpes viruses, measles, chicken pox, influenza, parainfluenza, etc.).

Polyoxidonium is an immunomodulator with a wide range of pharmacological effects on the body. This effect consists of immunomodulating, antioxidant, detoxifying and membrane-protective effects. The immunomodulatory effect of polyoxidonium is in the ability to activate macrophages, enhance the cooperative interaction between T and B lymphocytes, increase their functional activity, and significantly enhance antibody production.

Immunoglobulins.

Immunoglobulin preparations for intravenous administration, the so-called intravenous immunoglobulins, are widely used. Their use is indicated either as replacement therapy for primary and secondary immunodeficiencies, or for immunomodulatory treatment for autoimmune diseases

The mechanism of action of IVIG is associated with the neutralization of antigen and circulating antibodies, blockade of Fc receptors on macrophages and the classical pathway of complement activation, the elimination of circulating immune complexes and the modulation of the formation of pro-inflammatory cytokines. In addition, data were obtained on a change in the Th1 / Th2 balance towards Th1 and suppression of the synthesis of allo and autoantibodies by the feedback principle. The main indications for their appointment are primary and secondary immunodeficiencies, immune thrombocytopenic purpura, severe infectious diseases, prevention of infections after organ transplants, Guillain-Barrei syndrome, etc. For the purpose of passive specific immunotherapy, specific immunoglobulin or its fraction, the gamma globulindlin of intramuscular injection, are traditionally used: thistaphylococcal, antistreptococcal, antidiphtheria, against Pseudomonas aeruginosa, etc.

For example: Immunoglobulin anti-staphylococcal human

contains antitoxic Ig at a concentration of at least 20 IU / ml, which is 3-10 times higher than their normal blood serum content. Indications for use: purulent-septic processes, diseases of the musculoskeletal system (osteomyelitis) and other organs and systems .

The clinical use of immunomodulators.

Despite the frequently encountered point of view about the need to supplement therapeutic measures with an effect on the immune system, in clinical practice immunostimulating drugs are rarely included in the treatment program.

The feasibility of immunomodulating therapy is determined by the following factors:
1. The presence in patients of insufficient anti-infection protection (for example, recurrent infectious diseases).
2. Diseases with severe manifestations of endotoxemia (surgical diseases with purulent-septic complications, pancreatitis, burn disease, oncopathology, etc.).
3. The need to eliminate the effects of iatrogenic effects (immunosuppressive therapy, etc.).
4. The choice of an immunomodulating drug is determined by the stage of the disease (remission or exacerbation of the inflammatory process). For example, with acute inflammatory processes and septic conditions, immunomodulators such as polyoxidonium, galavit, and replacement therapy with intravenous immunoglobulins are recommended. During remission or in a sluggish course, treatment with lycopid, ribomunil, bronchomunal is justified, i.e. immunomodulators of microbial origin
5. Immunomodulators are prescribed in complex therapy simultaneously with etiotropic treatment.
6. The choice of an immunomodulatory drug and its administration is determined individually for each patient, depending on the severity of the underlying disease, concomitant pathology, and the type of immunological defect detected.
7. The main criteria for the appointment of immunomodulating drugs are the clinical manifestations of immunodeficiency.
8. The presence of a decrease in any indicator of immunity detected during an immunodiagnostic study in a practically healthy person is not an indispensable basis for the appointment of immunomodulating therapy. Such people should be registered in the appropriate treatment and prevention institution (observation group).
9. When carrying out immunorehabilitation measures, immunomodulators can be used as monotherapy, in particular for incomplete recovery after an acute infectious disease or in oncology practice.
10. When prescribing immunotropic therapy, it is advisable to
immunological monitoring.
Replacement therapy
Substitution therapy is an exposure method in which exogenous substances are introduced into the body that are missing or absent in the body. These treatment methods are quite aggressive methods of exposure to the human body and are carried out mainly in two clinical situations:
1. A genetic defect in which a stable absence or a sharp decrease in the substance being replaced is noted in the body;
2. Phenotypic damage to the body, accompanied by a pronounced defect in the immune system or other body tissues (massive burns, infections, etc.).
Replacement therapy methods include, for example, transfusion of immunoglobulins used monthly for X-linked agammaglobulinemia, or other immunodeficiencies and conditions accompanied by a lack of antibodies; administration of C1 inhibitor in congenital angioedema, transplantation of red bone marrow, etc.
Example: The use of intratect in the treatment of X-linked agammaglobuli-neemia.
When carrying out these measures, it must be remembered that replacement therapy is carried out according to vital indications, in connection with which it is necessary to achieve documented consent to the intervention, carefully explaining to the patient the possible complications and consequences of exposure.
In this case, there is often a risk of infection of the patient with viruses and prions from the drug. Therefore, when conducting replacement therapy, it is necessary to minimize this risk, for example, to use immunoglobulins with a certificate of prion safety or interferons of recombinant origin that do not contain human blood albumin.
Highly specific exogenous therapeutic antibodies
This treatment method is the introduction to a person of highly specific therapeutic antibodies. Differing in scientific novelty, it has a diverse spectrum of clinical situations when it is in demand quite widely.
1. Transplantology
Example: Orthoclone OKT3 is a monoclonal antibody that,

interacting with CD3, it blocks the activity of T-lymphocytes. This drug has been used in the prevention of acute kidney transplant rejection.
2. Autoimmune diseases
Remicade - blocks the activity of tumor necrosis factor. Is applied
the attraction of Crohn's disease, ulcerative colitis, rheumatoid arthritis, anklosing spondylitis.
3. Infectious diseases
Palivizumab - interacting with respiratory syn- glycoprotein F
cytovirus-forming virus neutralizes its activity and is used in prophylaxis in children at risk.
4. Oncology
Rituxan - interacting with CD20 induces apoptosis, antibody- and complement-dependent cell cytotoxicity. It is used in the treatment of non-Hodgkin lymphomas.
5. Allergic diseases
Omalizumab - interacting with IgE, binds it, preventing the degradation of mast cells and basophils. Used in the treatment of atopic bronchial asthma.
Antibacterial and antiviral drugs
Introducing adequate doses of antiviral or antibacterial drugs, there is a decrease in both the quantity and the negative impact of infectious pathogens on the immune system and the body as a whole. This favorably affects the functioning of the immune system and improves the quality of medical care (for example: treatment of HIV infection).
System adaptation
The elements of a positive impact on the immune system and the body as a whole are maintaining a healthy lifestyle, hardening, good nutrition, an adequate regime of physical activity, vitamin therapy, psychotherapy, etc. Adequate use of these methods allows you to maintain harmony between the human inner world and the environment.
GENERAL PRINCIPLES OF APPLICATION OF IMMUNOMODULATORS
1. Immunomodulators are used both in combination with antibiotics, antifungal, antiprotozoal or antiviral agents, thereby inflicting a “double blow” on the infectious agent, and as monotherapy for immunorehabilitation measures.
- It is advisable to prescribe immunomodulators early (from the first day of using a chemotherapeutic etiotropic agent).
- The severity of the effect of immunomodulatory therapy during treatment in the acute period of the disease is greater than in the stage of remission.
- The action of any immunomodulator is multifaceted: it is enough, for example, to activate macrophages, as their release of cytokines will set in motion the entire immune system.
2. A decrease in one of any immunity parameters detected during the assessment of the immune status of a practically healthy person does not necessarily serve as the basis for the appointment of an immunomodulating treatment. Dynamic monitoring of such a patient is shown.
IMMUNITY MULATORS
It is believed that their use leads to the activation of the immune system and increase immunity. This does not quite correctly reflect the target effect, since the immunity indicators under the influence of such agents do not exceed the level of the physiological norm, which means that there is no true stimulation. The experience that has been gained in clinical practice indicates that the direction and severity of the immune response depend on the initial level of the immune system, therefore, clinical improvement of the patient's condition and normalization of laboratory immunity indicators as a result of the use of immunoactive drugs is a manifestation of an immunomodulating effect the drug.
IMMUNOMODULATORS
Immunomodulators eliminate the imbalance of various parts of the immune system. They restore to a normal level reduced and at the same time reduce to a normal level increased immunity
The immunopharmacological effect of immunomodulators is manifested not only by a change in the number of cells and mediators of immunity, but also by the harmonization of mediator-receptor interactions at the level of cell membranes, activation of biochemical, synthetic and secretory processes in immunocompetent cells, optimization of cascade cytokine bioregulation that determines regulatory and effector functions.

Immunomodulators of microbial origin

The main pharmacological effects and mechanism of action

Pharmacological action - immunomodulatory. The main target for immunomodulators of bacterial origin are the cells of the innate immune system: mononuclear phagocytes, natural killer cells, B lymphocytes, polymorphic nuclear leukocytes, epithelial and dendritic cells, especially mature antigen-specific lymphocytes. In natural bacterial preparations, immunomodulation is manifested by activation of macrophages, stimulation of phagocytosis, induction of interferons, increase in the number of T-lymphocytes, activation of natural killer cells, production of anti-inflammatory cytokines, enhancement of proliferation of B-lymphocytes and production of specific antibodies to bacterial lysate or rib and membrane peptoglycans, increased synthesis and secretion of the mucous membrane of the respiratory tract, gastrointestinal tract and salivary glands of IgA, decrease blood concentrations of IgE, increase of the number lyso-tsima.

The mechanism of action of synthetic bacterial preparations, a typical representative of which is glucosaminyl muramyl dipeptide (lycopid *), is also associated with the rapid activation of innate immunity via] NOD2 receptors localized in the cytoplasm of cells of the immune system. It modulates the signal from the NOD2 receptor, which initiates the synthesis of cytokines [IL-1, TNF-α, CSF, interferon gamma (INF-γ)] and their secretion. This leads to an increase in the activity of macrophages, stimulation of phagocytosis, an increase in the activity of lysosomal enzymes in them, the formation of reactive oxygen species, the transition of existing antigen-specific cells of adaptive immunity to an activated state, followed by an increase in the effector functions of T-lymphocytes, natural killers and B-lymphocytes, activation native lymphocytes and their inclusion in the implementation of an adaptive immune response.

Glucosaminyl muramyl dipeptide (lycopid□) is characterized by a dose-dependent orientation and severity of the immunopharmacological effect. At doses of 1-10 mg, it increases the bactericidal and cytotoxic activity of monocytes, macrophages and lymphocytes, and at doses of 10-20 mg it inhibits the biosynthesis of pro-inflammatory cytokines.

In addition to the immunomodulatory effect, glucosaminyl muramyl dipeptide has anti-inflammatory, leukopoietic, detoxifying and hepatoprotective effects. The latter effect is associated with the ability of glucose-nyl muramyl dipeptide to activate the cytochrome P-450 systems in the liver.

Pharmacokinetics

The pharmacokinetics of immunomodulators in this group has been studied in glucosaminyl muramyl dipeptide (lycopid). Its bioavailability is 7–13%, Cmax is reached after 1.7 hours. Glucosaminyl muramyl dipeptide is metabolized to muramyl peptide fragments by lysozyme, and N-acetylmuramyl alanine amidase hydrolyzes the bond between the muramic acid residue of the oligosaccharide and the peptide moiety. Glucosaminyl muramyl dipeptide is excreted by the kidneys, intestines and lungs, T1 / 2 is 4.5 hours.

Indications

Acute chronic diseases and exacerbations of the upper and lower respiratory tract, prevention of their relapses. Secondary immunodeficiencies, accompanied by chronic, sluggish, recurrent infectious and inflammatory processes.

Contraindications

Hypersensitivity, pregnancy, lactation (IRS-19, imu-don), children's age (IRS-19 - up to 3 months; imudon - up to 3 years).

Side effect

Allergic reactions, nausea, vomiting, abdominal pain, diarrhea (imudon□, broncho-munal. IRS-19 * at the beginning of treatment can cause sneezing and rhinorrhea, and broncho-munal * and glucosaminyl muramyl dipeptide can cause an increase in body temperature. These phenomena pass with further treatment

Interaction

For natural bacterial immunomodulators, the interaction is not described. Glucosaminyl muramyl dipeptide (lycopid *), with simultaneous use, increases the clinical efficacy
antimicrobial, antiviral and antifungal drugs.

special instructions

It was noted that in case of clinical symptoms of bacterial infections, the possibility of prescribing antibacterial effects against the background of the continued use of IRS-19 should be considered. It is not recommended to use broncho-munal * in the first trimester of pregnancy. If necessary, use the drug during lactation should decide on the termination of breastfeeding. Broncho-munal * can only be started 4 weeks after vaccination with a live vaccine. It is not recommended to use broncho-munal * in acute intestinal diseases due to a possible decrease in the effectiveness of the drug.

Immunomodulators of plant origin

Echinacea purpurea juice juice (Immun) and potato sprout extract (Immunomax *) are included in the national formulary.

The main pharmacological effects and mechanism of action

Immunomodulatory and anti-inflammatory effects are inherent in drugs of this group. The pharmacological activity of echinacea preparations is determined by polysaccharides and their monomers, phenolcarboxylic acids and their derivatives, flavonoids, unsaturated hydrocarbons, unsaturated acid alkylamides. Immunomodulation of echinacea is associated with the activation of macrophages, accompanied by an increase in phagocytosis and intracellular killing of microorganisms, an increase in the production of interferons and IL-1, activation of natural killers and T-helpers, accelerated proliferation and transformation of B-lymphocytes into plasma cells, and increased antibody synthesis. Echinacea polysaccharides have a direct effect on macrophages and B-lymphocytes, while changes in the remaining parts of the immune system occur due to activation of the triggers of the immune response.

The anti-inflammatory effect of echinacea is associated with the inhibitory effect of polyunsaturated alkamides on the lipoxygenase and cyclooxygenase pathways of arachidonic acid metabolism, resulting in decreased synthesis of inflammatory mediators (leukotrienes and prostaglandins). Echinacea preparations are inferior to NSAIDs in the severity of the anti-inflammatory effect. They also eliminate drug-induced inhibition of leukopoiesis.

The mechanism of the immunomodulatory action of potato sprouts of the extract (immunomax) is different than that of echinacea. Being an acid peptidoglycan, potato sprout extract can integrate into the structures of cellular receptors of antigen-presenting cells, activate the mechanisms of rapid response of innate immunity and include adaptive immunity mechanisms to ensure an adequate response of the immune system in secondary immunodeficiencies manifested by the development of viral and bacterial infections. The immunomodulating effect is manifested by the activation of macrophages or monocytes, which secrete cytokines (IL-1β, IL-8, TNF-α) after 2-4 hours. Almost simultaneously, natural killers are activated. Their cytolytic activity increases 3 times. The extract does not have a direct effect on the neutrophilic granulocytes of potato germs. Their activation is achieved 24 hours after the use of the drug through IL-8. Strengthening the synthesis of antibodies against foreign antigens occurs due to the action of potato sprouts of the extract on the starting links of the immune system.

Pharmacokinetics

The pharmacokinetics of herbal preparations has not been studied.

Indications

Indications for Echinacea preparations are the prevention and treatment of influenza and colds, and for potato sprouts of the extract (immunomax *), immunodeficiency states caused by viruses, including herpes and human papillomas; chlamydia, mycoplasmas, ureaplasmas.

Contraindications

Contraindications for Echinacea preparations are hypersensitivity (including to plants of the family Asteraceae), progressive systemic diseases (tuberculosis, leukemia, systemic connective tissue diseases, multiple sclerosis, AIDS, HIV infection, autoimmune diseases), and potato sprout extract - hypersensitivity, lactation, children under 12 years old.

Side effect

Allergic reactions.

Interaction

It is described only for echinacea preparations. It is possible to use it simultaneously with antibiotics and other antimicrobial drugs. The drug in the form of drops contains ethanol and can change the

effect of cephalosporin derivatives and ethanol-containing drinks. Incompatible with immuno-depressants.

special instructions

Use during pregnancy and lactation is possible only after consultation with a doctor. When taking Echinacea in the form of drops with cephalosporin derivatives or ethanol-containing drinks, nausea, sweating, headache, palpitations may occur. Acceptance of an echinacea preparation containing ethanol is possible 3 days after the end of the course of treatment with the above cephalosporin derivatives.

Immunoregulatory peptides

The main pharmacological effects and mechanism of action

Immunoregulatory peptides have an immunomodulatory effect due to a change mainly in the number and functional activity of T-lymphocytes. They induce proliferation and differentiation of T-lymphocyte precursors into mature immunocompetent cells, normalize the ratio of their subpopulations, as well as the interaction of T- and B-lymphocytes, and activate the phagocytic function of neutrophils. Peptide immunoregulators restore the synthesis of the thymulin thymus hormone (immunofan *), stimulate the synthesis of cytokines, and activate innate immunity factors (neutrophils, monocytes, macrophages and natural killers). They inhibit the production of inflammatory cytokines IL-1, IL-6, IL-8 and TNF-α (hepon□), restore the synthesis of immunoglobulins (IgG, IgA, IgM) and inhibit the synthesis of IgE (immunofan).

Immunoregulatory peptides improve the course of cellular metabolism, increase the content of cyclic nucleotides (thymogen), stimulate the synthesis of ceruloplasmin, lactoferrin and increase catalase activity, normalize lipid peroxidation, inhibit the decomposition of phospholipids in the cell membrane, the formation of arachidonic acid and mediator Imunofan).

In addition to the immunomodulatory effect, preparations of this group have an anti-inflammatory and antioxidant effect.

Hepon * has an antiviral effect, which is associated with the ability of the drug to induce the production of α- and β-interferons.

Thymus extract (thymalinum) stimulates the processes of regeneration and hematopoiesis in case of inhibition.

Myelopid * refers to peptide immunomodulators of bone marrow origin, acting mainly on B-lymphocytes. It increases the mitotic activity of bone marrow cells and the formation of mature B-lymphocytes, activates humoral immunity. Myelopid * increases the number of B- and T-lymphocytes, activates phagocytosis. In addition to immunomodulatory effects, the drug exhibits an analgesic effect.

Pharmacokinetics

The pharmacokinetics of drugs of this group has not been studied in connection with their peptidic nature.

Indications

Secondary immunodeficiencies with a predominant lesion of the cellular component of the immune system of viral and bacterial etiology of various localization, opportunistic infections (imunofan *, hepon *), multiple sclerosis, inhibition of bone marrow hematopoiesis, lymphoproliferative diseases. Myelopid is indicated for secondary immunodeficiencies with a predominant lesion of the humoral immunity, accompanied by recurring purulent infections of various localization.

Contraindications

Hypersensitivity, atopic asthma, pregnancy. During lactation, you can not use gepon . Imunofan * is contraindicated in children under 2 years old, and gepon * - up to 12 years. Myelopid * is contraindicated in case of hypersensitivity and pregnancy with the presence of a Rhesus conflict.

Side effect

Allergic reactions.

When applying the thymus extract (tactivin), the development of hyperimmune cytolysis and exacerbation of purulent infections are possible.

Myelopid causes the following adverse reactions: dizziness, weakness, nausea, fever, flushing and soreness at the injection site.

Gepon did not have side effects.
Interaction
In clinical practice, no cases of interaction of preparations of immunoregulatory peptides with other drugs have been recorded.
Cytokine preparations
The main pharmacological effects and mechanism of action
Superlymph is a cytokine-complex drug with immunomodulating, anti-inflammatory, antioxidant, anti-bacterial and regenerative effects. Its immunomodulating effect is associated with the effect on the number and function of cells of innate immunity (neutrophils, monocytes, macrophages and natural killers). Super-lymph * accelerates the migration of phagocytes to the focus of infectious inflammation, activates all phases of phagocytosis, increases the cytotoxic properties of macrophages, stimulates the synthesis of IL-1 and TNF-α, and thereby activates the mechanisms of cellular and humoral immunity.
The presence in the superlymph of defensins, cathelicidins and other bactericidal substances of primary and secondary granules of leukocytes contributes to its antibacterial and antiviral effects.
The regenerating effect of superlymph is associated with its regulatory effect on collagen synthesis, as well as the proliferative activity of skin and periodontal fibroblasts, and stimulation of regeneration, which prevents the formation of rough scars.
Interleukin-1 beta (betaleukin) has a hemostimulating and immunostimulating effect. The drug induces the production of CSF, enhances the proliferation and differentiation of cells of various hematopoietic sprouts. The immunostimulating effect of interleukin-1 beta is due to activation of neutrophils, induction of differentiation of immunocompetent cell precursors, increased lymphocyte proliferation, synthesis of INF-γ and IL-2, and increased functional activity of NK cells.
Interleukin-2 (roncoleukin) has an immunomodulatory effect. It binds to specific receptors on target cells, stimulates the growth, differentiation and proliferation of T and B lymphocytes, reduces the level of spontaneous and activated apoptosis. It causes the formation of lymphokinactivated killers, stimulates the cytolytic activity of natural killers and cytotoxic T-lymphocytes. Interleukin-2 acts on other cells of the immune system indirectly through cytokines synthesized by target cells, which leads to the further development and completion of the antibacterial, antiviral, antifungal and antitumor immune responses.
Pharmacokinetics
Data on the pharmacokinetics of drugs in this group are not provided.
Indications
Secondary immunodeficiency states as a result of purulent-septic and purulent-destructive processes [interleukin-1 beta (betaleukin□)], sepsis and kidney cancer (interleukin-2), sluggish wound healing, unsatisfactory repair or excessive scarring (superlymph), leukopenia in-terleukin-1 beta).
Contraindications
Hypersensitivity. Interleukin-1 beta is contraindicated in septic shock, severe fever, interleukin-2 in autoimmune and decompensated cardiovascular diseases, pregnancy, and super-lymph in deep fistulas.
Side effect
Chills, hyperthermia, allergic reactions [interleukin-1 beta (betaley-kin), interleukin-2 (roncoleukin)], exacerbation of inflammatory phenomena in the area of the pathological process at the beginning of treatment within 1-2 days (super-lymph)
Interaction
Interleukin-2 is compatible with other drugs, and the interaction of interleukin-1 beta and superlymph is not described.
special instructions
If severe side effects occur on interleukin-1 beta, paracetamol, sodium metamizole, diphenhydramine (diphenhydramine), or a combination thereof, if necessary, glucocorticoids are used.
Rapid intravenous administration of interleukin-2 may be accompanied by manifestations of cardiovascular failure.
Interferon preparations and their inducers

Interferon preparations

The main pharmacological effects and mechanism of action

The preparations of α- and β-interferons have an immunomodulatory, antiviral and antiproliferative effect. Immunopharmacological effects are due to binding to specific receptors on the surface of the cells of the macroorganism and the launch of a complex cascade of intercellular interactions leading to interferon-dependent expression of numerous gene products and markers, including the main histocompatibility complex of class I, Mx2 '/ 5 protein '-oligoadenylate synthetase, beta2-microglobulin and neopterin. Interferon preparations stimulate the activity of macrophages and natural killers, the cytotoxic activity of T-killers.

The mechanism of antiviral action is to create protective mechanisms in cells not infected with the virus, which is achieved by changing the properties of cell membranes and preventing the virus from entering the cell. Interferons inhibit the processes of transcription and translation of the viral genome. They selectively activate 21.51-oligonucleotide synthetase and P1 kinase. Activated 21.51-oligonucleotide synthetase catalyzes the formation of 21.51-oligoadeglates, which increase the activity of endonuclease, which leads to the suppression of transcription of viral RNAs, i.e. to the destruction of viral i-RNA, and P1 kinase specifically blocks the translation of the protein of the virus-infected cell.

The antiproliferative effect of interferon preparations is due to direct mechanisms that cause changes in the cytoskeleton and cell membrane, regulate the processes of differentiation and cell metabolism, which, in turn, prevent the proliferation of cells, especially tumor cells. Interferons help modulate the expression of certain oncogenes (myc, sys, ras), which allows you to "normalize" the neoplastic transformation of cells and thereby inhibit tumor growth.

Pharmacokinetics

Interferons glycolize and have a single complex carbon-hydrogen fragment bonded to a nitrogen atom

Interferon preparations penetrate into breast milk, therefore, if necessary, the appointment of drugs during lactation should stop breastfeeding. From the bloodstream, they are eliminated by binding to cell receptors and subsequent penetration into the cells, as well as during the destruction and excretion of the kidneys.

Indications

Prevention and treatment of viral infections (influenza, acute and chronic viral hepatitis A, B, C, D, tick-borne encephalitis), oncopathology (hairy cell leukemia, multiple myeloma, non-Hodgkin lymphoma, cutaneous T-cell lymphoma, chronic myelogenous leukemia, Kaposi’s sarcoma against AIDS , kidney carcinoma, melanoma, genital warts, multiple sclerosis).

Contraindications

Hypersensitivity, severe allergic diseases, severe diseases of the cardiovascular system, severe disorders of the hematopoietic system and liver or kidney function, epilepsy and other central nervous system diseases, previous exposure to immunosuppressants, autoimmune diseases in the anamnesis, pregnancy, lactation, children age.

Side effect

Flu-like syndrome, dizziness, drowsiness, decreased cognitive function, decreased ability to concentrate (elderly patients or high doses), restless sleep,

anxiety, paresthesia, ataxia, impaired consciousness, changes in the EEG, optic nerve palsy, transient decrease or increase in blood pressure, arrhythmias, chest pain, leuko- and thrombocytopenia, dry mucous membranes, nausea, vomiting, allergic reactions.

Interaction

Reduce clearance and T1 / 2 of theophylline. Violate the metabolism of cimetidine, phenytoin, warfarin, diazepam, propranolol. Joint use with drugs that inhibit the function of the central nervous system, immunosuppressants, ethanol should be avoided. Decongestants increase the dryness of the mucous membranes when using interferon alpha-2 (fluferon *). Interferon alfa-2a (roferon A *) can enhance the neuro-, hemo- and cardiotoxic effects of drugs used earlier or simultaneously.

special instructions

In case of side effects from the central nervous system in elderly patients receiving high doses, treatment should be interrupted.
In patients with hepatitis C, during treatment, violations of the thyroid gland can sometimes be observed, expressed in hypoil or hyperthyroidism, therefore, the course of treatment should be started with the initially normal TSH content in the blood.
During the treatment period, caution must be exercised when driving motor vehicles and engaging in other potentially hazardous activities that require an increased concentration of attention and speed of psychomotor reactions.
Interferon Inductors
The main pharmacological effects and mechanism of action
Interferon inducers have immunomodulatory and antiviral effects, which are realized due to stimulation of the production of endogenous interferons. In addition, the inhibition of the translation of virus-specific proteins in infected cells is inherent in the drugs of this group, as a result of which the reproduction of DNA and RNA genomic viruses is suppressed.
Indications
Secondary immunodeficiencies, viral hepatitis A, B, C, encephalitis, encephalomyelitis, influenza and SARS, herpes and cytomegalovirus infection, chlamydia.
Contraindications
Hypersensitivity, pregnancy, lactation. Sodium oxodihydroacrydinyl acetate (neovir□) is contraindicated in severe renal failure and autoimmune diseases, and potato shoot extract (panavir *) - in severe kidney and spleen diseases. Contraindicated in children under 4 years of age [meglumine acridone acetate (cycloferon)], 7 years old (tilorone) and 18 years old (allokin-alpha).
Side effect
Allergic reactions, dyspeptic symptoms, short-term chills.
Interaction
Compatible with antibiotics, drugs used to treat viral and bacterial diseases.
Nucleic Acid Preparations
The main pharmacological effects and mechanism of action
Nucleic acid preparations have immunomodulatory, leukopo-stimulating, antioxidant and regenerating effects. The immunomodulatory effect is manifested by activation
phagocytosis, by increasing the functional activity of T-helpers and T-killers, improves the cooperation of T- and B-lymphocytes, their proliferation, activates the synthesis of antibodies.
Pharmacokinetics
Pharmacokinetics are described in sodium deoxyribonucleate (Derinat□). With its intramuscular administration, Cmax is reached after 0.5 hours, and T1 / 2 equals 72 hours. With repeated administration every 24 hours for 5 days, the drug accumulates in the blood and bone marrow. 8 days after the cessation of administration, the concentration in all organs and tissues decreases. It is excreted unchanged and in the form of metabolites mainly by the kidneys (60%) and partially by the intestines (15%).
Indications
Secondary immunodeficiencies, manifested by infectious and inflammatory diseases of the viral and bacterial etiology, leukemia and neutropenia.
Contraindications
Hypersensitivity, organic myocardial diseases with impaired conduction, liver and kidney failure, pregnancy, lactation, children under 7 years of age.
Synthetic immunomodulators
The immunostimulating effect of drugs of this group is manifested:
1) restoration of the antigen-presenting and regulatory function of macrophages, stimulation of phagocytosis [aminodihydrophthalazin-dione sodium (havavit), glutoxim *, inosine pranobex, azoximer bromide (polyoxidonium)];
2) a change in the level of redox systems and the dynamics of phosphorylation of key proteins of signal-transmitting systems and transcription factors (NF-kB and AP-1), primarily immunocompetent cells (glutoxim);

3) a differentiated effect on normal (stimulation of proliferation and differentiation) and transformed (induction of apoptosis - genetically programmed cell death) cells (glutoxim);
4) the stimulating effect on the cascade mechanisms of phosphate modification of the main proteins of signal-transmitting systems (glutoxim);
5) initiation of the cytokine system (including their endogenous production of IL-1, IL-6, TNF-α, erythropoietin), reproducing the effects of IL-2 by inducing the expression of its receptors (glutoxim *);
6) increasing the availability of inosine pranobex for lymphocytes and stimulating the proliferation of lymphocytes and the formation of cytokines;
7) a decrease in elevated and increased decreased levels of IL-1, IL-6 and TNF-α (azoximer bromide);
8) an increase in the cytotoxic activity of NK cells, especially with its initially lowered level (azoximer bromide, inosine pranobex);
9) elimination of cytopathogenic immune complexes (azoximer bromide);
10) increased antibody formation to T-dependent and T-independent antigens of both animal and microbial origin (azoximer bromide).
The anti-inflammatory effect of sodium aminodihydrophthalazinedione (galavit) is associated with the suppression of macrophage hyperactivity, a decrease in the excessive synthesis of TNF-α, IL-1, the production of reactive oxygen species and acute phase proteins.
The antiviral effect of inosine pranobex is associated with blockade of the reproduction of viral particles by damaging its genetic apparatus.
Pharmacokinetics
Glutoxim is unevenly distributed over the organs and tissues of the body: the maximum accumulation is in the liver, kidneys, organs of immunogenesis and hematopoiesis, the minimum in adipose tissue. Metabolized to amino acids. It is excreted by the kidneys in the form of metabolites.
Indications
Secondary immune deficiency on the background of acute and chronic diseases of various localization, viral and bacterial etiology, neurotic and psychosomatic disorders.
Contraindications
Hypersensitivity, pregnancy, lactation. Inosine pranobex is also contraindicated in gout, nephrourolithiasis, chronic renal failure, arrhythmias.
Side effect
Soreness at the injection site (azoximer bromide, glutoxim), nausea, vomiting, diarrhea, gastralgia, exacerbation of gout, hyperuricemia, dizziness, weakness, headaches (inosine pranobex), allergic reactions (gala-vit , inosine pranobex)
Interaction
Glutoxim is pharmaceutically compatible with water-soluble drugs. The effectiveness of inosine pranobex reduces immunosuppressants.
The rapid development of biotechnology has led to the creation of fundamentally new immunopharmacological agents, which are monoclonal antibodies
Drugs in this group are used only parenterally. The half-life depends on the stability of these immunopharmacological agents and elimination mechanisms. Protein molecules weighing less than 70 kDa are eliminated by the kidneys. The closer monoclonal antibodies are to human immunoglobulins, the longer their circulation and effect.
Mononuclear antibodies with an immunosuppressive effect can cause secondary immunodeficiencies. When using monoclonal antibody preparations, allergic reactions can occur or appear in the blood of the anti-body to these immunopharmacological agents, which leads to a decrease in their clinical effectiveness.
The intensive use of immunomodulators in wide clinical practice leads to the accumulation of evidence.
Clinical efficacy has been proven for IRS-19 (A, B) (prevention and treatment of rhinitis, pharyngitis, laryngitis and otitis), sodium deoxyribonucleate (derinat) (B) (rhinitis, sinusitis, aphthous stomatitis, impaired mucus integrity membranes of the nose, pharynx, oral cavity, etc.),

hepone * (B) (secondary immunodeficiency due to viral, bacterial and fungal intoxication with polypous rhinosinusitis, adenoiditis, pharyngomycosis, tonsillitis), interferon alpha-2 (fluferon) (C) (sinusitis of viral etiology).

At the end of 2006, research data were published to determine the effectiveness and safety of bacterial immunomodulators in 4 thousand children aged 6 months to 18 years with acute respiratory infections (colds, tonsillitis, pharyngitis, bronchitis and acute moderate otitis). When comparing groups of patients who received immunocorrectors or placebo, it was shown that the use of bacterial immunocorrectors reduces the incidence of acute respiratory infections in children by 40%. In the same randomized clinical trials, efficacy was not established for echinacea preparations used for prophylactic or therapeutic purposes.

They have evidence of clinical efficacy in chronic viral hepatitis B preparations of interferon alpha-2a and interferon alpha-2b (A).

Immunomodulators are used not only for secondary immunodeficiencies, manifested by infectious diseases, but also for sluggish diseases of the central nervous system, in particular multiple sclerosis and myasthenia gravis. There are several drug groups with immunomodulating activity that reduce the frequency of exacerbations in the remitting and remitting-progressive course of multiple sclerosis, as well as the degree of progression of disability in this disease (A). The immunomodulators are interferon beta-1a (rebif реб, avonex) (A, B), glatiramer acetate (A) and immunosuppressants azathioprine (D), mitoxantrone (A).

In myasthenia gravis, immunoregulatory peptides [alpha-glutamyl tryptophan (thymogen□), thioptin□, thymus extract (thymactide, thymalin□)] and immunosuppressants (azathio-prin, mycophenolate mofetil), cyclophosphamide are used for drug correction of immunopathogenesis IN).

Immunorehabilitation is a complex of therapeutic measures aimed at restoring the impaired functions of the immune system. The effect of immunorehabilitation can be obtained without a direct effect on the immune system, by treating pathological conditions that directly contribute to the development of immune imbalance.

There are several classifications of immunotropic drugs. The following classification is most often used in clinical practice:

CLINICAL-PHARMACOLOGICAL APPROACHES TO THE SELECTION AND APPLICATION OF MEDICINES FOR SECONDARY IMMUNO DEFICIENCIES

The goals of the treatment of secondary immunodeficiencies

• Restoring the physiological functioning of the immune system.
• Elimination of the clinical manifestations of the disease.
• Achieving complete recovery or prolonged clinical remission.
• Reducing the frequency of relapses and preventing exacerbations.
• Improving the quality of life.

The principles of the choice of drugs for the treatment of secondary immunodeficiencies

• The first group of choice for secondary immunodeficiencies are drugs that have an etiotropic effect against pathogens that have developed as a result of the loss of the body’s anti-infection and tumor defense by the immune system. These are antibacterial, antiviral and antitumor drugs.
• Immunomodulators are additional tools in the complex treatment of secondary immunodeficiencies. Their purpose is justified when the drugs of the first choice are not effective enough due to the inadequate clinical state of the functioning of the immune system, subject to
research principles of the appointment of etiotropic anti-infective and anti-tumor agents.

The main principles of the choice of immunomodulators

• The choice of immunomodulator is determined by the results of immunological studies and the clinical condition of the patient.
• It is advisable to prescribe immunomodulators as soon as possible, from the first day of using a chemotherapeutic etiotropic agent.
• A decrease in an immunity parameter detected by an immuno-diagnostic study in a practically healthy person does not necessarily serve as the basis for the appointment of an immunomodulating effect.

• Epidemiologically unfavorable situations of any infectious disease indicate the widespread use of immunomodulators for prophylactic purposes without assessing the immune status.
• The regimen and dose of immunomodulators is determined individually, adequately to the clinical manifestations of secondary immunodeficiency and a detected defect in the immune system.
• Immunomodulatory treatment should be carried out in courses, the number of which and the duration of the intervals are determined by the severity of clinical manifestations and the degree of violation of the immune system.
• Monitoring the effectiveness of immunomodulatory treatment is carried out laboratory, to restore immunity, and clinically.

Lesson purpose

The study of the main groups of immunotropic drugs and methods of immunocorrective effects on the human immunity system.

IMMUNOTROPIC PRODUCTS

The concept of immunopharmacology. History and features of the clinical use of drugs. The concept of immunomodulators, immunostimulants and immunosuppressants. The phenomenon of the "pendulum." Types of immunocorrection (replacement, stimulating, depressing

. Characteristics of individual groups. Indications and contraindications for use. Immunosuppressants as immunostimulants. Undesirable effects of immunosuppressive therapy. Control of immunosuppressive therapy.

. Classification of IMMUNITY MULTIERS:

. Characteristics of individual groups. Indications and contraindications for use.

. Nonspecific immunocorrection.

. The basic principles of the use of immunotropic drugs.

Classification of immunocorrective agents:

I. Immunomodulators

I. Products of physiological (biological) origin:

1. Immunoregulatory peptides obtained from the central organs of the immune system (thymus, bone marrow) - taktivin, thymostimulin, thymalin, thymococcal, thymomodulin, thymactide, thymoptin, vilosen, myeloid, splenin,

2. Cytokines (interferons, colony-stimulating factors, interleukins, monokines) - laferon, reaferon, roferon-A, intron-A, front, berofor, imukin, leukinferon, leukomax, granocyte, proleukin,

3. Immunoglobulins (specific and nonspecific) - alkimer, poly-bioline, etc.

II.Products of microbial origin:

1. Living bacteria - BCG;

2.Extracts - biostim, picybanil, levelax;

3. Lysates - bronchomunal, IRS-19, postpat, Imudon, bronchovax, diribiotin, rinovac, respivax, urostim;

4. Lipopolysaccharides - pyrogenal, prodigiosan;

5. Yeast polysaccharides - zymosan, sodium nucleinate;

6. Fungal polysaccharides - kestin, bestatin, lentinan, glucan;

7. Ribosomes + proteoglycan - ribomunyl;

8. Probiotics - blast, biosporin, linex.

III. Synthetic preparations (analogues of endogenous immunomodulators, immunomodulators of directional synthesis, known drugs with the properties of immunomodulators): thymogen, lycopide, diuciphone, levamisole (decaris), camantan, leacadine, polyoxidonium, groprinosin, isoprinosine, neovir, cyclovine -feron, copolymer1 (copaxone), lycopide, immunofan, polyoxidonium, sodium nucleate, etc.

IV.Vitamins and antioxidant complexes.

V. Herbal preparations: difur, blastophage, manax, immunal.

VI. Enterosorbents: Belosorb, Ensoral, Mycoton, Sillard, Anthralen.

preparations containing zinc, selenium, etc. and other trace elements.

VII. Immunosuppressants:

Antimetabolites

· Alkylating compounds

· Antibiotics

· Glucocorticoids

· Cyclosporins

· Antibodies and their constructs

VIII. Complex enzyme preparations: wobenzym, phlogenzym, wobemugos.

II. Immunosuppressants

· glucocorticoids, azathioprine (imuran), sandimmune, prograf, select, rapamycin, misoribine, brequinar, deoxyspergualin leflunomide, thymoglobin, limphoglobin, OCTZ, thymoglobulin, simulect.

Learning Theme Elements

1. Definition of the terms immunotherapy, immunoprophylaxis, immunostimulant, immunomodulator, immunosuppressant.

2. The basic principles of immunocorrective therapy.

3. Classification of immunocorrective drugs.

4. Immunocorrective drugs of different groups (indications and contraindications for use, the main side effects).

After mastering the material, the student should know:

1. Definition of the terms immunotherapy, immunostimulant, immunomodulator, immunosuppressant.

2. The main options for immunocorrective effects on the human body.

3. The main mechanisms of the effect of immunocorrective drugs on the human body.

4. The basic principles of immunotherapy.

5. The differences between immunomodulators, immunostimulants and immunosuppressants.

6. Classification of the main immunotropic drugs.

7. Properties and indications for the use of various classes of immunocorrective agents.

8. The basic principles of the use of immunocorrective drugs.

9. The possibilities of immunocorrection in various types of immunological pathology: immunodeficiencies, allergic and autoimmune diseases.

The student must be able to:

1. Understand the main groups of immunocorrective drugs.

2. Assign immunocorrective agents, taking into account the pathogenesis, phase and stage of the disease, and the mechanism of action of the immunocorrective drug.

3. To be able to justify the appointment of an immunocorrective drug.

Test questions of students' knowledge:

1. What is immunotherapy?

2. What are the main indications for immunotherapy you know?

3. What types of immunocorrective effects do you know?

4. What is an immunostimulant?

5. What principles of immunotherapy do you know?

6. What groups can be divided immunotropic drugs?

7. What are the main classes of immunotropic drugs, indications for use, side effects and contraindications.

Modern immunotherapy has several ways of exposure:

I. The use of immunomodulators.

II. Substitution therapy - the introduction into the body of immunity factors in the case of genetically or phenotypically caused by their insufficiency (the introduction of immunoglobulins, cytokines, etc.).

III.Introduction of highly specific preparations of exogenous therapeutic antibodies.

IV. Antibacterial and antiviral therapy.

V. Immunization with a given antigen:

Allergen-specific immunotherapy.

VI. System adaptation - a set of measures aimed at adapting the body to the environment (physiotherapy, hardening, diet, vitamin therapy, etc.).

VII. Efferent methods of exposure: hemosorption, plasma, cytopheresis, etc.

Viii. Physical methods: laser, ultraviolet and infrared irradiation of lymphoid organs and blood.

IX. Immune and genetic engineering: transplantation of organs, tissues and cells of the immune system, bone marrow, stem, dendritic and embryonic cells, gene therapy.

X. Immunosuppressive therapy.

The main mechanisms of action of immunotropic drugs:

1. Stimulation of the differentiation of immunocompetent cells due to the effect on the hematopoiesis system.

2. Interaction of immunotropic drugs with receptors of immunocompetent cells.

3. Stimulation or inhibition of the synthesis of cytokines.

4. Formation of specific active and passive immunity.

5. Replacement therapy.

6. Combined immunocorrecting effect and direct effect on antigen (antiviral effect).

Indications for immunotherapy:

1. Primary and acquired immunodeficiencies.

2. Allergic diseases.

3. Autoimmune diseases.

4. Oncological diseases.

5. Infectious diseases.

6. Conditions after allotransplantation.

7. Diseases accompanied by a violation of regeneration.

TESTS

1. A patient who has been suffering from bronchial asthma for 15 years has been referred to an immunologist for the appointment of immunocorrective therapy. An immunological examination revealed thymus-dependent immunodeficiency. What drug is most appropriate to start immunocorrection?

A. T-activin.

B. Interferon.

C. Cyclosporin A.

D. Gamma globulin.

E. Hydrocortisone.

2. Which of the following drugs is converted into a cytotoxic product.

A. –vincristine

B. –dactinomycin

C.! 5-florouracil

D. –lomustine

E. - paclitaxel

3. Which of the drugs is cytotoxic depending on the cell cycle

A.! Methotrexate

B. –dactinomycin

C. –cisplatin

D. –mechlorethamine

E. Doxorubicin

4. All of these drugs interfere with DNA transcription except:

A. - doxorubicin

B.! Tamoxifen

C. –cyclophosphamide

D. –mechlorethamine

E. –cisplatin

5. myelosuppression - very serious toxicity of all drugs except

A. –vinblastine

B. - cyclophosphamide

C. –cytarabine

D. –mechlorethamine

E.! L-asparaginase

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн, В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF DRUGS INHIBITION THE CNS FUNCTION

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF DRUGS STIMULATING CNS FUNCTION

Relevance of the topic.

Currently, the decisive role of disorders of the regulatory functions of the central nervous system (CNS) in the development of a number of somatic diseases is widely known. The latter include neurocirculatory (vegeto-vascular) dystonia, hypertension, coronary heart disease, atherosclerosis, diabetes mellitus, peptic ulcer of the stomach and 12 duodenal ulcer and other diseases called “diseases of the century”, in the genesis of which the leading role is played by chronic psycho-emotional stress. In this regard, a doctor of any specialty is faced with the need to use psychotropic drugs that correct both the processes of higher nervous activity and the autonomic functions of the central nervous system.

Medicines that affect emotions, the cognitive sphere and human behavior are called psychotropic. They entered practical medicine a little more than 30 years ago.

Medicines of this group include drugs that are different in chemical structure and mechanism of action. They are united by a normalizing effect on mental functions and human behavior, due to their ability to influence the cerebral cortex and subcortical structures, primarily on the limbic region, basal ganglia, and hypothalamus.

The main mechanisms of action of psychotropic drugs are based on their effect on neurotransmitter processes in the central nervous system, i.e. drugs can interact with receptors, change the processes of synthesis, release, deposition, inactivation of mediators.

Thus, psychotropic drugs compensate for psycho-vegetative disorders, contribute to the normalization of neuroendocrine abnormalities, have hypotensive, antiarrhythmic, antiemetic, antihistamine and anticonvulsant effects.

Motivational characteristic of the topic.

Psychotropic drugs have recently been increasingly used by doctors of various specialties. On the one hand, this is due to the constant increase in the number of neuropsychiatric diseases, on the other hand, the frequent secondary disorders of the central nervous system in many somatic diseases In addition, rational pharmacotherapy based on the effective and safe use of drugs should take into account the possible negative effects of non-psychotropic drugs on the central nervous system, which is not always taken into account by practical doctors. The study of this topic will allow students to more fully navigate the mechanisms of action of psychotropic drugs, to justifiably use them to control the pathogenesis of the disease, which ultimately will increase the effectiveness of the prevention and treatment of central nervous system disorders.

SUBSTANCES INFLUENCING THE CENTRAL NERVOUS SYSTEM

These are means that can affect the mental functions of a person (memory, behavior, emotions, etc.), and therefore they are used for mental disorders, for neurotic and neurosis-like disorders, states of internal stress, fear, anxiety, anxiety.

CLASSIFICATION OF PSYCHOTROPIC MEDICINES

1) Sedative.

2) Tranquilizers.

3) antipsychotics.

4) Anti-manic.

5) Antidepressants.

Sometimes, some authors refer to nootropic drugs (nootropics) as the sixth (6) group of psychotropic drugs.

We will begin the analysis of this group of drugs with sedatives.

Sedatives are a sedative. Sedative (sedative) drugs include:

1) low doses of barbiturates,

2) bromine and magnesium salts,

3) herbal preparations (valerian, motherwort, passionflower herbs, etc.).

All of them, causing a moderately calming effect, have an indiscriminate, simple, depressing effect on the cerebral cortex. In other words, sedatives enhance inhibitory processes in neurons of the cerebral cortex.

Sodium bromide and potassium bromide are most often used from bromine salts. Widely used drugs valerian in the form of infusions, tinctures, ex-tracts.

Sedatives are also motherwort herb preparations. Use tincture and tinctures motherwort. Passiflora drug - Novopassit. Infusions of ordinary hop, Quater's potion (valerian, bromides, menthol, etc.), magnesium ions (sulphate of magnesia).

Indications for use: sedatives are used for neurasthenia, hysteria, mild forms of neurosis, increased irritability, and insomnia associated with this.

Hop Melissa Peppermint Valerian

The second group of drugs from psychotropic drugs is a group of TRANQUILIZERS. Tranquilizers are modern sedatives with a selective effect on the human emotional sphere. The term tranquilizers comes from the Latin tranquillium - calm, peace. The psi-hotropic effect of tranquilizers is mainly associated with their effect on the libic system of the brain. In particular, tranquilizers reduce the spontaneous activity of hippocampal neurons. At the same time, they have a depressing effect on the hypothalamus and the activating reticular formation of the brain stem. Acting in this way, tranquilizers are able to reduce the state of internal tension, anxiety, fear, fear. Based on this, this group of funds is also called ANXIOLYTICS. The fact is that the Latin term anxius- or English "anxious" is translated as "anxious, full of fear, fear", and the Greek lysis - dissolution.

Therefore, in the literature the term anxiolytics is used as a synonym for tranquilizers, that is, means that can reduce the state of internal stress.

Due to the fact that these drugs are mainly used to treat patients with neurosis, they have their third main name, namely, anti-neurotic drugs.

Thus, we have three equivalent terms: tranquilizers, anxiolytics, anti-neurotic drugs that we can use as synonyms. You can still find synonyms in the literature: small tranquilizers, psychosedative drugs, ataractics.

Of the tranquilizers used in medical practice, benzodiazepine derivatives are most widely used, since they have a wide range of therapeutic effects and are relatively safe.

SIBAZON diazepam (Sibazonum; in the table. At 0, 005; in amp. 0, 5% solution of 2 ml); synonyms - diazepam, seduxen, relanium, valium. Preparations of the same group: chlozepide (elenium), phenazepam, nozepam, mezapam (orehotel).

The mechanism of action of benzodiazepine tranquilizers: in the body, in the territory of the central nervous system zones indicated above, benzodiazepines interact with the so-called benzodiazepine receptors, which are closely associated with GABA receptors (GABA - gamma-aminobutyric acid - inhibitory central nervous system mediator, inhibitory; glycine - also inhibitory CNS mediator; L-glutamic acid - an exciting mediator). When stimulating benzodiazepine receptors, activation of GABA receptors is observed. Therefore, the interaction of benzodiazepines with the same receptors manifests itself in the form of a GABA-mimetic effect.

All benzodiazepines that eliminate the feeling of emotional stress have similar properties, but vary in pharmacokinetics. More often than other drugs, diazepam or sibazon is used.

PHARMACOLOGICAL EFFECTS OF TRANQUILIZERS

(on the example of sibazon)

1) The main is their tranquilizing or anxiolytic effect, manifested in the ability to reduce the state of internal stress, anxiety, and mild fear. They reduce aggression and cause a state of sedation. At the same time, they eliminate both situational (associated with any event, specific action), and non-situational reactions. In addition, they have a pronounced sedative effect.

2) The next effect is their muscle relaxant effect, although the muscle relaxant effect of tranquilizers is weak. This effect is realized mainly due to the central action, but they also cause inhibition of spinal polysynaptic reflexes.

3) By increasing the threshold of a convulsive reaction, tranquilizers have anticonvulsant activity. It is believed that the anticonvulsant and myorelaxing activity of tranquilizers is associated with GABAergic action.

4) All benzodiazepine tranquilizers have a light hypnotic effect, and the NITRAZEPAM benzodiazepine tranquilizer has such a powerful hypnotic effect that it rightfully belongs to the group of sleeping pills.

5) Potentiating effect (enhance the effect of drugs that depress the central nervous system and analgesics). Benzodiazepines lower blood pressure, lower respiratory rate, and stimulate appetite.

INDICATIONS FOR USE:

1) as a remedy for the treatment of patients with primary neurosis (anti-neurotic drugs);

2) with neuroses due to somatic diseases (myocardial infarction, peptic ulcer);

3) for premedication in anesthesiology, as well as in the postoperative period; in dentistry;

4) with local spasms of skeletal muscle ("tick");

5) sibazon in injections (in / in, in / m); with convulsions as an anticonvulsant of various origins and with epileptic status, muscle hypertonicity;

6) as a light sleeping pill for some forms of insomnia;

7) with alcohol withdrawal syndrome in people suffering from chronic alcoholism.

SIDE EFFECTS

1) Benzodiazepines cause drowsiness during the day, lethargy, weakness, mild lethargy, decreased attention, and distraction. Therefore, they can not be assigned to drivers of transport, operators, pilots, students. Tranquilizers are best taken at night (in any case, 2/3 of the daily dose at night, and 1/3 of the dose at day).

2) Benzodiazepine tranquilizers can cause muscle weakness, ataxia.

3) Tolerance and physical dependence may develop.

4) Cancellation syndrome may develop, characterized by insomnia, agitation, depression.

5) Drugs can cause allergies, photosensitization, dizziness, headache, impaired sexual function, menstrual cycle, accommodation.

6) Tranquilizers have a cumulative ability.

Addiction and development of addiction is a reason for abuse of tranquilizers. This is their main drawback and big trouble.

In view of the above undesirable effects, the so-called “daytime tranquilizers” have been created, which have a significantly less pronounced muscle relaxant and general inhibitory effect. These include MEZAPAM (ore hotel, Germany). They act weaker in their tranquilizing effect, but most importantly, they cause side effects to a lesser extent. They have a sedative, anticonvulsant, muscle relaxant effect. Used for the treatment of patients with neurosis, alcoholism. Therefore, they are considered as “daytime” tranquilizers, less disturbing during the day (Table 0, 01).

Another drug, Phenazepam (tablets of 2.5 mg, 0, 0005, 0, 001), is a very powerful drug, like an anxiolytic and a tranquilizer that surpasses other drugs. In terms of duration of action, it is in first place among the above benzodiazepines, in action it is even close to antipsychotics. For phenazepam, it was shown that a decrease in it in blood plasma by 50% occurs after 24-72 hours (1-3 days). It is prescribed for very severe neuroses, which brings it closer to neuroleptics.

It is indicated for neurosis-like, psychopathic and psychopathic-like states, accompanied by anxiety, fear, emotional lability It is indicated for obsession, phobias, hypochondria syndromes. Used to stop alcohol withdrawal.

The propanediol derivative MEPROBAMAT or MEPROTAN has similar properties to benzodiazepines. Yields to the tranquilizer phenazepam. It has a sedative, muscle relaxant and anticonvulsant effect. Enhances the inhibitory effect of drugs for anesthesia, sleeping pills, ethyl alcohol, narcotic analgesics. It is well absorbed from the digestive tract. It inhibits a fast-new sleep, causes a strong aftereffect, is toxic, inhibits the respiratory center, and disrupts coordination. Affects blood, causes allergies.

The third group of psychotropic drugs are neuroleptics or antipsychotic drugs (neuron - nerve, leptos - gentle, thin - buckwheat.). Synonyms: large tranquilizers, neuroplegics. These are drugs for treating patients with psychoses.

PSYCHOSIS - a condition characterized by a distortion of reality (that is, delirium, hallucinations, aggressiveness, hostility, affective disorders). In general, this fits into the concept of productive symptomatology.

Psychoses can be ORGANIC or ENDOGENIC (schizophrenia, manic-depressive psychosis) and REACTIVE, that is, they are not independent diseases, but a condition that arose in response to shock. For example, during the earthquake in Armenia - mass psychoses. The basis of psi-hoz is of great importance a sharp increase in the sympathetic tone in the central nervous system, that is, an excess of catecholamines (norepinephrine, dopamine or dopamine).

The discovery and introduction into practice in the middle of the century of active psychotropic drugs of the group of antipsychotics is one of the largest achievements of medicine. This fundamentally changed the strategy and tactics of treating many mental illnesses. Before the advent of these drugs, the treatment of patients with psychosis was very limited (electroshock or insulin coma). In addition, antipsychotics are currently used not only in psychiatry, but also in the border areas of medicine - neurology, therapy, anesthesiology, surgery. The introduction of these funds has contributed to the development of basic research in the field of psychopharmacology, physiology, biochemistry, pathophysiology in order to understand the mechanisms of various manifestations of mental disorders.

The MECHANISM of the antipsychotic action of antipsychotics is not well understood. It is believed that the antipsychotic effect of antipsychotics is due to inhibition of the dopamine receptors (D receptors) of the limbic system (hippocampus, lumbar gyrus, hypothalamus).

The blocking effect on dopamine receptors is manifested by an antagonism with dopamine and dopaminomimetics (apomorphine, phenamine) both according to the behavioral reactions and at the level of individual neurons.

On preparations of neuronal membranes it was found that antipsychotics inhibit the binding of dopamine by its receptors.

In addition to blocking receptors sensitive to dopamine and noradrenaline, antipsychotics reduce the permeability of presynaptic membranes, disrupting the release of these biogenic amines and their reverse neuronal uptake (D-2 receptors). For some antipsychotics (phenothiazine derivatives) in the development of psychotropic effects, their blocking effect on serotonin receptors and brain M-

cholinergic receptors may be important. Thus, the main in the mechanism of action of antipsychotics is considered the blockade of D receptors.

By the chemical structure of antipsychotics belong to the following groups:

phenothiazine derivatives - chlorpromazine, etaperazine, trifthazine, fluorfezazine, thioproperazine or napeptyl, etc .;

2) derivatives of butyrophenone - haloperidol, droperidol;

3) derivatives of dibenzodiazepine - clozapine (leponex);
4) derivatives of thioxanthene - chlorprotixen (Truxal);
5) derivatives of indole - carbidine;
6) alkaloids of rauwolfia - reserpine.
Phenothiazine derivatives are the most widely used agents in the treatment of large psychoses.

The most typical representative of phenothiazine derivatives is aminazine or largactil (international name: chlorpromazine). Aminazinum (dragees for 0, 025; 0, 05; 0, 1; amp. For 1, 2, 5 and 10 ml - 25% solution).

Aminazine was the first drug of this group, synthesized in 1950. In 1952 he was introduced into clinical practice (Delay and Deniker), which laid the foundation for modern psychopharmacology. Phenothiazines have a three-ring structure in which 2 benzene rings are connected by sulfur and nitrogen atoms.

Since other antipsychotics of the phenothiazine group differ from aminazine only in strength and certain characteristics of the psychotropic effect, chlorpromazine should be discussed in detail.

BASIC PHARMACOLOGICAL EFFECTS OF AMINAZINE

1) A pronounced effect on the central nervous system. First of all, it is a neuroleptic effect, which can be described as the deepest sedative effect (supersedative) or an over-expressed tranquilizing effect. In this regard, it is understandable why this group of drugs was called "large tranquilizers" before.

In patients with large psychoses and agitation, aminosine causes a decrease in psychomotor activity, a decrease in motor-defensive reflexes, emotional calm, a decrease in initiative and arousal, without having a hypnotic effect (antipsychotic syndrome). The patient sits silently, he is indifferent to the surrounding events and the events around him, minimally reacting to external stimuli. Emotional dullness. Consciousness is maintained during this period.

This effect develops rapidly, for example, with parenteral administration (iv, iv) after 5-10 minutes and lasts 6 hours. About "is clarified by a blockade in the brain of adrenoreceptors and dopamine receptors.

2) The antipsychotic effect is realized by reducing the productive symptoms and the effect on the patient’s emotional sphere: reducing nonsense, hallucinations, and reducing the productive symptoms. The antipsychotic effect does not appear immediately, but gradually, after many days, mainly 1-2-3 weeks after daily use. It is believed that this effect is caused by the blockade of D-2 receptors (dopamine presynaptic).

3) Aminazine, like all phenathiazine derivatives, has a distinct antiemetic effect associated with blocking the chemoreceptors of the launch zone (trigger zone) located at the bottom of the IY ventricle. But it is not effective for vomiting caused by irritation of the vestibular apparatus or gastrointestinal tract. It eliminates the effect of apomorphine (a dopamine receptor stimulant) on the trigger zone in the medulla oblongata.

4) Aminazine inhibits the center of heat regulation. In this case, the final effect depends on the ambient temperature. Most often, due to an increase in heat transfer, slight hypothermia is observed.

5) A decrease in motor activity (muscle relaxant effect) is typical for chlorpromazine. At sufficiently high doses, a state of catalepsy develops, when the body and limbs for a long time remain in the position that they were given. This condition is due to the suppression of the descending facilitating effects of the reticular formation on spinal reflexes.

6) One of the manifestations of the effect of chlorpromazine on the central nervous system is its ability to potentiate the effects of analgesics, drugs for anesthesia, sleeping pills. This effect is also partially due to the inhibition of the bio-transformation of these drugs by chlorpromazine.

7) In high doses, chlorpromazine has a hypnotic effect (light, superficial sleep).

Aminazine, like all phenothiazines, affects peripheral innervation.

1) First of all, chlorpromazine has the expressed properties of an alpha-blocker, as a result of which it eliminates some of the effects of adrenaline and norepinephrine. Against the background of chlorpromazine, the pressor response to adrenaline decreases sharply or a "perversion" of the effect of adrenaline occurs and blood pressure drops.

2) In addition, some M-anticholinergic (i.e., atropine-like) properties are characteristic of chlorpromazine. This is manifested by a slight decrease in the secretion of salivary, bronchial and digestive glands.

Aminazine affects not only efferent, but also afferent innervation. With local action, it has a pronounced local anesthetic activity. In addition, it has a distinct antihistamine activity (blocks the histamine H-1 receptors), which leads to a decrease in vascular permeability, and is also an antispasmodic of myotropic action.

Characteristic for chlorpromazine effect on the cardiovascular system. First of all, this is manifested by a decrease in blood pressure (both systolic and diastolic), mainly due to alpha-adrenergic blocking action. Cardiodepressive effects, antiarrhythmic effect are noted.

Aminazine, in addition to its effects listed above on the nervous system and executive organs, has pronounced pharmacological effects on metabolism.

First of all, it affects the endocrine system. In women, it causes amenorrhea and lactation. Reduces libido in men (blocking D-receptors in the hypothalamus and pituitary gland). Aminazine blocks the release of growth hormone.

Aminazine is administered enterally and parenterally. With a single administration, the duration of action is 6 hours.

INDICATIONS FOR USE

1) Used as an ambulance for acute psychoses. According to this indication, it is administered parenterally. Aminazine and its analogues are most effective in arousing the patient, excitement, stress and other productive psychotic symptoms (hallucinations, aggression, delirium).

2) Previously used in the treatment of patients with chronic psychoses. Currently, there are more modern means, in the absence of which it can be used.

3) As an antiemetic with vomiting of central origin (with radiation, for example, with vomiting of pregnant women). Also with persistent hiccups, in the treatment of anticancer drugs.

4) In connection with the alpha-adrenergic blocking effect, they are used when stopping a hypertensive crisis. In neurology: in conditions with an increase in muscle tone (after cerebral stroke), sometimes with epileptic status.

5) In the treatment of drug dependence in relation to narcotic analgesics and ethyl alcohol.

6) In the treatment of patients with manic conditions

7) In operations on the heart and brain (hypothermic effect), with premedication, the same effect is used to eliminate hyperthermia in children.

SIDE EFFECTS

1) First of all, it should be noted that with prolonged administration of chlorpromazine in patients, deep inhibition develops. This effect is so overly pronounced that as it grows, the patient eventually turns into an emotionally "dumb" person. Aminazine can change behavioral reactions, accompanied by drowsiness, a violation of psychomotor functions. Lethargy, apathy develops.

2) Almost 10-14% of patients receiving chlorpromazine develop extrapyramidal disorders, extrapyramidal symptoms of parkinsonism: tremor (tremulous paralysis), muscle rigidity. The development of these symptoms is caused by a dopamine deficiency in the black nuclei of the brain that occurs under the influence of an antipsychotic.

3) Frequent adverse reactions to chlorpromazine are nasal congestion, dry mouth, palpitations. Due to the cholinolytic effect of phenothiazines (chlorpromazine, etc.), they cause vague visual perceptions, tachycardia, constipation, and suppression of ejaculation.

4) Hypotonic crises may develop, especially in the elderly. With intravenous administration, even death can occur.

5) In 0.5% of patients, blood disorders develop: agranulocytosis, thrombocytopenia, aplastic anemia. In a number of patients (up to 2%), cholestatic jaundice, various hormonal disorders (gynecomastia, lactation, menstrual irregularities), worsening diabetes, impotence.

6) Phenothiazines can cause either an increase or decrease in body temperature.

7) In psychiatric practice, one can see the development of tolerance, especially to sedative and antihypertensive action. Antipsychotic effect persists.

As already mentioned, chlorpromazine is a phenothiazine derivative. He was the first drug of this series. Subsequently, a whole series of compounds of this class and series were synthesized (meterazine, etaperazine, triftazil, thioproperazine or majeptil, fluorophenazine, etc.). In general, they are similar to chlorpromazine and differ from it only in the severity of individual properties, less toxicity and fewer side effects. Therefore, chlorpromazine is gradually being displaced from clinical practice by the aforementioned drugs.

In the past 10 years, the drug THIORIDAZINE (sonapax) has been widely used. It is inferior to aminazine in antipsychotic activity. In the preparation, the antipsychotic effect is combined with a calming effect without marked inhibition, lethargy, and emotional indifference. Very rarely causes extrapyramidal disorders. It is shown: with mental and emotional disorders, a sense of fear, tension, excitement.

Of great interest as antipsychotic agents are derivatives of butyrophenone. Of this series of compounds, haloperidol (halofen) is mainly used to treat patients with mental illness.

Haloperidolum (tab. At 0, 0015, 0, 005; 10 ml vials of 0, 2% - int .; ampoule - 1 ml - 0.5% solution). Its action occurs relatively quickly. With the introduction of the drug inside, the maximum concentration in the blood is already in 2-6 hours and remains at a high level of 3 days.

It has a less pronounced sedative effect and effect on the autonomic nervous system (alpha-adrenergic blocking, atropine-like and ganglion blocking effect less). In addition, antipsychotic activity is stronger than chlorpromazine, therefore it is of interest in patients with very strong excitement and mania.

The frequency of extrapyramidal reactions in the treatment of this drug is very high, so it does not have significant advantages over phenothiazines in the treatment of schizophrenia. Used in the treatment of patients with acute mental illness with the phenomena of hallucinations, delusions, aggression; with irreversible vomiting of any genesis or with resistance to other antipsychotics, as well as with sleeping pills, analgesics as a sedative.

DROPERIDOL belongs to the same group of drugs.

Droperidolum (amp. 5 and 10 ml of 0.25% solution, Hungary). It differs from galoperidol in short-term (10-20 minutes) feasible action. It has anti-shock and antiemetic effect. Reduces blood pressure, has an anti-arrhythmic effect. Droperidol is used mainly in anesthesiology for neuroleptanalgesia. In combination with a synthetic analgesic, fentanyl is part of the thalamonal preparation, which exhibits a quick antipsychotic and analgesic effect, leads to muscle relaxation, drowsiness. Used in psychiatry to stop reactive conditions. In anesthesiology: sedation during and after surgery. With endotracheal anesthesia. Contraindications: parkinsonism, hypotension, with the appointment of antihypertensive drugs.

At present, new antipsychotics have been created that practically do not cause extrapyramidal disorders. In this regard, one of the most recent drugs, CLOSAPIN (or leponex), is of interest. It has a strong antipsychotic effect with a sedative component in the absence of symptoms of parkinsonism. When using the drug, there is no such a sharp general inhibition as that of chlorpromazine. Sedation, developing at the beginning of treatment, which then passes. Clozapine is a derivative of dibenzodiazepine. It has high antipsychotic activity. Used in psychiatry to treat patients with manic-depressive psychosis and schizophrenia, with psychopathy.

It is believed that clozapine and classical antipsychotics (phenothiazines and butyrophenones) interact with different types of D receptors. In addition, closa-pin has a pronounced blocking activity against brain M-cholinergic receptors.

Clozapine is well tolerated, however, it is necessary to monitor the blood, because there is a risk of developing agranulocytosis, it is possible to develop tachycardia, collapse. Caution should be given to drivers, pilots and other categories of persons.

SULPIRIDE (eglonyl) is a moderate antipsychotic. It has an antiemetic, moderate antiserotonin effect, there is no sedative effect, there is no anticonvulsant activity, it has an antidepressant effect and some stimulating effect. Used in psychiatry (lethargy, lethargy, anergy), in therapy in the treatment of peptic ulcer, migraine, dizziness.

The fourth group of psychotropic drugs, which we will analyze very briefly, are ANTIMANIACAL MEDICINES.

MANIA - a painfully increased excited state, usually accompanied by an increase in mood, a desire to make speeches, etc.

From the Greek - mania - madness.

Mania is usually observed as one of the phases of manic-depressive syndrome (MDS).

In the treatment of patients with mania use:

1) antipsychotics;

2) lithium salts.

Antipsychotics are effective not only in mania, but also in general in agitated (severe excitement, agitation) states of various origins. Their action is manifested in general oppression, the development of apathy and drowsiness.

Lithium salts act more specifically. They have a pharmacotherapeutic effect only with mania, without causing general inhibition.

Lithium salts are used to treat and prevent mania.

The mechanism of action of lithium salts is not well understood. It is believed that they reduce the release of norepinephrine from nerve endings due to increased intracellular oxidative deamination and more active neuronal reuptake of the mediator. In addition, it is believed that lithium displaces sodium from the cells, as it is known, sodium provides depolarization, that is, the excitation of cells (neurons).

With the enteric administration of lithium salts, they are well absorbed from the small intestine. Lithium is excreted by the kidneys by filtration. The rate of lithium elimination can be slightly increased by increasing the content of sodium chloride in the diet. With a decrease in the introduction of sodium chloride or its excessive excretion, lithium is delayed in the body and this leads to intoxication (salt-free diet, the use of diuretics).

Various lithium salts are used: carbonate, chloride, iodite, acetate, nitrate. The most commonly used lithium carbonate.

Lithii carbonatus (tab. In the shell at 0, 3). Lithium carbonate has been used in the treatment of mental illness since 1949 (Cade). Lithium carbonate is administered only enterally.

As noted above, one of the most important indications for the use of lithium salts is the treatment of patients with mania. Lithium salts differ from antipsychotics:

1) a slower development of the effect (after 2-3 weeks), which dictates the use of antipsychotics in severe manic conditions at the beginning of treatment;

2) the difference between the action of lithium salts and antipsychotics lies in the fact that they have a more selective effect on mania, the absence of a sedative effect (does not cause lethargy, apathy in patients).

Of great importance is the effectiveness of lithium salts for the prevention of mania, as well as depression in MDP.

ADVERSE REACTIONS

It is necessary to take into account the small therapeutic latitude of lithium salts. This leads to the fact that the toxicity of these drugs is proportional to their content in serum. In this regard, their use requires regular monitoring of their content in the blood (not more than 1.6-2 meq / l).

Moderate toxicity is manifested by diarrhea, dyspeptic disorders, drowsiness, muscle weakness, tremor, ataxia, polyuria, thirst. Lithium carbonate can cause allergic reactions, blurred visual perceptions. Non-toxic goiter, hypothyroidism, changes in the ECG may develop.

Lithium salts are contraindicated in case of impaired renal excretory function, in case of thyroid gland diseases, with caution it is necessary to use the drug in case of peptic ulcer, cholecystitis.

ANTIDEPRESSANTS.

Use with a pathologically reduced mood. Antidepressants with a sedative effect are also called TIMOLEPTICS (from Greek - thymos - soul, spirit; leptos - gentle, delicate), and with a stimulant - TIMORETI-KAMI (Greek - ereto - annoy).

The successful correction of depression with medication is one of the most important achievements of psychopharmacology in recent years.

The cause of depression is impaired normal transmission of serotonin and no-radrenaline

CLASSIFICATION OF ANTIDEPRESSANTS

Briefly, it can be represented by the two main groups of funds that are most often used in the clinic.

1) Means that potentiate the action of monoamines (monoamines - tyrazine, serotonin).

Serotonin and norepinephrine reuptake inhibitors. In this group we will analyze two drugs: imizin, amitriptyline.

Serotonin-only Reuptake Inhibitors - Fluoxetine

Norepinephrine-only reuptake inhibitors - maprotiline

2) Monoamine oxidase inhibitors A and B - nialamide (nuredal).

The most widely used drugs are the first group, which are usually designated as

TRICYCLIC ANTIDEPRESSANTS.

IMIZIN (Imizinum; in the table at 0, 025; in amp. 1, 25% solution of 2 ml) is a typical representative of the drugs in this group and is used very often.

Other drugs: desipramine (norpramine), trimipramine, amitriptyline, nortriptyline (sirensan), protriptyline (vivactyl), nitroxazepine, etc.

Imizin has pronounced antidepressant properties, combined with a weak sedative effect. Sometimes, however, a psychostimulating effect (euphoria, agitation, insomnia) can be detected in imizin.

The mechanism of action by which tricyclic antidepressants act in humans is unknown. There are only hypotheses. One of them associates the antidepressant effect of imizin with its ability to inhibit the reverse neuronal uptake of norepinephrine. This leads to a large accumulation of the indicated mediator in the receptors, which enhances adrenergic effects. Imizin does not act on the activity of monoamine oxidase (MAO). In addition, imizin may activate serotonergic receptors, which is due to a violation of its neuronal and extraneuronal uptake. Strengthening the inhibitory effect of serotonin on the limbic system (amygdala complex) may be one of the important mechanisms of the antidepressant effect of imizine.

In addition, the central M-anticholinergic action of tricyclic antidepressants plays an important role.

PHARMACOLOGICAL EFFECTS

1) Tricyclic antidepressants have a pronounced effect on behavior. Imizin has an antidepressant effect. Improves mood, eliminates longing, unmotivated anxiety, suicidal thoughts, increases activity, desire for activity. In addition, it has some sedative effect.

2) Along with the central effects, imizin has some peripheral M-anticholinergic (atropine-like), papaverine-like (antispasmodic myotropic) and distinct antihistamine action.

When using imizine for depression, the therapeutic effect occurs after 2-3 weeks, and when using amitroptiline somewhat faster. Excreted by the kidneys, 90% bound to plasma proteins.

ADVERSE REACTIONS

Most often, side effects are associated: 1) with atropine-like properties (dry mouth, disturbance of accommodation, tachycardia, constipation, delayed diuresis). There may be phenomena: 2) orthostatic hypotension, collapse. With an overdose, tachycardia, arrhythmias. From the side of the psyche there can also be undesirable effects: either excessive sedation, or agitation, hallucinations, insomnia.

There may be a headache, allergic reactions, tremors, jaundice, leukemia.

The drug is contraindicated in glaucoma, with prostate adenoma. It can not be used together with MAO inhibitors.

AMITRIPTILIN (Amitriptylinum; in the table. At 0, 025; in amp. 1% solution of 2 ml) - the pharmacodynamics and pharmacokinetics are similar to imizine.

Along with the high antidepressant activity, amitriptyline also has psycho-sedative properties. He has no stimulating effect. It is superior to imizin in M-anticholinergic and anti-histamine action.

Amitriptyline is the most active antidepressant. Its therapeutic effect is detected after 10-14 days.

Side effects: constipation, tremors, muscle stiffness, dry mouth.

The second group of drugs INHIBITORS - MAO (IMAO - nialamide). Currently they are used quite rarely due to high hepatotoxicity. Therefore, when choosing, preference is given to antidepressants of the tricyclic series. But sometimes IMAO are also useful.

The mechanism of action of MAOI is due to the fact that these drugs inhibit the process of oxidative deamination of norepinephrine and serotonin, which leads to the accumulation of the latter in the brain tissue in significant quantities. Most drugs in this group block MAO irreversibly. Therefore, to restore MAO, it must be synthesized anew, which requires a certain time (up to 2 weeks).

Although the maximum effect of inhibition of MAO occurs within a few hours after absorption of MAO inhibitors, the antidepressant effect develops only after 7-14 days. It is possible that the influence of MAO inhibitors on the metabolism of aminobutyric acid may play a role.

PHARMACOLOGICAL EFFECTS

Along with antidepressant activity, MAO inhibitors are characterized by pronounced psychostimulant properties (euphoria, agitation, insomnia).

MAO inhibitors have hypotensive activity, which is associated with inhibition of the release of norepinephrine from the presynaptic ends of adrenergic fibers. Reduce pain with angina (block of the central links of the reflex paths from the heart).

Absorbed from the gastrointestinal tract well, eliminated by the kidneys.

SIDE EFFECTS

The drugs are relatively toxic. This is manifested mainly by the hepatotoxic effect (severe hepatitis). In addition, they stimulate the central nervous system (insomnia, euphoria, convulsions).

Antidepressants are widely used in the treatment of patients with the depressive phase of manic-depressive psychosis, as well as with neurotic and reactive depressions. Used in child psychiatry to correct the behavior of children in case of their mental underdevelopment, as well as for the treatment of enuresis.

There is the possibility of developing orthostatic collapse. It is necessary to carefully use them together with other neurotropic drugs (narcotic analgesics, indirect action adrenomimetics, antidepressants of the tricyclic series).

It is necessary to exclude foods containing tyrazine (cheese) from the patient's diet.

As MAO inhibitors, a large number of hydrazine derivatives were synthesized. But at present, few are used, in particular, NIALAMID. This is one of the least effective antidepressants (effect after 12-14 days). But low toxicity, which is its advantage. Of the non-hydrazine IMAO - TRANSAMINE (a strong MAO inhibitor - effect after 7-9 days). These drugs are contraindicated in diseases of the liver, kidneys, impaired cerebral circulation, with mental arousal.

Another group of drugs, recently the increasingly popular serotonin reuptake inhibitors - fluoxetine

CENTRAL NERVOUS SYSTEM STIMULANTS

Stimulants are conditionally divided into 4 large groups:

1. PSYCHOSTIMULATORS

a) psychomotor:

- caffeine; phenamine; Sydnocarb.

b) psychometabolic (nootropics):

- nootropil (piracetam); cerebrolysin; gamalon and others

2. ANALEPTICS

a) direct action:

- bemegrid; etimizol and others.

b) reflex action:

- cititon, etc.

c) mixed action:

- cordiamine and others.

3. SPINAL STIMULANTS

- strychnine;

- sekurenin and others.

4. GENERAL TONING AGENTS (ADAPTOGENS)

a) of plant origin: preparations of ginseng, eleutherococcus, aralia, golden root, maral's root, Bittner's balm, etc.

b) animal origin: pantocrine, etc.

PSYCHOSTIMULANTS and NOOTROPES

PSYCHOSTIMULATORS

Psychostimulants (or psychotonics, psychoanaleptics, psychomotor stimulants) increase mood, the ability to perceive external irritations, and psychomotor activity. They reduce the feeling of fatigue, increase physical and mental performance (especially when tired), temporarily but reduce the need for sleep (drugs that invigorate the tired body, called doping - from the English to dope - give drugs).

In contrast to drugs that depress the central nervous system, stimulants are less important, since they lack the selectivity of action. In addition, the stimulation of the central nervous system is accompanied by its subsequent inhibition.

CLASSIFICATION OF PSYCHOSTIMULATORS

1) Funds acting directly on the central nervous system:

a) stimulating mainly the cerebral cortex (xanthine alkaloids, phenamine, sydnocarb, methylphenamine, meridol, etc.);

b) stimulating mainly the medulla oblongata (corazole, cor-diamine, bemegrid, camphor, carbon dioxide);

c) stimulating mainly the spinal cord (strychnine).

2) Funds acting on the central nervous system reflexively (lobelin, veratrum, ni-cotin).

It should be remembered that such a division is conditional and when used in high doses, they can stimulate the central nervous system as a whole.

A typical representative of psychostimulants is Phenamine (amphetamine sulfate; tab. At 0, 005; drops in the nose, in the eye 1% solution). Chemically represents phenylalkylamine, that is, it is similar in structure to adrenaline and norepinephrine.

MECHANISM OF ACTION is associated with the ability to release NORADRENALINE and DOPAMINE from presynaptic endings. In addition, phenamine reduces the reuptake of norepinephrine and dopamine.

Phenamine stimulates the ascending activating reticular formation of the brain stem.

PHARMACOLOGICAL EFFECTS

CNS INFLUENCE

Powerful stimulator of the central nervous system. It increases mental and physical performance, improves mood, causes euphoria, insomnia, tremor, anxiety. In therapeutic doses, it has an awakening effect, eliminates fatigue, and increases physical capabilities. It stimulates the respiratory center and in this regard acts as an analeptic.

INFLUENCE ON THE CARDIOVASCULAR SYSTEM

Increases both systolic and diastolic blood pressure. In relation to the hypertensive effect of phenamine, tachyphylaxis is known.

SMOOTH MUSCULAR

Phenamine increases the tone of the sphincter of the bladder and relaxes the musculature of the bronchi, but only at high doses. Phenamine reduces appetite (on gi-potalamus), has some anticonvulsant effect (with Petit mal).

ADVERSE REACTIONS

An undesirable effect is the stimulation of the sympathetic nervous system (tachycardia, anxiety, headache, tremor, agitation, confusion, paranoid psychosis, angina attacks).

The drug causes drug dependence, mainly mental, cumulates. Tolerance may develop.

INDICATIONS FOR USE:

1) neurotic subdepression;

2) with narcolepsy, with catalepsy, to prevent pathological drowsiness (narcolepsy);

3) obesity;

4) as an analeptic for poisoning with narcotic analgesics.

Pyridrol and Meridol are similar to phenamine. They have no unwanted peripheral adrenomimetic effects.

In addition to phenamine, the active psychostimulant sydnocarb (mesocarb) also belongs to the group of phenylalkylsindononymonyms. This is an original domestic drug, slightly different in chemical structure from phenamine. In Russian clinics, Sydnocarb is currently the main psychostimulant. Compared with phenamine, it is significantly less toxic and does not show a pronounced peripheral sympathomimetic effect. The psychostimulating effect develops gradually, but it is longer, not accompanied by euphoria and motor excitement. As a rule, there is no tachycardia and a sharp increase in blood pressure. After the action of the drug, the patient does not experience general weakness and drowsiness. The drug is used for various types of asthenia, occurring with lethargy and lethargy, with apathy, decreased performance, hypochondria, and increased drowsiness.

The drug is used as a psychostimulant for asthenic and neurasthenic disorders in patients who have experienced intoxication, infection and brain injury, in some forms of psychosis.

In addition, sydnocarb is used for the relief of asthenic manifestations after the use of antipsychotics, tranquilizers, as well as in the treatment of patients with alcoholism (relief of asthenoneurotic reactions during the period of "withdrawal of alcohol", to reduce the phenomenon of withdrawal symptoms).

Sydnocarb is also used in the treatment of children with oligophrenia, accompanied by adynamia, spontaneity, lethargy, lethargy, asthenia.

Side effects. In case of an overdose, increased irritability, anxiety, loss of appetite are possible. In patients with psychosis, increased delirium and hallucinations are possible. A moderate rise in blood pressure is sometimes noted.

The drug is available in tablets at 0, 005; 0,01; 0, 025.

The industry also produces the combined preparation Sid-Nogluton, containing 0, 025 sydnocarb and 0, 1 glutamic acid. The latter potentiates the psychostimulating effect of sydnocarb.

Xanthine alkaloids (purine derivatives; metalxanthines), of which CAFEIN is a typical representative, also belong to agents stimulating mainly the cerebral cortex.

Xanthine alkaloids are found in several plants growing around the world. Three natural xanthine alkaloids were found in these plants: caffeine, theobromine, theophylline, which are purine bases. When heated with nitric acid, they form a yellow precipitate, from where the term xanthines originated (Greek - xanthos - yellow). Caffeine is found in tea leaves (Thea sinensis - 2%), in coffee seeds (Coffea arabica - 1-2%), in cocoa seeds (Theobroma acuminata), etc.

PHARMACOLOGICAL EFFECTS

Caffeine has the most pronounced effect on the central nervous system, followed by theophylline and theobromine. The effect of caffeine on higher nervous activity depends on the dose and type of nervous system. In small doses, caffeine increases the activity of the cortex, in large doses it inhibits it. In small doses, it helps to accelerate the thinking process and makes it clearer, brings clarity to thoughts, reduces drowsiness, fatigue and gives the ability to perform intellectually complex tasks. It reduces the reaction time, increases motor activity and fixes conditioned reflexes. These effects can be observed after 1-2 cups of coffee. One cup contains about 1,500 mg of caffeine.

Higher doses cause increased irritability, confusion, insomnia, headache, tremor. Theophylline in large doses can even cause cramps.

MEDULLA

High doses directly stimulate the respiratory, vasomotor centers and the center of the vagus nerve. This leads to increased breathing (rapid and aggravated), increased blood pressure, tachycardia. True, in large doses, tachy-cardia and arrhythmias occur, that is, its peripheral effect predominates (cardiac output increases).

SPINAL CORD

Very large doses increase the reflex excitability of the spinal cord and can lead to clonic seizures.

BLOOD VESSELS

Xanthines act on myotropic blood vessels, but this is a vasodilating effect for a short time. It cannot be used to treat peripheral vascular disease.

Xanthines have an ambiguous effect on various vascular regions. The latter helps with migraines. Caffeine has a weak myotropic antispasmodic effect on smooth muscle organs (bronchi, bile ducts). This is of great importance for the clinic. It has long been known that theophylline eliminates bronchospasm during anaphylactic shock, stimulates skeletal muscles, increases metabolism in them, and eliminates their fatigue.

Caffeine boosts CORE. Increases glycogenolysis, causing hyperglycemia. Increases lipolysis, releases adrenaline from the adrenal medulla.

DIURESIS

Xanthines increase diuresis. The strongest in this regard is theo-phyllin, then theobromine and caffeine.

Xanthines increase the volume, acidity and pepsin content in the gastric juice.

MECHANISM OF ACTION is associated with two directions:

1) xanthines inhibit cyclic nucleotide phosphodiesterase and prevent the transition of cAMP to 5-AMP;

2) cause changes in the distribution of calcium at the level of intracellular processes.

ADVERSE REACTIONS

1) Confusion, tremor, headache, insomnia. Tinnitus, headache, tachycardia, shortness of breath, arrhythmias. With these reactions, sedatives should be prescribed.

2) Ksptntiny rotiv is indicated for patients with peptic ulcer and gastritis.

3) Addiction develops to xanthines, to a greater extent - mental dependence, which, however, is not dangerous.

INDICATIONS FOR USE

To stimulate mental activity. With fatigue, in the presence of symptoms of asthenia, with migraine, hypotension. With distraction, impaired attention, exhaustion.

Caffeine is part of many combination drugs with non-narcotic and narcotic analgesics: citramon, panadol extra, solpadein, as well as ergot alkaloids - the drug cofetamine.

NOOTROPES, NOOTROPIC MEANS

The term is derived from the Greek - noos - thinking, tropos - aspiration, affinity. Means that have a special effect on the higher integrative functions of the brain, stimulate memory, learning, improve mental activity.

Improving mental, mental activity is the main effect of this group of drugs. This is manifested with mental deficiency associated with organic brain lesions.

The mechanisms of action of nootropic drugs at the neurophysiological level: the effect on transcanal and other types of polysynaptic evoked potentials recorded on the EEG.

The direction of action of nootropic drugs indicates their pronounced effect on the integrative activity of the brain and the processes of information transfer in the brain. Probably, under the influence of nootropics, the tetta-rhythm sets in various brain formations and information transfer processes in the brain. At the heart of the ability of nootropic drugs to improve learning processes and memory lies the process of increasing the level of spatial synchronization of the bio-potentials of the brain.

It should be noted that these drugs do not affect the higher nervous system of healthy animals and the psyche of a healthy person. They normally do not change many behavioral reactions, conditioned reflexes, bioelectrical activity of the brain, and motor activity.

The pharmacotherapeutic effect of nootropics at the molecular level under pathological conditions is based on a beneficial effect on neurometabolism and brain energy. Therefore, this group of drugs is also called psychome tabolic stimulants. The main nootropic drugs used in practice mimic the metabolic effects of β-aminobutyric acid (GABA).

The first drug synthesized abroad in the late 60s in the research laboratory of UCB (Belgium) was named NOOTROPIL. In our country there is an analogue - PIRACETAM (Piracetamum; in the table for 0, 2; in amp. 20% solution of 5 ml; capsules - 0, 4). It is a classic nootropic drug, therefore it is used most often by doctors of various specialties.

PHARMACOLOGICAL EFFECTS

Piracetam (nootropil) is a cyclic derivative of GABA. Nootropics improve the metabolism of brain cells and, above all, the metabolism of glucose and oxygen in them, increase the resistance of cells to hypoxia, improve blood supply to the brain, and the connection between the hemispheres. Nootropics increase memory, reduce fatigue. But the effects are manifested gradually, not immediately after administration. Piracetam has anticonvulsant activity, and in recent years its immunomodulating effects and immunopotentiating effects have also been described.

INDICATIONS FOR USE:

- in conditions after a concussion;

- in children with mental retardation, with varying degrees of oligophrenia; in children with impaired memory, attention, speech;

- old people, the elderly, in geriatrics to improve memory, mood;

- in chronic treatment of drug addicts, alcoholics;

- in patients after a stroke;

- Nootropics are indicated for enuresis in young children.

In addition, they are prescribed to potentiate the effects of immunostimulants.

AMINALON is a GABA preparation. Receive synthetically. GABA is a inhibitory neurotransmitter that plays an important role in the metabolic processes of nervous tissue. The drug stimulates tissue respiration, activates the enzymes of the Krebs cycle, improves the utilization of glucose by neurons.

Indications for use: vascular diseases of the brain, mental retardation in children.

Side effects of nootropics: brain stimulation can lead to irritation, sleep disturbance, dyspnea, anxiety in children, increased blood pressure, sexual excitability. Therefore, they are used in courses (2-3 weeks each).

In recent years, the group of nootropic drugs has expanded significantly. This is the Hungarian drug Cavinton (Gedeon Rihter), cerebrolysin, etc.

CAVINTON (tab. At 0, 005; amp. 0, 5% solution of 2 ml). Apovincamic acid ethyl ester (preparation of small periwinkle alkaloid).

Cavinton has the following effects:

1)dilates the vessels of the brain;
2) enhances cerebral blood flow, improves blood supply to the brain with an oxygen-home;
3) improves glucose utilization by neurons, promotes the accumulation of cAMP, ATP;
4) reduces platelet aggregation;
5) increases the content of catecholamines in the central nervous system.

It is used primarily in neurology for:

1) neurological and mental disorders associated with cerebrovascular accidents (stroke, trauma, sclerosis);
2) memory disorders;
3) dizziness;
4) aphasia;
5) hypertensive encephalopathy;
6) atherosclerosis of the retinal vessels, i.e. in ophthalmology, etc.
7) hearing impairment of toxic origin.

ANALEPTIC MEANS (ANALEPTICS)

By analeptic drugs (from the Greek analeptikos - restorative, firming) is meant a group of drugs that excite primarily the vital centers of the medulla oblongata - vascular and respiratory. In large doses, these drugs can excite the motor zones of the brain and cause seizures.

In therapeutic doses, analeptics are used for weakening vascular tone, for respiratory depression, for infectious diseases, in the postoperative period, etc.

Currently, the group of analeptics for localization of action can be divided into three subgroups:

1) Preparations directly, directly activating (revitalizing) the respiratory center:
- bemegrid; etimizol.
2) Means reflexively stimulating the center of respiration:
- cititon; lobelin.
3) Means of a mixed type of action, with both direct and reflective action:
- cordiamine; camphor; corazole; carbon dioxide.

Bemegrid (Bemegridum; in ampoules of 10 ml of a 0.5% solution) is a specific antagonist of barbiturates and has a “revitalizing” effect in case of intoxication caused by drugs of this group. The drug reduces the toxicity of barbiturates, relieves respiratory depression and blood circulation. The drug also stimulates the central nervous system, therefore it is effective not only for poisoning with barbiturates.

Bemegrid is used for acute poisoning with barbiturates, to restore breathing at the exit from anesthesia (ether, fluorotan, etc.), to remove the patient from a severe hypoxic state. The drug is administered intravenously, slowly until breathing, blood pressure, and pulse are restored.

Side effects: nausea, vomiting, cramps.

Among the direct-acting analeptics, the drug etimizol occupies a special place.

Etimizol (Aethimizolum; in the table. At 0, 1; in amp. At 3 and 5 ml of a 1% solution). The drug activates the reticular formation of the brain stem, increases the activity of neurons of the respiratory center, enhances the adrenocorticotropic function of the pituitary gland. The latter leads to the release of additional portions of glucocorticoid. At the same time, the drug differs from bemegrid in its mild inhibitory effect on the cerebral cortex (sedative effect), improves short-term memory, promotes mental work. Due to the fact that the drug promotes the release of glucocorticoid hormones, it again has an anti-inflammatory effect.

Indications for use. Etymizole is used as an analeptic, a respiratory stimulant for poisoning with morphine, non-narcotic analgesics, in the recovery period after anesthesia, with lung atelectasis. In psychiatry, its sedative effect is used in anxiety states. Given its anti-inflammatory effect, it is prescribed for the treatment of patients with polyarthritis and bronchial asthma, as well as an anti-allergic agent.

Side effects: nausea, dyspepsia.

Reflexively acting stimulants are H-cholinomimetics. These are cititon and lobelin drugs. They excite H-cholinergic receptors of the synocarotid zone, from where afferent impulses enter the medulla oblongata, thereby increasing the activity of neurons of the respiratory center. These funds act briefly, for several minutes. Clinically, there is an increase and deepening of breathing, an increase in blood pressure. Drugs are administered only intravenously. Use for the only indication - in case of carbon monoxide poisoning.

For agents of a mixed type of action, the central effect (direct excitation of the respiratory center) is supplemented by a stimulating effect on the chemoreceptors of the carotid glomerulus (reflex component). It is, as indicated above, cordiamine and carbon dioxide. In medical practice, carbogen is used: a mixture of gases - carbon dioxide (5-7%) and oxygen (93-95%). Assign in the form of inhalations, which increase the volume of respiration by 5-8 times.

Carbogen is used for overdose of general anesthetics, carbon monoxide poisoning, and asphyxiation of newborns.

As a respiratory stimulant, the drug Cordiaminum is used - a non-ogalene drug (prescribed as an official but 25% nicotinic acid diethylamide solution). The action of the drug is realized by stimulation of the respiratory and vasomotor centers.

Assign with heart failure, with shock, asphyxiation, intoxication.

DRUGS STIMULATING MOSTLY FUNCTIONS OF THE SPINAL CORD

In this group, two drugs are essentially used: strychnine and securinine.

Strychninum (Strichninum; powder; in ampoules of 1 ml of 0, 1% solution) is the main alkoloid of chilibuha seeds (vomit).

In medical practice, nitrate salt is used - strychnine nitrate.

In addition to strychnine, dry chilibuha extract and tincture of chibuha are also used.

Strychnine cramps

Strychnine and other chilibuha preparations excite the central nervous system and, first of all, increase reflex excitability. The patient's reflex reactions become more generalized. Strychnine improves the activity of the senses (vision, taste, hearing, tactile feeling), excites the vasomotor and respiratory centers, tones the skeletal muscles, myocardium.

Strychnine preparations are used as tonic agents with a general decrease in metabolic processes, rapid fatigability, and hypotension. weakening of cardiac activity due to intoxication and infections, with some functional disorders of the visual apparatus, with paresis and paralysis (diphtheria origin, for example), with atony of the stomach.

Side effects occur with an overdose and are manifested by tension of muscle groups (facial, occipital), shortness of breath, convulsions.

The preparation of securinin, obtained from the grass of securengi, is similar in nature to strychnine by the nature of its action, but less active (10 times). Used for asthenic conditions, paresis and paralysis, with hypo- and asthenic forms of neurasthenia, with impotence due to functional disorders.

GENERAL TONING AGENTS (ADAPTOGENS)

Preparations of this group by origin can be divided into means of plant and animal nature. More often, herbal remedies are used, namely various galenic preparations of plants (extracts of ginseng

root, extracts of leuzea, Rhodiola rosea or gold root, Eleutherococcus, tinctures of zamaniha, magnolia vine, Scutellaria zabaikalsky, Aralia). Of animal origin, we can name the drug pantocrine, obtained from antler reindeer, and produced as a neogalenic drug for oral (in drops) and parenteral administration.

The pharmacological effect of these drugs is due to the content of salinic glycosides-ginsenoids, essential oils, sterols, peptides and minerals in them. These biologically active substances bring a stimulating effect on the central nervous system, increase efficiency, regulate the functioning of the endocrine glands, moderate blood pressure, the level of atherogenic lipids (cholesterol) and glucose in the blood, activate the adrenal glands, the use of these drugs leads to reducing the incidence of acute respiratory infections, increasing the patient's resistance to viral and other infections, improving well-being and appetite.

These drugs are indicated for mental and physical stress during convalescence after prolonged and severe illnesses, in particular of an infectious nature (dysentery, typhoid and viral infections, etc.). Drugs are also prescribed for cancer patients in the rehabilitation period, after chemotherapy courses and radiation exposure.

As a rule, drugs are prescribed for a long time, within 1-2 months. Taking adaptogens is advisable in the morning, after breakfast. The appointment of these funds in the afternoon is not shown, because sleep disturbance in the form of difficulty in falling asleep is possible. In individuals, a manifestation of increased sensitivity to certain drugs is possible.

Anesthesia is a condition characterized by reversible general depression of the central nervous system, manifested by loss of consciousness, suppression of sensitivity (primarily pain), reflex reactions, muscle tone while maintaining vital functions (respiration, blood circulation, metabolism).

MECHANISMS OF ACTION for anesthesia are associated with the fact that they inhibit the interneuron (synaptic) transmission of excitation to the central nervous system. There is a violation of the transmission of afferent impulses, a change in cortical-subcortical relationships. Emerging functional disintegration of the central nervous system associated with impaired synaptic transmission causes the development of anesthesia.

The sequence of action of drugs for anesthesia on the central nervous system is as follows:

- cerebral cortex (consciousness);
- spinal cord (skeletal muscle);
- the medulla oblongata (vital centers - respiration, blood circulation).

Synaptic formations of different levels of the central nervous system and various morphofunctional organizations have unequal sensitivity to drugs for anesthesia. For example, synapses of the activating reticular formation of the trunk the brain are especially highly sensitive to drugs for anesthesia, while synapses of the centers of the medulla oblongata are most resistant to them. The difference in the sensitivity of synapses of different levels of the central nervous system explains the presence of certain stages in the action of general anesthetics.

SPECIFY THE CERTAIN STAGES OF ANNEASIS that are observed when using most drugs for anesthesia.

1st stage of analgesia, stunning, rush anesthesia. Analgesia - loss of pain sensitivity. From Greek. "an" is negation, algos is pain. The stage of analgesia begins from the moment the inhalation begins (if this is the route of administration) of the drug and continues until the patient loses consciousness. Thus, consciousness has been preserved in this stage. Sensitivity is reduced, reflexes and muscle tone are preserved. Only superficial operations are possible at this stage: opening a panaritium, abscess, tooth extraction, some obstetric operations (interventions).

2nd stage - the stage of excitation (delirium). It begins with loss of consciousness to a state of surgical anesthesia. At this stage, excitement, screaming, increased muscle activity, respiratory arrest, tachypnea, hyperventilation can be observed. Consciousness is absent, reflexes and tone are all intensified, (removal of inhibitory function of the cerebral cortex is observed).

Undesirable effects of this stage (motor excitement, increased skeletal muscle tone, vomiting) can be minimized by proper premedication.

Stage 3 - stage of surgical anesthesia. There are 4 levels of this stage: first - superficial; 2nd - easy; 3rd — deep; 4th — super deep surgical anesthesia. As the dose of the drug increases, anesthesia

deepens more and more. Anesthesia during extensive surgery is carried out at levels 2-3 of the 3rd stage. This stage is characterized by a gradual loss of reflexes, rhythmic breathing and relaxation of skeletal muscles. Reflexes are lost. Almost the loss of reflex from the eyelids and the development of rhythmic breathing indicates the onset of surgical anesthesia. Finally, the 4th stage is the stage of paralysis or the agonal stage. It is characterized by pronounced inhibition of the centers of the medulla oblongata. Complete paralysis of the respiratory muscles and diaphragm gradually develops, breathing stops, which is accompanied by a vasomotor collapse, - the heartbeats cease.

CLASSIFICATION OF MEDICINES FOR ANNESTHESIS

From the point of view of practical use of drugs for anesthesia are divided into 2 large groups:

1) funds for inhalation (through the lungs) anesthesia;

2) funds for non-inhalation anesthesia.

In turn, inhalation drugs for anesthesia are divided into:

- inhaled volatile liquids, ether for anesthesia, fluoro-tan are included here;
- gaseous agents for anesthesia - nitrous oxide, cyclopropane.

Means for non-inhalation anesthesia include: thiopental sodium, sodium hydroxybutyrate, ketamine, propanidide, diprivan.

We will analyze one of the main funds from the group of inhalation fluids - ether for anesthesia (Aether pro narcosi - a bottle of 100 ml and 150 ml).

The first inhaled general anesthetic - nitrous oxide - was discovered by Priestley in 1776, which accurately described its effects. In 1846, Morton proved the use of nitrous oxide for general anesthesia and demonstrated surgery under general anesthesia (USA). In 1847, N.I. Pirogov widely used ether anesthesia in surgical practice. By chemical structure it is diethyl ether. It is a colorless volatile liquid with a pungent odor and boiling point at t = 35 degrees. Ether for anesthesia has a pronounced activity, a sufficient breadth of therapeutic effects, relatively low toxicity. This is one of the safest means for anesthesia. It is an excellent general anesthetic with a wide breadth of action.

Advantages of the drug as a general anesthetic:

1) The ether for anesthesia has a pronounced activity, being a fairly strong means for anesthesia. When using ether, the stages of anesthesia are clearly expressed. The stage of analgesia is characterized by suppression of pain sensitivity, which is associated with inhibition of interneuronal transmission of excitation in afferent pathways and a decrease in the functional activity of neurons in the cerebral cortex; consciousness is preserved, orientation is disturbed. Being an excellent general anesthetic, it allows for some surgical procedures even when using concentrations that do not give complete surgical anesthesia (dislocation, reduction, delivery, etc.).

2) Ether for anesthesia provides deep analgesia. Causes surgical anesthesia without premedication.

3) The ether for anesthesia causes good muscle relaxation at the stage of surgical anesthesia, which facilitates the operation. Muscle relaxation is associated not only with the influence of the ether on the central mechanisms of regulation of muscle tone, but also with some inhibitory effect on the neuromuscular structure. Causing a curative effect on skeletal muscle, it provides sufficient muscle relaxation.

4) Having significant activity, ether, however, has a great breadth of action. It follows that ether is relatively safe for anesthesia even when used by inexperienced specialists.

5) Under the influence of ether, blood pressure does not change at levels 1 and 2 of surgical anesthesia and the myocardium is not sensitized to adrenaline, and therefore the drug does not provoke heart rhythm disturbances.

6) Slightly, in comparison with other general anesthetics, depresses breathing.

7) The ether lacks pronounced hepato- and nephrotoxicity.

8) Ether does not require the use of sophisticated equipment (mask anesthesia).

9) Economically, ether is a cheap anesthetic.

DISADVANTAGES OF ETHER AS A MEANS FOR ANNESTHESIS

1) For ether anesthesia, a prolonged stage of arousal is characteristic (up to 20-30 minutes). Anesthesia under its influence occurs slowly and is sometimes accompanied by strong excitement and increased motor activity.

2) Unpleasant entry, namely asphyxiation, an irritating odor increase salivation and secretion of the bronchial mucosa, which is accompanied by coughing and laryngospasm, and vomiting. There may even be reflex respiratory arrest, and the possibility of sensitization of baroreceptors during ether anesthesia sometimes leads to reflex cardiac arrest.
3) After operations under ether anesthesia, atelectasis and pneumonia (irritation, cooling of the lungs, dissolution of surfactant) may develop.
4) By activating the central links of the sympathoadrenal system and releasing adrenaline, it increases the heart rate (tachycardia).
5) Reflexively stimulated by n. vagus, which, in addition to cardiac arrest, can reduce the motor activity of the gastrointestinal tract.
6) Slow exit (awakening) from anesthesia. Persons with alcoholism have an ether tolerance, as a result of which anesthesia can be difficult.
7) The drug is unstable in the light, therefore it is stored in dark glass; explosive.

INDICATIONS FOR USE:

1) mononarcosis during operations on the organs of the abdominal cavity;

2) mixed anesthesia (anesthesia with a mixture: ether plus fluorotan);

3) combined anesthesia (induction anesthesia plus ether, plus muscle relaxant plus analgesics).

FLUOROTANE (Phthorothanum) in orange flasks of 50 ml each.

ADVANTAGES:

1) high activity as a general anesthetic (3-4 times more ether) ensures the achievement of the surgical stage of anesthesia;

2) anesthesia occurs quickly (3-5 minutes), with a short stage of arousal, which is weakly expressed;

3) anesthesia is easily controllable;

4) waking up the patient after 5-10 minutes;

5) a significant breadth of action of fluorotan;

6) satisfactory muscle relaxation;

7) does not irritate the mucous membranes;

8) inhibits the function of salivary, bronchial, gastric glands; relax the tone of the bronchi.

DISADVANTAGES: stimulates n. vagus, causes bradycardia (need atro-pin). Special equipment required. Blood pressure reduces (inhibits the vasomotor center and sympathetic ganglia. It increases bleeding and also directly affects myotropes in blood vessels. It causes cardiac arrhythmias, as it sensitizes the myocardium to adrenaline (noradrenaline, adrenaline, ephedrine, i.e., catecholamines cannot be administered; need a mesatone - alpha-adrenergic agonist.) In the postoperative period, it causes chills.

INDICATIONS FOR USE:

1) mononarcosis during operations on the organs of the chest and bronchial cavities;

2) combined anesthesia;

3) mixed anesthesia.

GAS PRODUCTS

Nitrous oxide, cyclopropane are related.

NITROGEN ACID (laughing gas) - practically non-toxic, does not have irritating properties. It has no negative effect on parenchymal organs. There are practically no side effects.

There is essentially one drawback - low activity. It causes anesthesia, a surgical stage, only in concentrations of 94-95 percent in inhaled air. It is impossible to use such concentrations (hypoxia develops). In practical anesthesiology, therefore, a mixture of 80 percent nitrous oxide and 20 percent oxygen is used. There is no necessary depth of anesthesia, there is no sufficient muscle relaxation. Only the initial level of the stage of surgical anesthesia is achieved. Therefore, nitrous oxide is combined with other drugs, for example fluorotane, thereby obtaining an azeotropic mixture (inseparably boiling mixture), as well as muscle relaxants. Rapid awakening is noted.

INDICATIONS FOR USE:

1) pure nitrous oxide gas is prescribed for rush anesthesia, i.e. for anesthesia at the stages of transportation (hip fracture, myocardial infarction, autopsy abscesses);

2) and in combination with fluorotan, as the main anesthesia for various extensive operations, with the addition of muscle relaxants for combined narcosis (nitrous oxide plus fluorotan plus muscle relaxant);

3) labor pain relief;

4) induction anesthesia.

CYCLOPROPANE is a colorless gas with a sweet smell and taste; chemically, it is trimethylene. Higher than nitrous oxide activity, deep anesthesia (20-25 percent in inhaled air). Fast entry (3-5 minutes), without stage of arousal. Does not affect the function of the liver and kidneys, causes pronounced muscle relaxation. Used for large surgical interventions on the chest and abdominal cavities. Can be used with artificial respiration. With cesarean section. It is used for induction anesthesia, combined, as well as for pain relief for short-term interventions. The main disadvantage is a cardiotropic effect leading to arrhythmias (bradycardia, ventricular extrapithelium), increased sensitization to myocardial adrenaline (anaprilin is necessary). It leads to a rise in blood pressure, promotes acidosis and hyperglycemia.

Means for non-inhalation anesthesia

These drugs are usually used parenterally, rarely - enteral. Most often, this is an intravenous route of administration.

The duration of action of drugs for intravenous anesthesia is classified:

1) short-term drugs (anesthesia duration up to 15 minutes) - propanidide (sombrevin), ketamine (ketalar, calypsol), propofol (di-privan);

2) average duration of action (duration of action - 20-50 minutes) - thiopental sodium, predion (viadryl);

3) long-acting (duration of action - 60 minutes or more) - sodium hydroxybutyrate.

1. PROPANIDID (epontol, sombrevin: in ampoules of 10 ml - 5% solution) a very rapid onset of anesthesia (after 30-40 seconds) without the stage of excitement. The stage of surgical anesthesia with a single injection of the drug into a vein lasts about 3 minutes, after another 2-3 minutes consciousness is restored. The short duration of the drug is due to its hydrolysis of cholinesterase blood plasma. If administered intravenously, it is possible to significantly increase the time of surgical anesthesia.

There are few side effects, most often these are allergic reactions. There is a moderate irritant effect, which is usually manifested by flushing and pain along the vein. Hyperventilation, slight tachycardia, slightly decreased blood pressure, muscle twitching may occur. Used for induction of anesthesia and short-term operations. It is convenient in outpatient practice, in dentistry (tooth extraction, acute pulpitis, especially if several teeth are dripped iv), for biopsy, reduction of dislocations, reposition of fragments, removal of sutures, during catheterization, bronchoscopy, etc.) .

2. KETAMIN (Ketaminum, vials of 10 ml, 20 ml (synonyms: ketalar, calypsol) - solutions are used for intravenous and intramuscular administration. Ketamine causes only general anesthesia and a mild hypnotic effect with partial loss of consciousness (state type neuroleptanalgesia). It is very important that ketamine does not develop surgical anesthesia. This condition is called “dissociative anesthesia.” It means that substances such as ketamine inhibit some formations of the central nervous system and do not affect others, that is, there is dissociation in them action.

Advantages:

1) a large breadth of therapeutic action;

2) rapid entry;

3) good analgesia.

With iv administration, the effect is caused after 30-60 seconds and lasts 5-10 minutes, and with iv muscle after 2-6 minutes and lasts 15-30 minutes.

There is no muscle relaxation, involuntary movements of the limbs can be observed. Pharyngeal, larynx, cough reflexes saved. Blood pressure rises, heart rate quickens. There may be hypersalivation, laryngospasm.

In the postoperative period, vivid but unpleasant dreams, psychomotor reactions, hallucinations are often not uncommon (it is necessary to administer a sibazon intravenously).

Apply for:

1) introduction to anesthesia (introductory);

2) for short-term painful manipulations (treatment of burn surfaces, cardiac catheterization and bronchoscopy), extraction of foreign bodies, in dentistry (pulpitis, opening phlegmon, etc.);

3) anesthesia in mass admission (IM);

4) combined (fluorotan plus muscle relaxants), during cesarean section.

Increases intraocular pressure, intracranial pressure.

DIPRIVAN (Diprivanum); international name - propofol. Aqueous isotonic white emulsion for intravenous administration, 0,01 in 1 ml. Means of ultra-short action.

Pharmacological effects: this is an ultra-short-acting anesthesia drug with a quick onset of effect (30 sec.) And a quick exit from narcosis.

Indications: a tool for induction of anesthesia, but also for maintenance (4-12 mg / kg / hour). It must be combined with analgesics (low analgesic activity).

Side effects:

1) hypotension;

2) temporary apnea;

3) upon exit from anesthesia - nausea, vomiting, headache, discoloration of urine, bronchospasm;

4) thrombosis, phlebitis.

Contraindications: intolerance, epilepsy (cautiously!), In case of violation of the cardiovascular system, kidneys, liver. You can't mix with anything except dextrase and lidocaine.

3. THIOPENTAL-SODIUM - sleeping pills and narcotic effects. With the on / in the introduction causes anesthesia after about 1 minute without the stage of excitation. The duration of action - 20-30 minutes - is rapidly destroyed in the liver. Naka is absorbed in large quantities in adipose tissue, insufficient muscle relaxation.

Since the intravenous route of administration, there is little opportunity to affect the nature of the effect after administration, that is, such anesthesia is poorly managed. The drug has a small breadth of therapeutic effect, depresses respiration (barbiturate), weak anal getics, weak muscle relaxation. Disadvantages: muscle twitching, laryngospasm, arousal n. vagus, increased secretion of glands.

Thiopental sodium should be administered very slowly, as it may cause a sharp inhibition of the respiratory and vasomotor centers, as well as the heart (apnea, collapse).

Used for: 1) induction of anesthesia and 2) short-term surgical interventions (as an independent tool). Atropine premedication is necessary. Bemegrid is a thiopental antagonist.

4. Predion or Viadril - a steroid, but does not possess hormonal properties. Used for induction of anesthesia, since its activity is low. Anesthesia after 5-15 minutes without stage of excitation. Duration - 20-30 m

Good muscle relaxation. Non toxic The main side effect of predion is an irritating effect (vascular endothelial damage, thrombosis, thrombophlebit).

5. SODIUM OXYBUTIRATE - (in ampoules of 10 ml of a 20% solution) is a synthetic analogue of the natural central nervous system metabolite. GABA is a natural inhibitory mediator, and GABA, i.e. sodium hydroxybutyrate, is its analogue (instead of the amino group, there is a hydroxyl group). It has a sedative, hypnotic, antihypoxic effect and causes anesthesia. The surgical stage of anesthesia occurs 30-40 minutes after iv administration. Therefore, it is well used in the form of rectal suppositories. When combined with other drugs for anesthesia and analgesics (weak analgesic activity) increases their activity. Causes pronounced muscle relaxation. Its activity is insufficient, therefore, it is administered in large doses (2, 0-4, 0). The stage of surgical anesthesia occurs after 30-40 minutes. The duration of anesthesia is 1, 5-3 hours. It can be used enteral (oral and rectal). Used for induction and combined anesthesia, for labor pain relief, with hypoxic cerebral edema, as an anti-shock agent.

ANALGESICS (ANNOXY MEDICINES)

These agents selectively reduce, suppress pain sensitivity, without significantly affecting other types of sensitivity and without disturbing consciousness (analgesia - loss of pain sensitivity; an - denial, algos - pain). Since ancient times, doctors tried to relieve the patient from pain. Hippocrates 400 BC e. wrote: "... the removal of pain is divine labor." Based on the pharmacodynamics of the corresponding drugs, modern painkillers are subdivided into 2 large groups:

II - narcotic analgesics or a group of morphine. This group of funds is characterized by the following points (conditions):

1) have a strong analgesic activity, allowing them to be used as highly effective painkillers;

2) these drugs can cause addiction, that is, addiction, drug dependence associated with their particular influence on the central nervous system, as well as the development of a painful condition (withdrawal) in people with developed dependence;

3) in case of an overdose, the patient develops a deep sleep, turning sequentially into anesthesia, coma and, finally, ending with a stop of the respiratory center. Therefore, they got their name - narcotic analgesics.

The second group of drugs is non-narcotic analgesics, the classic representatives of which are: aspirin or acetylsalicylic acid. There are a lot of drugs, but all of them are not addictive, because they have other mechanisms of action.

We will analyze the 1st group of drugs, namely the drugs of the morphine group or narcotic analgesics.

Narcotic analgesics have a pronounced inhibitory effect on the central nervous system. Unlike drugs that depress the central nervous system indiscriminately, it manifests itself as an analgesic, moderately hypnotic, antitussive effect, depressing the respiratory centers. In addition, most narcotic analgesics cause drug (mental and physical) dependence.

The most prominent representative of this group of funds, because of which this group got its name, is MORFIN.

Morphini hydrochloridum (tab. 0, 01; amp. 1% - 1 ml). Alkoloid morphine is isolated from opium (Greek - opos - juice), which is a frozen, dried-up lump of unripe capsules of sleeping pills (Papaver somniferum). The birthplace of poppy is Asia Minor, China, India, Egypt. Morphine got its name from the name of the ancient Greek god of dreams Morpheus, who, according to legend, is the son of the god of sleep Hypnos.

Morphine in opium contains 10-11%, which is almost half the share of all alkaloids in it (20 alkaloids). They have been used in medicine for a long time (5000 years ago as: anesthetic, antidiarrheal agent). Despite the synthesis of morphine carried out by chemists in 1952, it is still obtained from opium, which is cheaper and easier.

According to the chemical structure, all pharmacologically active opium alkaloids are either derivatives of Phenanthrene or derivatives of Isohin-Lin. The phenanthrene series alkaloids include: morphine, codeine, thebaine, etc. It is phenanthrene alkaloids that are characterized by a pronounced inhibitory effect on the central nervous system (analgesic, antitussive, hypnotic, etc.).

Derivatives of isoquinoline are characterized by a direct antispasmodic effect on smooth muscles. A typical isoquinoline derivative is paverin, which does not have any effect on the central nervous system, but affects smooth muscle, especially in the state of spasm. Papaverine acts in this case as an antispasmodic.

PHARMACOLOGICAL PROPERTIES OF MORPHIN

1. The effect of morphine on the central nervous system

1) Morphine primarily has an analgesic or analgesic effect, while the analgesic effect is exerted by doses that do not significantly change the functions of the central nervous system.

The analgesia caused by morphine is not accompanied by blurry speech, impaired coordination of movements, and the sense of touch, vibration sensitivity, and hearing are not weakened. The analgesic effect is the main one for morphine. In modern medicine, this is one of the most powerful painkillers. The effect develops a few minutes after the injection. More often, morphine is administered in / m, s / c, but it is also possible in / in. The action lasts 4-6 hours.

As you know, pain consists of 2 components:

a) the perception of pain, depending on the threshold of pain sensitivity of a person;

b) mental, emotional reaction to pain.

In this regard, it is important that morphine dramatically inhibits both components of pain. Firstly, it increases the threshold of pain sensitivity, thus reducing the perception of pain. The analgesic effect of morphine is accompanied by a feeling of well-being (euphoria).

Secondly, morphine alters the emotional response to pain. In therapeutic doses, it may not even completely eliminate the sensation of pain, but patients perceive it as something extraneous.

How and how does morphine effect these effects?

MECHANISM OF ACTION OF DRUG ANALGETICS.

In 1975, Hughes and Kosterlitz in the nervous system in humans and animals discovered specific "opiate" receptors of several types, with which narcotic analgesics interact.

Currently, 5 types of these opiate receptors are distinguished: mu, delta, kappa, sigma, epsilon.

It is with these opiate receptors that various endogenous peptides (produced in the body itself) that have high analgesic activity normally interact. Endogenous peptides have a very high affinity for these opiate receptors. The latter, as it became known, are located and function in various parts of the central nervous system and in peripheral tissues. Due to the fact that endogenous peptides have a high affinity, they are also referred to in the literature as LIGANDS in relation to opiate receptors, that is (from Lat. - ligo - I bind) that directly bind to receptors.

There are several endogenous ligands, all of them are oligo-peptides containing a different amount of amino acids and are combined under the name EN-DORPHINS (that is, endogenous morphins). Peptides containing five amino acids are called enkephalins (methionine-enkephalin, lysine-enkephalin). Currently, this is a whole class of 10-15 substances that have from 5 to 31 amino acids in their molecules.

Enkephalin, according to Hughes, Kosterlitz - is a "substance in the head."

Pharmacological effects of enkephalins:

- release of pituitary hormones;

- memory change;

- regulation of respiration;

- modulation of the immune response;

- anesthesia;

- a condition similar to catatonia;

- convulsive seizures;

- regulation of body temperature;

- control of appetite;

- reproduction functions;

- sexual behavior;

- reactions to stress;

- decrease in blood pressure.

MAIN BIOLOGICAL EFFECTS OF ENDOGENOUS OPIATES

The main effect, role, and biological function of endorphins is the inhibition of the release of "neurotransmitters of pain" from the central ends of afferent non-myelinated C-fibers (including norepinephrine, and acetylcholine, dopamine).

As you know, these pain mediators can be, first of all, substance P (peptide from amino acids), cholecystokinin, somatostatin, bradykinin, serotonin, histamine, prostaglandin. Pain impulses propagate along C- and A-fibers (A-delta fibers) and enter the posterior horns of the spinal cord.

When pain occurs, a special system of enkephalinergic neurons is normally stimulated, the so-called antinociceptive (anti-pain) system, neuropeptides are released, which has a inhibitory effect on the pain system (nociceptive) of neurons. The end result of the action of endogenous peptides on opiate receptors is an increase in the threshold of pain sensitivity.

Endogenous peptides are very active, they are hundreds of times more active than morphine. Currently, they are isolated in pure form, but in very small quantities, they are very expensive, while they are mainly used in experiments. But there are already results in practice. Synthesized, for example, the domestic peptide DALARGIN. The first results were obtained, and already in the clinic.

In the case of an insufficiency of the antinoceptive system (antipainergic energynergic), and this happens with an overly pronounced or prolonged harmful effect, pain must be suppressed with the help of painkillers - analgesics. It turned out that the site of action of both endogenous peptides and exogenous narcotic drugs are the same structures, namely the opiate receptors of the nociceptive (pain) system. In this regard, morphine and its analogues are opiate receptor agonists. Individual endo- and exogenous morphins act on different opiate receptors.

In particular, morphine acts predominantly on mu receptors, enkephalins on delta receptors, etc. ("responsible" for pain relief, respiratory depression, reduction in the incidence of CVS, immobilization).

Thus, narcotic analgesics, in particular morphine, playing the role of endogenous opiate peptides, being essentially imitators of the action of endogenous ligands (endorphins and enkephalins), increase the activity of the antinociceptive system and increase its inhibitory effect on the pain system.

In addition to endorphins, serotonin and glycine, which are synergists of morphine, function in this antinociceptive system. Acting mainly on mu receptors, morphine and other drugs of this group mainly suppress aching, pulling pain associated with the summation of nociceptive impulses coming from the spinal cord along a non-specific path to the non-specific nuclei of the thalamus, disrupting its spread to the upper frontal, parietal gyrus of the cerebral cortex (that is, the perception of pain), as well as to its other departments, in particular, to the hypothalamus, the amygdala complex, in which the vegetative, hormonal, emotional reactions form for pain.

By suppressing this pain, drugs inhibit the emotional reaction to it, as a result of which narcotic analgesics prevent dysfunctions of the cardiovascular system, the appearance of fear, and suffering associated with pain. Strong analgesics (fentanyl) are able to suppress the excitation of a specific nociceptive pathway.

By exciting enkephalin (opiate) receptors in other structures of the brain, endorphins and narcotic analgesics affect sleep, vigilance, emotions, sexual behavior, convulsive and epileptic reactions, and

autonomic functions. It turned out that almost all known neurotransmitter systems are involved in the implementation of the effects of endorphins and morphine-like drugs.

Hence the various other pharmacological effects of morphine and its preparations. So, the 2nd effect of morphine, a calming and sleeping pill. The sedative effect of morphine is very clear. Morpheus is the son of the god of sleep. The sedative effect of morphine is the development of drowsiness, some darkening of consciousness, a violation of the ability of logical thinking. Patients are easily awakened from sleep caused by morphine. The combination of morphine with hypnotic or other sedatives makes CNS depression more pronounced.

3rd effect - the effect of morphine on mood. There is a twofold influence. In some patients, and more often in healthy individuals, after a single injection of morphine, there is a feeling of dysphoria, anxiety, negative emotions, there is no pleasure, a decrease in mood. As a rule, this occurs in healthy individuals who do not have indications for the use of morphine.

With the repeated administration of morphine, especially if there are indications for the use of morphine, the phenomenon of euphoria usually develops: an increase in mood with a feeling of bliss, lightness, positive emotions, and pleasantness throughout the body. Amid drowsiness, decreased physical activity, difficulty developing concentration of attention develops, a feeling of indifference to the surrounding world arises.

Man’s thoughts and judgments lose their logical sequence, imagination becomes fantastic, vivid colorful pictures, visions (world of dreams, “high”) arise. Lost the ability to engage in art, science, creativity.

The occurrence of these psychotropic effects is due to the fact that morphine, like other analgesics of this group, directly interact with opiate receptors localized in the cerebral cortex, hypothalamus, hippocampus, and amygdala complex.

The desire to experience this condition again is the cause of a person's mental dependence on the drug. Thus, it is euphoria that is responsible for the development of addiction. Euphoria can occur even after a single injection.

The 4th pharmacological effect of morphine is associated with its effect on the hypothalamus. Morphine inhibits the thermoregulation center, which can lead to a sharp decrease in body temperature during morphine poisoning. In addition, the effect of morphine on the hypothalamus is also related to the fact that, like all narcotic analgesics, it stimulates the release of antidiuretic hormone, which leads to urinary retention. In addition, it stimulates the release of prolactin and growth hormone, but delays the release of luteinizing hormone. Under the influence of morphine, appetite decreases.

The 5th effect - morphine, like all other drugs of this group, has a pronounced effect on the centers of the medulla oblongata. This action is ambiguous, since it excites a number of centers, and the series depresses.

Inhibition of the respiratory center most easily occurs in children. Oppression of the respiratory center is associated with a decrease in its sensitivity to carbon-gas.

Morphine inhibits the central links of the cough reflex and has a pronounced antitussive activity.

Narcotic analgesics, like morphine, can help stimulate neurons in the chemoreceptor trigger (trigger) zone of the IY ventricular fundus, causing nausea and vomiting. The vomiting center itself morphine in large doses inhibits, therefore, repeated administration of morphine does not cause vomiting. In this regard, the use of emetics for poisoning with morphine is useless.

The 6th effect is the effect of morphine and its preparations on blood vessels. Therapeutic doses have little effect on blood pressure and the heart; toxic doses can cause hypotension. But morphine causes

the expansion of peripheral blood vessels, especially capillaries, partly due to direct action and partly due to the release of histamine. Thus, it can cause redness of the skin, increase its temperature, swelling, itching, sweating.

INFLUENCE OF MORPHINE ON THE GIT AND OTHER SMOOTHMUSCULAR BODIES

The effect of narcotic analgesics (morphine) on the gastrointestinal tract is mainly attributed to their increased activity of center n neurons. vagus, and to a lesser extent due to a direct effect on the nerve elements of the wall of the gastrointestinal tract. In this regard, morphine causes a strong spasm of the smooth muscle of the intestines, imocecal and anal sphincters and at the same time reduces motor activity, reducing peristalsis (GIT). The spasmogenic effect of morphine is most pronounced in the area of the duodenum and large intestine. The secretion of saliva, hydrochloric acid of gastric juice and secretory activity of the intestinal mucosa are reduced. The passage of feces is slowed down, the absorption of water from them increases, which leads to gaps (morphine constipation - an increase in the tone of all 3 muscle groups). Morphine and its analogues increase the tone of the gallbladder, contribute to the development of spasm of the sphincter of Oddi. Therefore, although the analgesic effect eases the patient's condition with biliary colic, the course of the pathological process itself is exacerbated.

INFLUENCE OF MORPHINE ON OTHER SMOOTHMUSIC EDUCATIONS

Morphine increases the tone of the uterus and bladder, ureters, which is accompanied by "urinary haste." At the same time, the visceral sphincter is reduced, which, if there is insufficient reaction to urges from the bladder, leads to urinary retention.

Morphine increases the tone of the bronchi and bronchioles.

INDICATIONS FOR USE OF MORPHIN

1) Acute pain, threatening the development of pain shock. Examples: severe trauma (fractures of the tubular bones, burns), relief of the postoperative period. In this case, morphine is used as an anesthetic, anti-shock agent. For the same purpose, morphine is used for myocardial infarction, pulmonary embolism, acute pericarditis, spontaneous pneumothorax. To relieve the sudden onset of pain, morphine is administered iv, which quickly reduces the risk of shock.

In addition, morphine as an analgesic is used for colic, for example, intestinal, renal, hepatic, etc. However, it must be clearly remembered that in this case, morphine is administered together with the antispasmodic atropine, and only when the doctor is confident in the correctness of the diagnosis.

2) Chronic pain in hopeless dying patients with a human purpose (example: hospices - hospitals for hopeless cancer patients; reception by the hour). In fact, chronic pain is a contraindication to the use of morphine. Only in hopeless, dying tumor carriers, doomed, the introduction of morphine is mandatory.

3) As a means of sedation during anesthesia, before anesthesia, that is, in anesthesiology.

4) As an antitussive for coughing, which threatens the life of the patient. According to this indication, morphine is prescribed for example, with extensive operations, chest injuries.

5) In acute left ventricular failure, that is, with cardiac asthma. In this case, the effect is due to a decrease in the excitability of the central nervous system and pathological dyspnea. It causes the expansion of peripheral vessels, as a result of which there is a redistribution of blood from the pulmonary artery system to the expanded peripheral vessels. This is accompanied by a decrease in blood flow and a decrease in pressure in the pulmonary artery and CVP. Thus, the work of the heart is reduced.

6) In acute pulmonary edema.

SIDE EFFECTS OF MORPHIN

The wide range of pharmacological effects of morphine also determines its numerous adverse reactions. This is, first of all, dysphoria, constipation, dry mouth, blurred thinking, dizziness, nausea and vomiting, depression of breath, headache, fatigue, paresthesia, bradycardia. Sometimes intolerance in the form of tremors and delusions, as well as allergic reactions are found.

CONTRAINDICATIONS FOR USE OF MORPHIN

There are no absolute ones, but there is a whole group of relative contraindications:

1) early childhood (up to 3 years) - the risk of respiratory depression;

2) in pregnant women (especially at the end of pregnancy, during childbirth);

3) with a variety of types of respiratory failure (emphysema, with bronchial asthma, with kyphoscoliosis, obesity);

4) with severe head injuries (increased intracranial pressure; in this case, morphine increases the intracranial pressure even more, causes vomiting; vomiting, in turn, increases intracranial pressure and thus forms a vicious circle).

In our country, a very powerful analgesic with a long-lasting effect has been created on the basis of morphine - MORPHILONG. It is a new drug containing morphine hydrochloride and narrowly fractionated polyvinylpyrrolidone. Morphilong as a result acquires a longer duration of action (22-24 hours of its analgesic effect) and a greater intensity of the effect. Side effects are less pronounced. This is its advantage over morphine (4-6 times longer than the duration of morphine). Used as a painkiller prolonged funds:

1) in the postoperative period;

2) with a pronounced pain syndrome.

OMNOPON (Omnoponum in amp. 1 ml - 1% and 2% solution). Omnopon is a newgalenic opium preparation in the form of a mixture of 5 opium alkaloids. It contains 48-50% morphine and 32-35% of other alkaloids of both the phenanthrene and isoquinoline series (papaverine). In this regard, omnopon has a lesser spasmogenic effect. In principle, the pharmacodynamics of omnopon is similar to that of morphine. However, they use omnopon anyway with atropine. Indications for use are almost the same.

In addition to morphine, omnopon, many synthetic and semi-synthetic drugs have found application in medical practice. These drugs were created for 2 purposes:

1) to get rid of poppy plantations;

2) so that addiction is not formed in patients. But this goal did not succeed, since all narcotic analgesics have common mechanisms of action (via opiate receptors).

Of significant interest is PROMEDOL, which is a synthetic drug derived from piperidine.

Promedolum (tab. - 0, 025; amp. 1 ml - 1% and 2% solution). It is 2-4 times inferior to morphine in analgesic activity. Duration of action is 3-4 hours. Less likely to cause nausea and vomiting, to a lesser extent depresses the respiratory center. Unlike morphine, promedol reduces the tone of the ureters and bronchial tubes, relaxes the cervix, and slightly enhances uterine wall contractions. In this regard, promedol is preferred for colic. In addition, it can be used during childbirth (according to indications, since to a lesser extent than morphine, it inhibits fetal breathing, and also relaxes the cervix).

In 1978, a synthetic analgesic appeared - MORADOL, which is a phenanthrene derivative in chemical structure. A similar synthetic drug is TRAMAL. MORADOL (butorphanol tartrate) with IM and IV administration provides a high degree of analgesic effectiveness, while analgesia occurs faster than with morphine (after 30-60 minutes, morphine after 60 minutes). The action lasts 3-4 hours. At the same time, it has significantly fewer side effects and, most importantly, a very low risk of developing physical dependence even with prolonged use, since moradol rarely causes euphoria (it acts primarily on other opiate delta receptors). In addition, respiratory depression is limited, even in large doses. Use: for the same indications as morphine, but in the case of long-term need for use. In therapeutic doses, it does not inhibit the respiratory center, it is safe for the mother and fetus.

Another synthetic representative of piperidine-phenanthrene derivatives is FENTANIL. Fentanyl has a very high analgesic activity, surpasses morphine in activity (100-400 times). A distinctive feature of fentanyl is the short duration of the analgesia caused by it (20-30 minutes). The effect develops after 1-3 minutes. Therefore, fentanyl is used for antipsychotics together with the antipsychotic droperidol (thalomonal).

This type of analgesia is used when the patient must be in consciousness, for example, with myocardial infarction. The form of anesthesia itself is very convenient, since the patient does not respond to pain irritation (analgesic effect) and is completely indifferent to everything that happens (the antipsychotic effect, consisting of a super sedative and strong tranquilizing effect).

Alone is the alkalioid opium CODEIN (Codeinum in the table at .015). As an analgesic, it is significantly weaker than morphine. Has a weaker affinity for opiate receptors. The antitussive effect of codeine is weaker than that of morphine, but it is quite sufficient for practice.

Advantages of codeine:

1) unlike morphine, it is well absorbed when taken orally;

2) codeine less depresses breathing;

3) causes less drowsiness;

4) has less spasmogenic activity;

5) dependence on codeine develops more slowly.

INDICATIONS FOR USE OF CODEINE:

1) with a dry, raw, unproductive cough;

2) the second stage of the fight against chronic pain in a cancer patient (WHO), according to a three-stage scheme. Codeine (50-150 mg after 5 hours) plus a non-narcotic analgesic, plus adjuvants (glucocorticoids, antidepressants, anticonvulsants, psychotropic, etc.).

Acute poisoning with morphine and morphine-like rats

Acute morphine poisoning can occur with an overdose of the drug, as well as with the accidental administration of large doses in addictive patients. In addition, morphine can be used for suicidal purposes. For adults, the lethal dose is 250 mg.

In acute morphine poisoning, the clinical picture is characteristic. The patient's condition is very difficult. First, a dream develops, passing into a stage of anesthesia, then a coma, leading to paralysis of the respiratory center.

The clinical picture consists primarily of respiratory depression, its decrease. The skin is pale, cold, cyanotic. A decrease in body temperature and urination is noted, at the end of poisoning - a decrease in blood pressure. Bradycardia develops, a sharp narrowing of the pupil (the point size of the pupil),

at the end of hypoxia, the pupil expands. Death occurs due to respiratory depression or shock, pulmonary edema and secondary infection.

TREATMENT of patients with acute morphine poisoning is based on the same principles as the treatment of acute intoxication with barbiturates. Aid measures distinguish specific and non-specific.

SPECIFIC ASSISTANCE MEASURES are associated with the introduction of specific morphine antagonists. The best antagonist is NALOXON (drug addict). In our country, there is practically no naloxone, and therefore they often use a partial antagonist - NALORFIN.

Naloxone and nalorphine eliminate the effects of morphine and its drugs on opiate receptors and restore normal CNS function.

Nalorfin, a partial antagonist of morphine, in its pure form (a single drug) acts as morphine (causes an analgesic effect, but is weaker, depresses breathing, gives bradycardia, narrows the pupils). But against the background of the administered morphine, nalorphine manifests itself as its antagonist. Nalorfin is usually used iv in a dose of 3 to 5 mg, if necessary, repeating injections after 30 minutes. Its effect literally occurs on the “tip of the needle” - during the first minute of administration. When overdosed, it can quickly -there is a withdrawal syndrome.

NON-SPECIFIC ASSISTANCE MEASURES are associated with the removal of non-absorbed poison. Moreover, gastric lavage should be done even with parenteral administration of morphine, since its partial release of the gastrointestinal mucosa into the intestinal lumen occurs. It is necessary to warm the patient, if convulsions occur, use anticonvulsants.

With deep respiratory depression produce artificial ventilation of the lungs.

CHRONIC MORPHINE POISONING, as a rule, is associated with the development of dependence on it. The development of addiction, drug addiction is naturally accompanied by the repeated administration of narcotic analgesics. Distinguish between physical and mental dependence.

A manifestation of the formed PHYSICAL DEPENDENCE on narcotic analgesics is the occurrence of withdrawal or withdrawal symptoms upon termination of repeated administration of morphine. The withdrawal syndrome consists of a number of characteristic signs: 6-10-12 hours after the last injection of morphine, the morphine rhinorrhea, lacrimation, terrible yawning, chills, goose bumps, hyperventilation, hyperthermia, mydriasis, muscle pain, vomiting, diarrhea, tachycardia, weakness, sweating, sleep disturbances, hallucinations, anxiety, anxiety, aggressiveness. These symptoms last for 2-3 days. To prevent or eliminate these phenomena, the addict is ready to do anything, even a crime. the drug leads a person to physical and mental degradation.

The mechanism of development of withdrawal is associated with the fact that narcotic analgesics, activating opiate receptors according to the feedback principle (as in endocrinology), inhibit the release, and maybe the synthesis of endogenous opiate peptides, gradually replacing their activity. As a result of the abolition of analgesics, insufficiency of both the previously administered analgesic and endogenous peptide occurs. Abstinence syndrome develops.

Previously, physical dependence develops mental dependence. The basis for the emergence of mental dependence are euphoria, sedation and an indifferent attitude to environmental disturbing people. In addition, repeated administration of morphine causes a very pleasant sensation in the abdominal cavity for the morphine, sensations of unusual heat in the epigastric region and lower abdomen, reminiscent of those with intense orgasm.

In addition to mental and physical dependence, there is a third sign of addiction - the development of tolerance, stability, and addiction. In this regard, the addict is constantly forced to increase the dose of the analgesic.

Treatment for morphine addiction is not fundamentally different from treatment for addiction to alcohol or barbiturates. The treatment of drug addicts is carried out in special institutions, but the results are not yet encouraging (units of percents). Frequent development of deprivation syndrome (withdrawal symptoms), relapse addiction.

There are no special tools. Use fortifying, vitamins. It's easier to prevent addiction than to cure. The danger of drug addiction is the main reason for limiting the use of these drugs in medicine. From pharmacies they are released only according to special recipes, drugs are stored according to list "A".

Non-narcotic analgesics are painkillers, analgesics that do not have a significant effect on the central nervous system, do not cause drug addiction and anesthesia. In other words, unlike narcotic analgesics, they do not have a sedative and hypnotic effect; euphoria, addiction and drug dependence do not occur with their use.

Currently, a large group of drugs has been synthesized, among which the so-called:

1) old or classic non-narcotic analgesics

2) new, more modern and more anti-inflammatory action - the so-called non-steroidal anti-inflammatory drugs – NSAIDs

The purpose of the lesson:

A. To learn the pharmacodynamics, pharmacokinetics, pharmacotoxicodin-miku psychotropic drugs / PLC /.

A) PSYCHOLEPTICS:

1. Antipsychotics (neuroplegics, antipsychotics). General characteristics. Classification:

1) Derivatives of phenothiazine (typical antipsychotics):

and aliphatic derivatives - chlorpromazine, levomepromazine;

b piperazine derivatives - etaperazine, triftazine, fluorophenazine, fluorophenazine decanoate;

in piperidine derivatives - neuleptyl.

2) Derivatives of butyrophenone - haloperidol, trifluperidol, droperidol.

3) Derivatives of diphenylbutylpiperidine - flushpirilen, pimozide.

4) Benzamide derivatives - sulpiride / eglonyl /, sultopride, thiapride, metoclopramide / cerucal, raglan /, amisulpride.

5) Derivatives of various chemical classes - reserpine, chlorprotixen, azaleptin.

2. Tranquilizers (anxiolytics). General characteristics. Classification:

1) Derivatives of 1,4-benzodiazepine - chlordiazepoxide, diazepam, phenazepam, nitrazepam, flunitrazepam, clonazepam, nozepam, mezapam, alprazolam, lorazepam, temazepam, gidazepam, etc.

2) Derivatives of different chemical groups - mebicar, grandaxin, amisyl, lithonite, phenibut, etc.

3. Psycho-sedatives. General characteristics. Classification:

1) herbal products - valerian, motherwort, pas siflora, corvalol, valocordin, corvaldin, novopassit, sedasen-forte, persen, cardiophyte, etc .;

2) bromides - sodium and potassium bromide;

3) complex combinations in the form of mixtures - Quater (infusion of valerian-n + infusion of mint + sodium bromide + magnesium sulfate + amidopyrine + caffeine), Ivanova-Smolensky (infusion of valerian + sodium bromide + amidopyrine + barbital-sodium) and other

B) PSYCHOANALEPTICS:

1. Antidepressants (timoleptics, timoanaleptics). General characteristics. Classification:

1) Monoamine oxidase (MAO) inhibitors - irreversible (nialamide) and reversible (pyrazidol, incazan, moclobemide, etc.);

2) Neuronal capture inhibitors:

a. non-selective action - tricyclic antidepressants (TAD): imipramine (imizine), clomipramine, amitriptyline, doxepin, azafen, desipramine; four-cyclic and other compounds - maprotiline, mianserin;

b. selective serotonin reuptake inhibitors (SSRIs) - fluosectin, fluvoxamine, sertraline, trazodone;

3) Derivatives of different groups - sidnofen, tianeptin.

2. Psychostimulants General characteristic. Classification:

1) Phenylalkylamines - amphetamine / phenamine /;

2) Sidnoniminy - Sydnocarb;

3) Derivatives of purine (xanthines) - caffeine, caffeine-sodium benzoate;

3. Neurometabolic stimulants or nootropics General characteristic. Classification:

1) pyrrolidone derivatives - piracetam / nootropil / and its analogues (aniracetam, etiracetam, etc.),

2) GABAergic - aminalon / gamalon /, picamilon, pantogam, phenibut, sodium hydroxybutyrate;

3) derivatives of different groups - membrane protectors (pyrididol / encephabol /, acefen); glutamatergic (memantine, glycine, nooglutil); neuropeptides (semax, ebiratide), etc.

C) PSYCHODISLEPTICS (psilosuibin, mescaline, lysergic acid diethylamide, etc.);

D) TIMOISOLEPTICS (lithium salts, valproic acid salts, carbamazepine, oxarbazepine, calcium channel blockers, etc.);

B. Know the main pathogenetic mechanisms that are the objects of drug exposure in:

A) neurocirculatory dystonia;

B) diencephalic crises;

C) encephalopathies;

D) sleep disturbances;

E) violations of thermoregulation (hyperthermia);

E) neurosis, asthenic conditions, manic-depressive psihozy, anxiety, psychomotor agitation, withdrawal syndrome (with alcoholism, drug addiction);

G) indomitable vomiting;

H) tetanus, epilepsy, Parkinson's disease

I) apnea, cardialgia, arrhythmias;

K) strokes

B. Be able to:

A) select and select the necessary drugs for a particular patient with the indicated pathology, select criteria for evaluating the therapeutic efficacy and safety of the psychotropic drugs used;

B) prescribe combination therapy;

C) justify and provide urgent medical assistance with:

1. diencephalic crisis;

2. psychomotor agitation;

3. hyperthermic crisis

Assignment for self-testing of the initial level

1. What are the most common psycho-emotional stressing influences (stress: hopeless situations, expectation, sleep deprivation, emotional pain, sexual deprivation), which are an important etiological factor in the development of "civilization diseases".

2. Describe the pathogenesis of the damaging effects of stress on the central nervous system, cardiovascular system and internal organs.

3. Determine the ways of pharmacological protection and correction of the psychosomatic reaction of a person with acute and chronic stress.

4. Formulate the main pathogenetic mechanisms of the development of mental disorders in patients with severe vascular and somatic pathology.

5. What are the drugs used in the treatment of somatogenic psychosis and depression.

6. List drugs that enhance mnemonic functions and adaptive capabilities of the brain.

7. List the indications for use, the rules for choosing and determining the dosage regimen for sedatives, tranquilizers, antipsychotics, antidepressant and nootropic drugs.

8. Indicate which of the psychotropic drugs can cause drug dependence.

9. What are the drugs with hypnosative and muscle relaxant effects.

10. What threatens with a deliberate or accidental overdose of tranquilizers or antipsychotics? What vital functions of the body in the first place need correction in case of poisoning with psychotropic drugs?

Control questions of the studied topic

1. What are the basic principles for the treatment of patients with neuropsychiatric disorders.

2. What are the principles for constructing a classification of PLC?

3. What sedative drugs have a predominantly psychotropic effect? What drugs have a predominantly organotropic effect?

4. Why are antipsychotics used mainly for psychosis, and tranquilizers are used more often for neurosis? Which of them have anti-arrhythmic and muscle relaxant effects?

5. Which PLCs have a pronounced M-anticholinergic effect, reduce the secretion of cerebrospinal fluid, and suppress cough?

6. What tranquilizer is useful for cardialgia, nausea?

7. What drugs for parenteral administration are used for an epileptic seizure?

8. What are the main effects of antipsychotics? What drugs have antihistamine and antihypertensive effects?

9. What drugs are used for antipsychotics, premedication before anesthesia?

10. What are the main side effects of psycholeptics?

11. What are your contraindications for prescribing antidepressants?

12. Why are MAO inhibitors incompatible with certain foods?

13. What are the indications for the use of psychostimulants?

14. What is the pharmacological effect of piracetam for strokes and coma?

15. What is the cause of the nootropic effect of cerebroprotectors?

16. What is the mechanism of action of normotimics (timotholeptics)?

17. What classes of drugs can be attributed to sleeping pills?

The list of practical works:

Homework.

1. Write down prescriptions for PLC (tableted, ampouled drug forms) presented in the section "Purpose of the lesson", indicate the spectrum of their pharmacological activity and indications for use.

2. Indicate and explain possible effective and undesirable combinations of PLC.

B. Independent work:

1. To supervise a thematic patient in the ward.

2. To study his medical history (data from examinations of specialists, records of the attending physician, laboratory and instrumental studies), a sheet of medical appointments and an expert assessment of the pharmacotherapy prescribed for the patient.

3. Write a protocol of independent work (see Appendix 1) for the choice of a psychotropic drug for the patient to be supervised, justify the appointment of combined drug therapy.

4. When examining a patient, highlight the signs characterizing the dysfunction of the central nervous system, reflect them in the clinical diagnosis.

5. Determine the group of psychotropic drugs needed to correct existing disorders.

6. Based on the theoretical knowledge of pharmacodynamics, propose a specific drug to the patient under supervision.

7. Choose the optimal dosage regimen for the drug, taking into account gender, age, body weight, route of administration and pharmacokinetics of the drug.

8. Select clinical criteria for evaluating the effectiveness and safety of the use of this psychotropic drug.

9. Make a forecast of side effects of drugs prescribed to the patient and outline a plan for their detection in the early stages.

10. Justify the duration of the main and supporting therapy.

11. To make a plan for urgent medical care for: diencephalic crisis, psychomotor agitation, hyperthermic crisis, dyscirculatory encephalopathy.

Control of the intermediate level of knowledge.

Solving situational tasks:

1. A patient, 31 years old, weighing 72 kg, suffers from neurocirculatory dystonia of a mixed cerebral-cardial, hypertensive type. Complaints of increased irritability, insomnia, frequent headaches, a feeling of lack of air, pain in the heart, tachycardia. Objectively: heart rate - 90 in 1 min, AKD - 140/90 mm Hg, limbs are pale, cold. Laboratory and instrumental examination data allow to exclude organic lesions of the central nervous system and cardiovascular system.

Prescribe a drug from the class of psychotropic drugs, justify your choice and mode of administration.

2. A patient, 47 years old, weighing 82 kg, suffers from hypertension II Art. Against the background of a hypertensive crisis with AKD - 240/140 mm Hg and heart rate - 98 in 1 min developed an acute violation of coronary circulation in the region of the anterior wall of the left ventricle. The patient is excited, not adequate.

Assign the correction of psychomotor agitation to this patient with an indication of the drug, its dose and route of administration.

3. A patient, 58 years old, weighing 53 kg, suffers from a hypertensive form of chronic pyelonephritis. Against the background of chronic alcoholism, sub-arachnoid hemorrhage occurred. On the second day of the hospital stay, delirium developed. The patient is agitated, gets up, resists attempts to examine and continue treatment, profanity.

Which PLC will you choose for stopping delirium in this patient? Indicate the dose and route of administration.

4. A patient, 80 years old, is undergoing treatment in the neurological department for severe disseminated atherosclerosis with predominant damage to the vessels of the brain, degree II encephalopathy. In the complex of therapeutic measures he receives therapy: Cavinton 2 ml intravenously in the morning, Piracetam 400 mg 3 times a day (at 9.00, 14.00 and 21.00), cerebrolysin 1.0 ml intramuscularly - in the afternoon. The patient complains of worsening night sleep.

Which of the prescribed medications can cause insomnia? Correct the therapy.

5. The girl, 13 years old, after a quarrel with her parents, took 30 tablets for suicidal purposes. relanium. Delivered to the hospital 2 hours after what happened in a state of deep stupor.

Give a prognosis of the clinical course of poisoning. What vital functions should you control first? Make a complete plan of treatment measures to save a teenager’s life.

6. Illness with manic-depressive psychosis will be removed in the warehouse for complex therapy haloperidol (0.0015 g 2 times a day), aminazine (0.025 g 3 times a day), azafen (0.025 1 time per day). After 2 days, the ear of the new one showed pain in the stomach, the temperature was 370C, and the residents of Zakarivnya shkiri.

Your little thought is given as I will become sick. Your recommendations. Відповідь overload.

7. A 48-year-old man who has been unemployed for a long time has been treated for alcohol depression. Then he developed hypertension and was assigned one of the traditional antihypertensive slow-acting drugs. In the process of treatment, he developed a persistent long-term deterioration of mood (a feeling of sadness, hopelessness, despair). One day he committed suicide. Could the medicine taken cause these symptoms? If so, which one?

8. Opioids: agonists and antagonists. It was decided to prescribe an opioid analgesic for a woman to give birth pain. What is the best substance in this case? What precautions should be taken? what

should be prescribed in case of accidental overdose of an opioid analgesic?

9. Patient S., aged 40, had a complication in the operation for gallstone disease under galantan anesthesia - malignant hyperthermia. What is the best way to reduce the muscle stiffness characteristic of this syndrome?

10. A patient undergoes inpatient treatment for schizophrenia. Receives haloperidol. By the end of the 1st month of treatment, the patient's condition improved markedly, delusional hallucinatory symptoms almost disappeared, but complaints of tremor and stiffness of movements appeared. An objective examination shows an increased tone of skeletal muscles. What complication developed in the patient, the mechanism of its development? Doctor tactics? What drugs from this group practically do not cause this complication?

11. A patient undergoes inpatient treatment for depression, receives amit-rptilin. As a result of treatment, the condition improved slightly, but there were complaints of dry mouth, visual impairment (difficulty viewing closely objects), constipation, and urinary retention. What is the cause of these symptoms? What drugs from this group of anti-depressants could be offered as an alternative to amitriptyline-well? Representatives of what other subgroups of antidepressants practically do not cause these side effects?

12. A patient was admitted to a hospital with cirrhosis. A history of chronic alcoholism and hospitalization for alcohol-related seizures. 1) What should be prescribed by the attending physician to prevent possible seizures caused by alcohol withdrawal syndrome?

TESTS

1. A patient was admitted to a hospital with cirrhosis. A history of chronic alcoholism and hospitalization for alcohol-related seizures. Choose from the following options

A. phenytoin (diphenin),

B. teturam,

C. chlordiazepoxide (elenium),

D. phenobarbital,

E. thiopental.

2. A man, 50 years old, was hospitalized in the intensive care unit with acute transmural myocardial infarction of the posterior diaphragmatic portion of the left ventricle. What drug is the least indicated?

A. Nifedipine.

B. Nitroglycerin.

C. Propranolol.

D. Fentanyl.

E. Morphine.

3. A sixty-year-old patient who suffers from hypertension and obesity, feels weakness in the right extremities, which intensifies throughout the day. The previous three days were observed short-term speech disturbances. Objectively: partial motor and sensory aphasia, right-sided spastic hemiparesis. What group of drugs should be prescribed for a patient to prevent the development of ischemic stroke?

A. Vitamins of group B.

B. Preparations of lipotropic action.

C. Anticonvulsants

D. Vasodilator drugs.

E. Tranquilizers.

4. In a 2-year-old boy who has been suffering from acute pneumonia with toxic syndrome for 3 days, tonic-clonic seizures arose against a background of an increase in body temperature to 40 ° C. What is the first aid measure to take first?

A. Mannitol 20% solution intravenously.

B. Magnesium sulfate 25% solution intravenously.

C. Hexenal 5% solution intravenously.

D. Seduxen 0.5% solution intramuscularly or intravenously.

E. Droperidol 0.25% solution intravenously or intramuscularly.

5. In addicts after the end of the drug there are severe mental, neurological and somatic disorders. What is the name of this symptom complex?

A. idiosyncrasy

B. Cumulation

C. Sensitization

D. Withdrawal syndrome

E. Tolerance

6. Against the background of alcohol intake in a patient receiving clonidine for the treatment of hypertension, there were signs of a sharp inhibition of the central nervous system. With what it can be connected?

A. idiosyncrasy

B. Summation of effects

C. Cumulation

D. Potentiation of effects

E. Intoxication

7. In complex therapy for chronic insufficiency, the patient was prescribed an analeptic, which also has a direct pacemaker and expectorant effect. Also, this medicine can be used outdoor for rubbing with arthritis. Indicate this drug.

A. Bemegrid

B. Cordiamine

C. Etymizole

D. Caffeine

E. Camphor

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

GENERAL PRINCIPLES OF ANTIBACTERIAL THERAPY

SPECTRA OF ANTIMICROBIAL ACTIVITY

CLASSIFICATION OF ANTIBACTERIAL MEANS

POSSIBLE COMPLICATIONS OF ANTIBACTERIAL THERAPY, THEIR PREVENTION AND TREATMENT

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF ANTIBIOTICS

Relevance of the topic.

The impressive successes associated with the introduction of antibacterial drugs into clinical practice are, without a doubt, one of the most significant achievements of 20th century medicine.

No wonder UNESCO attributed the discovery of penicillin by Alexander Fleming to the most significant events of the past century. The list of infections defeated by antibiotics is quite extensive, while the concept of the “incurability” of microbial diseases changed radically when the patient and the doctor were held captive by the modest possibilities of symptomatic therapy. Hundreds of millions of deaths were prevented using the active antimicrobial treatment method. The increase in human life expectancy is directly related to the introduction of antibacterial therapy in health care practice.

Unfortunately, this fame did a disservice. Achievements in the fight against many infections have developed confidence in the almost limitless possibilities of antibiotics, so they are often used even with the slightest hint of infection. It has become a good practice among the population, and doctors, not to leave a single condition without antibiotics, accompanied by an increase in body temperature or redness of the mucous membranes. Programs for antibiotic prophylaxis of infectious diseases were developed, and clinically healthy people were prescribed courses of antibiotic therapy. The powerful action of antibiotics that kill bacteria and slow their growth has reduced the number of sensitive strains, leading to the spread of resistant variants until they become the predominant representatives of the microbial flora. Today, the profile of antibiotic sensitivity to bacteria on the skin of people, in hospitals, in residential buildings is significantly different from the profile that was observed before the widespread introduction of antibiotics and even only 10 years ago. Multidrug resistance is usually found in bacteria that cause infections, as well as in commensal organisms that colonize the intestinal tract, skin and upper respiratory tract of a person. Resistant bacteria are the winners who survived the selection caused by antibiotics that occurs in all walks of life and in all population groups.

Moreover, against the background of an irrational, indiscriminate, unprofessional approach to vitally important medicines, not individual strains appeared, but new races of bacteria highly resistant to antibiotics.

Antimicrobials are the only class of drugs whose activity decreases over time. The increase in microbial resistance to antibiotics is justifiably called "the apocalypse of the twentieth century." Unfortunately, an immediate solution to this problem at the start of the 21st century seems absolutely unrealistic, since microorganisms have a significant advantage over antibiotics: representatives of the microbial world reproduce extremely quickly, which contributes to the selection of drug-resistant strains. The foregoing in the most urgent manner requires doctors to continuously improve their knowledge regarding antibiotic therapy. The ability to introduce modern scientific technologies to fight infections into practice, on the one hand, is the hallmark of a true professional, and on the other hand, it improves the well-being and quality of life of patients.

In the context of the current state of the problem of antibiotic therapy, Paracelsus's winged expression sounds very relevant: "The disease cannot adapt to the knowledge of the doctor."

Antibiotic therapy has firmly taken one of the leading places in the complex treatment of diseases, the main etiological factor of which are pathogenic microorganisms. Thanks to antibiotics, mankind has received formidable weapons against many previously dangerous infectious diseases. Over the past 30 years, a large number of antibiotics with various spectra of action have been synthesized and used in the clinic.

If at the beginning of the era of antibiotic use almost no mention was made of the possibility of complications of antibiotic therapy, then currently negative the properties of antibiotics are known even to non-specialists. The side effect of these drugs and various complications of antibiotic therapy is the subject of a significant number of special works, which indicates the seriousness and relevance of this problem.

Knowledge of possible adverse reactions during antibiotic therapy is important not only at the stage of prescribing antibiotics by a doctor, but also at the stage of direct execution of prescriptions.

Motivational characteristic of the topic.

ANTIBACTERIAL CHEMOTHERAPEUTIC 1

Antibacterial chemotherapeutic agents are characterized by two main properties:

1) selectivity of action in relation to certain types of pathogens, i.e. have a certain spectrum of antimicrobial action;

2) low toxicity to humans and animals.

Most often they are used for systemic infections in which resorptive drugs are required (administered enterally and parenterally). However, chemotherapeutic agents are prescribed locally; in this case, their absorption should be minimal. The latter is important for obtaining the most pronounced and persistent antimicrobial effect and to reduce the possibility of side effects. For the purpose of local action, the drugs are applied to the mucous membranes or to the skin, and also injected inside to affect the causative agents of intestinal infections (substances that are not absorbed from the digestive tract).

The use of antibacterial chemotherapeutic agents has its own characteristics. First of all, for successful treatment it is important to establish the causative agent of the disease and determine its sensitivity to those drugs that can be used as chemotherapeutic agents. If the causative agent of the disease is known, drugs with an appropriate spectrum of antibacterial action are selected. With an unknown pathogen, it is advisable to use substances with a wide spectrum or a combination of two drugs, the total spectrum of which includes probable pathogens.

It is necessary to begin treatment as soon as possible. At the beginning of the disease, microbial bodies are smaller and they are in a state of vigorous growth and reproduction. At this stage, microorganisms are most sensitive to the action of chemotherapeutic agents.

As indicated above, chemotherapeutic agents denote substances that have selective toxicity against certain pathogens of infectious and parasitic diseases. In addition to antibacterial drugs, these include antiviral, antifungal, antiprotozoal and anthelmintic drugs.

P. Ehrlich (1854-1915). Founder of chemotherapy for infections. Got the first effective antisyphilitic agent from the group of organic compounds of arsenic - salvarsan.

The principles of antibiotic therapy

Antibiotics are divided into groups and classes that differ in the spectrum of activity, pharmacodynamic and pharmacokinetic properties. The importance of antibiotics and the choice of a drug is based on several criteria. Consider the main ones.

Strict testimony

Reasonable indications for the appointment of an antibacterial drug.

Timely resolution of the need for combined antibacterial therapy.

Modern antibacterial therapy is carried out only when signs of an infectious process appear in the body with a highly probable or proven bacterial nature. Unreasonable use of antibiotics leads to an increase in microflora resistance and an increased risk of developing adverse reactions. Preventive antibiotic therapy is allowed only with:

• high risk of infection during operations;

• severe injuries;

• immunodeficiency.

Pathogen identification

The choice of a drug or combination of drugs, taking into account sensitivity to the causative agent of the infectious process.

The drug should be prescribed taking into account the spectrum and the degree of its antimicrobial activity against specific pathogens. To do this, a bacteriological study is conducted, which allows to establish the pathogen and its sensitivity to existing drugs. Without such an analysis, an antibiotic is prescribed taking into account regional data on the most likely pathogens and their resistance.

The choice of the most active and least toxic drug.

Dose, route and frequency of administration of the antibiotic

The drug is administered in a regimen that provides constant support for its therapeutic concentration in the focus of infection throughout the course of treatment.

Knowledge of the pharmacodynamics and pharmacokinetics of the antibacterial drug.

A significant role is also played by the choice of rational routes of administration of substances, given the fact that some of them are not completely absorbed from the gastrointestinal tract, poorly penetrate the blood-brain barrier, etc.

Doses of the preparations should be sufficient to ensure bacteriostatic or bactericidal concentrations in biological fluids and tissues. At the beginning of treatment, a shock dose is sometimes given in excess of the subsequent ones.

The optimal duration of treatment is very important. It should be borne in mind that clinical improvement (lowering the temperature, etc.) is not the basis for stopping the drug. If the necessary course of treatment has not been carried out, a relapse of the disease is possible.

For some infectious diseases, you have to resort to second courses of treatment.

Often, 2-3 antibacterial agents are prescribed simultaneously. However, it should be borne in mind that the combined use of such drugs should be sufficiently justified, since if the combination is incorrect, not only antagonism of substances with respect to antibacterial activity is possible, but also a summation of their toxic effects. The combination of drugs for chronic infections (for example, for tuberculosis) is most shown to prevent the development of resistance of bacteria to chemotherapeutic agents.

All these factors are determined depending on the ability of the drug to create the required effective concentration in the foci of infection.

The optimal method of administering antibacterial drugs depending on the patient's condition.

Consideration of the patient’s age, its anatomical and physiological characteristics and associated therapy.

Clinical Evaluation

Selection of criteria for evaluating the effectiveness of antibiotic therapy (clinical, laboratory and instrumental data).

Such an assessment should be carried out 2-3 days after the start of treatment. In the absence of regression of intoxication syndrome, a decrease in body temperature, and an improvement in overall well-being, it is necessary to clarify the correctness of the diagnosis and change of antibiotic.

Mandatory monitoring of side effects and complications of antibiotic therapy and their correction.

The following groups belong to antibacterial chemotherapeutic agents:

antibiotics,

sulfonamide preparations, quinolone derivatives,

synthetic antibacterial agents of different chemical structures, anti-syphilitic drugs, anti-tuberculosis drugs.

ANTIBIOTICS

Antibiotics From Greek. anti - against, bios - life.

are chemical compounds of biological origin that have a selective damaging or destructive effect on microorganisms. Antibiotics used in medical practice are produced by actinomycetes (radiant mushrooms), mold fungi, as well as some bacteria. This group of drugs also includes synthetic analogues and derivatives of natural antibiotics.

There are antibiotics with antibacterial, antifungal and antitumor effects.

Antibiotics that primarily affect bacteria. They are represented by the following groups:

1. Antibiotics with a β-lactam ring in their structure Penicillins Cephalosporins Carbapenems Monobactams

2. Macrolides - antibiotics, the structure of which includes a macrocyclic lactone ring (erythromycin, etc.), and azalides (azithromycin)

3. Tetracyclines - antibiotics, the structural basis of which are 4 condensed 6-membered cycles (tetracycline, etc.)

4. Derivatives of dioxiaminophenylpropane (chloramphenicol)

5. Aminoglycosides - antibiotics containing in the amino-sugar molecule (streptomycin, gentamicin, etc.)

6. Antibiotics from the group of cyclic polypeptides (polymyxins)

7. Lincosamides (clindamycin)

8. Glycopeptides (vancomycin, etc.)

9. Fusidic acid

10. Antibiotics for topical use Fyuzafyunzhin and others.

According to the spectrum of antimicrobial action, antibiotics differ quite significantly. Some affect mainly gram-positive bacteria (biosynthetic penicillins, macrolides), others affect mainly gram-negative bacteria (e.g. polymyxins, aztreonam). A number of antibiotics have a wide spectrum of action (tetracyclines, cephalosporins, chloramphenicol, aminoglycosides, etc.), including gram-positive and gram-negative bacteria and a number of other pathogens.

Antibiotics affect microorganisms, inhibiting their reproduction (bacteriostatic effect) or causing their death (bactericidal effect).

The following basic mechanisms of the antimicrobial action of antibiotics are known:

1) a violation of the synthesis of the bacterial cell wall (penicillins, cephalosporins act on this principle);

2) violation of the permeability of the cytoplasmic membrane (for example, poly-mixins);

3) violation of intracellular protein synthesis (this is how tetracyclines, levomycetin, aminoglycosides, etc. act);

4) impaired RNA synthesis (rifampicin).

The high selectivity of the action of antibiotics on microorganisms with their relatively low toxicity to a macroorganism, is obviously explained by the structural and functional organization of microbial cells. Indeed, the bacterial cell wall is fundamentally different in chemical composition from mammalian cell membranes. The bacterial cell wall consists of murein mucopeptide (contains N-acetyl-glucosamine, N-acetyl-muramic acid and peptide chains including some L- and D-amino acids). In this regard, substances that violate its synthesis (for example, penicillins) have a pronounced antimicrobial effect and practically do not affect the cells of the macroorganism. A certain role is probably played by an unequal number of membranes surrounding those active centers with which antibiotics can interact. So, unlike microorganisms in mammalian cells, in addition to the common plasma membrane, all intracellular organelles have their own, sometimes double membranes. Apparently, the differences in the chemical composition of individual cellular components are of great importance. Significant differences in the rate of growth and reproduction of cells of macro- and microorganisms, and therefore the rate of synthesis of their structural materials, should also be taken into account. In general, the problem of the selectivity of the action of antibiotics, as well as other antimicrobial agents, needs further study.

In the process of using antibiotics, the resistance of microorganisms to them can develop. It arises especially rapidly with respect to streptomycin, oleandomycin, rifampicin, relatively slowly with penicillins, tetracyclines and chloramphenicol, and rarely with polymyxins. Possible so-called cross-

resistance, which applies not only to the drug used, but also to other antibiotics that are similar in chemical structure (for example, to all tetracyclines). The likelihood of developing resistance decreases if the doses and duration of antibiotic administration are optimal, as well as with a rational combination of antibiotics. If resistance to the main antibiotic has occurred, it should be replaced by another, backup antibiotic.

By one or a number of properties, reserve antibiotics are inferior to the main antibiotics (they have less activity or more pronounced side effects, more toxicity or the rapid development of microorganism resistance to them). Therefore, they are prescribed only with the resistance of microorganisms to major antibiotics or with intolerance to the latter. Although antibiotics are characterized by high selectivity of action, nevertheless, they have a number of adverse effects on macroorganism. So, when using antibiotics, allergic reactions of an immediate and delayed type often occur (serum sickness, urticaria, angioedema, anaphylactic shock, contact dermatitis, etc.).

In addition, antibiotics may have a side effect of a non-allergic nature. The result of the direct irritating effect of antibiotics is dyspeptic symptoms (nausea, vomiting, diarrhea), pain at the site of intramuscular injection, the development of phlebitis and thrombophlebitis with intravenous injection of antibiotics. Adverse effects are also possible from the liver, kidneys, hematopoiesis, hearing, vestibular apparatus, etc.

For many antibiotics, the development of superinfection (dysbiosis) is typical, which is associated with the suppression of part of the saprophytic flora by the antibiotic, for example, the digestive tract. The latter may favor the multiplication of other microorganisms and fungi insensitive to this antibiotic (yeast-like fungi, Clostridium difficile, protea, Pseudomonas aeruginosa, staphylococci). Most often, superinfection occurs during treatment with broad-spectrum antibiotics.

Despite the widespread use of antibiotics in medical practice, the search for new, more advanced drugs of this type is being conducted on a fairly significant scale. The efforts of researchers are aimed at creating such antibiotics that would maximize the combination of positive qualities and were devoid of negative properties. Such “ideal” preparations should have high activity, pronounced selectivity of action, the necessary antimicrobial spectrum, bactericidal nature of action, permeability through biological membranes (including through the blood-brain barrier), and effectiveness in different biological environments. They should not cause the rapid development of resistance in microorganisms and sensitization of the macroorganism. The absence of side effects, minimal toxicity and a wide range of therapeutic effects - all this is also one of the basic requirements for new antibiotics. In addition, it is important that antibiotic preparations are technically available for manufacture at pharmaceutical plants and have a low cost.

Penicillins

Currently, the penicillin group is represented by a large number of drugs. Some of them are obtained from the culture medium on which certain strains of mold fungi (Penicillium), which are producers of penicillin, grow. These are the so-called biosynthetic penicillins. In addition, through the chemical modification of 6-aminopenicillanic acid, which is the structural basis of biosynthetic penicillins, a number of semi-synthetic penicillins have been created. On the differences in the ways of obtaining penicillins, as well as on a number of other signs, the classification given is based.

I. Preparations of penicillins obtained by biological synthesis (biosynthetic penicillins)

For parenteral administration (destroyed in the acidic environment of the stomach)

a) Short-term action Benzylpenicillin sodium salt Ben-zilpenicillin potassium salt

b) Long-acting benzylpenicillin novocaine salt

Bicillin-1 Bicillin-5

For enteral administration (acid resistant) - Phenoxymethylpenicillin

II. Semisynthetic Penicillins

For parenteral and enteral administration (acid resistant)

a) Resistant to penicillinase - Oxacillin sodium salt Nafcillin

b) A wide spectrum of action - Ampicillin Amoxicillin

For parenteral administration (they are destroyed in the acidic environment of the stomach) A wide spectrum of action, including Pseudomonas aeruginosa

Carbenicillin disodium salt

Ticarcillin

Azlocillin

For enteral administration (acid resistant)

Carbenicillin indanyl sodium

Carfecillin

Penicillins have a bactericidal effect. They affect only dividing cells. The mechanism of the antibacterial effect is associated with impaired synthesis of the components of the cell wall. It is believed that penicillins disrupt the late stages of cell wall synthesis, preventing the formation of peptide bonds due to inhibition of the transpeptidase enzyme.

a) Biosynthetic penicillins

There are several varieties of natural penicillins formed by mold fungi. In practical medicine, benzylpenicillin, produced in the form of a number of salts, has become very widespread.

Under industrial conditions, benzylpenicillin is obtained on liquid nutrient media in the so-called fermenters. Its producers are certain strains of Penicillium.

Benzylpenicillin is a monobasic acid, the structure of which includes β-lactam (l) and thiazolidine (t) cycles. By its nature, it is a cyclic dipeptide (L-cysteine and D-valine).

The activity of benzylpenicillin (as well as other antibiotics) can be determined by diffusion into agar. In this case, benzylpenicillin in various concentrations (in glass cylinders or in wells) is applied to Petri dishes with agar and zones of growth inhibition of the test culture for the test samples are determined in comparison with the standard. One unit of action (1 U) corresponds to an activity of 0.6 μg of pure crystalline benzylpenicillin (in the form of sodium salt).

Benzylpenicillin has a high antibacterial activity, but its spectrum of action is limited. The drug refers to antibiotics that act mainly on gram-positive bacteria.

Sensitive to it:

gram-positive cocci (staphylococci that do not produce penicillinase, streptococci, pneumococci),

gram-negative cocci (meningococci, gonococci),

diphtheria sticks (corynebacterium),

anthrax wands,

causative agents of gas gangrene and tetanus (clostridia),

spirochetes (including pale spirochete),

some pathogenic fungi (e.g. actinomycetes).

All benzylpenicillin salts are intended for parenteral use, as they are destroyed in the acidic environment of the stomach.

The highly soluble benzylpenicillin sodium and potassium salts act relatively briefly (3-4 hours). The latter explains the need for frequent injections of drugs, which significantly complicates their use. In this regard, the idea arose of creating long-acting drugs of benzylpenicillin. Research has evolved in two directions. One of them was based on the fact that benzylpenicillin is secreted from the body mainly by the kidneys by secretion of the renal tubules by the epithelium. Compounds were synthesized (for example, probenecid), which inhibit the secretion process and thereby delay benzylpenicillin in the body, prolonging its action. However, the effectiveness of such substances is limited and for this purpose they are practically not used.

The family of intestinal bacteria, acid-resistant mycobacterium tuberculosis, viruses, rickettsia, protozoa, yeast-like fungi are resistant to benzylpenicillin.

As long-acting preparations, the poorly soluble salts of benzylpenicillin (benzylpenicillin novocaine salt, bicillins) gained more importance. They are administered intramuscularly, and they are slowly absorbed from the injection site. Creating a depot of drugs in muscle tissue allows you to maintain the necessary concentration of antibiotics in the blood for a long time. Benzylpenicillin preparations do not penetrate the blood-brain barrier under normal conditions.

b) Semi-synthetic penicillins

Significant opportunities for the improvement of penicillins opened up with the separation of their structural basis - 6-aminopenicillanic acid.

Receive 6-aminopenicillanic acid by enzymatic cleavage (imidases) of benzylpenicillin, as well as by its chemical deacylation.

An important step was the preparation of penicillinase resistant penicillins. Semisynthetic penicillins with this property include oxacillin sodium salt, dicloxacillin, and some others. The value of these drugs is determined by the fact that they are effective against strains of staphylococci resistant to benzylpenicillin (due to the production of penicillinase by these strains).

Chemical modifications of 6-aminopenicillanic acid were carried out by attaching a variety of radicals to the amino group. Research was aimed at creating semi-synthetic penicillins with certain properties.

a) resistant to penicillinase (β-lactamase) produced by a number of microorganisms;

b) acid-resistant drugs that are effective when administered orally;

c) penicillins with a wide spectrum of action.

In oxacillin, resistance to penicillinase is combined with resistance in an acidic environment. According to the spectrum of antimicrobial action, it is similar to benzylpenicillin. A significant portion binds to blood plasma proteins (> 90%). The drug does not penetrate the blood-brain barrier. It is allocated mainly by kidneys. The frequency of administration is every 4-6 hours.

The group of drugs resistant to the action of penicillinase also includes nafcillin, which has a high antibacterial activity and penetrates the blood-brain barrier. It is secreted mainly with bile, to a lesser extent - by the kidneys. Enter enterally and parenterally.

Semi-synthetic penicillins of a wide spectrum of action are divided into the following groups:

I. Drugs that do not affect Pseudomonas aeruginosa

Aminopenicillins - Ampicillin Amoxicillin

β-Lactamases, long-existing bacterial enzymes, are the main protection of gram-negative microorganisms against β-lactam antibiotics. In the process of applying this group of antibiotics, β-lactamases were more often produced by many strains of Staphylococcus aureus, which was previously observed very rarely in these bacteria. In addition, Haemophilus influenzae and Neisseria gonorrhoeae, which previously did not produce this enzyme at all, became producers of β-lactamases. In the process of creating new β-lactam antibiotics, a modification of existing β-lactamases was noted, which "adapt" to more effective inactivation of new drugs. Currently, more than 100 varieties of β-lactamases have been described. Based on the primary structure, they are often divided into 4 groups (A, B, C and D). Groups A, B and D comprise a serine residue, and group B represents metallo-β-lactamases. The β-lactamase inhibitor clavulanic acid does not equally affect different groups of enzymes. The most effective inhibitor of group A is β-lactamase, slightly suppresses group D. The activity of β-lactamase of groups B and C does not change.

It is active against Pseudomonas aeruginosa (Pseudomonas aeruginosa) and various types of protea, both indole positive (P. vulgaris, P. morganii, P. rettgeri) and indole negative (P. mirabilis).

Note. Plus - the presence, minus - the absence of a specific property.

II. Drugs active against Pseudomonas aeruginosa

Carboxypenicillins Carbenicillin Ticarcillin Carfecillin

Ureidopenicillins Piperacillin Azlocillin Meslocillin

One of the aminopenicillins widely used in medical practice is ampicillin. It affects not only gram-positive, but also gram-negative microorganisms (salmonella, shigella, some protea strains, E. coli, Friedlander's bacillus, influenza bacillus). With respect to gram-positive bacteria, it is inferior in activity to benzylpenicillin (like all other semisynthetic penicillins), but surpasses oxacillin. It is destroyed by penicillinase and therefore ineffective against penicillinase-forming staphylococci. Ampicillin is acid resistant. It is not completely absorbed from the gastrointestinal tract (bioavailability ~ 40%) and slowly. It binds to plasma proteins to a small extent (10-30%). It penetrates the blood-brain barrier better than oxacillin. It is mainly excreted by the kidneys. Ampicillin is administered with an interval of 4-8 hours. The drug is low toxic and well tolerated by patients.

The combination drug Ampiox (ampicillin with oxacillin) is available.

Amoxicillin is similar in its activity and spectrum of action to ampicillin, but is more fully absorbed from the intestine. Enter it only enteral.

The listed semi-synthetic penicillins of a wide spectrum of activity, active against Pseudomonas aeruginosa, are destroyed by penicillinase.

Carbenicillin (piopen) is similar in its antimicrobial spectrum to ampicillin. It differs from it in that it actively acts on all types of protea and Pseudomonas aeruginosa (Pseudomonas aeruginosa).

In the acidic environment of the stomach, the drug is destroyed; slightly absorbed. Therefore, it is administered intramuscularly and intravenously. About 50% of the drug binds to plasma proteins. It penetrates poorly through the blood-brain barrier. It is excreted by the kidneys (secretion and filtration) and partially by the liver. Duration of action is 4-6 hours.

A new drug has been created - carbenicillin indanil sodium, which has acid resistance and is intended for enteral administration (for urinary tract infections).

Carfecillin and ticarcillin preparations are similar in their properties to carbenicillin. Carfecillin, unlike carbenicillin, is acid-resistant and is administered orally. Ticarcillin is slightly more active than carbenicillin, especially in terms of its effect on Pseudomonas aeruginosa.

The antibacterial activity of ureidopenicillins is similar to that of carboxypenicillins. In relation to Klebsiella, ureidopenicillins are more effective. According to the effect on Pseudomonas aeruginosa, drugs can be arranged in the following series (in decreasing activity): azlocillin = piperacillin> meslo-cillin = ticarcillin> carbenicillin.

An important problem is overcoming the resistance of a number of microorganisms to β-lactam antibiotics, which is caused by the ability of certain strains to produce β-lactamases. Based on these data, specific β-lactamase inhibitors (clavulanic acid, sul-bactam, tazobactam) that prevent the destruction of this group of antibiotics were synthesized. Inhibitors of β-lactamases are a part of a number of combined preparations (β-lactam antibiotics + β-lactamase inhibitors).

One of the commonly used drugs is Augmentin (amoxicillin + clavulanic acid). As already noted, amoxicillin is a broad-spectrum bactericidal β-lactam antibiotic. Clavulanic acid (produced by Streptomyces clavuligerus) is also a β-lactam derivative. However, her antibacterial effect is expressed to a very small extent. The main effect is competitive irreversible inhibition of a number of β-lactamases. The β-lactamases produced by some Enterobacteriaceae are not affected.

Augmentin has a wide antibacterial spectrum, including β-lactamase-producing gram-positive bacteria (staphylococci and most streptococci, including enterococci) and gram-negative bacteria (N. gonorrhoeae, N. meningitidis, N. influenzae, Gardenella vaginalis, Bordetella per Perella coli, Klebsiella pneumonia, Proteus mirabilis, Salmonella). High efficacy was noted in relation to many strains of anaerobic bacteria producing β-lactamases.

The drug is usually administered enterally 1 time per day. Absorbed well (74-92%). Bioavailability of about 70%. Substances and their metabolites are excreted by the kidneys.

It is used for infections of the respiratory tract, genitourinary tract, bacterial damage to the skin and soft tissues, bones, joints, and septic conditions.

Other combined preparations have been created: unazin (ampicillin + sulbactam), amoxiclav (amoxicillin + clavulanic acid), tazocin (piperacillin + tazobactam), etc.

A “atypical” preparation of penicillin, pommecillin, has been synthesized, acting mainly on gram-negative bacteria. It is a prodrug. In the body, it forms mecillins. Prescribe the drug inside, but it is poorly absorbed.

Semisynthetic penicillins oxacillin, dicloxacillin, nafcillin are the drugs of choice when infected with staphylococci producing penicillinase, i.e. resistant to benzylpenicillin. Oxacillin is administered orally and intramuscularly, nafcillin is administered orally, intramuscularly and intravenously.

Ampicillin, which has a wide spectrum of action, is of the greatest interest as a remedy for the treatment of diseases caused by gram-negative microorganisms or mixed flora. It is used orally for infections of the urinary, biliary, respiratory tract, gastrointestinal tract, in case of purulent surgical infection. Ampicillin sodium salt (pentrexil) is administered intramuscularly and intravenously. Amoxicillin has similar indications for use. Enter it enterally.

Carbenicillin, carfecillin, ticarcillin, azlocillin and other drugs of this group are especially indicated for infections caused by Pseudomonas aeruginosa, Proteus, Escherichia coli (with pyelonephritis, pneumonia, septicemia, peritonitis, etc.).

c) Side and toxic effects of penicillins

Penicillin toxicity is low, the breadth of therapeutic action is large. The main side effects include allergic reactions, which are observed in a significant number of patients (1-10%). They are associated with the formation of antibodies in the body. Allergic reactions usually occur a few days after the start of penicillin administration. However, these periods vary widely (from minutes to weeks). A correlation between the dose of penicillins, the time necessary for the development of allergic reactions, and the degree of their severity was not noted. The latter may be different. In some cases, allergic reactions are limited to skin rashes, dermititis, and fever. More severe forms are accompanied by swelling of the mucous membranes, arthritis, arthralgia, kidney damage, erythroderma and other disorders. A severe and rapidly developing allergic reaction, sometimes fatal, is anaphylactic shock2 (blood pressure drops, bronchospasm, abdominal pain, cerebral edema, loss of consciousness, and many other manifestations are possible).

Treatment of allergic reactions consists in the abolition of penicillin preparations, as well as in the administration of glucocorticoids (they have a pronounced anti-inflammatory and desensitizing effect), antihistamines (block histamine H1 receptors and eliminate the effects of histamine, which plays an important role in the development of allergic reactions), calcium chloride and a number of other agents. In anaphylactic shock, adrenergic agonists are administered intravenously, stimulating α- and β-adrenergic receptors (increase blood pressure, eliminate bronchospasm), epinephrine hydrochloride (which is the drug of choice) or ephedrine hydrochloride, as well as hydrocortisone, diphenhydramine, calcium chloride.

In addition, penicillins cause some side and toxic effects of a non-allergic nature. These include the irritating effect of pe-

Nitsillins. When taking drugs inside, they can cause inflammation of the mucous membrane of the tongue (glossitis), oral cavity (stomatitis), nausea, diarrhea. Intramuscular administration may be accompanied by pain, the development of infiltrates and aseptic necrosis of the muscle, and intravenous administration with phlebitis and thrombophlebitis.

Allergic reactions to penicillin preparations also occur in the medical personnel applying them and in persons engaged in their manufacture and packaging.

It usually occurs within 20 minutes after injection of penicillin preparations.

When using excessively high doses of the sodium salt of benzylpenicillin (especially endolumbar), a neurotoxic effect (arachnoiditis, encephalopathy) is possible. This complication sometimes occurs when prescribing the drug against the background of renal failure.

The toxic effect of penicillins in some cases adversely affects the activity of the heart. In single observations, the inhibitory effect of oxacillin on liver enzymes was noted. Reception of acid-resistant penicillins (especially a wide spectrum of action, for example, ampicillin) can be the cause of dysbiosis (more often than candidiasis).

Cephalosporins

A number of antibiotics were isolated from the fungus Cephalosporinum acremonium, including cephalosporin C. Its semisynthetic derivatives were called cephalosporins. These include cephalotin, cephalexin, cefaclor, cefotaxim, cefuroxime, cefoperazone, cefepime, ceftriaxone, etc. (table; see fig.). The chemical basis of these compounds is 7-aminocephalosporic acid.

Cephalosporins act bactericidal, which is associated with their inhibitory effect on cell wall formation. Like penicillin, they inhibit the activity of the enzyme transpeptidase, which is involved in the biosynthesis of the bacterial cell wall.

In structure, cephalosporins are similar to penicillins (see chemical structures). So, both groups of antibiotics contain a β-lactam ring (l). However, there are significant differences: the structure of penicillins includes a thiazole-lidine ring, and cephalosporins include a dihydrothiazine ring According to the antimicrobial spectrum, cephalosporins are broad-spectrum antibiotics. They are resistant to staphylococcal penicillinase, but many of the cephalosporins are destroyed by β-lactamases produced by certain gram-negative microorganisms (for example, Pseudomonas aeruginosa, Enterobacter aerogenes; this type of β-lactamase is often called cef-losporinase).

Cephalosporins are conventionally divided into 4 generations

Representatives of the first generation are especially effective against gram-positive cocci (pneumococci, streptococci, staphylococci). Some gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis) are also sensitive to them. They practically do not act on Pseudomonas aeruginosa, Enterobacter, Serratia marcescens, indole-positive protea, bacteroids (Bacteroides fragilis).

The spectrum of action of cephalosporins of the second generation includes that for drugs of the first generation and is supplemented by Enterobacter, indole-positive proteas. A number of drugs are also effective against Bacteroides fragilis and certain strains of Serratia (cefoxitin, cefmetazole, cefotetan). All drugs in this group are less active than drugs of the first generation in terms of their effect on gram-positive cocci. Pseudomonas aeruginosa is insensitive to them.

III The III generation of cephalosporins is characterized by a wider spectrum of action, especially in relation to gram-negative bacteria. On gram-positive cocci, they act to a lesser extent than cephalosporins of the second generation. For ceftazidime and cefoperazone, a pronounced effect on Pseudomonas aeruginosa was noted. Cefotaxime also acts on this pathogen, but to a small extent. Ceftizoxime and moxalactam have antibacterial activity against Bacteroides fragilis. This group of cephalosporins acts on Enterobacter, Serratia, as well as on strains of Haemophilus and Neisseria producing β-lactamases. An important property of most III generation cephalosporins (except cefoperazone and cefixix) is their ability to penetrate the blood-brain barrier.

IV generation cephalosporins have an even wider antimicrobial spectrum than III generation drugs. They are more effective against gram-positive cocci. They have high activity against cyanobacterial bacillus and other gram-negative bacteria, including strains producing β-lactamases. Bacteroids are slightly affected.

Based on the route of administration, cephalosporins are divided into 2 groups

For parenteral use - cephalotin cefuroxime ce-photaxime cefepim, etc.

For enteral administration of cefalexin cefaclor cefixime and others.

Most cephalosporins are poorly absorbed from the digestive tract. However, some drugs are absorbed quite well, and therefore they are administered enterally. The bioavailability of the latter corresponds to 50-90%. They accumulate in the blood at bactericidal concentrations, which provides the necessary pharmacotherapeutic effect.

Preparations of the first and second generation practically do not pass through the blood-brain barrier. At the same time, as already noted, many cephalosporins III knee-deep penetrate the brain tissue.

In the blood, cephalosporins partially bind to plasma proteins. Most drugs are excreted by the kidneys (by filtration and secretion), and some drugs are mainly excreted in the intestines (cefoperazone, cef-triaxone).

Half-life (t1 / 2) and dosage regimen are different for specific drugs of different generations

Sometimes cephalosporins are combined with a sulbactam β-lactamase inhibitor. This increases their effectiveness in the treatment of bacterial infections. One of these drugs is sulperazone (cefoperazone + sulbactam).

Cephalosporins are used for diseases caused by gram-negative microorganisms (for example, infections of the urinary tract), with infection with gram-positive bacteria in case of penicillin inefficiency or intolerance. In catarrhal pneumonia (pathogen - Friedlander's stick - Klebsiella pneumoniae), cephalosporins are the drugs of choice. For infections associated with Pseudomonas aeruginosa, ceftazidime and cefoperazone are prescribed. Ceftri-axon is the drug of choice for gonorrhea. For the treatment of meningitis caused by meningococci or pneumococci, drugs that pass through the blood-brain barrier, such as cefuroxime, cephalosporins of the third generation (except cefoperazone and cefixime), should be used. A number of drugs (cefoxitin, ceftisoxime) are effective for infection with bacteroids (Bacteroides fragilis).

Cephalosporins in a significant percentage of patients cause allergic reactions. Cross sensitization with penicillins is sometimes noted. Of the non-allergic complications, kidney damage is possible (observed mainly with the use of cephaloridine and cefradine). Mild leukopenia may occur. In addition, many drugs cause local irritant effects (especially cephalotin). In this regard, with intramuscular administration, pain, infiltrates may occur, and with intravenous administration, phlebitis. The possibility of superinfection should also be considered. Enterally administered drugs can cause dyspeptic symptoms. When prescribing certain drugs (cefoperazone, etc.), hypoprothrombinemia is sometimes noted.

OTHER ANTIBIOTICS IN THE STRUCTURE OF THE β-LACTAM RING

Carbapenems

Imipenem belongs to this group - a highly active semi-synthetic antibiotic with a wide spectrum of action. It is a derivative of thienamycin produced by Streptomyces cattleya. Effective against many aerobic and anaerobic bacteria. It inhibits the synthesis of the cell wall and, due to this, has a bactericidal effect. It is resistant to β-lactamases, but is destroyed by dehydropeptidase-1 of the proximal renal tubules. The latter explains the low concentration of the drug in the urine. To eliminate this imipenem deficiency, a dehydropeptidase-1 inhibitor called cilastatin was synthesized. Imipenem is currently used in combination with cilastatin. One such combination drug is thienam (primaxin). It is administered intravenously at intervals of 6 hours. In the gastrointestinal tract, imipenem is not absorbed. Of the side effects, nausea, vomiting, convulsions, allergic reactions are possible.

The antibiotic meropenem (meronem) also belongs to the group of carbapenems. It differs from imipenem by significant resistance to dihydropeptidase-1, and therefore, its combination with inhibitors of this enzyme is not required. Stable against most β-lactamases. The mechanism, nature and spectrum of antimicrobial action is similar to imipenem. t1 / 2 ~ 1.5 hours. About 2% binds to plasma proteins. It penetrates well through tissue barriers. It is metabolized in the liver. It is excreted mainly (~ 98%) by the kidneys. It is used for severe infections of various localization: pneumonia, peritonitis, meningitis, sepsis. The drug is also indicated in case of exacerbation of chronic bacterial bronchitis, with uncomplicated infection of the urinary tract, skin and its appendages. Enter intramuscularly and intravenously after 8 or 12 hours.

Of the side effects, allergic reactions, irritating effects at the injection site, dyspeptic symptoms, reversible leukopoiesis disorders, headache, and dysbiosis are possible.

Monobactams

This group includes the drug aztreonam isolated from the culture of Chromobacterium vialaceum. Resistant to β-lactamases produced by a number of gram-negative bacteria belonging to the groups Klebsiella, Pseudomonas, Serratia. It does not act on gram-positive bacteria and anaerobes. It inhibits

the synthesis of the cell wall and, due to this, has a bactericidal effect. Parenteral administration of aztreons. t1 / 2 ~ 1.7 h. It is excreted by the kidneys (secretion). Used for infections of the urinary tract, respiratory tract, skin, etc. Of the side effects, dyspeptic disorders, skin allergic reactions, headache, superinfection, rarely hepatotoxic effect are noted.

MACROLIDES AND AZALIDES

Antibiotics of this group at the core of their molecules contain a macrocyclic lactone ring associated with various sugars. Representatives of macrolides are erythromycin, oleandomycin, roxithromycin, clarithromycin, and azalides are azithromycin.

Erythromycin (erythran, erythrocin) is produced by Streptomyces erythreus. Gram-positive cocci and pathogenic spirochetes are most sensitive to it. However, its action spectrum also includes gram-negative cocci, diphtheria bacilli, pathogenic anaerobes, rickettsia, chlamydia, mycoplasmas, pathogens of amoebic dysentery, etc. Thus, erythromycin resembles benzylpenicillin in terms of its effect on various microorganisms, but its spectrum of action is somewhat wider .

The mechanism of action of erythromycin is the inhibition of protein synthesis by bacterial ribosomes. This is due to inhibition of the enzyme peptide translocase.

The drug is not completely absorbed from the gastrointestinal tract, but sufficiently to ensure that bacteriostatic concentrations are created in the blood and tissues. It should be borne in mind that in the acidic environment of the stomach, erythromycin is partially destroyed, therefore, it should be administered in acid-resistant capsules or in tablets (dragees) with a special coating that ensures the release of erythromycin only in the small intestine. The drug easily penetrates into various tissues, including through the placenta. In significant concentrations accumulates in phagocytes (like other macrolides). It does not enter the brain tissue under normal conditions. The duration of action is 4-6 hours. It is excreted in the bile and partially by the kidneys.

The use of erythromycin is limited, since the resistance of microorganisms to it is rapidly developing. Therefore, it is attributed to reserve antibiotics and is used in cases where penicillins and other antibiotics are ineffective. Erythromycin is prescribed orally (erythromycin base) and topically.

Erythromycin is a low-toxic antibiotic and relatively rarely causes side effects. Sometimes dyspeptic disorders, allergic reactions occur, superinfection is possible.

Similar properties and indications for use are olean-domicin. Its producer is Streptomyces antibioticus. Ole-andomycin is inferior to erythromycin in activity. The spectrum and mechanism of antimicrobial action are similar. The duration of action of oleandomycin is approximately 6 hours. Toxicity is low. It has a more pronounced irritant effect than erythromycin. Refers to antibiotics reserve. In medical practice, oleandomycin phosphate (oleandocin, romicil) is used inside.

Oleandomycin phosphate is released in combination with tetracycline (oletetrin) and tetracycline hydrochloride (sigmamycin, tetraolean).

In recent years, a number of semi-synthetic macrolides, clarithromycin, roxithromycin, etc., have been introduced into medical practice. By the mechanism of action, they are similar to erythromycin.

Clarithromycin (klacid) is 2-4 times more active than erythromycin against staphylococci and streptococci. Effective in infections caused by Micobacterium avium intracellulare and Helicobacter pylori.

It is well absorbed from the gastrointestinal tract, including after eating. The brain tissue does not pass. It is partially metabolized in the liver to form an active metabolite. It is allocated by kidneys. It acts longer than erythromycin. t1 / 2 for clarithromycin is about 3 times greater than for erythromycin.

Roxitromycin (rulide) is also an effective semisynthetic macrolide. It has a wide antibacterial spectrum of action. It is well absorbed when taken orally.

1 In erythromycin group macrolides, the basis of the structure is a 14-membered ring with an oxygen heteroatom. Azalides of the azithromycin type have a 15-membered ring with nitrogen and oxygen heteroatoms. The antibiotic josamycin (vilprafen) contains a 16-membered lactone ring.

2 Obtained enzymatically from a nutrient medium with a reduced chlorine content.

Azalides1 are chemically different from macrolides, but are similar in basic properties to them. One of the drugs in this group, azithromycin (sumamed), is 2-4 times less active in terms of its effect on staphylococci and streptococci than erythromycin, but is superior to the latter in terms of its effect on Haemophilus influenzae, as well as gram-negative cocci. It is poorly absorbed in the intestine, especially with the presence of food contents. Azithromycin is characterized by accumulation in high concentrations in cells - it can exceed concentrations in blood plasma by 10-100 times. It acts for a long time. t1 / 2 = 2-4 days (for erythromycin t1 / 2 = 2-5 hours). It does not pass through the blood-brain barrier. It is excreted by the kidneys unchanged.

Take enterally. Of the side effects, nausea, diarrhea are sometimes noted, hearing loss rarely occurs. Cost is higher than erythromycin.

A new antibiotic from the macrolide group is obtained - josamycin (wilp-rafen). Produced by Streptomyces narbonensis var. josamycetics. The main difference from other macrolides is a more rare development of microorganism resistance to it.

It should be noted that macrolides and azalides are effective against obligatory intracellular microorganisms - chlamydia, mycoplasmas and legionella, which can be the causative agents of the so-called "atypical" pneumonia.

TETRACYCLINES

Tetracyclines include a group of antibiotics, the structural basis of which is 4 condensed 6-membered cycles (see structures).

The following preparations are obtained biosynthetically (by fermentation): oxytetracycline dihydrate (terramycin, tetran, tarchocin) - producer Streptomyces rimosus, tetracycline (deschlorbiomycin) - producer Streptomyces aureofaciens2. Demeclocycline is produced by a mutant strain of Streptomyces aureofaciens.

Semisynthetic tetracyclines include metacyclin hydrochloride (rondomycin), doxycycline hydrochloride (vibramycin), minocycline, etc.

Tetracyclines have a wide spectrum of action. They are active against gram-positive and gram-negative cocci; causative agents of bacillary dysentery, typhoid fever; pathogenic spirochetes; causative agents of especially dangerous infections - plague, tularemia, brucellosis, cholera; rickettsia; chlamydia, some protozoa (pathogens of amoebic dysentery). Tetracyclines do not act on Proteus, blue-purulent bacillus, true viruses and pathogenic fungi. According to the effect on gram-positive microorganisms, they are inferior to penicillins. Tetracycline resistance is gradually developing1.

The mechanism of their antimicrobial action is associated with inhibition of intracellular protein synthesis by bacterial ribosomes. In addition, tetracyclines bind metals (Mg2 +, Ca2 +), forming chelate compounds with them, and inhibit enzyme systems. Tetracyclines have a bacteriostatic effect. Most active against breeding bacteria. All tetracyclines are similar in activity.

Tetracyclines are absorbed from the stomach and small intestine. Absorption is incomplete (especially after eating), but sufficient to provide bacteriostatic concentrations in the body. The

maximum plasma concentrations with the introduction of tetracyclines inside are achieved after 2-4 hours.

Tetracyclines form chelating compounds with calcium ions, iron, and aluminum, which are not absorbed. Therefore, the absorption of tetracyclines is disturbed when these ions (for example, calcium ions in milk and dairy products) are contained in food or substances that contain these ions (for example, antacids). In this regard, doxycycline and minocycline occupy a special place, which only to a small extent form chelate compounds with calcium ions and therefore the presence of food masses and calcium ions in the digestive tract does not affect their absorption, which occurs quickly and completely.

In circulating blood, a significant part of tetracyclines binds to plasma proteins (from 20 to 80%).

The most prolonged action is demeclocycline, doxycycline and meta-cyclin. According to the duration of action, tetracyclines are arranged in the following order: demeclocycline> doxycycline> metacyclin> oxytetracycline> tetra-cyclin.

Tetracyclines penetrate well through many tissue barriers, including through the placental. Certain quantities pass through the blood-brain barrier. However, when tetracyclines are introduced inside, their bacteriostatic concentrations in the cerebrospinal fluid usually do not accumulate. To do this, a very high content of antibiotics in the blood is required, which is easier to achieve with parenteral (especially intravenous) administration of drugs (for example, doxycycline hydrochloride). Minocycline practically does not penetrate the brain tissue.

Small amounts of tetracyclines are found in the liver and bones for a very long time.

Tetracyclines with urine and bile are secreted. Part of the tetracycline released with bile is re-absorbed from the small intestine. Doc-sicycline is excreted mainly with bile. Excrement determines up to 90% of the drug.

Tetracyclines have wide indications for use. They are effective for rickettsioses, typhus, pneumonia caused by mycoplasmas, infection with chlamydia (pneumonia, psittacosis, trachoma, etc.), with gonorrhea, syphilis, relapsing fever, brucellosis, tularemia, cholera, with bacillary and amoebic dysentery leptospirosis, etc. Tetracyclines are used in the development of resistance of microorganisms to penicillins and streptomycin or in sensitization of the patient to these antibiotics. They are prescribed more often inside with an interval of 4-8 hours. In addition, their soluble salts are administered parenterally (intravenously, intramuscularly, in the body cavity). Tetracyclines are not injected under the meninges, since they have an irritating effect. Locally they are used most often in ointments for eye diseases (especially with trachoma).

Tetracyclines have a number of adverse effects. So, they can cause allergic reactions. In this case, skin integuments are affected, mild fever is possible, etc. Allergic reactions to tetracyclines are observed much less frequently than to penicillins and cephalosporins.

Of the side effects of a non-allergic nature, the irritant effect (especially pronounced in oxytetracycline) should be noted first of all. When taking drugs inside, it is one of the main causes of dyspeptic symptoms (nausea, vomiting, diarrhea), glossitis, stomatitis and other disorders of the mucous membrane of the digestive tract. Due to the irritating effect, intramuscular injections are painful, intravenous infusion can lead to thrombophlebitis.

Tetracyclines have some hepatotoxicity (mainly oxytetracycline). With caution, tetracyclines should be prescribed in the second half of pregnancy and in children. This is due to the fact that tetracyclines are deposited in bone tissue, including in the tissues of teeth, and form chelating compounds with calcium salts. In this case, the formation of the skeleton is disturbed, staining and damage to the teeth occur.

One of the undesirable effects of tetracyclines (especially demeclocycline) is their ability to cause photosensitization1 and the associated dermatitis.

Typical for tetracycline metabolism. They inhibit protein synthesis (anti-anabolic effect), increase the excretion of sodium, water, amino acids, certain vitamins and a number of other compounds from the body.

Minocycline can cause vestibular disorders.

A characteristic complication in the treatment with tetracyclines is a super-infection. Being broad-spectrum antibiotics, tetracyclines suppress the saprophytic flora of the digestive tract and favor the development of candidiasis, superinfection with staphylococci, Proteus, Pseudomonas aeruginosa. The greatest concerns are staphylococcal enterocolitis and pneumonia, which can be very difficult. Inhibition of saprophytic flora is one of the reasons for the development of deficiency of B vitamins in patients (saprophytes are involved in their synthesis), which aggravates the defeat of the mucous membrane of the digestive tract caused by the irritating effect of tetracyclines and superinfection.

To prevent and treat candidiasis, tetracyclines are combined with the antifungal antibiotic nystatin. In addition, it is advisable to prescribe B vitamins simultaneously with tetracyclines. To suppress superinfection with staphylococci, Proteus or Pseudomonas aeruginosa, antimicrobials with an appropriate spectrum of action are used.

1 Cross-resistance is developed in relation to all preparations of the tetracycline series.

Pseudomembranous colitis2, which is treated with vancomycin, can occasionally develop.

In connection with the resistance of microorganisms developing in relation to known tetracyclines, the search for new derivatives of this group is logical. One of the latest advances is associated with the synthesis of glycyl cyclins. A promising compound of this series is tigecycline. Refers to tetracycline derivatives. It has high activity against gram-negative and gram-positive bacteria. Pseudomonas aeruginosa and Proteus are resistant to tigecycline. The drug is used for the ineffectiveness of many other antimicrobial agents associated with the development of resistance to them.

LEVOMYCETINE GROUP

The antibiotic chloramphenicol is produced by Streptomyces venezuelae. It is obtained from the culture fluid, as well as synthetically.

Levomycetin (chloramphenicol) has a wide spectrum of action, which includes gram-positive and gram-negative bacteria, including the family of intestinal bacteria, influenza bacilli, as well as rickettsia, chlamydia, pathogens of brucellosis, tularemia. Acid-resistant mycobacteria, Pseudomonas aeruginosa, Proteus, protozoa are little or completely insensitive to chloramphenicol.

The antimicrobial mechanism of chloramphenicol is associated with its effect on ribosomes and inhibition of protein synthesis. It also inhibits peptidyl transferase. These effects are manifested mainly by the bacteriostatic effect. The addiction of microorganisms to chloramphenicol develops relatively slowly.

Chloramphenicol is well absorbed from the gastrointestinal tract. The maximum plasma concentration is created after about 2 hours. To maintain bacteriostatic concentrations in the blood, chloramphenicol is prescribed with an interval of 6 hours. A significant portion of the antibiotic binds to plasma albumin. Chloramphenicol well penetrates into various tissues, including passing through the blood-brain barrier. In cerebrospinal fluid, the concentration of chloramphenicol is 2 times less than in plasma. Its main amount is subjected to chemical transformations in the liver. The resulting conjugates and about 10% of the unchanged drug are excreted by the kidneys.

Due to serious adverse effects in relation to blood formation (see below), chloramphenicol is usually referred to as reserve antibiotic; it is used only with the ineffectiveness of other antibiotics. The main indications for its use are typhoid fever, foodborne toxicoinfections (salmonella lesions) and rickettsioses. Sometimes it is used for diseases caused by sticks of influenza (for example, with meningitis, with infection of the urinary tract), with brucellosis and a number of other infections.

Chloramphenicol is usually taken orally. Levomycetin solutions and liniment are used topically1. For parenteral administration, chloramphenicol soluble succinate (chlorocide C) is released. It is administered subcutaneously, intramuscularly and intravenously.

As already noted, chloramphenicol can cause marked inhibition of hematopoiesis, accompanied by reticulocytopenia, granulocytopenia and, in severe cases, aplastic anemia, which usually ends fatal 2. Therefore, the use of chloramphenicol requires regular monitoring of the blood picture. To reduce the possibility of inhibition of hematopoiesis, an antibiotic should be prescribed for the shortest possible period of time. Repeated treatments are not recommended.

In some cases, allergic reactions are noted in the form of skin rashes, fever, etc.

Of the side effects of a non-allergic nature, irritation of the mucous membranes (nausea, diarrhea) most often occurs, including anorectal syndrome (with corresponding localization of irritation). The skin (rash, dermatitis) is also affected. Psychomotor disturbances, a depressing effect on the myocardium, are sometimes noted.

Severe intoxication with cardiovascular collapse often occurs in newborns and in the 1st month of life. This is due to the slow elimination of the antibiotic by the kidneys and the insufficiency of liver enzymes in children during this period.

When using chloramphenicol, superinfection (for example, candidiasis, infection with staphylococci, proteome) can develop.

It is believed that the cause of severe hematopoiesis caused by chloramphenicol is sensitization or idiosyncrasy (associated with genetically determined enzyme disease). At the same time, chloramphenicol also has a direct toxic effect on the bone marrow, depending on the dose of the substance

AMINOGLYCOSIDE GROUP

Aminoglycosides are divided into 3 groups:

1st generation - streptomycin, neomycin, monomycin, kanamycin;

II generation - gentamicin;

III generation - tobramycin, amikacin, sisomycin, netilmicin.

The main representatives of this group of antibiotics are streptomycin, neomycin, kanamycin, gentamicin, amikacin, tobramycin, sisomycin, monomycin, etc.

The mechanism of action of aminoglycosides is associated with their direct effect on ribosomes and inhibition of protein synthesis. For aminoglycosides, a bactericidal effect is characteristic.

Streptomycin is an antibiotic produced by Actinomyces globisporus streptomycini. In medical practice, streptomycin sulfate is used (see chemical structure). Streptomycin activity is defined in units of action (IU) and in weight units. 1 unit streptomycin base corresponds to 1 mcg.

Streptomycin has a wide range of antimicrobial effects. Most importantly, its inhibitory effect on mycobacterium tuberculosis, causative agents of tularemia, plague. In addition, it has a detrimental effect on pathogenic cocci, some protea strains, Pseudomonas aeruginosa, brucella and other gram-

negative and gram-positive bacteria. Anaerobes, spirochetes, rickettsiae, viruses, pathogenic fungi, and protozoa are insensitive to streptomycin.

Addiction develops relatively quickly to this antibiotic. In some cases, the formation of streptomycin-dependent strains is observed, for the growth and reproduction of which streptomycin is necessary.

From the gastrointestinal tract, the drug is poorly absorbed. When administered intramuscularly after 1-2 hours, streptomycin accumulates in plasma in maximum concentrations. It is distributed mainly extracellularly. Penetrates into the cavity of the peritoneum and pleura, during pregnancy - into the tissue of the fetus. Through the blood-brain barrier, as a rule, does not pass; with meningitis, the permeability of the blood-brain barrier to streptomycin increases. t1 / 2 ~ 2-4 h. Streptomycin is excreted mostly by the kidneys (by filtration) unchanged. An insignificant part is excreted with bile in the intestine.

Streptomycin sulfate is used mainly in the treatment of tuberculosis1. In addition, it is used in the treatment of tularemia, plague, brucellosis, urinary tract infections, respiratory organs, as well as other diseases. The drug is administered more often intramuscularly (1-2 times a day), as well as in the body cavity. In order to affect the intestinal flora of streptomycin, sulfate is administered orally. For injection under the meninges, only streptomycin-calcium chloride complex (a double salt of streptomycin hydrochloride and calcium chloride) is used. The latter has a less irritating effect than other streptomycin preparations. However, the toxicity of streptomycin-calcium chloride complex is significant.

The negative effects of streptomycin include non-allergic and allergic effects. The most serious is the ototoxic effect associated with damage to sensitive cells of the vestibular organ and the ear cochlea of the VIII pair of cranial nerves. Vestibular disorders and hearing loss occur. According to some authors, the use of calcium pantothenate reduces the possibility of these side effects. Streptomycin has nephrotoxicity. It has a depressing effect on neuromuscular synapses, which can cause respiratory depression. In addition, it has an irritating effect, and therefore his injections are painful.

When prescribing streptomycin preparations, allergic reactions are also noted (fever, skin lesions, eosinophilia, rarely anaphylactic shock, etc.). Against the background of streptomycin, superinfection is possible.

Locally, synthomycin is also used - a synthetic racemate of levomycetin. Chloramphenicol is a levorotatory isomer. Syntomycin consists of chloramphenicol and the dextrorotatory isomer. The latter does not possess antimicrobial activity.

Neomycin is a mixture of the neomycin A, B, and C antibiotics produced by Actinomyces fradiae. Available in the form of neomycin sulfate. It has a wide spectrum of action. Both gram-positive and gram-negative microorganisms are sensitive to it. It does not affect anaerobes, spirochetes, pathogenic fungi and viruses. The resistance of microorganisms to neomycin develops relatively slowly.

When ingested, the drug is poorly absorbed, so its effect with this route of administration is limited mainly by the digestive tract. Non-omicin is used to treat enteritis caused by susceptible to it.

microorganisms. Rationally, its use in the resistance of the corresponding pathogens to other antibiotics. Neomycin may be useful in preparing patients for surgery on the digestive tract (in order to partially "sterilize" the intestine). A positive quality is its high activity against Escherichia coli, some strains of Proteus and Pseudomonas aeruginosa. Of the side effects, dyspeptic disorders, allergic reactions, and candidiasis are possible.

Often, neomycin is used topically. It is prescribed for the treatment of infected wounds, a number of skin diseases (pyoderma, etc.), eye diseases (for example, conjunctivitis), etc. With intact skin

surface and mucous membranes, it is slightly absorbed. Outwardly, neomycin in some cases is used together with glucocorticoids (for example, with sinaflan or flu-methazone pivalate) 1. In this case, the antimicrobial effect is combined with anti-inflammatory.

Parenteral neomycin is not used due to its high toxicity in relation to the kidneys (protein appears in the urine) and the auditory nerve (there is tinnitus and hearing loss up to complete deafness). In addition, neomycin has curariform activity (it can cause depression and respiratory arrest).

The drug is contraindicated in diseases of the kidneys and auditory nerve.

Gentamicin is produced by Micromonospora purpurea and M. echinospora. Available in the form of gentamicin sulfate (garamycin).

It has a wide spectrum of action, including gram-positive and gram-negative bacteria. Of greatest practical interest is its activity against Pseudomonas aeruginosa, Proteus, Escherichia coli, as well as staphylococci resistant to benzylpenicillin. Resistance to gentin-qin develops slowly.

From the gastrointestinal tract, the drug is not sufficiently absorbed, therefore, for systemic action, it is prescribed intramuscularly. The maximum amounts of gentamicin in the blood plasma during this route of administration accumulate after 60 minutes. Antimicrobial concentrations remain in the body for 8-12 hours. Under normal conditions, gentamicin almost does not penetrate the blood-brain barrier. With meningitis, small concentrations are found in the cerebrospinal fluid. It is excreted by the kidneys mainly unchanged.

Gentamicin is used mainly for the treatment of diseases caused by gram-negative bacteria. The drug is especially valuable for urinary tract infections (pyelonephritis, cystitis), sepsis, wound infection, burns. Routes of administration: intramuscularly or externally.

Gentamicin is less toxic than neomycin. However, the main adverse effects typical of aminoglycosides are also observed with gentamicin. One of them is the ototoxic effect. Basically, gentamicin affects the vestibular branch of the VIII pair of cranial nerves. Hearing is less common. Nephrotoxicity is also less pronounced than with non-omycin. It has curariform properties.

The tobramycin (brulamycin) group is also an aminoglycoside group. Produced by Str. tenebrarius. It has a wide spectrum of action. Highly active against Pseudomonas aeruginosa. Effective antimicrobial concentrations after a single injection last for 6-8 hours. The drug is administered intramuscularly and intravenously. It is allocated mainly by kidneys. Indications for use are similar to those for gentamicin and are determined by the spectrum of antimicrobial action. It has nephro- and ototoxicity, but less pronounced than gentamicin.

Aminoglycosides also include the antibiotic sisomycin. Micromonospora inyoensis is produced. It has a wide spectrum of antimicrobial action similar to that of gentamicin. More active than the latter in relation to different types of Proteus, Pseudomonas aeruginosa, Klebsiella, Enterobacter

Sisomycin resistance develops slowly. Cross-resistance to all aminoglycosides also occurs.

1 Special ointments “Lokacorten-N”, “Sinalar-N” were issued (N indicates the presence of neomycin).

The drug is poorly absorbed from the digestive tract, therefore it is administered intramuscularly and intravenously. About 25% binds to plasma proteins. The frequency of administration in a clinical setting is 8 hours.

Indications for use and side effects are similar to those for gentamicin.

Among the most effective aminoglycosides is amikacin (amikin) 1. It is a derivative of kanamycin. Of all aminoglycosides, it has the widest spectrum of antimicrobial activity, including aerobic gram-

negative bacteria (including Pseudomonas aeruginosa, Proteus, Klebsiella, Escherichia coli, etc.) and Mycobacterium tuberculosis. Most gram-positive anaerobic bacteria are not affected. Resistant to many bacterial enzymes that inactivate aminoglycosides. It has ototoxicity and nephrotoxicity. Amikacin is administered intramuscularly and intravenously.

CYCLIC POLYPEPTIDES (POLYMIXINS AND OTHERS)

Chemically, polymyxins are a group of cyclic polypeptides. In our country, polymyxin M (in the form of sulphate), produced by Bac, is used. polymyxa Ross. In a number of other countries, polymyxin B and polymyxin E (colistin) were most prevalent.

In polymyxin M sulfate, the antimicrobial effect is predominantly expressed in relation to gram-negative bacteria: Pseudomonas aeruginosa, the family of intestinal bacteria (Escherichia coli, Shigella, Salmonella), as well as capsular bacteria, Pasteurella and Brucella, Influenza coli. Polymyxin M is resistant to pathogenic cocci, protea, pathogenic anaerobes, acid-resistant mycobacteria, diphtheria bacillus and some other pathogens.

The antimicrobial mechanism is associated with the damaging effect of polymyxin M on the cytoplasmic membrane. By disrupting its permeability, polymyxin M promotes the excretion of many components of the cytoplasm into the environment. Lysis of microorganisms occurs. A bactericidal effect is observed both at rest, and in the process of growth and reproduction of bacteria. Polymyxin M acts only on extracellularly located microorganisms.

Resistance to polymyxin M develops slowly, which is an undeniable advantage of the drug.

Polymyxin M sulfate is prescribed orally (high concentrations of the drug accumulate in the intestine; it is poorly absorbed from the gastrointestinal tract) and locally. It is not used parenterally, since with this route of administration it causes severe neuro- and nephrotoxic disorders. Enteral drug is used for enterocolitis caused by Pseudomonas aeruginosa, Escherichia coli, Shigella, as well as for sanitation before surgery. Topically, polymyxin M sulfate is effective in the treatment of purulent processes caused by pathogens sensitive to it (mainly gram-negative microorganisms, including Pseudomonas aeruginosa).

Side effects with enteric and topical administration of polymyxin M sulfate are rare. When administered, dyspeptic symptoms are possible, associated with some irritating effect of the drug. Sometimes superinfection occurs. Allergic reactions are practically not observed.

Contraindications to the appointment of polymyxin M sulfate are diseases of the kidneys.

Given the pronounced nephrotoxicity of this antibiotic, even if used internally or locally, it is necessary to systematically monitor renal function.

The new antibiotic daptomycin chemically resembles polymyxin. Belongs to cyclic lipopeptides. It is a semi-synthetic antibiotic obtained from the fermentation products of Streptomyces roseosporus. It binds to the cytoplasmic membrane of bacteria, causing their death. It has a bactericidal effect on gram-negative and gram-positive bacteria. Anaerobic bacteria have little effect.

Of the side effects, nausea, vomiting, muscle pain, myopathy, etc. are possible. Enter intravenously. It is used for the ineffectiveness of other anti-microbial agents.

LINKOSAMIDES

Clindamycin belongs to this group. It is an inhibitor of bacterial protein synthesis and usually acts bacteriostatically. It is active mainly against anaerobes (Bacteroides fragilis, etc.), streptococci and staphylococci. It is well absorbed from the intestines. It penetrates poorly through the blood-brain barrier. Metabolized in the liver. It is excreted by the kidneys and with bile.

It is used for infections caused by bacteroids, especially with the defeat of the Bacteroides fragilis of the abdominal cavity.

The most dangerous side effect is pseudomembranous colitis (diarrhea develops with mucous and bloody discharge, pain in the stomach, fever). This is one of the manifestations of dysbiosis associated with the action of the toxin Clostridium difficile, which can be found in the intestine. This complication is treated with vancomycin and metronidazole. Allergic reactions, liver damage, leukopenia are rarely observed.

Glycopeptides

The main drug of this group is vancomycin, which is a complex glycopeptide. It is produced by Streptomyces orientalis actinomycetes. It disrupts the synthesis of the bacterial cell wall and acts bactericidal. It has high activity against gram-positive cocci, including staphylococci resistant to methicillin and strains producing β-lactamases; acts on clostridia, including Clostridium difficile, as well as corynebacteria. It is poorly absorbed from the digestive tract. If a systemic effect is required, the drug is administered intravenously. It passes through the blood-brain barrier, especially with meningitis.

In addition, there is evidence that vancomycin affects the permeability of the cytoplasmic membrane and RNA synthesis.

Vancomycin is used for infections caused by gram-positive cocci resistant to penicillin, for enterocolitis, including pseudomembranous colitis.

The drug is toxic, which limits its use. It has ototoxicity and nephrotoxicity, can cause phlebitis. Allergic reactions, neutropenia, thrombocytopenia rarely occur.

The antibiotic teicoplanin belongs to the same group. Similar in properties to vancomycin. It acts for a long time. Enter once a day intramuscularly or intravenously.

FUZIDIC ACID

This is a narrow-spectrum antibiotic. It is used in the form of sodium salt. Mostly affects gram-positive bacteria. Inhibits bacterial protein synthesis. It acts bacteriostatically. It is well absorbed by enteral administration. In significant quantities accumulates in bone tissue. Metabolized in the liver. It is allocated with bile. It is used for staphylococcal infections resistant to penicillin, especially for osteomyelitis. Side effects: dyspeptic symptoms, skin rash, jaundice.

ANTIBIOTICS FOR LOCAL USE

For local exposure, an antibiotic fusafunjin (bioprox) with antimicrobial and anti-inflammatory effects is proposed. It is produced by a special strain of fungi Fusarium lateritium WR. By chemical structure, it refers to peptides. They release the drug in the form of aerosols for inhalation. It is effective against many cocci, some anaerobes, myoplasmas, fungi of the genus Candida. It is recommended for use in infections of the nasopharynx and respiratory tract. Of the side effects, an irritating effect is sometimes noted.

For topical application, an antibiotic mupirocin (bactro-ban) is also proposed. It is produced by Pseudomonasfluorescens. Inhibits protein synthesis. It has a bacteriostatic effect at low concentrations, and a bactericidal effect at high concentrations. To a small extent, absorbed from intact skin (0.25-0.3%). It is applied cutaneous or intranasally in the form of an ointment for damage to the skin and mucous membrane of the nasal passages with staphylococci (including t Side effects may be related to:

with hypersensitivity (allergic reactions, interstitial nephritis, vasculitis, fever),

toxic effect - nephrotoxicity, hepatotoxicity, ototoxicity, neurotoxicity ...,

gastrointestinal reactions,

hemorrhagic syndrome,

phlebitis,

electrolyte disturbances,

violation of alcohol tolerance,

chemotherapeutic effect of antibiotics:

(dysbiosis, superinfection,

Jarisch-Herxheimer syndrome.

Allergic reactions (immediate occurring up to 30 minutes, fast - 1–48 hours, delayed - after more than 48 hours) can develop with the use of any antibacterial drugs, but are most often observed with beta-lactam antibiotics and sulfonamides . Their occurrence is not associated with a pharmacological effect and does not depend on the dose of the drug, but the manifestations may increase with increasing dose. Allergic reactions necessarily occur again after repeated administration of the same or close in chemical structure antimicrobial agent, with the latent period becoming shorter and the symptoms more pronounced. Among the complications of antibiotic therapy, allergic reactions from mild skin lesions to anaphylactic shock are most common. According to information from 17 countries received by WHO, 1 case of death from anaphylactic shock accounts for 70 000 cases of antibiotic treatment. According to Kh.Kh. Planelles and A.N. Kharitonova (1968), summarizing 29 reports of domestic and foreign authors on this topic, the number of allergic reactions during treatment with penicillin ranged from 0.3 to 4.8%.

Cases of anaphylactic shock are possible in the treatment of various antibiotics, but in 90% of cases the cause of the shock is sensitization to penicillin.hose resistant to methicillin) and β-hemolytic streptococci.

There are reports of the development of shock with the introduction of aminoglycosides, levomycetin, tetracyclines, etc.

Among generalized allergic reactions, serum sickness syndrome should be mentioned, accompanied by fever, swollen lymph nodes, splenomegaly, eosinophilia, joint pain, urticaria, angioedema, etc. Serum sickness often occurs in cases of allergic reactions to penicillin. Serum sickness as a result of antibiotic therapy, as a rule, does not require special treatment and occurs after the termination of antibiotic therapy. In protracted cases, desensitizing therapy, the use of antihistamines and hormones are required.

Urticaria accounts for more than 1/3 of the complications arising from the use of antibiotics (in 2-4% of patients treated with penicillin). Perhaps the development of angioedema, edema of the brain and lungs. An allergic reaction may manifest as hemorrhagic vasculitis. Therapeutic measures for allergic complications are determined by their nature, and the urgency of carrying out is determined by the severity of the condition of the patients. Skin allergic reactions in most cases are easily treatable: as a rule, discontinuation of the drug and the use of antihistamines are sufficient. In rare cases, these reactions take a protracted course, which requires desensitizing therapy, in particular the appointment of corticosteroid hormones; generalized forms of exfoliative dermatitis sometimes end fatally. In severe cases, a combination of local and general allergic reactions, the use of antihistamines, calcium chloride, corticosteroids, proteolysis inhibitors is indicated. When angioedema extends to the larynx, tracheostomy is indicated. Antihistamines with mild skin manifestations in some cases allow, if necessary, to continue antibiotic therapy, which caused allergic reactions. In anaphylactic shock,

resuscitation measures should include the use of vasopressor, cardiac, hormonal, desensitizing and antihistamines, anti-shock blood substitutes. In anaphylactic shock caused by penicillin, intravenous administration of penicillinase at a dose (number of units) is shown, corresponding to the dose of penicillin administered after emergency measures were taken to remove the patient from collapse. To prevent complications of antibiotic therapy, tests are used for hypersensitivity to antibiotics: cutaneous, intradermal, conjunctival, etc. The diagnostic value of these samples should be treated critically, they are important in cases of positive results, but negative results do not exclude the possibility of sensitization. In addition, when conducting tests for sensitivity to antibiotics, there are severe complications, even deaths are described. The determination of hypersensitivity to antibiotics should begin with clarification of anamnestic data. It is important to find out whether the patient has been treated with antibiotics before and how he tolerated them, whether there were allergic manifestations during or after antibiotic therapy. Allergic (history of allergic (bronchial asthma, asthmatic bronchitis, allergic rhinitis, urticaria, etc.) and fungal (epidermophytia, ringworm, scab, microsporia, etc.) are clarified. In most cases, this information is sufficient to form an idea of the sensitization of the body and the possibility of initiating antibiotic therapy. Allergic reactions when using antibiotics occur when information about the possible sensitization of patients to antibiotics has not been clarified. Even when patients themselves indicated poor tolerance of antibiotics, increased sensitivity to them, the doctor did not take this information into account. We believe that the indications for special methods for determining the sensitization to antibiotics should be dubious medical history of poor tolerance of the drug or allergic or fungal diseases, despite the good tolerance of antibiotics in the past. Patients with various allergic diseases should be considered predisposed to allergic reactions to antibiotics. Anaphylactic type reactions are observed in them, and slow type reactions often occur equally with and without allergic diseases. Data on the development of allergic complications caused by penicillin therapy in patients with multivalent sensitization indicate the importance of an allergic history

Damage to the central nervous system when using antibiotics is rare. Neurotoxicity can manifest itself in visual impairment (aztreonam, chloramphenicol, isoniazid, ethambutol, ethionamide), taste (ampicillin, metronidazole, tetracycline), seizures (aztreonam, imipenem / cilastatin, metronidazole, quinolones, penicillin, penicillin, penicillin, penicillin, penicillin, penicillin, penicillin, penicillin, penicillin, penicillin) chloramphenicol, isoniazid, ethambutol, nitrofurantoin). The toxic effect on the central nervous system is especially pronounced when penicillin megadoses are used. If the concentration of the drug in the cerebrospinal fluid is higher than 10 μg / ml, a direct toxic effect on the brain is manifested. It can be expressed in motor excitement, convulsions, confusion. The use of high doses of semisynthetic penicillins can lead to similar complications. Aminoglycosides and vancomycin can cause damage to the auditory or vestibular apparatus. Hearing disorders when using streptomycin are more often observed in patients with kidney failure: after 2 weeks from the start of treatment, damage to the organ of hearing may occur. Hearing disorders usually occur 3-4 months after the start of treatment and develop gradually. Children under the age of 2 years are most sensitive to the ototoxic effect of aminoglycosides. Optic neuritis is rare. The effect of antibiotics on the organ of vision can be expressed in a violation of accommodation, with severe optic neuritis, their atrophy is possible. There are reports of the toxic effect of aminoglycosides, poly-myxin on peripheral nerves (polyneuritis) in 0.2-1% of clinical cases. The neuromuscular block is a serious complication caused by the neurotoxic effect of antibiotics (aminoglycosides, polymyxin). Describes (60 years) a sudden stop of breathing with the introduction of drugs into the abdominal cavity during laparotomy under ether anesthesia. The selectivity of the interaction of aminoglycosides (streptomycin, polymyxin) with muscle relaxants makes it possible to exclude such combinations not only during operations on the organs of the abdominal and chest cavities, but also during other interventions with the introduction of large doses of antibiotics (regional perfusion, prolonged infusion) in the treatment of purulent processes of various localization.

Hematologic syndromes constitute a small group of complications of antibiotic therapy. Peripheral blood changes are diverse and include eosinophilia, agranulocytosis, aplastic, hemolytic anemia, leukopenia, thrombocytopenia.

Hemorrhagic syndrome is caused by second-third-generation cephalosporins having an N-methylthiotetrazole ring: cefamandol, cefotetan, cefoperazone, moxalactam (disrupts the absorption of vitamin K in the intestine), as well as antiseptic penicillins: carbenicillin, less often - ticarcillin, less often - thrombocytes) and metro-nidazole (displaces coumarin anticoagulants from the bond with albumin). In rare cases, neuropenia / agranulocytosis occurs with the use of anti-pseudomonas penicillins, nitrofurans, sulfanilamides, rifampicin, more often with chloramphenicol (chloramphenicol). The effect of chloramphenicol on the blood formation of patients is rare, but with prolonged use of large doses, changes in the hematopoietic apparatus are possible. The negative effect of chloramphenicol on hematopoiesis should not be overestimated, but treatment should be carried out under the constant supervision of blood tests and, at the first sign of toxic action, discontinue the drug.

Almost all antibiotics, often tetracyclines, macrolides, lincomycin, have a side effect on the gastrointestinal tract. In the treatment with tetracycline, nausea, vomiting, abdominal pain, diarrhea, flatulence can be observed. When treating with tetracycline drugs, lincomycin, vomiting, diarrhea, and nausea are observed. Very rarely erosive gastritis, gastric bleeding (observed with gastroscopy in patients receiving chlortetracycline). Patients note dry mouth, burning tongue. In 2/3 of the observations, dyspeptic disorders in the treatment with tetracyclines were combined with skin rashes, which indicates the effect of allergic reactions on the functions of the gastrointestinal tract.

Pseudomembranous colitis occurs against the background of antibiotic therapy as endogenous superinfection (etiological factor Clostridium defficile) and is accompanied by severe diarrhea (4-6 times or more per day), bloody stools, cramping abdominal pain, fever (39-40 ° C), leukocytosis. The risk is highest when using lincomycin, clindamycin, ampicillin. When these signs appear, the antibiotic is canceled; prescribe vancomycin orally at 125 mg 4 times a day for 7 days or metronidazole orally at 250 mg 4 times a day for 7-10 days.

Pseudomembranous colitis often ends in death.

Kidney damage during antibiotic therapy may be allergic in nature or may be a result of direct nephrotoxicity. Interstitial nephritis (symptoms: hematuria, proteinuria, fever, rash, eosinophilia in the blood and urine, impaired renal function in 50% of cases) is often caused by semisynthetic penicillins (oxacillin, methicillin). The toxic effect on the kidneys (a decrease in renal function with an increase in the concentration of urea, creatinine in the blood) is most often manifested by the use of aminoglycosides, polymyxins, and vancomycin. Old age, hypotension, hypovolemia, liver disease, previous treatment with aminoglycosides, a combination of certain drugs (for example, aminoglycosides with diuretics) are predisposed to it.

Hepatotoxic effects (can occur in the form of cholestasis or hepatitis) develop with the use of anti-TB drugs, oxacillin and methicillin, aztreonam, tetracyclines, lincosamines, sulfanilamides. Preventive measures for the appointment of drugs with hepatotoxic effects are similar to those for other antibiotics with organotoxic properties: in case of damage to the liver parenchyma, the use of these drugs should be limited. For prophylactic and therapeutic purposes, the appointment of vitamins is indicated, especially group B. At the first signs of liver damage, the drug should be discontinued.

Hemolysis can develop under the influence of beta-lactam antibiotics, cotrimoxazole, trimethoprim (autoimmune hemolysis), as well as with the use of sulfonamides, nitrofurans, fluoroquinolones, cotrimoxazole, rifampicin due to hereditary deficiency in glucose-6-phosphate dehydrogen erythrocytes.

Phlebitis is possible with the intravenous use of almost all antibacterial agents, especially often (in decreasing order) with the introduction of monobactams, tetracyclines, vancomycin, polymyxin, cephalosporins.

Violation of tolerance to alcohol develops with the use of metronidazole, chloramphenicol and second-third generation cephalosporins having a methylthiotetrazole ring (cefamandol, cefoperazone,

cefotetan, cefmetazole). With the simultaneous use of alcohol, nausea, vomiting, dizziness, headache, hypotension, sweating are observed

Photosensitivity occurs with the use of fluoroquinolones, less often tetracyclines, sulfonamides, and is manifested by darkening of the skin in open areas of the body under the influence of sunlight (tanning, including burns).

The toxic effect of some antibiotics on the body requires special tactics of antibiotic therapy of bacterial infections in pregnant women and puerperas. In pregnant women, the dangers of exposure to the developing fetus should be taken into account, and in puerperas, the effect of antibiotics excreted in mother's milk on the baby. In the treatment of pregnant women with first-generation aminoglycosides, cases of damage in the newborn organs of the hearing, liver, kidneys, violation of the formation of the skeleton, teeth are described; in this regard, the use of chloramphenicol, tetracyclines, first-generation aminoglycosides is contraindicated 3-6 weeks before delivery. During pregnancy, if necessary, it is possible to prescribe second-generation antibiotics, primarily antistaphylococcal ones that do not have embryotoxic and teratogenic effects, i.e. semisynthetic penicillins and cephalosporins. When prescribing ampicillin, methicillin, oxacillin, zeporin, kefzol should focus on therapeutic doses, the excess of which is dangerous due to toxic effects on the fetus, especially in the early stages. In the treatment of purulent-inflammatory diseases in pregnant women, nursing mothers, tetracyclines, chloramphenicol, streptomycin, rifampicin, chloramphenicol are contraindicated. The administration of aminoglycosides is also inappropriate. It should be borne in mind that the indications for antibiotic therapy in this category of patients should not exceed the risk of the drug acting on the child, which can be expressed in sensitization, impaired formation of normal microflora, and the development of antibiotic resistance of the microbial flora. In cases of severe purulent infection, when nursing mothers need antibiotic therapy, the baby should be weaned during treatment or permanently. In such cases, it is necessary to provide adequate nutrition for the child with donor milk or artificial mixtures. With postpartum mastitis caused by Staphylococcus aureus, vancomycin, penicillin-resistant semi-synthetic penicillins are shown - oxacillin, ampicillin, methicillin, dicloxacillin, as well as cephalosporins, fusidine, lincomycin.

Among the adverse reactions of antibiotic therapy due to the direct chemotherapeutic effect of the drugs, one should mention the exacerbation reaction - toxic shock (Yarish-Herxheimer reaction), which occurs mainly in the treatment of patients with syphilis, typhoid fever, and brucellosis.

Under antibiotic therapy, as a result of the suppression of the competing microbial flora, opportunistic bacteria begin to multiply or the infection of their “dormant foci” worsens. Superinfection can be considered only those pathological conditions in which as a result of therapy the infectious process is eliminated and a new disease arises (the “pathology of therapy” according to I.V. Davydovsky, 1962) with special clinical manifestations and a new pathogen. The causative agents of the infection can be the natural inhabitants of the body (autoinfection) - Proteus, E. coli, pseudomonads, etc. Intestinal inhabitants as a result of antibiotic therapy in preparation for surgery can create favorable conditions for development due to the death of competitive flora. In cases of targeted suppression of the natural bacterial flora with antibiotics, it is extremely important to take into account the spectrum of action of the drugs used. One of the manifestations of superinfection during antibiotic therapy is candidiasis, which occurs in 1% of patients with diabetes who were treated with antibiotics for purulent-inflammatory diseases. Patients with diabetes are predisposed to candidiasis. Candidiasis is caused by Candida fungi, about 30 species of which exist in the body as commensals. The pathogenesis of generalized candidiasis has a complex mechanism, and it is difficult to explain their occurrence only by dysbiosis. The pathogenetic concept of the role of antibiotic therapy in the development of candidiasis can be formulated as follows. Long-term antibiotic therapy in certain background conditions and in the absence of appropriate preventive measures leads to a violation of the natural antagonism of microorganisms. As a result of suppression of the normal, antibiotic-sensitive saprophytic microflora, fungi multiply intensively and unhindered, which becomes the starting point in the development of the pathological process. The treatment of

candidiasis of any localization should be comprehensive and include both specific antifungal therapy and the use of vitamins, high-grade protein nutrition, in severe cases of blood transfusion, blood transfusion, protein blood substitutes, gamma globulin. Antifungal antibiotics (nystatin, levorin), iodides (iodides of potassium, sodium, tincture of iodine), aniline dyes (gentian violet, pioctanin, methylene blue, diamond green) are used as specific exposure agents; in addition, I use solutions of potassium permanganate, tannin, hexamethylenetetramine (urotropin), etc. Thus, adverse reactions to antibiotics depend on their group characteristics. Third-fourth generation cephalosporins can lead to superinfection with gram-positive bacteria, as well as Pseudomonas aeruginosa or fungi. Aminoglycosides are characterized by nephro- and neurotoxicity, which increases with the combination of these drugs with vancomycin or diuretics (dichlothiazide, ethacrylic acid). Aminoglycosides should be applied no more than 7 days. Fluoroquinolones are able to cause photodermatitis, their influence on the development of the skeleton is not excluded. Glycopeptides (vancomycin) have a nephrotoxic effect and can cause vascular reactions. Macrolides can cause disorders of the gastrointestinal tract, due to increased intestinal motility and increased tone

Antibacterial therapy (ABT) is often associated with a large risk for patients. The number of possible complications from the use of ABP when fully enumerated can take (and sometimes take) most of the standard annotation for ABP. Therefore, we decided to start with a clinical example. When using ABP, the following complications and adverse reactions are possible.

1. Allergic reactions. Allergic reactions, or hypersensitivity reactions, occur with the use of any antibacterial drugs, but are most often observed during treatment with β-lactam antibiotics and sulfonamides. These side effects are not associated with the pharmacological effects of drugs and are not dependent on the dose of the drug; they necessarily occur after repeated administration of an antibacterial agent that caused them or is close in chemical structure. By the speed of occurrence, immediate, quick and delayed reactions are distinguished, by severity - severe or life-threatening and moderate.

A. Immediate reactions (up to 30 minutes):

- Severe: anaphylactic shock, angioedema (Quincke's edema), bronchospasm;

- moderate: urticaria.

B. Quick reactions (1–48 hours):

- Severe: angioedema (Quincke's edema), bronchospasm;

- moderate: urticaria, skin itching, erythema, rhinitis.

B. Delayed reactions (> 48 hours):

- moderate: urticaria, polymorphic rash, erythema, arthritis, hemolytic anemia, eosinophilia, thrombocytopenia, leukopenia, agranulocytosis, interstitial nephritis, vasculitis, lupus-like syndrome, fever.

The most severe toxic-allergic reactions caused by antibiotics are:

- blood dysrasia - thrombocytopenia, leukopenia, megaloblastic anemia, methemoglobinemia;

- anaphylactic shock;

- Stevens-Johnson syndrome, Lyell's syndrome;

- pseudomembranous colitis; serum sickness, angioedema.

It is very important to anticipate the possible occurrence of these complications in order to prevent serious consequences in a timely manner.

Since β-lactam antibiotics (especially semisynthetic penicillins and cephalosporins (CS) of I – II generations) have allergenic properties, contraindications to their use are hypersensitivity to the antibiotics of the applied group and anaphylactoid reactions in history.

In such patients, all types of immune reactions can develop:

- immediate hypersensitivity, manifested by urticaria, laryngeal edema, bronchospasm (with or without hypovolemic shock);

- cytotoxicity, proceeding in the form of hemolytic anemia or thrombocytopenia;

- the formation of immune complexes in tissues with their subsequent damage;

- delayed hypersensitivity (skin rash, dermatitis, serum sickness).

Treatment of allergic reactions includes immediate withdrawal of the antibacterial drug, regardless of the severity of the reaction. Repeated administration of the same drug after elimination of symptoms is not allowed. With the development of severe reactions, the subsequent administration of compounds similar in chemical structure is also not allowed (for example, in the reaction to penicillin, other antibiotics with a β-lactam structure should not be prescribed - semisynthetic penicillins, cephalosporins, carbapenems, monobactams). In case of moderate reactions, in case of emergency, similar drugs are allowed, however, it is necessary to remember the possibility of cross-allergy: for example, the frequency of allergic reactions with cephalosporins is about 2%, however, in patients with hypersensitivity to penicillin, the risk of allergic reactions increases to 10%. If cross-allergy is possible, the first administration of an antibacterial drug should be carried out only under conditions guaranteeing the provision of emergency care; patient monitoring should be at least 2 hours

Treatment of patients with anaphylactic reactions includes specific measures aimed at counteracting the effects of vasoactive chemical allergy mediators, as well as general measures to eliminate impaired hemodynamics and respiratory function

Emergency measures for severe manifestations of sensitization to antibiotics are drug withdrawal and the immediate administration of adrenaline solutions (0.5-1.0 ml 0.1% subcutaneously or intramuscularly) or 0.1 ml 0.1% intravenously, sometimes repeatedly (after 10 –30 min), as necessary, to maintain blood circulation function. Drop-dose administration of no-radrenaline (5 mg per 500 ml of solvent) together with glucocorticosteroids (prednisone 60–120 mg or hydrocortisone 125–250 mg intravenously) is also recommended; calcium chloride (10 ml 10% intravenously slowly); antihistamines and desensitizing drugs, such as diphenhydramine, suprastin, tavegil and others in standard dosages.

2. Direct toxic effect of antibiotics. It is characterized by a number of clear signs: a) selectivity (each antibiotic has its own targets), drug administration is accompanied by individual clinical manifestations; b) the greatest likelihood of damage to an already pathologically altered organ (or tissue); c) dose and time dependence.

Neurotoxicity in the form of polyneuritis, the neuromuscular block is characteristic of aminoglycoside antibiotics, polymyxins, lincosamides, ristomycin, amphotericin B.

Visual impairment: aztreonam, isoniazid, chloramphenicol, ethambutol.

Taste disorder: ethionamide, ampicillin, amphotericin B, metronidazole, tetra-cyclin, ethambutol, cefamandol.

Seizures: aztreonam, imipenem, metronidazole, nalidixic acid, penicillins (in high doses), piperacillin, fluoroquinolones (in elderly patients or in combination with theophylline).

Hallucinations: cycloserine, chloramphenicol, gentamicin, isoniazid, nalidixic acid, tobramycin, ciprofloxacin.

Paresthesia: colistin, polymyxin B, streptomycin, chloramphenicol.

Peripheral neuropathy: polymyxin B, isoniazid, metronidazole, nitrofurantoin.

Ototoxicity: aminoglycosides (gentamicin), vancomycin.

Clinical manifestations of neurotoxicity:

a) auditory disorders:

- hearing loss - 2-12%;

- deafness - <0.5%;

b) vestibular disorders (1-3%):

- nausea, vomiting, dizziness, unstable gait, nystagmus.

Risk factors:

- renal failure;

- elderly age;

- combined use of aminoglycosides and loop diuretics (ethacrylic acid, to a lesser extent furosemide).

Treatment: antibiotic withdrawal, syndromic therapy using drugs of the diphenin group (pipolfen), vascular and metabolic therapy.

Nephrotoxicity (intracapillary glomerulonephritis, periarteritis, canalicular interstitial nephritis, renal failure) occurs when aminoglycosides, glycopeptides, polymyxins, some cephalosporins, amphotericin B, ristomycin, expired tetracyclines are used.

Symptoms: increased levels of urea and plasma creatinine; proteinuria; oliguria.

Predisposing factors: age> 60 years (especially in women); kidney disease; liver disease arterial hypotension; a decrease in diuresis due to prerenal factors (hypovolemia); aminoglycosides + vancomycin (+ cephalosporins of the 1st generation); aminoglycosides + thiazide diuretics; previous treatment with aminoglycosides.

Antibacterial agents causing kidney damage:

a) the most dangerous:

- AH;

- polymyxins;

- vancomycin;

b) less dangerous1:

- CA 1st generation;

- tetracyclines;

- rifampicin;

- co-trimoxazole

Prevention: correction of hypovolemia; increased renal blood flow; heart failure treatment; therapeutic monitoring; control of diuresis (at least 1 liter per day); correction of the dosage regimen (body weight, function-check); the introduction of a daily dose of aminoglycosides 1 time per day; short course of treatment.

Interstitial nephritis. Semi-synthetic penicillins (most often methicillin).

Symptoms: hematuria; proteinuria; fever; rash; eosinophilia in the blood and urine; impaired renal function (in 50% of complications).

Treatment: antibiotic withdrawal; glucocorticosteroids; dialysis treatment.

Hepatotoxicity. The appearance of toxic hepatitis is typical for taking amphotericin B; cholestasis - for macrolides and lincosamides; conjugation jaundice - for chloramphenicol.

Antibacterial agents with hepatotoxicity (in the order of decreasing the damaging effect): anti-tuberculosis drugs, oxacillin, methicillin, aztreonam, tetracyclines, lincosamines, sulfanilamides, co-trimoxazole.

With prolonged (more than 1 week) use of antibacterial agents with a hepatotoxic effect, it is necessary to regularly (once a week) monitor liver function (ACT, ALT, bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase).

Gastrointestinal toxicity. When taken orally, all antibiotics can cause damage to the gastrointestinal tract. In this case, gastritis, enteritis, erosion and ulcers occur. Taking tetracyclines (doxycycline) can lead to stomatitis, colitis and esophagitis. Side effects of the interaction of tetracyclines are often associated with the simultaneous intake of food and divalent metals. One or another violation of the gastrointestinal tract function is observed with different frequencies when using almost all antibacterial agents, mainly when taking the drug inside, which is called antibiotic-associated diarrhea. The frequency of development of these side effects depends not only on the chemical structure of the drug, but also on the dosage form, so the severity of side effects can vary even for the same drug made by different manufacturers. The most common gastrointestinal side effects are nausea, vomiting, diarrhea. Other symptoms may also be observed: anorexia, metallic taste in the mouth (metronidazole), abdominal pain (fluconazole, ketoconazole). The most serious side effect is pseudomembranous colitis caused by Clostridium difficile [31].

Since the 50s. XX century the widespread use of antibacterial drugs has led doctors to pay attention to serious side effects that occur when taking oral antibiotics, mainly in the form of intestinal lesions. The use of broad-spectrum antibiotics such as lincomycin and clindamycin led to diarrhea in 10% of patients, and in 1% it caused pseudomembranous colitis (MVP), characterized by ulcerative necrotic lesion of the intestine with the formation of a whitish plaque that resembles diphtheria.

Etiological factor: Clostridium difficile.

In 1935, when studying the intestinal microflora of newborns, the American microbiologists Hall and O'Toole isolated a new spore-forming anaerob belonging to the genus Clostridium and named C. difficile (“difficult” clostridia) due to significant difficulties in isolating and obtaining the culture. Due to the fact that this microbe was isolated from the feces of healthy newborns, it was initially considered as commensal, and its pathogenic properties have not been studied for a long time. Since the 50s. XX century the widespread use of antibacterial drugs made doctors pay attention to serious side effects that occur when taking oral antibiotics, mainly in the form of intestinal damage. The use of broad-spectrum antibiotics such as lincomycin and clindamycin led to diarrhea in 10% of patients, and in 1% it caused MVP, characterized by ulcerative necrotic lesion of the intestine with the formation of a whitish plaque resembling diphtheria.

MVP was first described by Finney in 1893. For many decades, it has been considered as a consequence of a variety of causes, in particular ischemia or viral infection. However, in 1977, Larson et al. reported the excretion of toxin from the stool of patients with MVP, which has a cytopathic effect in tissue culture. Soon, the pathogen producing this toxin was identified. It turned out to be the long-known C. difficile, which forced microbiologists and doctors to fundamentally reconsider their view of this microbe as an innocuous commensal. The incidence of diarrhea when using various antibiotics is maximum for amoxicillin / clavulanate - 10–25% and cefixime — 15–20%. Of other drugs, it can be caused by ampicillin in 5–10% of cases, clindamycin in 5–10%, cephalosporins (except cefixime) in 2–5%, macrolides in 2–5%, and tetracycline in 2–5 %, fluoroquinolones - in 1-2%, trimethoprim-sulfamethoxazole - in less than 1%.

Even vancomycin and metronidazole, which have been successfully used to treat C. difficile infection, can cause diarrhea caused by this pathogen in some patients. In developed countries, the most common cause of antibiotic-associated diarrhea was ampicillin and cephalosporins, due to their widespread use.

C. difficile is the cause of MVP in 100% of cases. Of all patients with antibiotic-associated diarrhea, its etiological role can be proved in 10–20% [31]. In most other cases, it is not possible to identify a specific pathogen, however, in 2-3%, C. perfringens and bacteria of the genus Salmonella are considered as etiological factors. The role of Candida albicans is controversial. Given the fundamentally different prognosis and management approaches, it is important for clinical practice to isolate diarrhea associated with or not associated with C. difficile infection. Nonspecific differential diagnostic criteria for the development of antibiotic-associated diarrhea are summarized in table. 1.

Intestinal colonization of C. difficile is observed in approximately 50% of newborns. The pathogenic properties of the pathogen do not appear until the end of the first year of life, due to a lack or underdevelopment of intestinal receptors for the toxins produced by it. At the same time, asymptomatic carriage of C. difficile is detected in a certain part of the adult population - from 1-3% in Europe to 15% in Japan.

The highest likelihood of colonization of the intestine is observed in individuals receiving oral antibiotics. Other risk factors include advanced age, abdominal surgery, chemotherapy. Often there is nosocomial infection, which is caused, on the one hand, by the frequent use of antibiotics in hospital patients, and on the other, by the contamination by bacteria and their spores of hospital equipment and instruments.

Pathophysiological processes leading to the occurrence of antibiotic-associated diarrhea that is not associated with C. difficile infection have not been adequately studied. Significant fluctuations in the incidence of diarrhea with the use of various antibacterial drugs are due to their pharmacokinetics.

So, the leadership of amoxicillin / clavulanate is probably due to the ability of clavulanic acid to enhance intestinal motility. Cefixime and cefopera zones accumulate in high concentrations in the colon due to incomplete absorption or enterohepatic circulation. The considered form of diarrhea usually stops on its own when the antibiotic is canceled or its dose is significantly reduced.

The pathogenesis of diarrhea due to C. difficile and its most severe form, MVP, has been studied much better. C. difficile diarrhea is a toxic infection caused by the action of two proteins with a molecular weight of 308 and 270 kDa, designated respectively as Toxin A and Toxin B. Toxin A is an enterotoxin with a relatively weak cytotoxic effect, while toxin B exhibits a pronounced cytotoxic effect in cell culture.

A characteristic feature of C. difficile infection is a significant variability of clinical manifestations - from asymptomatic carriage to fulminant forms of enterocolitis. The explanation of this fact by infection with strains with different ability to produce toxins does not stand up to criticism: the detection of significant concentrations of toxin in the feces is often observed in asymptomatic carriers.

Estimated protective factors may include different sensitivities of toxin-binding receptors, especially intestinal microflora, as well as different severity of the macroorganism's immune response. Information on this issue to this day remains controversial, which prevents the development of effective preventive measures, in particular vaccination.

Antibiotic-associated diarrhea debuts on average one week after the start of taking the antibacterial drug, although timing fluctuations can range from several hours to 4 weeks. Diarrhea, not associated with C. difficile, has no specific features, is manifested by mildly expressed relaxation of the stool with an increase in its frequency and does not require specific treatment.

As already indicated, MVP is the most severe form of C. difficile infection. The main clinical manifestation of the disease is diarrhea, in some cases with a frequency of stool up to 15-30 times a day. Most patients have constant or cramping abdominal pain in combination with fever, usually subfebrile, but sometimes reaching 40–41 ° C. Palpation tenderness moderate, mainly in the iliac regions. Leukocytosis ranges from 10,000 to 20,000 in 1 μl. However, in some patients, a myeloid reaction is observed with a leukocyte count of up to 60,000 in 1 μl and a sharp shift of the leukocyte formula to the left. Due to the significant loss of protein with feces, hypoalbuminemia develops. Inflammatory bowel changes reflect the presence of white blood cells in the feces. The especially severe course of MVP quickly leads to the development of a clinical picture of toxic megacolon. Later complications include electrolyte imbalance, dehydration, and development of protein-free edema. Perforation of the intestine is very rare. Expressed extraintestinal symptoms are also not characteristic, although cases of the development of polyarthritis involving large joints are described.

Diagnostic methods can be divided into two groups: those aimed at identifying morphological changes in the intestine and at detecting the etiological factor. Currently, there is a shift in emphasis towards the second group of methods, which allow for a significantly lower cost and greater safety for the patient to give direct access to etiotropic treatment.

Widely used in the 70–80s. XX century colonoscopy is currently rarely used. Of non-invasive methods, computer tomography is preferred, with which thickening of the intestinal wall and inflammatory effusion in the abdominal cavity are determined.

Obtaining a co-culture of C. difficile is associated with significant technical difficulties, which follows from the name of the pathogen. Moreover, this method has a fairly low specificity due to the widespread carriage of C. difficile among hospital patients and those taking antibiotics. In connection with this diagnostic method of choice, the detection of the toxin of the pathogen in the feces is recognized.

A prerequisite for treatment is the abolition of the antibacterial drug that caused diarrhea. Already in 1978, research groups in the United States and Great Britain reported the successful use of vancomycin in this disease. To date, vancomycin remains the drug of choice for the treatment of MVP. Its effectiveness is 95-100%. A feature of vancomycin is poor intestinal absorption, as evidenced by the high concentration of the drug in the feces when taken orally. The indicated property of vancomycin allows it to carry out antibacterial effects in MVP with maximum efficiency. In the vast majority of cases, against the background of treatment with vancomycin, the fever disappears after 24–48 hours, and by the end of 4–5 days diarrhea stops. The inefficiency of vancomycin makes one think of another cause of diarrhea, in particular, the onset of ulcerative colitis.

An alternative to vancomycin is metronidazole, the advantages of which include a significantly lower cost and no risk of selection of vancomycin-resistant enterococci. The effectiveness of the preparations is quite comparable, which allowed Zimmerman to take into account metronidazole, taking into account the noted advantages when analyzing the results of treatment of C. difficile infection, [4]. Bacitracin is another highly effective drug, but its high cost limits its widespread use.

A serious problem in the course of antibiotic therapy for C. difficile infection is relapse, which develops on average in 1/4 of patients (range from 5 to 50%) [4].

RECOMMENDATIONS FOR THE TREATMENT OF PRIMARY AND RECOVERY INFECT-CII C. DIFFICILE

1. Primary infection

A. Oral preparations:

a) vancomycin 125 mg 4 times a day for 7-14 days;

b) metronidazole 250 mg 3 times a day for 7-14 days;

c) bacitracin 25 000 units 4 times a day for 7-14 days

B. Oral administration is impossible (extremely serious condition, dynamic intestinal obstruction, intolerance):

a) metronidazole 500 mg intravenously every 6 hours;

b) vancomycin up to 2 g per day through a small intestine or rectal probe.

2. Multiple relapses

A. Vancomycin or metronidazole per os for 10-14 days, then:

a) cholestyramine 4 g 3 times a day + lactobacilli 1 g 4 times a day for 3-4 weeks;

b) vancomycin 125 mg every other day for 3 weeks.

B. Vancomycin + rifampicin for 7-14 days

B. Experimental methods:

a) Saccharomyces boulardii at 250 mg 2 times a day for 4 weeks;

b) immunoglobulin 400 mg / kg intravenously 1 time in 3 weeks;

c) rectal installations of fresh feces from a healthy donor - 50 g per 500 ml of physiological saline;

d) rectal installations of mixed bacterial co-culture from a healthy donor - 109 / ml, 2 ml per 180 ml of physiological saline.

According to Lipsett et al., In 0.4% of patients with a particularly severe course of MVP, the condition progressively worsens, despite the ongoing etiotropic and pathogenetic therapy, which forces them to resort to surgical intervention. The method of choice in such cases is total colectomy.

HEMATOTOXICITY

Hemorrhagic syndrome. Most commonly caused by the following ABPs:

- II – III generation cephalosporins having an N-methyl-thiotetrazole ring in their structure (cefamandole, cefmetazole, cefotetan, cefoperazone, moxalactam);

- antiseptic penicillins (carbenicillin> ticarcillin> ureidopenicillins);

- metronidazole (in combination with oral coumarin anticoagulants).

Causes of hemorrhagic syndrome:

- CS - violation of the absorption of vitamin K in the intestine;

- anti-pseudomonas penicillins - impaired function of platelet membranes;

- metronidazole - displacement of coumarin anticoagulants from the association with albumin.

Factors contributing to the development of hemorrhagic syndrome: old age, hypoalimentation, malignant neoplasms, extensive operations, cirrhosis of the liver, renal failure, hypoalbuminemia.

Neutropenia / agranulocytosis. Isolated cases of neutropenia up to the development of agranulocytosis are described with the use of carboxypenicillins, ureidopenicillins, nitrofurans, sulfonamides, rifampicin, somewhat more often with chloramphenicol. In order to quickly detect neutropenia with prolonged (more than 1 week) use of these drugs, it is necessary to regularly monitor the number of leukocytes and granulocytes in the blood.

Aplastic anemia. Most often observed with the use of chloramphenicol, less often - sulfa drugs. It is characterized by a violation of bone marrow function and is manifested by leukopenia, thrombocytopenia, anemia.

Hemolysis. It can develop with the use of various antibacterial drugs. According to the development mechanism (Table 2), autoimmune hemolysis and hemolysis are distinguished due to hereditary deficiency of glucose-6-phosphate dehydrogenase (G6-FDG) in red blood cells.

OTHER COMPLICATIONS

Phlebitis. They can develop with the intravenous use of almost all antibacterial agents, especially often with the use of monobactams, tetracyclines, vancomycin, polymyxin, cephalosporins. The treatment is symptomatic.

Violation of tolerance to alcohol. It develops with the use of metro-nidazole, chloramphenicol and cephalosporins of II – III generations having a methyl-thiotetrazole ring in their structure: cefamandole, cefoperazone, cefotetan, cefmenoxime, moxalactam (latamoxef), cefmetazole.

It manifests itself with disulfiram-like reactions while drinking alcohol (nausea, vomiting, dizziness, headache, tremor, hypotension, sweating). It is recommended to warn patients when prescribing these antibacterial drugs about the need to exclude alcohol.

Photosensitivity. Hypersensitivity to solar radiation can be observed with the use of fluoroquinolones, less often tetracyclines and sulfonamides, and is manifested by darkening of the skin in open areas of the body, the rapid development of tanning, severe skin burns. When using these drugs, patients should be advised not to be in direct sunlight, especially without clothes. During this period, physiotherapeutic procedures should also be excluded.

Electrolyte disturbances. Hypernatremia can develop with the use of carboxypenicillins and, to a lesser extent, ureidopenicillins due to the fact that the injectable forms of these drugs contain a sufficient amount of sodium:

- ticarcillin - 5.2 meq in 1 g;

- carbenicillin - 4.7 meq in 1 g;

- azlocillin - 2.17 meq in 1 g;

- piperacillin - 1.98 meq in 1 g;

- meslocillin - 1.85 meq in 1 g.

With the introduction of new antibiotics into the medical practice, third-generation cephalosporins, complications such as coagulopathy, disulfiram-like reactions that occur after alcohol intake in patients, and reactions associated with drug antagonism have appeared.

Fluoroquinolones with teratogenic properties are contraindicated in pregnant women.

For patients with incomplete skeletal formation, these drugs are also contraindicated because of their ability to inhibit the growth of cartilage. Tetracyclines can cause damage to bone tissue. The use of antifungal agents of the polyene series for the treatment of intestinal and local candidiasis (nystatin, levorin, amphotericin B) is often complicated by adverse reactions. Among these drugs, the most toxic is amphotericin B, which causes many undesirable effects (neuro-, nephro- and hematotoxic).

The Jarish-Herxheimer effect. Severe sepsis in various diseases is the clinical situation in which adequate antibiotic therapy should be built not only taking into account the antibiotic sensitivity of microorganisms and the pharmacokinetics of drugs, but also the intervention of antibiotics in a complex, and sometimes chaotic, mechanism for the development and maintenance of a generalized inflammatory reaction.

We would like to draw attention to this aspect of antimicrobial therapy, especially since it is little known to most practitioners. The effect of antimicrobials on the mass release of endotoxins by bacteria has been known since A. Jarish and K. Herxheimer, who described therapeutic shock. Of particular importance in these cases is the so-called secondary cytokinogenesis associated with the release of endotoxin under the influence of the bactericidal action of antibiotics (the Jarisch-Herxheimer reaction). In this regard, antibiotics have different potentials. Numerous studies have shown that the minimal risk of endotoxin release and secondary cytokinogenesis is associated with the use of antibiotics that have a fast bactericidal effect and cause the formation of spheroplasts, which are weak accumulators of endotoxicosis.

Patient B., 24 years old, was treated in the intensive care unit DOCMO from 08.19.91. until 09/10/91

Clinical diagnosis: cervical hemangioma, hemorrhagic shock, curettage of the uterus and extirpation of the uterus 08/15/91, thrombohemorrhagic syndrome, massive blood transfusion syndrome, cerebral edema, pulmonary edema, right-sided geo-motorax, right-sided lower lobe pneumonia, acute intestinal paresis, acute intestinal insufficiency , ulcerative stomatitis, sepsis, ulcerative gastroenterocolitis, recurrent DIC.

08/15/91, was admitted to the gynecological department, as heavy bleeding from the genital tract began. Curettage of the uterine cavity, conservative therapy, including blood transfusion, for an hour and a half without effect. In connection with the development of hemorrhagic shock, pulmonary edema, hypocoagulation, the patient was transferred to mechanical ventilation. An operation-resuscitation was performed - hysterectomy without appendages.

In the postoperative period, the patient was in a coma on mechanical ventilation with relatively stable hemodynamics, but with emerging multiple organ failure (acute renal failure in the stage of anuria, respiratory distress syndrome, cerebral edema).

08/19/91, due to the ineffectiveness of the therapy, the need for dialysis treatment, the patient is transferred to the intensive care unit Doktmo. During this period, the state of the hemostatic system is relatively stable: blood coagulation - 6 min - 6 min 35 s), prothrombin index - 64%, re-calcification time - 130 s, plasma tolerance to heparin - 876 s, Rutberg fibrinogen - 1 , 3 g / l, fibrinogen B - 1+, ethanol test - negative, fibrinolytic activity - 21.2%.

For 10 days, the patient underwent complex treatment, including mechanical ventilation through a tracheostomy cannula, correction of humoral status disorders, antibiotic therapy, modeling of detoxification of the body (3 sessions of arteriovenous hemodialysis, 6 sessions of ultraviolet irradiation of autologous blood, drainage of the thoracic lymphatic duct). As a result of the treatment,

the patient's condition improved: the phenomena of cerebral edema stopped and consciousness, spontaneous independent breathing, and kidney function recovered.

As antibacterial therapy, the patient received two antibiotics (carbenicillin, erythromycin), which were canceled on 08/29/91 and prescribed phos-famicin. After the start of taking the antibiotic during the day, the patient's condition was destabilized: sopor developed with a transition to a coma, tachypnea up to 34 in 1 min, tachycardia 120-140 beats / min. Blood pressure remained stable. Anuria developed again during the day. The state of the hemostatic system is a new wave of DIC: blood coagulation - 9 min 10 s - 10 min 45 s, prothrombin index 94%, recalcification time - 70 s, plasma tolerance to heparin - 360 s, Rutberg fibrinogen - 8.4 g / l, fibrinogen B - 4+, ethanol test - positive, fibrinolytic activity - 6%.

The patient continued intensive therapy, including lymphosorption, hemosorption, hemodialysis, AUFC, correction of homeostasis disorders. However, thrombohemorrhagic and purulent-septic complications, multiple organ failure syndrome progressed. 09/19/91, the patient died.

In this clinical case, the use of aggressive antibacterial therapy led to the release of not only endotoxins, but also secondary cytokines into the bloodstream and the development of a systemic reaction to aggression - a systemic inflammatory response syndrome (CVD). The initiators of the release of cytokines, enzymes, histamine, kinins, arachidonic acid, prostaglandins, nitric oxide are microbes and their toxins. Endotoxin, a lipopolysaccharide substance (LPS), is a major factor in initiating CVD. Its toxic effect is due to lipid A, which is part of the LPS. Aggressive antibiotic therapy leads to an avalanche-like entry into the bloodstream of endotoxin from destroyed microbes. The released endotoxin activates a number of biological systems, including the coagulation system, leading to the formation of multiple organ failure (PON). Damage to endothelial cells under the toxic effects of LPS endotoxin is of particular importance in the development of PON.

Fast bactericidal activity (death bacteria for 1 h) possess carbapenems and aminoglycosides. The risk of secondary cytokinogenesis is also minimal when using cefepime, ceftriaxone, piperacillin / tazobactam, amoxicillin / clavulanate, glycopeptides.

Antibiotics with a slow bactericidal effect (the death of bacteria after 2–4 h) - cefotaxime, monobactam (aztreonam) - contribute to a powerful release of endotoxins and highly active secondary cytokinogenesis. Fluoroquinolones occupy an intermediate position.

The practical significance of the phenomenon of antibiotic-induced release of endo-toxin cannot yet be fully appreciated, since there is no evidence-based clinical research on this issue. Nevertheless, data extrapolated from studies in the experiment cannot be overlooked when conducting antibiotic therapy.

The purpose of the lesson:

1. Learn the classification of antibiotics.

I. Classification of antibiotics by the mechanism of action□:

1 Antibiotics that violate the synthesis of microbial cell wall biopolymers: beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, monobactams), ristomycin, vancomycin, etc.

2 Antibiotics that violate the permeability of the membrane of the microbial cell: polyenes (nystatin, amphotericin B), polymyxins, etc.

3 Antibiotics that inhibit the synthesis of proteins of microorganisms: macrolides, aminoglycosides, tetracyclines, chloramphenicol, lincomycin, etc.

4 Antibiotics that disrupt the synthesis of nucleic acids: rifampicins, grise-ofulvin. Such a mechanism is mainly possessed by antitumor antibiotics and immunosuppressants.

II. Classification according to the spectrum of antibacterial action and chemical structure:

I With a predominant effect on gram-positive microflora:

1) Beta-lactam antibiotics:

And Penicillins:

a) biosynthetic - benzylpenicillin (potassium, sodium salt), bicillins, phenoxymethylpenicillin;

b) semi-synthetic - methicillin, carbenicillin, ampicillin, amoxicillin, amoxiclav, meslocillin, oxacillin, dicloxacillin, etc.

B. Cephalosporins:

1st generation - cefazolin (kefzol), cephalotin, cephalexin, cefaloridin and others;

2nd generation - cefuroxime, cefoxitin, cefaclor and others;

3rd generation - cefotaxime (claforan), cefixime, ceftriaxone, and others;

4th generation - cefepime, cefpirome, etc .;

In Other beta-lactam preparations (carbapenems and monobactams) - imipenem, aztreons, thienes.

2) Macrolides and azalides - erythromycin, roxithromycin, azithromycin (su-mamed).

3) Antibiotics for special indications - rifampicins, lincosamines (lincomycin, clindamycin), novobiocin, ristomycin, vancomycin, sodium fusidate, etc.

II With a predominant effect on gram-negative microflora:

1) Aminoglycosides - streptomycin, kanamycin, gentamicin, amikacin, sisomycin, tobramycin;

2) Polymyxins - polymyxin B and M.

III Acting on gram-positive and gram-negative flora:

1) Tetracyclines:

a) biosynthetic - tetracycline, oxytetracycline;

b) semi-synthetic - metacyclin, doxycycline (vibramycin);

c) combined - oletetrin.

2) Groups of chloramphenicol - chloramphenicol (chloramphenicol), syntomycin.

IV Acting on gram-positive and gram-negative microflora and applied locally - aminoglycosides (neomycin, monomycin), polymyxins, synthomycin, bacitracin, heliomycin, gramicidin.

V Antifungal - polyenes (nystatin, levorin, amphotericin B, amphoglucamine, mycoheptin), griseofulvin.

VI Antitumor - dactinomycin, daunomycin, mitomycin, rubomycin, bleomycin, etc.

2. Know:

I The basic principles of chemotherapy (rational choice of the drug, the start of treatment, route of administration, dose, interval of administration, duration of therapy, combination treatment, increase the immunological reactivity of the body).

II Evaluation criteria for chemotherapeutic agents.

III The main etiopathogenetic mechanisms of action of antibiotics, their pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics:

a) penicillin groups;

b) groups of cephalosporins;

c) groups of monobactams;

g) carbapenem groups;

e) aminoglycoside groups;

e) macrolide groups;

g) groups of tetracyclines;

h) chloramphenicol groups;

i) groups of lincosamides;

j) other groups (glycopeptides, rifampicin, polymyxins, etc.);

k) local and external use (bacitracin, baneocin, bioparox, gramicidin, heliomycin, bactroban);

ciprofloxacin, ofloxacin, pefloxacin, norfloxacin

X Complications of antibiotic therapy:

the development of allergic reactions (anaphylactic shock, Quincke's edema, urticaria, rhinitis, conjunctivitis, dermatit
b) the development of multiresistance in microorganisms (biological, species, secondary, persistent, cross);
the development of superinfection in the treatment of the primary disease (candamycinosis, staphylococcosis, hypovitaminosis)
direct organotropic toxic effects (neurotoxic, hepatotoxic, nephrotoxic, gastrointestinal disorders, damage to the hematopoietic apparatus, etc.);
the development of an exacerbation reaction (endotoxic);
mutagenic, teratogenic, embryotoxic effect.

3. Be able to:

1 Select a specific patient antimicrobial therapy, determine the criteria for the effectiveness and safety of its use;

2 Prescribe combination antibiotic therapy;

3 Provide urgent help with: pneumonia, septic shock, allergic shock, odontogenic sepsis.

4 Use disinfectants and antiseptics.

The task for self-checking the initial level.

1 List the pathogenetic mechanisms of action of antibiotics.

2 What are the main classifications of antibiotics.

3 List the main groups of antibiotics that have a bactericidal or bacteriostatic effect.

4 Give a classification of penicillins, cephalosporins, aminoglycosides, tetracyclines.

5 Antibiotics that suppress the vital activity of Pseudomonas aeruginosa: cephalosporins of the 3rd, 4th generation, aminoglycosides of the 2nd and 3rd generations, polymyxins, carbenicillin, etc.

6 What are the criteria that determine the choice of antibiotic for the treatment of the infectious process.

7 List the criteria for the effectiveness of the antibiotic.

8 Indicate the stages of the evaluation of the effect of the antibiotic in a temporary aspect. Doctor tactics at these stages.

9. What organs and systems are involved in the elimination of antibiotics and the significance of this process?

10 What features of the body should be considered when prescribing antibiotics?

11 What are the clinical and laboratory parameters characterizing the function of the kidneys, liver. What do they mean when choosing an antibiotic?

14 Justify the relevance of local and general use of nitro-midosol derivatives (metronidazole) in dental practice

15 Justify the features of antibacterial therapy for periodontitis, os-theomyelitis and septic state

16 What are the features of the appointment of antibiotic therapy in terms of the prevention of allergic complications

Control questions of the studied topic.

1 List the undesirable effects of antibiotic therapy, methods of their prophylaxis and treatment.

2 What are the clinical and pharmacological principles of the selection and selection of antibiotic in the treatment of an infectious process.

3 What are the principles underlying the classification of antibiotics.

4 Give a classification of penicillins.

5 What are the differences between semisynthetic penicillins from natural ones? Explain the principle of creating the form of “Ampioks”.

6 What features of the clinical effect are characteristic of carbenicillin?

7 In what cases should cephalosporins be chosen to suppress the infectious process? How are they classified as major side effects?

8. What are the general properties of penicillins and cephalosporins. What is of practical importance in the treatment of patients and the choice of combination therapy?

9 What antibiotics do cephalosporins not combine with?

10 How are aminoglycosides classified? Which drug of this group and in what dosage is most often used for infectious dental diseases?

11 Which drugs do not combine aminoglycosides?

12 Gentamicin is known to be excreted in breast milk. How do you rate gentamicin treatment for a nursing mother? Can breastfeeding be maintained?

13 What are the features of pharmacokinetics and pharmacodynamics of lincomycin?

14 In which disease are macrolides the first choice?

15 How are tetracyclines classified? What features of the pharmacokinetic effect are characteristic of tetracyclines?

16 Who should not use tetracyclines and why?

17 What antibiotics should not be given to pregnant women?

18 What antibiotics are most often used in children?

19 What are the features of the use of chloramphenicol? What side effects does chloramphenicol cause?

22 What is the algorithm for choosing an antibacterial drug in elderly people, taking into account concomitant pathology (damage to the kidneys, liver, cardiovascular system)?

Enumeration of practical work.

A**. Homework.**

1 Write down the prescriptions for antibiotics (for oral and parenteral administration) presented in the section “Purpose of the lesson”, indicate the principles of choice, explain the frequency and method of administration, the duration of treatment.

2 Mark possible effective and undesirable combinations of antimicrobial therapy.

B. Independent practical work in class.

1 To supervise a thematic patient in the ward.

2 To study the working history of the disease (data from laboratory and instrumental studies, conclusions of consultants) and the list of medical appointments.

3 Write a protocol of independent work on the selection and selection of the primary drug for the care patient and the rationale for the appointment of combination therapy.

4 To highlight the signs in a subjective and objective study of the patient, characterizing the presence of an infectious process, its localization, activity, prevalence. Write a clinical diagnosis of the disease.

5 Identify the group of drugs needed by the patient.

6 Based on the theoretical data of pharmacodynamics and their own observations, select drugs for the patient to be supervised.

7 Choose the optimal dosage regimen for drugs taking into account the characteristics of pharmacokinetics, pathogenesis of the disease, route of administration, age, body weight.

8 Select clinical and instrumental criteria for assessing the effectiveness and safety of the applied drugs, carry out an assessment.

9 To justify the need for combination drug therapy and suggest possible options for a safe combination of drugs.

10 Make a forecast of side effects of drugs prescribed to the patient and outline a plan for identifying them in the early stages.

11 Justify the duration of the main and maintenance therapy.

12 Create a plan for urgent medical care for: pneumonia, septic and allergic shock, odontogenic sepsis.

Control of the intermediate level of knowledge.

The solution of situational problems.

1 A 42-year-old patient was brought to the department with complaints of an increase in body temperature to 39.8 ° C, cough with a small amount of sputum, sweating. An objective examination: in the lungs on the right below the scapula, the zone of blunting of percussion sound, hard breathing, moist finely bubbly rales.

What is your diagnosis? Prescribe therapy, name the drug 1 line.

2 A 23-year-old patient with hospital-acquired right-sided pneumonia receiving treatment with benzylpenicillin at a dose of 6 million units per day, on the third day, subfebrile temperature remains, dullness of percussion sound, respectively, of the lower lobe of the lung, moist sonorous rales.

Tactics of patient management.

3 A 3-year-old child with pneumonia developed jaundice. The applicants emphasized that tetracycline was not given to the child. With a further clarification of the medical history, it was possible to find out that the child received ascorutin, rondomycin, calcium chloride, aspirin, and analgin.

Explain the cause of jaundice. Your conclusions, conclusions?

4 The doctor on call was summoned to a 27-year-old patient who was in the ward for pneumonia. Complains of weakness, dizziness. Objectively - covered with cold sweat, lips are cyanotic, pulse - 93 beats in 1 min., Rhythmic, weak filling, AKD - 90/55 mm RT. Art. The voice is a little hoarse. The nurse reported that 40 min. the next injection of penicillin was made to the patient.

What is your diagnosis? Indicate the option and severity of the patient's condition. Treatment plan. Prevention

5 A 38-year-old patient has rheumatism, an active phase, I degree of activity, recurrent rheumatic heart disease, mitral stenosis, HF I st. In the hospital, pharmacotherapy, benzylpenicillin, voltaren, ribocin, panangin, ranitidine is successfully carried out.

What antibiotic should be prescribed to the patient on an outpatient basis to prevent relapse of rheumatism?

6 A patient, 19 years old, complains of a dry cough, muscle pain, an increase in body temperature to 39 ° C. For a week, sore throat, subfebrile condition bothered. Objectively: harsh breathing. In the blood: L. - 7.0 • 109 / l, the leukocyte formula is normal. ESR - 26 mm / hour. X-ray data of the chest organs: increased pulmonary pattern, focal shadows of low intensity in the lower parts of the right lung.

Formulate a diagnosis. Treatment plan. Give a clinical and pharmacological evaluation of the prescribed treatment.

7 After the removal of the 8 tooth of the upper jaw on the right on the second day, the patient developed general weakness, fever up to 38.3 ° C, decreased appetite, swelling of the face on the right, and difficulty opening the mouth. Objectively: The mucous membrane of the gum adjacent to the hole is swollen, painful, hyperemic. A purulent complication after removal of the tooth was diagnosed.

Prescribe the optimal treatment, justify it

8 The baby is 10 months old. Due to non-compliance with personal hygiene rules, he developed aphthous gingivitis. Which antibacterial therapy you prefer - local or resorptive. Prescribe the necessary antimicrobial therapy. Justify its necessity and rationality.

9. A boy, 14 years old, weighing 53 kg, suffers from secondary chronic pyelonephritis with arterial hypertension, chronic renal failure of the first degree. Regarding another exacerbation of the disease (a protein sensitive to ampicillin was identified in the urine), ampicillin 500 mg 4 times a day is received intramuscularly, 0.2 g 4 times a day furazolidone 4 times a day. The patient constantly consumes a lot of dairy products (cheese, cottage cheese, sour cream). By the 10th day of treatment, lower back pain decreased, body temperature returned to normal, dysuric symptoms disappeared. However, there was a sharp headache of a diffuse nature, nausea, a sensation of pulsation in the back of the head. On examination, pallor of the skin is expressed, tachycardia - 130 strokes in 1 min, AKD - 200/120 mm RT. Art. (upon receipt of 150/95 mm RT. Art.). The residual nitrogen of the blood is 17.45 mmol / L (normal 14.3 - 25 mmol / L). Urinalysis according to Kakovsky-Addis: Er - 1.2 • 106 (normal to 1 • 106), L - 3.2 • 106 (normal to 2 • 106).

Justify the pathogenesis of the developed symptoms from the position of side effects of drugs taken by the patient. Give suggestions for treatment correction.

10. A patient, 34 years old, was admitted with complaints of pain in the lumbar region, dysuric phenomena, fever up to 37.5 - 38 ° C, chills. In addition, headaches, dizziness, and fatigue worry. During the examination: AKD - 180/110 mm RT. Art., in the urine - proteinuria - 0.5 g / l, white blood cells - 25 - 30 in the field of view, bacteriuria, cylindruria. In the blood - leukocytosis with a shift of the leukocyte formula to the left, ESR -18 mm / h.

Justify the diagnosis of the disease. Make a plan for further examination and treatment of the patient.

TESTS

1. Which of the following antibiotics do you prefer during a purulent-septic process that is localized in the bones of the lower jaw

A. lincomycin,

B. benzylpenicillin

C. bicillin-3

D. Gentamicin

E. synthomycin

2. A patient, 19 years old, complains of a dry cough, muscle pain, an increase in body temperature to 39 ° C. For a week, sore throat, sub-febrile condition bothered. Objectively: harsh breathing. In the blood: L. - 7.0 • 109 / l, the leukocyte formula is normal. ESR - 26 mm / hour. X-ray data of the chest organs: increased pulmonary pattern, focal shadows of weak intensity in the lower parts of the right lung. What drugs should be prescribed?

A. Aminoglycosides.

B. Sulfanilamides.

C. Penicillin antibiotics.

D. Cephalosporins II or III generation.

E. Macrolides.

3. A woman, 55 years old, complains of pain in the right hypochondrium, radiating under the right scapula associated with the intake of fatty foods, nausea, poor sleep. Sick with chronic cholecystitis for 12 years. Objectively: moderate flatulence, pain on palpation in the projection of the gallbladder, a positive symptom of Ortner. Body temperature - 37.7 ° C. In the blood: l. - 12.7 • 109 / l, p - 16%, ESR - 27 mm / hour. Microscopic examination of the second portion of the duodenal contents revealed a lot of mucus, epithelial cells, white blood cells. What antibacterial drug is most appropriate to prescribe a patient?

A. Chloramphenicol.

B. Penicillin.

C. Nitroxoline.

D. Ristomycin.

E. Ampicillin.

4. A man suffers from chronic heart failure II st .. Regularly takes furosemide three times a week. In connection with acute bronchopneumonia, the doctor prescribed combined pharmacotherapy. On the 5th day of her conduct, the patient's hearing deteriorated. What drug with joint use with furosemide led to hearing loss?

A. Mukaltin.

B. Linex.

C. Nystatin.

D. Tavegil.

E. Amikacin.

5. The onset of the girl’s disease, 18 years old, was sudden: chills, body temperature - 39 ° C, headache. A critical deterioration is noted for several hours. Objectively: the condition is extremely serious, adynamia, prostration, body temperature - 36 ° C, a numerous hemorrhagic rash on the limbs, trunk, buttocks. Meningial syndrome is moderate. Heart rate - 130 per minute. HELL - 60/20 mm RT. Art. On the eve of 3 days I felt a slight sore throat, stuffy nose. Which antibiotic is the drug of choice?

A. Gentamicin.

B. Penicillin.

C. Ampioks.

D. Chloramphenicol succinate

E. Cephalosporins.

6. In a 60-year-old man who suffers from chronic obstructive bronchitis for a long time and smokes a lot, a dry cough intensified, his body temperature increased to 37.5 ° C, and general weakness and fatigue appeared. Clinical and radiological data of pneumonia were not found. FEV - 70% of the norm. ESR - 37 mm / h. It is impossible to conduct bacteriological and microbiological examination. Is it appropriate to include which antibiotic in the complex treatment?

A. Carbenicillin.

V. Claforan.

S. chloramphenicol.

D. Tetracycline.

E. Benzylpenicillin.

7. After a clinical, radiological and laboratory examination of the patient, 35 years old, a preliminary diagnosis was made: atypical pneumonia of myoplasma etiology, moderate severity, DN I st. With which group of drugs is it advisable to start treatment?

A. Fluoroquinolones.

B. Cephalosporins.

C. β-lactam antibiotics.

D. Macrolides.

E. Aminoglycosides.

8. A man, 60 years old, is in the therapeutic department for right-sided croupous pneumonia. The patient's well-being under the influence of therapy improved. When can a patient be canceled antibiotics?

A. The day after normalization of temperature.

B. After complete resorption of the infiltrate.

C. After normalization of the blood picture.

D. On the 5th day of normalization of body temperature.

E. After the end of the symptoms of intoxication.

9. After treatment in a hospital and a sanatorium, a 10-year-old girl was discharged to the site who suffered a rheumatic attack, which proceeded with polyarthritis, skin erythema against the background of chorea. An increase in the content of acute phase indices and a high titer of anti-streptococcal antibodies were detected in the blood. At the moment, there are no signs of rheumatic process activity. What is the optimal bicillin prophylaxis regimen?

A. Bicillin prophylaxis only during intercurrent infections.

B. Bicillin-5 in combination with aspirin.

S. Bicillin-5 once every 3-4 weeks.

D. Bicillin-5 once a week.

E. Bicillin-5 in combination with prednisone.

10 A girl, 5 years old, was hospitalized in the nephrology department with severe swelling of the face, lower back, anterior abdominal wall, external genitalia, oliguria. Objectively: the skin is pale, dry, the liver 5 cm protrudes from under the edge of the costal arch, ascites. HELL - 90/50 mm Hg In urine: protein - 9.2 g / l, microhematuria, cylindruria. In the blood, ESR, hypoalbuminemia, hypercholesterolemia are sharply increased. What pathogenetic drug should be prescribed?

A. Freshly frozen plasma.

B. Prednisolone.

S. Veroshpiron.

D. Lasix.

E. Cyclophosphamide.

11. A boy, 10 years old, who suffered the first attack of rheumatism with manifestations of endomyocarditis and polyarthritis, was treated in a specialized department. Which of the drugs is appropriate to use for the secondary prevention of diseases in this case?

A. Bitsillin-3.

B. Bitsillin-5.

C. Bicillin-1.

D. Lincomycin.

E. Erythromycin.

12. The girl, 10 years old, was hospitalized for the next examination and treatment. Sick for 2 years. A week ago, after SARS, weakness, headache, swelling on the legs, in the lower back, on the face appeared. Body temperature - 37.6 ° C, blood pressure - 105/65 mm Hg. Art., heart rate - 86 per min. Loss of protein per day - 6 g, cylindruria, nocturia. In blood ESR - 44 mm / h, total protein - 45 g / l, α2-globulins - 27%. What is the main type of pathogenetic therapy for a child's disease?

A. Antibacterial therapy.

B. Anticoagulants.

C. NSAIDs.

D. Diuretics.

E. Glucocorticoids.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн, В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF SULFANILAMIDES.

Relevance of the topic.

After the brilliant discoveries of Erlich, all searches for drugs were shrouded in mystery. Specialists from leading pharmaceutical companies investigated each new compound without disclosing the results. In 1908, the Austrian chemist P. Helmo obtained p-aminobenzenesulfamide (sulfanilamide) from coal tar.

Later, Bayer chemist X. Gerlein found that the addition of sulfonamide to acidic dyes improves the color quality and proposed a new brick-red dye, chrysoidine.

Already in 1913, Bayer specialists established its ability to kill various bacteria. In 1932, the company IG Farbenindustri patented an orange-red substance with an unusual dye called streptozone.

In the laboratories of the company, it was studied in detail by the outstanding bacteriologist G. Domagk, who published his results in the famous article “Ein Beitrag zur Chemiotherapie der bacteriellen Infectionem” (“Contribution to the chemotherapy of bacterial infections”), which marked the birth of a new class of chemotherapeutic agents. Monopoly rights to streptozone (called pronounced or red streptocide) allowed IG Farbenindustria to capture the antimicrobial drug market.

But businessmen from pharmaceuticals did not attach importance to the discovery of P. Helmot and did not patent sulfonamide, and studies by the E. Fourno group from the Paris Pasteur Institute showed that the colorless fraction is the active principle of the pronzyl. Under the name "white streptocide", this drug has been widely circulated in many countries.

Drugs of this group are used for cases of antibiotic intolerance or microflora resistance, they are significantly inferior to antibiotics in activity, and in recent years their value for the clinic has been decreasing.

Sulfanilamides are close in structure to para-aminobenzoic acid.

Motivational characteristic of the topic.

Sulfanilamides (lat. Sulfanilamidum) is a group of chemicals derived from para-aminobenzenesulfamide - sulfanilic acid amide (para-aminobenzene sulfonic acid). Many of these substances have been used as antibacterial agents since the mid-twentieth century. para-Aminobenzenesulfamide - the simplest class compound - is also called white streptocide and is still used in medicine. Slightly more complex in structure, sulfonamide pronosil (red streptocide) was the first drug in this group and, in general, the first synthetic antibacterial drug in the world.

In 1934, G. Domagk discovered the antibacterial properties of pronounced. In 1935, scientists at the Pasteur Institute (France) found that it was the sulfonamide part of the molecule that had the antibacterial effect, and not the structure that gave it a color. It was found that the "active principle" of red streptocide is sulfanilamide, formed during metabolism (streptocide, white streptocide). Red streptocide went out of use, and on the basis of the sulfanilamide molecule, a large number of its derivatives were synthesized, of which some were widely used in medicine.

Sulfanilamides are antimicrobials derived from sulfanilic acid amide (white streptocide). Their discovery confirmed the prediction of P. Ehrlich about the possibility of selective damage to microorganisms by cytotoxic substances of a resorptive action. The first drug of this group pronosil (red streptocid) prevented the death of mice. infected with a tenfold lethal dose of hemolytic streptococcus

Dihydropteroic acid

Sulfanilamides act bacteriostatically, that is, they have chemotherapeutic activity in infections caused by gram-positive and gram-negative bacteria, some protozoa (pathogens of malaria toxoplasmosis), chlamydia (with trachoma, paratrachoma).

Their action is mainly associated with a violation of the formation by microorganisms of the growth factors necessary for their development - folic and di-hydropholic acids and other substances, the molecule of which includes para-aminobenzoic acid. The mechanism of action is associated with the structural similarity of the sulfanilamide fragment with para-aminobenzoic acid (PABA), a substrate of the enzyme dihydropteroate synthetase, which synthesizes dihydropteroic acid, which leads to competitive inhibition of dihydropteroate synthetase. This, in turn, leads to a disruption in the synthesis of dihydroperteric dihydrofolate, and then tetrahydrofolate, and as a result, to a violation of the synthesis of nucleic acids in bacteria.

On the basis of the sulfanilamide molecule in the second half of the 30s, many other compounds were synthesized (norsulfazole, ethazole, sulfazine, sulfacyl, etc.). The emergence of antibiotics has reduced interest in sulfonamides, however, they have not lost their clinical significance, now they are widely used "long-acting" (sulfapyridazine, sulfalene, etc.) and especially combination drugs (co-trimoxazole and its analogues, in the composition which, in addition to sulfonamide, includes trimethoprim).

To obtain a therapeutic effect, they must be prescribed in doses sufficient to prevent the possibility of using microorganisms of para-aminobenzoic acid contained in tissues. Inadequate doses of sulfonylamide preparations or discontinuation of treatment too early can lead to the emergence of resistant strains of pathogens that are not amenable to further action of sulfonamides. Most clinically significant bacteria are currently resistant to sulfonamides [4]. It is necessary to take into account that some drugs containing a para-aminobenzoic acid residue (for example, novocaine) can have a pronounced antisulfanilamide effect.

Antimicrobial spectrum of action

Sulfanilamides have a wide spectrum of antimicrobial activity, are active against gram-positive and gram-negative cocci, E. coli, Shigella, cholera vibrio, clostridia, protozoa (malarial plasmodium and toxoplasma), chlamydia; causative agents of anthrax, diphtheria, plague, as well as Klebsiella, actinomycetes and some other microorganisms.

The mechanism of action of sulfa drugs is a competitive antagonism with para-aminobenzoic acid (PABA). PABA is a compound necessary for the synthesis of folic acid by a microbial cell, without which the growth and reproduction of bacteria is impossible (PABA -> dihydrofolic acid -> tetrahydrofolic acid -> purine and pyrimidine bases -> RNA and DNA).

Classification of sulfanilamide drugs

Sulfonamides are classified according to the peculiarities of pharmacokinetics, in particular absorption in the digestive tract and the duration of excretion from the body:

I. Drugs that are well absorbed in the digestive canal:

- Preparations of short duration of action (T ½ - 8 hours), these are: etazole, norsulfazole, sulfadimezin;

- Medications of average duration of action (T ½ - 8-20 hours), these are: sulfazine, methylsulfazine;

- Long-acting drugs (T ½ - 24-48 hours), these are: sulfapyridine-zine, sulfadimethoxine, sulfamonomethoxin;

- Preparations of extra long action (T ½ - 65 hours), it is: sulfalene.

II. The drugs are practically not absorbed in the digestive tract (phthazine, phthalazole, sulgin).

III. Local drugs (streptocide, sulfacyl sodium).

IV. Combined preparations containing sulfanilamides (co-trimoxazole, salazolazine)

The duration of action of sulfonamides is due to labile reversible binding to albumin.

Pharmacokinetics:

1. routes of administration of sulfonamides: orally, i / m (sulfalen), iv (sulfacyl, norsulfazole), externally in the form of ointments (streptocid, silver sulfathiazole);

2. well absorbed in the gastrointestinal tract, except for SA, used to treat gastrointestinal infections;

3. bioavailability - 65 - 90%, and sulfonomethoxin -70 - 100%;

4. the maximum concentration in the blood plasma of SA of short action - after 1 - 2 hours, the average duration of action - after 2 - 4 hours, long and ultra-long action - after 4 - 8 hours;

5. The multiplicity of short-acting SA administration is 4–6 times, of average duration - 3–4 times, of long-term action - 1–2 times, and of ultra-long-term action - 1 time per day;

6. connection with plasma proteins - 50 - 90% (streptocid and sulfacyl - not more than 20%);

7. can displace other drugs from the connection with proteins ¬ manifestation of their side effects;

8. easily penetrate into the tissues and body fluids (into the lungs, tissues of the middle ear, tonsils, pleural, synovial, ascitic fluid);

9. Biotransformation of sulfonamides occurs in the gastrointestinal mucosa, liver and kidneys (sulfanilamide metabolites do not have antimicrobial activity);

10. When urine is acidified, sulfanilamides can precipitate and cause damage to the epithelium of the renal tubules;

11. sulfonamides are excreted mainly by glomerular filtration;

12. part of sulfonamides is present in the urine in the form of metabolites, and part is unchanged ® it is possible to use SA for the treatment of infections of the urinary tract;

13. sulfonamides of long and superlong action are excreted slowly with urine and retain a high concentration in blood plasma due to the high degree of binding to blood plasma proteins and intense reabsorption in the renal tubules;

14. local sulfonamides (non-absorbable SA) are excreted predominantly with feces, they are prescribed 4-6 times a day.

When combined with a protein, sulfonamides can displace other drugs or endogenous compounds such as bilirubin from the protein complex. Sulphanilamides can be displaced from the complex with proteins salicylates and other NSAIDs. From the blood, sulfonamides penetrate well into various body fluids and tissues. They can accumulate in tissues in which blood circulation is weakened. They pass well through the placental barrier and can cause methemoglobinemia and hyperbilirubinemia, especially in newborns. Metabolized in the liver by acetylation and glucuronidation (sulfadimethoxin) with the formation of inactive metabolites. If the drug undergoes acetylation slightly, then it is excreted from the body in an active state and can have an antimicrobial effect in the urinary tract (ethazole, urosulfan).

Sulfanilamides and their metabolites are removed mainly by filtration. Lipid-soluble sulfanilamides undergo reabsorption in the renal tubules after glomerular filtration, which, together with their ability to bind to plasma proteins, leads to a longer duration of action. Acetylated compounds are not reabsorbed by the kidneys, but under conditions of neutral or acidic pH, urine can form a precipitate (crystalluria) in the urinary tract. Glucuronides of sulfonamides are highly soluble in water and do not form a precipitate.

Side effect:

1. allergic reactions (cross-allergy with other SA, diuretics, antidiabetic drugs of sulfanylurea) skin rash, pruritus, photosensitivity of the skin, less common stomatitis, conjunctivitis, polyarteritis nodosa, Stevens-Johnson syndrome, anaphylactic shock;

2. with prolonged use, symptoms of folic acid deficiency in the body (dyspeptic disorders - nausea, vomiting, diarrhea, anorexia; muscle hypotrophy, blood disorders - neutropenia, leukopenia, thrombocytopenia);

3. When urine is acidified, hematuria, crystalluria and acute urinary retention (alkaline drinking or taking 5-15 g of sodium bicarbonate daily is recommended throughout the course of treatment with sulfonamides).

4. in patients suffering from liver diseases, more often in young children, when taking sulfonamides of long and superlong action, hyperbilirubinemia; in newborns, methemoglobinemia of newborn hypoxia;

5. neuritis accompanied by muscle weakness without loss of sensation;

6. combined drugs containing trimethoprim teratogenic effect;

7. in the second half of pregnancy, the risk of jaundice in newborns.

8. granulocytopenia, thrombocytopenia, megaloblastic anemia, intravascular hemolysis with the development of nuclear jaundice, methemoglobinemia, non-prayer jaundice

9. immunobiological reactions (intestinal dysbiosis).

Contraindications:

1. hypersensitivity;

2. a history of toxic and allergic reactions to sulfonamides;

3. hyperbilirubinemia (in children);

4. urolithiasis;

5. diseases of the hematopoietic system;

6. Decompensated heart failure;

7. Pregnancy and lactation.

Interaction with drugs of other groups:

Combinations of sulfonamides are not recommended:

1. with chloramphenicol, paracetamol, glucocorticosteroids, estrogens, androgens, vicasol, nicotinic acid, triiodothyronine hyperbilirubinemia;

2. with drugs with nephro- and hematotoxic effects;

3. with novocaine and novocainamide metabolism with the formation of para-aminobenzoic acid, a decrease in the antimicrobial activity of sulfonamides;

4. with drugs that are weak acids (acetylsalicylic acid, phenacetin, paracetamol, quinidine, furadonin, furazolidone, etc.) ® development of hemolytic anemia in patients with congenital deficiency of glucose-6-phosphate dehydrogenase enzyme;

5. with drugs displaced by sulfonamides from their association with proteins (oral antidiabetic drugs, hypoglycemia, anticoagulants of indirect action of bleeding);

6. for patients with acetyltransferase enzyme deficiency, the development of "lupus erythematosus syndrome" (headache, tachycardia, fever, skin rash, effusion into the pleural cavity, dyspeptic disorders

The purpose of the lesson.

To study scientifically based approaches to rational pharmacotherapy with drugs of the class of SLS and methods for monitoring the effectiveness and safety of their use in each patient.

1. The student must know:

a) a unified algorithm for the selection of antimicrobial drugs and methods for monitoring its effectiveness and safety;

b) the pharmacodynamics, nature and spectrum of the antimicrobial action of the following compounds:

Sulfanilamide drugs:

well absorbed in the digestive tract, which are used for systemic infections: norsulfazole, sulfadimethoxine (madribon), sulfadimezin, sulfadimethoxine, sulfapyridazine, sulfalene;

poorly absorbed from the digestive tract, which are used to treat intestinal infections: phthalazole;

combined:

- compounds with trimethoprim: cotrimoxazole (biseptol, bactrim, berlocide);

- Compounds with aminosalicylic acid: salazosulfanilamides;

for local and external use: streptocid, sulfacyl sodium (albucid), sulfargin, argosulfan.

in. pharmacokinetics of leading representatives of new groups of antimicrobial compounds and principles of choosing the routes of administration of these drugs;

d. the main biochemical mechanisms of the microbial cell, which are the object of drug exposure to SLS;

e. undesirable effects of the studied drugs, the principles of their early detection and prevention;

f. the main types of interaction between the studied antimicrobial agents and the principles of combination therapy based on this;

g. comparative characteristics of the leading representatives of the studied classes of antimicrobial compounds and the criteria for their selection in a particular patient;

h. age-specific features that should be considered when choosing the necessary chemotherapeutic agent, its dose and administration regimen.

The student must be able to:

a. select the necessary chemotherapeutic drug for a specific patient from the group of studied compounds, select the dose, regimen and route of administration of the drug;

b. highlight the criteria for therapeutic efficacy and safety of the drugs used;

s. select a drug for a particular patient from the group of sulfonamides taking into account the causative agent of the disease, localization of the infectious process, individual characteristics of the patient, select criteria for therapeutic efficacy and safety;

d. prescribe combination therapy;

e. having data on the concentration of creatinine in the blood serum (or on the creatinine clearance) be able to calculate in% the dose of the drug needed for this patient;

f. provide differential medical assistance for:

- acute pyelonephritis;

- acute gonorrhea;

- acute enterocolitis;

- acute giardiasis cholecystitis;

- anaerobic gas infection.

e. recognize the complications of antibiotic therapy and correct them.

Tasks for self-testing of the initial level.

1. List the main infectious diseases indicated for pharmacotherapy by representatives of the studied classes of antimicrobial agents.

2. What are the features of the course of infections of the genitourinary tract and gastrointestinal tract, which determine the choice of derivatives of the studied groups as antibacterial therapy.

3. Indicate the organs and systems involved in the elimination of the studied antimicrobial agents. What concomitant diseases require correction of the route of administration and dosage regimen?

4. Give a comparative assessment of the spectrum and nature of the antimicrobial action of chemotherapeutic drugs, derivatives: sulfonamide drugs,

5. What principle underlies the classification of SLS? How are sulfonamides divided according to their pharmacokinetic characteristics?

6. Which of the sulfa drugs have the broadest spectrum of action and are able to suppress the development of pathogens of toxoplasmosis, trachoma, as well as protea?

7. Describe the mechanism of antimicrobial action of SLS, drugs of the nitrofuran series, fluoroquinolones, hydroxyquinolines, imidazole, nalidixic, pipemidic, oxolinium acids.

8. What is the nature of the effects of SLS on microbial cells, bactericidal or bacteriostatic?

9. Describe the ability of various SLS to penetrate into organs, tissues and body fluids.

10. In what ways does the elimination of SLS from the body occur, on what does its speed depend?

11. Note the rate of elimination of SLS of short action, medium duration of action, long action.

12. What is the difference between the composition and action of the drug bactrim (biseptol, gro-septol, sulfatone, etc.) on microbial cells, from other SLS.

13. What are the main indications and principles of combination chemotherapy drugs of the studied groups.

14. What are the main clinical and laboratory criteria that are a guideline for monitoring the effectiveness and safety of the use of these groups of drugs.

15. Expand the mechanisms of the possible development of AB-resistance and AB-dependence, as well as methods of their prevention in conditions

16. What are the possible complications of eliminating acetylated SLS?

17. List the undesirable effects of sulfa drugs in relation to organs and systems of adults, children and pregnant women, what are the contraindications for their use.

Control questions of the studied topic.

1. List the clinical and pharmacological principles of the appointment of SLS.

a. What is the classification of SLS.

b. Explain the need for a shock dose of sulfonamide at the beginning of treatment.

in. What does the “plume” rule mean? What is its clinical feasibility?

d. Explain the need for a combination of SLS with antibiotics and other antimicrobial agents for severe infectious processes caused by polyvalent flora.

e. What are the criteria for the duration of treatment for SLS?

e. What are the forms of sulfanilamide preparations known to you.

g. Which SLS are used locally?

h. List drugs used for intestinal infections.

and. What are the parenteral drug SLS and the rules for their administration.

j. What are the criteria for the efficacy and safety of treatment for SLC?

l How to control the possibility of developing undesirable and side effects from the liver, kidneys, nervous system, and hematopoietic system during the treatment of SLC?

m. What are the drugs that can dramatically weaken the effectiveness of SLS due to the structural proximity to para-aminobenzoic acid.

n Determine the feasibility of co-administration of SLS and antibiotics of bactericidal action.

2. List the clinical and laboratory criteria for the effectiveness and safety of the treatment of acute pyelonephritis and acute enterocolitis.

Enumeration of practical work.

Homework.

1. Write down prescriptions for drugs (in all dosage forms) presented in the section “Purpose of the lesson”, indicate the points of action, the spectrum of diseases indicated for their purpose.

2. Indicate and explain possible cases of ineffectiveness of using SLS in infectious inflammatory processes of various localization.

B. Independent practical work in class.

1. Supervision of a thematic patient in the ward.

1. To study the medical history of the supervised patient (data from laboratory and instrumental studies, conclusions of consultants, records of the attending physician), a sheet of medical appointments.

2. Write a protocol of independent work on the selection and justification of the assigned value to the patient being supervised of one of the antimicrobial drugs considered in this topic.

3. In a subjective and objective examination, identify the patient with signs of an infectious disease, evaluate its severity and localization of the pathological process.

4. Based on the individual characteristics of pharmacodynamics and pharmacokinetics, as well as taking into account their own observations, choose one of the chemotherapeutic drugs for the patient to be supervised.

5. Choose the optimal dosage regimen for the drug, taking into account its pharmacokinetics, pathogenesis of the disease, route of administration, age, body weight.

6. To highlight the clinical and instrumental criteria for evaluating the effectiveness and safety of the applied tool.

7. Substantiate the feasibility of combined pharmacotherapy and propose possible options for a safe combination of drugs.

8. Make a forecast of side effects and outline a plan for their early detection.

9. Justify the duration basic and supportive therapy.

Explain the need for combined antibacterial and pathogenetic therapy for an infectious inflammatory process.

Control of the intermediate level of knowledge.

The solution of situational problems.

1. A patient, 34 years old, was admitted with complaints of pain in the lumbar region, dysuric phenomena, fever up to 37.5 - 38 ° C, chills. In addition, headaches, dizziness, and fatigue worry. On examination: AKD - 180/110 mm RT. Art., in the urine - proteinuria - 0.5 g / l, white blood cells - 25 - 30 in the field of view, bacteriuria, cylindruria. In the blood - leukocytosis with a shift of the leukocyte formula to the left, ESR -18 mm / h.

Justify the diagnosis of the disease. Make a plan for further examination and treatment of the patient.

2. A 43-year-old patient was admitted with complaints of pain in the lower abdomen, radiating to the perineum, accompanied by tenesmus, urinary frequency with pain, weakness, sleep disturbance, appetite. The body temperature is normal. A history of severe hypothermia. In the general analysis of urine - leukocytes 20 - 25 in the field of view, red blood cells - 8 -12 in the field of view, bacteria - completely in the field of view, oxalates in a small amount.

Diagnose the disease. What additional analyzes are needed for this? Select the circle of drugs effective in this pathology, the dosage regimen and route of administration.

3. A patient came to the admission department with complaints of severe weakness, pain in the lower abdomen, nausea, vomiting, and frequent loose stools. The stool is watery with a dirty greenish tint. On examination, the skin is pale, the tongue is dry, lined with a dirty white coating. Body temperature 38.5 ° C, pulse - 96 beats. in 1 min, AKD - 95/60 mm RT. Art. The abdomen on palpation is painful in the umbilical region, rumbling and splashing are noted.

To clarify the diagnosis, outline an examination plan for the patient. Write a comprehensive treatment plan. What groups of antibacterial agents are most effective for this pathology?

4. A child of 3 years old, weighing 18 kg, fell ill with acute tracheobronchitis. There is a dry cough with difficult to separate mucopurulent sputum. The scattered dry rales are heard, body temperature - 37.8 ° C, the roots of the lungs are densified.

Outline a plan of diagnostic measures necessary for the rational choice of antibacterial therapy, prescribe a drug from the group of short-acting sulfa drugs with an indication of its dosage regimen.

5. A patient, 35 years old, weighing 78 kg, was admitted to the department with a diagnosis of chronic obstructive bronchitis in the acute stage. A bacteriological study of sputum culture revealed a pathogenic strain of staphylococcus.

Assign the patient a medium-duration sulfanilamide preparation.

6. A patient, 37 years old, weighing 62 kg, is in the therapeutic department for acute left-side lower lobar bronchopneumonia. Penicillin therapy performed during the first week of treatment did not give results. The patient retains physical and radiological manifestations of the disease, fever. The result of the antibioticogram showed the sensitivity of the pathogenic flora to the drug sulfalene.

Prescribe a patient treatment with sulfalen for oral administration, for parenteral use.

7. A patient, 27 years old, is being treated in the gynecology department for exacerbation of chronic adnexitis. Within a week, he receives an injectable form of Biseptolum intravenously as an antibacterial agent 2 times a day (a 5 ml ampoule was diluted in 10 ml of a 0.9% sodium chloride solution). The patient notes severity in epigastrium, right hypochondrium, appearing on the 4-5th day of treatment, nausea, loss of appetite. An objective examination of the patient determines an increase in the liver by 4-5 cm, its edge is tightly elastic, painful on palpation.

Is a connection of manifestations of liver damage with the use of SLS possible? Assign the patient the necessary additional examination, give recommendations for further treatment.

8. A patient, 52 years old, suffers from urate diathesis, chronic pyelo-nephritis in the acute stage. For therapeutic purposes, Urolesan and Sulfalen were prescribed in doses adequate for this patient. However, on the third day of treatment, the patient increased pain in the lumbar region with radiation to the perineum, oliguria appeared, in the analysis of urine, the amount of protein, fresh and leached red blood cells, crystalluria increased.

Explain the reason for the deterioration of the patient. Give recommendations for further treatment.

9. A surgeon, 50 years old, weighing 96 kg, fell ill with acute bronchitis. He was treated on his own, taking orally ethazole 0.5 g in combination with ibu-profen 1 tablet. 3 times a day. On the 4th day of treatment, the condition improved, treatment was discontinued. After 3 days, the condition worsened sharply, and bilateral lower lobar multifocal bronchopneumonia was diagnosed.

Explain the causes of dissemination of the inflammatory process in the lung tissue during therapy, which were the disadvantages of the latter.

10. A girl of 8 years, within 10 days received sulfadimethoxin for acute tonsillitis. The disease was successfully cured. However, a control blood test revealed anemia and leukopenia, which were not previously determined.

Whether arising violations may be the result of treatment. Give recommendations for their elimination.

11. A 49-year-old patient complains of abdominal pain, bloating, and the periodic presence of fresh blood and mucus in watery feces. Revealed moderate anemia - HB-96 g / l, the number of red blood cells - 2.9 T / l. Fibrocolonoscopy was performed - the presence of ulcerative defects along the sigmoid and rectum. Diagnosed with ulcerative colitis.

Conduct adequate pharmacotherapy.

TESTS

1. Among the side effects caused by sulfonamides belongs syndrome

Lyella (toxic epidermal necrolysis). It ends lethally in:

A. 40% of cases

B. 100%

C. 1%

D. 5%

E. 70-80%

2. A 48-year-old patient with ulcerative colitis: pain along the intestines, flatulence, fresh blood in the feces, anemia (hemoglobin - 94 g / l, red blood cells - 2.8 T / l), ulcerative defects along the sigmoid colon with fibrocolonoscopy. Choose a remedy for treatment:

A. Sulfadimethoxin.

B. Sulfalen.

C. Phthalazole.

D. Co-trimoxazole.

E. Mesalazine.

3. A 28-year-old patient with acute cystitis was selected for the treatment of uroantiseptic, whose mechanism of action is to disrupt the activity of iron-containing microbe enzymes. Specify a drug that meets these requirements:

A. Biseptol.

B. Norfloxacin.

C. Urosulfan.

D. Nitrofurantoin.

E. Ampicillin.

6. A 63-year-old patient noted an allergic reaction to sulfanilamide preparations. What other groups of drugs are undesirable for use in the patient?

A. Narcotic analgesics.

B. Tetracyclines.

C. Furosemide, torasemide.

D. Magnesium sulfate.

E. Antihistamines.

7. In the treatment of sulfonamides, the principle of “shock doses” is used. For what purpose?

A. Extension of the spectrum of antimicrobial activity.

B. Reducing the risk of toxicity.

C. Increased competitive antagonism with PABA.

D. Decrease in duration of therapy.

E. All of the foregoing.

8 Which group of antimicrobials has the ability to disrupt the synthesis of purine and pyrimidine bases in a microbial cell?

A. Penicillin antibiotics.

B. Fluoroquinolones.

C. Cephalosporin antibiotics.

D. Nitrofurans.

E. Sulfanilamides.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

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3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF OXYCHINOLINS, FLUOROCHINOLONES

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF NITROFURANES, NITROIMIDAZOLE

Relevance of the topic.

The treatment of diseases etiologically associated with the infectious process remains today one of the most urgent tasks of modern medicine. At the same time, given the presence of a certain category of patients who cannot tolerate antibiotics, and on the other hand, the pharmacokinetics of sulfonamides, their distribution, as well as the activity spectrum, covering a wide range of microorganisms, such as chlamydia, protozoa, etc., make quite relevant is the use of other antimicrobial drugs. In this regard, thorough knowledge by clinical practitioners of the clinical pharmacology of fluoroquinolones, oxyquinolines, nitrofurans, metronidazole and other chemical groups is of great importance, due to the fact that they have a number of advantages over traditional antibiotics. These are the most widely used groups of antimicrobials. The wide spectrum of antimicrobial action of these drugs in combination with fairly low toxic properties, the presence of antiviral, antifungal and immunostimulating properties in some of them, as well as the relatively rare development of microbial flora resistance to them, make these drugs indispensable basic therapy for a wide range of infectious diseases of the gastrointestinal tract, urogenital pathology, postpartum infections, sepsis, diseases of the upper respiratory tract, etc. In this regard, knowledge of the pharmacodynamics, pharmacokinetics and pharmacotoxicodynamics of these drugs, the ability to use them in a particular the patient with maximum effectiveness and minimum side effects dictates the importance of studying this topic.

Motivational characteristic of the topic

OXYCHINOLINE DERIVATIVES

Oxyquinoline derivatives (O.p.) - synthetic antimicrobial agents that are derivatives of oxyquinoline. In medical practice, mainly derivatives of 8-hydroxyquinoline (nitroxoline, quinozole, quiniophon, enteroseptol) and 4-hydroxyquinoline (oxolinium acid) are mainly used.

Preparations of the group O. p. Have a wide spectrum of antimicrobial action and are highly active against gram-positive and gram-negative bacteria, including their strains resistant to antibiotics, sulfonamide drugs and other chemotherapeutic agents. The quiniophon acts on some protozoa (dysenteric amoeba, trichomonads, balantidia), and nitroxoline acts on yeast-like fungi of the genus Candida. Mechanisms of antimicrobial action of O. of item are not established.

According to a number of properties and practical use, preparations of O. p. Differ from each other. The most significant differences in their pharmacokinetics. Thus, the ciniophon is slightly absorbed from the gastrointestinal tract and, as a result, when administered orally, it accumulates in the intestinal lumen in high concentrations. At the same time, some preparations from O. p. (Nitroxoline, oxolinium acid) after oral administration are easily absorbed from the gastrointestinal tract into the blood and in significant quantities are excreted from the body in the urine unchanged. In connection with the indicated differences, pharmacokinetics that are poorly absorbed from the gastrointestinal tract of O. are effective mainly for intestinal infections, and well absorbed for infections of the urinary tract.

Indications for use of individual O. p. Are not identical. For example, quinio-phon is used mainly for the treatment of amoebic dysentery and sometimes in the complex treatment of ulcerative colitis. In

case of amoebic dysentery, a hiniofon is used together with anti-amoebic agents (emethine hydrochloride, tetracyclines), which act on amoebas that are parasitic in the intestinal wall, because it is active only against amoebas located in the intestinal lumen. Nitroxoline and oxolinic acid are used for pyelitis, pyelonephritis, cystitis, urethritis, prostatitis and for the prevention of infectious complications after operations on the kidneys and urinary tract or after diagnostic procedures (catheterization of the urinary tract, cystoscopy).

Many preparations of O. p. Are used for external use as antiseptics, because they have a wide spectrum of antimicrobial action. So, ciniophon as an antiseptic is used to treat purulent wounds, ulcers, burns and for washing and douching in gynecological and urological practice. Enteroseptol, together with glucocorticoids, is part of a number of official ointments (for example, Dermozolone ointment) used to treat infected eczema, pustular and fungal skin diseases. Chinosol can be used for disinfection of hands and douching, washing wounds, ulcers, etc. In addition, it has a spermatocidal effect, and therefore is used as a contraceptive (as part of the official contraceptive T vaginal suppository).

Common for the O. group, the manifestations of their side effects are dyspeptic disorders and allergic reactions. Other signs of a side effect of O. of item are not identical at various drugs. For example, oxolinium acid along with dyspeptic disorders and allergic reactions can cause headaches, sleep disturbances, general weakness, and tachycardia. Standing out with urine, nitroxoline stains urine in saffron yellow, which is not a reason for drug withdrawal. With prolonged use, the hiniofon causes the phenomena of iodism (conjunctivitis, cough, runny nose).

O.'s preparations of item are contraindicated at the increased sensitivity to them. Oxolinic acid is contraindicated in pregnancy, breast-feeding, and children under 2 years of age. This drug should be used with caution in patients with epilepsy, as well as in renal and liver failure. In patients with renal failure, nitroxoline is used with caution in order to avoid its cumulation.

Basic O. p., Their doses, methods of application, release form and storage conditions are given below.

Oxolinic acid (Acidum oxolinicum; synonym for Gramurin and others) is applied inside immediately after eating. Adults and children over 12 years of age are prescribed 0.5 g per dose, children from 2 to 12 years old - 0.25 g per dose 3 times a day. The course of treatment is from 7-10 days to 2-4 weeks. Release form: tablets on 0,25 g. Storage: list B.

Nitroxolin (Nitroxolinum; a synonym for 5-NOC, etc.) is prescribed by mouth for adults 0.1 g, in severe cases 0.15-0.2 g per reception 4 times a day. The maximum daily dose for adults should not exceed 0.8 g. The average daily dose for children over 5 years old is 0.2-0.4 g, for children under 5 years old - 0.2 g. The daily dose is divided into 4 receptions. The course of treatment is usually 2-3 weeks. If necessary, treatment courses are repeated after two week breaks. For preventive purposes, adults are prescribed 0.1 g per reception 4 times a day. Release form: tablets on 0,05 g, coated. Storage; List B, in a dry, dark place.

Hiniofon (Chiniofonum; synonym for yatren and others) is prescribed inside adults 0.5 g 3 times a day. The highest doses for adults inside: single 1 g, daily 3 g. For children, the drug is prescribed inside in the following daily doses: in the age of 1 year to 2 years - 0.1 g; from 2 to 3 years - 0.15 g; from 3 to 4 years - 0.2 g; from 4 to 5 years - 0.25 g; from 5 to 6 years - 0.3 g; from 6 to 8 years - 0.45 g; from 8 to 12 years old - 0.6 g; from 12 to 13 years - 0.7 g; from 13 to 15 years - 1 g; 16 years and older - 1.5 g. As an antiseptic, they are applied topically in the form of 0.5-3% solutions, 5-10% ointments and 10% powders. Release form: powder, tablets on 0,25 g. Storage: list B; in su-hom, protected from light.

Chinosol (Chinosolum; a synonym for oxyquinoline sulfate, etc.) as an antiseptic is applied externally in the form of solutions in concentration (1: 1000 - 1: 2000), as well as in the form of 5-10% ointments and 1-2% powders. As a contraceptive, they are used in the form of vaginal

suppositories "Contraceptin T", which are administered intravaginally before sexual intercourse. Release form: poro-shock. Storage: in well-closed containers.

Fluoroquinolones

When the first quinolones appeared, no one expected them to break into clinical medicine so swiftly and have a bright future. More than 40 years ago, nalidixic acid was accidentally synthesized from the antimalarial drug chloroquine. Nalidixic acid and the following series of preparations (roxoxacin, oxolinic and pyromidic acids, zinc-sacin, etc.) had moderate activity with respect to gram-negative microbes and poor absorption from the gastrointestinal tract (GIT), creating low concentrations in the blood, and therefore could not be used to treat systemic infections. However, due to the high concentrations created in urine and feces, they have found use in the treatment of urinary tract infections (MVP) and certain intestinal infections. In addition, in the course of clinical use, it was found that microbes quickly developed resistance to them, which also limited their use in the clinic.

The introduction of the pyrazinyl chain at position 7 of the core of naphthyridone or quinolone (e.g. pipemidic acid) led to some increase in antimicrobial activity against gram-negative bacteria, some expansion of the spectrum of action (including Pseudomonas spp. And some gram-positive microbes).

Fundamentally new prospects for creating drugs with increased antimicrobial activity appeared with the introduction of a fluorine atom at position 6. The first fluorine-containing drug was flumechin (1973), the creation of which indicated the possibility of increasing the activity of compounds of this class against gram-positive microbes.

A real achievement in the chemistry of fluoroquinolones was the synthesis of norfloxacin (fluorinated at position 6 of quinolone in combination with the piperazinyl ring at position 7): the drug was active against a wide spectrum of gram-negative bacteria and some gram-positive microbes. However, its pharmacokinetic properties are insufficient for use as a tool for the treatment of systemic infections. After receiving norfloxacin, intensive studies began on the synthesis of new compounds in the series of fluoroquinolones: starting in 1978 (patenting norfloxacin), many fluoroquinolones were obtained in the next 3-4 years, some of which are still used today - pefloxacin (1979), enoxacin (1980), fleroxacin (1981), ciprofloxacin (1981), ofloxacin (1982).

Over the past two decades, more than 30 drugs of the quinolone, naphthyridone and fluoroquinolone group have undergone clinical trials. Of these, 12 are proposed for widespread use in medical practice (table. 1). Fluoroquinolones, together with the latest generation cephalosporins and carbapenems, belong to the three main classes of broad-spectrum antimicrobial agents. One of the main advantages of fluoroquinolones is the presence of tablet dosage forms with high bioavailability.

Despite the wide antimicrobial spectrum and high activity, the disadvantage of early fluoroquinolones is insufficiently high activity against gram-positive cocci and some other microbes that are the causative agents of respiratory infections. In addition, the development of microbial resistance to fluoroquinolones, in particular S.aureus and P.aeruginosa, is noted.

Also, due to a large number of side effects, new fluoroquinolones (grepafloxacin) and new naphthyridones (tosufloxacin and trovafloxacin) are excluded from clinical use. A new generation of fluoroquinolones is expanding and constantly replenished with new drugs, which include levofloxacin and moxifloxacin. Thus, from a small group of drugs used to treat urinary tract infections, fluoroquinolones have become one of the dominant classes of antibiotics.

The history of the development of antibiotics of the quinolone class, of course, depended on their structure, which is based on two six-membered cycles. The chemical structure distinguishes quinolones (CH group in the eighth position) and naphthyridones (nitrogen atom in the eighth position). For fluoroquinolones, the presence of a fluorine atom in the sixth position is important.

The first quinolone preparations, nalidixic and pyromidic acids, were synthesized in the period 1962–1969. which coincided in time with the creation of ampicillin and gentamicin (table. 2).

If ampicillin and gentamicin are rightly called folk antibiotics, then the first quinolones can be mentioned only in a purely historical aspect.

Quinolone preparations, which were synthesized in the 70s of the last century, suffered the same fate. Few clinicians can remember today drugs such as cinoxacin or pipemidic acid, but cefazolin, which was introduced to the market in the same period, has not lost its significance to date.

In the future, the situation changed radically. Fluoroquinolone drugs created in the late 70s - mid 80s - norfloxacin, of-loxacin, ciprofloxacin - took their rightful place.

All quinolones are synthesized chemically, that is, they are not waste products of microorganisms. Nalidixic acid (4-quinolone-3-carboxylic acid) is the first antibacterial quinolone, which was introduced into clinical practice in 1963. It inhibits the growth of gram-negative bacteria and, to a lesser extent, gram-positive microorganisms. Nalidixic acid is a naphthyridone derivative, while the new quinolones, which are about a thousand times more active, are true quinolone compounds. All of them bind to the DNA gyrase enzyme, which is involved in the formation of new DNA molecules (Fig. 1) (the enzyme responsible for the topological organization of the bacterial cell. DNA gyrase takes part in the processes of DNA replication, genetic recombination and repair. In case of DNA gyrase blockade the genetic code of bacteria is destroyed, which leads to their death, and they are destroyed to such an extent that they are no longer able to recover among antibacterial agents, like cefotaxime, imipenem, aztreons synthesized at that time).

Historically, the first quinolones (nalidixic acid and oxolinic acid and cinoxacin close in chemical structure and properties) did not create systemic antibacterial concentrations and, thus, were used only as urinary antiseptics for 20 years.

A widespread drug of this group is norfloxacin. Unlike other fluoroquinolones, it creates high concentrations only in the digestive tract and urogenital tract. Bioavailability - 70%, half-life (t1 / 2 - 3-4 hours. Indications for use of this drug are interesting: infection with MVP, prostatitis, intestinal infections (shigellosis, salmonellosis), gonorrhea. "All genres are good, but boring," that is the drug is effective against many gram-negative bacteria, but not frequent inhabitants of the respiratory tract.

So, nalidixic acid inhibits many gram-negative bacteria in vitro at concentrations of 5–20 μg / ml. Significantly higher concentrations are required for the manifestation of its action in vivo. Most E. coli strains are sensitive to this drug, as are some strains of Enterobacter, Klebsiella, and Proteus mirabilis. Pseudomonas and most positive microorganisms - Staphylococcus aureus, pneumococcus and enterobacteria - are usually resistant.

Cross-resistance exists between nalidixic acid, oxolinic acid and cinoxacin. They are prescribed for oral administration, and they are almost completely absorbed from the gastrointestinal tract, broken down in the liver into biologically active and inactive compounds that are excreted by the kidneys. About 20% of the drug that enters the bloodstream is excreted in the urine in active form, and 80% in the form of inactive conjugates with glucuronic acid. The concentration of the active form of the drug in urine reaches 50-200 μg / ml.

The greatest difficulties with the use of these drugs are the rapid development of drug resistance to them. The emergence of resistant microorganisms in the treatment of these drugs is due to both the selection of resistant mutants in the microbial population and the superinfection of drug-resistant organisms of other strains or species. It is in connection with this circumstance that they are not considered highly effective for urinary tract infections.

Transmission by plasmids of resistance to nalidixic acid has not been established. There is no cross-resistance of pathogens to nalidixic acid and other antimicrobial agents of this group.

So, the only indication for the use of these drugs is a urinary tract infection caused by coliform organisms. The dose of nalidixic acid (nevigramone, negram, etc.) for adults is 1 g orally 4 times a day for 1-2 weeks (for children - 30-60 mg / kg per day). Oxolinic acid (dioxacin, gramramur, etc.) is prescribed at a dose of 0.75 g twice a day, and cinoxacin at a dose of 1 g / day.

Nalidixic acid excreted in the urine can cause a false-positive reaction to glucose, but it can also contribute to the occurrence of true hyperglycemia and glucosuria. Dyspeptic phenomena, skin rashes, photosensitivity, visual impairment, various phenomena from the central nervous system (CNS), including seizures, are sometimes noted. Quinolones inhibit the oxidative enzymes of the liver and can enhance the action of drugs metabolized by the cytochrome P450 system. In particular, under the influence of quinolones, the side effects caused by theophylline are enhanced. The toxic effect on the central nervous system is more characteristic of oxolinic acid.

However, new or, as they are also called, respiratory fluoroquinolones are not metabolized by the enzymes of the cytochrome P450 system, which means that they do not interact with warfarin and theophylline (and generally have a minimal degree of drug interactions).

Another characteristic toxicological feature of quinolones is the manifestation of arthropathy in young (growing) animals under experimental conditions, which manifests itself in the appearance of vesicles and erosion on the cartilaginous surface of the joints. Until now, there is no data on the appearance of this pathology in humans, nevertheless, quinolones are contraindicated in children and adolescents (during the formation of the skeleton), as well as in pregnant and lactating mothers.

A huge step forward was the transition from norfloxacin to the ci-profloxacin / ofloxacin group. In the process of studying this group of drugs, a number of 4-quinolone derivatives were synthesized. The compounds of this group turned out to be active antibacterial agents, the compounds containing an unsubstituted or substituted piperazine ring at position 7 of the quinolone nucleus, and a fluorine atom at position 6. These compounds are called fluoroquinolones (second-generation quinolones).

Monofluorinated compounds (ciproflocacin, ofloxacin, enoxacin, pefloxacin, amifloxacin, rufloxacin), di- (difloxacin, amef-loxacin) and trifluorinated compounds (fleroxacin, temafloxacin) are known to exist.

So, the second wave of development of quinolones is associated with the appearance of fluorinated compounds with low toxicity and much higher activity against a wide range of gram-negative microorganisms and some gram-positive pathogens (Staphylococcus aureus). These drugs have virtually no effect on streptococci. Ofloxacin exhibits antichlamydial activity only. Fluoroquinolones have improved pharmacokinetics, have forms for parenteral administration and, therefore, extended indications for use.

PHARMACOKINETIC AND CLINICAL SIGNIFICANCE OF RESPIRATOR TORCHEORHOLONES

Most fluoroquinolone preparations synthesized at the end of the 80s of the last century began to be regarded as competitors of III – IV generation cephalosporins. This was made possible thanks to a number of the following circumstances:

- a unique mechanism of action among antimicrobial agents - inhibition of the bacterial cell enzyme, DNA gyrase and, according to the latest data, topoisomerase IV;

- an extremely high degree of bactericidal activity against most microorganisms sensitive to them. While bacteriostatics such as macrolides and tetracyclines are mainly suitable for the treatment of mild and moderate infections, fluoroquinolones are suitable for the treatment of infectious diseases of any degree, including their severe forms;

- a wide spectrum of antimicrobial action, primarily in relation to gram-negative aerobic bacteria, a number of anaerobes, atypical microorganisms (chlamydia, mycoplasma, legionella), mycobacteria;

- high bioavailability when taken orally, good penetration into tissues, cells of a macroorganism, the ability to create concentrations close and exceeding serum;

- destruction of infectious agents by minimal release of various components of the bacterial cell (endotoxins), which rarely leads to the development of endotoxic shock;

- prolonged half-life, the presence of a post-antibiotic effect, which allows the use of a number of drugs once or twice a day;

- a good potentiating combination with other groups of antibacterial drugs (beta-lactams, aminoglycosides, macrolides, lincosamides, imidazoles);

- the possibility of use as an empirical therapy for severe infections in a hospital;

- low frequency of bacterial resistance to them, good tolerance, low frequency of side effects.

The ciprofloxacin developed in the laboratories of Bayer AG, registered and approved for use in many countries of the world since 1987, became the gold standard of the second generation quinolones. Since then, the drug has been used with great success to treat many infections. It is well absorbed in the digestive tract, its bioavailability is 80%, t1 / 2 - 4-6 hours. Tsiproflok-satsin (tsiprobay, tsifran) has a number of unique properties:

- a wide spectrum of action against clinically significant aerobic microorganisms;

- very good penetration into tissues (the concentration of the drug in tissues corresponds or exceeds the concentration in plasma);

- rapid bactericidal action at all stages of bacterial growth and the ability to act on intracellular microorganisms.

In parallel, resistance to other antibiotics usually does not develop, and ciprofloxacin is successfully used to treat infections caused by multiresistant microorganisms.

The disadvantages of this generation of drugs include low activity against pneumococci, chlamydia, mycoplasmas and anaerobes. Ofloxacin was the most active of the second generation quinolones against pneumococci and chlamydia. However, it is worse than ciprofloxacin on P.aeruginosa. The drug is almost completely absorbed in the digestive tract, bioavailability - 95-100%, t1 / 2 - 5-7 hours. Indications for use are significantly expanded, for example, lower respiratory tract infections (NDP) (exacerbation of chronic bronchitis, nosocomial pneumonia); infections of the profit center; prostatitis; intra-abdominal and pelvic infections (in combination with anti-anaerobic drugs); intestinal infections (shigillosis, salmonellosis); severe infections of the skin, soft tissues, wrinkles, joints; gonorrhea; tuberculosis (a drug of the second row); anthrax (treatment and prevention).

It is somewhat inferior in activity to ciprofloxacin and ofloxacin pefloxacin (abactal). The drug is almost 100% absorbed in the digestive tract. Absorption of fluoroquinolones in the gastrointestinal tract sharply worsens while taking antacids, sucralfate, preparations containing Ca, Mg, Al, Fe, Zn cations. Better than other fluoroquinolones, pefloxacin crosses the blood-brain barrier, t1 / 2 - 9–13 hours. More often than other fluoroquinolones can cause tendonitis. Indications for use are the same as for ofloxacin, plus secondary bacterial meningitis in neurosurgery.

Lomefloxacin (maxaquin) has less antimicrobial activity than other fluoroquinolones, especially in relation to pneumococci. The drug does not act on P.aeruginosa. Has a high bioavailability when taken orally (about 100%), t1 / 2 - 7-8 hours. Tolerated slightly worse than others fluoroquinolones. In particular, it often causes photosensitivity.

Indications for use are limited to NDP infections (exacerbation of chronic bronchitis of non-pneumococcal etiology); infections of profit centers. The drug is used in the complex treatment of tuberculosis, however, controlled clinical studies have not been conducted.

In general, preparations of this group have a number of significant advantages in comparison with quinolones of the first generation.

In pharmacodynamics - a wider spectrum of activity, including:

- staphylococci (including PRSA);

- gram-negative cocci (gonococcus, meningococcus, M.catarrhalis);

- gram-positive sticks (listeria, corynebacteria, anthrax pathogens);

- gram-negative bacilli of the Enterobacteriaceae family, including multi-resistant ones (E. coli, Salmonella, Shigella, Proteus, Enterobacter, Klebsi-Ella, Serration, Providence, Cytrobacter, Morganella), P.aeruginosa, as well as Campylobacter;

- individual drugs (cipro¬floxacin, ofloxacin, lomefloxacin, etc.) are active against M. tuberculosis;

- act on some intracellular microorganisms (legionella).

According to pharmacokinetics:

- create high concentrations in the blood and tissues when taken orally, bioavailability does not depend on the time of eating;

- penetrate well into various organs and tissues: lungs, kidneys, prostate;

- have a long t1 / 2, are prescribed 1-2 times a day for tolerance;

- unwanted reactions from the gastrointestinal tract and central nervous system are less common;

- can be used for kidney failure.

The microbiological characteristics of quinolones of the second generation can not always suit a practitioner:

- most streptococci (including pneumococci), enterococci, chlamydia, mycoplasma are insensitive to them;

- do not affect spirochetes, listeria and most anaerobes.

So, the antistreptococcal activity of the drugs of the ciprofloxacin / ofloxacin group is clearly small. Another disadvantage of this group of drugs is that they do not matter in the treatment of respiratory tract infections, in which pneumococci are also causative agents. And here the fundamental “watershed” takes place, explaining why new fluoroquinolone preparations appeared, which received another, almost official name, anti-pneumococcal fluoroquinolones. Unlike earlier fluoroquinolones, these drugs exhibit both anti-staphylococcal and anti-streptococcal activity, and they also affect enterococci. Antipneumococcal fluoroquinolones act on chlamydia and mycoplasma, as well as anaerobes. However, as specific anti-anaerobic drugs, their use is irrational. Thus, in terms of the spectrum of action, new fluoroquinolones are close to carbapenems, and given that all fluorinated quinolones penetrate very well into cells, it is clear what powerful weapon medicine received in the face of these drugs.

There is no doubt that the new fluoroquinolones, that is, generations III – IV, have overcome many of the shortcomings of the old fluoroquinolones. One of the first and main preparations of the third

generation was levofloxacin (tavanic), whose activity against pneumococci (including penicillin-resistant strains) and atypical pathogens was superior to previous classical fluoroquinolones

The increased anti-pneumococcal activity of levofloxacin allowed the US Food and Drug Administration to approve its use in community-acquired pneumonia caused by penicillin-resistant pneumococci. Levofloxacin was the first of the fluoroquinolones to receive such permission. Levofloxacin is an optically active left-rotating isloxacin isomer - L-ofloxacin. Levofloxacin is characterized by a wide spectrum of action similar to ofloxacin, however, it surpasses it in activity against gram-positive cocci. That is, he surpasses his predecessors in relation to streptococci, a number of representatives of enterobacteria. Compared with ofloxacin, it has a better pharmacological profile, a lower incidence of adverse reactions and better tolerance. Levofloxacin is more active than ofloxacin in relation to Haemophilus influenzae, Moraxella catarralis, Mycoplasma pneumoniae, and in relation to Chlamydia pneumoniae it is superior to ciprofloxacin

According to the results of the PROTEKT study (2001), levofloxacin is not inferior, and in some cases superior in its activity to penicillin, cefuroxime, clarithromycin, amoxicillin / clavulanate, which are traditionally considered effective in diseases caused by S. pneumoniae, M. catataris, H.influenzae. The drug has a high bioavailability when taken orally - about 100%, t1 / 2 - 6-8 hours. Levofloxacin penetrates well into the inflammatory exudate of the skin blister in humans: after a single injection of 500 mg, the average concentration in the exudate (3 mg / l) was reached after 3.7 hours, and the penetration rate into the inflammatory fluid was from 83 to 112%.

Good penetration of levofloxacin into the tissues of the respiratory tract is noted: after taking 500 mg, the average maximum concentration in the lung tissue was 11.3 mg / kg; the concentration of the drug in the lungs was 2.5–5 times higher than in plasma, and within 24 hours it significantly exceeded the minimum inhibitory concentration (MIC) for respiratory pathogens (S. pneumoniae, C. pneumoniae, M. catatarralis, H. influenzae) High concentrations of levofloxacin were found in the bronchial mucosa (penetration rate was 90–180% and epithelial lining fluid was 8–300%).

Indications for the use of levofloxacin are upper respiratory tract infections (URTIs) (acute sinusitis), NDP infections (exacerbation of chronic bronchitis, community-acquired pneumonia), infections of the MEP, infections of the skin and soft tissues, anthrax (treatment and prevention).

Levofloxacin penetrates well and accumulates in large quantities in the cells of a macroorganism: in neutrophils, lymphocytes, macrophages. The ratio of intracellular concentrations of levofloxacin in neutrophils to extracellular concentrations was 8.8, and in polymorphonucleocytes - 9.8.

The most important structures in the fluoroquinolone molecule in general and moxifloxacin in particular, which are responsible for antimicrobial properties, are the groups occupying positions 1, 7, and 8. The cyclopropyl group in position 1 provides activity against gram-negative microorganisms (Fig. 3). Attaching an additional ring at position 7 gives high activity in relation to gram-positive microflora, including pneumococci. The addition of a methoxy group at position 8 to the structure of the molecule led to an increase in activity against anaerobes without increasing the risk of potential phototoxicity.

Moxifloxacin (avelox) is superior to generation II quinolones in activity against pneumococci (including strains resistant to penicillin and macro-lids) and atypical pathogens (chlamydia, mycoplasma).

Unlike other fluoroquinolones, moxifloxacin acts well on non-spore forming anaerobes, including B.fragilis. Slightly inferior to cy-profloxacin in activity against gram-negative bacteria of the Enterobacteriaceae family and Pseudomonas aeruginosa. Oral bioavailability - 90%, t1 / 2 - 12–13 hours.

Indications for use relate to infections of the UDT (acute sinusitis), infections of the NDP (exacerbation of chronic bronchitis, community-acquired pneumonia), infections of the skin and soft tissues.

Like all fluoroquinolones, moxifloxacin acts bactericidal by blocking the synthesis of bacterial DNA, inhibiting the enzymes of the class of topoisomerases - DNA gyrase (topoisomerase II) and topoisomerase IV

Topoisomerase IV is another bacterial DNA enzyme (after DNA gyrase) and the second target for fluoroquinolones, which works in coordination with DNA gyrase, taking part in the general process of DNA replication. Topoisome-IV IV catalyzes decatinization - the cleavage of two linked DNA strands after replication, that is, the separation of daughter DNA molecules. DNA gyrase works in front of the replicative fork, removing an excess of positive supercoils, topoisomerase IV behind.

So, these enzymes perform strictly defined functions during the formation of the spatial structure of a DNA molecule during its replication: DNA gyrase catalyzes the unwinding (negative supercoiling) of DNA strands, and topoisomerase IV is involved in the separation (decatinization) of covalently closed circular DNA molecules. Inhibition of these enzymes disrupts the growth and division of a bacterial cell, which leads to its death.

Classical fluoroquinolones act only on one enzyme, while the second is not inhibited. It has been established that the main target for gram-positive microorganisms is topoisomerase IV, and for gram-negative pathogens, DNA gyrase. New fluoroquinolones adversely affect both enzymes, as a result of which their spectrum of action is significantly expanded.

The simultaneous effect on two enzymes significantly reduces the likelihood of the emergence of resistant strains of microorganisms, since the greater the activity of the drug against both enzymes, the lower the resistance level due to a mutation in the genes encoding one enzyme.

In general, the group of fluoroquinolone antibiotics is good, and a number of them have excellent pharmacokinetic parameters. First of all, the high bioavailability of this group of antibiotics is noteworthy. Moreover, if ofloxacin and pefloxacin, it ranges from 95-100%, then for levofloxacin it stably stays at the level of 100%.

The maximum concentration of fluoroquinolones in the blood ranges from 1.2 to 5.3, and in new fluoroquinolones it reaches a value of 5.0 or higher.

The effectiveness of a dose-dependent antibiotic can be predicted with the help of another pharmacodynamic parameter - the ratio of the area under the pharmacological curve (AUC) to IPC or MBC. AUC reflects a statement of the concentration of the drug in the blood from the time of its administration to the complete elimination from the body or within 24 hours after administration. The higher the AUC / IPC, the more effective the drug. It was established that the destruction of sensitive microorganisms is achieved with an AUC / IPC value of at least 30. For levofloxacin, the AUC / IPC is 50, that is, almost 1.7 times higher than the required value for pneumococci.

Fluoroquinolones are able to suppress the multiplication of microorganisms in concentrations below the IPC - the so-called subMPC effect. They also have a pronounced post-antibiotic effect (PAE) against gram-positive and gram-negative microorganisms, which is on average 2.

Recall that antibacterial drugs are dosed so that their concentrations in the focus of inflammation exceed the BMD of one or another pathogen. However, after the antibiotic concentration decreases below the MIC, the growth and multiplication of bacteria does not begin immediately. The period of their lack of activity is defined as PAE. Reliable evidence of this phenomenon in respiratory fluoroquinolones is extremely important. PAE has been proven in levofloxacin for pathogens such as S. pneumoniae, S. aureus, E. coli, S. epidermis, B. fragitis.

The PAE of moxifloxacin for various microorganisms is 1.2–3.1 hours at a concentration of 4 + MPC, and increases with increasing concentration of the drug. For example, the PAE for S. pneumoniae is 2.2 hours at a drug concentration of 4 + MPC and increases to 2.7 at a concentration of 10 + MPC.

Thus, fluoroquinolones of III – IV generations have opened up new perspectives in the treatment of infections of various localizations. In particular, in modern In addition to b-lactams and macrolides, new fluoroquinolones are recommended along with b-lactams and macrolides, especially in regions where multidrug-resistant pneumococci appeared.

The advantages of fluoroquinolones are the possibility of oral and parenteral administration, high activity and good tolerance, low risk of developing resistant strains. However, the extremely widespread use of fluoroquinolones in animal husbandry depicts the clinical futility of this group of drugs. During clinical studies and the widespread use of fluoroquinolones in medical practice, data have been accumulated showing a possible increase in the frequency of isolation of clinical bacterial strains with resistance to fluoroquinolones. Long-term treatment courses also contribute to the development of resistance. The frequency of spontaneous mutations to fluoroquinolones is very low. The emergence of acquired resistance in bacteria to fluoroquinolones is primarily associated with a change in the properties (sensitivity) of the two main target enzymes: a decrease in sensitivity to fluoroquinolones of DNA subunits of DNA gyrase and topoisomerase IV. It depends on the corresponding mutations in the genes encoding these enzymes.

The reason for the development of resistance to fluoroquinolones may be a violation of the transport systems of the cell. This is due to damage to the system of porin channels formed by the porin protein OmpF. Accordingly, the degree of passive diffusion of primarily hydrophilic fluoroquinolones (ciprofloxacin) decreases. It is also possible to change the structure of the lipopolysaccharide layer of the bacterial cell membrane and decrease the penetration of lipophilic fluoroquinolones (ofloxacin) into the cell. B-lactams, tetracyclines, chloramphenicol, amino glycosides and some other antibacterial drugs also penetrate the bacterial cell through porin channels. Therefore, if this transport route is violated, cross-resistance can develop simultaneously to fluoroquinolones and chemotherapeutic drugs of other structural classes. It should be borne in mind the possible high resistance to fluoroquinolones of methicillin-resistant staphylococcus strains. For example, in Australian hospitals, 16–24 to 80–100% of fluoroquinolone-resistant strains were isolated among methicillin-resistant staphylococci. Truly the future of quinolones depends on the future of resistance. Nevertheless, further changes in the structure of fluoroquinolones can lead to the creation of non-resistant drugs with a wider or narrower action.

For 60 years in medical practice and veterinary medicine, drugs derived from 5 nitrofuran have been used to treat bacterial and some protozoal infections. The antimicrobial activity of this class of chemical compounds was first established in 1944 by M. Dodd, W. Stillman and immediately attracted the attention of physicians. Studies have shown that among the numerous derivatives of furan, studied since the end of the 18th century, only compounds containing a nitro group (NO2) strictly in position of the 5th furan cycle are characterized by antimicrobial properties. Differences in the activity and spectrum of action of 5 nitrofurans with antimicrobial properties depend on the nature of the substituents in the position of the 2nd cycle (Fig. 1). The nitro group is essential for the manifestation of the antimicrobial properties of a number of chemical compounds, which is well demonstrated by the example of nitrofurans, nitroimidazoles and chloramphenicol; Interesting data were obtained on the high antimicrobial activity of 6-nitro derivatives of quinolone

NITROFURANES

Nitrofurans are the second after sulfonamides class of synthetic antibacterial drugs, proposed for widespread medical use. They are inferior in clinical efficacy to most antibiotics and are important mainly in the treatment of acute uncomplicated forms of urinary tract infection (nitrofurantoin,

furazidine), intestinal infections (nifuroxazide) and some protozoal infections - trichomoniasis and giardiasis (furazolidone, nifuratel).

Antimicrobial activity of nitrofurans, the relationship between structure and action, a possible mechanism of the antimicrobial effect and the results of application in medicine

Preparations of the nitrofuran group (more precisely, 5-nitrofuran) are classic synthetic chemotherapeutic agents with a wide anti-microbial spectrum of action. For use in medical practice in the 50-60s of the twentieth century, a number of different derivatives of 5-nitrofuran were proposed. Then, due to the introduction into clinical practice of a large number of highly effective chemotherapeutic drugs in other classes of chemicals that exceeded nitrofurans in terms of activity and had a number of advantages in pharmacokinetic and toxicological characteristics, interest in the drugs of this group decreased. Nevertheless, nitrofurans are still used in medical practice. The very first nitrofurans - nitrofurantoin (furadonin) and furazolidone and the furazidin (furagin) proposed somewhat later - are still of practical interest.

Nitrofurans are characterized by a fairly wide spectrum of action and are active in high concentrations in vitro against many gram-negative (E. coli, K. pneumoniae and others) and gram-positive bacteria, some anaerobes, and Candida fungi. Enterococci are insensitive. Resistant P.aeruginosa, most strains of Proteus, serration, Providence, acinetobacter. In addition, furazolidone and nifuratel are active against some protozoa (lamblia, trichomonads).

The mechanism of action of nitrofurans on a microbial cell consists of several factors. The drugs are oxygen acceptors and disrupt the process of cellular respiration; nitrofurans inhibit the activity of a number of respiratory enzymes of the cell (pyruvate oxidase, glutathione reductase, aldehyde dehydrogenase). Drugs undergo intracellular transformation: the nitro group is restored under the influence of bacterial flavoproteins. As a result, nitrofuran metabolites are formed, which have a cytotoxic effect. The cytotoxic effect of nitrofurans in combination with impaired cellular respiration determines the activity of certain drugs (furazolidone, nifuratel) in high concentrations not only against bacteria and protozoa (trichomonads, lamblia, dysentery amoeba), but also against fungi, including Candida genus. The drugs inhibit the biosynthesis of DNA of microorganisms and, to a lesser extent, RNA. The mechanism of action of nitrofurans cannot be considered completely deciphered, but it is specific only for drugs of this group. That is why nitrofurans are active against most strains of bacteria that are resistant to antimicrobials of other classes of chemicals.

Biological fluids (blood, blood serum, urine, cerebrospinal fluid, etc.) do not reduce the antibacterial activity of nitrofurans; the activity of the drugs does not change in the presence of paraaminobenzoic acid and novocaine. Nitrofuran antagonists are B vitamins, which can inhibit nitrofuran inhibition of the respiratory enzymes of the cell. Indicate the antagonism between certain nitrofurans (nitrofurantoin) and quinolones (nalidixic acid), which can reduce the therapeutic effect of quinolone; the mechanism of this phenomenon is not entirely clear.

By the mechanism of antimicrobial action, nitrofurans are close to antiseptics. However, unlike the latter, nitrofurans are less toxic (for human cells and experimental animals), have a chemotherapeutic effect in an in vivo experiment, can be used for systemic effects (usually orally), and therefore are considered in the group of chemotherapeutic anti-infectious drugs.

It is now clear that every antimicrobial drug and a new class of chemotherapeutic substances must be evaluated in terms of the frequency and level of development of drug resistance to them in clinical strains of microorganisms.

To nitrofurans resistance develops rather slowly in clinical strains of microorganisms, which is an important property of this class of antimicrobial substances. Resistance is cross-cutting only within a given class of substances. Bacterial strains resistant to sulfonamides, β-lactams, aminoglycosides, chloramphenicol, tetracyclines, fluoroquinolones remain sensitive to nitrofurans. However, in the

event of a violation of the transport systems of the cell, the development of cross-resistance between nitrofurans and other classes of chemotherapeutic drugs cannot be ruled out.

Analysis of the results of a wide study of clinical sensitivity bacterial strains to the spectrum of antimicrobial agents confirms the slow development of drug resistance of bacteria to nitrofurans, despite the use of these drugs in medical practice for almost 60 years. In a study in 1999, the sensitivity of microorganisms isolated from patients with urinary tract infections to 10 antimicrobials was shown the lowest level of enterobacteria resistance to fluoroquinolones (norfloxacin and ciprofloxacin) and nitrofurantoin (frequency of release of resistant strains mov was 2.6–2.9%). For ampicillin and co-trimoxazole, this indicator was at the level of 33.3 and 20.3%; for gentamicin and non-fluorinated quinolones, it was 4.4–5.9% [8].

Biochemical mechanisms of the development of drug resistance of bacteria to nitrofurans need to be studied.

The problem of drug resistance in relation to nitrofurans is currently not of clinical significance. Given the long-term use in medical practice (since 1944) and the isolation of nitrofuran-sensitive strains, it is possible to predict the further rather successful use of some drugs of this group in the clinic.

Pharmacokinetics Most nitrofurans after oral administration are fairly well absorbed, but the bioavailability of the drugs varies from 50 to 90–95%. Nifuroxazide is practically not absorbed. Nitrofurans do not provide the necessary therapeutic concentrations in the blood and tissues, since they are quickly excreted from the body, mainly by the kidneys, mainly by glomerular filtration. The half-life (T1 / 2) from the blood for most drugs is within 1 hour (for nitrofurantoin - 1 ± 0.2 hours). Plasma concentrations are low and, in addition, vary significantly. The therapeutic level of drugs (concentrations significantly exceeding the minimum inhibitory concentrations - MIC) is achieved only in urine and in the contents of the intestine. Depending on the metabolism of nitrofuran, the level of the active drug in the urine is also found in the body. Drugs that metabolize in the body to a lesser extent, accumulate in the urine in very high concentrations, which provide a bactericidal effect against the main causative agents of acute urinary tract infections (UTI). These include nitrofurantoin and furagin. These drugs are indicated for the treatment of UTI. Due to the rapid excretion in urine, the necessary therapeutic concentrations in the kidney tissue are not provided, which limits the effectiveness of the drugs in pyelonephritis, especially in chronic forms of the disease. With insufficient renal function, the elimination of nitrofurans is significantly slowed down. Furazolidone is extensively metabolized in the body, in the urine, an unchanged drug is determined within up to 5% of the dose taken. This nitrofuran is essential for the treatment of intestinal infections. Partially nitrofurans are excreted with bile. After oral administration, including due to excretion with bile, some nitrofurans provide high concentrations in the contents of the intestine. The maximum concentration in the intestinal contents is achieved with the use of nifuroxazide, primarily due to the low absorption of the drug after oral administration.

It is important that nitrofurans do not significantly alter the normal intestinal microflora; during nitrofuran therapy, no intensive development of fungi is noted.

Nitrofurans pass poorly through the histohematological barriers, some drugs (nitrofurantoin) in small amounts can pass into breast milk. It should be noted that a number of pharmacokinetic parameters for nitrofurans have not been adequately studied, including questions of penetration through histohematological barriers, in particular through the placental barrier.

Nitrofurans are metabolized mainly in the liver, partially in the muscle tissue and intestinal wall. In the process of metabolism, restoration of the nitro group occurs. Metabolites do not have an antimicrobial effect and are partially inactivated in the body. Metabolites in the form of amino derivatives of nitrofurans may be toxic.

Tolerance, adverse reactions, contraindications. Nitrofurans are characterized by a narrow therapeutic breadth and are used in low therapeutic doses. Recommended doses should be strictly observed. Exceeding dosages is associated with a significant risk of adverse reactions.

According to the toxicological characteristics in the experiment, nitrofurans differ from each other. Nitrofurantoin and nitrofural (furatsilin) are more toxic (LD50 when administered orally at a level of 166 mg / kg), furagin (furazidine) and furazolidone (LD50 2813 and 1807 mg / kg, respectively) are much better tolerated. Furagin is also characterized by the highest maximum tolerated dose (2000 mg / kg with a single administration of the drug intragastrically in experiments on mice)

When used in a clinic, the tolerability and nature of adverse reactions are generally the same for all nitrofurans.

Nitrofurans cause the same adverse reactions as other drugs.

From the gastrointestinal tract, pain and unpleasant sensations in the stomach or abdomen, loss of appetite, nausea, less often diarrhea and vomiting are noted.

From the liver, a transient increase in transaminases is possible.

Allergic reactions to nitrofurans can occur in the form of skin rash and itching, arthralgia and myalgia, eosinophilia, fever, very rarely - anaphylactic shock. Allergic reactions are cross-linked to all 5-nitrofuran derivatives.

The more rare adverse reactions specific to nitrofuranes and requiring special attention of a doctor include:

1) reactions from the respiratory system (acute pneumonitis - chest pain, cough, shortness of breath, fever) are more common in elderly patients, appear during the first week of treatment, usually reversible after treatment is stopped;

2) reactions from the nervous system in the form of dizziness, drowsiness and a state of fatigue, headache; the occurrence of polyneuropathies (numbness, tingling, burning of the skin of the face, peripheral neuropathies, muscle weakness);

3) hematological reactions (granulocytopenia, leukopenia, anemia, decreased platelet aggregation, very rarely hemolytic anemia).

The risk of adverse reactions increases with insufficient renal function and the use of drugs that block tubular secretion. In this case, the effectiveness of antibiotic therapy for urinary tract infections decreases (the necessary therapeutic concentrations in the urine are not provided) and, in addition, the risk of adverse reactions increases due to an increase in the blood concentration of not only the initial drug, but also its metabolites (despite partial elimination with bile). If liver function is insufficient, the risk of adverse reactions increases due to a decrease in the metabolism of the drug in the liver and an increase in the concentration of free nitrofuran in the blood. The risk of hematologic reactions during nitrofuran therapy is increased when used together with drugs that inhibit hematopoiesis in patients with glucose-6-phosphate dehydrogenase deficiency. Nitrofurans are contraindicated in children of the first month of life: due to the insufficient age development of enzyme systems, there is a high risk of hemolytic anemia.

It is necessary to note some features of adverse reactions depending on the drug. When treating with furazolidone and the simultaneous intake of alcohol, in some cases incompatibility with the type of disulfiram-like reactions is possible; the patient should not use alcoholic beverages during treatment and within 4 days after discontinuation of the drug. In addition, furazolidone acts as an inhibitor of monoamine oxidase (MAO), which, if the dosage of the drug is exceeded in some patients, can cause a sudden increase in blood pressure. The drug should not be used simultaneously with MAO inhibitors, including tricyclic antidepressants, avoid the use of products containing tyramine and

other vasoconstrictor amines. Nitrofurantoin should not be prescribed simultaneously with drugs that have a neurotoxic and hepatotoxic effect; when therapeutic doses are exceeded (from 10 mg / kg per day and above), a moderate delay in spermatogenesis is possible. Patients with respiratory diseases should be prescribed with caution under the supervision of a physician (risk of developing pneumonitis)

Indications for use. Immediately after the introduction into clinical practice, nitrofurans were recommended for the treatment of a wide range of infections. Currently, indications for the use of nitrofurans are strictly limited. Over the past 40–50 years, a large number of highly active antimicrobials have been developed with broad indications for use, which are much more active than nitrofurans.

The main field of application of nitrofurans as chemotherapeutic drugs in accordance with antimicrobial activity and pharmacokinetic properties is bacterial UTI, primarily acute uncomplicated processes, and some acute intestinal infections - bacterial diarrhea and shigellosis; in the treatment of cholera - in addition to rehydration and symptomatic therapy

In addition, three protozoal infections remain among the indications - trichomoniasis, giardiasis and intestinal amoebiasis. However, with protozoal infections, nitrofurans are less effective than drugs of the 5-nitroimidazole group

For the purpose of systemic action, drugs are prescribed orally.

Almost all nitrofurans can be used as local antiseptics for purulent bacterial infection (acute, uncomplicated). However, the low solubility of drugs significantly complicates the development of both injectable forms of nitrofurans and optimal dosage forms for topical application.

Evaluation of antibacterial properties and chemotherapeutic activity showed that furagin potassium salt is characterized by a fairly wide antibacterial spectrum, exhibits chemotherapeutic activity (experiments in mice and rabbits) in models of septicemia caused by staphylococcus, E. coli and salmonella, in a model of peritonitis caused by association staphylococcus and E. coli.

Potassium furagin salt was significantly better (faster and more fully) absorbed after oral administration, and after rapid excretion from the blood in the urine, higher concentrations of furagin were achieved than after administration of the main furagin. Furagin was highly active, in particular, against gram-positive cocci, the causative agents of purulent-inflammatory processes, and its potassium salt was used parenterally for the treatment of some generalized forms of purulent infection. A fixed, convenient parenteral dosage form of potassium furagin has not been released. Potassium salt of furagin in the form of a 1% solution more successfully (in comparison with other nitrofurans) was used topically for the treatment of purulent wounds and burns and for administration into the cavity.

Contraindications

Allergic reactions to nitrofurans.

Renal failure (nitrofurantoin, furazidine).

Severe liver disease (furazolidone).

Glucose-6-phosphate dehydrogenase deficiency.

Pregnancy - III trimester (nitrofurantoin).

Newborn.

Warnings

Allergy. Cross to all nitrofuran derivatives.

Pregnancy. The use of nitrofurantoin during pregnancy is possible only in the II trimester. Data on the use of other nitrofurans in pregnancy are insufficient to recommend their use.

Lactation. Nitrofurans are able to pass into breast milk. Due to the immaturity of enzyme systems in newborns and the associated risk of hemolytic anemia, nitrofurans are not recommended for nursing women.

Pediatrics. Nitrofurans should not be used in newborns due to the immaturity of the enzyme systems and the associated risk of hemolytic anemia.

Geriatrics. In the elderly, it is necessary to use with caution in connection with possible changes in kidney function. Dose reduction may be required. The risk of developing pneumonitis and peripheral polyneuropathies increases.

Impaired renal function. Nitrofurantoin and furazidine are contraindicated in renal failure, since in this case they do not create therapeutic concentrations in the urine, they cumulate and can have a toxic effect.

Impaired liver function. With the initial pathology of the liver, the risk of hepatotoxic action increases. Other concomitant diseases. The risk of peripheral polyneuropathies increases with anemia, diabetes mellitus, electrolyte imbalance, and vitamin B. For the purpose of prevention, B vitamins should be prescribed.

Drug interactions

The activity of nitrofurantoin and furazidine decreases under the influence of quinolones.

When combined with chloramphenicol, the risk of inhibition of blood creation increases.

When combined with alcohol, furazolidone can cause a disulfiram-like reaction.

With the simultaneous use of furazolidone, which is an MAO inhibitor, with other MAO inhibitors, sympathomimetics, tricyclic antidepressants, or foods containing tyramine, there is a risk of hypertensive crisis.

Application principles

Take orally after a meal, drink plenty of water (100-200 ml).

Strictly observe the regimen and treatment regimen throughout the course of therapy, do not skip the dose and take it at regular intervals. If you miss a dose, take it as soon as possible; do not take if it is almost time for the next dose; do not double the dose. Withstand the duration of therapy, especially with streptococcal infections.

Consult a doctor if improvement does not occur within a few days or new symptoms appear.

Do not drink alcoholic beverages during furazolidone therapy and within 4 days after its withdrawal.

During therapy with furazolidone, foods and drinks containing tyramine (cheese, beer, wine, beans, smoked foods) should not be consumed in a large number.

During treatment with furazolidone, medications for the treatment of cough and colds should not be taken without a doctor's prescription.

Use caution in case of dizziness.

Nitrofurantoin and furazidine can stain the urine in a rusty yellow or brownish color. Furamag® ("OlainFarm") - the original combined dosage form of 5-nitrofuran furagin with improved solubility and optimized pharmacokinetic and toxicological properties.

Features of the mechanism of antimicrobial action, activity spectrum, pharmacokinetic and toxicological properties, as well as physicochemical parameters of the group of nitrofurans, determine the possibilities and their significance for clinical practice.

5-Nitroimidazoles - antimicrobial agents for the treatment of bacterial and protozoal infections

The drugs of the 5-nitroimidazole group (5-NIMZ) are highly active antimicrobial drugs with a wide spectrum of action for the systemic treatment of infections caused by obligate anaerobic bacteria and a number of infectious diseases caused by protozoa. 5-NIMZ are also active against certain representatives of facultative anaerobes (microaerophiles) and, accordingly, are effective in infections caused by these microorganisms.

In terms of chemical structure, 5-NIMZ are synthetic low-molecular compounds containing a nitro group (NO2) at the position of the 5th imidazole ring (see figure). By their biological properties and the mechanism of antimicrobial action, 5-NIMZ fundamentally differ from pharmacological preparations of other chemical groups and imidazole derivatives with antifungal activity. Imidazole antimycotics have a more complex chemical structure, and the nitro group or any other substituents are absent in the structure of their molecule in the imidazole ring.

The antiprotozoal activity of nitroimidazoles was first established in 1956 with a compound called azomycin, which was 2-nitroimidazole. As a result of further exploratory studies, it was shown that it was 5-nitroimidazole derivatives that showed the highest antimicrobial activity. Moreover, at the first stages of the study, only antiprotozoal activity was established in these compounds. In 1957, 5-NIMZ was synthesized - metronidazole, which was already used in the clinic for treating trichomonas infection in 1960 and still remains highly effective in this infectious disease. A detailed study of the biological and antimicrobial properties of metronidazole also established its high activity against obligate anaerobes. Over the following years, intensive searches were carried out for new compounds in the series of analogues of metronidazole. As a result, a number of new highly effective drugs were also developed with high activity against anaerobic bacteria and some protozoa. All the most active drugs used in clinical practice necessarily have a nitro group in the position of the 5th imidazole cycle, and some differences in their biological properties are associated with a modification of the structure of substituents at positions 1 and 2 of the cycle (i.e., according to R1 and R2 and; see figure). The structure of these substituents determines the difference in the physicochemical properties of the preparations and, accordingly, the features of their action. The drugs practically do not differ in spectrum and degree of activity, a number of differences are associated with pharmacokinetic and some toxicological properties (in particular, in interaction with alcohol) and developed dosage forms. All drugs of the 5-NIMZ group are poorly soluble compounds, which complicates the development of injectable dosage forms. At the same time, high bioavailability and optimal distribution in the body make it possible to successfully use 5-NIMZ for the purpose of systemic oral administration.

Based on the antimicrobial and optimal pharmacological and toxicological properties, the most widely used and used in medical practice are three drugs of the 5-NIMZ group - metronidazole - MDZ, tinidazole - TDZ and ornidazole - ODZ. From the point of view of the chemical structure, the drugs differ in the nature of the substituents in R1

They are characterized by the widest indications for use. In addition, in medical practice, preparations of secnidazole, nimrazole, ternidazole, satranidazole and some others are used. However, they are not used as widely as the first three, since they do not have significant (fundamental) advantages in terms of the spectrum of activity and degree of activity in comparison with MDZ, TDZ, and DLZ. The difference can be mainly in pharmacokinetic properties (for

example, secnidazole, satranidazole - in terms of duration of action) and in indications for use, mainly with protozoal infections (trichomoniasis).

The lecture uses materials from reviews and monographs in which the interested reader will find the necessary links to the primary sources (see recommended literature).

Antimicrobial activity and antimicrobial mechanism against obligate anaerobic microorganisms and microaerophiles

Nitroimidazoles are active against most gram-positive and gram-negative obligate anaerobic bacteria, spore-forming and non-spore-forming, as well as against anaerobic cocci. Of greatest importance is activity against bacteroids, primarily against Bacteroides fragilis, and various representatives of Clostridium spp. Propinibacterium acnes strains are resistant to nitroimidazoles. By their action on anaerobic bacteria, 5-NIMZ are comparable to clindamycin protected with b-lactams (amoxicillin / clavulanate, piperacillin / tazobactam), they are somewhat inferior to carbapenems (meropenem, imipenem, ertapenem), and some new fluoroquinoloxenofenacin) The difference in activity depends on the properties of the strains.

Of the microaerophiles (facultative anaerobes), 5-NIMZ are active against Helicobacter spp., Moreover, activity against Helicibacter pylori (H. pylori) is of the greatest importance for the clinic. In addition, drugs are active against Gardnerella vaginalis.

The spectrum of action of 5-NIMZ in relation to anaerobic bacteria includes:

• Bacteroides spp., Including B. fragilis, B. distassons, B. ovatus, B. thetaiotamicron, B. melaninigenicus, B. vulgatus, B. caccae, B. uniformis;

• Fusobacterium spp., Eubacterium spp;

• Clostridium spp., Including Clostridium perfringens, Clostridium difficile;

• Peptococcus spp., PeptoStreptococcus spp.

In relation to the listed non-spore-forming anaerobic bacteria, the range of the minimum inhibitory concentration (MPC) of metronidazole is in the range of 0.01–256 mg / l, the range of MPC90 is in the range of 0.1–4–6.2 mg / l. The activity against fusobacteria and eubacteria is within the MPC90 range of 0.5–4 mg / L. The drug is highly active in relation to various spore-forming anaerobes of Clostridium spp .: MPC90 range 1.6–4 mg / L. At the same time, it should be noted that some highly resistant strains are isolated, for example, C. perfringens strains with IPC up to 128 mg / L.

Ornidazole exhibits very high activity against non-spore-forming and spore-forming anaerobes: the MPK90 range for this 5-NIMZ is 0.1–1.6 mg / l.

In accordance with their activity against anaerobic bacteria, MDZ, TDZ and ODZ are highly effective in the treatment of anaerobic infection; MDZ is most widely used in clinical practice, although two other drugs are no less effective.

An important property of MDZ, TDZ, and ODZ is activity against H. pylori microaerophile: the IPC range is from 0.125 to 32 mg / L. The activity of 5-NIMZ in relation to H. pylori was very important for the eradication of this microorganism in combination therapy of gastric ulcer, duodenal ulcer, and gastric lymphoma. Less studied is the activity of 5-NIMZ against H. heilmanii; this microaerophile is rarely a cause of the above infectious processes.

5-NIMZ are active against another microaerophile - Gardnerella vaginalis. The range of MPC is from 1 to more than 128 mg / l, MPC90 4–128 mg / l. This activity has a certain value in the treatment of bacterial vaginosis, however, the value of 5-NIMZ in this pathology is primarily associated with their direct effect on the obligate anaerobic flora.

Activity against causative agents of protozoal infections

Among the causative agents of protozoal infections, 5-NIMZ are sensitive:

Trichomonas spp., Trichomonas vaginalis, Entamoeba hystolytica, Giardia lamblia (Lamblia intestinalis), Balantidium coli, some strains of Leishmania spp.

The activity of the drugs is high and is within the IPC range of 0.3–6 mg / L. More resistant strains of Giardia lamblia. MDZ ensures the death of trophozoids G. lamblia in concentrations from 1 to 50 mg / L.

Under the action of 5-NIMZ on protozoa, the degree of activity depends not only on the current dose of the drug and the sensitivity of the strain, but also from exposure. The trichomonacid effect of metronidazole in 90% of Trichomonas vaginalis cells is manifested at a concentration of 2.5 mg / L and exposure for 24 hours. In experiments with Entamoeba histilytica, morphological changes in protozoan cells with a concentration of 1-2 mg / L metronidazole are observed after 6–20 h, a complete protistocidal effect at these concentrations occurs after 24 hours. At a concentration of 0.2 mg / l, a complete protistocidal effect is recorded only after 72 hours.

5-NIMZ are not active against all groups of aerobic bacteria, including microorganisms with intracellular localization, spirochetes, rickettsia; not active against plasmodia of malaria, do not affect pathogens of mycoses, viruses and prions.

Antimicrobial mechanism

Nitroimidazoles are drugs with a bactericidal and protistocidal type of action and belong to DNA-tropic compounds with selective activity against microorganisms having nitroreductase enzyme systems capable of reducing the nitro group. These drugs, unlike most other antimicrobial agents, show their effect only after transformation in the cells of bacteria or protozoa. Nitroreductases catalyze the interaction of proteins of the ferridoxin group with nitro compounds in the microbial cell. As a result of the action of nitroreductases, active metabolites of 5-NIMZ are formed in the cell, which have a bactericidal and protistocidal effect. The target of these metabolites are DNA and RNA cells and cellular proteins. Active reduced forms of drugs disrupt DNA replication and protein synthesis in the microbial cell. This process is simultaneously accompanied by the formation of free radicals, which also have a damaging effect on DNA.

The following 4 stages are considered in the antimicrobial effect of 5-NIMZ:

• penetration of the drug into the microbial cell,

• restoration of the 5-NIMZ nitro group under the action of microbial cell enzyme systems,

• antimicrobial action of reduced products and the action of free radicals,

• removal from the cell of the formed intracellular transformation products.

5-NIMZ are characterized by rapid bactericidal (protistocidal) action. The range of bactericidal concentrations of the three main preparations of this group in relation to 50 strains of B. fragilis was in the range of 0.03–2 mg / L, and for most of these strains it was in the range of 0.25–1.0 mg / L. The dependence of the bactericidal effect on concentration was established. The values of the minimum bactericidal concentration (MBC) in relation to most anaerobic bacteria are equal to or exceed MPC by 2–4 times. Bactericidal concentrations of 5-NIMZ are significantly lower than those achieved in the body (in blood and tissues) at therapeutic doses of drugs, and characterize the high bactericidal activity of these compounds. The drugs provide a pronounced post-antibiotic effect (PAE), in particular, the PAE for MDZ in relation to anaerobic bacteria, depending on the current concentration, is determined within 3 hours.

Drug resistance, its mechanisms and clinical significance

Microorganisms may develop drug resistance to 5-NIMZ. The frequency of development of resistance to MDZ, TDZ, ODZ and other drugs of this group and the level of this resistance differ significantly depending on the type of microorganism and the effectiveness of the applied doses and treatment regimens

The development of resistance is primarily associated with a decrease in the activity of nitroreductases of the microbial cell and, accordingly, with a decrease in the intracellular biotransformation of drugs. As a result, the formation of complexes with DNA, the processes of formation of free radicals and the concentration of cytotoxic metabolic products are reduced. The development of resistance to 5-NIMZ, as well as to other antimicrobial agents, may also be associated with a violation of cell transport systems (decreased permeability of the cell wall in anaerobes and microaerofl and the cell membrane in protozoa), including the ejection phenomenon.

Acquired drug resistance to 5-NIMZ is not yet a clinical problem, since in the body, at the right dosages (!), Serum and tissue concentrations of drugs are created that are significantly higher than BMD and MBC. The degree of resistance must be very high (BMD more than 32 mg / l) in order to exceed the level of drug concentrations in the course of treatment. For example, when assessing the sensitivity of bacteria strains of the B. fragilis group to various antimicrobial agents, all strains were sensitive to MDZ and chloramphenicol, less than 1% of the strains were resistant to imipenem and ticacillin / clavulanate, 4–5% were resistant to clindamycin and cefoxitine, 11.5% - to piperacillin and moxalactam, 56–68% - to cefoperazone and ceftazim-dime (G. Cucbaral et al., 1988).

In protozoa and obligate anaerobic microorganisms, resistance to 5-NIMZ, as a rule, develops relatively rarely.

Of greatest clinical importance is the development of resistance to 5-NIMZ, in particular to metronidazole and tinidazole, in H. pylori. These two drugs most often, along with proton pump inhibitors, macrolides (clarithromycin), amoxicillin or tetracycline, are used in the treatment of gastric ulcer with the aim of eliminating the pathogen. Monitoring the sensitivity of H. pylori to MDS and clarithromycin over 5 years showed a significant increase in resistance to MDS. In 1991, 9% was isolated, and in 1995 - already 26.6% of MDZ-resistant strains. At the same time, resistance to clarithromycin increased much more slowly. In another study over the same period, the frequency of isolation of resistant strains to MDS increased from 22 to 55.3% (T. Alacron et al., 1996; J. Joseph, M. Sung, 1996).

Pharmacokinetics

5-NIMZ are characterized by optimal pharmacokinetic properties. Important are the high bioavailability of drugs in the range of 80-100% and rapid absorption when taken orally. This eliminates the need to widely use parenteral administration, which is usually used only for severe forms of anaerobic or mixed aerobic-anaerobic infections, including infections of the central nervous system (CNS) and extra-intestinal amoebiasis. Preparations of this group bind slightly to plasma proteins (by 10–20%), have a large distribution volume, penetrate well into body fluids and tissues, and provide high tissue concentrations.

The bioavailability of MDZ is at a level of 100%, the maximum concentration after oral administration is achieved after 1-2 hours and is, depending on the dose, from 6 to 40 mg / l; binding to plasma proteins - up to 20%, T1 / 2 - 9 (6–10) hours. When administered repeatedly, it accumulates. The bioavailability of TDZ is in the range of 90%, binding to plasma proteins is up to 10%, T1 / 2 is 10-14 hours. It is cumulated with repeated administrations. The bioavailability of ODD is up to 90%, protein binding is at the level of 13-15%, the maximum concentration is reached within 3 hours, the plasma concentration at therapeutic doses is from 6 to 36 mg / l, T1 / 2 in - less than 13 hours, accumulates during repeated administrations, already at the dosage regimen every 12 hours

In addition, 5-NIMZ penetrate well through the blood-brain and placental barriers, into breast milk, and are actively secreted by saliva and gastric juice. In cerebrospinal fluid, depending on the degree of inflammation of the meninges and the administered dose of the drug, 40 to 80% of the concentration of 5-NIMZ in the blood is determined. With meningitis, the concentration of MDZ in the cerebrospinal fluid may correspond to serum. During the course of treatment for 14 days in the cerebrospinal fluid 1.5 hours after the injection, an average of 14.7 + 7.4 mg / L MDS was determined (daily dose of the drug is 2.4 g). High concentrations of drugs in the cerebrospinal fluid, an average of 30.3 + 10.2 mg / l, were recorded 1.5 hours after the administration of 2 g of TDZ and 1.5 g of ODZ (F.Jokini, I.Jokini, 1981, etc.)

5-NIMZ provide high concentrations in brain tissue, which significantly distinguishes this group of drugs from most other antibacterial agents and is important for the treatment of purulent-inflammatory processes in brain tissue and abscesses and brain tissue lesions in extraintestinal amoebiasis.

Concentrations of 5-NIMZ in various tissues and body fluids with the use of therapeutic doses, including oral administration, reach 70–94% of serum concentrations.

5-NIMZ slowly removed from the body. As indicated above, the half-life for MDZ is in the range of 6–10 hours, for TDZ and ODZ - 10–14 hours. Some other drugs of this group are excreted even more slowly, for example, secnidazole and satranidazole — T1 / 2 - up to 20 hours It should be remembered that the elimination of drugs sharply lengthens in newborns and, for example, for MDS can reach 25 hours. The drugs accumulate during the course of treatment. Slow elimination of 5-NIMZ is partly associated with reabsorption of drugs in the renal tubules (TDZ). Prolonged action, good penetration into organs, tissues and body fluids in combination with high serum concentrations and bactericidal activity allow in some cases successful treatment with a single dose once, which completely eliminates the cumulative effect.

The drugs are well absorbed when administered rectally and intravaginally; this justifies the indications for their use in candles and globules. At the same time, with these routes of administration, the drugs also have a direct local effect on the pathogen.

5-NIMZ is metabolized in the liver. The main metabolites are their hydroxy derivatives, which are characterized by antianerobic and antiprotozoal activity and are also eliminated from the body as slowly as the initial preparation. Accordingly, an increase in the antimicrobial effect (joint action) is observed, although these metabolites are somewhat less active than the initial 5-NIMZ. In addition to active, metabolites are formed that do not have an antimicrobial effect.

The drugs are excreted mainly by the kidneys - up to 60–85% of the dose taken (depending on the drug). At the same time, from 4 to 12–20% is an unchanged drug, and the rest are various metabolites; from 6 to 15% of the administered dose is excreted unchanged with bile and feces.

Clinic Application

High antianerobic and antiprotozoal activity in combination with favorable pharmacokinetics allows the use of 5-NIMZ in almost any localization of the infection.

MDZ, TDZ and DLZ are important highly effective drugs for the treatment of severe generalized forms of anaerobic and mixed aerobic-anaerobic infections, including CNS infection. Drugs are also widely used to treat protozoal infections. Some 5-NIMZ are included in the combined treatment regimen of gastric and duodenal ulcers.

The most widely used in clinical practice for anaerobic and protozoal infections is MDZ, which, despite its "long clinical experience" (40 years), remains highly effective. The largest number of different dosage forms have been developed for MDZ - for oral, intravenous, rectal, intravaginal, topical administration.

TDZ and DLD are more often used to treat protozoal infections, but with no less success, these 5-NIMZ can be prescribed for anaerobic infections. The use of TDZ is somewhat limited by the absence of injectable dosage forms necessary for generalized infections (anaerobic, extraintestinal amoebiasis). Unfortunately, the injection form of DLD is not registered in Russia.

The main indications for the use of nimorazole and secnidazole are protozoal infections, mainly trichomoniasis. Dosage forms - only tablets for oral administration, injection forms are not developed. Ternidazole is available only for intravaginal administration in a combined dosage form in combination with neomycin, nystatin, and prednisolone. In this case, local action is primarily realized, but (taking into account the absorption of ternidazole), the general resorption effect should be borne in mind.

Treatment of various forms of purulent-inflammatory processes caused by anaerobic microorganisms

5-NIMZ are indicated in monotherapy for anaerobic infections (a rather rare situation in clinical practice), but, as a rule, they are most often used for mixed aerobic-anaerobic infections, including infections:

• skin (including pink and vulgar acne), soft tissues, joints;

• CNS, including brain abscesses, meningitis;

• intra-abdominal (peritonitis, intraperitoneal abscess, liver abscess, gallbladder infection);

• in the pelvic area (endometritis, pelvioperitonitis, tubo-ovarian abscess, infection after cesarean section, infected abortion), with bacterial vaginosis;

• in the colorectal region;

• respiratory tract (lung abscess, empyema, pleural pneumonia);

• oral cavity, peridental tissues;

• endocarditis;

• bacteremia caused by bacteroids, primarily

Bacteroides fragilis.

With the above forms and localization of purulent infection, as a rule, a mixed aerobic-anaerobic infection occurs, therefore 5-NIMZ (mainly MDZ) should be used only in combination therapy schemes. Currently, a large number of antimicrobial agents have been developed in antibiotic groups with high antianerobic activity, especially against bacteroids. Therefore, in monotherapy regimes, for example, carbapenems or protected penicillins can be used, since these drugs are simultaneously active against anaerobic and aerobic flora. Details of antibiotic therapy and prophylaxis of infections with anaerobic etiology are considered in monographs by N.A. Efimenko et al. (2004) and S.V. Sidorenko and S.V. Yakovleva (2003).

An important area of application of 5-NIMZ, taking into account anti-anaerobic activity, is the prevention of infection during surgical interventions in the abdominal cavity, in colorectal surgery, and dental practice in operations in the oral cavity. There is an obvious need to include 5-NIMZ in prophylactic regimens at risk of developing anaerobic infection.

In cases of developed severe forms of infection, parenteral administration of 5-NIMZ is indicated at the first stages, and with clinical improvement, it is justified to carry out treatment according to the step therapy regimen - intravenously / orally.

It must be emphasized that 5-NIMZ are well combined with chemotherapeutic drugs of other chemical groups.

In mixed bacterial infections, 5-NIMZ can be used in conjunction with b-lactams, aminoglycosides, fluoroquinolones, macrolides, vancomycin, chloramphenicol, sulfonamides, co-trimoxazole and its analogues, as well as for indications in combination with anti-tuberculosis drugs tami. At the same time, when choosing drugs for the combined treatment of bacterial infections, it is necessary to take into account (as indicated above) both anti-anaerobic properties and the degree of activity against anaerobes of those antibacterial agents that are supposed to be prescribed simultaneously with 5-NIMZ.

5-NIMZ go well with antimycotics and antiviral agents.

For empirical therapy of aerobic-anaerobic or anaerobic infections, a number of schemes are proposed with the inclusion of 5-NIMZ, namely:

• for central nervous system infections - benzylpenicillin or third generation cephalosporins + injectable 5-NIMZ, orally - preferably TDZ; fluoroquinolones + 5-NIMZ;

• with intra-abdominal infections and infections of the pelvic cavity - cephalosporins of the II or III generation + 5-NIMZ;

• for infections of the lower respiratory tract (lung abscess, pleural empyema, aspiration pneumonia) - benzylpenicillin or third generation cephalosporins + 5-NIMZ.

5-NIMZ, primarily MDZ, are successfully used to treat bacterial vaginosis. The cause of this pathology is a violation of the vaginal ecosystem and activation of growth and reproduction of both obligate anaerobes and Gardnerella spp. This microaerophile is well associated with obligate anaerobes. Gardnerella spp. Growth inhibition. is largely a consequence of the normalization of the vaginal biocenosis as a result of the suppression of the multiplication of anaerobes. Nevertheless, one cannot exclude the direct direct effect of 5-NIMZ on gardnerella, especially in the case of strains with a fairly high sensitivity to 5-NIMZ. There is positive experience with the use of DLD in the treatment of bacterial vaginosis.

The bactericidal properties of 5-NIMZ allow the use of these drugs locally as part of ointments, creams and gels for the treatment of some forms of purulent skin infection (pink and vulgar acne) and wound infection (non-healing wounds, trophic ulcers). Local action is also manifested with intravaginal administration of suppositories or globules.

Treatment of protozoal infections In protozoal infections, 5-NIMZ is usually used orally. An exception is the generalized form of amoebiasis (systemic amoebiasis) with damage to the internal organs when intravenous administration of the drug is necessary.

Indications for the use of 5-NIMZ for protozoal infections:

• trichomoniasis in men and women, both clinically expressed and symptom-free, including the prevention of infection in the sexual partner;

• amoebiasis - an acute intestinal form of amoebic dysentery and mainly extraintestinal amoebiasis, including amoebic liver abscess or brain tissue abscess; with asymptomatic amoebic dysentery and cystic carriage, amoeba 5-NIMZ are less effective, as they are well absorbed from the gastrointestinal tract (GIT) and do not always provide the necessary drug concentration in the intestinal lumen with these forms of amoebiasis;

• giardiasis (acute and chronic forms);

• balantidiasis.

The high therapeutic efficacy of 5-NIMZ in trichomoniasis, amoebiasis, giardiasis, established in clinical trials of the 70-80s of the last century, is confirmed by publications of recent years. The question of the choice of the drug is discussed primarily for the treatment of trichomoniasis (M.A. Gomberg, A.M. Soloviev, 2003). According to the recommendations of WHO and the Federal guidelines for the use of medicines (Issue IV, 2003), MDZ is considered as the drug of choice. At the same time, there are a number of advantages in ODD compared with MDZ: efficacy in patients in cases where metronidazole was not effective, and better tolerance. In the guidelines for the diagnosis and treatment of the most common sexually transmitted infections (STIs) and associated diseases (approved by the Russian Association of Obstetricians and Gynecologists, 2000) with urogenital trichomoniasis, the following are recommended as the drugs of choice: 1) for uncomplicated forms of infection ODZ (1.5 g once) or TDZ (2.0 g once) and 2) in complicated forms - ODZ (0.5 g every 12 hours for 10 days). MDZ, TDZ, nimorazol, secnidazole are considered in alternative regimens.

In the framework of this publication, unfortunately, it is impossible to give an exhaustive review of the very extensive clinical materials on the use of 5-NIMZ in the treatment of protozoal infections.

Clinical data as a whole indicate a slow increase in resistance to 5-NIMZ in protozoa. At the same time, it seems that the rather widespread use of MDS in Trichomonas infection in a number of regions can lead to the appearance of resistant strains of Trichomonas with a BMD of 100 μg / ml or higher (H. Gillette, G. Schmid et al., 1999). Of undoubtedly great interest is the study of the laws of development of resistance in protozoa to 5-NIMZ.

The use in combination therapy of gastric ulcer and duodenal ulcer

Of the 5-NIMZ, two drugs - MDZ and TDZ - are used in complex therapy for the eradication of H. pylori in patients with peptic ulcer of the stomach or duodenal ulcer and with gastric lymphoma. It should be borne in mind that all antibacterial drugs used in this pathology are not effective enough in monotherapy, including 5-NIMZ. It is necessary to use both proton pump inhibitors and antibacterial drugs according to the developed schemes. Recently, there has been an increase in the resistance of the pathogen to 5-NIMZ, which reduces the effectiveness of combination therapy. The most effective are considered schemes with clarithromycin and 5-NIMZ. Proton pump inhibitors are required for all circuits.

Pseudomembranous colitis

Due to the high activity of 5-NIMZ against Clostridium difficile, this group of drugs is indicated for the treatment of pseudomembranous colitis and necrotic colitis caused by this microorganism. The drugs have a direct bactericidal effect on pathogens, but do not neutralize their toxins. In addition, 5-NIMZ are also used for some chronic inflammatory bowel diseases, namely for ulcerative colitis and Crohn's disease, in which anaerobic flora can be activated.

Recommended doses of drugs in the treatment of anaerobic and protozoal infections and possible dose changes in case of impaired renal and hepatic function are presented in table. 2, 3

Tolerance, interaction, adverse reactions, contraindications

All 5-NIMZ when used in recommended therapeutic doses, as a rule, are well tolerated with different routes of administration. The frequency of undesirable reactions does not exceed this indicator for fluoroquinolones and b-lactams. Severe life-threatening adverse reactions that are characteristic only for this group of drugs have not been described for 5-NIMZ. Possible adverse reactions, mostly of the same type.

The following adverse reactions may occur with 5-NIMZ therapy.

From the gastrointestinal tract - an unpleasant (metallic) taste and / or dry mouth, nausea, diarrhea, abdominal pain, vomiting.

From the side of the central nervous system - headache, dizziness, impaired sleep and coordination of movements, ataxia, with an overdose - depressive reactions, peripheral neuropathies, convulsive reactions.

Skin-allergic - rashes, skin itching.

From the hematopoietic system - leukopenia, neutropenia.

Local reactions in the area of the introduction of solutions - phlebitis, thrombophlebitis, pain.

With the external use of dosage forms containing 5-NIMZ, the possibility of the development of photodermatitis should be considered.

With intravaginal administration of drugs, itching, burning in the vagina / vulva, swelling of the vulva, the appearance or intensification of secretions, and increased urination are possible.

In the treatment of 5-NIMZ, the cross-sectional nature of allergies to all drugs of this group should be taken into account, and in young children, the risk of cumulation due to a slowdown in drug withdrawal. In severe renal failure, as well as in elderly patients due to age-related insufficiency of liver function, a dosage reduction should be considered. In violation of the metabolic function of the liver, an increase in the concentration of drugs in the blood is possible above the therapeutic and, accordingly, the risk of adverse reactions due to an overdose.

With caution, 5-NIMZ should be used in patients with central nervous system diseases (with a tendency to convulsive reactions and organic central nervous system diseases) and for diseases of the hematopoietic system (risk of developing leukopenia, neutropenia).

When using MDZ and TDZ, it is possible to stain urine in a dark color due to the properties of metabolites. Urine does not turn dark when using ODZ. 5-NIMZ enhance the effects of oral anticoagulants. With the simultaneous use of 5-NIMZ with inducers of microsomal enzymes (phenobarbital, rifampicin), the concentration of 5-NIMZ in blood and tissues decreases, when used together with inhibitors of microsomal systems of the liver, in particular with H2 receptor blockers (cimetidine) , - is rising.

MDZ, TDZ, secnidazole, nimorazole inhibit in the body the enzyme aldehydhydrogen dehydrogenase and therefore are incompatible with alcohol, as they cause di-sulfiramine-like reactions. Ornidazole does not affect the activity of aldehyde dehydrogenase, therefore it is compatible with alcohol, which is very important for maintaining the quality of life of patients.

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The purpose of the lesson.

To study scientifically based approaches to the rational pharmaco-therapy of fluoroquinolones, nitrofurans, oxyquinolines and other chemical groups and methods for monitoring the effectiveness and safety of their use in each patient.

1**. The student must know:**

a) a unified algorithm for the selection of antimicrobial drugs and methods for monitoring its effectiveness and safety;

b) the pharmacodynamics, nature and spectrum of the antimicrobial action of the following compounds:

nitrofurans: furatsilin, furazolidone, furadonin, nitrofurantoin, nifuroxazide;

oxyquinolines: nitroxoline, chlorchinaldol;

quinolones: oxolinic acid;

nalidixic acid negram, nevigramone;

pipemidic acid: palin, pimidel;

nitroimidazoles: metronidazole (trichopolum, metrogil, flagyl), ornidazole, tinidazole, secnidazole.

quinoxaline derivatives (dioxidine, quinoxidine).

a) the pharmacokinetics of leading representatives of new groups of antimicrobial compounds and principles for choosing the routes of administration of these drugs;

b) the main biochemical mechanisms of the microbial cell, which are the object of drug exposure to SLS;

c) undesirable effects of the studied drugs, the principles of their early detection and prevention;

d) the main types of interaction between the studied antimicrobial agents and the principles of combination therapy based on this;

e) a comparative description of the leading representatives of the studied classes of antimicrobial compounds and the criteria for their selection in a particular patient;

f) age-specific features that should be considered when choosing the necessary chemotherapeutic agent, its dose and administration regimen.

2**. The student must be able to:**

a) select a specific patient from the group of compounds studied the necessary chemotherapeutic drugs, select the dose, mode and route of administration of the drug;

b) highlight the criteria for therapeutic efficacy and safety of applied drugs;

c) select a specific patient from the group of sulfonamides taking into account the causative agent of the disease, localization of the infectious process, individual characteristics of the patient, highlight the criteria for therapeutic efficacy and safety;

d) prescribe combination therapy;

e) having data on the concentration of creatinine in the blood serum (or on the creatinine clearance) be able to calculate in% the dose of the drug needed for this patient;

f) provide differential medical assistance with:

- acute pyelonephritis;

- acute gonorrhea;

- acute enterocolitis;

- acute giardiasis cholecystitis;

- anaerobic gas infection.

e. recognize the complications of antibiotic therapy and correct them.

Tasks for self-testing of the initial level.

1. List the main infectious diseases indicated for pharmacotherapy by representatives of the studied classes of antimicrobial drugs.

2. What are the features of the course of infections of the genitourinary sphere and gastrointestinal tract organs that determine the choice of antibiotic therapy for the derivatives of the studied groups.

3. Indicate the organs and systems involved in the elimination of the studied antimicrobial agents. What concomitant diseases require correction of the route of administration and dosage regimen?

4. Give a comparative assessment of the spectrum and nature of the antimicrobial action of chemotherapeutic drugs, derivatives: drugs of the nitrofuran series, fluoroquinolones, hydroxyquinolines, imidazole, oxolinium acids.

5. What are the main indications and principles of combination chemotherapy with the drugs of the studied groups.

6. What are the main clinical and laboratory criteria that are a guideline for monitoring the effectiveness and safety of the use of these groups of drugs.

7. Expand the mechanisms of the possible development of AB-resistance and AB-dependence, as well as methods of their prevention in conditions

8. List the undesirable effects of drugs of the nitrofuran series, fluoroquinolones, oxyquinolines, imidazole, oxolinic acid in relation to organs and systems of adults, children and pregnant women, what are the contraindications for their use.

Control questions of the studied topic.

1. List the clinical and pharmacological principles of the appointment of antimicrobial drugs.

2. List the drug from the nitrofuran group. Give their comparative characteristics (the most clinically significant differences in PK, undesirable reactions, indications for use).

3. List the drug from the imidazole group. Give their comparative characteristics (the most clinically significant differences in PK, adverse reactions, indications for use).

4. Features of the use of nitrofurans depending on the physiological state of the patient (age, pregnancy, lactation), concomitant pathology and drug therapy.

5. What are the features of microflora resistance to nitroimide-ashes.

6. Features of the use of nitroimidazoles depending on the localization of the pathology and pathogen (infection of the oral cavity, abscesses of the brain, lungs, infection in the abdominal cavity and pelvis, STIs, H. pylori eradication).

7. The most important recommendations for patients while taking nitroimidazole.

8. The most important recommendations for patients while taking nitrofuran preparations.

9. The place of nitrofurans in clinical practice - modern ideas.

10. The most common examples of erroneous administration of nitrofurans.

11. List the clinical and laboratory criteria for the effectiveness and safety of the treatment of acute pyelonephritis and acute enterocolitis.

12. Tell us about the main pharmacokinetic differences between the individual representatives of the nitrofuran series and suggest the optimal pharmacotherapy regimen taking into account gender, age, and pathogenesis of the disease.

13. Give a clinical and pharmacological evaluation of the antimicrobial action of derivatives of oxyquinolines in comparison with derivatives of the nitrofuran series, reflecting their general properties and features.

14. Give a general description of the derivatives of oxyquinolines used in infectious diseases, reflect the criteria for the effectiveness and safety of therapy.

15. Give the clinical and pharmacological characteristics of the derivatives of oxychinolines used for infections of the genitourinary tract (nitroxoline), reflect the criteria for the effectiveness and safety of the therapy.

16. Suggest optimal pharmacotherapy regimens for the most frequent acute and chronic infectious diseases of the genitourinary sphere, indicating the routes, doses and modes of administration of these uroseptics, criteria for the effectiveness and safety of therapy.

17. Disclose the mechanisms of the antimicrobial action of metronidazole, the characteristic differences between its pharmacokinetics and pharmacodynamics from other chemotherapeutic agents and indicate the main criteria for its effectiveness and safety.

18. Justify the choice of the dosage form of metronidazole with an indication of the routes, doses and regimen of administration for: anaerobic gas infection; acute trichomoniasis; peptic ulcer in the acute stage.

19. Indicate the main combinations, both increasing the antimicrobial activity of the studied compounds, and the most dangerous in terms of possible complications. Discover the mechanisms of side effects.

20. Formulate the significance of the leading pharmacokinetic characteristics in the rational choice of representatives of this class of antimicrobial drugs, the tactics and dosage regimen, and the assessment of efficacy and safety.

Enumeration of practical work.

Homework.

1. Write down prescriptions for drugs (in all dosage forms) presented in the section “Purpose of the lesson”, indicate the points of action, the spectrum of diseases indicated for their purpose.

2. Indicate and explain possible cases of ineffectiveness of using SLS in infectious inflammatory processes of various localization.

B. Independent practical work in class.

Supervision of a thematic patient in the ward.

1. To study the medical history of the supervised patient (data from laboratory and instrumental studies, conclusions of consultants, records of the attending physician), a sheet of medical appointments.

2. Write a protocol of independent work on the selection and justification of the assigned value to the patient being supervised of one of the antimicrobial drugs considered in this topic.

3. In a subjective and objective examination, identify the patient with signs of an infectious disease, evaluate its severity and localization of the pathological process.

4. Based on the individual characteristics of pharmacodynamics and pharmacokinetics, as well as taking into account their own observations, choose one of the chemotherapeutic drugs for the patient to be supervised.

5. Choose the optimal dosage regimen for the drug, taking into account its pharmacokinetics, pathogenesis of the disease, route of administration, age, body weight.

6. To highlight the clinical and instrumental criteria for evaluating the effectiveness and safety of the applied tool.

7. Justify the feasibility of combination pharmacotherapy and propose

possible options for a safe combination of drugs.

8. Make a forecast of side effects and outline a plan for their early detection.

9. Justify the duration of the main and supporting therapy.

10. Explain the need for combined antibacterial and pathogenetic therapy for an infectious inflammatory process.

The solution of situational problems.

1. A boy, 14 years old, weighing 53 kg, suffers from secondary chronic pyelonephritis with arterial hypertension, chronic renal failure of the first degree. Regarding another exacerbation of the disease (a protein sensitive to ampicillin has been identified in the urine), 500 mg ampicillin is administered intramuscularly 4 times a day, and inside, furazolidone 0.2 g 4 times a day. The patient constantly consumes a lot of dairy products (cheese, cottage cheese, sour cream). By the 10th day of treatment, lower back pain decreased, body temperature returned to normal, dysuric symptoms disappeared. However, there was a sharp headache of a diffuse nature, nausea, a sensation of pulsation in the back of the head. On examination, pallor of the skin is expressed, tachycardia - 130 strokes in 1 min, AKD - 200/120 mm RT. Art. (upon receipt of 150/95 mm RT. Art.). The residual nitrogen of the blood is 17.45 mmol / L (normal 14.3 - 25 mmol / L). Urinalysis according to Kakovsky-Addis: Er - 1.2 • 106 (normal to 1 • 106), L - 3.2 • 106 (normal to 2 •106).

Justify the pathogenesis of the developed symptoms from the position of side effects of drugs taken by the patient. Give suggestions for treatment correction.

2. A patient, 34 years old, was admitted with complaints of pain in the lumbar region, dysuric phenomena, fever up to 37.5 - 38 ° C, chills. In addition, headaches, dizziness, and fatigue worry. During the examination: AKD - 180/110 mm RT. Art., in the urine - proteinuria - 0.5 g / l, white blood cells - 25 - 30 in the field of view, bacteriuria, cylindruria. In the blood - leukocytosis with a shift of the leukocyte formula to the left, ESR -18 mm / h.

Justify the diagnosis of the disease. Make a plan for further examination and treatment of the patient.

3. A patient, 43 years old, was admitted with complaints of pain in the lower abdomen radiating to the perineum, accompanied by tenesmus, frequent urination with pain, weakness, sleep disturbance, appetite. Body temperature is normal. A history of severe hypothermia. In the general analysis of urine - leukocytes 20 - 25 in the field of view, red blood cells - 8 -12 in the field of view, bacteria - completely in the field of view, oxalates in a small amount.

Diagnose the disease. What additional analyzes are needed for this? Select the circle of drugs effective in this pathology, their dosage regimen and route of administration.

4. A patient, 26 years old, was admitted with complaints of pain, burning in the genital area, copious discharge of a whitish-gray color, foamy, with an evil smell. A history of a week ago random sexual intercourse. The native preparation of the separated urethra revealed the presence of Trichomonas.

List drugs that are effective in this disease. Suggest treatment options.

5. The patient came to the admission department with complaints of severe weakness, pain in the lower abdomen, nausea, vomiting, and frequent loose stools. The stools are watery with a dirty greenish tint. On examination, the skin is pale, the tongue is dry, lined with a dirty white coating.

Body temperature 38.5 ° C, pulse - 96 beats. in 1 min, AKD - 95/60 mm RT. Art. The abdomen on palpation is painful in the umbilical region, rumbling and splashing are noted.

To clarify the diagnosis, outline an examination plan for the patient. Write a comprehensive treatment plan. What groups of antibacterial agents are most effective for this pathology?

6. A patient with an extensive lacerated wound of the lower leg was delivered to the surgical hospital. The general condition is severe: severe intoxication, high fever, confused consciousness. Upon examination of the wound - gray color of damaged tissues, severe swelling, bronze color of the surrounding skin. Subcutaneous crepitus is characteristic. When radiography is detected, an accumulation of gas under the skin and along the affected muscles.

What is your diagnosis? Make a drug treatment plan. With which anti-bacterial drug it is necessary to begin treatment of the patient, choose the drug form and the optimal dosage regimen.

7. A child of 3 years old, weighing 18 kg, fell ill with acute tracheobronchitis. A dry cough with difficult to separate mucopurulent sputum is disturbing. You are heard scattered dry rales, body temperature - 37.8 ° C, the roots of the lungs are densified.

Outline a plan of diagnostic measures necessary for the rational choice of antibacterial therapy, prescribe a drug from the group of short-acting sulfa drugs with an indication of its dosage regimen.

8. A patient, 35 years old, weighing 78 kg, was admitted to the department with a diagnosis of chronic obstructive bronchitis in the acute stage. A bacteriological study of sputum culture revealed a pathogenic strain of staphylococcus.

Prescribe a patient from the group of antimicrobial drugs of medium duration.

10. A patient, 27 years old, is being treated in the gynecology department for exacerbation of chronic adnexitis. For a week, as an anti-bacterial agent, he receives an injectable form of Biseptolum intravenously 2 times a day (a 5 ml ampoule was diluted in 10 ml of a 0.9% sodium chloride solution). The patient notes severity in epigastrium, right hypochondrium, appearing on the 4-5th day of treatment, nausea, loss of appetite. When about the liver by 4-5 cm, its edge is tightly elastic, painful on palpation.

Is a connection of manifestations of liver damage with the use of antimicrobial drugs? Assign the patient the necessary additional examination, give recommendations for further treatment.

TESTS

1. What is the average duration of eradication therapy for Helicobacter pylori infection with peptic ulcer of the stomach and duodenum?

A. 7-10 days

B. 1-2 days

C. 3-5 days

D. 11-14 days

E. 15-20 days

2.From the following antiulcer drugs, select drugs that are part of the Helicobacter pylori eradication regimen:

A. Sucralfat

B. Misoprostol

S. Gastrocepin

D. Almagel

E Metranidazole

3. The mechanism of the antimicrobial action of nitrofuran derivatives is due to:

A. Violation of the synthesis of nucleic acids.

B. Inhibition of the activity of respiratory enzymes.

C. Impaired function of iron-containing enzymes.

D. Antagonism with para-aminobenzoic acid.

E. Impaired synthesis of the microbial wall.

4. A 48-year-old patient with ulcerative colitis: pain along the intestines, flatulence, fresh blood in the feces, anemia (hemoglobin - 94 g / l, erythrocytes - 2.8 T / l), ulcerative defects along the sigmoid colon with fibrocolonoscopy. Choose a remedy for treatment:

A. Sulfadimethoxin.

B. Sulfalen.

C. Phthalazole.

D. Co-trimoxazole.

E. Mesalazine.

5. A 28-year-old patient with acute cystitis was chosen for the treatment of uroanti-septic tank, the mechanism of action of which is to disrupt the activity of iron-containing microbial enzymes. Indicate the drug that meets these requirements:

A. Biseptol.

B. Norfloxacin.

C. Nitroxoline.

D. Nitrofurantoin.

E. Ampicillin.

6. A 51-year-old patient with exacerbation of chronic pyelonephritis and symptomatic arterial hypertension was prescribed treatment, including furagin, 2 tablets 4 times a day. What dietary recommendations can prevent a hemodynamic disorder in a patient?

A. Limit the use of cottage cheese, cheese.

B. Limit the use of meat products.

C. Limit the use of fish products.

D. Limit the use of coffee and tea.

E. Gluten-free diet.

7. A 26-year-old patient with complaints of pain, burning in the genitals, copious foamy discharge of white-gray color. In the native preparation, Trichomonas. Specify a drug for etiotropic treatment:

A. Co-trimoxazole.

B. Tinidazole.

C. Nitroxoline.

D. Lincomycin.

E. Cefepim.

8. A 63-year-old patient noted an allergic reaction to sulfanilamide preparations. What other groups of drugs are undesirable for use in the patient?

A. Narcotic analgesics.

B. Tetracyclines.

C. Furosemide, torasemide.

D. Magnesium sulfate.

E. Antihistamines.

9. The use of metronidazole in the treatment of duodenal ulcers is due to:

A. Inhibition of growth and reproduction of H. pylori.

B. Inhibition of gastrin synthesis.

C. Stimulation of mucosal regeneration processes.

D. Stimulating the synthesis of gastroprotective prostaglandin.

E. Activation of anabolic processes.

10. Which of the following drugs is not used to treat giardiasis?

A. Ornidazole.

B. Tinidazole.

C. Metronidazole.

D. Clotrimazole.

E. Secnidazole.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF ANTIVIRAL AND ANTIFUNGAL DRUGS

Relevance of the topic

Viruses are non-cellular life forms that have their own gene and are capable of reproducing only in the cells of more highly developed creatures. Viruses are characterized by two forms of existence: extracellular and intracellular (reproducing). Viruses in composition differ in two large groups: simple and complex. The former consist only of protein and nucleic acids, while complex viruses along with these components contain lipids and carbohydrates in the form of glycoproteins. Viruses are characterized by a wide variety of forms of nucleic acids, including those forms of RNA and DNA that are absent in cellular life forms.

Propagation of viruses occurs in the cell. Many viruses are absorbed by the cell through pinocytosis. Once in the cage, they are released from the shell. The first stages of the development of viruses in the cell in general terms are that the so-called early proteins are built, i.e. proteins are enzymes necessary for the virus to replicate their nucleic acids. The so-called late proteins are involved in the

formation of protein shells of daughter virospores. Of the enzymes in viruses containing DNA, one of the first to synthesize RNA polymerase, which builds informational RNA on DNA strands. This RNA enters the ribosomes of the strand and other proteins of the viral particle are synthesized.

Viruses containing RNA synthesize a polymerase catalyzing the synthesis of new particles of viral RNA; this RNA goes to the ribosomes and controls the synthesis of the capsid protein. A virus containing RNA does not need DNA to reproduce and transmit genetic information.

Viruses are fundamentally different from all other organisms. We will name their most important features:

• The body does not have a cellular structure.

• They can exist only as intracellular parasites and cannot multiply outside the cells of those organisms in which they parasitize.

• Contain only one type of nucleic acid - either RNA or DNA (all cellular organisms contain both DNA and RNA at the same time). No ribosomes.

• No metabolism. It uses energy derived from metabolism in the host cells. They have a very limited number of enzymes, use the metabolism of the host, its enzymes, the energy obtained by metabolism in the cells of the host.

• Mature virospores (“spores” of viruses) can exist outside the host cell; during this period, they show no signs of life.

Currently, about 200 forms of animal viruses, 170 plant viruses and 50 viruses parasitizing in bacteria are known. They are combined in 20-25 families.

According to modern concepts, viruses lie on the border of “living” and “nonliving,” these are extracellular life forms that can penetrate certain living cells and multiply only within them.

The genetic apparatus of viruses is represented by various forms of nucleic acids; no other life forms have such a variety. In all living organisms, except viruses, the genetic apparatus consists of a double-stranded molecule of deoxyribonucleic acid (DNA), and ribonucleic acid (RNA), which acts as an information carrier in cells, is always single-stranded. In viruses, there are all possible variants of the device of the genetic apparatus: single and double-stranded RNA, single and double-stranded DNA. Moreover, the viral RNA and viral DNA can be either linear or ring-locked.

By the beginning of the XXI century, more than 1000 different viruses were investigated that cause diseases such as influenza, herpes, hepatitis, smallpox, polio, cytomegalovirus infection, encephalitis, measles, etc. In general, about 80% of the currently registered infections, cause viruses. The first places by the mass of the lesion are occupied by acute respiratory diseases, influenza, viral hepatitis, now AIDS has also been added to them. Widespread viral diseases in animals. Well-known epidemics of viruses in birds, sheep, cows. As a result of the visna virus epidemic, in the 30s and 40s of the last century, Icelanders were forced to slaughter more than one hundred and fifty thousand animals. The bird leukemia virus caused a loss to the US poultry industry in 1955 in the amount of over $ 60 million. Widespread cattle leukemia virus infection is known. In some countries of the world they are infected with over 80% of cows and bulls.

Viral diseases are very diverse and depend on the nature of viruses, their virulence, ways of penetration into the body and overcoming the body's natural protective barriers. Infection can occur through air, food, milk, water, through various objects, through the bite of blood-sucking arthropods (mosquitoes, mosquitoes and ticks).

Influencing them with the help of a medicine will not damage the cells of a macroorganism, it is almost impossible. In most cases, the use of antiviral drugs is ineffective, and the risk of undesirable

effects is very high. Antiviral agents - drugs with a small breadth of therapeutic effect. Maximum efficiency can be achieved when used prophylactically or locally when it is possible to create a high concentration.

One of the factors of the cell's natural defense against viruses is the production of interferon, a substance that creates the cell's resistance to the virus, although this is a short-term protective effect.

In recent decades, there has been a significant increase in fungal diseases. This is due to many factors and, in particular, to the widespread use in medical practice of broad-spectrum antibiotics, immuno-depressants and other groups of drugs

In connection with the growth trend of fungal diseases (both superficial and severe visceral mycoses associated with HIV infection, cancer and hematological diseases), the development of resistance of pathogens to existing drugs, the identification of types of fungi that were previously considered non-pathogenic (currently while about 400 species of fungi are considered potential pathogens of mycoses), the need for effective antifungal agents has increased.

Antifungal agents (antimycotics) drugs that have a fungicidal or fungistatic effect and are used to prevent and treat mycoses.

For the treatment of fungal diseases, a number of drugs are used that are different in origin (natural or synthetic), spectrum and mechanism of action, antifungal effect (fungicidal or fungistatic), indications for use (local or systemic infections), methods of administration (inside, parenteral, external) .

Most fungi are resistant to antibacterial drugs. Only a few chemical compounds have an inhibitory effect on fungi pathogenic to humans, and most of them are very toxic. The need for effective antifungal drugs has become particularly relevant due to the sharp increase in the number of local and disseminated mycoses in patients with immunodeficiency.

Motivational characteristic of the topic

HISTORY OF CREATION OF ANTIVIRAL DRUGS.

The first drug proposed as a specific antiviral agent was thiosemicarbazone, the virucidal effect of which was described by G. Domagk (1946). The drug of this group thiocetosone has some antiviral activity, but is not effective enough; it is used as an anti-tuberculosis drug. Derivatives of this group 1, 4-benzoquinone-guanyl-hydrazinothio-semicarbazone called "pharyngosept" (faringosept, Romania) are used in the form of "perlingual" (absorbable in the oral cavity) tablets for the treatment of infectious diseases of the upper respiratory tract (tonsillitis, stomatitis, etc. .)

Subsequently, methisazone was synthesized, which effectively suppresses the reproduction of smallpox viruses, and in 1959, nucleoside idoxuridine, which turned out to be an effective antiviral agent, suppresses the herpes simplex virus and vaccines (vaccine disease). Side effects with systemic use have limited the possibility of widespread use of idoxuridine, but it has remained as an effective tool for topical use in ophthalmic practice for herpetic Kerotitis. Following idoxuridine, other nucleosides began to be obtained, among which highly effective antiviral drugs were identified, including acyclovir, ribamidine (ribovirin) and others. In 1964 amantadine (midantine) was synthesized, then remantadine and other derivatives of adamantane proved to be effective antiviral agents. An outstanding discovery was the discovery of endogenous interferon and the establishment of its antiviral activity. Modern DNA recombination technology (genetic engineering) has opened the possibility of widespread use of interferons for the treatment and prevention of viral and other diseases.

An outstanding event was the discovery of endogenous interferon and the establishment of its antiviral activity. Until 1957, interferons were considered as a curious biological phenomenon. The

period 1957 - 1967 was devoted to the study of the general laws of production and the action of interferon. In the process of this work, the universality of the formation of this protein by cells of all vertebrates (from fish to humans) was established and the basic methods for its preparation and purification were developed.

In 1967, the leading role of high molecular weight double-stranded RNAs in the induction of interferon was proved and the search for the most active drugs with the prospect of clinical use was begun.

Over the next thirteen years (1967 - 1980), the anti-turologenic effect of interferon and its inducers was studied, experimentally justifying the principles of interferon superinduction. At the same time, the existence of a complex multicomponent production mechanism and the action of interferon was theoretically justified, which subsequently culminated in the identification of genes and information RNA for interferon and enzymes that carry out its action. The 80s were marked by such major events in the study of interferon and its inducers:

1) the doctrine of the interferon system has finally taken shape;

2) with the help of genetic engineering methods, promising interferon preparations for clinical use have been obtained;

3) the multiplicity of interferon genes is proved (in humans, their number approaches 30);

4) the indications and contraindications for the clinical use of interferons and their inducers are determined.

In the years 80 - 90, it was found that the action of a number of immunostimulating and antiviral agents (prodignosan, half-dan, arbidol, etc.) is associated with their interferogenic activity, i.e., their ability to stimulate the formation of endogenous interferon.

Domestic researchers have developed a number of synthetic and natural (herbal) preparations for systemic and topical use in viral diseases (bonafton, arbidol, oxolin, deuteriformin, tebrofen, alpizarin, etc.). It has now been established that the action of a number of immunostimulating and antiviral agents is associated with their interferon activity, i.e. ability to stimulate the formation of endogenous interferon.

Year Event

1946 Proposed as an antiviral agent thiosemi-carbazone. Action described by G. Domagk

50th Open metisazon

1957 Discovered by interferon Isaacs and Lindenman.

1957–1967 The general patterns of production and the action of interferon are studied. The universality of the phenomenon of the formation of this protein by cells of all vertebrates (from fish to humans) has been established and the basic methods for its preparation and purification have been developed

1959 Idoxuridine active against herpes simplex virus is discovered.

1964 Synthesized adamantane, then remantadine and other derivatives of adamantane

1970 Tiloron, interferon inducer discovered

1967–1980 The antiturogenic effect of interferon and its inducers was studied, the principles of superinduction of interferon were experimentally substantiated

80–90 years It has been established that the action of a number of immunostimulating and antiviral agents (prodignosan, half-dan, arbidol, etc.) is associated with their interferogenic activity, that is, their ability to stimulate the formation of endogenous interferon

The process of reproduction (reproduction) of viruses includes the following stages

1. Adsorption occurs through the interaction of glycoprotein receptors-capsid spikes with cell receptors. The specific interaction of viral proteins with the surface receptors of the infected cell explains the "tropism of viruses" to a specific type of macroorganism cell. Adsorption also depends on ionic attraction

2. The penetration of the virus into the cell (viropexis) occurs in two ways: by injection of viral RNA (DNA) or by vacuolization

3. Deproteinization ("stripping") of the viral particles leads to the release of the viral genome. The destruction of the capsid occurs under the action of lysosomal cell enzymes. Modified viral particles lose their infectious properties

4. Replication - the formation of daughter copies of the virus genomes

5. The assembly of daughter populations of the virus

6. Release of daughter virions - the final stage of reproductive cycle

Thus, viruses are obligate intracellular parasites that are not capable of independent reproduction. The synthesis of viral proteins and the reproduction of copies of the viral genome provide the biosynthetic processes of the host cell. Therefore, the creation of chemotherapy drugs that can selectively destroy a viral particle and not damage the cells of a macroorganism is one of the most difficult tasks of pharmacology. A detailed study of the reproductive cycle of viruses made it possible to establish their structural and morphological features and synthesize etiotropic antiviral agents. So, in the process of reproduction, viruses produce a number of enzymes that differ from human cell enzymes. These virus-specific enzymes are targeted by many antiviral drugs. The activity of drugs can be directed to other distinctive features of viral particles. Therefore, it is advisable to consider antiviral drugs taking into account the points of application of their action in the cycle of reproduction of viruses. In view of this, the most popular classification of antiviral agents according to the mechanism of action.

Antiviral Classification

I. Drugs acting on extracellular forms of the virus:

- oxolin;

- arbidol-lens.

II. Viropexis inhibitors (M2-channel blockers):

- amantadine (midantan, symmetryl, verigit-K, adamantine, amandine, amantane, an-tadine);

- remantadine (rimantadine, meradan, algir, polirem).

III. Neuraminidase Inhibitors:

- zanamivir (relenza);

- oseltamivir (tamiflu).

IV. Drugs that inhibit the reproduction of the virus:

1. Inhibitors of DNA (RNA) -polymerase viruses:

- acyclovir (acigerpin, acyclovir, vivorax, herpevir, herperax, herpesin, zovirax, xorovir, lovir, medovir, supra-viran, cycloviral, sedico, citivir);

- ganciclovir (cymeven);

- vidarabine;

- ribavirin (virazole, rebetol, Meduna ribavirin, ribamidil), etc.

2. Reverse transcriptase inhibitors:

a) . Abnormal nucleoside:

- abacavir (ziagen);

- didanosine (videx);

- lamivudine (Zeffix, epivir Three Ti See);

- stavudine (zerit) -,

- zalcitobin (hivid);

- zidovudine (retrovir AZ and Ti, thymazide, azidothymidine).

b). Preparations of non-nucleoside structure:

- efavirenz;

- nevirapine (viramune).

3. Inhibitors of proteases:

- aprenavir (agenerase);

- indinavira sulfate (crixivan);

- saquinavir (inviraz, fortovaz).

V. Inhibitory maturation of viruses:

- metisazon (marboran, kemoviran, viruzona)

VI. Interferons and inducers of interferons.

Classification of antiviral drugs by origin:

• nucleoside analogues - zidovudine, acyclovir, vidarabine, ganciclovir, trif-luridine;

• derivatives of lipids - saquinavir;

• derivatives of adamantane - midantane, remantadine;

• derivatives of ladol carbolic acid - foscarnet;

• thiosemicarbazone derivatives - methisazone;

• drugs produced by macroorganism cells - interferons.

The distribution of antiviral drugs depending on the direction of their action.

DNA viruses:

• herpes simplex virus - acyclovir, vilaciclovir, foscarnet, vidarabine, trifluridine;

• cytomegalovirus-ganciclovir, foscarnet;

• virus of herpes zoster and chicken pox - acyclovir, foscarnet;

• smallpox virus - methisazane;

• hepatitis B virus and C-interferons.

RNA viruses:

• human immunodeficiency virus - zidovudine, didanosine, zalcitabine, saqui-navir, ritonavir;

• influenza virus type A - midantan, remantadine;

• influenza virus types B and A-arbidol;

• respiratory syncytial virus-ribamidil.

Antiviral drugs can be divided, depending on the type of disease, into groups:

• Influenza drugs (remantadine, oxolin, etc.)

• Antiherpetic and anti-cytomegalovirus (tebrofen, riodoc-sleep, etc.)

• Medicines that affect the human immunodeficiency virus (azidothymidine, phosphanoformate)

• Broad-spectrum drugs (interferons and interferonogens)

Mashkovsky M.D. proposed the following classification of antiviral drugs:

A) Interferon

• Leukocyte interferon from human blood donation.

• Purified α-interferon obtained from donated blood.

• Recombinant α2-interferon produced by the bacterial strain of pseudomonad, in the genetic apparatus of which the human leukocyte α2-interferon gene is integrated.

• Recombinant interferon alfa-2v.

• Recombinant human β1-interferon.

Inductors of interferon:

• Half-dan a powder or porous mass of white color, has immuno-stimulating activity, ie ability to stimulate the production of endogenous interferon and has an antiviral effect.

• Neovir - an action similar to that of a half-dan.

B) Derivatives of amantadine and other groups of synthetic compounds

• Remantadine. It is used as an anti-Parkinsonian drug, it indicates a preventive effect against influenza infection caused by certain strains of viruses.

• Adapromin. Close to remantadine.

• Datiforin. Similar to remantadine.

• Arbidol. An antiviral drug that has an inhibitory effect on influenza A and B.

• Bonaphton. It has antiviral activity against the herpes simplex virus and some adenoviruses.

• Oxolin. It has virucidal activity, is effective for viral diseases of the eyes, skin, viral rhinitis; has a prophylactic effect in influenza.

• Tebrofen. It is used as an ointment for viral diseases of the eyes, as well as for skin diseases of a viral or presumed viral etiology. It can also be used to treat flat warts in children.

• Riodoxol. It has antiviral optimality and has an antifungal effect.

.Florenal. Opens a neutralizing effect against viruses.

Metisazon. It suppresses reproduction of the main group virus: it has prophylactic activity against smallpox virus and facilitates the course of post-vaccination complications, delays the spread of the skin process, and promotes faster drying of effeorations. There is evidence of the effectiveness of metisazon in the treatment of recurrent genital herpes.

C) Nucleosides:

• Idoxuridine. Applied with keratitis in ophthalmology.

• Acyclovir. Effective against herpes simplex viruses and herpes zoster. It has an immunostimulating effect.

• Ganciclovir. Compared to acyclovir, ganciclovir is more effective and, in addition, acts not only on the herpes virus, but also on cytomegalovirus.

• Famciclovir. It has the same functions as ganciclovir.

• Ribamidil. Ribamidil, like acyclovir, has antiviral activity. Inhibits the synthesis of viral DNA and RNA.

• Zidovudine. An antiviral drug that inhibits the replication of retroviruses, including human immunodeficiency virus (HIV).

D) Antiviral drugs of plant origin:

• Flacoside. Obtained from the velvet leaves of the Amur family of root. The drug is effective against DNA viruses.

• Alpidarin. Obtained from Alpine Koneermena grass and yellowing penny, legume family. Effective against herpes DNA viruses. The inhibitory effect on the reproduction of the herpes simplex virus is manifested mainly in the early stages of the development of the virus.

• Cholepin. Purified extract from part of the plant mepedecium penny, legume family. It has antiviral activity against DNA viruses of the herpes group.

• Ligosin. Apply for herpetic skin diseases.

• Gossypol. The product obtained from the processing of cotton seeds or from the roots of cotton, the family of malvaceae. The drug has activity against various strains of viruses, including dermatotropic strains of the herpes virus. It has a weak effect on gram-positive bacteria.

According to the sources of production and chemical nature, they are divided into the following groups:

1) interferons (endogenous origin and obtained by genetic engineering, their derivatives and analogues);

2) synthetic compounds (amantadines, arbidol, bonafton, etc.);

3) substances of plant origin (alpizarin, flacoside, etc.).

Antiviral agents will be reviewed in accordance with the proposed classification.

I. Drugs acting on extracellular forms of the virus

The main application of the first group of antiviral agents is the treatment and prevention of influenza and acute respiratory viral infections (ARVI). ARVI is a group of diseases similar in clinical and epidemiological characteristics. Acute respiratory viral infections account for about 75% of all infectious diseases. The wide spread of SARS is facilitated by the airborne infection, the absence of a persistent immunity to repeated infections, as well as the wide variety and frequent mutations of the SARS pathogens. Among the 200 known pathogens of the disease, of course, the leading role belongs to influenza viruses. Influenza is registered everywhere and poses the greatest epidemic danger. Every tenth adult in the world gets the flu every year. During epidemic outbreaks, influenza is associated with high mortality, especially in young children and the elderly. Occupying a major place in the structure of acute respiratory viral infections, influenza reduces the reactivity of the immune system and is often complicated by pneumonia, otitis media, pyelonephritis, and damage to other organs.

There are three varieties of the influenza virus - A, B, C. These are RNA-containing viruses of the Orthomixoviridae family. Large epidemics and pandemics are caused by type A virus. The unpredictability of epidemics is due to antigenic variability of viruses, leading to a partial or complete change in group and strain determinants - hemagpyutinin and neuraminidases. Hemagglutinin and neuraminidase are glycoprotein spikes that penetrate the supercapsid of the virus. These spikes are necessary for the adhesion of the virus on the membrane and its penetration into the cell

In this case, hemagglutinin ensures the fusion of the capsid with the cell membrane and lysosome membranes, and neuraminidase recognizes and interacts with the surface receptors of the cell. In addition, neuraminidase, by cleaving neuraminic acid from daughter virions and the cell membrane, ensures the exit of viruses from the cell (Fig. 3d). An important role in the morphogenesis of the virus is played by M-protein. On the one hand, the M-protein surrounds the nucleocapsid and protects the virus genome, on the other hand, the M-protein integrates into the cell membrane and modifies

On modified M-protein sections of the membranes, the assembly of additional virus populations occurs, followed by the formation of M-channels and the release of daughter virions from the cell.

Among chemotherapeutic agents for the prevention of influenza and acute respiratory viral infections, the intranasal use of oxopine ointment is still popular. The drug is also effective in adenoviral keratoconjunctivitis, herpetic keratitis, viral skin lesions (shingles), rhinitis of viral etiology.

Mechanism of action: oxolin binds to the guanine bases of the nucleic acids of a virus particle located outside the cell - "virucidal action.

When applied topically, oxolin ointment can cause irritating effects. Oxolinic ointment for nasal and external use is released at 0.25% - 1.0 and 3% - 1.0.

Among the modern anti-influenza drugs is the inducer of interferon arbidop-pans. Arbidol is active against influenza A and B viruses and reduces the risk of acute respiratory viral infections by 7.5 times.

The mechanism of action of the drug is complex and consists of the following links:

inhibits the fusion of the lipid membrane of the virion with the membranes of human cells - "prevents the penetration of the virus into the host cell.

• inhibits the translation of virus-specific proteins in infected cells - "inhibits the reproduction of viruses.

The antiviral effect of the drug enhances its interferonogenic and immunomodulatory activity. Arbidol has been proven to stimulate cellular and humoral immunity. The antioxidant activity of arbi dol also matters. A good therapeutic effect and the absence of side effects allows you to prescribe Arbidol-Lance for the prevention and treatment of influenza and SARS for adults and children from two years of age. For the prevention of influenza and acute respiratory viral infections, the drug is used at an age dose during the epidemic 2 times a week for three weeks, in contact with patients - daily for 10-14 days. The use of arbidol for therapeutic purposes should be started in the first hours of the disease 4 times a day (every 6 hours) for 3-5 days. The drug is available in capsules of 0.1 for adults and tablets, coated at 0.05 for children.

II. Viropexis inhibitors (M2 channel blockers)

M, β-protein blockers are adamantane derivatives: amantadine and rimantadine

In the mechanism of the antiviral action of adamantane derivatives, the key reaction is their interaction with the M-protein of the influenza virus. This, in turn, violates the following two stages of reproduction of a viral particle:

1. Suppress the fusion of the envelope of the virus with endosome membranes - "disrupt the deproteinization of viral particles -" prevent the transfer of the virion genetic material to the cytoplasm of the host cell -> inhibit the early stage of specific reproduction of the virus

2. Violate the incorporation of M-protein into the membrane of the host cells - "prevent membrane modification -" inhibit the assembly of added virions

Midantan, a well-known anti-Parkinsonian drug, is not used as an antiviral drug in our country. Rimantadine was created on the basis of amantadine, which is more active and less toxic than its predecessor. Rimantadine is well absorbed when taken orally and, better than amantadine, penetrates the secrets of the respiratory tract. The antiviral effect of rimantadine is longer than that of midantan. Ri-mantadine is produced in Russia under the brand name Remantadine in 50 mg tablets. Remantadine inhibits the reproduction of a large number of strains of influenza A viruses and reduces the toxic effect of influenza B on the body. The drug is active against tick-borne encephalitis viruses. In this regard, rimantadine is used not only for influenza, but also for the prevention of tick-borne encephalitis of viral etiology. With prophylactic use, the effectiveness of rimantadine with influenza is 70-90%. For prevention, take 0.05 1 time per day, for 10-15 days.

For therapeutic purposes, rimantadine is prescribed no later than 48 hours from the onset of the first signs of the disease, and then resistance develops to it. This is due to the fact that the main mechanism of action of the drug is due to a violation of the penetration of the virus into the cells and blockade of the nuclear phase of reproduction. At later stages of the reproduction of the virus, rimantadine acts to a much lesser extent. Therefore, at the height of the disease, when the virus "has time" to integrate into the genome of the host cell, the drug is not effective. The treatment regimen is as follows: 1 day 300 mg once, 2 days 200 mg and 3 days 100 mg. 0.1 g 3 times in the first day; on the 2nd and 3rd days - 0.1 g 2 times a day and on the 3rd day - 0.1 g once a day. The duration of the course should not exceed 5 days in order to avoid the emergence of resistant forms of the virus. For children from 1 year to 7 years, rimantadine is replaced with apygir (syrup). The drug is a combination of rimantadine with sodium alginate, which provides a constant concentration of rimantadine in the blood and reduces its toxic effect.

In most cases, rimantadine is well tolerated. In 3-6% of patients, adverse reactions from the central nervous system or gastrointestinal tract can be noted. Rimantadine should be used with caution in the elderly, with severe violations of liver function, as well as in individuals with increased convulsive readiness (for example, with epilepsy).

III. Neuraminidase Inhibitors

A new direction in the development of influenza drugs is the creation of inhibitors of viral neuraminidase. As mentioned earlier, neuraminidase (sialidase) is one of the key enzymes involved in the replication of influenza viruses of types A and B. When the inhibition of neuraminidase is violated, the virus penetrate into healthy cells. Due to the special mechanism of action, neuraminidase inhibitors prevent the spread of infection from a sick person to a healthy one. In addition, neuraminidase inhibitors are able to reduce the production of cytokines (IL-1 and tumor necrosis factor), inhibiting the development of a local inflammatory reaction and weakening such systemic manifestations of a viral infection as fever, muscle and joint pain, loss of appetite. We add that neuraminidase inhibitors reduce the resistance of viruses to the protective effect of the secretion of the respiratory tract, which prevents the further spread of the virus in the body.

Neuraminidase Inhibitors

Drug Dosage Forms Side Effects

Donkey tamivir

(Tamiflu) Capsules 0.075 Powder for suspension preparation. Dyspepsia, bronchitis, headache, eating bone, insomnia.

Zanamivir

(Relenza) Powder for inhalation 5 mg / kg dose. Rarely - bronchospasm, shortness of breath, allergic reactions.

The first representatives of neuraminidase inhibitors are otep-tamivir and zanamivir. Zanamivir is a structural analogue of sialic acid, a natural substrate of viral neuraminidase and has the ability to compete with it for binding to the active sites of the enzyme. Thus, the principle of competitive antagonism underlies the mechanism of action of zanamivir. Due to its high toxicity and low bioavailability when taken orally, the drug is used by inhalation. Zanamivir is recommended for the treatment of uncomplicated influenza in people over 12 years of age with a period of the appearance of clinical symptoms no more than 36 hours.

The oral neuraminidase inhibitor oseltamivir (Tamiflu) is active against all clinically relevant strains of the influenza virus, including bird flu (H5N1). Virus resistance to the drug does not occur. Moreover, according to clinical studies, the sensitivity of influenza viruses to Tamiflu increases over time. Oseltamivir is a prodrug and, under the influence of intestinal and liver esterases, turns into an active metabolite of carboxylate, which is well distributed into the main foci of influenza infection.

Mechanism of action: the carboxylate combines with a hydrophobic "pocket" of the active site of the influenza virus neuraminidase - it blocks the ability of the latter to cleave sialic acid residues from the surface of the infected cell - "the penetration and exit of new virions from the cell is inhibited

Oseltamivir is registered as a drug for seasonal influenza prophylaxis in adults and children older than 1 year.

The recommended prophylactic dose of the drug is 75 mg per day for 4-6 weeks, and the therapeutic dose is 75-150 mg twice a day for 5 days. The drug is well tolerated, has high bioavailability and systemic effect. To date, oseltamivir is the only drug officially recommended by the WHO in the event of an influenza pandemic. Thus, oseltamivir fully confirms the status of the main antiviral drug

assigned to the WHO drug on August 23, 2007. Oseltamivir is manufactured by F. Hoffmann-LaRoche (Switzerland) under the brand name Tamiflu in 75 mg capsules.

Thus, an important advantage of neuraminidase inhibitors over blockers of M-channels (amandatin, rimantadine) is their activity against two types of influenza virus - A and B.

IV. Drugs that inhibit the reproduction of the virus

Preparations that inhibit the reproduction of the virus are represented by a large group of highly effective agents. By the chemical structure, these medicinal substances are derivatives of nucleosides. Recall that purine and pyrimidine bases belong to nucleosides. In turn, nucleosides arranged in a specific order form nucleic acids (DNA and RNA).

Due to the similar chemical structure, drugs from the group of abnormal purine and pyrimidine bases are embedded in the nucleic acids of viruses and disrupt their function. In addition, nucleoside analogues inhibit virion DNA polymerase, which blocks the replication of daughter viral particles. Thus, the principle of competitive antagonism underlies the mechanism of action of abnormal nucleosides.

Inhibitors of DNA (RNA) -virus virus polymerase

1. Inhibitors of PH K-polymerase of viruses

Ribavirin is active against many RNA and DNA viruses. The drug has a complex, finally unclear mechanism of action. It is believed that it blocks the RNA polymerase of viruses, which disrupts the synthesis of ribonucleoproteins of messenger RNA. Thus, ribavirin blocks the early stages of viral transcription. When inhaled, the drug creates high concentrations in the secrets of the respiratory tract. Taking into account the toxicity of ribavirin and limited data on its clinical effectiveness, the drug should be prescribed only in case of positive results of serological tests confirming the presence of respiratory syncytial viral infection (RSV). However, the drug has been shown to be effective in treating viral hepatitis. It is applied by inhalation using a nebulizer, only in a hospital setting. Before the procedure, the contents of the vial are dissolved in 300 ml of sterile water for injection (the concentration of the solution used is 20 mg / ml). Inhalations are carried out within 12-18 hours daily, the course of treatment is 3-7 days.

2. Inhibitors of DNA polymerase viruses

DNA-containing viruses are the causative agents of herpetic viral infection. Herpesviral diseases (from the Greek Herpes - creeping) are among the common human viral infections. The most famous representatives of this group - herpes simplex viruses of types 1 and 2 (HSV-1 and HSV-2) - cause damage to the mucous membranes. Primary infection with herpes simplex virus type 3 (Varicella zoster, HZV) occurs as chicken pox (varicella), and relapses cause shingles (zoster). A fourth type of herpes virus, better known as the Epstein-Barr virus (EBV), causes infectious mononucleosis. A characteristic feature of the herpes simplex virus type 5 BMS) is its ability to form giant, or cytomegal cells. Therefore, the herpes simplex virus type 5 is called cytomegalovirus. Thus, herpes viruses cause acute and latent infections, and also have a certain oncogenic potential.

Most modern antiherpetic agents are abnormal nucleosides. Anti-herpes drugs inhibit viral DNA polymerase more actively than the host cell polymerase. Lesions caused by the herpes simplex virus type 1 usually go away on their own and require only local events. Therapy is recommended to be started at the prodrome stage (itching). In this case, the development of the bubble stage can be completely prevented. For the treatment of infections caused by herpes simplex viruses and Varicella zoster virus, the following antiherpetic drugs are prescribed for topical and external use.

In the treatment of herpetic keratitis, the analogue of thymidine idoxuridine (Oftan Ida) has proved its effectiveness. When applied topically, the drug can cause irritation and allergic reactions. Available in plastic dropper bottles in the form of a solution for eye drops of 0.1% - 10 ml.

The universal representative of abnormal nucleosides is acyclovir. The drug is indicated for the treatment of herpes infection and the prevention of recurrence of the disease. The undoubted advantage of acyclovir is a wide range of antiherpetic activity. So, the drug is prescribed for infection with VEB, HSV-1 and HSV-2. Acyclovir is effective for herpes zoster and cytomegalovirus infection. At the same time, severe side effects that develop with the resorptive action of acyclovir limit its use.

Vapatsikpovir (valtrex) in its main characteristics is close to acyclovir, but differs from it in greater bioavailability during enteral administration. Valaciclovir is a prodrug, and in the human body it turns into acyclovir, which provides the antiherpetic effect of the drug. Valacyclovir is active against all types of herpes viruses.

Another representative of antiherpetic - famciclovir (famvir) after oral administration quickly turns into the active metabolite penciclovir. The advantage of penciclovir is its activity against recently identified strains of herpes simplex viruses resistant to acyclovir. In addition, the administration of famciclovir significantly reduces the severity and duration of postherpetic neuralgia in patients with herpes zoster. The drug is well tolerated.

Currently, penciclovir, also known as fenistil and pencivir, is becoming increasingly popular. Being a synthetic analogue of the acyclic guanine nucleoside, penciclovir is highly specific for herpes-infected cells. Like acyclovir, penciclovir is activated in the cell by phosphorylation, but the latter in the activated form is more stable and therefore the duration of action of penciclovir is longer than that of acyclovir. As a result of a longer exposure to the infected cell, penciclovir is effective at any stage of herpes simplex, including blister. At the same time, the drug reduces the formation time of the crust by 30%, and the healing process occurs 1-2 days faster (on average - 4 days). Quickly relieves pain and other symptoms of labial herpes (itching, burning, redness, tingling, etc.). Penciclovir is active against herpes simplex viruses (Herpes simhlex) and herpes simplex virus type 3 (Varicella zoster).

In some cases, Vidarabine is prescribed to treat a complicated infection caused by the Varicella zoster virus. The drug is successfully used for herpetic encephalitis and herpetic keratoconjunctivitis. With topical use of vidarabine, irritation, pain, photophobia, allergic reactions are possible. The drug is neurotoxic, causes leukopenia and thrombocytopenia.

The basis for the treatment of cytomegalovirus infection is ganciclovir or foscarnet sodium. Ganciclovir, which is similar in chemical structure to the acyclo virus, is a synthetic analogue of guanine. Ganciclovir is active against all types of herpes viruses, but is prescribed only for cytomegalovirus infection, since taking ganciclovir often leads to severe impairment of the functions of various organs and systems.

Virus DNA polymerase inhibitors include sodium foscarnet, an antiviral agent for external use. It has a virologostatic effect on herpes simplex viruses of the first and second type and influenza A viruses. It is active against oncogenic viruses, hepatitis B virus and some retroviruses. When applied topically, the drug does not cause side effects.

Reverse transcriptase inhibitors

Reverse transcriptase is an enzyme involved in the reproduction of viruses of the Retroviridae family. Reverse transcriptase (or revertase) provides the reverse direction of the flow of genetic information - not from DNA to RNA, but, on the contrary, from RNA to DNA, in connection with which the family got its name (Fig. 4). Retroviruses include the human immunodeficiency virus (HIV). Two lymphotropic retroviruses, HIV-1 and HIV-2, cause HIV infection. The first type of

human immunodeficiency virus, previously called HTLV-3 or LAV, is considered the main causative agent of the disease. The late manifest stage of HIV infection is AIDS (Acquired Human Immunodeficiency Syndrome). HIV infection is characterized by progressive disorders of the immune response as a result of prolonged circulation of the virus in lymphocytes, macrophages and cells of the human nervous tissue.

Tropism of the virus to the cells of the immune system is provided by glycoprotein spikes embedded in the supercapsid. It is well known that these glycoproteins interact with CD4 receptors located on the membrane of immunocompetent cells. After adsorption and penetration into the cell, HIV "undresses" and the virion RNA is released into the cytoplasm. Retrovirus RNAs do not exhibit infectious properties, but serve as a matrix for the synthesis of a DNA molecule using RNA-dependent DNA polymerase (reverse transcriptase, revertase), which is part of a viral particle. The synthesized double viral DNA molecule is transported to the cell nucleus and is inserted into the DNA of the host cell using cell integrase. The integrated DNA molecule is transcribed by cellular DNA-dependent RNA polymerase to form viral RNA. A part of RNA molecules is used to form mature virions, another part of viral RNA is a matrix for synthesizing host proteins of structural proteins and enzymes of daughter virions on ribosomes of cells. It is important that viral proteins are synthesized in the form of long polymer chains of precursor proteins that are "cut" into individual structural proteins by viral proteases.

Thus, in the process of reproduction of the retrovirus, two virus-specific enzymes (reverse transcriptase and protease) are formed, which are the target for the action of drugs used in the treatment of HIV infection.

1. Abnormal nucleosides - reverse transcriptase inhibitors

Of the drugs used in the treatment of HIV infection, virus reverse transcriptase inhibitors have attracted great attention. As can be seen from fig. 5, nucleoside derivatives of this group of drugs, getting into the infected cell are phosphorylated.

Non-nucleoside reverse transcriptase inhibitors 5. The mechanism of action of antiretroviral drugs

The resulting active metabolites by the principle of competitive antagonism inhibit the reverse transcriptase of virions. As a result, the formation of daughter RNA virus from proviral DNA is disrupted. The latter suppresses the synthesis of mRNA and viral proteins, which provides a therapeutic effect.

Representatives of the first generation, stavudine and zidovudine, have a low selective effect on viral enzymes and inhibit human DNA polymerase. As a result, the synthesis of myochondrial DNA of human cells is inhibited, which leads to the defeat of almost all systems of organs. So, stavudine and zidovudine are characterized by suppression of hematopoiesis and the development of leukopenia, thrombocytopenia and anemia. Pancytopenia and bone marrow hypoplasia are possible. From the digestive system, ano-rexia, taste perversion, abdominal pain, diarrhea, hepatomegaly, fatty dystrophy of the liver, increased levels of bilirubin and liver transaminases are possible. Damage to the central nervous system is manifested by depression and convulsions.

Pamivudine is highly selective for reverse transcriptase of the virus. The drug does not inhibit bone marrow cells and has a less pronounced cytotoxic effect. In addition, lamivudine is characterized by high bioavailability (80-88%) and is active against HIV strains resistant to zidovudine. Lamivudine is used to treat viral hepatitis B.

2. Non-nucleoside reverse transcriptase inhibitors

Non-nucleoside HIV reverse transcriptase inhibitors in macroorganism cells do not phosphorylate and inhibit the RNA-dependent DNA polymerase of virions uncompetitively due to direct interaction with the catalytic center of the enzyme

Protease inhibitors

Inhibitors of viral proteases by the principle of competitive antagonism inhibit HIV proteases. As a result, viral enzymes lose their ability to cleave the precursor polyproteins necessary for virus replication. This leads to the formation of inactive viral particles. HIV protease inhibitors include drugs listed in the table.

Unfortunately, available antiviral agents do not cure patients radically, but only delay the development of the disease. Therefore, the most effective use of antiretroviral drugs in the first 6-8 months from the onset of the disease. The combined use of protease inhibitors with nucleoside and / or non-nucleoside HIV reverse transcriptase inhibitors is advisable. Endogenous and exogenous interferon preparations have proven effective in the complex treatment of AIDS.

V. Virus maturation inhibitors

A striking representative of this group of funds is the metison. Methazone inhibits the assembly of virions, as it blocks the synthesis of viral structural protein. The drug is active against smallpox viruses and is used to prevent smallpox, as well as to reduce the complications of anti-smallpox vaccination. Since smallpox is currently rare, the drug is almost never used. At the same time, metisazon is of interest in connection with a special mechanism of action and pronounced antiviral activity. It is possible that new highly effective antiviral agents will be synthesized on the basis of metisazon, and it will become the pioneer of a new group of drugs. This is all the more interesting because there is evidence of the effectiveness of the drug in the treatment of recurrent genital herpes. The drug is well tolerated and administered orally.

VI. Interferons and inducers of interferons

Interferon preparations are widely used for the treatment and prevention of viral infections. Discovered interferons were relatively recent. In 1957, Isaacs and Lindenmann discovered that cells infected with the influenza virus begin to produce and release into the environment a special protein that prevents the proliferation of viruses. Subsequently, this protein received the name interferon (lat. Inter - between, death + ferre - bear). The following definition is currently recognized:

Interferons are low molecular weight proteins of the cytokine group synthesized by human cells in the process of a protective reaction to foreign agents.

Interferons (IFN) have a pronounced species specificity and are one of the most important factors in protecting the body during primary viral infection. Not only viruses are capable of inducing IFN synthesis, but also bacteria, mitogenic and antigenic effects. More than 20 interferons are known that differ in structure and biological properties. All human cells are able to synthesize interferons, but their main source is immune cells. Therefore, there are three main varieties of interferons:

1. alfa-interferon (leukocyte) - produced by leukocytes;

2. beta) -interferon (fibroblast) - produced by fibroblasts;

3. gama)-interferon (lymphocytic or immune) - is synthesized by lymphocytes.

According to their functional activity, interferons are combined in two types. Type I includes a-IFN and R-IFN.

• IFN-a is intended for free circulation and protection of organs remote from the pathogen introduction sites.

• IFN-R acts locally, preventing the spread of the virus from its places of introduction.

This group of glycoproteins is characterized by pronounced antiviral activity.

The mechanism of action of interferons includes the following points:

1. Suppression of transcription of viral proteins.

2. Inhibition of viral protein translation.

3. Suppression of protein metabolism.

4. Violation of the assembly and maturation of the viral particle.

An important property of interferons is their ability to activate the synthesis of protective enzymes in human cells that block the replication of viral DNA and RNA. The complex mechanism of action provides interferons with a wide spectrum of antiviral activity. Moreover, it is believed that resistance to interferon in viruses does not occur. The immunomodulatory activity of interferons enhances their antiviral effect, and this effect is most pronounced in a representative of type II interferons, IFN-y.

All interferons, along with the antiviral effect, have antitumor and immunomodulatory effects. The spectrum of pharmacological activity of IFN determines the main indications for their purpose: complex therapy of infectious diseases, oncological pathology, immunodeficiencies of various origins and other conditions, accompanied by a decrease in the production of interferon cells of the macroorganism. A pronounced suppression of interferon genesis is also characteristic of chronic viral infections. In addition, studies have found that in children and the elderly, especially in the cold season, interferon is formed more slowly and in less quantity. There are two ways to increase the concentration of interferons in the body:

1. The introduction of exogenous interferon preparations (IFN itself)

2. Introduction of inducers of the synthesis of interferons (preparations of endogenous interferon).

As antiviral agents, a-interferon preparations are mainly used. At the same time, at present, all three varieties of human interferons have been obtained by genetic engineering. Recombinant and natural interferon preparations include:

1. Interferon alpha - 2b;

2. Interferon beta - 1a;

3. Interferon - lb;

4. Combined preparations containing several IFN;

5. Complex preparations including cytokines and other biologically active substances along with IFN.

Exogenous interferon preparations are widely used for the treatment and prevention of influenza. IFN is successfully used in the complex treatment of herpes infection, viral hepatitis and AIDS. Note that interferon therapy is not without drawbacks. So parenteral administration of IFN drugs for severe viral infections leads to serious side effects. In addition, interferons are inaccessible for widespread use in practical medicine, as they are poorly represented on the pharmaceutical market in Russia, and the cost of such drugs is very high.

Interferon preparations

1. Alfainterferon (interlock, CHLI) Ampoules and vials of 2 ml in dry form (activity 1000 MR, 4 doses)

2. Viferon Ointment

3. Grippferon Vial containing 5 or 10 ml of recombinant a-2 IFN with an activity of at least 10,000 IU / ml.

4. Reaferon (realdiron) Ampoules with lyophilized powder, containing 0.5; 1; 3; 5 million ME.

5. Human leukocyte IFN for injection Ampoules with lyophilized powder for injection (a-IFN mixture, activity 0.1; 0.25; 0.5 or 1 million ME).

6. Intron-A Vials with lyophilized powder for injection, containing 1, 3, 5, 10 and 30 million IU of human recombinant a-2 IFN ointment containing 5 million ME in 1 g.

An alternative to interferon therapy are interferon inducers.

Interferon inducers are substances of natural and synthetic origin that cause the production of endogenous IFN in the cells of a macroorganism. Despite the variety of interferon inducers, their pharmacological activity is largely due to the effects of IFN:

1). Induction of the synthesis of interferons;

2). Immunomodulatory effect;

3) .Stimulation of nonspecific protective mechanisms of the body;

4). Antiviral effect.

The following drugs belong to endogenous interferon preparations or interferon inducers:

I. Natural products:

Aktipol, Arbidol-Lens, Poludan, Amixil.

II. Preparations of synthetic origin:

Copaxone-teva, Isoprinosine, Galavit, Gepon, Derinat, Immunomax, Lycopid, Polyoxidonium, Dekaris.

III. Herbal remedies:

Echinacea hexal (immunal, immunorm,)

Phytopreparations of combined composition: Original Bittner Balm, Sinupret, Tonsilgon.

Due to similar immunopharmacological mechanisms of action, interferon inducers have indications for use common with IFN. Endogenous interferon preparations are prescribed for the treatment and prevention of viral infections. In addition, IFN inducers are used in the complex treatment of infectious diseases of another etiology and for the correction of weakened immunity (including immunodeficiency states).

A special place is the pharmacotherapy of viral hepatitis. So, the number of carriers of viral hepatitis in the world exceeds 1 billion. Considering the great social significance of this infectious disease, a few words about the modern chemotherapy drugs used to treat viral hepatitis. Viral hepatitis is a group of polyetiological anthroponotic liver lesions with various mechanisms and pathways of transmission of the pathogen. For the first time, distinguished domestic therapist S.P. Botkin (1888) suggested separating infectious hepatitis from other liver lesions. Currently, 8 types of viral hepatitis pathogens have been isolated and studied.

Over the past 30 years, the main principle of the treatment of viral hepatitis has been intensive and prolonged interferon therapy. Its effect is expressed in the reduction of intoxication, the number and severity of complications and the neutralization of the pathogen virus. In some cases, interferon

inducers are prescribed. At the present stage, the treatment of viral hepatitis includes the appointment of etiotropic drugs such as vidarabine, pamivudine and ribavirin (see earlier). An important part of the complex therapy of viral hepatitis is symptomatic treatment. In general, the rational pharmacotherapy of viral hepatitis remains a challenge. Therefore, the possibility of immunoprophylaxis of the disease attracts much attention.

In conclusion, a few words about other treatment options for the most common viral infections. So, in the treatment of various forms of herpetic infection, almost all known interferon inducers of local and systemic action are used. For example, with herpetic infection, hypicirrhizic acid (epigen intimate) is used. Glycyrrhizic acid stimulates the formation of IFN and interacts with the structures of the virus, changing the phases of the viral cycle. The drug improves tissue regeneration and has an anti-inflammatory and analgesic effect. Glycyrrhizic acid is active against DNA and RNA viruses, including herpes simplex viruses, herpes zoster, human papillomas and cytomegaloviruses. The drug is well tolerated.

Currently, the company Allofarm has developed and introduced into production an innovative drug allomedin. The main active ingredient of the new drug is the alloferon-3 peptide. Preclinical studies have established that active substances - peptides from the group of allostatin - increase the antiviral and antitumor immunity of the body. Clinical trials have shown that the use of alloferon in relapsing herpes increases the relapse-free period to six months or more. The use of the drug at the beginning of the disease eliminates unpleasant symptoms within a few hours and stops herpetic eruptions. We add that allomedin is also indicated for the treatment of viral papilloma. The drug is available in the form of Allomedin gel.

It should be mentioned the domestic drug antigrippin, which is a balanced mixture of acetylsalicylic acid, ascorbic acid, rutin, metamizole, diphenhydramine, calcium gluconate. In case of influenza and acute respiratory viral infections with adaptive and therapeutic purposes, adaptogens are widely used - general restorative agents of plant origin (preparations of ginseng, eleutherococcus, Chinese magnolia vine, lure, aralia, rhodiola, echinacea, Kalanchoe). For the treatment of influenza caused by viruses of type A and B, a synthetic drug from the class of bicyclotenes deutiforin is used. Adapromin is used as a therapeutic and prophylactic agent for influenza A and B - 0.2 g once a day for 4 days, for emergency prophylaxis in the outbreak 0.1 g once a day for 5-10 days.

For respiratory infections, immunomodulators are widely used: ribomunyl, broncho-torment, IRS-19, chmudon, etc. They increase the concentration of γ-IFN and interleukin-2 (IL-2), which contributes to the development of a more stable immune response. The intranasal use of such interferon preparations as Alphainterferon (interlock, CHLI), Viferon, Grippferon and Reaferon (realdiron) allows preventing the development of the disease. With topical application of IFN, no side effects were detected. Homeopathic remedies comprise a separate group of anti-influenza drugs: aflubin, allicor, flu-gel, iflucid, tonsilgon, traumeel, flu, engistol, EDAS 903 granules, EDAS 131 drops, nazentropfen C, AGRI adult and children.

A promising antiviral drug is recently developed pleconaril in the United States. In vitro studies and in experiments on animals revealed its activity against enteroviruses and rhinoviruses. The data from the first placebo-controlled studies indicate the effectiveness of the drug in respiratory infections and enteroviral meningitis.

Despite the rather extensive list of drugs, viral diseases remain poorly controlled infections. This is due to the lack of radical methods of therapy and the development of virus resistance. The maximum effectiveness of antiviral therapy is achieved with a comprehensive treatment.

INTERFERONS

Antiviral activity.

Interferons are cytokine-like mosquitoes with antiviral, immunomodulatory and antiproliferative effects. They are synthesized by cells under the influence of various factors and trigger biochemical mechanisms to protect cells of the same animal species from viruses. The human body produces three groups of interferons with antiviral effects - alpha (more than 18 representatives), beta and gamma. The recombinant interferons alpha used in clinical practice are non-glycosylated proteins with a molecular weight of about 19,500.

Synthesis of interferon alpha can occur in almost all cells. Trigger stimuli for the formation of interferons can be viruses, double-stranded RNA, some cytokines (including IL-1, IL-2, TNF) and other factors. Interferon y is produced only by T and NK lymphocytes when they are stimulated by mitogen antigens and some cytokines. The functions of interferons alpha and betta are diverse: they have antiviral and antiproliferative effects; enhance the cytotoxic activity of T-lymphocytes, NK-lymphocytes and macrophages; increase the expression of HLA class I antigens and other surface antigens. Interferon gamma is less active against viruses, but has a stronger immunomodulating effect: it activates macrophages, stimulates the expression of HLA class II antigens and mediates local inflammatory reactions.

Interferons inhibit the reproduction of most animal viruses, but they act weakly on many DNA-containing viruses. Data on antiviral activity of interferons vary greatly depending on the virus and the method of analysis. The biological activity of interferons is usually determined by their antiviral effect in cell culture and expressed in international units (ME) in accordance with generally accepted standards.

Mechanism of action.

The binding of interferons to specific cellular receptors activates intracellular signal transmission, in which Janus kinases and STAT transcription factors are involved. As a result, the STAT protein complex is cleaved from the receptor and transferred to the cell nucleus, where it interacts with genes that carry an interferon-sensitive regulatory element. Thus, the synthesis of more than two dozen proteins is launched, the action of which is aimed at suppressing the virus. Interferons act on all the main stages of virus reproduction: penetration into the cell and undressing, synthesis of viral mRNA, translation of viral proteins, assembly and exit of the virus from the cell. The most formidable property of interferons for many viruses is the suppression of the synthesis of viral proteins. Interferons induce the production of 2 ′, 5′-oligoadenylate synthetases and PKR protein kinases. In the presence of double-stranded RNA, 2 ′, 5′-oligoadenylate synthetases form 2 ′, 5′-oligoadenylates, which, in turn, activate ribonuclease L, which cleaves both viral and cellular single-stranded RNAs. PKR protein kinase selectively phosphorylates and thereby blocks the translation initiation factor eIF2a, without which the synthesis of viral proteins is impossible. In addition, it can trigger apoptosis. Interferons also induce phosphodiesterase, which cleaves part of the TPH K molecule, which prevents the elongation of the polypeptide chain. Depending on the type of virus, interferons can act at various stages of its reproduction. Some viruses can inhibit the production of enzymes induced by interferons or reduce their activity. Thus, one of the mechanisms of hepatitis C virus resistance to interferons is due to the ability of this virus to inhibit PKR protein kinase (Francois et al., 2000).

Complex interactions exist between interferons and other components of the immune system. Interferons can act on the virus directly or indirectly - due to changes in the immune response. For example, by increasing the expression of HLA antigens, they stimulate the lysis of infected cells with cytotoxic T lymphocytes. In addition to the antiviral effect itself, interferons participate in some general body reactions to a viral infection, including pathological immune reactions accompanied by tissue damage.

Pharmacokinetics

When interferons are taken orally, it is not possible to detect them in plasma, and the level of 2 ′, 5′-oligoadenylate synthetase in lymphocytes almost does not increase (Wills, 1990). But with a / m or s / c administration, interferon a is absorbed by more than 80%. The serum concentration of interferon a is dose dependent; 4-8 hours after administration, it reaches a maximum, and after 18-36 hours it returns to its original level. With a single introduction, level 2 ′, 5′- oligoadenylate synthetase in blood lymphocytes (an indicator of the biological activity of interferon) begins to increase after 6 hours and remains above the initial level for 4 days. 24 hours after the administration of interferon a, the antiviral activity of blood lymphocytes becomes maximum, and then slowly (within 6 days) returns to the initial level. The absorption of interferon y with i / m or s / c administration is less constant, and the serum concentration of interferon with this administration is low, although the level of 2 ′, 5′-oligoadenylate synthetase in blood lymphocytes may increase. The distribution volume of interferon a is on average 31l. With systemic use, low concentrations of interferon are found in the secrets of the respiratory tract, CSF, aqueous humor and the brain.

Since the effect of interferons lasts long enough, it is difficult to judge it on the basis of usual pharmacokinetic parameters. With iv administration, the dynamics of elimination of interferon α from plasma is complex and is described by several exponential functions (Bocci, 1992). T1 / 2 of interferon a is about 40 minutes, and of recombinant Riu interferons is about 4 hours and 30 minutes, respectively. The elimination of interferons from plasma depends on their distribution in the body, uptake by cells and decay, which occurs mainly in the liver and kidneys. Only a very small number of interferons are excreted in the urine.

The addition of an inert polymer of polyethylene glycol to interferons significantly slows their elimination from plasma. The resulting long-acting interferons (conjugated interferons, or peginterferons) can be administered only 1 time per week. In addition, the addition of polyethylene glycol reduces the immunogenicity of protein preparations. With an increase in the molecular weight of polyethylene glycol, T1 / 2 of the drug increases, its renal clearance and relative antiviral activity decrease. In large clinical trials, the efficacy of two conjugated interferons was studied. Peginterferon a-2b was obtained by adding a linear polyethylene glycol molecule with a molecular weight of 12,000 to interferon a-2b. T1 / 2 of such a preparation was increased from 2-3 to 54 hours (Glueetal., 2000). Peginterferon-2a contains an ether of branched polyethylene glycol with a molecular weight of 40,000; its T1 / 2 is still higher - an average of 77 hours. About 70% of peginterferon a-2b and most of pegininterferon a-2a are eliminated by hepatic metabolism. Side effects. A few hours after the administration of interferons (at a dose of 1-2 million IU or more), a flu-like syndrome often occurs with fever, chills, headache, myalgia, arthralgia, nausea, vomiting and diarrhea (Dusheiko, 1997). The fever usually lasts no more than 12 hours, when taking antipyretic drugs before the introduction of interferon, it is less pronounced. In most cases, interferon tolerance improves over time. An influenza-like condition, discomfort at the injection site and leukopenia occurred in almost half of patients with genital warts with the introduction of interferon in warts.

With systemic use, interferon can cause inhibition of blood formation (neutropenia and thrombocytopenia), disorders of the central nervous system (drowsiness, confusion, behavioral changes, rarely epileptic seizures), severe asthenia with increased fatigue and weight loss, autoimmune disorders (in including chronic lymphocytic thyroiditis), less often - cardiovascular disorders (arterial hypotension and tachycardia). These side effects inhibit dose escalation. Sometimes there is an increase in the activity of liver enzymes and triglycerides in the blood, alopecia, proteinuria and azotemia, interstitial nephritis, and the formation of autoantibodies. In children treated with interferon, personality changes and alopecia often occur (Sokal et al., 1998). Occasionally, when interferons are administered, neutralizing antibodies are generated to them, and then further treatment becomes useless (Antonelli et al., 1991). The introduction of interferons can adversely affect reproductive function. Their safety during pregnancy has not been established.

Interferons slow down the inactivation of certain drugs (for example, theophylline) by microsomal liver enzymes. As a result, the serum concentration of such drugs rises. Inhibition of hematopoiesis caused by other drugs (for example, zidovudine), against the background of the introduction of interferons, may increase.

Tolerance of conjugated interferons is not worse than usual: treatment should be canceled in 6-11% of cases. However, according to some studies, conjugated interferons are more likely to cause fever, nausea, and an inflammatory reaction at the injection site. It is not clear yet whether the accumulation and prolonged residence of polyethylene glycol in the body is dangerous.

ANTI-INFLAMMATORY DRUGS

Arbidol is a derivative of indolecarboxylic acid. The mechanism of action of the drug consists of suppressing the reproduction of the influenza virus, the effect on the synthesis of IFN, increasing the number of T-lymphocytes and the functional activity of macrophages, as well as the antioxidant effect.

The drug penetrates unchanged in both uninfected and infected cells and is determined in the nuclear and cytoplasmic fractions. Arbidol inhibits the process of fusion of the lipid viral envelope with endosome membranes (at pH 7.4), leading to the release of the viral genome and the beginning of transcription. Unlike amantadine and rimantadine, Arbidol inhibits the release of the nucleocapsid itself from external proteins, neuraminidase, and the lipid membrane. Thus, Arbidol acts in the early stages of viral reproduction.

The drug does not have strain specificity (in cell cultures, it inhibits the reproduction of influenza A virus by 80%, influenza B virus by 60% and influenza C virus by 20%, and also affects bird flu virus, but weaker than for the reproduction of human influenza virus strains).

The synthesis of IFN is increasing, starting from taking 1 tablet to 3 tablets. However, a further increase in the level of IFN when taking Arbidol is not observed. A rapid increase in IFN synthesis can have a preventive effect when taking the drug before the onset of the flu.

Arbidol has an immunomodulatory effect, leading to an increase in the total number of T-lymphocytes and T-helpers. Moreover, the normalization of these indicators was observed in patients with an initially reduced number of CD3 and CD4 cells, and in individuals with normal functioning of the cellular immunity component, there were practically no changes in the number of T-lymphocytes and T-helpers. Moreover, the use of Arbidol does not lead to a significant decrease in the absolute number of T-suppressor lymphocytes - thus, the stimulating activity of the drug is not associated with inhibition of the function of suppressor cells. Arbidol increases the total number of macrophages with absorbed bacteria and the phagocytic number. It is assumed that the activating stimuli for phagocytic cells were cytokines and, in particular, IFN, the production of which increases under the influence of the drug. The content of natural killers - NK cells is also increasing, which allows us to characterize the drug as an inducer of activity of natural killers

The drug is rapidly absorbed from the gastrointestinal tract (GIT). T1 / 2 is 16–21 hours. It is excreted unchanged with feces (38.9%) and urine (0.12%). During the first day, 90% of the administered dose is excreted.

Drug interactions of Arbidol with other drugs in the literature are not described.

Almost the only side effects of the drug are allergic reactions. The drug is approved for use from 2 years of age.

Arbidol has a fairly wide range of antiviral effects and is used for the prevention and treatment of influenza types A and B, including those complicated by bronchitis and pneumonia; acute respiratory

infections (ARVI); chronic bronchitis, pneumonia, recurrent herpetic infection; in the postoperative period - to normalize the immune status and prevent complications.

Amantadine and rimantadine are derivatives of adamantane. Both drugs even in small doses inhibit the reproduction of virus A. Their antiviral activity is due to two mechanisms.

Firstly, they act at an early stage of viral reproduction, suppressing the "undressing" of the virus. The primary target for these drugs is the influenza A virus M2 protein, which forms an ion channel in its shell. Suppression of the function of this protein leads to the fact that protons from endosomes cannot get inside the virus, the dissociation of ribonucleide and the exit of the virus into the cytoplasm are blocked.

Secondly, they can act at the stage of virus assembly, apparently due to changes in the processing of hemagglutinin. This mechanism is possible in some strains of viruses.

Among wild strains, resistance to drugs is rare, but resistant strains are obtained from patients taking them. The sensitivity and resistance of viruses to amantadine and rimantadine cross.

Both drugs are well absorbed when taken orally, have a large volume of distribution. Most amantadine is excreted unchanged in the urine. The half-life (T1 / 2) in young people is 12-18 hours, in the elderly it almost doubles, and in case of renal failure it increases even more. Therefore, the dose of the drug must be reduced even with a slight change in kidney function. Rimantadine is actively metabolized in the liver, T1 / 2 averages 24–36 hours, 60–90% of the drug is excreted in the urine as metabolites.

When taking both drugs, minor dose-related disorders from the gastrointestinal tract (nausea, loss of appetite) and central nervous system (CNS) (irritability, insomnia, impaired concentration) are most often noted. When taking high doses of amantadine, a significant neurotoxic effect is possible: confusion, hallucinations, epileptic seizures, coma (these effects may be enhanced while taking H1-blockers, M-anticholinergics, psychotropic drugs and ethanol). Safety during pregnancy has not been established. Allowed to use from the age of 7.

The drugs are used for the prevention and treatment of influenza A. Their use during influenza epidemics helps to avoid infection in 70–90% of cases. In people with uncomplicated influenza A, treatment with drugs over an age-related period of 5 days, begun at an early stage of the disease, reduces the duration of fever and general symptoms by 1–2 days, accelerates recovery, and sometimes shortens the period of virus isolation.

Oseltamivir is an inactive precursor, which in the body turns into an active metabolite - oseltamivir carboxylate. It is a transitional analogue of sialic acid and a selective inhibitor of the neuraminidase of influenza A and B. In addition, it suppresses strains of the influenza A virus that are resistant to adamantane derivatives.

Influenza virus neuraminidase cleaves the terminal residues of sialic acids and, thus, destroys the receptors located on the surface of cells and new viruses, i.e., facilitates the exit of the virus from the cell at the end of reproduction. The active metabolite of oseltamivir causes changes in the active center of neuraminidase and inhibits its activity. Aggregation of viruses on the cell surface occurs and their spread slows down.

Resistant strains of influenza A virus are found in 1-2% of patients taking the drug. No resistant strains of the influenza B virus have been found to date.

When taken orally, the drug is well absorbed. Eating does not affect its bioavailability, but reduces the risk of side effects on the digestive tract. The drug undergoes enzymatic hydrolysis in the digestive tract and liver with the formation of an active metabolite. The volume of distribution of the

drug is close to the volume of fluid in the body. T1 / 2 of oseltamivir and its active metabolite is 1-3 and 6-10 hours, respectively. Both compounds are excreted mainly by the kidneys unchanged.

When taken orally, slight discomfort in the abdomen and nausea are possible, which decrease when taking the drug with food. Gastrointestinal disorders usually go away after 1-2 days, even if the patient continues to take the drug. There are no clinically significant interactions of oseltamivir with other drugs. The drug is used in children older than 1 year.

Oseltamivir is used to treat and prevent flu. Prophylactic administration of oseltamivir during epidemics reduces the incidence rate both among those vaccinated with the influenza vaccine and among those unvaccinated. In the treatment of influenza with this drug, recovery occurs 1–2 days earlier, and the number of bacterial complications decreases by 40–50%.

ANTIHERPETIC DRUGS

Herpes simplex virus type 1 causes damage to the skin, mouth, esophagus and brain; herpes simplex virus type 2 causes damage to the external genitalia, rectum, skin and meninges. The first of the approved antiherpetic drugs was vidarabine (1977). However, due to its high toxicity, it was used to treat diseases caused by the herpes simplex virus and Varicella – zostervirus only for health reasons. Since 1982, acyclovir has been used to treat patients with a less severe course of the disease.

Acyclovir is the acyclic analog of guanosine, and valaciclovir is the L-valine ester of acyclovir. Acyclovir inhibits the synthesis of viral DNA after phosphorylation of viral thymidine kinase inside infected cells. The acyclovir triphosphate formed in the cell is inserted into the DNA strand synthesized in the host cell, which leads to the cessation of the growth of the viral DNA strand. The DNA molecule, which contains acyclovir, binds to DNA polymerase, irreversibly inactivating it.

Virus resistance may result from a decrease in viral thymidine kinase activity and a change in viral DNA polymerase. A change in enzyme activity results from mutations.

The oral bioavailability of acyclovir is only 10–30% and decreases with increasing dose. Unlike acyclovir, the bioavailability of valaciclovir when administered orally reaches 70%. The drug quickly and almost completely turns into acyclovir. Acyclovir penetrates many biological fluids, including the contents of vesicles in case of chickenpox, cerebrospinal fluid, accumulates in milk, amniotic fluid and placenta. Its concentration in the vaginal contents varies widely. The serum concentration of the drug in the mother and newborn is approximately the same. Through the skin, the drug is practically not absorbed. T1 / 2 of acyclovir averages 2.5 hours in adults, 4 hours in newborns, and can increase up to 20 hours in patients with renal failure. The drug is almost completely excreted by the kidneys unchanged. During pregnancy, the pharmacokinetics of drugs does not change.

Acyclovir is generally well tolerated. When applying ointment based on polyethylene glycol, irritation of the genital mucosa and a burning sensation are possible. When taken orally, the drug occasionally causes headache, dizziness, rash, and diarrhea. Renal failure and a neurotoxic effect are even less common. Side effects of valaciclovir are similar to those of acyclovir - nausea, diarrhea, headache; high doses can cause confusion, hallucinations, kidney damage and, very rarely, thrombocytopenia. With intravenous administration of large doses of acyclovir, renal failure and CNS lesions may develop.

Famciclovir itself is inactive, but the first passage through the liver quickly turns into penciclovir.

Penciclovir is an acyclic analogue of guanosine. The mechanism of action of the drug is similar to the mechanism of action of acyclovir. Like acyclovir, penciclovir acts mainly on herpes simplex and Varicella – zostervirus viruses. Clinic resistance to penciclavir is rare.

Unlike penciclovir, whose bioavailability when taken orally is only 5%, famciclovir is well absorbed. When taking famciclovir, the bioavailability of penciclovir increases to 65–77%. Eating with the

drug slows down the absorption of the latter, but in general, bioavailability does not decrease. The distribution volume of penciclovir is 2 times the volume of fluid in the body, T1 / 21/2 increases to 9.9 hours. The drug is easily removed during hemodialysis.

Acyclovir is well tolerated, but sometimes headache, nausea, diarrhea, urticaria can occur, and in older people - hallucinations and confusion. Topical preparations may cause contact dermatitis and ulceration.

The safety of the drug during pregnancy, as well as its interaction with other drugs, has not been established.

Ganciclovir is an acyclic analogue of guanosine. The mechanism of action of the drug is similar to the mechanism of action of acyclovir. Active against all herpes viruses, but most effective against cytomegalovirus.

The bioavailability of ganciclovir when taken orally with food is 6–9% and slightly less when taken on an empty stomach. Valganciclovir is well absorbed and rapidly hydrolyzed to ganciclovir, the bioavailability of which increases to 61%. When taking valganciclovir with food, the bioavailability of ganciclovir increases by another 25%. With normal renal function, T1 / 2 is 2–4 hours. More than 90% of the drug is excreted by the kidneys unchanged. With renal failure, T1 / 2 increases to 28–40 hours.

The main dose-limiting side effect of ganciclovir is inhibition of hematopoiesis (neutropenia, thrombocytopenia). In 5-15% of patients, CNS lesions of varying severity (from headache to seizures and coma) are noted. With intravenous administration, phlebitis, azotemia, anemia, rash, fever, a change in the biochemical parameters of the liver, nausea, vomiting, eosinophilia are possible.

In laboratory animals, the drug had a teratogenic and embryotoxic effect, irreversibly impaired reproductive function. Cytostatic drugs increase the side effect of ganciclovir on the bone marrow.

Valacyclovir is a prodrug in the body that quickly and almost completely turns into acyclovir, which, after phosphorylation, acquires a specific activity. Acyclovir is a structural analogue of purine nucleosides (normal DNA components), interacts with viral DNA polymerase and blocks the reproduction of viruses. Selective antiherpetic activity is due to the affinity for Herpes simplex, Varicella zoster and Epstein-Barr virus thymidine kinases. Under the action of thymidine kinase, the virus is transformed into acyclovir monophosphate, with the participation of human cell guanylate kinase, into acyclovir diphosphate and then into the active form of acyclovir triphosphate. Triphosphate blocks viral DNA replication due to competitive inhibition of viral DNA polymerase and inhibition of DNA strand elongation. In vitro acyclovir is active against Herpes simplex viruses type 1 and 2, Varicella zoster (less active than against Herpes simplex due to more efficient phosphorylation with the corresponding thymidine kinase), Epstein-Barr virus, CMV and human herpes simplex virus 6.

Idoxuridine is an iodine-containing analogue of thymidine. The mechanism of antiviral action is not fully understood. It is known that phosphorylated derivatives of the drug integrate into viral and cellular DNA, but inhibit only viral DNA replication. At the same time, the DNA becomes more fragile, it is easily destroyed, errors occur more often during its transcription. Resistant strains are isolated from patients with herpetic keratitis treated with idoxuridine. The drug is allowed only for topical use. When using it, pain, itching, inflammation and swelling in the eye area, allergic reactions are possible.

AIDS MEDICINES

The reproduction of the human immunodeficiency virus (HIV), the causative agent of STI-Yes, can only be stopped by very active and targeted treatment, affecting the metabolic processes of the virus in the infected cell (A). First, the nucleocapsid of the virus through glycoproteins binds to the CC) 4-

molecule of the T helper. Then the capsid protein enters the case, which begins the process of fusion of the capsid with the cell membrane. In an infected cell, viral RNA must first be translated into DNA; it also occurs with the help of the viral reverse transcriptase enzyme. Double-stranded DNA is inserted into the target cell genome using the viral integrase enzyme. Next is the replication of the virus. Virus DNA controls the synthesis of viral RNA and proteins (reverse transcriptase and integrase, as well as structural proteins located on the inside of the viral envelope). The products of protein synthesis are polypeptides - precursor proteins that carry a fatty acid (myristic acid) at the N-terminus, with the help of which they are attached to the inside of the plasmalemma of the target cell. Then the viral particle is separated ("budded") from the cell. During this process, the polypeptide containing the protease is cleaved into individual proteins with specific functions.

Nucleoside reverse transcriptase inhibitors.
These include zidovudine, stavudine, zalcitabine, didanosine, and lamivu-din. These substances are nucleosides with an abnormal sugar residue, which is then phosphorylated. Abnormal triphosphates block reverse transcriptase and can cause viral DNA chain breakage. Drugs are administered orally. They differ in side effects (for example, leukopenia when taking zidovudine, peripheral neuropathy or pancreatitis when taking other drugs) and the mechanism of development of resistance. For the treatment of AIDS, a combination of two drugs of this group and one non-nucleoside inhibitor, or one or two HIV protease inhibitors, is used.
To date, six nucleoside reverse transcriptase inhibitors are approved for use by the FDA, which differ from each other in phosphorylation mechanisms and side effects. Among these drugs, there are both time-tested (for example, zidovudine and didanosine), and relatively recently approved by the FDA (abacavir). They tried to use nucleoside reverse transcriptase inhibitors in the form of monotherapy or in combinations of two drugs, but now they are part of reliable treatment regimens, including 3-4 drugs. Recent studies have shown that nucleoside reverse transcriptase inhibitors can cause lactic acidosis, severe hepatomegaly and fatty liver.
II. HIV protease inhibitors.
The drugs interfere with the cleavage of the inactive precursor protein and, consequently, the maturation of the virus. Apply orally.
Saquinavir can be called an abnormal peptide. Its bioavailability is limited. Other protease inhibitors: ritonavir, indinavir, nelfinavir, amprenavir. They are characterized by high bioavailability; inhibit the activity of CYP, so it is necessary to take into account possible interactions with drugs. With prolonged use, redistribution of adipose tissue in the body and metabolic disorders (hyperlipidemia, insulin resistance, hyperglycemia) are possible.
Almost all HIV protease inhibitors allowed for use sharply inhibit the reproduction of HIV-1, and after 4–12 weeks of monotherapy, the concentration of HIV-1 RNA in plasma decreases by a factor of 100–1000. An exception is saquinavir in hard gelatin capsules, which, due to their low bioavailability, are prescribed together with ritonavir. The relative effectiveness of each of the drugs separately has not been established, since comparative studies of them were almost not carried out. When a powerful HIV protease inhibitor is prescribed in combination with two nucleoside reverse transcriptase inhibitors to previously untreated patients, 60-95% of them do not detect viral plasma RNA in plasma. The ineffectiveness of such combinations in most, if not all, cases is due to the fact that patients do not follow the treatment regimen.
III. Fusion Inhibitors.
Enfuvirtide is a peptide that inhibits the necessary spatial change in the fusion protein through specific binding to it.
It is a backup therapeutic agent.
The emergence of multiresistant strains of HIV requires the development of new antiretroviral drugs that act not only on reverse transcriptase or HIV protease, but also on other molecular targets. They act on different stages of the HIV life cycle: the adsorption and fusion of the virus with the cell membrane, the incorporation of its genetic material into the genome of the host cell and assembly. Another possible direction is HIV regulatory protein blockers (in particular, Tat). It is hoped that at least some of the new drugs will suppress the reproduction of resistant strains of HIV, give fewer side effects and allow less frequent use than current ones.

Clinical trials of drugs acting on the fusion of HIV with the membrane of the host cell are already in progress. It has been accidentally discovered that peptides similar to the short sequences of the gp41 glycoprotein inhibit the incorporation of HIV into cells (Jiangetal., 1993; Wildetal., 1994). These peptides disrupt the interaction between the terminal regions of N36 and C34 of the gp41 glycoprotein. One of these peptides - T-20 (or DP-178), consisting of 36 amino acids, binds to the hydrophobic gap of the helical N-terminal portion of the (N36) gp41, which is coiled, thereby blocking the fusion of HIV with the membrane and its penetration into the cell. The concentration of T-20, which inhibits the reproduction of HIV-1 by 50%, is 50-60 nmol / L (Sodroski, 1999). In a preliminary clinical trial, T-20 was administered iv for 2 weeks in the form of monotherapy to 16 HIV-infected patients. Moreover, in half the cases, the concentration of viral RNA decreased by two orders of magnitude (Kilby et al., 1998), which exceeds the effect of standard drug combinations (Richman, 1998; Rimsky et al., 1998; Sodroski, 1999). T-20 resistant strains of HIV result from mutations in the gp41 gene (Rimsky et al., 1998). T-20 tests are being conducted in combination with other drugs. The disadvantage of T-20 is that, as a large peptide, it is not absorbed when taken orally; therefore, it has to be administered s / c or iv (2 times a day). Searches are being conducted for inhibitors of the fusion of HIV with a cell with a lower molecular weight that can be absorbed in the digestive tract.

GENERAL CHARACTERISTICS OF ANTIFUNGIC AGENTS

Antifungal drugs, or antimycotics, are a fairly extensive class of diverse chemical compounds, both of natural origin and obtained by chemical synthesis, which have specific activity against pathogenic fungi. Depending on the chemical structure, they are divided into several groups that differ in the characteristics of the activity spectrum, pharmacokinetics and clinical use in various fungal infections (mycoses).

The history of the discovery of antifungal agents

Fungal diseases have been known for a very long time, since antiquity. However, the causative agents of dermatomycosis, candidiasis were detected only in the middle of the 19th century, by the beginning of the 20th century. pathogens of many visceral mycoses have been described. Before antimycotics appeared in medical practice, antiseptics and potassium iodide were used to treat mycoses.

In 1954, antifungal activity was discovered in the well-known since the late 40s. XX century polyene antibiotic nystatin, in connection with which nystatin has become widely used to treat candidiasis. The antibiotic griseofulvin turned out to be a highly effective antifungal agent. Griseofulvin was first isolated in 1939 and was used for fungal diseases of plants, was introduced into medical practice in 1958 and was historically the first specific antimycotic for the treatment of dermatomycosis in humans. For the treatment of deep (visceral) mycoses, another polyene antibiotic, amphotericin B (was obtained in purified form in 1956), was started to be used.

Major successes in the creation of antifungal agents date back to the 70s. XX century. When imidazole derivatives were synthesized and put into practice - II generation antimycotics - clotrimazole (1969), miconazole, ketoconazole (1978), and others. Triazole derivatives (itraco-nazole - synthesized in 1980, fluconazole - synthesized in 1982), the active use of which began in the 90s, and allylamines (terbinafine, naphtha-fin).

IV generation antimycotics - new drugs already registered in Russia or undergoing clinical trials - liposomal forms of polyene antibiotics (amphotericin B and nystatin), triazole derivatives (voriconazole - created in 1995, posaconazole - registered in Russia at the end 2007, ravukonazole - not registered in Russia) and echinocandins (caspofun-gin).

Classification and general characteristic of mycoses

Depending on the location of the lesions, mycoses are divided into four groups:

• systemic, or deep mycoses, characterized by damage to internal organs involving various tissues (coccidioidosis, histoplasmosis, cryptococcosis, North American and South American blastomycosis) in the pathological process;

• subcutaneous, or subcutaneous mycoses, characterized by damage to the skin, subcutaneous tissue, fascia and bones (sporotrichosis, chromomycosis, madu-romycosis);

• epidermomycosis, characterized by damage to the epidermis, hair and nails (dermatomycosis);

• superficial mycoses, characterized by damage to the hair and superficial stratum corneum of the epidermis (keratomycosis, multicolored lichen - malassesiosis, black lichen - cladosporiosis, white pedestrian - trichosporosis and black pedestrian - pedraiosis.

The causative agents of deep and subcutaneous mycosis are usually found in the soil. The entry gates of infection with different mycoses are different. Systemic mycoses develop after inhalation of the pathogen spores, and subcutaneous ones after the direct entry of spores or mycelial fragments into the skin wound.

Deep mycoses resemble chronic bacterial infections caused by mycobacteria or actinomycetes. Primary lesions usually affect the lungs and occur in the form of acute pneumonia. Chronic forms are less common. They slowly progress and are characterized by the formation of suppurative wounds or granulomatous lesions; sometimes there are pulmonary caverns and the pathological process extends to the pleura. The causative agents of deep mycoses can spread hematogenously throughout the body, forming metastatic abscesses or granulomas in any organs and tissues.

With systemic mycoses, as a rule, an allergy is observed with the development of HRT. However, these diseases are not contagious, i.e. not transmitted from person to person or from animal to person. Before the discovery of antifungal polyene antibiotics, deep disseminated mycoses ended, as a rule, with death. Some of the causative agents of systemic mycoses are classified as dangerous (Coccidioides immitis, Histoplasma capsulatum) due to their high contagiousness. In addition to cryptococcosis, other deep mycoses are endemic infections.

Subcutaneous mycoses. The disease begins imperceptibly and slowly progresses with the formation of subcutaneous abscesses and granulomas, often reaching the skin surface, forming in the form of chronic, ulcerative, draining lesions. The infection can spread along the lymphatic tract and be accompanied by suppurative, granulomatous lesions in the regional lymph nodes. The disease often leads to disfigurement of parts of the body and often ends fatally, although the dissemination of the pathogen to the internal organs is rare.

Subcutaneous destructive abscesses, spreading to soft tissues, fascia and bone tissue, are called mycetomas (maduromycosis, or “Madura leg”, by the name of the locality of Madura in India, where this mycosis was first described). They are characterized by the formation of fistulas with purulent discharge. In the latter (as in abscesses), granules or drusen are often found, which are parts of the colonies of the corresponding pathogens. Similar abscesses can also be caused by bacteria of the genus Nocardia, Actinomyces.

Epidermomycoses are chronic infections that rarely occur in a severe form. The causative agent is Microsporum gypseum. Dermatomycetes come closer to the category of obligate parasites of humans and animals transmitted by the contact of healthy individuals with patients or with pieces of affected hair and epidermal scales. Inflammatory foci at the site of infection in most cases are local in nature and are not subject to destruction. People with epidermomycosis usually develop HRT. Diseases are mild and asymptomatic, acute and chronic forms are possible. The prognosis in untreated cases is not difficult. Superficial mycoses are relatively rare diseases. They are characterized by minimal reactions of the microorganism to the pathogen localized in the nails, hair or the stratum corneum of the epidermis.

Opportunistic mycoses is a group of mycoses that are caused by conditionally pathogenic fungi from the genera Absidia, Aspergillus, Candida, Mucor, Penicillium and others in immunodeficient individuals ..

Classification of antimycotics

Antifungal Antibiotics

Polyenes

• Tetraenes: natamycin.

• Heptaenes: amphotericin B, nystatin, levorin, mycoheptin, trichomycin.

Nonpolyenic antibiotics

• Grizzans: griseofulvin.

Azoles

• imidazoles

1st generation: clotrimazole, miconazole, isoconazole, bifonazole, amicazole.

- 2nd generation: econazole, thioconazole, butoconazole, fenticonazole.
- 3rd generation: ketoconazole, oxyconazole, sulfonazole.
• Triazoles: itraconazole, fluconazole, voriconazole, terconazole, fluconone-zol.
Allylamines: naftifin, terbinafine, butenafine.
Pyrimidines: flucytosine, cyclopirox.
Iodine preparations: iodine, potassium iodide, povidone-iodine.
Aniline dyes: brilliant green, gentian violet, methylene blue, fucorcin.
Morpholines: amorolfine.
Arenas
• Halogenated phenols: galaprogin, nitrophenol.
• Thiocarbonates: tolnaftate, tolcyclate.
Glucan synthesis inhibitors: caspofungin, mycofungin, anidulafungin.
Bis-Quaternary ammonium salts: decamine.
Derivatives of undecylenic acid: undecylenic acid, copper undecylinate, zinc undecylinate.
Carboxylic acids: octicyl.
Derivatives of boric acid: boric acid, sodium tetraborate.
Herbal preparations: anmarin.
Antifungal agents differ in the following parameters:
By the origin of antifungal drugs: natural or synthetic;
According to the spectrum and mechanism of action;
By antifungal effect: fungicidal and fungistatic;
According to indications for use: for the treatment of local or systemic fungal diseases;
By the method of administration: for oral administration, for parenteral administration, for external use
In clinical practice, antifungal agents are divided into 3 main groups:
Preparations for the treatment of deep (systemic) mycoses.
Preparations for the treatment of epidermophytosis and trichophytosis.
Candidiasis preparations
Polyenes:
Nystatin
Levorin
Natamycin
Amphotericin B
Amphotericin B liposome
Azoles:
For systemic use
Ketoconazole
Fluconazole
Itraconazole
For topical use
Clotrimazole
Miconazole
Bifonazole
Econazole
Isoconazole
Oxyconazole
Allylamines:
For systemic use
Terbinafine
For topical use
Naphthyne
Preparations of different groups:
For systemic use

Griseofulvin
Potassium iodide
For topical use
Amorolfin
Cyclopirox
The need for the use of antifungal drugs has recently increased significantly due to an increase in the prevalence of systemic mycoses, including severe life-threatening forms, due primarily to an increase in the number of patients with immunosuppression of various origins. It is also important to carry out invasive medical procedures more frequently and to use (often unjustified) powerful wide-spectrum AMPs.
Polyenes
Polyenes, which are natural antimycotics, include nystatin, levorin, and natamycin, applied topically and internally, as well as amphotericin B, used primarily for the treatment of severe systemic mycoses. Liposomal amphotericin B is one of the modern dosage forms of this polyene with improved tolerance. It is obtained by encapsulating amphotericin B in liposomes (fat vesicles formed when phospholipids are dispersed in water), which ensures the release of the active substance only in contact with fungal cells and is intact with respect to normal tissues.
Mechanism of action
Polyenes, depending on the concentration, can have both fungistatic and fungicidal effects due to the binding of the drug to ergosterol of the fungal membrane, which leads to a violation of its integrity, loss of cytoplasm and cell death.
Activity spectrum
Polyenes have the widest spectrum of in vitro activity among antifungal drugs.
For systemic use (amphotericin B), Candida spp is sensitive. (resistant strains are found among C. lusitaniae), Aspergillus spp. (A.terreus may be resistant), C.neoformans, pathogens of mucomycosis (Mucor spp., Rhizopus spp. And others), S.schenckii, pathogens of endemic mycoses (B.dermatitidis, H.capsulatum, C.immitis, P. brasiliensis) and some other mushrooms.
However, when applied topically (nystatin, levorin, natamycin), they act mainly on Candida spp.
Polyenes are also active against some protozoa - trichomo-nad (natamycin), Leishmania and amoeba (amphotericin B).
Fungi-dermatomycetes and pseudo-allesheria (P. boydii) are resistant to polyenes.
Pharmacokinetics
All polyenes are practically not absorbed in the digestive tract and when applied topically. Amphotericin B with iv administration is distributed into many organs and tissues (lungs, liver, kidneys, adrenal glands, muscles, etc.), pleural, peritoneal, synovial and intraocular fluid. Poor passes through the BBB. Slowly excreted by the kidneys, 40% of the administered dose is excreted within 7 days. The elimination half-life is 24–48 hours, but with prolonged use, it can increase up to 2 weeks due to cumulation in the tissues. The pharmacokinetics of liposomal amphotericin B is generally less understood. There is evidence that it creates higher peak blood concentrations than standard. It practically does not penetrate the kidney tissue (therefore, less nephrotoxic). It has more pronounced cumulative properties. The elimination half-life averages 4-6 days, with prolonged use, an increase of up to 49 days is possible.
Adverse reactions
Nystatin, Levorin, Natamycin
(for systemic use)
Gastrointestinal tract: abdominal pain, nausea, vomiting, diarrhea.
Allergic reactions: rash, itching, Stevens – Johnson syndrome (rarely).
(topical application)
Irritation of the skin and mucous membranes, accompanied by a burning sensation.
Amphotericin B
Reactions to IV infusion: fever, chills, nausea, vomiting, headache, hypotension. Prevention measures: premedication with the introduction of NSAIDs (paracetamol, ibuprofen) and antihistamines (diphenhydramine).

Local reactions: pain at the site of infusion, phlebitis, thrombophlebitis. Prevention measures: administration of heparin.
Kidneys: impaired function - decreased diuresis or polyuria. Control measures: monitoring the clinical analysis of urine, determining the level of creatinine in blood serum every other day during an increase in dose, and then at least twice in Week. Prevention measures: hydration, exclusion of other nephrotoxic drugs.
Liver: possible hepatotoxic effect. Control measures: clinical and laboratory (transaminase activity) monitoring.
Electrolyte imbalance: hypokalemia, hypomagnesemia. Control measures: determination of the concentration of serum electrolytes 2 times a week.
Hematological reactions: most often anemia, less commonly leukopenia, thrombocytopenia. Control measures: a clinical blood test with a determination of the platelet count 1 time per week.
Gastrointestinal tract: abdominal pain, anorexia, nausea, vomiting, diarrhea.
Nervous system: headache, dizziness, paresis, impaired sensation, tremors, cramps.
Allergic reactions: rash, itching, bronchospasm.
Amphotericin B liposome
Compared with a standard drug, it causes less anemia, fever, chills, hypotension, less nephrotoxicity.
Indications
Nystatin, Levorin
Candidiasis of the skin, oral cavity and pharynx, intestines.
Candidiasis vulvovaginitis.
(Preventive use is ineffective!)
Natamycin
Candidiasis of the skin, oral cavity and pharynx, intestines.
Candidiasis vulvovaginitis.
Candidiasis balanoposthitis.
Trichomonas vulvovaginitis.
Amphotericin B
Severe forms of systemic mycoses:
invasive candidiasis
aspergillosis
cryptococcosis,
sporotrichosis,
mucormycosis,
trichosporosis
Fusarium
pheogyphomycosis,
endemic mycoses (blastomycosis, coccidioidosis, paracoccidioidosis, histoplasmosis, penicilliosis).
Candidiasis of the skin and mucous membranes (topically).
Leishmaniasis.
Primary amoebic meningoencephalitis caused by N. fowleri.
Amphotericin B liposome
Severe forms of systemic mycoses (see amphotericin B) in patients with renal insufficiency, with the ineffectiveness of the standard drug, with its nephrotoxicity, or pronounced reactions to IV infusion that cannot be stopped by premedication.
Contraindications
For all polyenes
Allergic reactions to drugs of the polyene group.
Additionally for amphotericin B
Impaired liver function.
Impaired renal function.
Diabetes.
All contraindications are relative, since amphotericin In practice, it is always used for health reasons.

Warnings

Allergy. There is no evidence of cross-allergy to all polyenes, however, in patients with an allergy to one of the polyenes, other drugs of this group should be used with caution.

Pregnancy. Amphotericin B passes through the placenta. Adequate and strictly controlled studies of the safety of polyenes in humans have not been conducted. However, in numerous reports on the use of amphotericin B at all stages of pregnancy, an adverse effect on the fetus was not recorded. It is recommended to use with caution.

Lactation. Data on the penetration of polyenes into breast milk are not available. Adverse effects were not observed in breast-fed infants. It is recommended to use with caution.

Pediatrics. To date, no serious specific problems associated with the assignment of polyene to children have been reported. In the treatment of oral candidiasis in children under 5 years of age, it is preferable to prescribe a suspension of natamycin, since the buccal administration of nystatin or levorin tablets may be difficult.

Geriatrics. In connection with possible changes in kidney function in elderly people, an increased risk of nephrotoxicity of amphotericin B is possible.

Impaired renal function. The risk of nephrotoxicity of amphotericin B is significantly increased, therefore liposomal amphotericin B is preferred.

Impaired liver function. A higher risk of the hepatotoxic effect of amphotericin B is possible. It is necessary to compare the possible benefits of the application and the potential risk.

Diabetes. Since amphotericin B solutions (standard and liposomal) for iv infusion are prepared on a 5% glucose solution, diabetes is a relative contraindication. It is necessary to compare the possible benefits of the application and the potential risk.

Drug interactions

With the simultaneous use of amphotericin B with myelotoxic drugs (methotrexate, chloramphenicol, etc.), the risk of anemia and other hematopoiesis increases.

With the combination of amphotericin B with nephrotoxic drugs (aminoglycosides, cyclosporine, etc.), the risk of severe renal dysfunction increases.

With the combination of amphotericin B with non-potassium-sparing diuretics (thiazide, loop) and glucocorticoids, the risk of developing hypokalemia, hypomagnesemia increases.

Amphotericin B, causing hypokalemia and hypomagnesemia, can increase the toxicity of cardiac glycosides.

Amphotericin B (standard and liposomal) is incompatible with 0.9% sodium chloride solution and other solutions containing electrolytes. When using systems for iv administration, established for the introduction of other drugs, it is necessary to rinse the system with 5% glucose solution.

Patient Information

When using nystatin, levorin and natamycin, strictly observe the regimen and treatment regimens throughout the course of therapy, do not miss a dose and take it at regular intervals. If you miss a dose, take it as soon as possible; do not take if it is almost time for the next dose; do not double the dose. Withstand the duration of therapy. Observe the rules for storage of drugs. Do not use expired drugs.

Azoles

Azoles are the most representative group of synthetic anti-mycotics, including drugs for systemic (ketoconazole, fluconazole, itracon-zol) and local (bifonazole, isoconazole, clotrimazole, miconazole, oxyconazole, econazole). It should be noted that the first of the proposed “systemic” azoles - ketoconazole - after the introduction of itraconazole into clinical practice, practically lost its importance due to its high toxicity and has been used locally more often lately.

Mechanism of action

Azoles have a predominantly fungistatic effect, which is associated with the inhibition of cytochrome P-450-dependent 14α-demethylase, which catalyzes the conversion of lanosterol to ergosterol, the main structural component of the fungal membrane. Local preparations when creating high local concentrations against a number of fungi can act fungicidal.

Activity spectrum

Azoles have a wide spectrum of antifungal activity. The main causative agents of candidiasis (C. albicans, C. parapsilosis, C. tropicalis, C. lusitaniae and others), Aspergillus spp., Fusarium spp., C. neoformans, dermatomycetes (Epidermophyton spp., Trichophyton spp.) Are sensitive to itraconazole. , Microsporum spp.), S. schenckii, P.boydii, H. capsulatum, B. dermatitidis, C. immitis, P. brasiliensis and some other fungi. Resistance is often found in C.glabrata and C.krusei.

Ketoconazole is close in spectrum to itraconazole, but does not affect Aspergillus spp.

Fluconazole is most active against most causative agents of candidiasis (C. albicans, C. parapsilosis, C. tropicalis, C. lusitaniae and others), cryptococcus and coccidioid, as well as dermatomycetes. Blastomycetes, histoplasmas, paracoccidioids and sporotrix are somewhat less sensitive to it. Does not affect as-pergillas.

Topically used azoles are mainly active against Candida spp., Dermatomycetes, M.furfur. Act on a number of other fungi that cause superficial mycoses. Some gram-positive cocci and corynebacteria are also sensitive to them. Clotrimazole is moderately active against certain anaerobes (bacteroids, G. vaginalis) and Trichomonas.

Pharmacokinetics

Ketoconazole, fluconazole and itraconazole are well absorbed in the digestive tract. At the same time, the absorption of ketoconazole and itraconazole requires a sufficient level of acidity in the stomach, because, reacting with hydrochloric acid, they are converted into highly soluble hydrochlorides. The bioavailability of itraconazole, prescribed in the form of capsules, is higher when taken with food, and in the form of a solution - on an empty stomach. Peak blood concentrations of fluconazole are reached after 1–2 hours, and ketoconazole and itraconazole after 2–4 hours.

Fluconazole is characterized by a low degree of binding to plasma proteins (11%), while ketoconazole and itraconazole bind to proteins by almost 99%.

Fluconazole and ketoconazole are relatively evenly distributed in the body, creating high concentrations in various organs, tissues and secrets. Fluconazole crosses the BBB and the blood-brain barrier. Levels of fluconazole in CSF in patients with fungal meningitis make up 52–85% of plasma concentration. Ketoconazole passes poorly through the BBB and creates very low concentrations in the CSF.

Itraconazole, being highly lipophilic, is distributed mainly in organs and tissues with a high fat content: liver, kidneys, omentum. It can accumulate in tissues that are particularly prone to fungal infections, such as skin (including the epidermis), nail plates, lung tissue, genitals, where its concentration is almost 7 times higher than in plasma. In inflammatory exudates, itraconazole levels are 3.5 times higher than plasma levels. At the same time, itraconazole practically does not penetrate into "aqueous" media - saliva, intraocular fluid, CSF.

Ketoconazole and itraconazole are metabolized in the liver, mainly excreted in the digestive tract. Itraconazole is partially excreted with the secretion of the sebaceous and sweat glands of the skin. Fluconazole is only partially metabolized, excreted by the kidneys mainly unchanged. The half-life of ketocazole is 6–10 hours, itraconazole is 20–45 hours, and does not change with renal failure. The half-life of fluconazole is 30 hours, with renal failure it can increase up to 3-4 days.

Itraconazole is not removed from the body during hemodialysis, the concentration of fluconazole in plasma during this procedure is reduced by 2 times.

Topical azoles create high and fairly stable concentrations in the epidermis and underlying affected skin layers, and the created concentrations are superior to BMD for the main fungi that cause skin mycoses. The most long-lasting concentrations are typical for bifonazole, whose half-life from the skin is 19–32 hours (depending on its density). Systemic absorption through the skin is minimal and has no clinical significance. With intravaginal administration, absorption may be 3–10%.

Adverse reactions

Common to all system azoles

Gastrointestinal tract: abdominal pain, impaired appetite, nausea, vomiting, diarrhea, constipation.

CNS: headache, dizziness, drowsiness, visual impairment, paraesthesia, tremor, convulsions.

Allergic reactions: rash, pruritus, exfoliative dermatitis, Stevens-Johnson syndrome (more often with fluconazole).

Hematologic reactions: thrombocytopenia, agranulocytosis.
Liver: increased activity of transaminases, cholestatic jaundice.
Additionally for itraconazole
Cardiovascular system: congestive heart failure, arterial hypertension.
Liver: hepatotoxic reactions (rare)
Metabolic disorders: hypokalemia, edema.
Endocrine system: impaired corticosteroid production.
Additionally for ketoconazole
Liver: severe hepatotoxic reactions, up to the development of hepatitis.
Endocrine system: violation of the production of testosterone and corticosteroids, accompanied in men by gynecomastia, oligospermia, impotence, in women - menstrual irregularities.
Common to local azoles
With intravaginal administration: itching, burning, hyperemia and swelling of the mucous membrane, vaginal discharge, increased urination, pain during intercourse, burning sensation in the penis of the sexual partner.
Indications
Itraconazole
Dermatomycosis: epidermophytosis, trichophytosis, microsporia.
Pityriasis versicolor.
Candidiasis of the esophagus, skin and mucous membranes, nails, candida paronychia, vulvovaginitis.
Cryptococcosis
Aspergillosis (with resistance or poor tolerance to amphotericin B).
Pseudo-allesheriosis.
Theogyphomycosis.
Chromomycosis.
Sporotrichosis.
Endemic mycoses.
Prevention of mycosis in AIDS.
Fluconazole
Invasive candidiasis.
Candidiasis of the skin, mucous membranes, esophagus, candida paronychia, onychomycosis, vulvovaginitis.
Cryptococcosis
Dermatomycosis: epidermophytosis, trichophytosis, microsporia.
Pityriasis versicolor.
Sporotrichosis.
Pseudo-allesheriosis.
Trichosporosis.
Some endemic mycoses.
Ketoconazole
Candidiasis of the skin, esophagus, candida paronychia, vulvovaginitis.
Pityriasis versicolor (systemically and locally).
Dermatomycosis (topically).
Seborrheic eczema (topically).
Paracoccidioidosis.
Topical azoles
Candidiasis of the skin, oral cavity and pharynx, candidiasis vulvovaginitis.
Dermatomycosis: trichophytosis and epidermophytosis of smooth skin, hands and feet with limited lesions. With onychomycosis, they are ineffective.
Pityriasis versicolor.
Erythrasma
Contraindications

An allergic reaction to drugs of the azole group.
Pregnancy (systemically).
Breastfeeding (systemically).
Severe hepatic impairment (ketoconazole, itraconazole).
Age up to 16 years (itraconazole).
Warnings
Allergy. There is no evidence of cross-allergy to all azoles, however, in patients with an allergy to one of the azoles, other drugs in this group should be used with caution.
Pregnancy. Adequate studies of the safety of azoles in humans have not been conducted. Ketoconazole passes through the placenta. Fluconazole may interfere with estrogen synthesis. There is evidence of teratogenic and embryotoxic action of azoles in animals. Systemic use in pregnant women is not recommended. Intravaginal use is not recommended in the first trimester, in others - no more than 7 days. For external use, care must be taken.
Lactation. Azoles penetrate into breast milk, and fluconazole creates the highest concentration in it, close to the level in blood plasma. Systemic use of azoles in breastfeeding is not recommended.
Pediatrics. Adequate studies of the safety of itraconazole in children under 16 years of age have not been conducted, therefore it is not recommended for use in this age group. In children, the risk of hepatotoxicity of ketoconazole is higher than in adults.
Geriatrics. In older people, due to age-related changes in renal function, a disturbance in the excretion of fluconazole is possible, as a result of which a dosage regimen may be necessary.
Impaired renal function. In patients with renal failure, excretion of fluconazole is impaired, which may be accompanied by its cumulation and toxic effects. Therefore, with renal failure, correction of the dosage regimen of fluconazole is required. Periodic monitoring of creatinine clearance is required.
Impaired liver function. Due to the fact that itraconazole and ketoconazole are metabolized in the liver, in patients with impaired function, their cumulation and the development of hepatotoxic effects are possible. Therefore, ketoconazole and itra-conazole are contraindicated in such patients. When using these antimycotics, it is necessary to conduct regular clinical and laboratory monitoring (transaminase activity monthly), especially when prescribing ketoconazole. Strict control of liver function is also necessary in people with alcoholism, or receiving other drugs that can adversely affect the liver.
Heart failure. Itraconazole can contribute to the progression of heart failure, therefore, it should not be used to treat skin mycoses and onychomycoses in patients with impaired cardiac function.
Hypokalemia. With the appointment of itraconazole, cases of hypokalemia, which was associated with the development of ventricular arrhythmias, are described. Therefore, with its prolonged use, monitoring of the electrolyte balance is necessary.
Drug interactions
Antacids, sucralfate, anticholinergics, H2 blockers and proton pump inhibitors reduce the bioavailability of ketoconazole and itraconazole, as they reduce acidity in the stomach and disrupt the conversion of azoles to soluble forms.
Didanosine (containing the buffer medium necessary to increase the pH of the stomach and improve absorption of the drug) also reduces the bioavailability of ketoconazole and itraconazole.
Ketoconazole, itraconazole and, to a lesser extent, fluconazole are cytochrome P-450 inhibitors, therefore, they can disrupt the metabolism of the following drugs in the liver:
oral antidiabetic (chlorpropamide, glipizide, etc.), the result may be hypoglycemia. Strict control of blood glucose is required with possible dosage adjustment of antidiabetic drugs;
indirect anticoagulants of the coumarin group (warfarin, etc.), which can be accompanied by hypocoagulation and bleeding. Laboratory monitoring of hemostasis indices is necessary;
cyclosporine, digoxin (ketoconazole and itraconazole), theophylline (fluco-nazole), which can lead to an increase in their concentration in the blood and toxic effects. Clinical control and monitoring of drug concentrations are necessary with a possible correction of their dosage. There are recommendations for reducing the dose of cyclosporine by 2 times since the concomitant administration of itraconazole;

terfenadine, astemizole, cisapride, quinidine, pimozide. An increase in their concentration in the blood may be accompanied by a prolongation of the QT interval on the ECG with the development of severe, potentially fatal ventricular arrhythmias. Therefore, combinations of azoles with these drugs are unacceptable.

The combination of itraconazole with lovastatin or simvastatin is accompanied by an increase in their concentration in the blood and the development of rhabdomyolysis. During treatment with itraconazole, statins should be withdrawn.

Rifampicin and isoniazid increase the metabolism of azoles in the liver and lower their plasma concentrations, which can cause treatment failures. Therefore, azoles are not recommended for use in combination with rifampicin or isoniazid.

Carbamazepine reduces the concentration of itraconazole in the blood, which may be the reason for the inefficiency of the latter.

Cytochrome P-450 inhibitors (cimetidine, erythromycin, clarithromycin, etc.) can block the metabolism of ketoconazole and itraconazole and increase their concentration in the blood. The simultaneous use of erythromycin and itraco-nazole is not recommended in connection with the possible development of cardiotoxicity of the latter.

Ketoconazole disrupts the metabolism of alcohol and can cause disulfi-like reactions.

Application principles

Azole preparations should be taken with a sufficient amount of water when taken orally. Ketoconazole and itraconazole capsules should be taken during or immediately after a meal. With reduced acidity in the stomach, these preparations are recommended to be taken with drinks that have an acidic reaction (for example, with cola). It is necessary to observe intervals of at least 2 hours between doses of the indicated azoles and drugs that lower acidity (antacids, sucralfate, anticholinergics, H2 blockers, proton pump inhibitors).

During treatment with systemic azoles, you can not take terfenadine, asimizol, cisapride, pimozide, quinidine. In the treatment of itraconazole - lovastatin and simvastatin.

Do not drink alcoholic beverages during treatment.

Strictly observe the regimen and treatment regimens throughout the course of therapy, do not miss a dose and take it at regular intervals. If you miss a dose, take it as soon as possible; do not take if it is almost time for the next dose; do not double the dose. Withstand the duration of therapy.

Do not use expired drugs.

Do not use azoles systemically during pregnancy and lactation. Intravaginal use of azoles is contraindicated in the first trimester of pregnancy, in others - no more than 7 days. In the treatment of systemic azoles, reliable methods of contraception should be used.

Before starting intravaginal use of azoles, carefully study the instructions for use of the drug. During pregnancy, discuss with the doctor the possibility of using the applicator. Use only special swabs. Observe personal hygiene. It should be borne in mind that some intravaginal forms may contain latex-damaging ingredients. Therefore, one should refrain from using barrier contraceptives from latex during treatment and within 3 days after its completion.

Avoid getting topical preparations on the mucous membrane of the eyes, nose, mouth, open wounds.

In the treatment of foot mycoses, it is necessary to carry out antifungal treatment of shoes, socks and stockings.

Consult a doctor if improvement does not occur at the time indicated by the doctor or if new symptoms appear.

Allylamines

Allylamines, which are synthetic antimycotics, include terbinafine, used internally and topically, and naphthyphine, intended for local use. The main indications for the use of allylamines are dermatomycoses.

Mechanism of action

Allylamines have a predominantly fungicidal effect associated with impaired ergosterol synthesis. Unlike azoles, allylamines block earlier stages of biosynthesis, inhibiting the enzyme squalene epoxidase.

Activity spectrum

Allylamines have a wide spectrum of antifungal activity. Dermatomycetes (Epidermophyton spp., Trichophyton spp., Micro-sporum spp.), M. furfur, candida, aspergillus, histoplasma, blastomycetes, cryptococcus, sporotrix, and chromomycosis pathogens are sensitive to them.
Terbinafine is also active in vitro against a number of protozoa (some types of Leishmania and trypanosomes).
Despite the wide spectrum of activity of allylamines, only their effect on the causative agents of dermatomycosis is of clinical importance.
Pharmacokinetics
Terbinafine is well absorbed in the digestive tract, and the bioavailability is practically independent of food intake. Almost completely (99%) binds to plasma proteins. With its high lipophilicity, terbinafine is distributed into many tissues. Diffusing through the skin, and also standing out with the secrets of the sebaceous and sweat glands, creates high concentrations in the stratum corneum of the epidermis, the nail plates, hair follicles, and hair. It is metabolized in the liver, excreted by the kidneys. The elimination half-life is 11–17 hours, increases with renal and hepatic insufficiency.
When applied topically, systemic absorption of terbinafine is less than 5%, naphthyne - 4-6%. The preparations create high concentrations in various layers of the skin, exceeding the BMD for the main causative agents of dermatomycosis. The absorbed portion of naftifin is partially metabolized in the liver, excreted in the urine and feces. The elimination half-life is 2-3 days.
Adverse reactions
Terbinafine inside
Gastrointestinal tract: abdominal pain, impaired appetite, nausea, vomiting, diarrhea, changes and loss of taste.
CNS: headache, dizziness.
Allergic reactions: rash, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome.
Hematologic reactions: neutropenia, pancytopenia.
Liver: increased activity of transaminases, cholestatic jaundice, hepatic failure.
Others: arthralgia, myalgia.
Terbinafine topically, naphthyne
Skin: itching, burning, hyperemia, dryness.
Indications
Avoid getting topical preparations on the mucous membrane of the eyes, nose, mouth, open wounds.
In the treatment of foot mycoses, it is necessary to carry out antifungal treatment of shoes, socks and stockings.
Consult a doctor if improvement does not occur at the time indicated by the doctor or if new symptoms appear.
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Terbinafine is also active in vitro against a number of protozoa (some types of Leishmania and trypanosomes).
Despite the wide spectrum of activity of allylamines, only their effect on the causative agents of dermatomycosis is of clinical importance.
Pharmacokinetics

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Reverse reactions
Terbinafine inside
Gastrointestinal tract: abdominal pain, impaired appetite, nausea, vomiting, diarrhea, changes and loss of taste.
CNS: headache, dizziness.
Allergic reactions: rash, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome.
Hematologic reactions: neutropenia, pancytopenia.
Liver: increased activity of transaminases, cholestatic jaundice, hepatic failure.
Others: arthralgia, myalgia.
Terbinafine topically, naphthyne
Skin: itching, burning, hyperemia, dryness.
Indications
Dermatomycosis: epidermophytosis, trichophytosis, microsporia (with a limited lesion - topically, with a widespread - inside).
Mycosis of the scalp (inside).
Onychomycosis (inside).
Chromomycosis (inside).
Candidiasis of the skin (local).
Pityriasis versicolor (local).
Contraindications
An allergic reaction to drugs of the allylamine group.
Pregnancy.
Lactation.
Age up to 2 years.
Warnings
Allergy. There is no evidence of cross-allergy to terbinafine and naftifine, but patients with an allergy to one of the drugs should use the other with caution.
Pregnancy. Adequate safety studies of allylamines have not been conducted. Use in pregnant women is not recommended.
Lactation. Terbinafine passes into breast milk. Use in breast-feeding is not recommended.
Pediatrics. Adequate safety studies in children under 2 years of age have not been conducted, so it is not recommended to use in this age group.
Geriatrics. In older people, due to age-related changes in kidney function, terbinafine excretion may be impaired, as a result of which a dosage regimen may need to be adjusted.
Impaired renal function. In patients with renal failure, the excretion of terbinafine is impaired, which may be accompanied by its cumulation and toxic effects. Therefore, with renal failure, correction of the dosing regimen of terbinafine is required. Periodic monitoring of creatinine clearance is necessary.
Impaired liver function. Possible increased risk of hepatotoxicity of terbinafine. Adequate clinical and laboratory monitoring is required. With the development of severe impaired liver function during treatment with terbinafine, the drug should be discontinued. Strict control of liver function is necessary in alcoholism and in people receiving other drugs that can adversely affect the liver.
Drug interactions

Inducers of microsomal liver enzymes (rifampicin, etc.) can enhance the metabolism of terbinafine and increase its clearance.
Inhibitors of microsomal liver enzymes (cimetidine, etc.) can block the metabolism of terbinafine and lower its clearance.
In the situations described, correction of the dosage regimen of terbinafine may be required.
Application principles
Terbinafine can be taken orally, regardless of the meal (on an empty stomach or after eating), should be washed down with plenty of water.
Do not drink alcoholic beverages during treatment.
Strictly observe the regimen and treatment regimens throughout the course of therapy, do not miss a dose and take it at regular intervals. If you miss a dose, take it as soon as possible; do not take if it is almost time for the next dose; do not double the dose. Withstand the duration of therapy. Irregular use or premature termination of treatment increases the risk of relapse.
Do not use expired drugs.
Do not use allylamines during pregnancy and lactation.
Avoid getting topical preparations on the mucous membrane of the eyes, nose, mouth, open wounds.
In the treatment of foot mycoses, it is necessary to carry out antifungal treatment of shoes, socks and stockings.
Consult a doctor if improvement does not occur at the time indicated by the doctor or if new symptoms appear.
Drugs of different groups
Griseofulvin
One of the earliest natural antimycotics with a narrow spectrum of activity. It is produced by the fungus of the genus Penicillium. It is used only for dermatomycoses caused by dermatomycetes.
Mechanism of action
It has a fungistatic effect, which is due to inhibition of the mitotic activity of fungal cells in metaphase and impaired DNA synthesis. Selectively accumulating in the "prokeratin" cells of the skin, hair, nails, griseofulvin gives the newly formed keratin resistance to fungal infection. The cure occurs after a complete replacement of infected keratin, so the clinical effect develops slowly.
Activity spectrum
Dermatomycetes are sensitive to griseofulvin (Epidermophyton spp., Trichophyton spp., Microsporum spp.). Other mushrooms are stable.
Pharmacokinetics
Griseofulvin is well absorbed in the digestive tract. Bioavailability increases when taken with fatty foods. The maximum concentration in the blood is observed after 4 hours. High concentrations are created in the keratin layers of the skin, hair, and nails. Only a small fraction of griseofulvin is distributed into other tissues and secrets. Metabolized in the liver. It is excreted in feces (36% in active form) and in urine (less than 1%). The elimination half-life is 15–20 hours, with renal failure it does not change.
Adverse reactions
Gastrointestinal tract: abdominal pain, nausea, vomiting, diarrhea.
Nervous system: headache, dizziness, insomnia, peripheral neuritis.
Skin: rash, itching, photodermatitis.
Hematologic reactions: granulocytopenia, leukopenia.
Liver: increased activity of transaminases, jaundice, hepatitis.
Other: oral candidiasis, lupus-like syndrome.
Indications
Dermatomycosis: epidermophytosis, trichophytosis, microsporia.
Mycosis of the scalp.
Onychomycosis.
Contraindications
Allergic reaction to griseofulvin.
Pregnancy.

Impaired liver function.
Systemic lupus erythematosus.
Porphyria.
Warnings
Pregnancy. Griseofulvin crosses the placenta. Adequate studies of safety in humans have not been conducted. There is evidence of teratogenic and embryotoxic effects in animals. Use in pregnant women is not recommended.
Lactation. Adequate safety data are not available. Use during breastfeeding is not recommended.
Geriatrics. In older people, due to age-related changes in liver function, an increase in the risk of hepatotoxicity of griseofulvin is possible. Strict clinical and laboratory monitoring is required.
Impaired liver function. Due to the hepatotoxicity of griseoful-wine, regular clinical and laboratory monitoring is necessary when it is prescribed. In case of impaired liver function, it is not recommended to prescribe. Strict control of liver function is also necessary in alcoholism and in people receiving other drugs that can adversely affect the liver.
Drug interactions
Inducers of microsomal liver enzymes (barbiturates, rifampicin, etc.) can enhance the metabolism of griseofulvin and weaken its effect.
Griseofulvin induces cytochrome P-450, therefore, it can enhance liver metabolism and, therefore, weaken the effect:
indirect anticoagulants of the coumarin group (prothrombin time control is necessary, dose adjustment of the anticoagulant may be required);
oral antidiabetic drugs, (control of blood glucose with a possible dose adjustment of antidiabetic drugs);
theophylline (monitoring its concentration in the blood with possible dose adjustment);
estrogen-containing oral contraceptives. This can be accompanied by intermenstrual bleeding, amenorrhea, and the occurrence of an unplanned pregnancy. Therefore, during treatment with griseofulvin and within 1 month after its completion, it is necessary to use additional or alternative methods of contraception.
Griseofulvin enhances the effects of alcohol.
Application principles
Griseofulvin should be taken orally during or immediately after a meal. If you are using a low fat diet, you should take griseofulvin with 1 tablespoon of vegetable oil.
Do not drink alcoholic beverages during treatment.
Strictly observe the regimen and treatment regimens throughout the course of therapy, do not miss the dose and take it at regular intervals. If you miss a dose, take it as soon as possible; do not take if it is almost time for the next dose; do not double the dose. Withstand the duration of therapy. Irregular use or premature termination of treatment increases the risk of relapse.
Do not use expired drugs.
Use caution in case of dizziness.
Do not undergo direct insolation.
Do not use griseofulvin during pregnancy and lactation.
During treatment with griseofulvin and for 1 month after the end, do not use only estrogen-containing oral preparations for contraception. Be sure to use additional or alternative methods.
In the treatment of foot mycoses, it is necessary to carry out antifungal treatment of shoes, socks and stockings.
Consult a doctor if improvement does not occur at the time indicated by the doctor or if new symptoms appear.
Potassium iodide
As an antifungal drug, potassium iodide is used orally in the form of a concentrated solution (1.0 g / ml). The mechanism of action is precisely unknown.
Activity spectrum
Active against many fungi, but the main clinical value is the effect on S.schencii.
Pharmacokinetics

Quickly and almost completely absorbed in the digestive tract. It is distributed predominantly into the thyroid gland. It also accumulates in the salivary glands, the mucous membrane of the stomach, and mammary glands. Concentrations in saliva, gastric juice and breast milk are 30 times higher than in blood plasma. Excreted mainly by the kidneys.
Adverse reactions
Gastrointestinal tract: abdominal pain, nausea, vomiting, diarrhea.
Endocrine system: changes in thyroid function (appropriate clinical and laboratory monitoring is necessary).
Iodism reactions: rash, rhinitis, conjunctivitis, stomatitis, laryngitis, bronchitis.
Others: lymphadenopathy, swelling of the submandibular salivary glands.
With the development of severe HP, the dose should be reduced or the dose should be temporarily discontinued. After 1-2 weeks, treatment can be resumed at lower doses.
Indications
Sporotrichosis: cutaneous, cutaneous-lymphatic.
Contraindications
Hypersensitivity to iodine preparations.
Hyperthyroidism.
Thyroid tumors.
Warnings
Pregnancy. Adequate safety studies have not been conducted. Use in pregnant women is possible only in cases where the intended benefit prevails over the risk.
Lactation. Concentrations of potassium iodide in breast milk are 30 times higher than plasma levels. During treatment, breast-feeding should be discontinued.
Drug interactions
When combined with potassium preparations or potassium-sparing diuretics, hyperkalemia may develop.
Patient Information
Potassium iodide should be taken orally after a meal. A single dose is recommended to be diluted with water, milk or fruit juice.
Strictly observe the regimen and treatment regimens throughout the course of therapy, do not miss the dose and take it at regular intervals. If you miss a dose, take it as soon as possible; do not take if it is almost time for the next dose; do not double the dose. Withstand the duration of therapy. Irregular use or premature termination of treatment increases the risk of relapse.
Consult a doctor if improvement does not occur at the time indicated by the doctor or if new symptoms appear.
Amorolfin
Synthetic antimycotic for topical use (in the form of nail polish), which is a derivative of morpholine.
Mechanism of action
Depending on the concentration, it can have both fungistatic and fungicidal effects due to a violation of the structure of the cell membrane of fungi.
Activity spectrum
It is characterized by a wide spectrum of antifungal activity. Candida spp., Dermatomycetes, Pityrosporum spp., Cryptococcus spp. Are sensitive to it. and a number of other mushrooms.
Pharmacokinetics
When applied topically, it penetrates well into the nail plate and the nail bed. Systemic absorption is negligible and has no clinical significance.
Adverse reactions
Local: burning, itching or irritation of the skin near the nail, nail discoration (rarely).
Indications
Onychomycosis caused by dermatomycetes, yeast and molds (if no more than 2/3 of the nail plate is affected).
Prevention of onychomycosis.
Contraindications

Hypersensitivity to amorolfine.
Pregnancy.
Lactation.
Age to 6 years.
Warnings
Pregnancy. Adequate safety studies have not been conducted. Use in pregnant women is not recommended.
Lactation. Adequate safety data are not available. Use during breastfeeding is not recommended.
Pediatrics. Adequate safety studies have not been conducted. Use in children under 6 years is not recommended.
Drug interactions
Systemic antimycotics enhance the therapeutic effect of amorolfin.
Patient Information
Carefully read the instructions for use.
Strictly observe the regimen and treatment regimens throughout the course of therapy.
Withstand the duration of therapy. Irregular use or premature termination of treatment increases the risk of relapse.
During treatment, it is not recommended to use cosmetic nail polish and false nails.
When working with organic solvents, protective impervious gloves must be worn.
Regularly grind all changed nail tissue. Nail files used to treat affected nails should not be used to treat healthy nails.
Consult a doctor if improvement does not occur at the time indicated by the doctor or if new symptoms appear.
Observe storage rules.
Cyclopirox
A synthetic topical antifungal drug with a wide spectrum of activity. The mechanism of action is not installed.
Activity spectrum
Candida spp., Dermatomycetes, M.furfur, Cladosporium spp. Are sensitive to cyclopirox. and many other mushrooms. It also acts on some gram-positive and gram-negative bacteria, mycoplasmas and trichomonads, but this does not have practical value.
Pharmacokinetics
When applied topically, it quickly penetrates into various layers of the skin and its appendages, creating high local concentrations 20-30 times higher than BMD for the main pathogens of superficial mycoses. When applied to large areas, it can be slightly absorbed (1.3% of the dose is found in the blood), binds to plasma proteins by 94–97%, and is excreted by the kidneys. The half-life is 1.7 hours.
Adverse reactions
Local: burning, itching, irritation, peeling or flushing of the skin.
Indications
Dermatomycosis caused by dermatomycetes, yeast and mold fungi.
Onychomycosis (if no more than 2/3 of the nail plate is affected).
Fungal vaginitis and vulvovaginitis.
Prevention of fungal infections of the feet (powder in socks and / or shoes).
Contraindications
Hypersensitivity to cyclopirox.
Pregnancy.
Lactation.
Age to 6 years.
Warnings
Pregnancy. Adequate safety studies have not been conducted. Use in pregnant women is not recommended.
Lactation. Adequate safety data are not available. Use during breastfeeding is not recommended.

Pediatrics. Adequate safety studies have not been conducted. Use in children under 6 years is not recommended.
Drug interactions
Systemic antimycotics enhance the therapeutic effect of cyclopirox.
Application principles
Carefully study the instructions for use of the prescribed dosage form of the drug.
Strictly observe the regimen and treatment regimens throughout the course of therapy.
Withstand the duration of therapy. Irregular use or premature termination of treatment increases the risk of relapse.
During treatment, it is not recommended to use cosmetic nail polish and false nails.
When working with organic solvents, protective impervious gloves must be worn.
In the treatment of onychomycosis, all altered nail tissue should be regularly stitched. The files used to treat affected nails cannot be used to treat healthy nails.
Avoid contact with solution and cream in the eyes.
The vaginal cream must be injected deep into the vagina using the attached disposable applicators, preferably at night. A new applicator is used for each procedure.
Table. Antifungal drugs.
Main characteristics and features applied
Boric Acid (Acidum Boricum)
Mechanism of action Boric acid has antibacterial, antifungal, antiparasitic and astringent effects. The acid coagulates proteins of the microbial cell, disrupts the permeability of the cell membrane, a 2-4 percent solution of boric acid delays the growth and development of bacteria, 5% inhibits the processes of phagocytosis. Preparations containing boric acid also have insecticidal and irritating effects.
Pharmacokinetics Boric acid penetrates well through the skin and mucous membranes, especially in young children, can accumulate in tissues, is slowly excreted from the body - about 50% is excreted in the urine in 12 hours, the remainder is excreted within 5-7 days. With repeated applications, it accumulates.
Place in therapy. Boric acid in the form of an ointment can be used for pediculosis. A 3% solution is used for lotions with weeping eczema, dermatitis, 0.5-3% alcohol solutions are used to treat the affected areas with pyoderma, eczema, diaper rash. A 10% solution in glycerin is used for diaper rash and colpitis. Boric acid is part of a number of combined preparations.
Tolerance, side effects. When using boric acid, especially in case of overdose, prolonged use and impaired renal function, acute and chronic toxic reactions (nausea, vomiting, diarrhea, skin rash, desquamation of the epithelium, headache, confusion, convulsions, oliguria, in rare cases - a shock condition).
Contraindications The use of boric acid is contraindicated in patients with impaired renal function, nursing mothers for treatment of the mammary glands, children (especially newborns), pregnant women and individuals with individual intolerance, as well as with damage to large areas of the skin. Since boric acid is well absorbed when it enters the mucous membranes, it is not recommended to rinse the cavities with it.
SOLUTION IODINE 5% (SOLUTIO IODI SPIRITUOSA)
Mechanism of action. Iodine preparations have a fungicidal effect on many fungi, but the main clinical value is their activity against Sporotrix schenckii. In addition, they have a wide spectrum of antimicrobial activity against gram-positive cocci and gram-negative bacteria, viruses and protozoa. Iodine ions are able to oxidize phospholipids of the cell wall of fungi, leading to the appearance of gaps in the cell membrane, as a result of which the transmembrane ion potential is violated. The fungal cell dies due to the release of K + ions and the entry of Na + ions with water. Elemental iodine binds to the amino groups of cellular proteins and forms iodamines, causing protein coagulation and cell death.
Pharmacokinetics Iodine alcohol solution is applied externally. When in contact with the skin or mucous membranes, 30% turns into iodides, the rest - into active iodine. When applied to vast surfaces, it is absorbed in significant quantities.

Place in therapy. Iodine alcohol solution is used in dermatovenerology for fungal and viral infections of the skin, trichomoniasis.
Contraindications When applied topically, iodine can cause a chemical burn of the skin or mucous membranes, symptoms of iodism (acne, wines, angioedema, conjunctivitis, lacrimation, salivation, stomatitis, rhinitis, laryngitis, bronchitis).
Iodine preparations are contraindicated in case of their individual intolerance, urticaria, furunculosis, acne, Dühring's herpetiform dermatitis, hyperthyroidism, adenoma and other tumors of the thyroid gland, severe kidney diseases, renal failure, pregnancy, breast-feeding, during the neonatal period.
Iodine is chemically incompatible with essential oils, ammonia solutions, mercury preparations, and oxidizing agents. With the simultaneous use of 2 or more iodine preparations, the risk of side effects increases.

The purpose of the lesson.

A Assimilate the pharmacokinetics, pharmacodynamics and pharmacotoxicodynamics of PRO-TYPHO-FOAM drugs
1. General characteristics.
2. Classification:
A. Drugs for the treatment of dermatomycosis:
• azoles (for topical use - clotrimazole, miconazole, for systemic - ketoconazole, intraconazole, etc.);
• antibiotics (griseofulvin, etc.);
• acids (salicylic, benzoic);
• dyes (brilliant green, methylene blue, fucorcin);
• iodine preparations (alcohol iodine solution, potassium iodide);
• preparations of various chemical groups (undecine, zincundane, mycoseptin, nitrofungin, naftifin, cyclopirox, terbina-fin, tolnaftate, etc.)
B. Drugs for the treatment of candidiasis:
• polyene antibiotics (nystatin, levorin, mycoheptin, topically amphotericin B);
• azoles (for topical use of clotrimazole, miconazole; for systemic use - ketoconazole, etc.);
• representatives of other groups (decamine, cyclopirox, etc.)
B. Preparations for the treatment of systemic mycoses: polyene antibiotics
II generation (local, course 3-4 days): econazole, thioconazole;
III generation (both for local and systemic therapy, 1 time per day): ketoconazole (nizoral), sulfonazole, oxyconazole;
2) Derivatives of triazole: fluconazole (diflucan), itracon-zol, fluoronazole, terconazole (fungistat).
4. The mechanisms of action of individual groups. Undesirable effects.
ANTI-VIRAL DRUGS
Antiviral Classification
I. Drugs acting on extracellular forms of the virus:
- oxolin;
- arbidol-lens.
II. Viropexis inhibitors (M2-channel blockers):
- amantadine (midantane, symmetrel, verigit-K, adamantine, amandine, amantane, an-tadine);
- remantadine (rimantadine, meradan, algir, polirem).
III. Neuraminidase Inhibitors:
- zanamivir (relenza);
- oseltamivir (tamiflu).
IV. Drugs that inhibit the reproduction of the virus:
1. Inhibitors of DNA (RNA) -polymerase viruses:
- acyclovir (acigerpine, acyclovir, vivorax, herpevir, herperax, herpesin, zovirax, xorovir, lovir, medovir, supra-viran, cycloviral, sedico, citivir);
- ganciclovir (cymeven);
- vidarabine;
- ribavirin (virazole, rebetol, Meduna ribavirin, ribamidil), etc.
2. Reverse transcriptase inhibitors:

a) . Abnormal nucleoside:
- abacavir (ziagen);
- didanosine (videx);
- lamivudine (Zeffix, epivir Three Ti See);
- stavudine (zerit) -,
- zalcitobin (hivid);
- zidovudine (retrovir AZ and Ti, thymazide, azidothymidine).
b). Preparations of non-nucleoside structure:
- efavirenz;
- nevirapine (viramune).
3. Inhibitors of proteases:
- aprenavir (agenerase);
- indinavira sulfate (crixivan);
- saquinavir (inviraz, fortovaz).
V. Inhibitory maturation of viruses:
- metisazon (marboran, kemoviran, viruzona)
VI. Interferons and inducers of interferons.
Classification of antiviral drugs by origin:
• nucleoside analogues - zidovudine, acyclovir, vidarabine, ganciclovir, trif-luridine;
• derivatives of lipids - saquinavir;
• derivatives of adamantane - midantane, remantadine;
• derivatives of ladol carbolic acid - foscarnet;
• thiosemicarbazone derivatives - methisazone;
• drugs produced by macroorganism cells - interferons.
The distribution of antiviral drugs depending on the direction of their action.
DNA viruses:
• herpes simplex virus - acyclovir, vilaciclovir, foscarnet, vidarabine, trifluridine;
• cytomegalovirus-ganciclovir, foscarnet;
• virus of herpes zoster and chicken pox - acyclovir, foscarnet;
• smallpox virus - methisazane;
• hepatitis B virus and C-interferons.
RNA viruses:
• human immunodeficiency virus - zidovudine, didanosine, zalcitabine, saqui-navir, ritonavir;
• influenza virus type A - midantan, remantadine;
• influenza virus types B and A-arbidol;
• respiratory syncytial virus-ribamidil.
Antiviral drugs can be divided, depending on the type of disease, into groups:
• Influenza drugs (remantadine, oxolin, etc.)
• Antiherpetic and anti-cytomegalovirus (tebrofen, riodoc-sleep, etc.)
• Medicines that affect the human immunodeficiency virus (azidothymidine, phosphanoformate)
• Broad-spectrum drugs (interferons and interferonogens)
Mashkovsky M.D. proposed the following classification of antiviral drugs:
A) Interferon
• Leukocyte interferon from human blood donation.
• Purified α-interferon obtained from donated blood.
• Recombinant α2-interferon produced by the bacterial strain of pseudomonad, in the genetic apparatus of which the human leukocyte α2-interferon gene is integrated.
• Recombinant interferon alfa-2v.
• Recombinant human β1-interferon.
B) Inductors of interferon:
• Half-dan - a powder or porous mass of white color, has immuno-stimulating activity, ie ability to stimulate the production of endogenous interferon and has an antiviral effect.
• Neovir - an action similar to that of a half-dan.

C) Derivatives of amantadine and other groups of synthetic compounds
• Remantadine. It is used as an anti-Parkinsonian drug, it indicates a prophylactic effect against influenza infection caused by certain strains of viruses.
• Adapromin. Close to remantadine.
• Datiforin. Similar to remantadine.
• Arbidol. An antiviral drug that has an inhibitory effect on influenza A and B.
• Bonaphton. It has antiviral activity against herpes simplex virus and some adenoviruses.
• Oxolin. It has virucidal activity, is effective for viral diseases of the eyes, skin, viral rhinitis; It has a preventive effect in case of flu.
• Tebrofen. It is used as an ointment for viral diseases of the eyes, as well as for skin diseases of a viral or presumed viral etiology. It can also be used for the treatment of flat warts in children.
• Riodoxol. It has antiviral optimality and has an antifungal effect.
9. Florenal. Opens a neutralizing effect against viruses.
10. Metisazon. Suppresses reproduction of the virus of the main group: it has prophylactic activity against smallpox virus and facilitates the course

post-vaccination complications, delays the spread of the skin process, contributes to a faster drying of effeora. There is evidence of the effectiveness of metisazon in the treatment of recurrent genital herpes.

D) Nucleosides:

• Idoxuridine. Applied with keratitis in ophthalmology.

• Acyclovir. Effective against herpes simplex viruses and herpes zoster. It has an immunostimulating effect.

• Ganciclovir. Compared to acyclovir, ganciclovir is more effective and, in addition, acts not only on the herpes virus, but also on cytomegalovirus.

• Famciclovir. It has the same functions as ganciclovir.

• Ribamidil. Ribamidil, like acyclovir, has antiviral activity. Inhibits the synthesis of viral DNA and RNA.

• Zidovudine. An antiviral drug that inhibits the replication of retroviruses, including human immunodeficiency virus (HIV).

D) Antiviral drugs of plant origin:

• Flacoside. Obtained from the velvet leaves of the Amur family of root. The drug is effective against DNA viruses.

• Alpidarin. Obtained from Alpine Koneermena grass and yellowing penny, legume family. Effective against herpes DNA viruses. The inhibitory effect on the reproduction of the herpes simplex virus is manifested mainly in the early stages of the development of the virus.

• Cholepin. Purified extract from part of the plant mepedecium penny, legume family. It has antiviral activity against DNA-containing viruses of the herpes group.

• Ligosin. Used for herpetic skin diseases.

• Gossypol. Product obtained from the processing of cotton seeds or from the roots of cotton, the family of malvaceae. The drug has activity against various strains of viruses, including dermatotropic strains of the herpes virus. It has a weak effect on gram-positive bacteria.

According to the sources of production and chemical nature, they are divided into the following groups:

1) interferons (endogenous origin and obtained by genetic engineering, their derivatives and analogues);

2) synthetic compounds (amantadines, arbidol, bonafton, etc.);

3) substances of plant origin (alpizarin, flacoside, etc.).

B Be able to:

1 Select the necessary drugs for a specific patient with the indicated pathology, highlight the criteria for therapeutic efficacy and safety;

2 Prescribe combination therapy;

3 To justify and provide urgent differential medical assistance with:

1) acute systemic mycoses;

2) acute systemic dermatomycosis

Control questions of the studied topic.

1 Classification of antimycotic drugs by chemical structure

2 Features of the classification of antiviral drugs

3 What are the main pharmacodynamic effects of antimycotic drugs? Explain their clinical significance.

5 What is the general mechanism for the development of the pharmacodynamic effects of antiviral drugs?

7 What are the main mechanisms of action of antiviral drugs?

8. What are the basic principles for choosing antiviral drugs and antimycotic drugs?

9 What are the criteria for evaluating the effectiveness of their application?

20 What methods and criteria for determining the safety of treatment of antiviral drugs and antimycotic drugs do you know ?.

Enumeration of practical work.

A**. Homework.**

1 Write down recipes for LR (tablets and / or capsules, ampoules) presented in the section “Purpose of the lesson”, indicate the point of application of the action, the spectrum of diseases (syndromes) indicated for their purpose.

2 Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1 To supervise a thematic patient in the ward.

2 To study the working history of the disease (subjective, objective - physical and laboratory-instrumental data, conclusions of consultants) and a list of medical appointments.

3 Write a protocol of independent work on the selection and selection of a basic drug for the patient to be supervised and the rationale for the appointment of combined drug therapy.

4 To highlight the signs in a subjective and objective study of the patient, characterizing the presence of the inflammatory process, the main syndromes characteristic of inflammation, fever and pain; write a clinical diagnosis of the disease.

5 Identify the group of drugs needed by the patient.

6 Based on the theoretical pharmacodynamics data and own observations, select specific drugs for the patient to be supervised.

7 Choose the optimal dosage, pathogenesis of the disease, route of administration, age, body weight.

8 Select clinical and instrumental criteria for assessing the effectiveness and safety of the applied drugs, carry out an assessment.

9 To justify the need for combination therapy and suggest possible options for a safe combination of drugs.

10 Make a forecast of side effects of drugs prescribed to the patient and outline a plan for identifying them in the early stages.

11 Justify the duration of the main and maintenance therapy.

12 Draw up a plan for urgent medical care for: acute rheumatoid arthritis; fit of gout.

Control of the intermediate level of knowledge.

The solution of situational problems.

1. Hvoromu L., 20 rock, from the GDVZ (pharyngitis, rhinitis) and increased temperature of up to 390C for the prevention of bacterial accelerated signs of biseptol.

Evaluate the variability of tactics. Your recommendations.

2. A 42-year-old patient was brought to the department with complaints of fever up to 39.8 ° C, cough with a small amount of sputum, sweating. An objective examination: in the lungs below the scapula, the area of blunting of percussion sound, hard breathing, moist small-bubbling rales, fungi of the genus Candida were found in the analysis of sputum.

What is your diagnosis? Prescribe therapy, name the drug 1 line, what antifungal drugs you offer.

3. The patient is 23 years old, with hospital-acquired right-sided pneumonia receiving treatment with benzylpenicillin at a dose of 12 million units. per day, on the third day, subfebrile temperature, dullness of percussion sound, respectively, of the lower lobe of the lung, moist sonorous rales are maintained.

In complex therapy, prescribe the optimal antifungal drug

4. A 32-year-old woman was admitted to the treatment department with complaints of an increase in body temperature up to 38.50 C, cough with a small amount of yellow sputum, sweating. Objectively: in the lungs to the left below the angle of the scapula, the area of dullness of percussion sound, weakened vesicular breathing, moist small-bubble rales. The doctor on duty prescribed a patient benzylpenicillin sodium i / m 4 times a day for 2500000 units.

Formulate a preliminary diagnosis. Assign the necessary follow-up examination to the patient. Evaluate the medical tactics of the doctor on duty. If necessary, adjust the pharmacotherapy. Specify methods for monitoring the effectiveness of treatment in a hospital. Prescribe an antimycotic drug

TESTS

1. Antifungal action among the listed antibiotics has:

A. Kefzol

B. Fluconazole

C. Rifampicin

D. Streptomycin

E. Lincomycin

2. The patient after prolonged use of the drug prescribed for acute respiratory illness, the following symptoms occurred: headache, dizziness, tinnitus, nausea, pain in the epigastric region. What drug could cause a similar clinical picture?

A. Vitamin C.

B. Acetylsalicylic acid.

C. Naphthyzine.

D. Bromhexine.

E. Midantan.

3. All of these drugs interfere with DNA transcription except

A. - doxorubicin

B Tamoxifen

C. cyclophosphamide

D. mechlorethamine

E. cisplatin

4. Myelosuppression is a very serious toxicity of all drugs except:

A. vinblastine

B. cyclophosphamide

C. cytarabine

D. mechlorethamine

E. Acyclovir

5. Antiviral drugs with immunostimulating effect

A.! Acyclovir

B. Remantadine.

C. Adapromin

D. Datiforin

E. Zidovudine

6. Antiviral drugs of plant origin:

A. Flacoside

B. Ganciclovir.

C. Famciclovir.

D. Ribamidil.

E. Zidovudine.

7. Onychomycosis is a disease that manifests itself:

A. Fungal infection of the fingernails

B. Candidiasis of the inguinal folds

C. Black dots on broken hair

D. Erosions and cracks in the corners of the mouth

E. Dry cough, headache, hyperthermia.

8. Choose a drug for the treatment of candidal lesions of the mucous membranes of the genital organs:

A. Nystatin

B. Fluconazole

C. Metronidazole

D. Tetracycline

E. Linex

9. Patient 26 years old with common herpes. Select a medication for the treatment of this patient:

A. Acyclovir

B. Fluconazole

C. Levofloxacin

D. Metronidazole

E. All of the above drugs for complex therapy are used.

10. Which of the following drugs is used for helminthiases?

A. Amikacin

B. Diakarb

C. Amphotericin B

D Levamisole

E. Nitroxoline

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF MEDICINES IN ANESTHESIOLOGY AND REANIMATOLOGY

Relevance of the topic

Anesthesiology (other Greek ἀν- - negative prefix, αἴσθησις - sensitivity and λόγος - teaching) - a branch of medicine that studies the means and methods of providing anesthesia (that is, loss of sensitivity, including pain) for various acute pain syndromes , shock conditions, injuries, surgical interventions.

Anesthesiology is closely connected with resuscitation, as the anesthesiologist also has to solve the problem of maintaining life support parameters (respiration, blood circulation) during anesthesia.

Motivational characteristic of the topic

Anesthesiology is a specialty that requires very serious theoretical training and continuous practical improvement.

In 1846, it was proved that with the help of ether, you can turn off consciousness and at the same time eliminate the reaction to pain caused by the operation. This was done on October 16 by Thomas Morton. Such a state was called by N. I. Pirogov "insensitivity." The terms “anesthesia” and “general anesthesia” were widely used for its designation. Often they are used as synonyms, but there are differences between them.

General anesthesia is an artificially induced reversible state of the body, in which mental reactions are turned off and the reaction to pain and other harmful irritations is reduced or absent.

Anesthesia is a deeper inhibition of body cells, and not just nerve cells. This condition is also reversible if the anesthesia was not excessively deep. But still N.I. Pirogov wrote that from deep anesthesia to death is one step.

That is why it is better to use the term "general anesthesia" - the elimination of pain, discomfort and prevention of other harmful effects of the operation - uncomfortable position, immobility, blood loss, respiratory depression, etc.

To achieve the state of general anesthesia, pharmacological preparations, some physical agents (electric current, cold) and even hypnosis are used. Such a variety of means creates difficulties: to indicate the characteristics of a particular anesthesia method, the name of the drug is used - general anesthesia with ether, fluorotane, ketamine, and the way this substance is introduced into the body. For example, if a substance is injected into a vein, then such anesthesia is called intravenous, if through “the lungs, it is called inhalation (from Latin, ingalarae - I inhale).

Indeed, in many ways, the features of general anesthesia are determined by both the substance (general anesthetic) and the method of its administration. With the inhalation method, it is easier to control the concentration of the substance and thereby the depth of general anesthesia. But with the intravenous method, anesthesia occurs more smoothly, it is pleasant for the patient.

The most important unit of general anesthesia, based on the following principles: how is the state of general anesthesia achieved - with the help of one pharmacological substance or a combination of several substances, several methods? Does this combination satisfy the requirements of “ideal” anesthesia? Whether it is general anesthesia alone or a combination of drugs, these requirements are as follows. General anesthesia should

1) provide the best conditions for surgical intervention: create good muscle relaxation, prevent a reaction to pain and other irritations of the central, autonomic and peripheral nervous system, reduce blood loss, maintain the defenses of the patient;

2) to be safe for the patient, that is, not to exert harmful effects, but, on the contrary, to protect the body from the harmful factors of operations;

3) to be controlled, that is, if necessary, to quickly provide deeper inhibition of reflexes, to relax muscles well, to lower or increase blood pressure, etc. But if necessary, quickly restore consciousness and protective reflexes, for example, coughing.

It is clear that to fulfill all these requirements with a single substance is very difficult. However, at present, for one reason or another, it is necessary to carry out general anesthesia using one general anesthetic. This is called monoanesthesia (from Latin mono - the only one), or mononarcosis.

However, in most cases, to achieve these goals, a combination of substances and methods is used, for example, nitrous oxide and fluorotane, barbiturates and ether. Even more often with large complex operations, the introduction of a general anesthetic is combined with drugs that do not affect the central nervous system at all. Thus, a combination of a general anesthetic with special substances that interrupt the transmission of excitation from a nerve to a muscle is widespread. These substances are called muscle relaxants (muscle relaxants). They will be described in detail below.

Such anesthesia is called combined, or multicomponent. Consciousness and the reaction to pain with such anesthesia are turned off using general anesthetics, and muscle relaxation is achieved by other methods - using muscle relaxants and local anesthesia. In this case, a general anesthetic can be administered in small safe concentrations and successfully protect the patient from the harmful effects of the operation.

But still, general anesthesia is based on the effect of general anesthetics (narcotic substances). Therefore, in order to master combined combined anesthesia, it is necessary to perfectly master the technique of general anesthesia with the help of one general anesthetic - monoanesthesia.

It should be emphasized that general anesthesia with ether differs significantly from general anesthesia with fluorotan or sodium thiopental. But they have a main common feature - the stage of general anesthesia. Most clearly these stages are expressed during general anesthesia with ether.

Stage is a special period of general anesthesia, which differs in its clinical features - the effect on the nervous system, respiration, blood circulation - from other stages. These features are manifested in changes in reactions (reflexes): the reaction of the pupils to light, the size of the pupils, the reaction of the pupils to pain irritation, the features of lacrimation, the nature of the pulse, blood pressure and breathing, and the degree of muscle relaxation.

Currently, with any general anesthesia, there are 4 stages:

1) addiction;

2) excitement;

3) surgical;

4) awakening.

Some authors identify another stage of overdose. But it is only the final phase of the surgical stage, and its most severe signs - impaired breathing and blood circulation - can develop at any stage if complications arise.

Stage I - addiction, or analgesia.

At this stage, the body is saturated with a general anesthetic. Consciousness is saved and only at the end of the stage begins to blur. At the same time, the feeling of pain decreases. This part of the stage is called the phase of analgesia, which is well expressed under the action of ether. This stage is used for small operations, such as opening abscesses.

When using ether, stage I lasts from 3 to 8 minutes. Its duration largely depends on the preparation of the patient, the state of his central nervous system. At first, the patient may be agitated, hypersensitive to any irritants. Ether is an annoying substance. Sudden inhalation of its vapor can cause reflex respiratory arrest and even heart failure.

This stage I, which is long and fraught with complications, is a big drawback of general anesthesia with ether. Therefore, they try to bypass this stage and introduce other general anesthetics into the anesthesia, providing a faster, smoother and more pleasant for the patient introduction to the state of general anesthesia.

II stage - excitement.

As soon as consciousness is lost, the stage of excitement sets in. A typical manifestation of it is involuntary movements of arms and legs, sometimes incoherent cries of individual words. Vomiting may occur, and if the stomach has not been emptied before general anesthesia begins, then the vomit is ejected into the oral cavity, outward and aspirated into the airways. The stage of excitement is especially dangerous for patients with arterial hypertension, since blood pressure rises sharply at this time.

This stage is characteristic of general ether anesthesia. Excitation can be reduced by a good preparation of the patient. The stage of excitement is actually absent when using other drugs for general anesthesia - barbiturates, fluorotan. These substances are also used for the introductory period.

Stage III - surgical.

The stage begins after the end of arousal, and it is it that is the goal of general anesthesia in surgery. Surgical interventions can be performed at this stage. Stage III can be divided into phases depending on the degree of CNS depression and reactions to painful irritation.

At the beginning of the surgical stage, the suppression of reactions to pain is still insufficient. The patient is calm, the excitement is over, but a motor reaction and muscle tension occur on the skin incision. Superficial operations (herniation, incision of the abscess) can be done at this time. But as soon as muscle relaxation is required, this depth will be insufficient. The beginning of the surgical stage is called the first phase - stage III1. Together with the stage of addiction and arousal, it is included in the concept of superficial general anesthesia.

The main signs of stage III1 are an even, calm pulse, normal blood pressure, calm breathing, lacrimation, preservation of the corneal reflex and the reaction of the pupil to light and skin incision. The last two reflexes are checked as follows: at the time of the incision, the pupil expands, and when illuminated with a flashlight or a laryngoscope bulb, it narrows.

With further deepening of general anesthesia, reactions to the incision disappear — both movements and pupil dilation. The pupil’s response to light also decreases. But lacrimation persists, and the muscles can still be tense. The pulse quickens; breathing becomes more superficial, but it still provides good gas exchange; HELL remains stable.

This is stage III2, or the stage of medium depth of general anesthesia. It is they who strive to achieve when conducting general anesthesia with ether. It is safe and provides good conditions for surgical intervention.

Further saturation of the body with ether leads to complete relaxation of the muscles, depression and even the disappearance of all or almost all reflexes, a significant deterioration in breathing and blood circulation. A little more ether - and the pupils will expand. Now they will no longer respond to light! The pulse will become filamentous. Breathing will almost stop, and then death may occur. General anesthesia, instead of saving the patient, will kill him. This stage cannot be allowed.

Only sometimes, when it is impossible to carry out combined general anesthesia, and it is urgent to perform an operation that requires deep muscle relaxation, can anesthesia be deepened for a short time to this stage. But at the same time, auxiliary ventilation of the lungs is necessarily carried out and they continuously monitor the activity of the heart.

Attention should be paid to one feature of the middle and deep stages of general anesthesia with ether, and other general anesthetics. Surgery of the abdominal organs requires good muscle relaxation. It would seem that for this you need to deepen general anesthesia. However, in the deep stage (IIIc) not only the abdominal muscles, but also the respiratory intercostal muscles relax. Now breath is carried out mainly due to the diaphragm. Her excursions increase, and the diaphragm “pushes” the abdominal organs. This creates the appearance of poor muscle relaxation. And attempts to relax the muscles by increasing the concentration of ether or another substance lead to an overdose. An experienced specialist seeks to conduct general anesthesia in stage III2, and to provide relaxation of the muscles of the abdominal cavity due to the correct position of the patient on the operating table.

With deep anesthesia, the centers of respiration and blood circulation, the heart muscle, blood flow in the liver, kidneys, and adrenal glands are depressed. Ether can cause respiratory arrest, fluorotane - cardiac arrest. But the result is one - death! Therefore, at the first signs of an overdose, it is necessary to stop the flow of a general anesthetic, check whether the effects of the overdose are associated with complications of general anesthesia (tongue retraction, regurgitation), and stop the operation. Once again, the general anesthetic can be started and the operation can only be continued when all signs of an overdose disappear.

Stage IV Awakening.

When they stop injecting a general anesthetic into the body, it begins to be excreted through the lungs (inhaled substances) or kidneys (non-inhalation substances). Part of the general anesthetic is retained in fat depots, part is decomposed by the liver. Therefore, in obese patients, with poor liver and kidney function, the stage of awakening may be delayed.

General anesthesia is becoming more superficial, as they say, "relieved." The stages go in the reverse order: III3, III2, III1, excitement and, finally, consciousness returns. This period is very responsible, since it can last a long time, especially in these groups of patients and after prolonged operations.

At this time, agitation, vomiting, retraction of the tongue and other complications may occur, which, if left unattended, will lead to death.

The course of other types of general anesthesia differs from the clinic of general anesthesia with ether. But the sequence and general characteristics of the stages are preserved, although some stages, for example, excitations, may not appear externally. The main thing to remember is that the clinic depends not only on the dose of general anesthetic, but also on ensuring normal breathing and blood circulation, and preventing complications. The task and goal is to achieve such anesthesia that will provide the necessary conditions for the operation, but not harm the patient.

Medicines in anesthesiology and rhenimatology

1. Means for sedation

Anticholinergic drugs

Hypnotics and tranquilizers

Benzodiazepines

Barbiturates

Zolpidem, zopiclone, zaleplon

Other sleeping pills and tranquilizers

Antihistamines

Antipsychotics

Narcotic analgesics

Narcotic antagonists and partial agonists

2. Means for the prevention of aspiration, postoperative nausea and vomiting

H2 blockers

Proton pump inhibitors

Antacids

Serotonin Receptor Antagonists

Metoclopramide

3. Means for the prevention of thromboembolic complications

Heparin

Low molecular weight heparins

Other direct anticoagulants

Indirect anticoagulants

4. Chemoprophylaxis

5. Means for inhalation anesthesia

6. Means for non-inhalation anesthesia

Barbiturates

Benzodiazepines

Narcotic analgesics

Ґ2-adrenoreceptor agonists

Other drugs for non-inhalation anesthesia

7. Muscle relaxants - components of general anesthesia

Depolarizing muscle relaxants

Non-depolarizing muscle relaxants

8. Means to accelerate recovery after anesthesia

Benzodiazepine Antidotes

Opiate Antidotes

Antidotes of non-depolarizing muscle relaxants

9. Means for local anesthesia

Local anesthetics

Narcotic analgesics for regional anesthesia

Adrenergic agonists for regional anesthesia

10. Means for postoperative analgesia

Narcotic analgesics

Central analgesics

Non-narcotic analgesics

11. Means for infusion therapy

Blood components and preparations

Whole blood

Blood components

Blood products

Artificial Colloidal Solutions

Dextrans

Hydroxyethyl starch preparations

Gelatin preparations

Crystalloid solutions

Balanced Saline

Means for correcting the acid-base state

Antihypoxic crystalloid solutions

12. Intensive care products

Bronchodilators

Glucocorticoid hormones

Vasopressor (adrenomimetic) agents

Cardiotonic drugs

Phosphodiesterase Inhibitors

Calcium sensitizers

Antianginal drugs

Nitrates

Antihypertensive drugs

ACE inhibitors

Ganglion blocking agents

Antiarrhythmic drugs

Effective with supraventricular tachyarrhythmia

Effective with ventricular tachycardia

Effective for supraventricular and ventricular arrhythmias

Bradyarrhythmias

in-blockers

Cardiac Glycosides

Diuretics

Loop diuretics

Osmodiuretics

Procoagulants

Vitamin K

Fibrinolysis inhibitors

Thromboplastin activators

Hemophilia Remedies

Antiproteinase agents

Inhalation anesthetics

General properties

Inhalation anesthetics such as nitrous oxide, halotane, enflurane8, isoflurane, sevoflurane and desflurane * are commonly used.

Clinical effect: loss of consciousness, reduction of pain and decreased muscle tone

Pharmacodynamics: at the cellular level, the point of application of the effects of inhalation anesthetics is the double phospholipid layer of neuronal membranes. Due to their lipophilicity, they penetrate through the double layer and violate the permeability of cell membranes. This interferes with the operation of ion transport channels and other functional proteins.

Pharmacokinetics

Inhaled anesthetics are mostly excreted unchanged with exhaled air. Depending on the type of anesthetic, its various fraction is metabolized in the liver through cytochrome P450-dependent processes. As a result of metabolism, fluorides, chlorides, bromides and organic halogen compounds are formed. Nitrous oxide is partially reduced by intestinal microflora to nitrogen.

Nitrous oxide

In a liquid state, they are stored in gray steel cylinders under a vapor pressure of 51 atm. and 20□C. The condition of the contents of the cylinders can only be determined by weighing, so do not rely on the readings of the cylinder pressure gauge.

N2O (l) = (actual mass - empty cylinder mass) x500.

Flavourless, does not irritate mucous membranes.

Pharmacokinetics: partially restored by intestinal microflora to nitrogen. The minimum alveolar concentration (MAC) can only be achieved under hyperbaric conditions (approximately 105%).

Mechanism of action: weak anesthetic with good analgesic potential, without muscle relaxant effect.

Dosage regimen: up to 70% mixed with oxygen. Do not use alone to induce or to maintain anesthesia.

Side effects

• A slight risk of cardiac depression in patients with coronary artery disease, possibly myocardioprotective effect.

• May lead to an increase in ICP.

• With prolonged use or repeated short-term use, megaloblastic bone marrow suppression (agranulocytosis) or the development of neurological disorders (funicular myelosis) is possible. Nitrous oxide oxidizes the cobalt atom of vitamin B12, disrupting the exchange of methionine and folic acid. In patients with chronic vitamin B12 deficiency (pernicious anemia), nitrous oxide cannot be used.

• Postoperative middle ear dysfunction in patients with impaired Eustachian tube function is possible.

• Increased cuff pressure of the endotracheal tube due to diffusion of nitrous oxide (measure cuff pressure).

• Possible teratogenic effects in early pregnancy.

• Promotes postoperative nausea and vomiting.

• The solubility of nitrous oxide in the blood is about 34 times greater than nitrogen — a noticeable increase in volume in all expandable, gas-filled spaces (interferes with intestinal operations and worsens postoperative restoration of intestinal functions). For ophthalmic surgeries using SF6 gas, nitrous oxide should be stopped for 20 minutes.

• Dangers of hypoxia due to diffusion of nitrous oxide before removing from anesthesia, increase FiO2 to 1.

Contraindications: preparation for artificial insemination, patients with immunosuppression, chronic vitamin B12 deficiency, chronic left ventricular failure, Eustachian tube obstruction.

The effect of the "second gas"

It appears with the introduction of an inhaled anesthetic in addition to a high concentration of nitrous oxide; due to the more rapid achievement of a sufficient alveolar gas concentration, induction in anesthesia is faster.

Halotan

At room temperature it is in a liquid state; it is necessary to use a specially arranged evaporator, thymol is added as a stabilizer.

Pharmacokinetics: slow biotransformation with a high level of metabolism.

Mechanism of action: reversible oppression of consciousness, perception and reflexes.

Dosage regimen: MAK - 0.75 vol.%; MAC at 70% N20 - 0.3 vol.%; therapeutic concentration - 0.2-1.5 vol.%.

Side effects

• Arrhythmogenic effect (especially in combination with catecholamines and theophylline), negative inotropic effect (- drop in MOS).

• Vasodilation (lowering blood pressure), increased intracranial blood volume with an increase in ICP.

• Dose-dependent respiratory depression, increased bronchial secretion, bronchodilation (mainly in patients with asthma or COPD).

• Decreased uterine tone.

• Reduced blood flow in the kidneys and glomerular filtration rate (GFR).

• Rarely - hepatotoxicity, since halotane reduces blood flow in the liver. Caution: hypotension in patients with liver damage.

• Conclusion: in adults, halotane anesthesia is not performed.

Halotan Hepatitis

Rarely, approximately 1:35 000, sometimes occurs after some time. Risk groups: age> 40 years, repeated halotan anesthesia, female, obesity (mnemonic rule: fat, female, forty, fertile). Possible mechanism of pathogenesis: immunotoxic and cytotoxic reactions. Diagnosis: a pronounced increase in the concentration of blood transaminases, eosinophilia, fever, jaundice; detection of antibodies to trifluoroacetic acid; it is impossible to histologically differentiate with viral hepatitis. Forecast: high mortality.

Contraindications: MH (pay attention to data on predisposition and belonging to a risk group), heart failure.

Drug interaction: decreased muscle tone and increased action of non-depolarizing muscle relaxants (less pronounced than isoflurane, enflurane

! Slight irritation of the mucous membranes and the pleasant smell of halotane make this anesthetic preferable for mask anesthesia in young children with a slight severity of cough reflex and laryngos-pasm compared to isoflurane, enflurane8 and desflurane *. ! Due to its high toxicity, it is rarely used at present; displaced by other inhalation anesthetics (sevoflurane).

Enfluran

At room temperature it is in a liquid state; A special vaporizer must be used.

Mechanism of action: reversible oppression of consciousness, perception and reflexes.

Dosage regimen: MAK - 1.68 vol.%; MAC at 70% N2O - 0.6 vol.%; therapeutic concentration - 0.2-3.0 vol.%.

Side effects

• Decrease in the threshold of convulsive readiness (occur when

> 2 vol.%).

• Decreased renal perfusion and GFR (nephrotoxic, depending on the duration of anesthesia).

• Negative inotropic effect with a drop in cardiac output (less than halotane).

• Vasodilation with a decrease in blood pressure.

• An increase in blood volume in the cranial cavity with an increase in ICP.

• Dose-dependent respiratory depression and bronchodilation are less pronounced than in isoflurane and halothane.

• Decreased uterine tone.

• Ethereal odor, slight irritation of the mucous membranes. Contraindications: renal failure, severe heart

insufficiency, MH (take into account data on predisposition and belonging to a risk group), increased ICP.

Drug interaction: muscle relaxation and increased action of non-depolarizing muscle relaxants.

Isoflurane

The trade name is foran *, packaged in 250 ml bottles. At room temperature it is in a liquid state; a special vaporizer must be used.

Pharmacokinetics: low metabolic rate in the body. Mechanism of action: reversible inhibition of consciousness, perception and reflexes.

Dosage regimen: MAK - 1.15 vol.%; MAC at 70% N20 - 0.5 vol.%; therapeutic concentration - 0.2-2.5 vol.%.

Side effects

• Negative inotropic effect with a decrease in cardiac output (less than that of halothane and enflurane8).

• Vasodilation with a decrease in blood pressure.

• In patients with coronary artery disease at high doses (MAC> 1), the phenomenon of coronary robbery is possible.

• Increased heart rate.

• Dose-dependent respiratory depression, bronchodilation (the same strength as that of halothane).

• Ethereal odor, slight irritation of the mucous membranes.

• When inhaled into anesthesia with isoflurane, increased salivation and laryngospasm are noted.

• Discrete increase in blood volume in the cranial cavity with an increase in ICP. With hypocapnia on the background of isoflurane anesthesia (MAC <1), ICP may decrease.

• Decreased uterine tone.

• Possible cardioprotective effect.

Contraindications: severe heart failure, MH (take into account data on predisposition and belonging to a risk group), increased intracranial pressure

Drug interaction: pronounced muscle relaxation (stronger than that of halothane) and increased effect of non-depolarizing muscle relaxants.

Sevoflurane

The trade name is Sevoran , packaged in 250 ml vials.

At room temperature it is in a liquid state, it is necessary to use a special evaporator.

Mechanism of action: reversible oppression of consciousness, perception and reflexes.

Pharmacokinetics

Metabolic rate <4%; formation of free and bound fluorine (fluorine concentration> 50 μmol / L, which exceeds the level of toxic dose of fluorine). However, compared with methoxyflurane8, the development of impaired renal function has not been proven.

The formation of a large amount of compound A, a nephrotoxic decomposition product of sevoflurane, in contact with dry soda lime, low fresh gas flow and high temperatures. Attention: it is necessary to monitor the drying of soda lime, to prevent a decrease in humidity in the breathing circuit by installing a continuous gas flow, to pay attention to the sudden heating of the CO2 absorber.

Dosage regimen: MAK50 (%) - 2.05; MAK50 (%) at 70% N2O - 1.1, therapeutic concentration - 0.66-3 vol.%;

Side effects

• Slight negative inotropic effect. Rarely tachycardia (significantly less pronounced than when using desflurane * and isoflurane). The coronarodilating effect is weaker than that of isoflurane.

• In patients with coronary artery disease with high MAC (> 1.5), the phenomenon of coronary robbery is possible.

• Vasodilation with a decrease in blood pressure.

• Dose-dependent respiratory depression.

• May cause MH.

• A slight increase in blood supply to the brain with an increase in ICP.

• Possible cardioprotective effect.

Contraindications: severe heart failure, MH (take into account data on predisposition and belonging to a risk group), increased intracranial pressure, hypersensitivity to halogen-containing inhalation anesthetics in the anamnesis, drug

Drug interaction: muscle relaxant effect and increased action of non-depolarizing muscle relaxants.

Due to the absence of airway irritation and an unpleasant odor, it is ideal for masked anesthesia in children.

• Due to the low distribution coefficient in the blood / alveolar air, rapid induction into and withdrawal from anesthesia is possible.

• Probably an early appearance of pain (take into account with postoperative analgesia).

• Patients with renal failure, newborns, and infants should not be given Sevoflurane due to the possible accumulation of fluorides.

• Often, after sevoflurane anesthesia, children develop severe excitement and agitation (additional intravenous administration of midazolam may be required).

Desflurane *

The trade name is Supran *. Packed in 240 ml vials.

It is necessary to use only a special evaporator for desflurane-on *, since its boiling point is 22.8 ° C

Pharmacokinetics: the metabolic rate is very low (0.02%).

Mechanism of action: reversible oppression of consciousness, perception and reflexes.

Dosage regimen: Therapeutic concentration (MAK50 vol.%): Depends on age, general condition and combination with other anesthetics or opioid analgesics.

Side effects

• Slight dose-dependent negative inotropic effect. With rapid administration - tachycardia, increased blood pressure and heart rhythm disturbances.

• Vasodilation with a decrease in blood pressure.

• Dose-dependent respiratory depression, laryngo- and bronchospasm (sharp, irritating airways odor).

• Some increase in blood supply to the brain with an increase

ICP.

• May cause MH.

Drug interaction: muscle relaxation and increased action of non-depolarizing muscle relaxants.

Contraindications: MH (take into account data on predisposition and affiliation to the risk group), increased intracranial pressure, hypersensitivity to halogen-containing inhalation anesthetics in history, ischemic heart disease; patients in whom an increase in heart rate and blood pressure are an unpredictable risk.

Excellent controllability of desflurane anesthesia and significant superiority in elimination (low coefficient of gas distribution in blood / alveolar air). Due to severe irritation of the respiratory tract, it is not used for mask administration in anesthesia in children and patients with a tendency to bronchoconstriction.

Desflurane * is recommended for routine use only when performing general anesthesia using the minimum or small flow method, with a large stream of fresh gas, the use of desflurane * is uneconomical.

Desflurane , like enflurane and isoflurane, forms a large amount of carbon monoxide when interacting with dry natron lime (with CO poisoning, there are no pronounced changes in pulse oximetry and skin color) - update soda lime at least 1 time per week.

Anesthetics for intravenous administration

Sleeping pills

An additional administration of opioid analgesics (for example, fentanyl) is necessary, since sodium thiopental, etomidate8, ketamine and propofol do not have an analgesic effect.

Thiopental sodium

Trade name - thiopental *, 1 ampoule - 0.5 g (or 1 g) of dry matter; 1 bottle - 2.5 or 5 g of dry matter; diluted with water; usually a 2.5% solution is used (for example, 0.5 g of sodium thiopental in 20 ml of solution).

Pharmacokinetics

• For parenteral use only; The elimination half-life is 9-16 hours, the volume of distribution is 2.5 l / kg, the connection with plasma proteins is 50-80%; excreted from the body after a slow, but almost complete oxidation in the liver. The onset of action is 20-60 s after administration.

• A short duration of action (5-10 minutes after intravenous administration of the initial dose) is associated with the movement of a substance from the central nervous system to skeletal muscle and adipose tissue. Repeated injections of the drug lead to a significant increase in the duration of anesthesia.

Mechanism of action: thiobarbititurate with a good narcotic and weak analgesic and muscle relaxant effect. Oppression of the central nervous system, especially the reticular formation. With an increase in dose - a smooth sequential transition: sedation - sleep - anesthesia - coma.

Indications: often used for anesthesia in "ordinary" patients.

Dosage regimen: a single dose for induction in anesthesia is 3-7 mg / kg (200-500 mg) intravenously for 30 s (depending on the individual action).

Side effects

• Dose-dependent inhibition of the cardiovascular system with a decrease in blood pressure (must be entered slowly), vasodilation, decrease in cardiac output.

• Dose-dependent respiratory depression up to apnea.

• The release of histamine, cough, laryngo-and bronchospasm.

• Rarely - pain at the injection site due to irritation of the vascular wall when administered intravenously.

• Prevention: preliminary administration of fentanyl (0.05-0.1 mg intravenously).

• An alternative is intravenous regional anesthesia. At the same time, blood flow to the extremities with already available venous access is stopped. Intravenously, 20 mg of a 2% solution of lidocaine is administered (for example, 1 ml of 0.2% xicain *); survive for 20 s. Then the tourniquet is removed and after about 30 seconds thiopental sodium is introduced.

Contraindications: porphyria (sodium thiopental leads to an increase in porphyrin synthesis and can provoke an attack); allergy to barbiturates, especially in patients with bronchial asthma and urticaria, decompensated heart failure, acute myocardial infarction, severe liver damage, shock.

Drug interaction: induces microsomal liver enzymes, thereby accelerating the metabolism of corticosteroids, phenytoin, digitoxin, fenprocoumone *. Inhibits metabolism

Etomidate8

The trade name is etomidate-lipuro *, an ampoule (10 ml) contains 20 mg (in soybean oil), hypnomidate8: an ampoule (10 ml) contains 20 mg.

Pharmacokinetics

• The action occurs in 15-20 s, the duration of action is 2-3 minutes longer at high doses, the distribution volume is 2.5-4 l / kg; connection with plasma proteins - 75%. It is excreted after almost complete metabolization (esterase, oxidative N-dealkylation) with the formation of inactive metabolites.

• Loss of action associated with the ingestion of a substance from the blood to the central nervous system, lungs and liver. From there, thisidate8 is rapidly excreted and accumulates in muscle and adipose tissue.

Mechanism of action: narcotic effect without analgesic and myo-relaxing effect. Oppression of the central nervous system, especially the reticular formation.

Dosage regimen

For induction in anesthesia - 0.15-0.3 mg / kg (10-20 mg) intravenously.

The dosage of subsequent injections depends on the clinical effect (up to 80 mg - 4 ampoules).

Side effects

• Pain when administered intravenously (etomidate8 is preferred in soybean oil). Prevention: pre-enter fentanyl (0.05-0.1 mg intravenously). Alternative: intravenous regional anesthesia. Stop the blood flow in the limbs with imposed venous access; 20 mg of lidocaine is injected intravenously in a 2% solution (for example, 1 ml of 0.2% xicaine *), wait 20 seconds, remove the tourniquet, and approximately 30 seconds later this is administered.

• Myoclonus and dyskinesia. Prevention is the preliminary administration of fentanyl.

• Dose-dependent respiratory depression. Rarely - apnea.

• A slight decrease in ICP.

• With prolonged sedation with the help of thisidate, the biosynthesis of cortisone is inhibited.

Contraindications: allergy to thisidate8 (rare).

Interactions: antihypertensive drugs (possibly a strong decrease in blood pressure).

Anesthesia drug for intravenous administration with minimal effect on hemodynamics. Does not release histamine.

• Use caution in patients with a tendency to seizures: although etomidate8 has some anticonvulsant effects, prolonged myoclonus, seizures, and epileptiform EEG changes have been observed after intravenous administration of etomidate.

• Accidental injection of the drug into the artery usually does not lead to complications.

• Large breadth of therapeutic effect.

Propofol

The trade name is Diprivan , ampoules (20 ml) contain 200 mg of propofol, soybean oil, purified egg phosphatide (white emulsion), injection bottles (50 ml) contain 500 mg.

Pharmacokinetics

• The elimination half-life is 30-60 minutes, the distribution volume is 4-12 l / kg, the connection with plasma proteins is 97%, excretion after quick conjugation with glucuronic or sulfuric acid. The effect occurs within 30-45 s after intravenous administration, the duration of action after one injection is about 5 minutes, due to redistribution and inactivation in the liver. Duration of action - 5 minutes.

• A short duration of action (a few minutes after intravenous administration) is associated with the drug getting from the blood to the central nervous system, lungs, liver and subsequent rapid redistribution with deposition in muscle and then adipose tissue

Mechanism of action: a rapidly metabolized narcotic drug of short action without an analgesic effect for intravenous administration. Oppression of the central nervous system, especially the reticular formation. With increasing doses - a smooth sequential transition: sedation - sleep - anesthesia - coma.

Indication: induction in anesthesia and its maintenance.

Dosage regimen

• A single dose for administration to anesthesia of 1.2-2.5 mg / kg intravenously (80-180 mg). Enter slowly, adjust the dose depending on the individual action of the drug.

• Subsequent doses to maintain anesthesia: 25-50 mg bolus or infusion.

• Continuous administration: with a perfuser, 500 mg of propofol 0.1-0.2 mg / (kgxmin) = 6-12 mg / (kghh); 400-800 mg / h =

40-80 ml / h.

Side effects

• Respiratory depression up to apnea.

• With rapid administration and high doses, it has a pronounced negative effect on hemodynamics (reduced cardiac output and blood pressure).

• Hyperkinesis occurs more often than with thiopental sodium, less often - etomidate8.

• Reduced ICP.

• The appearance of distant (within a few hours) epileptiform attacks, in patients with epilepsy, seizures are possible.

• Pain in the injection area. Prevention: pre-enter fenta-nil (0.05-0.1 mg intravenously). Alternative: intravenous regional anesthesia. Stop blood flow in the limbs with superimposed venous access; 20 mg of lidocaine is administered intravenously in the form of a 2% solution (for example, 1 ml of a 2% xicaine solution *), they wait 20 seconds. The tourniquet is removed and propofol is administered after about 30 seconds.

Drug interaction: potentiation of the action of antihypertensive drugs; lipophilic opioids (fentanyl, alfentanil *, sufentanil *) leads to an increase in the concentration of propofol in the blood.

Contraindications: decompensated cardiopulmonary diseases.

Due to the rapid destruction of the substance in the liver, cumulation during repeated administrations is usually not observed; at the end of anesthesia, rapid awakening sets in with a clear consciousness.

• The release of histamine does not occur and the level of cortisol in the plasma does not decrease (which occurs with prolonged use of etomidate8).

• With prolonged use, metabolites may stain urine in a dark brown or green color.

• At a dose of> 6 mg / (kg hh), the concentration of triglycerides in the blood should be monitored for a long time and the intake of fats with an auxiliary substance (soybean oil) should be monitored.

Ketamine

Trade name - ketanest8 5 mg / ml injection: 1 ampoule contains 5 ml, 1 injection bottle contains 20 ml; ketanest8 25 mg / ml injection: 1 ampoule contains 2 ml, 1 injection vial contains 10 or 50 ml; ketamine 50 mg / 100 mg / 500 mg; curamed *: 1 ampoule contains 5 ml = 50 mg (1% solution), ampoule contains 2 ml = 100 mg (5% solution), 1 ampoule contains 10 ml = 500 mg (5% solution).

Pharmacokinetics: for parenteral administration only. The effect occurs 30 seconds after intravenous administration, 5-10 minutes after intramuscular administration. The duration of action is 5-15 and 10-25 minutes, respectively. The elimination half-life is 2.5-4 hours, the distribution volume is approximately 4 l / kg, binding to plasma proteins is 20-50%. In the liver, it transforms into partially pharmacologically active metabolites, followed by conjugation.

Mechanism of action

• Chemical affinity for hallucinogens. First, it inhibits the thalamo-neocortical, then the reticular and limbic systems. Dissociated anesthesia develops: although it seems that irritation of the sensory organs is perceived by the patient, but does not reach his consciousness. The patient freezes in a certain position of the body according to the cataleptic state, accompanied by amnesia and analgesia.

• Reflexes and spontaneous breathing are largely preserved.

Indications

Induction in anesthesia and its maintenance according to certain indications.

Repeated short-term anesthesia, for example, in patients with burns; for non-contact patients, ketamine can be administered intramuscularly.

Analgesia and sedation in combination with sedatives

Dosage regimen (for ketamine)

• Introduction to anesthesia: 1-2 mg / kg (70-150 mg) slowly (longer than 1 min) intravenously or 5-10 mg / kg (350-700 mg) intramuscularly.

• Repeated doses: according to circumstances, intravenously or intramuscularly - separate injections of half the initial dose.

• Through perfusion: 1-4 mg / (kghh). A 50 ml injection bottle contains 25 mg / ml pure or 250 mg per 50 ml 0.9% sodium chloride solution 15-150 mg / h = 0.6-6 ml / h.

Attention: on the recommendation of the manufacturer, it is necessary to enter only half the dose when using ketanest8, in clinical practice this is most often neglected. The S-enantiomer and ketamine racemate have approximately the same dose / effect ratio.

Side effects

• Activation of the sympathetic nervous system with increased blood pressure, tachycardia, increased myocardial oxygen demand, bronchodilation, increased uterine tone, increased intraocular pressure (IOP) and ICP.

• Increased salivation.

• Dyskinesia, increased muscle tone.

• Unpleasant (up to perceived as threatening) dreams, hallucinations.

• Arousal in the awakening phase.

• If administered too quickly, respiratory depression up to apnea.

Contraindications

• Manifestations of heart failure, coronary heart disease, mitral, aortic stenosis.

• Arterial hypertension.

• Hyperthyroidism, pheochromocytoma.

• Increased intracranial pressure, head injury, intracranial tumor.

• Penetrating eye damage.

• Mental illness.

• Preeclampsia, eclampsia (see 15.3.5).

Drug interaction

• Potentiation of the effects of drugs that increase blood pressure and heart rate (catecholamines, theophylline, pancuronium bromide8).

• Increased blood pressure and tachycardia may increase with the simultaneous use of thyroid hormones.

• Diazepam increases the duration of action inhibition of ketamine metabolism in the body.

! In ketaneste8 of the enantiomers of ketamine, only (S) -ketamine-HC1 is present, which provides anesthetic and analgesic effects, but there are no changes worth mentioning in the effectiveness of this drug.

• Due to the psychotomimetic effect, ketamine mononarcosis is not used. Instead, ketamine is used for ataralgesia (sedation and analgesia) in combination with benzodiazepines, while maintaining spontaneous breathing with oxygen supplied through a mask or probe.

• Large breadth of therapeutic effect.

• No organotoxicity.

• Ketamine crosses the placental barrier.

Example

• Premedication with the atropine anticholinergic to eliminate hyper salivation of 0.5 mg intramuscularly or intravenously.

• Midazolam (for example, dormicum *) for administration in an individual dose, for example 0.15-0.2 mg / kg (10-15 mg) intravenously.

• After that - ketamine in a dose of 35-100 mg intravenously.

• If necessary, subsequent injections after 10 minutes.

• In case of spontaneous breathing - apply O, in a volume of 2-4 l / min.

• Quiet, darkened room for waking up.

Opioid Analgesics

Opioid analgesics are all substances that can bind to and activate various peripheral and central opioid receptors.

• Complete agonists (morphine-like analgesics): fentanyl, pethidine *, peritramide8, tilidine8, tramadol.

• Analgesics with mixed action (antagonist agonists): pentazocine8.

• Partial agonists: buprenorphine.

The full naloxone antagonist eliminates the effects of opioid analgesics (buprenorphine is the exception). The effect occurs 2-3 minutes after intravenous administration, the duration of action depends on the dose and is 1-4 hours.

Effects and Side Effects Central

• Analgesia, sedative, antitussive effects, respiratory depression, miosis, nausea and vomiting, decreased central sympathetic tone, increased cerebrospinal fluid pressure (CSF) due to hypoventilation.

• When taking pentazocine8 - dysphoria (for example, fear, nightmares, hallucinations), increased sympathetic tone with increased pressure in the pulmonary artery.

Peripheral: spasmogenic effect on smooth muscle cells of the gastrointestinal tract and urinary tract (slowing down gastric emptying, spastic stasipipation, urinary retention, stagnation of secretion in pancreatic and biliary tracts). The release of histamine, primarily with the use of morphine, is accompanied by bronchospasm and vasodilation.

Respiratory depression

When titrating a dose of a narcotic analgesic, it is necessary to maintain a balance between pain-induced enhancement of external respiration and oppression of the respiratory center by opioids. Consequence: there is no respiratory depression. With a change in pain, it is important to adjust the dose in time.

Contraindications

Obstetrics: cesarean section (before umbilical cord cutting); cerebral edema, head injury (increased intracranial pressure). Exception: with controlled mechanical ventilation and hyperventilation, bronchial asthma (bronchospasm).

! Take special care: with biliary colic, postcholecystectomy syndrome (spasmogenic effect), hypovolemia, taking antihypertensive drugs (increased decrease in blood pressure), impaired liver function (danger of cumulation), myxedema (increased sensitivity of the body), Addison’s disease (increased sensitization) ! Pregnancy, childbirth, breastfeeding. Opioid analgesics that cross the placenta and breast milk can cause respiratory depression in the fetus and newborn. That is why, for

the treatment of pain during pregnancy, it is preferable to use pethidine at a dose of 75-100 mg intramuscularly (for example, dolantin , see 5.2.2, 22.3.1).

Alfentanil

(To be registered as a narcotic drug.) Trade name - rapifen *: 1 ampoule (2 ml) contains 1,088 mg of alfentanil * -HCL (= 1 mg of alfentanil *); the ampoule (10 ml) contains 5.44 mg of Alfentanil * - HCL (= 5 mg of Al-Fentanyl *).

Pharmacokinetics: the onset of action occurs 30 seconds after intravenous administration, the duration of action is 15-20 minutes, the connection with plasma proteins is 90%. After inactivation, the liver is excreted in the urine.

Mechanism of action: A complete opioid receptor agonist.

Indications: intravenous and combined anesthesia for short surgical interventions.

Dosage regimen

Initial dose (anesthesia): 15 mcg / kg (1 mg / 70 kg).

Maintenance dose: 7-15 mcg / kg (0.5-1 mg / 70 kg).

Side effects: respiratory depression, decreased blood pressure, bradycardia, chest stiffness, bronchospasm, nausea, vomiting, constipation, urinary retention, mi-oz.

Contraindications: pregnancy and lactation.

Drug interaction: with drugs that depress the central nervous system (potentiation of effects).

The duration of action is less than that of fentanyl.

The power is 3-4 times less than that of fentanyl.

Chest rigidity can be avoided or reduced by slow intravenous administration of the drug (during this, talk with the patient until the effect of the drug begins).

Antidote: naloxone (see 5.2.3).

Buprenorphine hydrochloride

(To be registered as a narcotic drug.)

Trade name - buprenorphine: 1 ampoule (1 ml) contains 0.324 mg of bu-renorphine hydrochloride (= 0.3 mg of buprenorphine) for intramuscular and intravenous administration.

1 tablet contains 0.216 mg of buprenorphine hydrochloride (= 0.2 mg of buprenorphine) under the tongue; temgestic forte: 1 tablet contains 0.432 mg of buprenorphine hydrochloride (= 0.4 mg of buprenorphine) under the tongue. Transdermal: patch (transdermal system) transtek 35, 52.5 and 70 μg / h.

Pharmacokinetics: oral bioavailability is only 20% after the first passage through the liver. With the recommended sublingual use, systemic bioavailability is 60%, the distribution volume is 2 l / kg, binding to plasma proteins is 96%; 10% of the substance is excreted by the kidneys unchanged, the rest (partially after N-dealkylation in the liver) - in the form of conjugates of glucuronic acid or unchanged with bile (enterohepatic circulation). The onset of action occurs 30 seconds after intramuscular injection or sublingual administration, 10-15 minutes after intravenous administration, 12-15 hours after gluing the transdermal patch. Duration of action: sublingually - 8-10 hours;

intramuscularly and intravenously - 5-6 hours; transdermally - 72 hours. The analgesic effect of buprenorfin hydrochloride in the skin depot continues for 12-15 hours after the patch is removed.

Mechanism of action: partial agonist of opioid receptors (partial μ-agonist, k-antagonist).

Indications: severe acute and chronic pain.

Dosage regimen - single doses:

• sublingual: 0.2-0.4 mg, not more than 1 time in 6-8 hours;

• intramuscularly and intravenously: 0.15-0.3 mg, not more than 1 time

at 6-8 hours;

• epidural: 0.15-0.3 mg (the effect occurs 10 minutes after administration, the duration of action is 15-20 hours,

• transdermal: after individual titration and sedation with opioid analgesics. The patch can be cut.

The daily dose of 35 μg / h in the patch = 30-60 mg of morphine (daily dose of morphine inside).

Maximum daily dose: dosage above 5-8 mg / day does not lead to further strengthening of the effect (ceiling effect).

Side effects: sedation, dizziness, stiffness, nausea and vomiting, spastic obstipation, urinary retention, pressure drop, bradycardia, decrease in pulmonary pressure, respiratory depression.

Contraindications: hypersensitivity, pregnancy and lactation.

Drug Interactions substances of central action.

• An increase in the action of MAO inhibitors (with hypertension, fever, confusion and agitation, convulsive attacks) is likely.

• The effects of pure opioid receptor agonists (fentanyl, morphine, pethidine , pyritramide8) may decrease with the competitive inhibition of opioid receptors by buprenorphine hydrochloride.

! The most common side effects of buprenorphine hydrochloride are less pronounced than the similar effect of morphine. Very strong analgesic: the analgesic potential of buprenorphine hydrochloride with sublingual administration at a dose of 0.2-0.6 mg or with intramuscular administration of 0.3-0.6 mg corresponds to 10 mg of morphine.

Ceiling effect: the use of doses in excess of the recommended daily doses does not significantly increase the effect.

Cancellation syndrome: due to the high affinity for receptors, it may develop after a latency period of 1-2 weeks.

The duration and intensity of action may increase with liver failure (metabolized in the liver). In this case, reduce the dose.

Antagonist: due to pronounced affinity for opioid receptors, it is not affected by naloxone; antidote - a central analeptic of doxapram * [dopram : ampoule (5 ml) contains 100 mg]. Dosage regimen: 0.5-1.5 mg / kg intravenously, through a perfuser 200 mg in 50 ml of 0.9% sodium chloride solution; the rate of administration of 60-180 mg / h = 15-45 ml / h.

Buprenorphine hydrochloride is also available as subutex * tablets for sublingual administration (0.4 mg / 2 mg / 8 mg), but they are prescribed only when indicated for replacement therapy.

Fentanyl

(To be registered as a narcotic drug.)

Trade name - fentanyl *: 1 ampoule (2 ml) contains 0.157 mg of fenta-nyldihydrogen citrate (= 0.1 mg of fentanyl); the ampoule (10 ml) contains 0.785 mg of fentanyldihydrogen citrate (= 0.5 mg of fentanyl). Transdermal: Durogesic patch 12, 25, 50, 75 and 100 μg / h. Through the mucous membranes: Actik nipple * 200, 400, 600, 800, 1200 and 1600 mcg.

Pharmacokinetics

• Parenteral: the half-life, depending on the dose, is 1-6 hours. At high doses or with repeated administration, the half-life is extended due to cumulation and the limited ability of the liver to metabolize.

• Distribution volume 3 l / kg, binding to plasma proteins 80%; 5% of the substance is excreted by the kidneys unchanged, the rest - after oxidative N-dealkylation in the liver. The onset of action is noted a few seconds after administration.

• The duration of action after a single parenteral administration of 20-30 minutes is associated with the redistribution of the lipophilic substance from the well-circulated areas (brain) into tissues with less blood flow (muscles, adipose tissue).

• Transdermal: onset of action - approximately 12 hours after application. Duration about 72 hours. After removing the patch, the effect persists for 12 hours due to the deposition of fentanyl in the skin.

• Through the mucous membranes: bioavailability of 50%. The action occurs in 3-5 minutes (rapid absorption through the mucous membrane of the oral cavity + slow absorption of fentanyl, swallowed with saliva in the digestive tract). The maximum plasma level is reached within 20-40 minutes. Duration of action is 2.5-5 hours.

Mechanism of action: opioid receptor agonist, full μ-agonist. Indications

Parenteral: analgesia of patients on mechanical ventilation, combined intravenous anesthesia, severe pain (for example, with myocardial infarction).

Transdermal: chronic pain requiring relief from opioid analgesics.

Through the mucous membranes: allowed in the treatment of pain associated with the decay of the tumor.

Dosage regimen

Initial dose (anesthesia): 1.5-4.5 mcg / kg (0.1-0.3 mg / 70 kg).

Maintenance doses: 1-3 mcg / kg (0.07-0.2 mg / 70 kg).

Continuous administration: 5 ampoules of fentanyl of 0.5 mg in a syringe of lineoma-ta per 50 ml (0.05 mg / ml), start the administration from 1-2 ml / h, increase the infusion rate by 1-2 as needed ml / h

Transdermal: after individual titration and sedation with opioid analgesics. Transdermal patch can be cut. A daily dose of 25 μg / h in the patch corresponds to 60 mg of morphine (daily dose of morphine when taken orally).

Through the mucous membrane of the oral cavity: a fentanyl-containing plate is moved forward and backward for 15 minutes along the most extensive surface of the mucous membrane of the oral

cavity. It must not be absorbed or chewed. To calculate the dosage: one plate contains 200 μg, which corresponds to 10 mg of morphine inside.

Side effects: respiratory depression, decreased blood pressure, bradycardia (rear wall infarction), constipation, urinary retention, nausea, vomiting, miosis.

Contraindications: pregnancy and lactation (crosses the placental barrier). Taking drugs that depress the central nervous system (potentiation of action).

Drug interaction

Drugs that depress the central nervous system, and alcohol: increased depression of the central nervous system. Antihypertensive drugs, antipsychotics, benzodiazepines: increased hypotensive effect.

Verapamil, clonidine, urapidil8: increased bradycardia. Propofol: increased plasma concentration of propofol. ! Very strong analgesic: 0.05-0.1 mg of fentanyl corresponds

10 mg of morphine intravenously. ! Severe respiratory depression: should not be prescribed high

doses, if there is no possibility of intubation and mechanical ventilation. ! Dose-dependent recoil effect: hours after the last administration of fentanyl, respiratory depression is possible again (reduce the dose of fentanyl in patients on mechanical ventilation in time). ! Antidote: Naloxone

Morphine

(To be registered as a narcotic drug.)

Parenteral administration: for example, 1 ampoule (1 ml) contains 10 mg of morphine, 1 ampoule (1 ml) - 20 mg of morphine, 1 ampoule (5 ml) - 100 mg of morphine, 1 ampoule (10 ml) - 200 mg of morphine (for subcutaneous and intravenous administration).

Pharmacokinetics: the action develops 10 seconds after intravenous administration, duration - 90 minutes; 1/3 of the drug binds to plasma proteins; possesses hydrophilic properties; 10% is excreted by the kidneys unchanged; the rest is predominantly after combining with glucuronic acid in different parts of the morphine molecule, while morphine-6-glucuronide is formed in a small amount, which has an analgesic effect. With renal failure, this substance accumulates → it is necessary to reduce the dose.

Mechanism of action: A complete opioid receptor agonist.

Indications: postoperative analgesia, severe pain, congestion in the lungs with acute left ventricular failure.

Dosage regimen

• Single dose: depending on how severe the pain is, the most common dosage regimen is every 2-4 hours.

• Subcutaneous: 10-30 mg.

• Intravenous: 5-10 mg. Dilute every 2.5-5 mg in 5 ml of water for injection *, inject slowly. The advantage of fractional intravenous administration: after cessation of administration, a more rapid decrease in the concentration of the substance in the blood and attenuation of respiratory depression are noted than with subcutaneous use.

• Through a perfuser: 1 ampoule contains 100 mg = 100 mg in 50 ml of 0.9% sodium chloride solution at a rate of 1-4 mg / h = 0.5-2 ml / h (if necessary, you can increase the rate of administration; maximum daily dose not limited

Side effects

• Respiratory depression (depending on the rate of administration).

• Nausea and vomiting.

• Central vagus nerve stimulation with myosis and bradycardia.

• Direct vasodilation with a decrease in blood pressure, peripheral venous congestion.

• The release of histamine with vasodilation and a decrease in blood pressure, profuse sweating, bronchospasm in patients with asthma.

• Increased smooth muscle tone with spastic constipation, urinary retention, spasm of the sphincter of Oddi and the risk of biliary colic and pan-creatitis.

Contraindications: hypersensitivity to morphine, biliary colic, acute hepatic porphyria, pregnancy, lactation (only for strict indications).

Drug interaction

• Drugs that depress the central nervous system, and alcohol: increased depression of the central nervous system.

• Indirect anticoagulants: increased bleeding tendency.

• Diuretics: increased orthostatic hypotension, reduced diuresis.

• Isoniazid: enhances the effects of morphine.

• MAO inhibitors: enhance the effects of morphine.

• Neostigmine methyl sulfate: enhances the effects of morphine.

! Morphine - a standard for assessing the strength and profile of opio-

idic analgesics. ! It is advisable to prescribe morphine for cardiac arrest, since it, by developing peripheral venous stasis, limits blood flow to the lungs and reduces the feeling of lack of air. ! Antidote: naloxone.

Petidine * (meperidine)

(To be registered as a narcotic drug.) The trade name is dolantin *. 1 ampoule (1 ml) contains 50 mg. 1 ampoule (2 ml) contains 100 mg, for subcutaneous, intramuscular and intravenous administration. Suppositories of 100 mg, drops (1 ml = 25 drops) of 50 mg.

Pharmacokinetics: oral bioavailability of about 50% (metabolized during the first passage through the liver). The half-life of 24-48 hours; the effect develops 5-7 minutes after intravenous administration, 10 minutes after subcutaneous administration, 15-30 minutes after ingestion or rectal administration. Duration of action is 3-4 hours; distribution volume - 4.2 l / kg; binding to plasma proteins - 50%. 5-25% of the substance is excreted by the kidneys unchanged (more with acidic urine); the rest is metabolized in the liver, resulting in the formation of a metabolite of norpetidine (half-life of 20 hours), which has an analgesic effect (2 times weaker than pethidine *) and provokes convulsions (action 2 times stronger than pethidine)

With renal failure, there is a danger of cumulation.

Mechanism of action: an opioid receptor agonist with analgesic, sedative and antitussive effects.

Indications: acute, very strong pain, for example, with myocardial infarction, acute cases of glaucoma, postoperative pain; trembling after anesthesia, chills after transfusion, trembling from the cold.

Dosage regimen - single dose:

• inside, subcutaneously, intramuscularly: 25-150 mg;

• intravenously: 25-100 mg, administered slowly (0.5-2 ml in 1-2 minutes), can be repeated every 2-3 hours

Side effects

• In doses equivalent in strength to the action of morphine, a comparable respiratory depression.

• Smaller than morphine antitussive effect (poorly suited for bronchoscopy).

• Stronger than morphine, pronounced sedation and euphoria.

• Smaller than morphine spasmogenic effect.

• Nausea and vomiting (often), constipation, mixed complaints.

• Very little effect on uterine contractility.

• Vasodilation with hypotension and reflex tachycardia with too rapid intravenous administration.

Contraindications: hypersensitivity to pethidine *, acute hepatic porphyria.

Drug interaction

• Medicines that depress the central nervous system, alcohol: increased sedation and respiratory depression.

• Acceleration of elimination and shortening of action while taking microsomal enzymes (phenobarbital, phenytoin, carbamazepine, rifampicin) with inducers.

• Antacids enhance the action of pethidine *, anticholinergics (atropine) enhance anticholinergic effects, TCAs increase central nervous system depression, barbiturates increase the toxicity of pethidine *, isoniazid enhance the effects of pethidine * and anticholinergic effects, oral contraceptives enhance the effect of pethidine, inhibitors Mn methyl sulfate enhances and prolongs analgesia, nitrates enhance the hypotensive effect of pethidine .

• Long-term use of glucocorticoids leads to an increase in IOP.

! About 75-100 mg of pethidine * corresponds to 10 mg of morphine.

! Petidine * is one of the oldest synthetic opioid analgesics, it is prescribed as often as morphine. ! During pregnancy and lactation, it is used only according to strict indications.

Antidote: naloxone.

Pyritramide 8 (To be registered as a narcotic drug.) Trade name - dipidolor8. 1 ampoule (2 ml) contains 22 mg of pyrithramide salt 8 (= 15 mg of pyritramide 8) for intramuscular and intravenous administration.

Pharmacokinetics: duration of action 4-6 hours. Onset of action 15 minutes after intramuscular injection, 5 minutes after intravenous injection.

Mechanism of action: an opioid receptor agonist with analgesic, sedative and antitussive effects.

Indications: severe and very severe acute and chronic pain.

Dosage regimen - single dose:

• intramuscularly: 15-30 mg;

• intravenously: 7.5-22.5 mg (average dose 0.1-0.3 mg / kg), if necessary, can be repeated every 6 hours.

Side effects

• At doses corresponding to morphine by the degree of analgesia, respiratory depression comparable to morphine is observed, more pronounced than morphine's sedative effect. Very rarely (compared with morphine), nausea and vomiting occur.

• Almost no pronounced cardiovascular side effects (bradycardia).

• Constipation, urinary retention, bronchospasm, arterial hypotension (especially with too fast intravenous administration).

Contraindications: hypersensitivity to pyritramide8, acute hepatic porphyria; during pregnancy and lactation - only according to strict indications.

Drug interaction: substances of central action - increased sedation and respiratory depression.

! Approximately 15 mg of pyritramide8 corresponds in analgesic effect to 10 mg of morphine. There is no euphoria.

Very often prescribed in the postoperative period. Antidote: naloxone.

Remifentanil 8

(To be registered as a narcotic drug.)

The trade name is Ultiva8: ampoules with 1.1 mg of remifentanil-la8 hydrochloride powder (= 1 mg of remifentanil8); ampoules with 2.2 mg of remifent-nil8 hydrochloride powder (= 2 mg of remifentanil8); ampoules with 5.5 mg of remifen-tanil8 hydrochloride powder (= 5 mg of remifentanil8).

Dissolve in distilled water or in a 5% glucose solution, inject intravenously.

Pharmacokinetics: for parenteral administration only; distribution volume 200-400 ml / kg; has a slight lipophilicity; binding to plasma proteins of 70%; the onset of action after 1-1.5 minutes, an effective half-elimination period of 3-10 minutes (does not depend on the dose and duration of infusion). It is metabolized by esterases, independent of pseudocholinesterase, not excreted by the liver, does not accumulate, the main metabolite does not have affinity for opioid receptors and is excreted by the kidneys.

Mechanism of action: selective agonist of opioid μ receptors with a strong analgesic, sedative, antitussive effect.

Indications: with intravenous and combined anesthesia for the introduction of anesthesia and its maintenance.

Dosage regimen: since the frequency of development of chest rigidity correlates with the dose and rate of infusion, bolus administration is not recommended. Enter through continuous infusion.

Side effects: skeletal muscle rigidity (stiffness of the chest), vagus nerve stimulation with a decrease in blood pressure during vasodilation and bradycardia, respiratory depression, nausea, vomiting, constipation, urinary retention.

Contraindications

• There is insufficient evidence of action during pregnancy and lactation. By analogy with other opioid analgesics, it can be assumed that remintentanil8 crosses the placental barrier and is excreted in breast milk.

• There is no data on the use in children under two years of age.

• Not intended for epidural, intraspinal and intrathecal administration, as it contains glycine (an exciting neurotransmitter).

Drug interaction: centrally acting substances - enhancing the sedative effect and respiratory depression; strengthening the antihypertensive effect of antihypertensive agents, antipsychotics of the phenothiazine series and benzodiazepine derivatives; potentiates heart rate reduction (for example, when taking verapamil, diltiazem, clonidine, urapidil8).

The power of analgesia is comparable to fentanyl.

Virtually no effect on hemodynamics.

No need to adjust the dose for renal or hepatic

insufficiency. ! Due to the very fast onset of action and the short half-life, the effect is “On / Off”.

• Advantages: very good controllability (suitable for both short-term and long-term interventions) with the ability to quickly wake up the patient; there is no postoperative respiratory depression and recoil effect.

• Disadvantages: it does not have an aftereffect, so you need to start adequate postoperative analgesic therapy in advance (with long-term operations about 20 minutes before completion).

Hypnotics are administered before fentanyl infusion.

Remifentanil8 residues in the infusion system, when flushed, can cause the effects of opioids (respiratory depression!).

Do not administer through a single infusion system with blood, serum or plasma, since nonspecific esterases contained in blood products can lead to hydrolysis of remifentanil8 and, as a result, shorten its effect.

In Germany, they have been used since 1996. A comprehensive description of remifentanil8, including in comparison with other opioid analgesics, is not yet possible.

Antidote: naloxone The half-life of naloxone is longer than remyfentanyl8

Sufentanil

(To be registered as a narcotic drug.)

Trade name - Suffent: an ampoule (5 ml) contains 0.375 mg of sufentanil dihydrogen citrate * (= 0.250 mg of sufentanil = 50 μg / ml), for intravenous administration; Suffent Mitte *: an ampoule (10 ml) contains 0.075 mg of sufentanil dihydrogen citrate * (= 0.05 mg of sufentanil = 5 μg mg / ml),

for intravenous administration; epidural sulfate *: an ampoule (2 ml) contains 0.015 mg of sufentanyl dihydrogen citrate * (= 0.01 mg of sufentanil = 5 μg mg / ml) for epidural administration.

Pharmacokinetics: only for parenteral administration, highly lipophilic compound, binding to plasma proteins up to 90%, half-life - 2.5 hours with a wide range of vibrations. It undergoes oxidative N-dealkylation and O-demethylation in the liver and small intestine.

Mechanism of action: agonist of opioid μ receptors, with cough suppressant, very pronounced analgesic and moderate sedative effect.

Indications: induction in anesthesia and its maintenance. As an analgesic component in analgesia (for example, in patients with mechanical ventilation).

Dosage regimen

For anesthesia with combined anesthesia for

0.3-1 mcg / kg (20-70 mcg).

Repeated doses: every 30-40 minutes bolus at 0.3-0.7 mcg / kg (20-50 mcg) or through a perfus at 20-70 mcg / h.

Analgesic sedation: initial bolus injection of 10 mcg, then through perfusion at a speed of 35-100 mcg / h.

Epidural: sufentanil 10-15 μg each (the effect occurs after about 5 minutes, the duration of action is 4-6 hours). For a good distribution of sufentanil * enter in a sufficient volume of liquid: dilute in a bolus dose of local anesthetic or in 5-10 ml of 0.9% sodium chloride solution.

Side effects: respiratory depression, vagus nerve stimulation with a decrease in blood pressure due to vasodilation and bradycardia, increase

stitching of smooth muscle sphincters, skeletal muscle stiffness (stiffness of the chest), nausea, vomiting, constipation, urinary retention.

Contraindications: pregnancy and lactation, since sufentanil * overcomes the placental barrier and penetrates into breast milk, acute liver-night porphyria, children up to a year.

Drug interaction

• Drugs that depress the central nervous system, and alcohol: increased oppression of the central nervous system.

• Antihypertensive drugs, antipsychotics, benzodiazepines: increased decrease in blood pressure.

• Verapamil, clonidine, urapidil: increased bradycardia.

• Propofol: increased concentration of propofol in plasma.

! The analgesic effect is about 3-10 times more powerful than fentanyl: approximately 0.01 mg of sufent corresponds to 10 mg of morphine.

It has less effect on hemodynamic stability than fentanyl.

Awakening is faster than after fentanyl injection.

Pronounced sedative effect, the drug can be used as the only component for analgesic sedation.

Very large therapeutic latitude (100 times greater than that of fenta-nil).

When the estimated need for sufentanil * is less than 0.05 mg (duration of operation <3 hours), diluted sufentanil * (sufenta mite *) is used, since it is better to dose the drug and its consumption becomes more economical.

Antidote: naloxone.

Naloxone

Trade name - narcanti8: ampoule (1 ml) contains 0.4 mg of naloxone.

Pharmacokinetics

• Low bioavailability when taken orally (metabolized during the first passage through the liver), therefore, only parenteral administration is justified.

• The half-life of 1-1.5 hours, the volume of distribution of 5 l / kg.

• Binding to plasma proteins 50%.

Elimination through oxidation and conjugation with glucuronic acid in the liver; the effect occurs 1-2 minutes after intravenous administration.

• The duration of action depends on the concentration of the administered opioid analgesic.

Mechanism of action: a complete antagonist of opioid receptors that blocks all the effects of opioid analgesics and does not have its own pharmacological effects in a wide therapeutic range.

Indications: postoperative respiratory depression caused by opioids; caused by opioids and synthetic narcotic drugs (e.g., fentanyl, methadone8, pentazocin8, dextropropoxyphene *, tilidine8) respiratory depression and twilight consciousness.

Dosage regimen

Postoperative respiratory depression: fractional administration of 0.1-0.4 mg intravenously.

In case of an overdose of opioid analgesics: titrate the dose in accordance with the clinical effect; the initial dose is 0.4-2 mg intravenously every 2-3 minutes up to a total amount of about 10 mg.

Side effects: with an overly sharp suppression of the effects of opioid analgesics - dizziness, vomiting, profuse sweating, tachycardia, muscle hypertonia, tremor, seizures, asystole. In patients with opioid analgesic dependence, acute withdrawal syndrome.

! Due to the short half-life, the condition of the patient should be carefully monitored and, if necessary, repeated injections are possible: the recoil effect is possible.

If there is no clinical effect after the administration of 10 mg of naloxone, an overdose of opioids is doubtful.

Benzodiazepines

Diazepam

The trade name is Valium8: Ampoule (2 ml) contains 10 mg. Pharmacokinetics

• The effect occurs in 1-2 minutes, the duration of action depends on the dose, up to many hours; in high doses - cumulation.

• The half-life of 24-57 hours.

• Biotransformation in the liver to partially active metabolites.

• Mechanism of action: has affinity for specific benzodiazepine receptors, has sedative, anxiolytic, anticonvulsant and muscle relaxant effects.

Indications: premedication, addition to opioids, sedation during regional anesthesia and painless interventions (endoscopy), as an anticonvulsant.

Dosage regimen

Intravenously: 0.15-0.45 mg / kg, dosed according to the clinical effect.

Inside: 5-15 mg. Side effects

• Respiratory depression (especially with excessively rapid administration).

• Reduced blood pressure (especially in combination with opioid analgesics).

• Anterograde amnesia.

• Irritation of veins and thrombophlebitis with intravenous administration; intramuscular injection is most often painful.

• Episodic paradoxical reactions in elderly patients. With repeated injections, there is a danger of cumulation. Contraindications: myasthenia gravis, acute intermittent porphyria, intolerance to benzodiazepines.

! Antagonist: flumazenil (anexate *).

Dosage regimen: initial dose of 0.2 mg, increase by 0.1 mg until a sufficient effect is achieved (maximum - 1 mg). Penetrates through the placental barrier.

Flunitrazepam

The trade name is Rohypnol8: a coated tablet contains 1 mg of flunitrazepam, an ampoule (1 ml) contains 2 mg of flunitrazepam (contains 30 mg of benzyl alcohol as a preservative); the ampoule with the solvent contains 1 ml of water for injection *.

Pharmacokinetics: distribution volume 2.2-4 l / kg, plasma protein binding 80%, the duration of action depends on the dose and can reach many hours, the half-life of unchanged active substances is 10-30 hours; 95% of the substance is metabolized by conversion in the liver to partially active metabolites (7-amino metabolite with a half-life of 20-30 hours), excretion by 90% by the kidneys, 10% with bile.

Mechanism of action: 1,4-substituted benzodiazepine derivative with predominant hypnotic as well as sedative, anxiolytic, anticonvulsant and muscle relaxant effects, has high affinity for CNS benzodiazepine receptors and enhances GABAergic inhibitory mechanisms (GABA - gamma-aminobutyric acid).

Indications: sleeping pills, used for anesthesia and intensive care, for sedation in anesthesiology, with clinically significant sleep disorders.

Dosage regimen Premedication

• Inside: 0.5-1 mg in the evening on the eve of surgery immediately before going to bed.

• Intramuscularly: 1-2 mg 30-60 minutes before induction in anesthesia. Introduction to anesthesia: 0.015-0.03 mg / kg intravenously (corresponding to 1-2 mg).

Side effects: respiratory depression, decreased blood pressure during peripheral vasodilation, anterograde amnesia, episodic paradoxical reactions in elderly patients, allergic and anaphylactic

reactions, local thrombophlebitis with intravenous administration. If accidentally introduced into the artery - the danger of necrosis.

Contraindications: hypersensitivity to benzodiazepines or benzyl alcohol, a history of drug dependence, psychosis, myasthenia gravis, severe chronic hypercapnia, acute intermittent porphyria, newborns (due to benzyl alcohol), pregnancy and lactation.

Drug interaction: increased central sedative effect of other drugs (anesthetics, analgesics, antipsychotics, tranquilizers, antidepressants, sleeping pills) and alcohol.

There is a danger due to the long half-life

cumulation. ! Penetrates through the placental barrier.

In renal or hepatic insufficiency, it is necessary to reduce the dose.

The intravenous flunitrazepam solution contains 10% ethanol.

Antagonist: flumazenil (anexate *). Dosage regimen: initial dose of 0.2 mg, increase by 0.1 mg until a sufficient effect is achieved (max-max - 1 mg).

Midazolam

Trade name - dormicum *: ampoule (1 ml) contains 5 mg; ampoule (3 ml) contains 15 mg; an ampoule (5 ml) contains 5 mg; the ampoule (10 ml) contains 50 mg, the tablet contains 7.5 mg.

Pharmacokinetics: water-soluble benzodiazepine derivative (has less irritating effect on the wall of the veins than diazepam). The effect occurs 3 minutes after administration, the duration of action is 45-90 minutes, the elimination half-life is 1.5-2.5 hours. Biotransformation: to inactive metabolites in the liver.

Indications: premedication, addition to opioids, sedation during regional anesthesia and painless interventions (endoscopy), as an anticonvulsant.

Dosage regimen: dose slowly and individually (administered bolus, intravenously, 0.5-1 mg each). For sedation, 0.1-0.15 mg / kg is administered intramuscularly; adults 7.5-15 mg by mouth; small children 0.3 mg / kg rectally; 0.4 mg / kg orally.

Side effects: respiratory depression (especially with rapid administration), decreased blood pressure (especially in combination with opioids), antegrade amnesia, episodic paradoxical reactions in elderly patients.

Contraindications: see. "Diazepam".

The antagonist is flumazenil (anexate *); dosage see "Diazepam": antagonist.

Flumazenil

Trade name - Anexat *: ampoule (5 ml) contains 0.5 mg.

Pharmacokinetics: due to the low bioavailability when taken orally (25% due to metabolism when passing through the liver), only parenteral administration is justified. The half-life is approximately 50 minutes, increases with hepatic insufficiency; distribution volume 0.95 l / kg, plasma protein binding 50%; eliminated by the liver. The onset of action 1-2 minutes after intravenous administration. The duration of action depends on the concentration of the benzodiazepine anxiolytic taken internally (competitive antagonism).

Mechanism of action: imidazobenzodiazepine (no internal activity), a competitive blocker of benzodiazepine receptors.

Indications

• First of all, severe poisoning with benzodiazepines (for differential diagnosis and treatment).

• Short term cessation of long-term patient sedation on mechanical ventilation for neurological examination.

• Suppression of paradoxical reactions to the introduction of benzodiazepines.

• Coma with hepatic encephalopathy (controversial indications). Dosage regimen: the initial dose of 0.2 mg is intravenously bolus, then 0.1 mg is added as needed until the patient regains consciousness. The maximum total dose is about 1 mg, although overdose is not observed even with 100 mg.

Side effects: nausea and vomiting, a sense of fear, fluctuations in blood pressure and heart rate, rarely - manifestations of withdrawal symptoms (convulsive seizures, symptomatic psychoses).

Contraindications

Absolute: epilepsy, taking benzodiazepines as an adjunctive therapy.

Relative: pregnancy, lactation, children.

! In case of liver failure, reduce the dose.

Due to insufficient clinical data, pregnant and lactating mothers, as well as children under 15 years of age, should be prescribed only for strict indications.

After administration of the drug, it is necessary to continue monitoring for a long time, since the half-life of flumazenil is much shorter than that of benzodiazepines.

Muscle relaxants

The mechanism of action, indications and contraindications -

Muscle relaxants (arranged in increasing duration of action)

Alcuronium Chloride

Trade name - alloferin : ampoule (5 ml) contains 5 mg; ampoule (10 ml) contains 10 mg.

Pharmacokinetics: onset of action 3-4 minutes after administration, duration of action 20-30 minutes, excreted by the kidneys.

Mechanism of action: non-depolarizing (competitive blocker of acetylcholine receptors of the neuromuscular synapse) muscle relaxant of medium duration.

Indications: intubation, perioperative anesthesia and mechanical ventilation.

Dosage regimen - single dose:

• recurrence: 0.025-0.05 mg / kg (adults 2-3 mg);

• intubation: 0.2-0.3 mg / kg, after intubation with suxamethonium chloride (initial) 0.16 mg / kg, subsequent injections of 0.03 mg / kg every 15-25 minutes.

Side effects: histamine release with bronchospasm and cutaneous erythema.

Contraindications: myasthenia gravis, Lambert-Eaton syndrome, allergic diathesis (relative), acute intermittent porphyria.

Drug interaction

Neuromuscular blockade is enhanced by aminoglycosides, colistin; polymyxin B, amphotericin B, benzodiazepines, thiazide diuretics, furosemide, ethacrylic acid, quinidine, ganglion blockers, magnesium sulfate, lithium salts. Lowers blood pressure when combined with halotane. Antagonists are acetylcholinesterase inhibitors. ! It does not cross the placental barrier.

! With renal failure, remember about delayed excretion.

! The substance decomposes in the light; do not store at> 8 ° C.

Atracuria besylate

Trade name - Tracrium : ampoule (2.5 ml) contains 25 mg of atracuria besylate; the ampoule (5 ml) contains 50 mg of atracuria besylate.

Pharmacokinetics: the onset of action occurs depending on the dose administered - after 2 minutes at a dose of 0.3 mg / kg and after 1 minute at 0.6 mg / kg. The half-life of 20-30 minutes, Hoffman elimination (spontaneous decomposition of muscle relaxant), by hydrolysis by esterases and partially by the kidneys unchanged. Decomposition products - laudanosine, acrylate and alcohol.

Mechanism of action: non-depolarizing muscle relaxant (competitive blocker of the acetylcholine receptors of the neuromuscular synapse).

Indications: medium-duration muscle relaxant for intubation, perioperative anesthesia and mechanical ventilation. Dosage regimen - adults and children over 1 month:

• intubation: 0.5-0.6 mg / kg intravenously (35-50 mg);

• subsequent injections: 0.1-0.2 mg / kg intravenously (10-15 mg). Side effects: histamine release with redness of the skin, bronchospasm, decreased blood pressure, tachycardia and anaphylaxis with laryngospasm.

Contraindications: myasthenia gravis, hypovolemic shock, asthma, allergic diathesis.

Drug interaction

It interacts with other drugs that lead to an extension or enhancement of neuromuscular blockade, such as antiarrhythmic drugs, antibiotics, acetazolamide, β-blockers, diuretics, ganglioblockers, inhaled anesthetics (e.g., halothane, isoflurane, enflurane8), calcium channel antagonists , ketamine, lithium salts and magnesium sulfate.

In an alkaline medium, it loses activity (for example, when mixed with sodium thiopental, do not mix in one syringe!).

! Antagonist: acetylcholinesterase inhibitors (for example, neostigmine at a dose of 0.5-5 mg intravenously) with additional administration of atropine (0.5-1 mg intravenously). To date, there is no evidence of a negative effect on the condition of patients with acute intermittent porphyria, as well as the possibility of the development of MH.

In case of impaired liver or kidney function, dose adjustment is not required.

Cisatracuria besylate

The trade name is Nimbex *: an ampoule (2.5 ml) contains 6.7 mg of cisatracuria besilate (= 5 mg of cisatracuria) for intravenous administration, an ampoule (5 ml) contains 13.4 mg of cisatracuria besilate (= 10 mg of cisatracuria) for intravenous administration.

Pharmacokinetics: for parenteral administration only; the volume of distribution is approximately 160 ml / kg; at a dose of 0.15 mg / kg, the effect develops 2 minutes after administration; the duration of the action is about 45 minutes, the half-life is about 24 minutes. Hoffman elimination (spontaneous decomposition of muscle relaxant), with the formation of inactive metabolites, as well as through hydrolysis of esterases. Decay products - laudanosine (compared with atracuria besylate, only 10% of the total amount decomposes), acrylate and alcohol.

Mechanism of action: non-depolarizing muscle relaxant (competitive blocker of the acetylcholine receptors of the neuromuscular synapse). One of the ten stereoisomers of atracuria.

Indications: a muscle relaxant of medium duration, used for intubation, perioperative muscle relaxation and

Mechanical ventilation

Dosage regimen Intubation: 0.1-0.15 mg / kg. Repeated doses: 0.03 mg / kg. Side effects

• Redness of the skin or eczema, bronchospasm, decreased blood pressure, bradycardia.

• In patients with intensive care, individual cases of muscle weakness and / or myopathy have been reported. Rarely, cramps. However, in these patients, concomitant diseases were discovered that could lead to convulsions, for example, head injury, hypoxic encephalopathy, cerebral edema, viral encephalitis, uremia. A causal relationship cannot be established.

• Very rarely - severe anaphylactic reactions due to one or more anesthetics.

Contraindications: myasthenia gravis, hypersensitivity to atracuria besylate, other muscle relaxants (cross-reactions) and sulfobenzene acid, pregnancy and lactation, children under 2 years old.

Drug interaction

• Enhance neuromuscular blockade: antiarrhythmic drugs, antibiotics, β-blockers, diuretics, ganglion blockers, inhalation anesthetics, calcium channel antagonists, ketamine, lithium salts and magnesium sulfate.

• The effect decreases with prolonged use of phenytoin or carbamazepine.

• Incompatibility with propofol and alkaline solutions (for example, thiopental).

4-5 times more powerful than atracuria.

There are no signs of ganglion-blocking or m-anticholinergic action; accordingly, it does not violate the stability of hemodynamics.

There is no need to reduce the dose for impaired liver or kidney function.

You can not enter through the same infusion system together with blood, serum or plasma, since nonspecific esterases of blood preparations can lead to hydrolysis of cisatracuria and weakening its effect.

Antagonist: acetylcholinesterase inhibitors (for example, neostigmine methyl sulfate at a dose of 0.5-5 mg intravenously) with additional administration of atropine (0.5-1 mg intravenously).

Rocuronium bromide

The trade name is Esmeron *: an ampoule (5 ml) contains 50 mg of rocuronium bromide for intravenous administration, an ampoule (10 ml) contains 100 mg of rocuronium bromide for intravenous administration.

Pharmacokinetics: for parenteral administration only; distribution volume about 228 ml / kg; onset of action 60 s after administration at a dose of 0.6 mg / kg; duration of action is approximately 30-40 minutes; the elimination half-life is about 97 minutes. After biotransformation, the liver is excreted mainly with bile; up to 30% with urine.

Mechanism of action: non-depolarizing muscle relaxant (competitive blocker of acetylcholine receptors of the neuromuscular synapse).

Indications: medium-duration muscle relaxant for intubation, perioperative muscle relaxation and mechanical ventilation.

Dosage regimen

Intubation dose: 0.6 mg / kg.

Repeated doses: 0.075-0.15 mg / kg.

Side effects: anaphylactic or allergic reactions are possible.

Contraindications: myasthenia gravis, Lambert-Eaton syndrome, transferred poliomyelitis, hypersensitivity to other muscle relaxants (cross-reactions) and bromides. There is no data on the use during pregnancy and lactation; clinical information on use in children younger than 3 months of age is also absent.

Drug interaction

• Strengthen neuromuscular blockade: antiarrhythmic drugs, antibiotics, barbiturates, β-blockers, diuretics, ganglion blockers, inhalation anesthetics, ketamine, lithium salts and magnesium sulfate.

• Weakening effect: with prolonged use of phenytoin, carbamazepine, corticosteroids or theophylline.

• Incompatible with dexamethasone, diazepam, furosemide, sodium hydrocortisone succinate , soluble insulin, sodium thiopental, vancomycin.

! Due to the rapid onset of action, suxamethonium chloride is being discussed as an alternative.

! It has a higher affinity for the muscles of the vocal folds compared to skeletal muscles, which means an open glottis even before achieving sufficient general surgical muscle relaxation.

! Virtually no effect on hemodynamics.

! It is necessary to reduce the dose for liver failure; renal failure is clinically less significant.

Antagonist: acetylcholinesterase inhibitors (for example, neostigmine methyl sulfate at a dose of 0.5-5 mg intravenously) with additional administration of atropine (0.5-1 mg intravenously).

Suxamethonium Chloride

Trade name - listenone *: ampoule of 1% solution (5 ml) contains 50 mg; the ampoule of a 2% solution (5 ml) contains 100 mg; the ampoule of a 5% solution (2 ml) contains 100 mg.

Pharmacokinetics: the half-life after intravenous injection is about 3 minutes; elimination by decomposition to choline and succinic acid by pseudocholinesterase in the liver and plasma. The onset of action after 30-60 s after administration, the duration of action after a single injection is about 5 minutes.

Mechanism of action: inhibition of neuromuscular transmission of excitation through depolarization of the postsynaptic membrane.

Indications: short-term muscle relaxation for intubation, bronchoscopy, electroconvulsive therapy. To avoid muscle fasciculations, 1-2 minutes prior to succinylcholine injection, a non-depolarizing muscle relaxant is introduced (precurarization).

Dosage regimen: single dose for intubation 1-1.5 mg / kg intravenously.

Side effects

• Initially, arterial hypotension and bradycardia are possible (later partially replaced by tachycardia and increased blood pressure).

• Hypersalivation and enhanced bronchial secretion.

• Hyperkalemia with the penetration of potassium into the extracellular space.

• Myoglobinemia, myoglobinuria due to rhabdomyolysis (rarely).

• MH (rarely).

• Increased pressure in the digestive tract. (Attention: pregnant women in the later stages, patients with obesity, intestinal obstruction and diaphragmatic hernia.) Prevention - the introduction of atropine or precurarization.

• The release of histamine with the danger of bronchospasm (rarely).

• Muscular fasciculations as a result of asynchronous depolarization (muscle pain the next day).

• An increase in the duration of action with a genetically determined decrease in the activity of pseudocholinesterases (frequency 1: 3000).

• Increased IOP and ICP.

Contraindications: burns, neuromuscular disorders (such as myotonia, poliomyelitis), penetrating eye injuries, increased intracranial pressure, hyperkalemia, decreased cholinesterase activity (limited destruction).

Drug interaction: increased neuromuscular blockade with aminoglycosides, amphotericin B, β-adrenergic blockers, quinidine, lidocaine.

! Patients with decreased cholinesterase activity should be monitored for a long time. Alternative: administration of 45-180 mg of serum cholinesterase *, the effect occurs after about 10 minutes. Isolated cases of fatal outcomes due to non-treatable bradycardia are described. Since these cases can be explained in advance by not diagnosed muscle diseases, suxamethonium chloride is administered only according to strict indications.

Parasympathomimetic effects (bradycardia, hypersalivation) can be limited if atropine is previously administered.

Precuralization (the introduction of small doses of non-depolarizing muscle relaxants) can reduce muscle fasciculations.

If possible, one should refrain from repeated injections to avoid the “double block” (an additional property of suxamethonium chloride, which leads to inhibition of depolarization). Does not penetrate the placental barrier.

Vecuronium bromide

Trade name - Norkuron : bottle = 10 mg in 217 mg of dry matter; dilute in 4 ml of a 0.9% solution of sodium chloride or water for injection .

Pharmacokinetics: for parenteral administration only; the half-life of about 1 hour; the volume of distribution is approximately 0.3 l / kg. Elimination is mainly unchanged with bile (70%), the rest is excreted in the urine (15%) and after hydroxylation in the liver. The effect develops 1-3 minutes after administration, the duration of action after the first injection is 20-30 minutes, with repeated injections longer.

Mechanism of action: competitive blockade of n-cholinergic receptors of the neuromuscular synapse (non-depolarizing).

Indications: muscle relaxation for intubation, perioperative muscle relaxation and mechanical ventilation.

Dosage regimen: single dose.

Precursorization: 0.01-0.02 mg / kg (1-1.5 mg) intravenously.

Intubation: 0.08-0.1 mg / kg (5-7 mg) intravenously.

Repeated doses: 0.02-0.05 mg / kg (1.5-3.5 mg) intravenously.

Side effects: slight m-anticholinergic effect (tachycardia, moderate increase in blood pressure). In the early postpartum period - a significant lengthening of the neuromuscular blockade.

Contraindications: liver failure, hypersensitivity to vecuronium bromide or bromine preparations, myasthenia gravis, Lambert-Eaton syndrome, severe electrolyte imbalance.

Drug interaction: increased neuromuscular blockade when combined with aminoglycosides, β-blockers, quinidine, clindamycin, slow calcium channel antagonists, local anesthetics, loop diuretics, tetracycline, with hypokalemia, and also with a high concentration of magnesium or lithium. ! Due to excretion with bile, it is indicated for renal failure.

Side effects are less than pancuronium bromide.

Antagonist: acetylcholinesterase inhibitors (for example, neostigmine methyl sulfate at a dose of 0.5-5 mg intravenously) with additional administration of atropine (0.5-1 mg intravenously).

It can be used during pregnancy, because the drug does not penetrate the placental barrier due to low lipophilicity.

Local anesthetics

Mechanism of action

Local anesthetics reversibly block the spread of action potential along nerve fibers, preventing the onset of a sensation of pain without impaired consciousness.

The sensitivity of certain types of nerve fibers to the blocking action of local anesthetics is different. Thin fibers turn off earlier than thick ones. From here arises a sequence of loss of sensitivity: pain, temperature, tactile, pressure. The effect attenuation occurs in the reverse order - pain sensitivity returns last.

The less myelinated the nerve fiber, the less it is protected from the effects of a local anesthetic and the faster it undergoes anesthesia. The exception is myelinated preganglionic autonomous B-fibers (innervate the smooth muscles of the vascular wall), which are blocked before all other nerve fibers, including thin ones.

With spinal and epidural anesthesia, blockade leads to vasodilation, followed by a decrease in blood pressure.

Pharmacological properties

The ability to diffuse: anesthetics diffuse in the form of a free base. The active form of the local anesthetic molecule is the cation; therefore, the concentration of cations determines the distribution of the blockade. The alkaline environment of the solution promotes better penetration of the local anesthetic, and acidic (for example, infected tissue) - reduces the proportion of cations, and a smaller amount of local anesthetic reaches the nervous tissue.

Analgesic potential: determined by the degree of lipophilicity.

Quality of analgesia: depends on the concentration of local anesthetic; low concentration analgesia (loss of pain sensitivity), high concentration anesthesia (loss of tactile sensitivity).

Motor blockade: more pronounced and occurs earlier with a high concentration and lipophilicity of the anesthetic.

Onset time: Depends on the diffusion distance, local anesthetic concentration, fat solubility and the presence of vasoconstrictors.

Duration of action: determined primarily by lipophilicity and the degree of binding to proteins, less - by the size of the molecule. The duration of action the longer, the greater the selected concentration. Table Classification of local anesthetics (examples of drugs) by duration of action

Short duration of action (30-60 min) Average duration of action (60-120 min) High duration of action (up to 400 min)

Procaine (procaine) Lidocaine (xylocaine). Mepivacaine (scando-nest). Prilocaine (xi-lonest) Tetracaine (gerviros). Boopi-wacaine (carbostezin). Ropi-wacaine (napropin)

After injection of a local anesthetic, the patient does not feel separate noses, but cries out when the skin is cut.

Reason: blockade is still insufficient. In this case, individual irritations are not perceived, but with prolonged stimulation, individual impulses pass and the patient feels pain (significantly mitigated).

Treatment: wait, re-inject a local anesthetic, perform analgesia with sedation, for example, midazolam in a dose of 2-4 mg (dormicum *), if necessary, add 1-3 ml of a “cocktail” (1 ml = 0.5 mg mid zolam and 10 mg ketamine).

Distribution of analgesia: Depends on diffusion and volume of distribution (volume and rate of administration).

Total dose: may vary depending on the concentration and volume of the injected solution. Increasing the dose accelerates the onset of action, increases its duration and the success of anesthesia. (Attention: you can not sharply increase the volume)

Adding vasoconstrictors to the anesthetic solution: (epinephrine 1: 200 thousand) reduces blood circulation in the tissue and anesthetic resorption, thereby accelerating the onset of the effect and increasing the duration of action.

Addition of CO2: with an increase in acidity in nerve fibers, the onset of the effect and the depth of analgesia increase (debatable).

Addition of bases (bicarbonate): if the pH and the proportion of undissociated molecules increase, diffusion is facilitated, and the action of the anesthetic occurs earlier.

A combination of several local anesthetics: earlier their effects appear, the duration of action increases, and toxicity decreases.

! An increase in the concentration of local anesthetic with a constant volume (for example, 10 ml of a 0.5% solution of bupivacaine instead of 10 ml of a 0.25% solution of bupivacaine) leads to an increase in the amount of anesthetic administered and the onset of the effect.

! An increase in the volume of the solution with a constant total amount of anesthetic (20 ml of a 1% solution of mepivacaine instead of 10 ml of a 2% solution of mepivacaine) leads to a more rapid spread of the drug from the injection site to the adjacent areas.

! Heating a local anesthetic solution (for example, when wearing trousers in a pocket) accelerates the onset of the effect.

Elimination of anesthetics from the field of action and biotransformation

A local anesthetic in the form of a free base (non-dissociated form) quickly diffuses into the surrounding tissues, penetrates into the blood vessels and is removed from the injection area. In addition, due to vasodilation, anesthetic resorption occurs very quickly (if vasoconstrictors have not been administered).

Local ether type anesthetics (e.g. procaine, tetracaine)

In the bloodstream, drugs are cleaved by plasma pseudocholinesterase; decay products do not have anesthetic effect, are not toxic in the resulting doses; destruction occurs in the liver (with the exception of cocaine).

The destruction rate of procaine (1 mg / min) and tetracaine (0.25 mg / min) results in a very short half-life. Because of this, with accidental intravascular administration, a high plasma concentration remains for a very short time. Attention: with a deficiency of pseudocholinesterases or with their low activity, a clinically significant lengthening of the half-life period is noted.

Amide type local anesthetics (lidocaine)

• They undergo biotransformation in liver cells: oxidative hydroxylation with monooxygenases and enzymatic hydrolysis of carboxyl esterases (with the exception of prilocaine). The process proceeds more slowly than cleavage by esterases.

The half-life of 1.5-3.5 hours; the induction of microsomal liver enzymes (for example, barbiturates) accelerates metabolism, and a decrease in liver perfusion or disease slows down. Kidney disease does not affect the excretion of local anesthetics.

Supplementary vasoconstrictor administration

Epinephrine

• Trade name suprarenin : ampoule (1 ml) contains 1 mg (1: 1000).

• Dosage regimen: 1: 200 thousand - 0.1 mg = 0.1 ml per 20 ml of local anesthetic (tuberculin syringe); maximum dose 0.25 mg = 0.25 ml epinephrine 1: 1000.

Ornipressin

• Trade name - sandoz POR 8 ; 1 Unit per 10 ml of local anesthetic.

• Pharmacokinetics: the effect develops more slowly than epinephrine. Because of this, concentration is often increased, which increases the risk of side effects.

Mechanism of action: the introduction of vasoconstrictors not only increases the duration of local action of the anesthetic with a decrease in perfusion in the intervention area, but also prevents large concentrations of the drug from entering the bloodstream.

Side effects

Epinephrine: in high doses - reflex apnea, increased blood pressure, in low doses - the risk of lowering blood pressure.

Ornipressin : increased blood pressure, angina pectoris, bradycardia, pallor of the face (centralization of blood circulation). Incompatible with halotane!

Contraindications

With anesthesia in the region of the terminal arteries (fingers and toes, ears, penis), there is a danger of gangrene with circular administration.

Arterial hypertension, glaucoma (angle-closure), mitral stenosis, gestosis, thyrotoxicosis, diabetes mellitus, arteriosclerosis, myocardial disease, paroxysmal tachycardia, arrhythmia with a tendency to tachycardia, ischemic heart disease, treatment of TCA.

Epinephrine should not be administered during halotane anesthesia due to

dangers of heart rhythm disturbance. ! Vasoconstrictors enter the bloodstream → it is necessary to remember the side effects (Table 5-7). Ornipressin * is less toxic than epinephrine.

Side effects and complications

The higher the dose of local anesthetic, the higher its plasma concentration and, accordingly, the risk of side effects

HELL - blood pressure. BCC is the volume of circulating blood. CNS - Central nervous system. Heart rate - heart rate. ECG - electrocardiography.

The stronger the anesthetic effect, the higher the toxicity to the central nervous system.

Side effects and complications of the use of local anesthetics and adjuvants

The higher the concentration of the anesthetic in the plasma and the faster the increase in this concentration, the greater the risk of central side effects and the more severe the reactions.

The degree of toxicity (to reduce): tetracaine, bupivacaine, ropiva-cain, lidocaine, mepivacaine, prilocaine, procaine.

Allergy

Allergic reactions to local anesthetics are very rare, and only to ether-type substances. The severity of an allergic reaction does not depend on the dose administered.

Pathogenesis

• Many amino esters are derivatives of para-aminobenzoic acid, which some patients are allergic to. Para-amino benzoic acid is formed by cleavage of tetracaine and procaine with pseudo-cholinesterase.

• With the destruction of the amino amides of bupivacaine, ropivacaine, lidocaine, mepivacaine, prilocaine, paraaminobenzoic acid does not form. However, some preparations contain a preservative methyl 4-hydroxybenzoate (methylparaben), which may be allergenic due to the paragroup contained in the molecule (xylocaine0, xylonest , meaverine , scandonest).

Clinical manifestations: allergic dermatitis (redness of the skin, itching), asthmatic attacks, anaphylactic shock.

Treatment: if there is a history of allergy to local anesthetics in case of allergic diathesis, preoperative prophylaxis with antihistamines (dimetinden, for example, fenistil) is carried out, the patient is constantly monitored during the operation. Central nervous system reactions

Pathogenesis: Small-sized molecules of local anesthetics easily penetrate the blood-brain barrier (BBB) rapid accumulation in the central nervous system.

Clinical manifestations

• Two-phase course: with a low content of anesthetic in plasma - an inhibitory and anticonvulsant effect; higher concentrations lead to excitement.

• Signs of a preconvulsive state: anxiety, dizziness, auditory and visual disturbances, tinnitus, formation (tongue, lips), metallic taste in the mouth, blurred speech, trembling, muscle twitching.

! With a further increase in the concentration of local anesthetic, convulsions and respiratory arrest develop; with intravascular administration of an anesthetic, convulsions can occur without any preliminary symptoms. ! During the first 20-30 minutes after injection of a local anesthetic, it is necessary to carefully monitor the patient (verbal contact!). An unexpected anxiety of a patient is most often an early sign of central nervous system intoxication! Analeptics of central action (for example, acetazolamide, in particular diamox *) should not be administered: they are contraindicated for intoxication with a local anesthetic! Cardiovascular Reactions

The most common side effect is a violation of myocardial conduction (expansion of the QRS complex, blockade). Direct negative inotropic effect prevails. This may be accompanied by a reduction in the force of contractions by 25% with a strong decrease in blood pressure.

The order of development of cardiovascular side effects: bradycardia, arterial hypotension (decreased cardiac output), sometimes arrhythmias, blockade, asystole.

The vasodilating effect of local anesthetics does not have a toxic effect on the cardiovascular system and hemodynamic parameters. Methemoglobinemia

Methemoglobin is not able to carry oxygen. Normally, all methemoglobin that is formed in a red blood cell, glucose-6-phosphate dehydrogenase is converted back to hemoglobin.

Pathogenesis: enzyme deficiency (5-20% of patients from southern Europe and Africa) leads to pathological sensitivity to methemoglobin-forming poisons and a tendency to hemolytic crises after the administration of various drugs (e.g., antiarrhythmic drugs, sulfonamide diuretics).

Diagnosis: reduced recovery of methemoglobin in red blood cells with methylene blue.

Using pulse oximetry by the two-wave method, only oxyhemoglobin and deoxyhemoglobin (functional saturation) can be measured. The pathological forms of hemoglobin (methemoglobin, carbhemoglobin, sulfhemoglobin) and fetal hemoglobin are not detectable and are not taken into account when calculating saturation. That is why functional saturation based on the results of pulse oximetry, for example, at a high concentration of methemoglobin, is significantly higher than the actual saturation. ! All complications are treatable! The necessary conditions

Equipment: venous access, apparatus for anesthesia or mechanical ventilation, tools for intubation.

Prepare injectable drugs: sedatives - diazepam, midazolam; vasopressor drugs - amesinia methyl sulfate 0 (supratonin).

Drugs that should be ready for any local anesthesia: suxamethonium chloride (e.g., listenone), atropine, orciprenaline (e.g., alupent), electrolyte solutions, β-blockers (e.g., metoprolol), norphenefrin0 (e.g. novadral0).

Clinical application

Regional anesthesia

• Peripheral: blockade of individual nerves, blockage of nerve trunks or plexuses

• Central: lumbar, caudal, thoracic epidural anesthesia high, medium, low spinal anesthesia, sacrum block

Superficial anesthesia

Localization: the mucous membrane of the nasal cavity, mouth, pharynx, tracheo

bronchial system, esophagus, genital tract.

Choice of substance: 4% lidocaine solution or 2% gel (for example, xyloka-in0), 2% mepivacaine gel (for example, meaverine), 2% tetracaine solution.

Pharmacokinetics: the maximum effect develops after about 5 minutes, the duration of action is from 15-30 minutes (lidocaine) to 60 minutes (tetracaine), a relatively high plasma concentration occurs in a short time.

Infiltration Anesthesia

• Localization: extravasal, intradermal, subcutaneous, intramuscular; special form - intravenous regional anesthesia

• Choice of substance: 1% lidocaine solution (xylocaine 0) or 1% mepivacaine solution (scandonest) is preferred.

Example of calculating the maximum dose from mg in ml (bupivacaine)

Maximum single dose: 150 mg = 30 ml of 0.5% bupivacaine (1% solution contains 1 g of active substance in 100 ml).

Conversion of percent in mg:% x 10 x ml = total amount (mg). 30 ml 0.5% bupivacaine: 0.5 x 10 ml x 30 = 150 mg.

Prevention of Thromboembolism and Anticoagulants

Despite the fact that the risk of spinal hematomas during regional anesthesia near the spinal cord usually remains low (according to Tryba et al. - 1: 200 thousand), in case of blood coagulation disorders this complication may have neurological consequences for the patient. That is why the issue of spinal or epidural anesthesia during treatment with anticoagulants (or when planning such treatment) remains controversial.

Anticoagulants and surgery

• If the patient is taking acetylsalicylic acid or using low doses of unfractionated or low molecular weight sodium heparin for the prevention of thrombosis at certain time intervals, he can be given regional anesthesia

• When prescribing prophylactic doses of heparin sodium, it is not necessary to conduct a blood coagulation test.

• At least 8 hours should elapse between subcutaneous injection of low molecular weight sodium heparin and placement or removal of an epidural catheter (prevention of hemorrhagic complications). Low molecular weight sodium heparin can be administered on the evening before surgery for the prevention of thromboembolism, which does not interfere with regional anesthesia.

• When combining several anticoagulants, care must be taken, since it is not possible to accurately assess the risk of bleeding.

Already existing anticoagulation therapy with vitamin K antagonists and sodium heparin is a contraindication for puncture or removal of the epidural catheter.

• If you need to perform a puncture for a patient who plans to administer sodium heparin during surgery, you must postpone the operation for at least 12 hours. Performing an epidural puncture on the evening before surgery helps to avoid delay.

Bupivacaine

Trade name - carbostezin : 0.25, 0.5 and 0.75% solution; bupivacaine-voelm : 0.25, 0.5 and 0.75% solution; 1 ml contains 2.5, 5 and 7.5 mg of bupivacaine hydrochloride, ampoules of 5 ml and 20 ml.

Mechanism of action: local anesthetic.

Indications: therapeutic conduction anesthesia, conduction anesthesia for long-term operations, sympathetic block, spinal, epidural anesthesia.

Dosage regimen: recommended maximum doses of 150 mg (up to 60 ml of 0.25% solution, or 30 ml of 0.5%, or 20 ml of 0.75%), in children and adults in serious condition - 2 mg / kg .

Side effects: see 5.4.5.

Contraindications: severe violations of the action potential, hypersensitivity to local amide type anesthetics, cardiogenic and hypovolemic shock, should be used with caution in patients with liver diseases.

Drug interaction: weakens the effect of sulfonamide diuretics. Lidocaine

Trade name xylocaine 0.5, 1, and 2% solution: 1 ml of the drug contains 5, 10 or 20 mg of lidocaine hydrochloride with or without a vasoconstrictor, 10 ml ampoules and 50 ml vials; lidocaine hydrochloride 1% brown (5 ml) contains 50 mg of lidocaine hydrochloride in water for injection .

Mechanism of action:

Indications: infiltration anesthesia, conduction anesthetics

syria, sympathetic blockade, therapeutic and diagnostic blockades, spinal anesthesia.

Dosage regimen

• In adults with normal body weight (70 kg), the maximum dose is 200 mg (40 ml of 0.5% solution, or 20 ml of 1%, or 10 ml of 2%).

• In children and adults in serious condition - no more than 2.9 mg / kg; lidocaine hydrochloride 1% brown: in children do not exceed a dose of 7 mg / kg.

Contraindications: severe violations of the action potential, hypersensitivity to local amide type anesthetics, cardiogenic and hypovolemic shock, use with caution in patients with liver diseases (vasoconstrictors).

Drug interaction: weakens the effect of sulfonamide diuretics.

Mepivacaine

Trade name - meaverine *, 0.5, 1 and 2% solution: 1 ml contains 5, 10 or 20 mg of mepivacaine hydrochloride; ampoules of 2 and 5 ml.

Mechanism of action: weak vasodilator effect, the effect is longer than that of lidocaine.

Indications: 0.5% solution for infiltration anesthesia and 1% for conduction anesthesia, sympathetic blockade, neurological treatment; 2% for conduction anesthesia.

Dosage regimen

• In adults with normal body weight (70 kg), the maximum dose is 300 mg (up to 60 ml of 0.5% solution, or 30 ml of 1%, or 15 ml of 2%).

• In children and adults in serious condition, no more than 4 mg / kg (with interventions in the ENT region - 200 mg).

Contraindications: severe violations of the action potential, hypersensitivity to local amide type anesthetics, cardiogenic and hypovolemic shock, use with caution in patients with liver diseases.

Drug interaction: weakens the effect of sulfonamide diuretics. Prilocaine

Trade name - xylonest *, 0.5, 1 and 2% solution: 1 ml contains 5, 10 or 20 mg of prilocaine hydrochloride, 10 ml ampoules, 50 ml vials.

Mechanism of action: weak vasodilating effect, no cumulation - reintroduction is possible.

Indications: infiltration anesthesia, conduction anesthesia, sympathetic blockade, therapeutic and diagnostic blockades.

Dosage regimen

• In adults with normal body weight (70 kg), the maximum dose is 400 mg (80 ml 0.5%, or 40 ml 1%, or 20 ml 2%).

• In children and adults in serious condition, not more than 3.8 mg / kg.

• In patients with anemia, impaired alveolar gas exchange and coronary insufficiency, the maximum dose is 400 mg.

Side effects: with severe anemia, an increase in the concentration of methemoglobin is possible. Contraindications

Severe disturbances in the conductivity of the action potential, hypersensitivity to local amide type anesthetics, cardiogenic and hypovolemic shock, should be used with caution in patients with liver diseases.

Due to the formation of methemoglobin, it is not used in the following risk groups: anesthetic aid in obstetrics in newborns and premature babies, with a deficiency of glucose-6-phosphate dehydrogenase (history!).

Drug interaction: weakens the effect of sulfonamide diuretics.

Methemoglobinemia

Pathogenesis: the formation of o-toluidine with inhibition of the restoration of metgeoglobin to hemoglobin and an increase in the concentration of methemoglobin. The use of prilocaine in doses of more than 600 mg (prolonged epidural anesthesia) is prohibited, the maximum concentration is observed 2-3 hours after injection. Clinical manifestations: cyanosis of the skin at a concentration of hemoglobin of 3-5 g / dl (approximately 15-20% of total Hb).

Treatment: 10 ml of a 2% solution of methylene blue intravenously (repeat 1-2 times) or 10 ml of 0.2% thionine * (catalysis *) intravenously; with insufficient glucose-6-phosphate dehydrogenase, toluidine blue is introduced, since methylene blue will lead to increased methemoglobinemia.

Procaine

Trade name - novocaine *, l and 2% solution: 1 ml of the drug contains 10 or 20 mg of procaine hydrochloride, packaged in 2 and 5 ml ampoules, 50 ml vials.

Mechanism of action: the delay in the onset of the effect, the duration of the action is less than with identical doses, for example, lidocaine.

Indications: infiltration anesthesia, peripheral blockade.

Dosage regimen: 500 mg each (50 ml of 1% solution or 25 ml of 2%).

Side effects: see 5.4.5. Essential anesthetic. Belongs to the least toxic local anesthetics (methemoglobinemia, see. "Prilocaine").

Contraindications: allergy to procaine, benzoic acid, sulfonamides, combination with sulfonamides, acetylcholinesterase inhibitors, deficiency of pseudocholinesterase activity, circulatory failure of III and IV degrees, cardiac arrhythmias (bradyarrhythmia, AV block), myocardial infarction.

Drug interaction: weakens the effect of sulfonamide diuretics; acetylcholinesterase inhibitors increase the concentration of procaine in the plasma. Ropivacaine

Trade name - napin *, 0.2, 0.75 and 1.0% solution; 1 ml contains 2, 7.5 or 10 mg of ropivacaine hydrochloride. Ampoules of 10, 20, 100 and 200 ml.

Mechanism of action: local anesthetic.

Indications: infiltration anesthesia, conduction anesthetics

syria, epidural anesthesia, analgesic therapy. Dosage regimen: single dose:

• epidural anesthesia for surgical interventions: <250 mg (15-25 ml of 0.75% solution, 15-20 ml of 1% solution);

• lumbar epidural anesthesia for the treatment of acute pain: <10-20 ml of a 0.2% solution;

• with prolonged epidural infusion for postoperative analgesia and analgesia in obstetrics <6-10 ml / h of a 0.2% solution;

• for small nerve blocks and infiltration anesthesia 1-100 ml of 0.2% solution.

Contraindications: intravenous regional anesthesia, hypersensitivity to local amide type anesthetics, paracervical anesthesia in obstetrics, hypovolemia, severe renal and hepatic insufficiency, partial or complete AV block, children under 12 years of age.

Drug Interactions: Slow calcium channel blockers (e.g. fluvoxamine, verapamil) increase the concentration of ropivacaine in the blood.

Other medicines

Antiarrhythmic drugs Atropine

Trade name - atropine sulfate, 1 ml of solution contains 0.5 mg.

Pharmacokinetics: duration of action: 30-120 min; 50% is excreted in urine.

Mechanism of action: m-anticholinergic. It causes pupil dilation (mydriasis), inhibition of salivation and sweating, bronchodilation, has a positive chronotropic effect on the myocardium, inhibits gastrointestinal motility, and relieves bladder spasm.

Indications

• Bradyarrhythmias.

• Decreased tone of the parasympathetic nervous system for diagnostic or therapeutic interventions (gastroscopy, gastric lavage, pleural puncture), anesthesia (debatable).

• Antidote for poisoning with parasympathomimetics (for example, neostigmine methyl sulfate) or FOS (E 605).

Limitation of indications: for grade III AV block, 0.5 mg of orcy-prenaline0 is introduced into 50 ml of a 0.9% sodium chloride solution through a perfuser (alupent0) to alleviate the condition before setting up an EX.

Dosage regimen

0.25-0.5 mg intravenously, repeated dose up to 2 mg (with the exception of grade III AV block and intoxication).

In case of poisoning with organophosphorus compounds: the initial dose is 50-100 mg intravenously, until the symptoms of parasympathetic activation disappear (miosis!), Then through the perfuser 500 mg = 50 ml at a rate of 0.5-20 ml / h, depending on the symptoms.

Side effects: dry mouth, constipation, paralytic intestinal obstruction, glaucoma attacks, mydriasis, urination disorders (urinary retention), redness of the skin, fever, supraventricular and ventricular tachyekstrasi-stolii (rare), confusion

Contraindications

None in life-threatening conditions.

In other cases: glaucoma, tachyarrhythmias, acute pulmonary edema, impaired urination with the presence of residual urine, mechanical gastrointestinal stenosis.

Drug interaction

Potentiation of action: all substances with anticholinergic action, for example, antihistamines, antiparkinsonian drugs, tri- and tetracyclic antidepressants, antipsychotics, quinidine, disopyramide 0.

Weakening of the effect: a decrease in the motility of the gastrointestinal tract when taking antagonists of dopamine receptors (for example, metoclopramide).The introduction of 0.04 mg / kg intravenously completely blocks the cardiotropic effects of the vagus nerve (with a mass of 50 kg 2 mg intravenously).

In case of poisoning with organophosphorus compounds, obidoxime * is additionally administered at a dose of 0.25 mg intravenously.

With intravenous administration, ventricular fibrillation is possible.

In the first 1-2 minutes, paradoxical bradycardia is possible. ! Atropine fever.

In case of overdose or intoxication (belladonna), AV blockade may occur.

Antidote: neostigmine methyl sulfate at a dose of 0.01-0.035 mg / kg intravenously slowly.

Ipratropium bromide

The trade name is itrop0, the ampoule (1 ml) contains 0.5 mg of the drug, the tablet contains 10 mg.

Pharmacokinetics: low oral bioavailability due to poor absorption in the digestive tract; the time to reach a 50% concentration in plasma is 3.5 hours, the volume of distribution is 2.5 l / kg, binding to plasma proteins is 20%; after intravenous administration, up to 50% of the substance is excreted unchanged by the kidneys, the remainder is metabolized in the liver.

Mechanism of action: blocks the receptors of postganglionic parasympathetic neurons, with inhibition of the muscarinic-like effects of acetylcholine.

Indications: bradyarrhythmias (sinus bradycardia), bradyarrhythmias with blockade of the sinus node, AV block II degree with Wenckebach periodics, absolute bradyarrhythmias with atrial fibrillation.

Dosage regimen

Inside: individually in the range of 2-3 times at 10, 15 or 20 mg / day.

Intravenously: single dose - 0.5 mg. Side effects:

Contraindications

Absolute: glaucoma, prostate hyperplasia, gastrointestinal stenosis.

Relative: early pregnancy

Drug interaction: potentiation of the action of all substances with a cholinolytic effect, for example, antihistamines, antiparkinsonian drugs, TCAs, antipsychotics, quinidine, disopyramide 0.

Quaternary ammonium compound does not penetrate the central nervous system and

It does not cause central side effects. ! Antidote: physostigmine 0.01-0.05 mg / kg intravenously slowly (anticholium). Lidocaine as an anti-arrhythmic drug

Trade name - xylocaine 0, 2% solution, ampoule (5 ml) contains 100 mg, special ampoule (5 ml) contains 1000 mg.

Pharmacokinetics: oral bioavailability is low due to the pronounced effect of the first passage through the liver, therefore only intravenous administration is justified. The half-life of 1.6 hours (phase α is 15 minutes), the volume of distribution is 1.5 l / kg, binding to plasma proteins of 65%, is biotransformed in the liver: mostly through the formation of a pharmacologically active metabolite of monoethylxylidide (half-life of 3 hours) to inactive meta-pains. The effect develops 1-2 minutes after intravenous administration, the duration of action after one injection is about 15-20 minutes, the therapeutic plasma concentration is 2-5 mg / l (8.5-21.5 μmol / l).

Mechanism of action

• Class IB antiarrhythmic.

• Rest potential - 0, spontaneous diastolic depolarization (automatism) 1, fast action potential 1, depolarization rate 1, excitation conductivity 1, action potential duration 1, effective refractory period 1, general refractory period T, slow action potential effects - 0, the power of contractions 1, a decrease in the level of catecholamines.

• The area of antiarrhythmic action: the sinus node + atria 0, the AV node 0, the bundle of His - 0, the ventricles - +.

Indications: ventricular extrasystole, ventricular tachycardia, prevention of ventricular arrhythmias in case of myocardial infarction, ventricular arrhythmias due to glycoside poisoning, TCA poisoning, mechanical irritation of the myocardium with ventricular extrasystoles, tirycardia pir-et-de-point)

Dosage regimen

Intravenously: the initial dose is 100 mg, repeated injections are possible after 5-10 minutes.

Through perfuser: one special ampoule contains 5 ml = 1000 mg of the drug in 50 ml of 0.9% sodium chloride solution, at a rate of 2-4 mg / (kg / h). With a body weight of 70 kg - 12-240 mg / h = 6-12 ml / h. ! In severe heart failure, shock, or liver failure, the dose should be reduced to 50% of the maximum (6 g / day).

Side effects: heart failure, ventricular extra-systole, ventricular fibrillation, sinus node weakness syndrome, AV block, tremor, confusion, convulsive seizures, coma.

Contraindications: intolerance to local anesthetics, AV blockade with a replacement ventricular rhythm.

Drug interaction: enhances the negative inotropic effect of antiarrhythmic drugs, cimetidine, propanolol, halothane.

It is well tolerated by patients and is characterized by controllability (a very short half-life). First-line antiarrhythmic agent for ventricular arrhythmias. ! It can be used during pregnancy (see 15.2.4). ! Perhaps a combination with antiarrhythmic drugs of classes IA, II, III, IV. ! When idioventricular rhythm in the framework of myocardial infarction is usually not used. ! Lidocaine significantly inhibits the automatism of additional pacemakers, do not enter with AV blockade with a replacement ventricular rhythm. ! Constantly monitor the concentration of K + in serum. ! Elimination of the liver slows down with low cardiac output.

Orciprenaline

The trade name is Alupent0, the ampoule (1 ml) contains 0.5 mg of the drug, the ampoule (10 ml) contains 5 mg, the tablet contains 20 mg.

Pharmacokinetics: the half-life (in plasma) with a single administration is 2 hours, the half-elimination period is much longer. Binding to plasma proteins 10%, excreted by the kidneys unchanged after conjugation with sulfuric acid. Mechanism of action: β1-, p2-adrenergic agonist.

Indications: sinus bradycardia; digitalis bradycardia; absolute bradyarrhythmia with atrial fibrillation, bradycardic conduction disturbances (for example, AV block II degree), an antidote for poisoning with β-adrenoblockers.

Dosage regimen

Intravenously: 1 ampoule of 0.5 mg in 10 ml of 0.9% sodium chloride solution (1:10 dilution): 5-10 ml, re-administration is possible.

Through perfuser: 1 ampoule = 5 mg (10 ml) in 50 ml of 0.9% sodium chloride solution at a rate of 10-30 mg / min = 6-18 ml / h.

! Subcutaneous, intramuscular and intubation tubes are also allowed.

Side effects: decreased blood pressure due to peripheral vasodilation, tachycardia, ventricular extrasystole, ventricular fibrillation, headache, tremor, psychosis, nausea; allergic skin reactions are possible.

Contraindications: obstructive cardiomyopathy, asystole, bronchial asthma (it is better to use β2-adrenergic agonists). Use with caution in acute myocardial infarction.

Drug interaction: reduces the antihypertensive effect of antidiabetic agents.

Poorly managed drug ("only someone who knows him well" uses alupent). With bradycardia, it is preferable to first use epinephrine. Tachyphylaxis

Antidote: β-blockers.

Pindolol

The trade name is Wisken *, the ampoule (2 ml) contains 0.4 mg of the drug, and the tablet is 5 mg.

Pharmacokinetics: oral bioavailability of 85%, half-life of 3-4 hours, volume of distribution - 2 l / kg, binding to plasma proteins - 60%; elimination - 50% by the kidneys unchanged, the rest is oxidized in the liver with the formation of inactive metabolites.

Mechanism of action

β-blocker, antiarrhythmic agent of class II.

Non-selective, pronounced internal activity, in addition, non-specific (quinidine-like) action on the membrane during poisoning.

Area of antiarrhythmic action: sinus node+, atria +, AV node++, His bundle 0, ventricles 0.

Indications: hyperkinetic cardial syndrome; sinus tachycardia with hyperthyroidism; supraventricular estrasystole; atrial tachycardia with a change in conductivity, especially with an overdose of digitalis; paroxysmal atrial tachycardia; atrial flutter and atrial fibrillation with good conduction; ventricular extrasystole caused by adrenergic agents; recurrent ventricular fibrillation as part of resuscitation measures; obstructive cardiomyopathy; arterial hypertension.

Dosage regimen

Intravenously: 2 ml = 0.4 mg, slowly, after 20 minutes, repeated injection of 1 ml = 0.2 mg.

Inside: 3 mg per day, 5 mg. Side effects and contraindications

Rhythm disturbances with a tendency to bradycardia, increased heart failure, bronchial obstruction, fatigue, depression, increased peripheral circulation disturbances (Raynaud's phenomenon), allergies, decreased blood pressure, nausea, diarrhea, constipation, muscle weakness.

With a sharp abolition of β-blockers, there is a danger of a withdrawal syndrome with tachycardia, angina pectoris, heart attack and cardiac arrhythmias → it is necessary to slowly reduce the dose. β-blockers can trigger spastic angina pectoris. ! Do not inject intravenously with slow calcium channel blockers. Use caution when combined with antiarrhythmic drugs IA and III classes with strong inhibition of conductivity. ! During pregnancy, it is better to use selective

β1-blockers.In severe renal failure, it is necessary to reduce the dose

Verapamil

The trade name is isoptin *, an ampoule (2 ml) contains 5 mg of the drug, ampoule (20 ml) contains 50 mg, a tablet contains 40, 80 or 120 mg, a tablet with a slow release (retard) contains 120 or 240 mg the drug.

Pharmacokinetics: oral bioavailability of 20% (due to pronounced metabolism during the first passage through the liver; bioavailability increases to 40% with prolonged use due to saturation of

hepatic metabolism); The half-life at the beginning of treatment is 4.5 hours, with prolonged use - 9 hours; distribution volume - 4 l / kg, binding to plasma proteins - 90%; elimination - destruction in the liver to inactive (norverapamil) and inactive metabolites.

Mechanism of action

Class IV antiarrhythmic: slow calcium channel blocker.

Area of antiarrhythmic action: sinus node+, atria +, AV node ++, His bundle - 0, ventricles - 0.

Indications

Paroxysmal supraventricular tachycardia, supraventricular tachycardia with a change in conductivity, atrial fibrillation with a one-to-one, supraventricular extrasystole with ischemia, arterial hypertension, ischemic heart disease, Prinzmetal angina, hypertrophic obstructive cardiomyopathy.

The blockade of the tachycardic action of β-adrenergic agonists during medication weakening of contractions during childbirth and therapy with theophylline.

Dosage regimen

Intravenously: 1 ampoule = 5 mg slowly for 2-3 minutes, re-administration is possible after 15 minutes.

Through perfuser: 2 ampoules of 20 ml = 100 mg in 50 ml of 0.9% sodium chloride solution at a rate of 2-5 ml / h.

The maximum dose of 10 mg / h = 5 ml / h; The maximum daily dose is 100 mg!

The therapeutic plasma concentration is 0.02-0.1 mg / L (0.04-0.2 μmol / L).

Side effects: AV block, bradycardia, heart failure, decreased blood pressure, constipation. Rarely: allergy, gynecomastia, gingival hyperplasia.

Contraindications: severe heart failure, sinus weakness syndrome, sinoatrial and AV block II and III degrees, atrial fibrillation and flutter in Wolff-Parkinson-White syndrome. Do not use in early pregnancy

Drug interaction: digoxin (increase in plasma glycosides), anticoagulants and antiplatelet agents (risk of bleeding due to inhibition of platelet aggregation), β-blockers (increased effect).

Atrial fibrillation and flutter in Wolf-Parkinson-White syndrome, with the possibility of "one

to one ”with ventricular tachycardia or ventricular fibrillation.

• Do not administer intravenously with β-blockers.

• Do not combine with antiarrhythmic drugs that strongly inhibit conductivity.

• Weak efficacy in sinus tachycardia, hence weak efficacy in postoperative sinus tachycardia.

• In case of liver failure, the dose should be reduced.

• Do not mix with alcohol-containing solutions - precipitation.

Antidote: volume administration, atropine, orciprenaline .

Cardiac Glycosides

Mechanism of action: a positive inotropic effect when calcium enters the myocardial cells, lengthening of the atrial refractory period (negative chronotropic effect) and slowing of AV conduction (negative dromotropic effect), which leads to a reduction in heart rate in supraventricular tachycardia. Enhancing pulse generation (positive batmotropic effect). For antiarrhythmic action, higher doses are needed than for positive inotropic.

Indications: supraventricular tachycardia, especially absolute tachyarrhythmia with atrial fibrillation or flutter, chronic heart failure III-IV FC (functional class).

Contraindications: hypertrophic obstructive cardiomyopathy, sinus node weakness syndrome (in the absence of EX), AV block II and III degrees, hypokalemia, hypercalcemia, Wolff-Parkinson-White syndrome with atrial fibrillation (inhibition of conduction in the extra bundle).

Before intravenous administration, monitor the concentration of K + and in case of decrease, first make up for it.

With hypercalcemia, the side effects of cardiac glycosides increase.

Do not prescribe for Wolff-Parkinson-White syndrome with atrial flutter or atrial fibrillation, since, due to the acceleration of aberrant conduction, ventricular tachycardia or ventricular flutter may occur. Drugs of choice for simultaneous administration with quinidine (reduce the anticholinergic effects of quinidine).

Side effects

• AV block, bradycardia, ventricular arrhythmias (attention: first of all, with hypokalemia), atrial tachycardia with blockade (typical rhythm disturbance in case of overdose).

• Nausea, vomiting, fainting.

• Confusion, impaired color vision, headache, neuralgia.

• Rarely - exanthema, eosinophilia, thrombocytopenia, gynecomastia.

Digitoxin

The trade name is Digimerk, the ampoule contains 0.1 or 0.25 mg, the tablet contains 0.1 mg, the mini-tablet contains 0.07 mg of the drug.

Pharmacokinetics: oral bioavailability of 90%, half-life - 7.5 days, the degree of decrease in concentration - 7%, distribution volume - 0.5 l / kg, binding to plasma proteins - 95%. Elimination: 25-30% of the kidneys in unchanged form, the rest undergoes biotransformation in the liver to pharmacologically weakly acting metabolites. The onset of action is 30-120 minutes after intravenous administration, 3-5 hours after ingestion. The therapeutic plasma concentration is 13-25 μg / L (17-33 nmol / L).

Dosage regimen

Intravenously: a saturating dose of 0.8-1.6 mg, depending on body weight. The initial dose is 0.1-0.5 mg, then inject 0.2 mg every 6 hours until a therapeutic effect is achieved. In case of rhythm disturbances with a tendency to tachycardia, the total saturating dose is administered within 24 hours.

Inside: digitalization by taking 0.07 mg 4 times a day for 4 days, then a maintenance dose of 0.05-0.1 mg 1 time per day.

Drug interactions: phenobarbital, phenytoin, spironolactone and rifampicin weaken the effect of digitoxin due to the induction of microsomal enzymes. Derivatives of coumarin, sulfonylurea and heparin sodium enhance its effect.

! If possible, do not use Anti-Dot during pregnancy: cholestyramine(quantalan) inside reduces the half-life of digoxin by half (4 x 8 g = 4 x 2 packets per day). With the introduction of digitalis-antidote BM (see 8.3.6), the effects of glycoside are immediately neutralized. 80 mg of digitalisantidot BM neutralize 1 mg of digitoxin. A concentration of digitoxin in plasma of 10 μg / L corresponds to a dose of 1 mg glycoside after final distribution.

Digoxin

The trade name is Novodigal *, an ampoule (2 ml) contains 0.4 mg, a tablet contains 0.2 mg, a small tablet contains 0.1 mg of the drug.

Pharmacokinetics: oral bioavailability (in the form of methyldigoxin as acetyl or acetyl or methyl group is cleaved in the intestines and liver) about 85%; elimination half-life - 36 hours; the degree of decrease in concentration is 20%; the volume of distribution is 6-7 l / kg, binding to plasma proteins - 25%; elimination: 60-80% of the kidneys unchanged, the rest with bile, partially after biotransformation in the liver. The onset of action is 10-30 minutes after intravenous administration, 2-3 hours after ingestion. The therapeutic plasma concentration of 0.7-2.0 μg / L (0.9-2.6 nmol / L).

Dosage regimen

Intravenously: a saturating dose of 0.8 mg 2 times a day on the first day, then a maintenance dose of 0.2-0.3 mg / day is prescribed. With tachycardia (fast digitalization): the initial dose is 0.4 mg, then a saturating dose of 0.8-1.6 mg is administered within 24 hours (under the supervision of an ECG monitor!).

Inside: 0.2 mg 3 times a day for 3 days, then 0.2 mg 1 time per day.

Drug interaction

• Amiodarone, quinidine, flecainide *, nifedipine, phenytoin, propafenone and verapamil increase the level of digoxin in plasma.

• When using diuretics or corticosteroids, an increase in the action of digoxin with hypokalemia is noted (primarily cardiac side effects!).

• Penicillins and salicylates improve digoxin absorption. Antacids, colestyramine ?, metoclopramide, neomycin, paraaminosalicylic acid, sulfasalazine reduce digoxin absorption.

• Thyroid hormones weaken the effect of digoxin.

• With the simultaneous introduction of antiarrhythmic drugs that significantly inhibit conduction, the blockade intensifies.

! Digoxin solution for intravenous administration contains 9.8 vol.% Ethanol.

! In renal failure, the dose should be reduced and the concentration of the drug in the plasma should be monitored.

Use during pregnancy, with the appointment of minimum doses

Antidote: 80 mg of antibodies to digitalis preparations bind 1 mg of digoxin within 6 hours. The concentration of digoxin in plasma of 1 μg / l corresponds to the administered dose of 1 mg. With supraventricular arrhythmias associated with digoxin, β-blockers are recommended, with ventricular tachycardia, phenytoin or lidocaine is recommended.

Antihypertensive drugs

Clonidine

The trade name is catapresan, 1 ml of the solution contains 0.15 mg of clonidine.

Pharmacokinetics: onset of action 5-10 minutes after intravenous administration, duration of action - 1-4 hours, half-life - 8 hours.

Mechanism of action: central stimulation of a2-adrenergic receptors, peripheral blockade of a2-adrenergic receptors.

Indications: arterial hypertension, alcohol delirium (sympatholysis).

Dosage regimen

Intravenously: dilute 1 ml of the drug in 9 ml of a 0.9% sodium chloride solution (1 ml = 0.015 mg), the initial dose is 0.03 mg, slowly injected.

Through perfuser: dilute 3 ampoules in 50 ml of 0.9% sodium chloride solution, inject at a rate of 1-5 ml / h.

Side effects: initial increase in blood pressure, bradycardia, dry mouth, sedation.

Contraindications: sick sinus syndrome with bradycardia, pheochromocytoma. During pregnancy only for strict indications

Drug interaction

• Strengthening the effects of alcohol, diuretics, sleeping pills, antipsychotics, vasodilators.

• Weakening of the action of TCAs with hypotensive effect.

! Hypertensive crises with an initial increase in blood pressure; with a sharp discontinuation of the drug - the development of arterial hypertension.

Dihydralazine *

The trade name is Nepressol *, an ampoule (2 ml) contains 25 mg of dihydralazine *.

Pharmacokinetics: elimination half-life of 1-2 hours, duration of action - 6 hours.

Mechanism of action: a vasodilator with a direct myotropic effect on smooth muscle cells of the vascular wall.

Indications: hypertensive crisis, arterial hypertension. The drug of choice during pregnancy.

Dosage regimen

Intravenously: dilute the contents of 1 ampoule in 10 ml of a 0.9% solution of sodium chloride, inject 2 ml fractionally under constant monitoring of blood pressure; second injections every 5-10 minutes.

Through perfuser: 3 ampoules per 50 ml of 0.9% sodium chloride solution; at a speed of 1-5 ml / h = 1.5-7.5 mg / h.

Side effects: reflex tachycardia, angina pectoris, leukopenia, drug-induced systemic lupus erythematosus, orthostatic hypotension, headache.

Drug interaction: antihypertensive agents (increased effect).

Contraindications: acute myocardial infarction. ! No dose reduction required for renal failure. ! Combination with β-blockers and nitroglycerin gives a good effect. Antidote: with an excessive decrease in blood pressure - the introduction of a volume of fluid.

Nifedipine

Trade name - Adalat *, 5 mg vials (50 ml), 5, 10 and 20 mg capsules; 10 mg tablets; 20 mg retard tablets, 20 mg quick-acting tablets.

Pharmacokinetics: rapidly absorbed by sublingual administration. Bioavailability of 65%, after complete biotransformation in the liver is excreted in urine; half-life of 2 hours

Mechanism of action: slow calcium channel blocker.

Indications: unstable angina (pre-infarction state, vasos-pastic angina, Prinzmetal angina, rest angina), myocardial infarction with spastic component (recurrent ST elevations), hypertensive crisis, pulmonary embolism.

Dosage regimen

Inside: 1 capsule (10 mg), bite under the supervision of a doctor, put under anesthesia under the tongue of patients.

Through perfuser: 1 vial contains 5 mg = 50 ml; 6.3-12.5 ml / h = 0.63-1.25 mg / h; preliminary bolus administration of 0.5-1 mg in 5 minutes = 5-10 ml in 5 minutes = 60-120 ml / h for 5 minutes

Side effects: tachycardia, negative inotropic effect, the “stealing phenomenon” (debatable!), Nausea, vomiting, itching, impaired liver function, decreased blood pressure due to the expansion of peripheral vessels, “hot flashes”, headache, edema of the lower limbs, allergies, phlebitis with intravenous administration.

Contraindications: severe heart failure, arterial hypotension, pregnancy .

Drug interaction: with β-blockers, cimetidine - lowering blood pressure.

Antidote with an excessive decrease in blood pressure: the introduction of a fluid volume, dopamine may be used.

Nitroglycerine

Trade name - nitrolingual *, ampoule (5 ml) contains 5 mg, ampoule (25 ml) contains 25 mg, ampoule (50 ml) contains 50 mg of the drug, pump-action spray / pocket spray / N-spray contains 0.4 mg / inhalation ; 0.2 mg, 0.8 mg and 1.2 mg capsules for sustained release, 2.5 mg sustained release capsules.

Mechanism of action

• Reduces blood pressure by direct vasodilation of predominantly venous vessels.

• Short half elimination period.

• For controlled hypotension, it is often not effective enough. Dosage regimen: 50 mg / 50 ml through a perfuser; initial dose

1-2 mcg / (kgxmin). Sodium nitroprusside

The trade name is Niprus, the ampoule contains 60 mg of sodium nitroprusside.

Pharmacokinetics

• When sodium nitroprusside is destroyed, cyanide is formed, which, with the help of thiosulfate, turns into thiocyanate. Sodium nitroprusside, cyanide and thiocyanate are excreted by the kidneys.

• Advantage of the drug: good controllability (quick start of action and weakening of the effect within a few seconds after cessation of administration), half-life of 2 minutes.

Mechanism of action: reduces blood pressure by direct action on smooth muscle cells of the vascular wall dilation of both arterioles and venules.

Dosage regimen

Intravenously: 60 mg of the drug in 500 ml of 5% glucose solution; the rate of drip infusion is determined depending on the clinical need. Or 60 mg in 50 ml of a 5% glucose solution through a perfuser at a rate of 0.3-8 μg / (kgxmin), which corresponds to approximately 1-28 ml / h in a patient weighing 70 kg in a heavy condition.

With the introduction of more than 2 μg / (kgxmin) combined with sodium thiosulfate in a ratio of 1:10, for example, sodium thiosulfate 10% or C-hydril, in an ampoule - 1 g of the drug. Dosage regimen: 0.5 mg / (kg / h).

Side effects: the risk of thiocyanide poisoning, especially with renal failure (cyanide groups disrupt tissue respiration - tissue hypoxia - shock). The most important laboratory symptom is increasing metabolic acidosis according to the results of the analysis of the gas composition of the blood. Reflex tachycardia, muscle twitches.

Drug interaction: narcotic, antihypertensive drugs, vasodilators, sedatives increase the decrease in blood pressure.

The strongest vasodilator.

Always enter in a shielded container. ! Antidote

• In case of cyanide intoxication 4-DMAP (4-dimethylaminophenol) l mg / kg methemoglobin-forming agent. Since cyanide has a greater affinity for methemoglobin than for cytochrome oxidase, it is released from the bond with cyanide. 15 minutes after the administration of DMAP at a dose of 150 mg / kg, an injection of sodium thiosulfate should be given - acceleration of renal elimination of sulfur-bound cyanide (in the form of thiocyanate).

• With an excessive decrease in blood pressure, dopamine must be administered.

Furosemide

The trade name is Lasix, the ampoule (2 ml) contains 20 mg of the drug, the ampoule (4 ml) contains 40 mg, the solution for infusion (25 ml) is 250 mg, the tablet contains 40 or 500 mg.

Pharmacokinetics: onset of action after 2-5 minutes, maximum effect 20-60 minutes after intravenous administration; the duration of action is about 2 hours, bioavailability when taken orally 70%, binding to plasma proteins 98%, elimination by the kidneys 67%.

Mechanism of action: loop diuretic, blocks NaCl transport in the ascending knee of the Henle loop; reduces venous tone and pressure in the pulmonary artery.

Indications: pulmonary edema, right ventricular failure, acute increase in pressure in the pulmonary artery, fluid retention in case of liver and kidney diseases, edema during burns, hypertensive crisis, hypercalcemia, hyperkalemia, poisoning (forced diuresis).

Dosage regimen

Intravenously: 40 mg slowly, repeat until the desired effect is achieved.

Through perfuser: with severe renal failure, 2 ampoules of 25 ml = 500 mg each at a rate of 50-100 mg / h = 5-10 ml / h, the maximum daily dose of 2000 mg.

Side effects: hypokalemia (attention: acute myocardial infarction, digitalis preparations - arrhythmias), hypocalcemia, metabolic alkalosis, decreased blood pressure, hemoconcentration (increased creatinine in the blood due to dehydration), thrombophilia, allergies (sulfonamide derivative), photophobia, photophobia spasms of the calf muscles, a feeling of pressure in the head, profuse sweating, hyperuricemia, vasculitis, anemia, leukopenia, thrombocytopenia. Provokes acute porphyria.

Drug interaction: antidiabetic agents (decrease in blood glucose concentration decreases), antihypertensive drugs (blood pressure decreases), aminoglycosides (increased nephrotoxicity), non-depolarizing muscle relaxants (potentiation of muscle relaxation), glucocorticoids (additional excretion of potassium), cardiac glycosides (with potassium deficiency enhances the effect of glycosides), lithium salts (increased lithium concentration - increased cardio and nephrotoxicity), NSAIDs (reduce the effect of furosemide), salicylates (salicylate toxicity increases), theophylline (potentiation of action), pressor amines (for example, epinephrine - weakening of the action of amines).

Contraindications: hypovolemia, hyponatremia, severe hypokalemia, impaired liver function (precoma and hepatic coma), hypersensitivity to sulfonamides (cross-reactions), renal failure with anuria. When pregnancy is prescribed according to strict indications

Caution: arterial hypotension.

Before intravenous administration, eliminate urination disorders.

Careful monitoring of the concentration of electrolytes, creatinine and sodium hydrogencarbonate in the blood with intravenous administration.

In pulmonary edema, the initial effect is manifested even before the appearance of diuresis by reducing the tone of the veins and pressure in the pulmonary artery.

A strong and abrupt change in fluid balance in the body should be avoided. Intravenous administration of high doses is permissible only according to vital indications (pulmonary edema).

Blood clotting drugs

Aprotinin

The trade name is trasilol, an ampoule (5 ml) contains 100 thousand KIU ~ 14 mg, an ampoule (10 ml) contains 200 thousand KIE ~ 28 mg, an ampoule (50 ml) contains 500 thousand KIE ~ 70 mg aprotinin.

(KIE - unit of kallikrein inactivator, intravenous administration).

Pharmacokinetics: for parenteral administration only; the volume of distribution is about 20 l, binding to plasma proteins is 80%. Initial half-life (distribution in the extracellular space) 0.3-0.7 hours; The elimination half-life is 5–10 hours; it accumulates in the kidneys and in a small amount in the cartilaginous tissue, practically does not enter the CSF and penetrates very limitedly through the placental barrier. Elimination occurs by lysosomal cleavage in the kidneys to inactive proteins and amino acids excreted in the urine (in case of impaired renal function, a dose reduction is not necessary!).

Mechanism of action: a polypeptide obtained from the lungs of a bull, an inhibitor of serine proteases, forms reversible complexes with trypsin, kallikrein, plasmin, protein C and a plasmin streptokinase complex, at the same time it has a platelet-stabilizing effect.

Indications: bleeding with hyperfibrinolytic disorders of hemostasis, hemostatic disorders, for example, postoperative, post-traumatic, with extracorporeal circulation, peripartally, complications of thrombolytic therapy.

Dosage regimen: allergic reactions are possible, therefore initially blockers of H1 and H2 receptors are initially administered, then 10 thousand KIU (= 1 ml) are injected and the patient is monitored for 10 minutes.

Hyperfibrinolytic bleeding: 500 thousand KIE intravenously (not faster than 10 ml / min), then 200 thousand KIE intravenously every 4 hours

Acute bleeding after thrombolytic therapy: according

1-2 million KIU for 10-20 minutes intravenously, then 70-100 thousand KIU / h intravenously.

Extracorporeal circulation: initial dose of 2 million KIU for 20 minutes intravenously, then 500 thousand KIU / h intravenously until the end of the operation. In addition, 2 million KIUs are introduced into the volume of filling of the heart-lung machine.

Primary hyperfibrinolysis: 500 thousand -1 million KIE intravenously.

Side effects: allergic or anaphylactic reactions, transient increase in plasma creatinine concentration, local thrombophlebitis.

Contraindications: caution with the previous use of aprotinin and / or allergic diathesis, in the first trimester of pregnancy.

Drug Interactions: Synergist of heparin sodium, but may cause resistance to it; depending on the dose, inhibits the effects of fibrinolytics.

! Consider monitoring heparin therapy.

! Plasma concentrations> 200 KIU / ml increase APTT but not

thrombin time. ! Coagulation time increases in systems activated by celite (hemochrom), but not in systems activated by kaolin (hemo-tech).

Do not mix in the same syringe with other medicines.

Tranexamic acid

Trade name cyclocapron. Ampoules (5 ml) of 500 mg for intravenous administration; coated tablets, 500 mg each.

Pharmacokinetics: it has sufficient bioavailability both with parenteral administration and with oral administration. The elimination half-life of 2 hours is excreted in the urine unchanged, with renal

insufficiency dosage adjustment is needed.

Mechanism of action: amino acid with antifibrinolytic properties (synthetic derivative of lysine); binds proteases that convert plasminogen to plasmin.

Indications: bleeding with generalized or local hyperfibrinolysis.

Dosage regimen

At 10-15 mg / kg IV bolus, followed by infusion at 1 mg / (kg / h). In acute bleeding: 1-2 g bolus, then infusion at 5 mg / (kg / h).

Contraindications: massive hematuria originating from the upper urinary tract (risk of ureteral obstruction).

Side effects: hypotension, color vision disorders, with prolonged treatment - myopathy, rhabdomyolysis, nausea, vomiting, redness of the skin.

Cyclocapron is incompatible with blood products and penicillin-containing infusion solutions.

Catecholamines

β-adrenergic agonists

Mechanism of action: relaxation of the smooth muscles of the bronchi, uterus and blood vessels (vasodilation with decreased blood pressure and reflex tachycardia), increased mucociliary clearance, increased ejection fraction of the right ventricle, and improved diaphragm contractility. Increased basal metabolic rate (caloric effect), increased glycogenolysis in muscles (hyperglycemia), lipolysis (increased content of free fatty acids in the blood)

Due to β1-adrenergic action, there is a great danger of arrhythmias! Intravenously, β2-adrenergic agonists are administered only to patients younger than 45 years old, without heart disease, with heart rate <130 per minute. Careful observation is required! Contraindications

Absolute: hyperthyroidism, hypertrophic obstructive cardiomyopathy, tachycarditis heart rhythm disturbances.

Relative: acute myocardial infarction, severe coronary artery disease, changes in blood glucose concentration.

Side effects

Often: palpitations, tachycardia, decreased blood pressure, muscle tremors (tremors), anxiety, nausea, sleep disturbances; hypokalemia (fenoterol, salbutamol, terbutaline), a paradoxical decrease in pO2 by 10% is possible due to an increase in the ventilation-perfusion ratio.

Rarely: impaired glucose utilization in diabetes mellitus, it is necessary to control the concentration of glucose in the blood. Angina pectoris, ventricular fibrillation. Epinephrine

Trade name adrenaline; ampoules (1 ml), 1 mg of the drug.

Pharmacokinetics: elimination half-life of 3-10 minutes, duration of action 3-5 minutes, distribution volume 0.3 l / kg; 1-10% is excreted by the kidneys in an unchanged form, re-uptake by adrenergic neurons is possible, but most are oxidized, methylated and conjugated with glucuronic and sulfuric acids in the liver.

Mechanism of action: sympathomimetic, agonist of all adrenergic receptors. In high doses, it primarily stimulates α-adrenergic receptors. Positive foreign, chrono, batmodromotropic effect on the heart; decrease in diastolic blood pressure (effect of stimulation of β2-adrenergic receptors). Low doses of epinephrine increase heart rate (by reflex activation of the vagus nerve?), While high doses reduce it again. Brain perfusion and O2 consumption with continuous administration of the drug increase dose-dependently without changing the resistance of the brain vessels. In most cases, there is an improvement in coronary blood flow.

Indications: the drug of choice during resuscitation measures (ventricular fibrillation, asystole, low-release syndrome; see 8.2.1 (in such situations, orciprenaline is usually not prescribed).

Dosage regimen

Intravenously: with zero blood pressure in the patient: 1 mg diluted 1:10, injected fractionally (2-4-6-10 ml) or diluted twice (1: 100) and injected 2-4 ml. Not for subcutaneous or intramuscular use!

Through perfuser: 0.01-0.4 μg / (kgxmin) 5 ampoules should be diluted with 0.9% sodium chloride solution to 50 ml = 100 μg / ml, in order to avoid unwanted bolus administration, it is best to infuse through separate clearance of the CVC.

Side effects: tachycardia, ventricular extrasystole, ventricular fibrillation, angina pectoris due to increased heart rate, increased blood glucose and blood pressure, tremor, decreased K + concentration.

Contraindications: obstructive cardiomyopathy.

Drug interaction: antidiabetic drugs (weakening the effect), halotane (amplification of cardiac arrhythmias), TCA (increased sympathetic activity), β-adrenergic blockers (the effects are opposite to the effects of epinephrine; lowering blood pressure).

With AV block, is it better to prescribe orciprenaline ?. ! During resuscitation, always administer sodium bicarbonate prior to administration.

! It is possible to administer through an endotracheal tube: dilute one ampoule in 10 ml of 0.9% sodium chloride solution, inject in a volume of 10 ml.

Dobutamine

Trade name - dobutrex ?, vial for injection (dry matter) = 250 mg.

Dobutrex? liquid: injection vial (20 ml) contains 250 mg.

Pharmacokinetics: elimination half-life of about 2 minutes, duration of action 1-5 minutes, distribution volume 0.2 l / kg, excreted after methylation and conjugation with glucuronic acid.

Mechanism of action: β1-, β2- and α-adrenoreceptor agonist, does not affect dopamine receptors. With simultaneous stimulation of β2 and α-adrenergic receptors, the predominant effect is an increase in cardiac output without a significant change in blood pressure. An increase in heart rate and pulmonary blood flow depends on the dose. Reduces pre- and afterload on the right and left ventricles, pulmonary vascular resistance and pulmonary artery pressure.

Indications: increased pre- and afterload in case of heart failure (acute or chronic), circulatory disturbance of extracardiac origin. With concomitant arterial hypotension, a combination with an α-adrenomimetic (vasoconstrictor), for example, dopamine (medium and high doses), norepinephrine, is possible.

Dosage regimen

Intravenously: 2.5-12 mcg / (kgxmin).

Side effects: tachycardia, arrhythmias, one-to-one treatment for atrial fibrillation, angina pectoris. Contraindications

Absolute: diseases in which normal filling and / or emptying of the ventricles is difficult due to mechanical causes (for example, with pericardial effusion, obstructive cardiomyopathy).

Relative: myocardial ischemia, hypovolemia. Drug Interaction: increased need for insulin preparations; β-blockers weaken the positive inotropic effect and cause peripheral vasoconstriction. ! Not intended for oral, enteral, subcutaneous or intramuscular administration. ! Do not dissolve in

alkaline solutions (pH> 8). ! It acts synergistically with sympathomimetics-vasoconstrictors, such as dopamine, norepinephrine. ! With continuous administration> 72 hours, tachyphylaxis occurs. ! Increased pulmonary blood flow, decreased right ventricular afterload, decreased pulmonary pressure, decreased left ventricular afterload.

! You should always compensate for a possible lack of volume, since the development of tachycardia with subsequent myocardial hypoperfusion is likely (due to shortening of diastole and low diastolic pressure).

Dopamine

The trade name is dopamine Giulini 50 *, the ampoule contains 5 ml = 50 mg; dopamine Nutterman *: ampoule (10 ml) contains 50 mg; dopamine Giulini 200 *: am-pool (10 ml) contains 200 mg; dopamine 200 Nutterman *: ampoule (5 ml) contains 200 mg; dopamine Giulini 250/500 *: ampoule (50 ml) contains 250 or 500 mg of the drug.

Pharmacokinetics: elimination half-life of 2-8 minutes, duration of action - 1-2 minutes, distribution volume - about 0.89 l / kg. Elimination is carried out through partial biotransformation into norepinephrine (at low doses up to 25%), as well as oxidation, methylation and conjugation with glucuronic acid.

Mechanism of action: dose-dependent stimulation of dopamine, α- and β1-adrenergic receptors.

Low doses: stimulation of dopamine and β1-adrenergic receptors, as well as indirect β2-stimulation due to the release of norepinephrine. Myocardial contractility and blood pressure do not change, OPSS decreases (dopaminergic arterial vasodilation), MOS does not change or increases slightly (improvement of organ perfusion).

Medium doses: stimulation of dopamine and β1-adrenergic receptors, indirect β2-stimulation. Myocardial contractility and blood pressure increase slightly, OPSS and renal blood flow do not change.

High doses: stimulation of dopamine and α-adrenergic receptors. Myocardial contractility, blood pressure, OPSS (generalized vasoconstriction) and MOS increase; renal blood flow is reduced.

Indications: heart failure due to increased pre-load with a decrease in blood pressure, increased perfusion of the kidneys, liver, and area of the celiac trunk (including the intestine).

Dosage regimen: the drug is not effective for enteral administration or ingestion. Do not inject subcutaneously or intramuscularly.

Low doses: 0.5-5 mcg / (kgxmin) (patient weighing 60 kg). Through perfuser: 250 mg per 50 ml of 0.9% sodium chloride solution = 5 mg / ml, 1-3.5 ml / h.

Average doses: 6-9 mcg / (kgxmin) via perfusion at a rate of 4-7.2 ml / h.

High doses: 10 mcg / (kgxmin) via perfusion at a rate of 8-16 ml / h.

Side effects: tachycardia, arrhythmias, angina pectoris, a sign of overdose - an increase in heart rate of more than 25 per minute (differential diagnosis with hypovolemia).

Drug interaction: guanethidine (enhanced effects), MAO inhibitors (it is necessary to reduce the dose of dopamine to 1/10 of the original).

Do not dissolve in alkalis (pH> 8), do not administer through one catheter

with sodium bicarbonate or haloperidol (loss of effect). ! Before using dopamine, compensate for any

lack of bcc. ! Synergism with dobutamine.

Tachyphylaxis (- interruptions in treatment are necessary). ! Caution for bleeding from an ulcer (increased bleeding).

“Ricochet effect”: arterial hypotension after withdrawal. In high doses: oliguria, circulatory disorders in the limbs with the possible development of necrosis, as well as excessive production of lactate. Due to increased pulmonary and peripheral resistance, it is necessary to combine the drug with nitrates or nifedipine.

Accidental near-venous administration: 5-10 mg of phentolamine diluted 1: 10, administered subcutaneously.

Antidote: in case of overdose, it is enough to stop the administration of the drug (short half-life).

Norepinephrine

The trade name is norepinephrine *, an ampoule (1 ml) contains 1 mg of the drug.

Pharmacokinetics: elimination half-life of 1-3 minutes, duration of action - 1-2 minutes, volume of distribution - 0.3 l / kg. Elimination: 3-15% of the kidneys unchanged, re-uptake by adrenergic neurons is possible, but most are methylated, oxidized, conjugated with glucuronic and sulfuric acids.

Mechanism of action: β1- and α-adrenoreceptor agonist.

Indications: septic shock, decreased OPSS (for example, due to the release of histamine in anaphylactic shock). Antidote for overdose of vasodilator tori.

Dosage regimen

Initial dose: 0.3 mg intravenously, do not enter subcutaneously or intramuscularly.

Through perfuser: 0.05-0.3 mcg / (kgxmin). Dilution: 3 or 5 ampoules in a 0.9% sodium chloride solution up to 50 ml = 60 or 100 μg / ml; to avoid unwanted bolus administration, it is best to administer a CVC through a separate lumen.

Drug interaction: TCA (increased sympathomimetic action), antidiabetic drugs (weakening effect), halothane (cardiac arrhythmias).

To think over therapy at centralization of blood circulation, acrocyanosis, anuria. ! The combination with dobutamine with reduced OPSS can cause hypotension (pulmonary artery catheterization!). ! Reduced renal blood flow leads to oliguria. ! Increased end diastolic pressure in the left ventricle.

With paravasal administration, the formation of necrosis is possible, immediately introduce 0.9% sodium chloride solution.

With cardiogenic shock, coronary circulation improves.

Alcoholic delirium (sympathomimetic symptoms are reduced).

Antidote: receptor blocker (tolazoline?).

Dexpanthenol

The trade name is bepanten *, 5 g contains 250 mg of dexpanthenol.

Indications: prevention of conjunctival lesions during operations, wounds, conjunctival and corneal burns, conjunctivitis, rhinitis.

Dosage regimen: lay a strip of ointment 1 cm long for a veco. Side effects: allergic manifestations (rarely). ! When using the ointment as an ointment for the nose, do not use the same tube for the eyes.

5.5.8. Calcium preparations

The trade name is Calcium Sandoz, 10 ml contains 2.25 mmol Ca2 +.

Indications

• Metabolic disorders and calcium deficiency: tetany, spasmophilia, pregnancy, lactation, fractures.

• The need for the appointment of urticaria, allergic edema, and electromechanical dissociation to increase the inotropic effect is questionable.

• Before hemodialysis in renal failure with severe hypo-calciumemia.

• Intoxication CCl4, oxalic acid, fluorides, lead. Dosage regimen

Adults: 10 ml injected slowly intravenously for 10 minutes, repeat as needed. Children: 2-5 ml intravenously.

Side effects: with too rapid administration, nausea, vomiting, sensation of heat, hypotension, heart rhythm disturbances.

Contraindications: hypercalcemia, severe renal failure, digitalis, shock.

Drug interaction: increased effects of cardiac glycosides. Attention: the introduction of epinephrine against a background of increased concentration of Ca2 + can lead to severe cardiac arrhythmias. ! Always evaluate the concentration of calcium in combination with the concentration of plasma albumin and BOR. ! Do not mix with phosphates.

GENERAL ISSUES OF MODERN INFUSIOLOGY

Liquid solutions intended for introduction into the body through a blood vessel are called infusion solutions.

Mandatory properties for infusion solutions are:

• fluidity,

• non-toxicity in a therapeutic dose, both for blood components and for organs,

• fairly easy dosage

• neutrality of the infusion medium, especially for various drugs,

• relative stability of the solutions used.

Classification of infusion solutions and purpose

According to the main characteristics of infusion media, several groups of solutions are distinguished. In different classifications, there are from 4 to 6 groups. But the so-called “working” classification looks more acceptable. Here, all infusion solutions are divided as follows.

• crystalloids.

• colloids.

• preparations of blood components.

It is based on belonging to inorganic and organic substances, as well as the possession or not of oncotic properties, which determines their properties and indications for use.

It is known that in the process of intensive therapy, often the main "nosological" diagnosis fades into the background, and the symptoms of complications of the disease itself, or of irrational, insufficiently balanced medical measures, emerge on the first. And because of how quickly and correctly the doctor will solve suddenly arising and unexpectedly changing situational tasks at the scene of the incident, during transportation, in the emergency room and at the patient's bedside, the outcome of the struggle for life depends. In this case, the urgency of the action of drugs directly depends on the route of its introduction into the body. And today there is no other way of administering a drug that is more suitable for quickly achieving the effect than intravascular infusion. It is difficult to disagree with the statement that "without it [infusion-transfusion therapy] there would simply not exist not only anesthesiology, but also all medicine in general"

The need for infusion-transfusion therapy is high at all stages of medical care: in multidisciplinary hospitals - in 30-40% of patients, in victims of accidents and catastrophes - up to 80%, in people in the departments of anesthesiology and intensive care, this figure reaches 100%.

Historical background on infusion therapy. The idea of introducing fluids into the bloodstream was expressed in 1616 by the discoverer of blood circulation William Harvey. After 1819, when the English surgeon J. Blondell performed the first blood transfusion from person to person, other doctors began to follow him, but the outcomes were not always optimistic, since it was not known about the existence of blood groups. By the middle of the XIX century, faced with serious difficulties of blood transfusion, they began to look for blood substitutes.

In 1830, on the advice of the chemist Herman, acidified water was injected into a vein with cholera, followed by saline solutions to cholera patients, in rare cases, by doctors Orlovsky and Thomas Latta in 1832.

In 1897, Quinton proposed using seawater for infusion. In 1936, A.A. Babsky and A.G. Sosnovsky in Odessa

Considering that the ratio of sodium, potassium and calcium in the blood of mammals approximates that in seawater, in 1940 they produced in the Odessa laboratory an AM-4 Babsky solution (aquamarinae). Other poly-ionic saline solutions were also proposed (Tyrode, Normozol, Norm, tutofusin, Kharkiv uk-rinfuzin, Leningrad solution No. 3 of Petrov and Filatov, as well as tablets for its preparation in front-line conditions, TsOLIPK Moscow salt infusion, etc.). In the postwar years, the study of infusion solutions continued, primarily to compensate for blood loss in hypovolemic shock.

TASKS OF MODERN INFUSIOLOGY

Previously, infusion therapy was considered an integral part of transfusiology - the science of blood transfusion and blood substitutes. Now transfusion of donated blood and its components is undergoing a conceptual review in connection with the increased threat of the transfer from the donor to the patient of viral infections such as hepatitis and AIDS, the cure of which is very problematic today. In surgery, where indications for transfusion therapy are especially frequent, even a direction called "bloodless surgery" has appeared, the main principle of which is the maximum compensation for blood loss due to artificial solutions that can perform most of the main functions of the blood, up to oxygen transport. And modern infusion therapy performs such multifaceted functions and has such a set of media with specific properties that transfusion therapy is rather one of the parts of infusion therapy, although transfusion has its own problems, in particular, those that make it related to transplantology.

Thus, infusion therapy is firmly included in the medical practice of doctors of various clinical specialties, and for patients who are in critical condition, it is an integral component of intensive

care. An indication for its purpose is the need to replenish water, protein and electrolytes lost by the body when it is impossible or difficult to receive them naturally through the digestive canal.

The main tasks of infusion therapy are as follows:

1. replenishment of intravascular and intercellular fluid ¬ volume (volume correction);

2. correction of violations of water metabolism and KShchS;

3. providing parenteral nutrition;

4. regulation of the rheological properties of blood;

5. correction of cell deficiency and individual blood components;

6. the introduction of drugs.

The versatility of modern infusion therapy is provided by such a wide variety of infusion preparations that there is a need to improve their classification. Classifications of infusion preparations according to their chemical structure were previously proposed. Thus, for example, the classification of A.N. Filatova and F.V. Balluseca (1973):

1. crystalloids:

a) saline solutions;

b) carbohydrates and alcohols;

2. colloids:

a) polysaccharides and polyalcohols;

b) synthetic polymers;

c) biopolymers;

g) proteins;

e) complex solutions.

However, firstly, to date, a number of drugs with a different chemical structure have been synthesized, and secondly, classification according to this principle is more important for pharmacological production. For clinical purposes, functional classification is more convenient.

There are 3 groups of funds:

to deal with shock,

for detoxification,

for parenteral nutrition

BASIC PRINCIPLES OF WATER-ELECTROLYTE EXCHANGE

Water, quantitatively the most important component of the body, is of fundamental importance for the body as an environment and a participant in the exchange of substances. The water content in people is different, individual. She, in particular, provides diverse metabolic processes in the body:

1) surrounds intracellular structures in cells and ensures their general activity;

2) carries out an exchange between cells;

3) is a transport medium in the exchange of substances between the outside world and active cells;

4) is involved in thermoregulation.

The total body water is usually divided into several sectors:

1. Intracellular.

2. Extracellular:

a) interstitial;

b) vascular.

The exchange of water in the body occurs as follows. During the day a person drinks about 1.2 liters of water, about 1 liter enters his body with food, about 300 ml of water is formed during the oxidation of nutrients. Under normal water balance, the same amount of water (about 2.5 l) is excreted from the body: by the kidneys (1–1.5 l), by evaporation by the skin (0.5–1 l) and the lungs (about 400 ml), and it is also excreted in feces (50-200 ml).

Water exchange is closely related to salt metabolism. About 90% of substances dissolved in the extracellular medium are electrolytes. In physiological terms, the most important of these are sodium, potassium, chlorine, and bicarbonate ions. Electrolytes, diffusing between sectors, help maintain a constant ion gradient, while non-diffusing colloids that do not penetrate the capillary membrane determine the direction, diffusion rate, and amount of ions moving.

The movement of water in liquid spaces follows several physiological principles: osmolality is the number of particles in 1 liter of solution, and osmolality is the assignment of particles to 1 kg of water. The average blood water content is 92% by volume; therefore, osmolality = osmolarity / 0.92. In clinical practice, these concepts are identical. Osmolarity is created by osmotically active substances - sugars, amino acids, urea, CO2, etc., which create osmotic pressure:

Osm = 1.86 x Na + glucose + 2 x urea nitrogen + 9

The pressure necessary to counteract the movement of water along a concentration gradient through a semipermeable membrane is called the osmotic pressure:

OD = osmolality x 19.3.

The total osmotic pressure, which is created by conventional concentrations of plasma components, is 5620 mm Hg. (291.2 mosmol / kg x 19.3 mm Hg / mosmol / kg H2O). If we compare the osmotic pressure of Ringer's solution of lactate (RL) (5268 mmHg) and physiological solution of sodium chloride (5944 mmHg), it becomes clear that the Ringer's solution of lactate replaces a slightly smaller volume of plasma than physiological solution, since less osmotic dilution of the plasma leads to the movement of water from the extracellular space into the intracellular in accordance with the osmotic gradient.

Osmolality of normal plasma is a fairly constant value and is equal to 285–295 mosmol / kg. Of the total plasma osmolality, only 2 mosmol / kg is due to the presence of proteins dissolved in it. Thus, the main components providing plasma osmolality are sodium and chlorine (about 140 and 100 mosmol / kg, respectively).

Plasma proteins, albumin and gamma globulins determine the colloid osmotic pressure of plasma (oncotic pressure). Oncotic pressure is less than 1% of the total osmotic pressure, but proteins are osmotically active and very important in terms of maintaining the volume of circulating plasma (CPP). Albumin restricts the movement of water into the interstitial space, despite the large concentration gradient (40 and 10 g / l). This allows you to maintain CPI and the volume of interstitial fluid.

The close relationship between water, electrolyte and acid-base equilibrium is determined by the physicochemical law of electroneutrality. This law consists in the fact that the sum of positive charges in all water spaces is equal to the sum of negative charges. Constantly occurring changes in the concentration of electrolytes in aqueous media are accompanied by a change in electric potentials with subsequent recovery. Thus, with dynamic equilibrium, stable concentrations of cations and anions are formed. A graphic image of this law can be presented in the form of a Gamble diagram

The content of anions in any water sector is equal to the content of cations. Violation of this principle leads to water-electrolyte and acid-base imbalances. For example, an increase in the concentration of chlorine decreases the concentration of bicarbonate (the main buffer), which leads to metabolic acidosis. If we assume that the sum of the concentrations of small plasma cations (potassium, calcium, magnesium) - the fluctuation limits are not large - is approximately 11 meq / l and equal to the sum of the concentrations of the residual anions, then the electrolyte equilibrium can be represented as follows:

[Na +] = [Cl-] + the sum of the bases,

sum of bases = [Na +] - [Cl-].

In clinical practice, the water-electrolyte balance mainly depends on the distribution of electrolytes such as sodium, chlorine, bicarbonate.

The distribution of water and electrolytes obeys not only the laws of osmolality. The presence of a sodium concentration gradient in the extra- and intracellular spaces and a negative intracellular charge could provide a force capable of moving sodium toward the cell. In reality, this does not happen, since such a force is balanced by another, acting in the opposite direction and called the sodium pump. The energy of the sodium pump, which is a specific property of the cell membrane, is provided by the hydrolysis of ATP and is aimed at expelling sodium from the cell. The same energy promotes the movement of potassium into the cell.

The constancy of the volume and osmolality of extracellular fluid is supported by regulatory mechanisms, the main effector of which are the kidneys. Irritation of osmoreceptors of the hypothalamic region (with increased blood osmolarity), as well as left atrium volume receptors (with a decrease in blood volume) enhances the release of vasopressin (ADH) by the supraoptic and paraventricular hypothalamic nuclei. Vasopressin enhances the reabsorption of water in the tubules of nephrons.

Irritation of the receptors of the renal arteriole leading to the kidney (with a decrease in renal blood flow, blood loss) and sodium receptors of the dense spot of the juxtaglomerular complex (with sodium deficiency) enhances the synthesis and release of renin. Angiotensin II formed under the influence of renin increases adrenal gland release of aldosterone, which increases sodium reabsorption. A decrease in extracellular fluid volume and angiotensin also stimulate the thirst center located in the lateral region of the hypothalamus.

Antidiuretic and antinatriuretic mechanisms are opposed by diuretic and natriuretic. The main acting factors of these mechanisms are renomedullary renal prostaglandins and an atrial natriuretic factor (ANF, atriopeptide). ANF is produced in atrial cells and is a peptide of 28 amino acids. It increases diuresis and natriuresis, relaxes the smooth muscles of blood vessels and lowers blood pressure. The content of ANF in the atrium and its secretion into the blood increases under the influence of taking excess water and sodium chloride, stretching the atria, with an increase in blood pressure, and also with the stimulation of α-adrenergic receptors and vasopressin receptors

Regulation of water metabolism is closely related to the state of volemia and the intensity of peripheral blood circulation, vascular permeability, and the ratio of hydrostatic and colloid osmotic pressure in the lumen of the capillary and interstitial space.

The dynamics of the fluid balance in the body is determined by the Starling equation:

Q = K (Pc - Pi) - r (pc - pi),

where Q is the transvascular fluid flow, depending on the balance of forces contributing to the filtration [K (Pc- Pi)] is the first component, and reabsorption [(r (pc - pi)] is the second component; K - filtration coefficient is the amount of filtrate passing through 100 g of tissue per minute with increasing pressure per mm Hg; Pc is the hydrostatic pressure in the capillaries; Pi is the hydrostatic pressure in the interstitium; pc is the oncotic pressure of the plasma; pi - oncotic pressure in the interstitium; r - reflection coefficient, describes the permeability of the membranes n.

As applied to practice, it follows from the Starling equation that the volume of each water sector depends on changes in hydrostatic and colloidal osmotic pressure. Hypoproteinemia (hypoalbuminemia), on the one hand, leads to a decrease in oncotic pressure and a decrease in CP, and on the other hand to interstitial edema. An increase in hydrostatic pressure, for example, with high-volume infusions of crystalloid, will also lead to interstitial edema with normal or increased CP.

CLASSIFICATION OF INFUSION SOLUTIONS

Infusion solutions are water-based drugs used for parenteral therapy to replenish and maintain water-electrolyte balance and ensure optimal body metabolism

There are various classifications of infusion solutions. According to the mechanism of therapeutic action, they are divided into the following groups: hemodynamic blood substitutes; detoxification blood substitutes; preparations for parenteral nutrition; regulators of water-salt metabolism and acid-base balance; blood substitutes with oxygen transfer function; infusion antigi-poxants and blood substitutes of complex action. According to one of the modern classifications, the following types of infusion solutions are distinguished:

1. Volume-substituting solutions (plasma substitutes and blood). The main purpose of their application is the rapid restoration of plasma and globular volumes, improving blood rheology.

2. Basic infusion solutions of glucose and electrolytes. They are used to maintain water-electrolyte balance.

3. Corrective infusion solutions, including molar solutions of electrolytes and sodium bicarbonate, designed to correct violations of the hydroionic and acid-base balance.

4. Solutions of diuretics. The main purpose of their use is the restoration of diuresis, the prevention of renal failure and detoxification.

5. Solutions - oxygen carriers (perftoran, metafusol), increasing the oxygen capacity of the blood and normalizing the normal oxygen regime of the body and metabolism.

6. Means of parenteral nutrition, which are substrates for energy supply.

Since in this paper we are talking about infusion solutions used during surgery, solutions for parenteral nutrition, oxygen carriers and diuretics are not considered.

Factors affecting the volume of intraoperative infusion therapy:

- volume of intravascular fluid before surgery;

- heart function before surgery;

- anesthesia method;

- pharmacology of anesthetic;

- position on the operating table;

- thermoregulation;

- infusion therapy during surgery;

- the duration of the operation;

- localization of the operation;

- method of operation;

- ischemia of internal organs;

- heart function during surgery;

- permeability of capillaries;

- endotoxemia;

- pro-inflammatory cytokines; sepsis;

- allergic and anaphylactic reactions.

Over the past 40 years, a huge number of points of view on infusion therapy during

Complications of infusion therapy

1. local hematomas and tissue necrosis, damage to adjacent organs and tissues (during puncture, catheterization), phlebitis and venous thrombosis (due to the high osmolarity of the solutions, their low temperature, low pH), embolism;

2. water intoxication, salt fever, edema, dilution acidosis, hypo and hyperosmolar syndrome;

3. reactions to infusion therapy: hyperthermia, anaphylactic shock, chills, circulatory disorders;

4. overdose of drugs (potassium, calcium, etc.);

5. complications associated with blood transfusion, transfusion reactions (30 min - 2 h), hemolytic reactions (10-15 min or more), massive blood transfusion syndrome (more than 50% of BCC per day);

6. overload of the circulatory system due to the excess of the injected solutions, the high rate of their administration (swelling of the cervical veins, bradycardia, expansion of the borders of the heart, cyanosis, cardiac arrest, pulmonary edema are possible);

7. pulmonary edema due to a decrease in colloid osmotic pressure in the plasma and an increase in hydrostatic in the capillary (hemodilution with water over 15% bcc).

The purpose of the lesson.

To learn

I- Pharmacokinetics, pharmacodynamics. pharmacotoxicodynamics of general anesthetics:

1. inhalation drugs:

nitrous oxide, halotane, enflurane. isoflurane, methoxyflurane, diflurane. Sevoflurane

2. intravenous drugs:

ketamine, thiopental, etomidate, midazolam, propofol.

III pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of drugs used for major violations of water-electrolyte metabolism:

o r-ry crystalloid:

- glucose 5%, 10%, 40% solutions;

- sodium chloride (NaCl) 0.9%, 2%, 5%, 10% solutions;

- potassium chloride (KCl) 7.5% solution;

- magnesium sulfate (MgSO4) 5%, 10%, 20%, 25% solutions; magnesium citrate (magnesol), potassium and magnesium asparaginate

- calcium chloride (CaCl2) 5%, 10% solutions;

- calcium gluconate 5%, 10% solutions;

- polyionic solutions: (acesol, disol, lactasol, trisol, chlorosol, ringer's solution);

- glucose salt solutions: (glucosolan, rehydron), dexoride, Tata Dexin;

o colloidal plasma substitutes:

- high molecular weight (polyglucin, albumin);

- medium molecular weight (reopoliglyukin, gelatin, neo-hemodesis, poly-des);

- low molecular weight (mannitol, sorbitol, reogluman).

pharmacodynamics, pharmacokinetics, pharmacotoxicodynamics of drugs used to correct various violations of the CRR:

a) drugs used to correct acidosis - alkaline solutions (sodium bicarbonate and trisamine);

- metabolic therapy (vitamins: B1, B2, B6, B12; lyic acid and ascorbic acid; essentials); antihypoxants (sodium oxybutyrate, cytochrome, O2); microcirculation enhancing agents (reopoliglyukin pentoksifillin, neogemodez, buflomedil, naftidrofuril)

b) drugs used to correct alkalosis - acid solutions (0.1 n hydrochloric acid solution, ascorbic acid); amino acids (lysine, arginine); chlorides (potassium, calcium, sodium); diuretics (ammonium chloride, diacarb);

Know:

a) leading pathogenetic mechanisms in the main violations of water-electrolyte metabolism, which are the subject of drug exposure.

d) undesirable effects of drugs used to normalize the disturbed water-electrolyte balance;

c) the principles of combining these drugs;

e) criteria for the effectiveness and safety of the proposed drugs.

f) the main pathogenetic mechanisms of impaired regulation of the thyroid gland, which are the object of drug exposure in:

- metabolic acidosis;

- respiratory acidosis;

- mixed respiratory and non-respiratory acidosis;

- mixed multidirectional violations of the CRR;

- metabolic and respiratory alkalosis.

basic pathogenetic mechanisms of action, basic pharmacological effects and principles of rational choice and purpose of general anesthetics

Be able to:

a) select the necessary drug for a particular patient, highlight the criteria for its therapeutic effectiveness and safety;

b) select and prescribe, if necessary, combined therapy;

c) substantiate and provide urgent medical assistance aimed at normalizing the disturbed water-electrolyte balance with:

- hyperglycemic (hyperosmolar) coma;

- hyperglycemic (ketoacidotic) coma;

- infectious toxic shock;

- acute posthemorrhagic hypovolemia;

- threatening pulmonary edema, brain;

- toxicosis of pregnancy;

- burn disease.

- keto-and lactic acidotic coma;

- severe hypoxic conditions,

Renal failure

- indomitable vomiting and diarrhea, sepsis, hypoperfusion, poisoning.

The task for the self-test of the initial level:

1. List the diseases and syndromes accompanied by the most pronounced disturbances in the water-electrolyte balance in the body.

2. Identify the pathophysiological and pathochemical mechanisms of these disorders.

3. Indicate the clinical and laboratory instrumental criteria characterizing the violation of the water-electrolyte balance.

4. List the main groups of drugs used to correct extracellular and intracellular dehydration, extracellular and intracellular hyperhydration, hypo- and hypernatremia, hypo- and hyperkalemia, hypo- and hypercalcemia, hypo- and hypermagnesemia, hypo- and hyperchloremia.

5. What determines the osmolarity of blood plasma, under what conditions is it disturbed?

6. Explain the importance of leading pharmacokinetic parameters in the individual choice of drugs that normalize the water-electrolyte balance.

7. What concomitant diseases can complicate the ongoing corrective pharmacotherapy of disturbed water-electrolyte balance?

8. The use of which common drugs can lead to severe disturbances in the water-electrolyte balance in the body. Suggest a scheme for the prevention of such disorders.

10. Indicate the normal limits of extracellular fluid in the human body.

12. What are the four main systems that make up the buffer capacity of body fluids.

13. What is the role of pathology of the broncho-pulmonary system in the violation of homeostasis?

14. What is the role of the kidneys in the regulation of CRR?

15. Which organ in the human body is the main supplier of hydrochloric acid?

16. In which section of the digestive tract is sodium bicarbonate produced?

17. What types of acidosis do you know?

18. What types of alkolosis do you know?

19. List the tools used to correct the CRR during its shift to the acidic or alkaline side.

20. For what pathology are shifts in the body's thyroid gland observed?

Control questions of the studied topic

1. What are the clinical and pharmacological criteria for the selection and selection of drugs used for the correction of EBV disorders.

2. What principles are the basis for the classification of drugs used to correct VEB?

3. State the causes, development mechanisms, the clinic of water depletion and how to correct it.

4. Indicate the causes, development mechanisms, clinic and drug therapy of acute dehydration.

5. Justify the pharmacotherapy of chronic dehydration.

6. Define the concept of “osmotic pressure of biological fluids” (osmolarity and osmolality) and describe how to correct its disturbance.

7. Indicate the causes, development mechanism, hyperhydration clinic and methods of its treatment.

8. Describe the causes and methods of treatment of disorders of sodium metabolism.

9. The physiological significance of potassium and methods for correcting types of metabolic disorders.

10. List the reasons and indicate the methods of correction of metabolic disorders of calcium, magnesium.

11. State the diagnostic signs of hyperphosphatemia and hypophosphatemia, indicate the methods of principles for their correction.

12. Give the clinical and pharmacological characteristics of polarizing solutions.

13. Describe the clinical and pharmacological characteristics of crystalloid solutions.

14. Indicate the clinical and pharmacological characteristics of the main colloidal plasma substitutes.

15. What is the classification of drugs for anesthesia.

15. List the indications and contraindications for general anesthesia.

16. What are the signs and stages of anesthesia.

17. Indicate the main pharmacological effects of narcotic drugs.

18. Highlight the stages of anesthesia, criteria for assessing its depth and safety, as well as the principles of dosing anesthesia

19. Make a comparative description of funds for inhalation and non-inhalation anesthesia

20. What are the features of the action and use of non-inhalation narcotic drugs.

21. What are the main clinical effects of inhaled anesthetics on organs and systems?

22. Why are most inhaled anesthetics potentially dangerous with increased intracranial pressure?

23. What is the main disadvantage of nitrous oxide?

24. What combination of drugs used together with nitrous oxide for antipsychotics is the most rational and effective?

25. For what purpose isoflurane, halothane, and enflurane are prescribed for intrauterine manipulation and obstetrics?

Enumeration of practical work.

Homework.

1. Write down the prescriptions for drugs presented in the section “Purpose of the lesson”, indicate the point of application of the action, the range of diseases (syndromes) that are indicative of their purpose.

2. Indicate and explain possible combinations of drugs used in violation of VEB, as well as the possibility of their interchange.

Independent work in class.

1. To supervise a thematic patient in the ward.

2. To study his medical history (data from laboratory and instrumental studies, conclusions of consultants) and a list of medical appointments.

3. Write a protocol of independent work of choice for a given patient with drugs that correct VEB disorders (see Appendix 1).

4. In a subjective and objective study of the patient, identify signs that characterize the violation of VEB.

5. Determine the group of drugs necessary for the patient to correct the revealed violations of VEB.

6. Choose a specific drug, its dose and mode of administration.

7. To highlight the clinical and instrumental criteria for assessing the effectiveness and safety of the drugs used.

8. Justify the need for combination drug therapy and suggest possible options for a safe combination of drugs.

9. Make a forecast of possible side effects from the use of these drugs and outline a plan for their early detection and prevention.

10. Justify the duration of the main and supporting therapy.

11. What are the clinical and pharmacological criteria for the selection and selection of drugs used to correct violations of the CRR.

What principles are laid in the basis of the classification of drugs used for correction of CSR?

13. Describe the clinical signs of an overdose of 4% sodium bicarbonate solution when administered intravenously.

14. In connection with what shifts in homeostasis during repeated vomiting are potassium, calcium and sodium chlorides prescribed?

15. Justify the appointment of B vitamins in complex therapy for ketoacidotic coma.

16. For what purpose in clinical practice are inhalations of an oxygen-air mixture and hyperbaric oxygenation?

17. Justify the appointment of sodium oxybutyrate to a patient admitted in a state of asthmatic status.

18. Describe the mechanism for the correction of alkalosis when ingested ammonium chloride.

19. Why should lactic acidosis therapy be aimed at eliminating the underlying cause?

20. What is the correction of acidosis, which is based on: sepsis, poisoning, hypoperfusion?

Control of the intermediate level of knowledge.

The situational tasks:

1. A patient, 42 years old, weighing 67 kg, suffering from a severe form of insulin-dependent diabetes mellitus, against the background of chronic alcoholism, was admitted to the endocrinology department in a coma. The deterioration came after an alcoholic excess. The skin is pale, dry, hot. BH - 40 in 1 min. The breath is deep, noisy; Heart rate - 110 in 1 min, heart sounds are muffled. The abdomen is swollen, peristalsis is sluggish. Blood sugar 32 mmol / L. Acetone in the urine (++++).

Explain the probable genesis of coma, draw up a plan for additional examination and urgent care to the patient.

2. A patient, 67 years old, weighing 86 kg, was admitted to the therapeutic department in connection with a sharp decompensation of NK. Suffers from severe disseminated atherosclerosis; IHD: angina of tension and rest, atherosclerotic cardiosclerosis, atrial fibrillation, persistent tachysystolic form. During the examination, a spontaneous closed valve pneumothorax was diagnosed, which caused the decompensation of the NK to the level of the NK II B st. with constantly progressing pulmonary-heart failure

What violations from the side of the thyroid gland should be expected in the help of this patient? (Make an action plan based on his stay in a multi-disciplinary hospital).

3. The patient, 38 years old, weighing 65 kg, was admitted to the therapeutic department in connection with the exacerbation of chronic cholecystic pancreatitis. Does the patient suffer from epigastric pain, repeated vomiting with bile, sharp weakness of this patient? What research and calculations should be performed for their targeted correction? What should be done to provide a radical, head-spinning. Objectively: pale, cold, clammy sweat. Respiration is frequent, superficial. AKD - 100/50 mm RT. Art .. Heart rate - 92 in 1 min. The abdomen is painful in the upper half, there

are no symptoms of peritoneal irritation, peristalsis is preserved. The doctor on duty prescribed treatment with anticholinergics, antispasmodics, non-narcotic analgesics (all drugs are administered parenterally), in addition, 200 ml of 4% sodium bicarbonate solution is administered intravenously. Contrary to the expectation of the doctor after the measures taken, the patient's condition worsened. Intensified nausea, vomiting, weakness, dizziness, AKD - 90/50 mm RT. Art., heart rate 106 in 1 min.

Explain the reason for the deterioration. What did the doctor on duty not take into account? Assign correction of existing violations of the CRR with the indication of drugs and their administration.

4. A patient, 14 years old, weighing 47 kg, was admitted to the department in connection with a moderate seizure of persistent bronchial asthma. The patient is pale, mucous cyanotic, severe expiratory dyspnea, a mass of polymorphic dry rales is heard over the lungs, AKD - 140/90 mm Hg Heart rate -108 in 1 min. The patient was administered intravenously: solution of aminophylline 2.4% - 10.0 ml; prednisone - 25 mg; no-spa - 2 ml.

Should therapy be supplemented with a remedy that corrects the CSR?

5. A boy, 5 years old, after eating a large amount of fatty foods felt bad. Nausea, vomiting, headache appeared. The urine reaction is sharply acidic; exhaled breath with the smell of acetone.

What is the drug that you would prefer for the relief of ketoacidosis in a child. Justify your choice.

6. During the fluorotan anesthesia, the patient developed a collapse. To increase blood pressure, he was given intravenous adrenaline. Soon after, the patient developed ventricular fibrillation of the heart. Why did the patient develop collapse and what are the causes of ventricular fibrillation after administration of adrenaline? What was necessary to enter to restore blood pressure?

7. Immediately after intravenous administration of a solution of sodium thiopental sodium to the patient, the doctor began surgical intervention in the oral cavity. In response to the manipulation, the patient developed a strong cough and there were signs of asphyxiation (blueness of the face, difficulty breathing) What are these complications associated with? What mistake did the doctor make? How could these complications be avoided? Help measures?

8. A patient, 42 years old, weighing 67 kg, suffering from a severe form of insulin-dependent diabetes mellitus, against the background of chronic alcoholism, was admitted to the endocrinology department in a coma. Deterioration came after an alcoholic excess. The skin is pale, dry, hot. BH - 40 in 1 min. The breath is deep, noisy; Heart rate - 110 in 1 min, heart sounds are muffled. Belly swollen, peri-staltics sluggish. Blood sugar 32 mmol / L. Acetone in the urine (++++).

Explain the probable genesis of coma, draw up a plan for additional examination and urgent care to the patient.

9. A patient, 67 years old, weighing 86 kg, was admitted to the therapeutic department due to a sharp decompensation of NK. Suffers from severe disseminated atherosclerosis; IHD: angina of tension and rest, atherosclerotic cardiosclerosis, atrial fibrillation, persistent tachysystolic form. During the examination, a spontaneous closed valve pneumo-thorax was diagnosed, which caused the decompensation of NK to the level of NK II B st. with constantly progressing pulmonary heart disease.

What abnormalities on the part of the CSR should be expected in this patient? What research and calculations should be performed for their targeted correction? What should be done to provide radical care to this patient? (Make an action plan based on his stay in a multi-disciplinary hospital).

10. A patient, 14 years old, weighing 47 kg, was admitted to the department in connection with a moderate seizure of persistent bronchial asthma. The patient is pale, mucous cyanotic, severe expiratory dyspnea, the mass of polymorphic dry rales is heard over the lungs, AKD - 140/90 mm Hg

Heart rate -108 in 1 min. The patient was administered intravenously: solution of aminophylline 2.4% - 10.0 ml; prednisone - 25 mg; no-spa - 2 ml.

Should therapy be supplemented with a CBS corrective?

11. A boy, 5 years old, after eating a large amount of fatty foods felt bad. Nausea, vomiting, headache appeared. The urine reaction is sharply acidic; exhaled breath with the smell of acetone.

What is the drug that you would prefer for the relief of ketoacidosis in a child. Justify your choice.

12. Patient P., 65 years old, was delivered to the cardiac resuscitation unit 1 hour after the development of an uncurable anginal attack. When examining a patient in a forced orthopnea, the skin is pale, slight acrocyanosis of the lips. No swelling. In the lungs, single fine-bubbling rales. Heart sounds are muffled. Heart rate - 58 in 1 minute, the pulse is irregular (up to 8 extrasystoles per minute). AKD - 105/65 mm Hg ECG: acute myocardial infarction of the anterior wall of the left ventricle, frequent ventricular extrasystole, P - Q 0.2 s, QRS 0.1 s, Q - T 0.42 s.

Formulate a diagnosis. What are the resuscitation measures. Choose the most optimal antiarrhythmic drug for this patient with an indication of the dose and route of administration. Indicate the mechanism of its action and possible side effects.

TESTS

1. Systolic pressure drops after the administration of any of the following substances:

A. phenylephrine

B. dopamine

C. ephedrine

D.Reserpine

E.Norepinephrine

2. Metabolic alkalosis is characteristic of:

A. Sodium bicarbonate

B. Ethacrylic acid

C. Ranitidine

D. Sucralfate

3. Non-inhalation short-acting anesthetic

A. Thiopental sodium,

B. Nitrous oxide

C. Fluorotan

D. Zopiclone

4. With pulmonary edema to reduce bcc

A. Furosemide

B. Veshpiron

C. Hypothiazide

D. Amiloride

E. Triampur

5. In acute hypercalcemia

A. Furosemide

B. Spironolactone

C. Amiloride

D. Triampur

E. Veroshpiron

6. Metabolic acidosis occurs when applied

A. Acetazolomide

B. Spironolactone

C. Amiloride

D. Triampur

E. Veroshpiron

6. A patient in a swoon with a sharp respiratory depression and cardiac activity, a decrease in tendon reflexes was delivered to the admission department. According to his wife accompanying him, he recently suffered from insomnia and took sleeping pills for the night. What kind of drug is needed for emergency treatment?

A. Unitiol.

B. Bemegrid.

C. Dipiroxim.

D. Atropine sulfate.

E. Adrenaline.

7. A patient in a fainting condition was delivered to the emergency department. The skin is cold, the pupils are narrowed, breathing with difficulty, periodic according to the Cheyne-Stokes type, blood pressure is reduced, the bladder is full. What happened poisoning?

A. Non-narcotic analgesics.

B. Tranquilizers.

C. Narcotic analgesics.

D. M-anticholinergic.

E. M-cholinomimetics

8. A 42-year-old patient was hospitalized in the surgical department with a closed pelvic fracture in shock. What blood substitute should be prescribed for infusion antishock therapy?

A. Haemodesis.

B. Intralipid.

C. Isotonic sodium chloride solution.

D. Plasma.

E. Polyglukin.

9. The main drugs for removing from burn shock will be:

A. Effective analgesia and administration of glucocorticoids.

B. Effective analgesia and transport immobilization.

C. Effective analgesia and cooling of burns

D. Effective analgesia and infusion therapy.

E. Effective analgesia and administration of cardiac glycosides.

10. The victim was dragged out from under the rubble of the destroyed house after 6 hours. On examination: syndrome of prolonged compression of both limbs, decompensated ischemia of the II stage, a comprehensive intensive care is carried out. What infusion solutions are most appropriate to use at the prehospital stage?

A. Ringer's solution, Lactosol.

B. 10% glucose solution.

C. Gelatinol, Albumin.

D. Isotonic solution of sodium chloride, sodium bicarbonate.

E. Freshly frozen plasma.

11. The patient, 47 years old, has clinical death, on the ECG - asystole. Against the background of general resuscitation measures, which medication should be administered first?

A. Atropine.

B. Sodium bicarbonate.

C. Calcium chloride.

D. Lidocaine.

E. Adrenaline.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison’s principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

GENERAL PRINCIPLES OF TREATMENT OF POISONING BY MEDICINES

ANTIDOTIC THERAPY

Relevance of the topic.

Modern pharmacology is dynamic and reflects the progress of biomedical and pharmaceutical sciences. Every year, dozens of new original medicines, hundreds of drugs with new trade names in various dosage forms, enter the pharmaceutical market. As the number of drugs increases, helping patients becomes more complicated. It must be remembered that drugs along with the therapeutic effect can cause a number of side effects, ranging from trivial (mild nausea and vomiting) to fatal (aplastic anemia, anaphylactic shock and others, which can lead to the death of the patient).

The mortality rate of patients undergoing inpatient treatment as a result of side effects or drug overdoses is less than 1% (WHO Chronicle). However, drugs become easily accessible to the ordinary consumer who does not have a medical education, as a result of which about 5% of cases of emergency hospitalization, due to poisoning, are associated with the development of side effects of drugs.

Medications are a common cause of poisoning, especially in children. To prevent accidents, keep medicines out of the reach of children. In adults, drug poisoning is possible due to accidental overdose and as a result of attempted suicide.

Studies have shown that in our time there are a large number of people who have a long-formed habit of reaching for a medical panacea at the first "signals" of an illness of their body: headaches, diarrhea, or simply insomnia. Undoubtedly, we simply are not able to not use the inventions of medicine, but at the same time it should be done wisely, and only according to the instructions of the attending doctor and, of course, know the reasonable measure in tablets, because otherwise you can simply become a victim of severe intoxication.

Motivational characteristic of the topic

Causes of drug poisoning All drugs that have at least some real effect on the body can do harm under certain circumstances. If the substance has no contraindications, side effects and can be taken in any dosage - this is, with a high degree of probability, a placebo drug (i.e. not a drug at all). Drug poisoning can occur when: the dosage of the drug is incorrectly selected. The child was prescribed an adult dose, or an anorexic girl 40 kg of live weight was prescribed a dose calculated for an adult man. This situation arises quite often, since manufacturers themselves indicate in the instructions not the amount of active substance per unit mass of the body, but abstract concepts - to children, adults. A competent doctor often titrates (selects) the dose, regardless of the manufacturer's recommendations; concomitant diseases and the condition of organs that remove the active substance from the body are not taken into account. Almost any drug is excreted by the liver and / or kidneys. Consequently, with diseases of these organs, the elimination of the drug slows down, the body accumulates and poisones; the doctor’s recommendations on the combination of the drug with food, alcohol, etc. are not followed; self-medication takes place. Uncontrolled intake of over-the-counter, and even more so, prescription drugs quite often ends sadly, up to a fatal outcome; distraction is pronounced - elderly people often confuse drugs, especially with a large number of various diseases; pills and capsules are available and attractive to children. Some medicines look very “delicious.” Drug poisoning can be both acute and chronic. What can be poisoned Most often, poisoning occurs due to the uncontrolled intake of non-specific anti-inflammatory drugs (NSAIDs): analgin, diphenhydramine, aspirin, paracetamol. They drink them to stop the pain, but the dosage, as a rule, is selected in relation to pain, and not to the capabilities of your own body. Most often, this situation occurs in patients with arthrosis, hernias, as well as migraine or migraine-like headaches. In addition, advertising of teas against colds has recently intensified - teraflu, coldflu, flucold, etc. Few people know that when using these "harmless" complex drugs, acute reactive hepatitis often occurs. It is enough to drink 6-10 bags of this “joy” per day, and it will be very difficult to save a person from a fatal outcome, and health will be undermined for the rest of his life. Medications to be taken with caution

Poisoning with drugs is possible due to violation of dosage, the use of expired tablets. In general, drug poisoning can be obtained for a number of various reasons:

• Violation of dosages

• The use of tablets whose shelf life has expired

Uncontrolled treatment

• Combination of incompatible medicines

• Erroneous medications

Basic principles of treatment and prevention of drug poisoning.

Classification of Toxic Substances (S):

1. By belonging to certain classes of chemical compounds: barbiturates, benzodiazepines, cyanides.

2. By origin: non-biological nature (acids, alkalis, salts of heavy metals), toxic waste products of some MB (botulinum toxin), plant origin (alkoloids, glycosides), animal origin (snake venoms, bees)

3. According to the degree of toxicity: a) extremely toxic (DL50 <1 mg / kg) b) highly toxic (1-50) c) highly toxic (50-500) d) moderately toxic (500-5000) e) slightly toxic (5000-15000) e) practically non-toxic (> 15.000)

4. According to the toxicological effect: a) nerve-paralytic (bronchospasm, suffocation) b) skin-resorptive c) general toxic (hypoxic stomachs, coma, paralysis) d) suffocating e) tear and irritating e) psychotropic (violation of mental activity, consciousness)

5. Depending on the scope of primary use: industrial poisons, pesticides, household poisons, chemical warfare agents, medicinal substances.

6. Depending on the toxicity of drugs: list A - drugs, the purpose, use, dosing and storage of which, due to their high toxicity, should be carried out with great care. The same list includes drugs that cause drug addiction; list B - drugs, the purpose, use, dosage and storage of which should be carried out with caution in connection with possible complications when they are used without medical supervision.

Selectively toxic effect of drugs.

A) cardiotoxic: cardiac glycosides, potassium preparations, antidepressants

B) neurotoxic: psychopharmacological agents, oxyquinolines, aminoglycosides

C) hepatotoxic: tetracyclines, chloramphenicol, erythromycin, paracetamol

D) nephrotoxic: vancomycin, aminoglycosides, sulfonamides

D) gastroenterotoxic: steroidal anti-inflammatory drugs, NSAIDs, reserpine

E) hematotoxic: cytostatics, chloramphenicol, sulfonamides, nitrates, nitrites

G) pneumotoxic

Toxicokinetics - studies the absorption, distribution, metabolism and excretion of drugs taken in toxic doses.

The entry of toxic substances into the body is possible a) enteral b) parenteral. The speed and completeness of absorption reflects the rate of development of the toxic effect and its severity.

Distribution in the body: Vd = D / Cmax - the actual volume in which the toxic substance is distributed in the body. Vd> 5-10 l / kg - OM is difficult to remove (antidepressants, phenothiazines). Vd <1 L / kg - OM is easier to remove from the body (theophylline, salicylates, phenobarbital).

Overdose - a change in pharmacokinetic processes: solubility, protein binding, metabolism ® a significant increase in the free fraction of drugs ® toxic effect.

Kinetics of the first order with increasing concentration of drugs passes into the kinetics of zero order.

Toxigenic stage - detoxification therapy, somatogenic stage - symptomatic therapy.

Toxicodynamics. The main mechanisms of toxic action:

A) mediator: direct (by the type of competitive blockade - FOS, psycho-mimetics) and indirect (activators or inhibitors of enzymes)

B) interaction with biomolecules and intracellular structures (hemolytic substances)

C) metabolism by the type of lethal synthesis (ethyl alcohol, thiophos)

D) enzymatic (snake venoms, etc.)

Types of action: local, reflex, resorptive.

Classification of poisoning:

1. Etiopathogenetic:

a) accidental (self-medication, erroneous reception)

b) deliberate (for the purpose of suicide, murder, development in a victim of a helpless state)

2. Clinical:

a) depending on the rate of development of poisoning: acute (single or short-time intake of a toxic dose of the substance), adequate (delayed development of the clinical picture after a single dose), chronic

b) depending on the manifestation of the main syndrome: CVS damage, DS damage, etc.

c) depending on the severity of the patient's condition: mild, moderate, severe, extremely severe

3. Nosological: takes into account the name of the drug, the name of the group of substances

The general mechanism of death in case of poisoning:

A) defeat CVS:

1) decrease in blood pressure, peripheral vascular hypovolemia, collapse, brady - or tachycardia (tricyclic antidepressants, beta-blockers, calcium channel blockers)

2) arrhythmias (ventricular tachycardia, fibrillation - tricyclic antidepressants, theophylline, amphetamine)

B) damage to the central nervous system: stupor, coma respiratory depression (drugs, barbiturates, alcohol, hypno-sedative drugs)

B) cramps, muscle hyperreactivity and rigidity hyperthermia, myoglobinuria, renal failure, hyperkalemia

Toxicological triad:

1) duration of use, dose and substance ® history.

2) assessment of the state of consciousness by symptoms: respiration, blood pressure, body temperature

3) laboratory rates

Basic principles of treatment

Uncontrolled treatment

• Combination of incompatible medicines

• Erroneous medications

Basic principles of treatment and prevention of drug poisoning.

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Toxicological triad:

1) duration of use, dose and substance ® history.

2) assessment of the state of consciousness by symptoms: respiration, blood pressure, body temperature

3) laboratory rates

Basic principles of treatment

I. First aid: artificial respiration, cardiac massage, anti-shock therapy, monitoring of water-electrolyte balance

II. Delayed absorption and removal of non-absorbed OM from the body:

Purpose: to stop contact with OM

Parenteral route:

a) through the lungs:

1) stop inhalation
2) irritating substances (ammonia, formaldehyde) ® fix active movements, warm, give oxygen and antifoam agents (ammonia antifoam vinegar, and formaldehyde - dilute ammonia solution)
b) through the skin: wash off with a copious amount of warm water with soap or detergent, specific antidotes, neutralization and termination of the exposure to organic matter on the skin (FOS: wash with water, remove with 10-15% hydrochloric alcohol or 5-6% hydrogen carbonate solution sodium with water; phenol-crezole: vegetable oil or ethylene glycol, but not petroleum jelly, KMNO4: 0.5-1% solution of ascorbic acid or equal volumes of 3% hydrogen peroxide and 3% solution of acetic acid, CCl4, turpentine gasoline: warm soapy water)
c) when injected into a limb: tourniquet above the injection site
d) in case of contact with eyes: rinse with warm saline or milk for 10-20 minutes, instill a local anesthetic; acid and alkali cannot be neutralized. Mandatory consultation of an ophthalmologist.
2. Enteral route: free the stomach from OM, accelerate passage
a) removal of OM:
1) pre-intake of water. You can not take milk (with the exception of corrosive poisons) and ethanol (with the exception of methanol).
2) vomiting - indicated mainly for poisoning with large tablets or capsules that cannot pass through the probe. It can be provoked reflexively or by vomiting (NaCl: 1 tablespoon per 1 glass of water; Ipecac syrup: adults 2 tablespoons, children 2 teaspoons; mustard: 1-2 teaspoons per glass of water; apomorphine: 5-10 mg / kg subcutaneously , except for children under 5 years old). Do not induce vomiting after administration: organic solvents - danger of inhalation, detergents - foaming, convulsive agents - danger of aspiration, caustic substances - damage to the esophagus)
3) probe gastric lavage - is an emergency and mandatory measure. The stomach is washed if from the moment of poisoning no more than 4-6 hours have passed, sometimes up to 10 hours; in case of poisoning with acetylsalicylic acid - after 24 hours. Pre-intubate the patient with a tube with an inflatable cuff: in a coma in the absence of a cough and laryngeal reflex. The stomach is washed with water or saline at 30 ° C, the procedure takes 4 hours or more. At the end of washing - activated carbon and sodium sulfate.
b) reduced absorption from the digestive tract: activated carbon inside after emptying the stomach + sodium or magnesium sulfate. Features of measures to reduce absorption:
1) organic solvents: do not induce vomiting, washing the stomach after intubation, activated charcoal + liquid paraffin
2) detergents: do not induce vomiting and rinse the stomach, give plenty of water + antifoam agents (simethicone)
3) acids and alkalis: vomiting cannot be caused; gastric lavage through a tube lubricated with vegetable oil after the administration of narcotic analgesic is the only indication for giving milk. In case of acid poisoning - antacids, in case of alkali poisoning - citric or acetic acid.
III. Removal of absorbed OM from the body
If the substance is absorbed and has a resorptive effect, the main efforts should be aimed at removing it from the body as soon as possible. For this purpose, forced diuresis, peritoneal dialysis, hemodialysis, hemosorption, blood replacement, etc. are used.
a) forced diuresis (conditions: sufficient renal blood flow and glomerular filtration; pour in and pour 20-25 liters in 24 hours)
b) peritoneal hemodialysis

c) hemosorption
d) exchange blood transfusion
e) forced hyperventilation
The method of forced diuresis is a combination of water load with the giving of active diuretics (furosemide, mannitol). In some cases, alkalization or acidification of urine (depending on the means of the substance) contributes to a more rapid release of the substance (due to a decrease in its re-absorption in the renal tubules). By the method of forced diuresis, only free substances unrelated to proteins and blood lipids can be removed. When using this method, electrolyte balance should be maintained, which can be disturbed due to the removal of a significant amount of ions from the body. In acute cardiovascular failure, severe impaired renal function and the risk of developing edema of the brain or lungs, forced diuresis is contraindicated.
In addition to forced diuresis, hemodialysis or peritoneal dialysis is used. During hemodialysis (artificial kidney), blood passes through a dialyzer having a semi-impermeable membrane, and is largely freed from toxic substances not associated with proteins (for example, bar bitrates). Hemodialysis is contraindicated in a sharp decrease in blood pressure.
Peritoneal dialysis consists in "washing" the peritoneal cavity with a solution of electrolytes. Depending on the nature of the poisoning, certain dialysis fluids are used that contribute to the most rapid removal of substances into the peritoneal cavity. Along with the dialysis solution, antibiotics are administered to prevent infection. Despite the high efficiency of these methods, they are not universal, since not all chemical compounds are well dialyzed (i.e., they do not pass through the impermeable dialyzer membrane during hemodialysis or through the peritoneum during peritoneal dialysis).
A successful method of detoxification is hemosorption. In this case, toxic substances in the blood are adsorbed on special sorbents (for example, on granular activated carbon coated with blood proteins). This method allows you to successfully detoxify the body when poisoning with antipsychotics, tranquilizers, organophosphorus compounds, etc. It is important that this method is effective in cases where the drugs are poorly dialyzed (including substances associated with plasma proteins) and hemodialysis does not give a positive result. .
In the treatment of acute poisoning, blood replacement operations are also used. In such cases, bloodletting is combined with transfusion of donated blood. The most shown use of this method for poisoning with substances that act directly on the blood, for example, causing methemoglobin formation (this is how nitrites, nitrobenzenes, etc. act). In addition, the method is very effective in case of poisoning with high molecular weight compounds that are tightly bound to plasma proteins. Blood replacement surgery is contraindicated in case of severe circulatory disorders, thrombophlebitis.
Sometimes, for the purpose of detoxification, the lymph (lymphorrhea) is removed through the thoracic lymphatic duct. Lymphodialysis, lymphosorption are possible. These methods are not of particular importance in the treatment of acute poisoning with drugs.
If the poisoning occurred due to substances released by the lungs, then forced breathing is one of the important ways to treat such intoxication (for example, by means for inhalation anesthesia). Hyperventilation can be caused by a respiratory stimulant carbogen, as well as artificial respiration.
Strengthening the biotransformation of toxic substances in the body during the treatment of acute poisoning does not play a significant role.
IV. Neutralization of the absorbed toxic substance
If it is established which substance caused the poisoning, resort to de-toxicity of the body with the help of antidotes.
Antidotes are drugs used for the specific treatment of chemical poisoning. These include substances that inactivate poisons, either through chemical or physical interactions, or due to pharmacological antagonism (at the level of physiological systems, receptors, etc.). So, when poisoning with heavy metals, compounds are used that form non-toxic complexes with them (for example, unity-ol, D-penicillamine). Antidotes are known that react with a substance and release a substrate (for example, cholinesterase reactive oximes; antidotes are similarly used in case of poisoning with metge-moglobin-forming substances). Pharmacological antagonists are widely used in acute poisoning

(atropine in case of poisoning with anticholinestics; various drugs; nalorphine in case of morphine poisoning). Typically, pharmacological antagonists compete with the same receptors as the substances that caused the poisoning.
The earlier treatment of acute antidote poisoning is started, the higher its effectiveness. With the developed lesions of tissues, organs and systems of the body and in the terminal stages of poisoning, the effectiveness of antidote therapy is small.
Antidotes: 1) toxicotropic - binding, neutralizing and preventing the absorption of OM: acting on the principle of activated carbon, acting on the chemical principle (unitiol, penicillamine, pentacin)
2) toxicokinetic - accelerate the biotransformation of OM (trimedoxy-ma bromide, sodium thiosulfate, ethanol, AO)
3) pharmacological - atropine, naloxone
4) immunological antidotes
Unitiol, succimer - binds heavy metals, metalloids, cardiac glycosides. Esmolol binds theophylline, caffeine. Calcium trisodium penototate - forms complexes with divalent and trivalent metals
Symptomatic therapy of functional disorders.
An important role in the treatment of acute poisoning is played by symptomatic therapy. It becomes especially important in case of poisoning with substances that do not have specific antidotes.
First of all, it is necessary to maintain vital functions - blood circulation and breathing. For this purpose, cardiac glycosides are used; substances that regulate the level of arterial pressure; agents that improve micro-circulation in peripheral tissues; often use oxygen therapy and sometimes respiratory stimulants. If undesirable symptoms appear that aggravate the patient's condition, they are eliminated with the help of appropriate drugs. Thus, seizures can be stopped with a tranquilizer sibazon, which has a pronounced anticonvulsant activity. With brain edema, dehydration therapy is carried out (with the help of mannitol, glycerol). Pain is treated with analgesics (morphine). Much attention should be paid to the acid-base condition and, if there are violations, carry out the necessary correction of it. In the treatment of acidosis, solutions of sodium bicarbonate, trisamine are used, and with alkalosis, ammonium chloride. It is equally important to maintain water - electrolyte balance.
Thus, the treatment of acute poisoning with drugs includes a complex of detoxification measures in combination with symptomatic and, if necessary, resuscitation therapy
Barbiturate poisoning. Pathogenesis (mechanism) of barbiturate poisoning. Clinic (signs) of barbiturate poisoning.
Of the drugs, barbiturate poisoning occupy a prominent place in frequency of use in domestic suicidal attempts.
Depending on the duration of action, barbiturates of long duration (8-12 hours - phenobarbital), medium (6-8 hours - barbital (veronal), barbital-sodium (medial), etc. and short-acting (4-6 hours - etaminal sodium (Nembutal). A lethal dose for these drugs is considered to be a concentration in the blood of more than 0.1 g / L. The severity of the condition of the sufferer is enhanced by concomitant diseases, especially the liver and kidneys.
The pathogenesis of poisoning with barbiturates. Barbiturates have a selective toxic effect on the central nervous system, which is manifested by inhibition of the function of the cerebral cortex due to the effect on the metabolism of nerve cells through a decrease in their oxygen consumption and disturbances in the cytochrome system, which, in turn, leads to a disorder in the formation of acetylcholine and, consequently, specifically, impaired transmission of nerve impulses in the central nervous system.
Toxic effects on the stem and medulla oblongata lead to loss of consciousness and the onset of coma, to a violation of the respiratory function of the central genesis, which is manifested by a decrease in DO and MOD; paralysis of the vasomotor center, a harbinger of which is the collapoid state; to the disappearance of pain, tactile and tendon reflexes; to metabolic disorders, increased heat transfer, lower body temperature; inhibition of diuresis, and oliguria helps to increase the level of residual nitrogen in the blood; to vagotonia, which is manifested by increased secretion in the bronchi.
The cardiovascular system. Toxic doses of barbiturates reduce the contractility of the myocardium and vascular smooth muscle tone, which, in turn, helps to reduce UO, MOS, CVP, and a drop in PSS and blood pressure. Barbiturates in high concentrations have a direct effect on the capillary bed - its

permeability increases, which is fraught with the appearance of complications in the form of pulmonary edema and brain. Subsequently, this pathological cascade causes the rapid appearance of trophic disorders in the form of bullous dermatitis and necrotic dermatomyositis, proceeding as rapidly developing bedsores.
Clinic (signs) of barbiturate poisoning.
There are 4 main clinical syndromes: 1. Coma and other neurological disorders. 2. Respiratory disorders. 3. Dysfunction of the CVS. 4. Trophic disorders and impaired renal function.
The development of a coma in severe poisoning with barbiturates.
Moderate and deep stunning, stupor and moderate coma (synonym: coma I) do not have any specific signs.
For deep coma (synonym: coma II), specific signs are pronounced hypersalivation, bronchorrhea of varying degrees. It is possible respiratory failure due to retraction of the tongue or aspiration of vomit, BUT ANGULATION OF RESPIRATION OF THE CENTRAL GENESIS IS NOW AVAILABLE. Tachycardia is noted, but there is no pronounced hemodynamic disturbance. On the ECG, in addition to compensatory sinus tachycardia, diffuse changes in the myocardium can be detected. Arterial hypotension, oliguria. Specific “barbituric spindles” appear on the EEG. A high concentration of barbiturates is observed in blood plasma
For transcendental coma (synonym: coma III), the hallmark is a RESPIRATION OF THE CENTRAL GENESIS due to inhibition of the respiratory center and the rapid development of bullous dermatitis.
Emergency care for barbiturate poisoning. First aid for barbiturate poisoning.
It should be noted that in the treatment of barbiturate poisoning, the formerly previous traditional method of treating with large doses of analeptics (cordiamine, caffeine, etc.) proved to be ineffective with a deep barbituric coma and even dangerous due to the possible development of convulsive conditions and respiratory complications, therefore, these drugs can be used only in patients with mild poisoning.
The pathogenetic method of treatment should be considered accelerated release of the body from barbiturates by the method of forced diuresis, and if there are signs of respiratory failure, transfer the patient to mechanical ventilation. The widespread use of this method in the treatment of patients with severe barbiturate poisoning has produced a kind of revolution in toxicology, comparable to the era of antibiotics in surgery. So, while the mortality rate in patients with severe coma during treatment with respiratory analeptics was 20-30%, while in the treatment with forced diuresis in combination with mechanical ventilation, this figure decreased by about 10 times and currently amounts to 2-3%.
The method of forced diuresis is carried out in combination with the alkalization of plasma with 4% sodium bicarbonate solution for the fastest removal of barbiturates from the blood. It should be emphasized the importance of replenishing blood electrolytes with this method of treatment and indicate contraindications (persistent collapse, cardiac asthma, acute renal failure, circulatory failure IIB — III century). Monitoring of the therapy is carried out by determining CVP, hematocrit, plasma electrolytes, diuresis and, of course, the concentration of barbiturates in the blood and urine. Transfer of the patient to mechanical ventilation is carried out according to generally accepted indications
In patients with severe poisoning, hemosorption is the most effective way to purify blood from barbiturates. It should be noted that this method is effective both for poisoning with barbiturates and psychotropic drugs that are poorly excreted from the body during hemodialysis.
For the treatment of the hypoxic state of the central nervous system, large doses of vitamins are recommended: B1 - 2-4 ml of 2.5% solution, B6 - 8-10 ml of 5% solution, B12 - up to 800 mcg, C - up to 10 ml 5 % solution, nicotine mid for 5% solution of glucose up to 15 mg / kg of weight per day.
1. Indications for the complex treatment of barbiturate poisoning include vascular agents (dopamine, etc.), glucocorticoids, antibacterial agents, cardiac glycosides, etc. 2. Nicotinamide is not used for sedation with sedatives.
Poisoning with tranquilizers (benzodiazepine derivatives). Non-delayed care (first aid) for poisoning with tranquilizers.

Derivatives of benzodiazepine include elenium (chlordiazepoxide, napotone, librium), diazepam (seduxen), oxazepam (tazepam), and radedorm (eunoktin). These drugs enter the bloodstream, absorbed in the digestive tract. Natural detoxification occurs in the liver, excretion from the body - with urine and feces. The lethal dose is 1-2 g. Toxic concentration in the blood is 5-20 mg / l, the lethal - 50 mg / l.

Toxic effect. Psychotropic and neurotoxic, due to inhibition of the central nervous system, weakening of the processes of excitation of subcortical formations, inhibition of intercalated neurons of the spinal cord and thalamus (central muscle relaxation).

Clinical signs and diagnosis of poisoning with tranquilizers are similar to those described above for poisoning with barbiturates.

Emergency care (first aid) for poisoning with tranquilizers is also similar to the above, with the exception of a slight nuance - forced diuresis is performed without alkalizing the plasma.

Prevention of acute poisoning

The main task is the prevention of acute poisoning. To do this, it is necessary to prescribe drugs reasonably and properly store them in medical institutions and at home. So, medicines should not be kept in cabinets or in the refrigerator where food is located. Storage locations for medicines should not be accessible to children. It is impractical to keep drugs at home in which there is no need. Do not use medicines that have expired. Used drugs must necessarily have appropriate labels with names. Naturally, taking drugs should only be recommended by a doctor, strictly observing their dosage. Self-medication is unacceptable, since it is often the cause of acute poisoning and other adverse effects. The observance of the rules for storing chemicals and working with them at chemical and pharmaceutical enterprises and in laboratories involved in the manufacture of drugs is important. Fulfillment of all these requirements can significantly reduce the incidence of acute drug poisoning.

The purpose of the lesson. To learn the general principles of emergency care in acute poisoning. Know the pharmacotherapy of extreme conditions. To understand the pharmacodynamics of drugs used for emergency care.

Lesson purpose

To learn

A. General relief measures for ACUTE POISONING:

1. Prevention of further intake of poison in the body (removal of non-absorbable poison). Measures for the penetration of non-absorbed poison into the body (when it enters the skin and mucous membranes, when it enters the stomach and intestines, by inhalation): washing, neutralization, binding, oxidation, adsorption, precipitation.

2. Acceleration of elimination of non-absorbed poison from the body (in case of poisoning with volatile substances, remove it from the poisoned atmosphere): forced diuresis, blood transfusion, creation of an appropriate pH environment in urine, peritonial dialysis, hemodialysis.

3. The concept of antidote therapy. Classification of antidotes:

a) physical and chemical; c) functional; d) immunological (anti-toxic serum). The use of specific antidotes:

opioids - naloxone;

barbiturates and anesthesia - bemegrid;

methanol - ethyl alcohol;

benzodiazepines - flumazenil;

salts of heavy metals - unitiol, acetylcysteine, complexones (EDTA, tri-long, penicillamine, etc.);

magnesium sulfate - calcium chloride;

iron preparations - deferoxamine;

bromides - sodium chloride;

dichloroethane - acetylcysteine;

cardiac glycosides - unitiol, acetylcysteine, complexones (EDTA, trilong, etc.), potassium preparations (panangin);

muscarin - atropine;

FOS - cholinesterase reactivators (dipiroxim, aloxime, isonitrosine);

non-depolarizing muscle relaxants - proserin;

direct anticoagulants protamine sulfate;
indirect anticoagulants vikasol;
cyanides - methylene blue (chromosmon).
4. Symptomatic therapy of functional disorders in acute poisoning:
a) in case of respiratory failure of various etiologies: respiratory center depression, airway obstruction, bronchospasm, larynx and lung edema, respiratory muscles paralysis;
b) with hypoxia of various etiologies: respiratory and circulatory disorders, hemolysis, blockade of respiratory enzymes, hemoglobin change;
c) in case of impaired cardiac activity: myocardial damage, impaired conduction, sudden cardiac arrest;
d) in case of violation of vascular tone: a drop in blood pressure (poisoning with sleeping pills, ganglioblockers, sympatho- and adrenolytics, myotropic drugs), increased blood pressure (poisoning with vasoconstrictors, analeptics, phenamine);
e) with a convulsive syndrome (poisoning with analeptics, anticholinestics, N-cholinomimetics, phenothiazine derivatives, insulin, strychnin, and other convulsive poisons).
B. Essential first aid drugs in EXTREME CONDITIONS.
1. In acute decompensation of chronic heart failure - cardiac glycosides and non-glycoside cardiotonics.
2. In acute vascular insufficiency - adrenomimetics, analeptics, glucocorticoids.
3. In pulmonary edema - nitrates, saluretics, vasodilators, glycosides, neuroleptics, narcotic analgesics, antifoam agents, ganglion blockers.
4. With a spasm of smooth muscles of the abdominal cavity organs (renal, hepatic, intestinal colic) - anticholinergics, myotropic antispasmodics, non-narcotic and narcotic analgesics.
5. With hypertensive crisis - antihypertensive drugs.
6. With anaphylactic shock - adrenaline, glucocorticoids in high doses, antihistamines.
7. With hyperglycemic coma - short-acting insulin, depending on the level of hyperglycemia, alkaline solutions, cocarboxylase, potassium salts.
8. With hypoglycemic coma - hypertonic glucose solutions, adrenaline, glucocorticoids.

Test questions.

1. What are the basic principles for the treatment of acute drug poisoning?
2. Which laxatives are most rationally prescribed in the system of measures for the treatment of acute poisoning with drugs?
3. What agents contribute to the detoxification of substances in the body?
4. What agents should be prescribed to accelerate the excretion of substances by the kidneys?
What substances should be used for poisoning with narcotic analgesics?
6. What substances are used in acute heart failure associated with drug poisoning?
7. What drugs are used for poisoning with narcotic, sleeping pills, ethyl alcohol?
8. What substances should be prescribed for poisoning with analeptics?
9. What substances should be prescribed for poisoning with M-cholinomimetic agents?
10. What substances are antagonists of antidepolarizing muscle relaxants?
11. What substances are used for cardiac glycoside poisoning?
12. What remedy is used in case of overdose of neodikumarin?
13. What substances are used for cyanide poisoning?
14. What drugs should be prescribed for the resorptive action of salts of heavy metals and arsenic?
15. What substances are prescribed to prevent the absorption of salts of heavy metals from the gastrointestinal tract?
16. What substances are used for poisoning with anticholinesterase substances (FOS, etc.)?
17. What substances are used for an overdose of insulin?
18. What substances are used for atropine poisoning?

Control questions of the studied topic

1. The basic principles of the treatment of acute poisoning with drugs.

2. Measures of assistance in case of poisoning, depending on the route of poison entry into the body (in case of poisoning by gaseous substances, when poison enters the skin or mucous membranes, into the gastrointestinal tract, parenterally).
3. The neutralization of the poison with its resorptive effect, antidote therapy, the use of functional antagonists, stimulators of physiological functions, drugs that normalize acid-base balance, blood transfusion and blood-replacing fluids.
4. Acceleration of the removal of poison from the body.
Enumeration of practical work.
A. Homework.
1. Write down the prescriptions for drugs presented in the section “Purpose of the lesson”, indicate the point of application of the action, the spectrum of diseases (syndromes) that are an indication of their purpose.
2. Indicate and explain possible combinations of drugs used in violation of VEB, as well as the possibility of their interchange.
Control of the intermediate level of knowledge.
The task.
1. Write down an opiate receptor antagonist for morphine poisoning.
2. Write out a remedy for stopping a hypertensive crisis.
The solution of situational tasks:
1. A patient, 42 years old, is in a therapeutic hospital with a diagnosis of Rheumatism of the active phase, stage II activity, recurrent carditis, aortic valve insufficiency, CH-II B stage. Within one month, he takes digitoxin 1 tablet (0.0001 g) 2 times a day. Heart rate decreased from 90 beats. in 1 min to 50 beats. in 1 min. However, during the last week shortness of breath, swelling on the legs intensified, daily diuresis decreased, and liver distance from under the costal arch increased.
What was the reason for the deterioration of the patient? What types of hypertension should be prescribed to reduce the severity of decompensation?
On the 3rd day of treatment with digoxin, the patient revealed: pulse - 50 beats. in 1 min, extrasystoles as bigeminia.

Formulate a diagnosis. Patient treatment plan. Give the clinical and pharmacological rationale for the prescribed drugs.

The task. Make an annotation for the group of M-anticholinergic drugs used to stop hepatic and renal colic.

1. Pharmacological group

2. Classification

3. The chemical formula of the main representative

4. Pharmacodynamics

5. Indications

6. Undesirable effects

The task. Prescribe a prescription for a hypotensive drug for hypertensive crisis from the group of phosphodiesterase inhibitors.

The task. Offer an equivalent substitute for drugs not available in the pharmacy and indicate the most common synonyms: corglycon, cordiamine, clonidine, papaverine, drotaverine.

The task. Make an annotation on the main group of antianginal drugs that reduce the oxygen demand of the myocardium and improve its blood supply in case of angina attack.

1. Pharmacological group.

2. Classification.

3. Pharmacodynamics.

4. Pharmacokinetics.

5. Undesirable effects.

The task. Write a prescription for a drug for forced diuresis in case of various poisonings.

The task. Offer an equivalent replacement for drugs not available in the pharmacy and indicate the most common synonyms: ethacrylic acid, norepinephrine, dopamine, chlorpromazine, pentamine, prednisolone

TESTS

1. During treatment, the patient was prescribed strophanthin, the average rate of saturation, but the symptoms of digital intoxication developed: vomiting, extrasystoles, and visual impairment. What drug can lead to a worsening of the patient's condition, and therefore it must be canceled?

A. Panangin.

B. Unitiol.

C. Calcium chloride.

D. Diphenin.

E. Reviewed.

2. An overdose of salicylates leads to the following EXCEPT

A. nausea vomiting

B. Tinnitus

C.hyperventilation

D Increase in blood PH

3. The patient was injected with a solution of morphine hydrochloride under the skin for the purpose of pain relief during traumatic shock. What is the mechanism of the analgesic effect of this drug?

A. Change in the emotional coloring of pain.

B. Blockade of peripheral sensitive receptors.

C. Interaction with opioid receptors.

D. Violation of the conduction of impulses along afferent nerves.

E. Inhibition of the formation of mediators of pain in peripheral tissues.

4. A patient with acute morphine intoxication was given naloxone, which quickly improved her condition. What is the inhibitory mechanism of action of this drug?

A. Blockade of sigma-opiate receptors.

B. Blockade of the GABA receptor.

C. Blockade of serotonin receptors.

D. Blockade of benzodiazepine receptors.

E. Competitive blockade of adrenergic receptors.

5. In the admission department the patient entered in a swoon. The skin is cold, the pupils are constricted, breathing is difficult, there is a periodicity of breathing according to the Cheyne-Stokes type, blood pressure is reduced, the urinary bladder is full. Diagnosis: morphine poisoning. What drug should be used as an antagonist?

A. Naloxone.

B. Bemegrid.

C. Caffeine.

D. Unitiol.

E. Sodium thiosulfate.

7. In the pharmacy area, a young man was found to have fainted: periodic breathing, slow heart rate, reflexes, except for the knee, are suppressed, the pupils are narrowed. 15 ampoules of morphine solution were found near the patient. What manipulations should be applied first?

A. Introduce an antiarrhythmic agent.

B. Rinse the stomach with potassium permanganate solution.

C. Make an enema.

D. Induce a gag reflex.

E. Introduce a diuretic.

6. For an urgent surgical intervention, the patient in the surgical department was called an anesthetist who performed neuroleptanalgesia. Which of the following drug combinations is used for this?

A. Droperidol + fentanyl.

B. Promedol + sibazon.

C. Analgin + diazepam.

D. Haloperidol + fentanyl.

E. Droperidol + sibazon.

8. A patient, 30 years old, was taken to the admission department after a car accident with a hip fracture. The patient has sharply reduced blood pressure 70/40, weak pulse, increased pain response. What needs to be introduced to the patient for the prevention of traumatic shock?

A. Morphine.

B. Paracetamol.

C. Pentazocine.

D. Analgin.

E. Papaverine.

9. Patient with asthma during an asthma attack uses the drug Berotek recommended by the pharmacist. After the tenth inhalation, tachycardia and pain in the heart region with irradiation to the left scapula occurred during the first day. What can be related to these phenomena?

A. Overdose.

B. Bronchospasm.

C. Insufficient selectivity of the drug against an overdose.

D. Inadequate selectivity of drugs.

E. Psychogenic factors.

10. List the general principles for the treatment of acute poisoning:

A. Cessation of further ingestion of a toxic substance into the body

B. Maximum reduction in the concentration of toxic substances in the body

C. Treatment and prevention of various complications

D. Ensuring the normal functioning of vital organs and systems

E. All of the above

11. In a 3-year-old child who was taken to the hospital, a co-pink state, a sharp decrease in muscle tone, inhibition of tendon and periosteal reflexes are recorded, myosis is detected, and pupils respond to light. Corneal reflexes saved. The pulse is frequent, weakened. HELL - 80/50 mm RT. Art. Parents suspect that the child swallowed the pill. What kind of tablet medicine is poisoned by such a clinical picture?

A. Barbiturates.

B. β2-adrenergic agonists.

C. Tranquilizers.

D. Antihypertensive drugs.

E. Atropine-like drugs.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison’s principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod’s clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн, В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

INTERACTION OF MEDICINES

Relevance of the topic.

For the treatment of various diseases, in clinical practice quite often two or more drugs are simultaneously used simultaneously, which increases the effectiveness of complex pharmacotherapy with correctly selected ingredients included in the combination.

The chemical and pharmaceutical industry supplies more than two thousand drugs to the country's pharmacy network, many of which are combined. The possibility of joint use of drugs included in the drug is justified by experimental studies and clinical observations. The scientifically substantiated rational combination of etiotropic, pathogenetic and symptomatic agents is a positive side of modern drug therapy, because in this case the doses of individual drugs are reduced, which leads to a weakening of their toxic effects, at the same time, the therapeutic effect of drugs is strengthened (potentiated).

On the other hand, the often insufficiently substantiated prescription of drugs causes damage to the entire complex of treatment or does not give the desired therapeutic effect.

Theoretical and practical (clinical) aspects of the interaction of drugs are extremely relevant, since in recent years there have been increasing reports of interactions between medicines, cases of

complications arising from this, sometimes even fatal, have been described. The cause of the undesirable effects of the interaction can be, firstly, physical, chemical or physicochemical incompatibility and, secondly, biopharmaceutical and pharmacokinetic interactions in the body, associated with the influence of one substance on the absorption, transport, distribution, conversion and elimination of another drug , and on the features of its pharmacodynamics.

The mechanism of drug interaction is complex. F. Hansen (1974) proposed dividing the mechanisms of drug interaction into three groups:

1) pharmacokinetic interactions, when some drugs can affect the biotransformation of other drugs; these are interactions that change the process of absorption of drugs in the digestive apparatus, or their binding to a blood plasma protein;

2) pharmacological interactions in which two drugs have an additive or synergistic effect; in both cases, the basis of the effect is the mutual action of drugs on the same or different structures (tissue receptors);

3) various interactions that are not included in the above categories.

E. G. Ariens and L. I. Simons propose to divide the interaction of drugs by quantitative result into cooperative (summation, or potentiation) and antagonistic. From a clinical point of view, the pharmaceutical, pharmacokinetic and pharmacodynamic phases of interaction are distinguished. Due to the fact that the interaction reaction occurs both between the substances themselves and their effects, it is more convenient (more rational) to talk about two types of interaction: chemical and pharmacological. Pharmacological interaction, in turn, is divided into pharmacokinetic and pharmacodynamic (I.S. Chek-may, 1980).

Physico-chemical interaction occurs in the digestive apparatus between drugs, food products and digestive enzymes, as well as in blood plasma or intercapital fluid with proteins, lipoproteins, carbohydrates, biometals and other substances. It is based on physicochemical laws, as a result of which color and dispersion change, precipitate precipitates, damp mixtures form, colloidal (solution) composition changes, and, as a result of a chemical reaction, inactivation of the drug.

Alkaloids as highly effective agents are often used to treat various diseases and are prescribed by doctors in conjunction with other drugs in powders, potions, eye drops, lotions, etc. Among alkaloids, papaverine, quinine, apomorphine hydrochloride precipitates most often. strychnine nitrate. At the same time, caffeine-sodium benzoate, pilocarpine hydrochloride, codeine phosphate, scopolamine hydrobromide, form less precipitates when interacting with other substances. For example, in a medicine containing sodium bicarbonate, papaverine hydrochloride and tincture of valerian, pH 9.0. The base of papaverine precipitates even at a pH of 6.4. Salts of weak organic nitrogen bases (dibazole, dicain, diphenhydramine, novocaine, promedol, thifen, ethacridine lactate, etc.) undergo changes in alkaline media similar to alkaloids. In eye drops containing sodium sulfacyl and dicaine, it drops out sediment of local anesthetic.

Hydrobromic and hydroiodic salts are poorly soluble in many alkaloids and nitrogen bases. Thus, in drops containing codeine phosphate, sodium bromide and adoniside, the precipitate also precipitates in the form of codeine hydrobromide. Cardiac glycosides easily form precipitates with salts of alkaloids and heavy metals, tannins. Therefore, in drops containing tincture of lily of the valley, motherwort And hawthorn extract, tannins of the latter precipitate cardiac glycosides of lily of the valley.

When drugs enter the digestive apparatus, their reaction is possible not only between themselves, but also with food, as well as with the secret of the stomach and intestines, i.e., pharmacokinetic interaction is already manifested.

So, it was found that the calcium contained in milk forms a complex with tetracyclines and ergocalciferol, dramatically reducing their healing properties. The activity of anticoagulant therapy (neodicumarin, pepilin) depends on the presence of vitamin K in the food (cabbage, spinach, etc.), because there is an antagonistic interaction between these substances. The antimicrobial properties of sulfonamide are significantly weakened when used with food. The blood level of griseofulvin depends on the amount of lipids in food. Ethanol is known to alter the resorption, metabolism, or pharmacological activity of antihypertensive, antianginal agents, anticoagulants, hypnotics, phenothiazine derivatives, antihistamines, and antibacterial drugs. With the simultaneous use of substances that disrupt absorption or accelerate the passage of glycosides through the intestines (neomycin, antacids, cholestyramia), the bioavailability and effectiveness of cardiac glycosides decrease.

Upon receipt in blood plasma, most drugs bind reversibly to plasma albumin, acting as a kind of depot (reservoir) with large fluctuations depending on the concentration of the drug (inactive, ineffective and toxic). The strength of the complex and its kinetic properties significantly affect the possibility of drug interaction in the process of their transport to tissues. Weak bases bind to proteins faster and more firmly, although their degree of affinity is small, so the percentage of bound drug in plasma and tissues is relatively constant. Drugs having a pH of less than 7.0 are easily replaced in the protein bond by other drugs, leading to an increase in their concentration at the receptors. Clofibrate and tolbutamide reduce the connection of cardiac glycosides with blood proteins. Since the connection of substances with a protein is the reverse process and obeys the law of the acting masses, it is possible to displace one compound by another (butadion and sulfanilamide preparations can replace neodicumarin in its complex with protein and significantly increase the anticoagulant effect of the latter). Drugs also interact in the process of their metabolism in the body. More than two hundred drugs are known that accelerate the metabolism of pharmacological agents in the liver by enhancing (inducing) the activity of microsomal enzymes of the endoplasmic reticulum of the liver (phenobarbital, chlorpromazine, methanine, antihistamines, oral antidiabetic and anticonvulsants, sex hormones) . Coffee and tea contribute to the acceleration of drug metabolism. Substances that inhibit the activity of microsomal liver enzymes, halogen-containing compounds and others increase the duration of the action of drugs whose metabolism occurs in this organ. Nicotinamide increases the number of oxidized and reduced forms of nicotinamidadene indium diuklertides in this organ and is therefore used to treat poisoning with barbiturates, cardiac glycosides and other substances. The manifested pharmacodynamic interactions of drugs are characterized either by synergism or antagonism

Quite often, pharmacological interaction is an obstacle to the complex treatment of various diseases. For example, para-aminobenzoic acid derivatives (novocaine, dicaine, anesthesia) are genuinely pharmacologically incompatible with sulfanilamide preparations; with the simultaneous use of these compounds, the antimicrobial properties of sulfonamides are almost completely lost.

A kind of drug interaction is their incompatibility; it can be physical, chemical and pharmaceutical.

Physical incompatibility is due to insufficient solubility, immiscibility, volatility, adsorption or coagulation of the active principles, a change in the colloidal composition, wetting or melting of the mixture. As a result of the physical incompatibility of the selected ingredients, the pharmacotherapeutic value of the entire combination is lost, the dosage accuracy is impaired, drug administration is difficult, the physical properties and appearance of the finished dosage form are changed. For example, in a mixture of tincture of valerian, camphor and cordiamine, a precipitate of camphor is formed, insoluble in an aqueous medium of a cordiamine solution. As a result of improper selection of the solvent, a precipitate drops in the nasal drops containing 1 g of menthol and 10 ml of glycerol, since menthol dissolves in glycerol only in a ratio of 1: 500. Menthol crystals irritate the nasal mucosa. Due to the insufficient solubility of substances in solvents, a poorly selected mixture can have a harmful effect. When using ear drops containing crystalline phenol and

liquid paraffin, cases of chemical burns of the tympanic membrane by precipitating insoluble excess of phenol are described.

Chemical incompatibility arises as a result of a chemical reaction (oxidation, reduction, hydrolysis, double exchange, etc.) of substances with each other. As a result of chemical incompatibility, the therapeutic value of the drug composition is lost or its effect changes, and the newly formed compounds may be toxic. Acids and drugs with an acid reaction form precipitates with salts of the purine alkaloids, antibiotics, licorice root preparations, alkaline reactants.

When describing the interaction of drugs, one should dwell on the possibilities of simultaneously administering several drugs orally and parenterally. If the incompatibility of drugs is not proven, it is more appropriate to prescribe them inside with a short (up to 1 hour) break. It is possible to administer several substances in one syringe only after special experimental studies.

Theoretically, various aspects of drug interaction are not always scientifically substantiated. So, the phenomena of chemical and pharmacological interaction of vitamins are well known. At the same time, several vitamins are usually found in food products (vegetables, fruits, etc.), however, incompatibility phenomena are not observed. Further research is needed to clarify the various aspects of drug interactions.

The study of the mechanisms of drug interaction is one of the possible ways to increase the effectiveness of combination therapy.

To identify and study the largest possible number of possible combinations of drugs, joint efforts by a clinician of pharmacologists are necessary.

Motivational characteristic of the topic

INTERACTION OF MEDICINES

By the interaction of drugs is understood the change in the effectiveness and safety of one drug with its simultaneous or sequential use with another drug, as well as xenobiotics, food, alcohol, and smoking. Of clinical importance are drug interactions that alter the effectiveness and safety of pharmacotherapy.

The interaction of drugs, leading to an increase in the effectiveness and safety of pharmacotherapy, is the basis for the rational combination of drugs

The interaction of drugs can lead to a decrease in the effectiveness of pharmacotherapy, while talking about irrational combinations of drugs. For example, almost all NSAIDs reduce the effectiveness of ACE inhibitors in hypertension and heart failure.

The basis of potentially dangerous combinations of drugs is the interaction of drugs, leading to a decrease in the safety of pharmacotherapy. Potentially dangerous combinations of drugs constitute a serious clinical problem. According to various authors, from 17-23% of combinations of drugs prescribed by doctors are potentially dangerous. Only 6-8% of patients receiving potentially dangerous combinations of drugs develop side effects. At the same time, according to statistics in the USA alone, 160,000 patients die every year from the side effects of drugs. The cause of death of a third of them is the interaction of drugs, usually associated with the use of potentially dangerous combinations of drugs. In addition, the side effects arising from the use of potentially dangerous combinations are also a serious economic problem, since the cost of their treatment is half the cost of the treatment of all drug complications.

TYPES OF INTERACTION OF MEDICINES

Depending on the mechanism, distinguish:

1. Pharmaceutical drug interactions.

2. Pharmacological interactions of drugs.

pharmacokinetic interaction of drugs.

pharmacodynamic interaction of drugs.

pharmacotoxicodynamic drug interactions.

• Pharmacokinetic interaction - the effect of one drug on the pharmacokinetic processes (absorption, distribution, metabolism, excretion) of another. As a result of pharmacokinetic interaction, the concentration of drugs in the blood plasma changes, and, consequently, its interaction with specific target molecules (receptors, enzymes, ion channels, etc.).

• Pharmacodynamic interaction - the effect of one drug on the process of generation and realization of the pharmacological effect of another, while the concentration of drugs in the plasma may not change. Most often, with pharmacodynamic interaction, one drug interferes with the mechanism of action of another.

PHARMACOKINETIC INTERACTION OF MEDICINES

Pharmacokinetic interaction of drugs can occur when they are absorbed, distributed, metabolized, and excreted metabolic products.

Drug Interactions upon Absorption

Changes in absorption through the digestive tract of some drugs under the influence of others can occur by various mechanisms. The main mechanisms are:

• the formation of chelated and complex compounds;

• a change in the pH of the gastric or intestinal contents;

• effect on the normal intestinal microflora;

• damage to the intestinal mucosa or effect on its functions

These changes can lead to a weakening or increased absorption of drugs from the digestive tract. As a rule, the interaction of drugs during absorption develops when they are taken simultaneously, or if the interval between doses of drugs is less than 2 hours. If the interval between doses of drugs is more than 4 hours, then interaction at the level of absorption is almost impossible. The interaction with absorption is especially significant for drugs with a short half-life (less than 12 hours) and for drugs whose pharmacological effect develops only when the maximum therapeutic concentration is quickly reached. This is due to the fact that even a slight decrease in the absorption intensity of such drugs leads to the achievement of only subtherapeutic concentrations, and therefore, to a decrease in the effectiveness of pharmacotherapy. This applies before

total to sleeping pills and non-narcotic analgesics. At the same time, a change in absorption practically does not affect the bioavailability of drugs with a long half-life (at least 12 hours). Below are the most significant mechanisms of drug interaction during absorption.

The formation of complex and chelate compounds

The essence of this mechanism is that during the interaction of drugs in the gastrointestinal tract, non-absorbable complexes and chelate compounds can form. So, activated carbon and antacids significantly inhibit the absorption of almost all drugs. Therefore, the appointment of activated carbon is an integral component of the treatment of poisoning with drugs (barbiturates,

benzodiazepines, etc.). It is known that the combined use of fluoroquinolones (ciprofloxacin, levofloxacin, etc.) with antacids and a gastroprotector sucralfate leads to the ineffectiveness of antibiotic therapy. This is due to the formation in the gastrointestinal tract of nonabsorbable chelating compounds of fluoroquinolones with magnesium, aluminum, calcium, sucralfate. Tetracycline forms non-absorbable chelating compounds in the gastrointestinal tract with aluminum, calcium, zinc, magnesium, salts of bismuth, iron and other metals, with all divalent and trivalent cations. Therefore, the absorption rate of tetracycline decreases with its combined use with antacids, bismuth preparations, as well as with calcium-rich foods (milk and dairy products), and as a result, therapy with this antibiotic becomes less effective. At the same time, the formation of nonabsorbable chelating compounds of tetracycline with iron leads to both a decrease in the effectiveness of antibiotic therapy and ineffectiveness of therapy with iron preparations. The ion-exchange resins used to treat hyperlipidemia (colestyramine) can form non-absorbable complexes and, therefore, reduce the absorption of the most diverse drugs (anticoagulants, digoxin, thiazide diuretics, thyroid hormones and fat-soluble vitamins), as a result of which blood concentration may decrease significantly. Such interactions of drugs during absorption can be avoided if a medication interval of at least 4 hours is made between drug intake.

Change in pH of gastric contents

Lipophilic nonionized drugs are better absorbed in the digestive tract than hydrophilic ionized ones. Most drugs are weak acids or weak bases, therefore, an increase in the pH of the gastric contents leads to an increase in the ionization of drugs - weak acids, and

decrease in ionization of drugs - weak bases. Under these conditions, the absorption of the former is inhibited, and the latter is enhanced. Therefore, drugs (antacids, histamine H2-receptor blockers, proton pump inhibitors) that change the pH of gastric contents affect the absorption of other drugs used in conjunction with them. So, ketoconazole and other antifungal drugs - derivatives of azole (weak acids) are practically not absorbed, and therefore, are ineffective if the patient uses them together with histamine H2 receptor blockers or proton pump inhibitors. By the same mechanism, the effectiveness of other drugs is also reduced - weak acids (indirect anticoagulants, acetylsalicylic acid, digoxin, sulfonamides, nitrofurans) when used together with antacids. Thus, the combined use of antacids with barbiturates (weak acids) leads to an almost complete elimination of the hypnotic effect of the latter. In contrast, increasing the pH of gastric contents when taking antacids increases the absorption of the oral sugar-lowering drug glibutide (weak base) by about 25%, which increases the likelihood of developing hypoglycemia. Drugs in the form of enteric-soluble tablets can be absorbed faster when the pH of the gastric contents increases, since dissolution of the membrane in such an environment occurs faster, before the drug reaches the small intestine. Such interactions of drugs during absorption can be avoided if drugs are prescribed with an interval of at least 4 hours.

Change in the state of normal microflora of the gastrointestinal tract

Normal microflora of the gastrointestinal tract is actively involved in absorption some drugs (digoxin, estrogens, etc.). Antibacterial drugs, especially of a wide spectrum of action, suppressing the normal microflora of the gastrointestinal tract, can alter the absorption of drugs. It is well known that Eubacterium lentum (a representative of the normal intestinal microflora) metabolizes to inactive products about 10% of digoxin taken orally. The combined use of digoxin with erythromycin leads to an increase in the concentration of digoxin in the blood, which can lead to the development of side effects up to glycosidic intoxication. Another example is the decrease in the effectiveness of oral contraceptives when used together with broad-spectrum antibiotics. It is well known that ethinyl estradiol contained in oral contraceptives undergoes enterohepatic recirculation: after absorption, ethinyl estradiol is metabolized (conjugated) in the liver, then

conjugates with bile enter the intestine, where, under the action of normal microflora enzymes, they are hydrolyzed to ethinyl estradiol, which is again absorbed. When using broad-spectrum antibiotics

that suppress the normal microflora, enterohepatic recycling of ethinyl estradiol is impaired, as a result of which the contraceptive effectiveness of the drugs containing it decreases.

Damage to the intestinal mucosa

Cytostatics prescribed as a component of chemotherapy for malignant tumors can damage the intestinal mucosa, which slows down the absorption of drugs. Cyclophosphamide, vincristine, and procarbazine can inhibit the absorption of digoxin, reducing its effectiveness. To avoid this phenomenon, digoxin in capsule form should be prescribed. Damage to the intestinal mucosa is the main cause of malabsorption of iron, cyanocobalamin, and folic acid when used together with neomycin and antibacterial drugs from the polymyxin or tetracycline group.

Gastrointestinal motility changes

Changes in the motility of the gastrointestinal tract can lead either to an acceleration or to a slowdown in the absorption of drugs. The rapid evacuation of gastric contents under the action of prokinetics (metoclopramide, domperidone) accelerates the absorption of certain drugs (ethanol, paracetamol, tetracycline, diazepam, cyclosporine, propranolol, lithium salts, etc.), since they reach the small intestine faster. The concentration of cyclosporine in plasma increases by about 30% when it is taken together with prokinetics metoclopramide, as metoclopramide accelerates gastric emptying. The use of such a combination can lead to the rapid development of side effects of cyclosporine (nephrotoxicity, hepatotoxicity and hematotoxicity). The rational combined use of metoclopramide with non-narcotic analgesics. Metoclopramide accelerates the release of non-narcotic analgesics into the small intestine, where they are intensively absorbed. As a result, the maximum concentration in blood plasma is quickly achieved, the onset is accelerated and the severity of the analgesic effect is increased.

With the simultaneous use of slowly absorbed drugs (digoxin, cimetidine, etc.) and prokinetics, the effect is opposite. For example, the bioavailability of slowly dissolving digoxin is reduced by 20% if it is taken simultaneously with metoclopramide. Acceleration of gastrointestinal motility and a decrease in the time it takes for drugs to pass through it slows down absorption and reduces the bioavailability of drugs. Erythromycin, laxative drugs can increase gastrointestinal motility. Anticholinergic drugs, narcotic analgesics, histamine H1 receptor blockers, phenothiazine antipsychotics have the opposite effect (lengthening the passage of drugs through the digestive tract).

Weakened gastrointestinal motility accelerates absorption and increases the bioavailability of drugs (cardiac glycosides, iron preparations), increasing the risk of side effects. For example, with the combined intake of gastrointestinal tract-weakening preparations with acetylsalicylic acid, the contact time of the latter with the gastric mucosa increases and the risk of ulceration (ulcerogenic effect) increases.

Effect on glycoprotein P activity

Glycoprotein P “ejects” absorbable drugs from enterocytes into the intestinal lumen. Glycoprotein P has drugs - substrates, inhibitors and inducers. The combined use of glycoprotein P inhibitors with its substrates leads to more complete absorption and an increase in the concentration of the latter in the blood, which increases the risk of side effects. Thus, quinidine and verapamil (powerful inhibitors of glycoprotein P) increase the concentration of digoxin (substrate) in the blood when taken together, which increases the risk of side effects of digoxin, up to digital intoxication. On the other hand, the use of substrates of glycoprotein P together with its inducers reduces the bioavailability and concentration of substrates in blood plasma, causing their low efficiency. For example, St. John's wort preparations reduce the concentration of digoxin in blood plasma.

Drug Interactions in Distribution

After absorption of drugs, blood flow is carried to organs and tissues of the body, where their pharmacological targets are localized. The distribution of drugs depends on the state of hemodynamics in organs and tissues. So, with a decrease in cardiac output in patients with heart failure, renal perfusion decreases, and loop diuretics have an insufficient diuretic effect, since they do not reach the point of their application (the ascending knee of the Henle loop). If with the help of drugs with a positive intropic effect (cardiac glycosides, dobutamine, etc.), cardiac output and renal perfusion are increased, then the diuretic effect of loop diuretics will increase.

Of greatest clinical significance is the interaction of drugs at the level of communication with blood proteins. A number of drugs are characterized by high

affinity for plasma proteins. In this case, weak acids bind to albumin, and weak bases to α-1-acid glycoprotein. Communication with proteins is broken if drugs with a higher affinity for them appear in the blood. Such drugs displace their competitor from the protein bond. This frequently occurring mechanism of drug interaction causes an increase in the free or active fraction of the drug that binds to proteins worse, enhancing its pharmacological effect (including side effects). This interaction mechanism gains clinical significance if the drug has a small distribution volume (less than 35 l) and binds to blood proteins by more than 90%. If the drug binds to blood proteins by less than 90%, then its displacement from communication with proteins will not lead to a significant change in the concentration of the free fraction in the blood. If a drug has a large volume of distribution (more than 35 l), then an increase in the concentration of its active fraction is leveled out by "leaving" the tissue. It should be noted that this interaction is usually short-term, since drugs are rapidly metabolized and excreted. Examples of drugs that have a very high affinity for plasma proteins and have a small distribution volume: phenytoin (binds to protein by 90%, distribution volume of 35 l), tolbutamide (binds to protein by 96%, distribution volume of 10 l) and warfarin (binds to 99% protein, distribution volume 9 l). These drugs are displaced from the association with blood proteins by sulfonamides, acetylsalicylic acid and phenylbutazone. Increased concentration of displaced drugs in the blood may cause side effects. So, salicylates, phenylbutazone and clofibrate increase the frequency of internal bleeding, displacing indirect anticoagulants from warfare due to protein [warfarin, acenocoumarol (syncumar), phenindione (phenylin)].

LS inhibitors of glycoprotein P increase the penetration of its substrates through histohematological barriers and, in particular, through the BBB. For example, quinidine (an inhibitor of glycoprotein P) promotes the penetration of antidiarrheal drugs Loperamide through the BBB, which can cause morphine-like side effects (dry mouth, miosis, respiratory depression). Domperidone crosses the BBB, causing extrapyramidal disorders, when used together with cyclosporine (an inhibitor of glycoprotein P).

Drug Interactions in Biotransformation

More than 300 drugs are known that affect the metabolism of other drugs. Moreover, they are able to both increase the activity of enzymes of the metabolism of drugs (induction), and suppress it (inhibition)

Induction of the biotransformation enzyme is an absolute increase in its quantity and (or) activity due to the action of a certain chemical agent and, in particular, drugs. This is accompanied by hypertrophy of the endoplasmic reticulum, in which most of the metabolic enzymes are localized. Induction can undergo both phase I biotransformation enzymes (cytochrome P-450 isoenzymes) and phase II enzymes (UDP-glucuronyl transferase, etc.). Enzyme inducing drugs do not have obvious structural similarities, but are characterized by some common features:

• tend to dissolve in fats (lipophilic);

• serve as substrates of enzymes (which they induce);

• they usually have a long half-life. Various substrates are able to induce isoenzymes of cytochrome P-450 with unequal molecular weight, substrate specificity, immunochemical and spectral characteristics. In addition, the intensity of induction of biotransformation enzymes can vary significantly in different people (for example, the same substrate increases the activity of drugs biotransformation enzymes in different individuals by 15-100 times).

The main mechanisms of induction of biotransformation enzymes:

• The molecules of the inducer directly affect the regulatory region of the gene, which leads to the induction of the enzyme biotransformation of drugs. This mechanism is most characteristic for autoinduction - an increase in the activity of an enzyme that metabolizes a xenobiotic under the action of the xenobiotic itself. Autoinduction is considered as an adaptive mechanism developed in the process of evolution to inactivate xenobiotics, including plant origin. So auto-induction in relation to the cytochromes of the subfamily IIB has phytoncide of garlic dialyl sulfide. Typical autoinductors among drugs are barbiturates (inducers of isoenzymes of cytochrome P-450 3A4, 2C9, subfamily IIB).

• Molecules of the biotransformation enzyme drugs are stabilized due to the formation of a complex with some xenobiotics (ethanol, acetone). For example, ethanol induces the isoenzyme of cytochrome P-450 2E1 at all stages of its formation from transcription to translation. It is believed that the stabilizing effect of ethanol is associated with its ability to activate the phosphorylation system in hepatocyte via cAMP. The induction of the cytochrome P-450 2E1 isoenzyme associated with starvation and diabetes mellitus is associated with the same mechanism. In this case, ketone bodies act as inductors of the cytochrome P-450 2E1 isoenzyme.

The activity of cytochrome P-450 isoenzymes 1A1, 3A4, 2B6 increases with the interaction of the inducer molecule with specific receptors belonging to the class of proteins - transcription regulators.

Induction leads to an acceleration of the biotransformation of drugs, substrates of the corresponding enzymes, and, as a rule, to a decrease in their pharmacological activity. Among the inducers of enzymes of biotransformation of drugs, rifampicin (an inductor of cytochrome P-450 1A2, 2C9, 2C19, 3A4, 3A5-7 isoenzymes) and barbiturates (cytochrome P-450 isozyme inducers 1A2, 2B6, 2C8, 2C9, 2C, are most widely used in clinical practice). 3A4, 3A5-7). Unlike barbiturates, the development of the inducing effect of which takes several weeks, rifampicin acts quickly (the induction of biotransformation enzymes with its appointment can be detected after 2-4 days), and the maximum reaches its effect after 6-10 days. Induction of enzymes caused by rifampicin and barbiturates can lead to a decrease in the pharmacological efficacy of indirect anticoagulants (warfarin, acenocumarol, phenindione), cyclosporine, glucocorticoids, ketoconazole, theophylline, quinidine, digitoxin and dose adjustment (which requires an increase in dosage).

It should be emphasized that when canceling the inducer of enzymes of biotransformation of drugs, the dosage of the combined drug should be reduced, since its concentration in the blood increases. An example of this interaction is the combination of indirect anticoagulants and phenobarbital. The cause of bleeding during treatment with indirect anticoagulants in 14% of cases is the abolition of drugs that induce biotransformation enzymes.

Inhibition of drugs biotransformation enzymes - inhibition of the activity of metabolic enzymes under the influence of drugs and xenobiotics.

The main mechanisms of inhibition of enzymes of biotransformation of drugs:

• binding to the regulatory region of a gene that regulates the synthesis of a specific isoenzyme of P-450 cytochrome (cimetidine, fluoxetine, omeprazole, fluoroquinolones, macrolides, sulfonamides, etc.);

• metabolic competition consists in the fact that some drugs with high affinity (affinity) for certain isoenzymes of cytochrome P-450 (verapamil, nifedipine, and

pin, quinidine), inhibit the biotransformation of drugs with lower;

• direct inactivation of cytochrome P-450 isoenzymes and inhibition of the interaction of cytochrome P-450 with NADP-H-cytochrome P-450 reductase (fumarocoumarins of grapefruit and lime juice).

A decrease in the activity of drugs biotransformation enzymes under the action of appropriate inhibitors leads to an increase in the blood concentration of drugs (enzyme substrates) and an increase in their half-life, which causes the development of side effects. Some inhibitors affect several isoforms of biotransformation enzymes at once. To inhibit several enzyme isoforms at once, large concentrations of the inhibitor may be required.

Thus, the antifungal drug fluconazole inhibits the activity of the cytochrome P-450 2C9 isoenzyme at a dose of 100 mg / day, and when the dose is increased to 400 mg, the activity of the cytochrome P-450 3A4 isoenzyme is also suppressed. In addition, the higher the dose of the inhibitor, the faster its effect occurs and the brighter it is expressed. Inhibition in general develops faster than induction; usually it can be registered after 24 hours from the moment of drug administration. The rate of inhibition of the enzyme activity is also affected by the route of administration of the LS inhibitor: with intravenous administration, the interaction develops faster.

Consider several clinically relevant examples of this mechanism of interaction.

• Inhibitors of the cytochrome P-450 1A2 isoenzyme include fluoroquinolones: ciprofloxacin and, to a lesser extent, norfloxacin. The combined use of theophylline preparations with the listed fluoroquinolones leads to a 4-5-fold increase in theophylline concentration in the blood and to a sharp increase in cardiotoxicity, therefore, theophylline should not be combined with ciprofloxacin, enoxacin and norfloxacin. The absence of the inhibitory effect of other fluoroquinolones on CYP1A2 is explained by the presence in their molecules of radicals at positions N1 and C7, which do not allow contact with CYP1A2. Thus, lo-mefloxacin at position C7 has a 3-hydroxy-4-methylpiperazine group, therefore it does not inhibit CYP1A2 and can be used safely with theophylline preparations.

• The combined use of the indirect anticoagulant warfarin (substrate of the cytochrome P-450 2C9 isoenzyme) with sulfonamide preparations (inhibitors of the cytochrome P-450 2C9 isoenzyme) enhances the anticoagulant effect and increases the risk of hemorrhagic complications. Therefore, for

a combination of warfarin with sulfonamides recommend strict control of the international normalized ratio (INR) - at least 1-2 times a week.

• Macrolide antibiotics inhibit the cytochrome P-4450 3A4 isoenzyme. Macrolides differ in their ability to inhibit CYP3A4. In the classification proposed by P. Periti et al. (1992), macrolides are divided according to their ability to inhibit CYP3A4 into 3 groups:

Group 1 strong CYP3A4 inhibitors (erythromycin and troleandomycin);

Group 2 moderate CYP3A4 inhibitors (clarithromycin); 3rd group - macroleads that do not inhibit CYP3A4 (azithromycin).

• The combined use of cytochrome P-450 3A4 isoenzyme substrates with only macrolides of the 1st and 2nd groups can lead to side effects. For example, the combined use of macrolides of the 1st and 2nd group with histamine H1 receptor blockers (astemizole *, terfenadine *, etc.) in 10% of cases leads to cardiotoxicity, manifested by prolongation of the QT interval according to ECG, which increases the risk the occurrence of life-threatening ventricular tachycardia of the “pirouette” type (bidirectional spindle-shaped ventricular tachycardia).

Many drugs can affect the intensity of hepatic blood flow, a “limiting” factor in the biotransformation of drugs with high liver-night clearance, which are characterized by the “first pass” effect (see Chapter 1, “Clinical Pharmacokinetics”). Therefore, drugs that reduce the value of hepatic blood flow inhibit the biotransformation of drugs with high liver-night clearance, increasing their bioavailability.

It is known that β-blockers (propranolol, etc.), reducing the intensity of hepatic blood flow, inhibit their own metabolism, as well as the biotransformation of lidocaine, chlorpromazine, verapamil, etc. The concentration of these drugs in blood plasma rises, and side effects can occur effects. It should be noted that in order to enable this mechanism of interaction, it is necessary a few days from the date of administration of β-blockers. Among β-blockers, pro-pranolol has the greatest effect on hepatic blood flow.

Drug Interactions in Excretion

When excreting drugs, they interact with each other, changing the parameters of glomerular filtration, tubular secretion and reabsorption.

Changing glomerular filtration

GFR-lowering drugs usually lower filtration pressure, decreasing the volume of circulating blood, or lowering the blood pressure or tone of the renal arteries. The concentration of drugs that are eliminated from the body primarily by passive filtration increases with their combined use with drugs that reduce GFR. At the same time, the incidence of side effects also increases.

For example, a decrease in GFR when taking furosemide leads to inhibition of the filtration of aminoglycoside antibiotics, an increase in their concentration in the blood, and an increase in nephrotoxicity. At the same time, nephrotoxic drugs themselves (for example, aminoglycosides) can reduce the number of functioning glomeruli and reduce GFR, which leads to the accumulation in the body of drugs used together with them, for example digoxin.

Changes in tubular secretion

Many drugs are actively secreted in the proximal tubule of the nephron. Lipophilic drugs are secreted using glycoprotein R, hydrophilic, as well as drug metabolites - through transporters of organic anions (OAT, OTPP) and cations (OST). A decrease in the activity of these specific systems can lead to an increase in blood concentration of drugs, the main way of eliminating them. - tubular secretion. Competition of endogenous substances (e.g. uric acid) and drugs or their metabolites (benzylpenicillin, probenicide *, NSAIDs, methotrexate, sulfonamides and cephalosporins) for transport systems may lead to the development of clinically significant drug interactions

NSAIDs, inhibiting OAT2, OAT3, OAT4 of the proximal renal tubules, inhibit the active secretion of methotrexate, increasing its concentration in blood plasma and increasing the risk of side effects (myelotoxicity, etc.). The ability of probenicide * to inhibit OAT1 of proximal renal tubules, while inhibiting tubular secretion of penicillins, was previously widely used to increase the effectiveness of β-lactam antibiotics.

Changing tubular reabsorption

Filtered and secreted drugs are reabsorbed in the distal part of the renal tubule and in collecting ducts, and only non-ionized drug molecules are reabsorbed. The acidity of the medium changes the degree of ionization of drugs, therefore, the acidity of primary urine is significantly affected by their results. the action of other drugs. With acidification of urine, reabsorbium of weak bases is reduced, and with alkalization, weak acids.

PHARMACODYNAMIC INTERACTION OF MEDICINES

Pharmacodynamic interaction - a change in the pharmacological effects of one drug under the influence of another, not accompanied by a change in its concentration in the blood and communication with target molecules (receptors, enzymes, ion channels, etc.). The pharmacodynamic interaction of drugs is clinically manifested by their antagonism or synergism.

• Antagonism - the interaction of drugs that depresses or eliminates part or all of the pharmacological effects of one or more drugs.

• Synergism - the unidirectional effect of drugs, providing a stronger pharmacological effect than the action of each drug separately.

The following types of synergism are distinguished:

sensitizing effect - the result of a synergistic interaction of drugs, in which the pharmacological effect of one drug is enhanced by another that does not have this pharmacological effect;

additive effect is the result of a synergistic drug interaction, in which the pharmacological effect of the combination is greater than the action of one of the components, but less than the expected effect of their sum;

summation of action - the result of a synergistic interaction of drugs, in which the pharmacological effect of a combination of drugs is approximately equal to the sum of each of them;

potentiation is the result of a synergistic drug interaction, in which the final pharmacological effect of a combination of drugs is greater than the sum of the effects of each component of the combination.

Synergistic pharmacodynamic interaction

The synergistic interaction is based on the unidirectional effect of jointly used drugs. Here are some examples of synergistic pharmacodynamic interactions. The β-adrenoblocker propranolol and the verapamil blocker of slow calcium channels reduce myocardial contractility (negative inotropic effect) and heart rate (negative chronotropic effect), inhibit atrioventricular conductivity, etc. The combined use of these drugs enhances these pharmacological effects - the combination of propranolol and verapamil is potentially dangerous

An example of a clinically significant interaction of this kind is the effect of NSAIDs on the effectiveness of antihypertensive drugs. NSAIDs weaken the hypotensive effect of most antihypertensive drugs (ACE inhibitors, diuretics, β-blockers). In addition, in patients with heart failure with NSAIDs, the frequency of decompensations increases, which, apparently, is associated with a decrease in the effectiveness of the applied diuretics and ACE inhibitors. The mechanism of these phenomena is the inhibition of the synthesis of vasodilating prostaglandins in the kidneys with NSAIDs.

A synergistic or antagonistic pharmacodynamic interaction, depending on the mechanism underlying it, can be direct and indirect (indirect).

Direct pharmacodynamic interaction

In direct pharmacodynamic interaction, both drugs affect the same biosubstrate: specific target molecules (receptors, enzymes, ion channels, etc.), systems of "secondary" mediators, transport mediator systems. The following are examples of direct pharmacodynamic interaction.

Interaction at the level of specific target molecules

In case of an overdose of β-adrenergic blockers (hypotension, bradycardia, atrial ventricular conduction disturbance, etc.), a dobutamine β1-adrenergic receptor agonist is used, which displaces

the β-adrenergic blocker from the connection with β1-adrenergic receptors and eliminates its pharmacological effects.

Intermediary Interoperability

Secondary intermediaries (messengers) that carry signals from receptors in effector cells include cAMP, cGMP, inositol triphosphate, etc. Theophylline and

agonists of β2-adrenergic receptors f2-adrenergic agonists). This combination is used to enhance the bronchodilator effect with insufficient effectiveness of β2-adrenergic agonist monotherapy.

β2-adrenergic agonists stimulate β2-adrenergic receptors of the smooth muscles of the bronchi; as a result of signal transmission through Gs-proteins, they increase the activity of adenylate cyclase, which intensively converts ATP into cAMP, a secondary mediator of receptor signal transmission. An increase in the intracellular concentration of cAMP leads to the activation of cAMP-dependent protein kinases that phosphorylate and, thus, reduce the kinase activity of myosin light chains. The latter ceases to phosphorylate the light chains of the myosin contractile protein, while myosin loses its ability to connect with actin and the smooth muscle cells of the bronchi remain in a relaxed state. There is a bronchodilator effect.

Theophylline, inhibiting phosphodiesterase (an enzyme that destroys cAMP), increases the concentration of intracellular cAMP. The combined use of β2-adrenergic agonists and theophylline leads to an even greater increase in the concentration of cAMP in the smooth muscle cells of the bronchi, enhancing the bronchodilator effect.

Interaction at the level of transport mediator systems

The combined use of antidepressants MAO inhibitors with sympathomimetics (amphetamine, ephedrine) - leads to severe hypertensive crisis, which may be accompanied by delirium and cardiac arrhythmias. When taking sympathomimetics from the ends of the sympathetic nerves, an excessive amount of norepinephrine is released, which accumulates in them as a result of inhibition of MAO.

Another example is the occurrence of “serotonin syndrome” when using the following drug combinations: MAO inhibitors and antidepressants - serotonin reuptake inhibitors, MAO inhibitors and tricyclic antidepressants, MAO inhibitors and tryptophan. These interactions lead to excessive accumulation of serotonin in the central nervous system, as a result of which the “serotonin syndrome” occurs - fever, ataxia, convulsions, etc.

Indirect (indirect) pharmacodynamic interaction

This type of drug interaction is realized with the inclusion of various biological substrates and can be carried out at the level of effector cells, tissues, organs, and functional systems. The following are examples of indirect pharmacodynamic interactions at various levels.

Effector cell level interaction

β2-adrenergic agonists, especially in high doses, lose their selectivity for β2-adrenergic receptors, stimulate β1-adrenergic receptors of the sinus node of the cardiac conduction system. This leads to stimulation of adenylate cyclase through the Gs protein and activation of cAMP synthesis. An increase in the intracellular concentration of cAMP leads to the activation of cAMP-dependent protein kinases, which phosphorylate calcium membrane channels, facilitating their opening. This creates a flow of calcium ions from the extracellular space into the cardiomyocytes, which plays the role of a “calcium spark” for the massive release of calcium ions from the intracellular depot (sarcoplasmic reticulum). An increase in the concentration of intracellular calcium in the cardiomyocytes of the sinus node leads to an increase in heart rate - tachycardia. Verapamil, blocking slow calcium channels in the cells of the sinus node, eliminates this effect of β2-adrenergic agonists. Therefore, verapamil is used to attenuate tachycardia caused by the use of β2-adrenergic agonists.

Another example of indirect pharmacodynamic interaction at the effector cell level is the weakening of the antibacterial activity of bactericidal antibiotics (β-lactam antibiotics, aminoglycosides, etc.) when used together with bacteriostatic antibiotics (tetracyclines, macrolides, lincosamides, etc.). This is due to the fact that bactericidal antibiotics act on dividing bacterial cells. When bacterial cell division is suppressed by bacteriostatic antibiotics, the number of fissile bacteria - targets for bactericidal antibiotics - decreases, and therefore their antibacterial activity also weakens.

Effector organ level interaction

Many drugs have organotoxicity - the ability to infect certain organs. It is potentially dangerous to jointly use drugs that have a toxic effect on the same organ. Such combinations of drugs should be avoided, and in case of urgent need for their use, it is necessary to carefully monitor the functional state of the corresponding organ. Some drugs with organotoxicity are given in table.

Effector Functional System Interaction

During pharmacotherapy of arterial hypertension, in order to increase the effectiveness of antihypertensive therapy, they resort to a combination of drugs with different mechanisms of action. For example, a combination of thiazide diuretics (hydrochlorothiazide, etc.) and ACE inhibitors (captopril, ena-lapril, etc.) is considered effective and safe. With this combination, the hypotensive effect is potentiated, which allows you to normalize blood pressure.

INTERACTION OF MEDICINES WITH FOOD

Food can change both the pharmacokinetics and pharmacodynamics of drugs.

Pharmacokinetic interaction of drugs with food

The pharmacokinetic interaction of drugs taken orally with food occurs mainly at the level of absorption. When taken together with food, absorption slows down and the bioavailability of some drugs decreases and the absorption of other drugs accelerates (see Table 5-6). For example, when taking non-narcotic analgesics (acetylsalicylic acid, paracetamol, etc.) with food, the development of anesthetic action slows down. The antiallergic effect develops longer if histamine H1 receptor blockers are taken with food. Recommendations for the use of drugs depending on food intake are given in table.

Slowing down the absorption of some drugs contributes to a certain qualitative composition of food. This may be due to the effect of certain products on the pH of the stomach.

For example, products that enhance the secretion of hydrochloric acid in the stomach (tomatoes, fruit juices, caffeinated drinks), slow down the absorption and reduce the bioavailability of erythromycin and semisynthetic penicillins (ampicillin, oxacillin, amoxicillin). When alkalizing the contents of the stomach with certain food products (milk and dairy products), antifungal drugs - imidazole derivatives (clotrimazole, ketoconazole, etc.) are ionized, which reduces their bioavailability.

The composition of food may include components that form nonabsorbable chelating compounds and complexes with drugs. So, calcium-rich foods (milk, cheese, ice cream, yogurt and other dairy products) inhibit the absorption of tetracyclines and ciprofloxacin. The predominance of animal fats in food can increase the bioavailability of lipophilic drugs. The increased content of animal fats in food provides a more complete absorption of theophylline, while carbohydrate-rich foods reduce its absorption. This must be considered when prescribing oral prolonged dosage forms of theophylline.

In some cases, it is specifically recommended to take drugs during meals to reduce the risk of side effects. For example, to reduce the ulcerogenic effect of NSAIDs and glucocorticoids (with long-term use of course), they should be taken with food or washed down with milk. Food does not significantly affect the absorption of certain drugs.

The components of some products affect the biotransformation of drugs. For example, flavonoids of grapefruit juice inhibit the cytochrome P-450 3A4 isoenzyme. A glass of grapefruit juice 2 times slows down the clearance of nifedipine (a substrate of the cytochrome P-450 3A4 isoenzyme) taken orally, provoking severe arterial hypotension and tachycardia.

Fruit juices affect the activity of not only cytochrome P-450 isoenzymes, but also transporters and are able to change the pharmacokinetics of drugs

So, orange juice induces the OATP-C transporter and almost 2 times reduces the maximum concentration of atenolol in the blood, which is accompanied by a less pronounced decrease in heart rate.

Patients should be warned about the inadmissibility of drinking drugs with fruit juices

Inducers of the cytochrome P-450 1A2 isoenzyme include nutrition products such as broccoli, Brussels sprouts, and well-fried meat. The effectiveness of theophylline (a substrate of the cytochrome P-450 1A2 isoenzyme) in patients who regularly consume these products is reduced due to its intense metabolism. It was shown that some varieties of honey induce the cytochrome P-450 3A4 isoenzyme, which can reduce the effectiveness of drugs undergoing biotransformation under the influence of this isoenzyme.

Pharmacodynamic interaction of drugs with food

The pharmacodynamic interaction of drugs with food can also be direct and indirect.

Direct interaction at the level of specific target molecules occurs with the combined use of indirect anticoagulants [warfarin, acenocumarol (syncumar *), phenindione (phenylin *)] and vegetables rich in vitamin K (spinach, lettuce, cabbage, radish, turnip, Brussels sprouts, broccoli, asparagus). As is known, the effect of indirect anticoagulants is associated with inhibition of the formation of reduced vitamin K, which is necessary for the synthesis of blood coagulation factors (II, V, IX, X). The listed products replenish the reserves of vitamin K and reduce the anticoagulant effect of these drugs, reducing their effectiveness. Therefore, when prescribing indirect anticoagulants, it is necessary to inform patients about the need to limit the use of the above vegetables.

Direct pharmacodynamic interaction at the level of transport mediator systems occurs when antidepressants from the group of MAO inhibitors are used together with foods rich in sympathomimetic tyramine. Under the action of tyramine from the ends of the sympathetic nerves, an excessive amount of norepinephrine is accumulated, which accumulates as a result of suppression of MAO. In this case, a pronounced hypertensive crisis develops, which can be accompanied by delirium and rhythm disturbances of the heart. Tyramine is found in large quantities in certain types of cheese (Camembert, Cheddar, Mozzarella, Parmesan), soy sauce, Salami sausage, chicken, sauerkraut, bananas, avocados, raisins , beer, wines sherry and riesling. Before the appointment of MAO inhibitors, patients should be warned about the need to strictly follow an appropriate diet.

Some food products may enter into indirect pharmacodynamic interaction with drugs. So, the use of foods with a high content of sodium chloride (sausages, ham, canned meat and fish, bacon, salted and smoked fish, etc.) can

to reduce the hypotensive effect of antihypertensive drugs (diuretics, β-blockers, slow calcium channel blockers, ACE inhibitors, etc.). Potassium-rich foods (dried fruits, apricots, jacket potatoes, bananas, figs, orange juice, etc.) can provoke hyperkalemia with spironolactone, ACE inhibitors, angiotensin receptor antagonists.

Thus, food can have a diverse effect on the pharmacokinetics and pharmacodynamics of drugs, which must be taken into account when conducting pharmacotherapy

INTERACTION OF MEDICINES WITH TOBACCO

By the prevalence of smoking, Russia is one of the first places in the world. Among the male population, the prevalence of smoking is 63.2%, among the female - 9.7% (Oganov R.G. et al., 1998).

Tobacco smoke contains more than a hundred different chemical compounds that have a diverse effect on the human body. The effect of the components of tobacco smoke on the pharmacokinetics and pharmacodynamics of certain drugs is known, which must be taken into account when conducting pharmacotherapy in smokers. The greatest influence on the pharmacokinetics of drugs is exerted by PAHs from tobacco smoke. The pharmacokinetic interaction of drugs with PAHs is carried out at the level of biotransformation, since PAHs induce the isoenzyme of cytochrome P-450 1A1 (localized in the lungs) and 1A2 (localized in the liver). Induction under the influence of PAHs of the cytochrome P-450 1A2 isoenzyme in the liver is of clinical importance, and the biotransformation of the substrates of this isoenzyme: theophylline, mexiletine, caffeine, pentazocine, propranolol, flecainide *, est-radiol and a number of psychotropic drugs will accelerate , which leads to a decrease in their concentration in the blood and a decrease in pharmacological effectiveness. This requires the appointment of smokers of these drugs in large doses.

Of all the components of tobacco, nicotine has the most significant effect on the pharmacodynamics of drugs. Indirect pharmacodynamic interaction of β-blockers with nicotine is known. Nicotine stimulates the N-cholinergic receptors of the cells of the adrenal medulla and sympathetic ganglia and causes the release of adrenaline and norepinephrine. Moreover, the effect of β-blockers can be leveled, which reduces the hypotensive and antianginal effect and requires an increase in the dose of β-blockers. The inadequate analgesic effect of these drugs in smokers is sometimes associated with indirect pharmacodynamic interaction of narcotic analgesics and nicotine.

INTERACTION OF MEDICINES WITH PHYPHOTHERAPA-MI

According to various authors, from 20 to 30% of patients who receive certain drugs for a long time, they also independently take various non-prescription drugs and biologically active additives containing plant materials (herbal preparations). Of these, only 20-25% report this to their attending physician. The interaction of drugs with medicinal plants is not well understood. Separate reports of clinically significant interactions of this kind have been published. According to some reports, side effects with the combined use of drugs and herbal remedies are found in 16% of cases, however, there is no exact information on the frequency and nature of interactions of drugs with herbal remedies.

To prevent the development of undesirable drug reactions and prevent a decrease in the efficacy of drugs that may result from such interactions, during pharmacotherapy, the doctor should actively collect information from the patient about the use of herbal remedies.

The interaction of drugs with herbal remedies can be both pharmacokinetic and pharmacodynamic and can be carried out at various levels. The pharmacokinetic interaction between drugs and phytopreparations at the level of biotransformation is best studied. In vitro and in vivo studies have demonstrated the effect of various medicinal plants on the activity of cytochrome P-450 isoenzymes (inhibition and induction). Phytopreparations containing those listed in the table. plants affect the pharmacokinetics of drugs metabolized by these isoenzymes

In half the cases, side effects occur with the combined use of drugs with herbal remedies containing St. John's wort. Hypericum perforatum reduces the effectiveness of digoxin, indirect anticoagulants, cyclosporine, amitriptyline, indinavir. Perhaps an increase in theophylline concentration in the blood, a high risk of cardiotoxic effect. When taking antidepressants from the group of serotonin reuptake inhibitors, St. John's wort preparations are categorically contraindicated in patients. When prescribing indirect anticoagulants and antiplatelet agents with Gingo bifolia, garlic or angelica preparations, special care should be taken and blood clotting indicators (INR, APTT) should be

carefully monitored, since such combinations can lead to hemorrhagic complications. Many herbal remedies (especially those produced as “diet pills”) contain laxative medicinal plants (senna, sabur, buckthorn, joster, aloe), while increasing the passage rate of intestinal contents can reduce the bioavailability of many drugs and reduce the effectiveness of pharmacotherapy.

Some known clinically significant interactions of drugs with medicinal plants are given in table.

DRUG INTERACTIONS WITH ETHANOL

A high level of ethanol consumption (alcohol, ethyl alcohol) remains, which is 7.57 liters per year in terms of absolute alcohol per capita (Koshkina EA, 1999). According to the Ministry of Health, 20% of the population is drunk, and 1.5% suffer from alcoholism. It is known that the interaction of drugs with ethanol can lead to serious complications, and even death. Ethanol can enter into both pharmacokinetic and pharmacodynamic interactions with drugs.

Pharmacokinetic interaction of drugs with eta-nolol

The pharmacokinetic interaction of drugs with ethanol occurs mainly at the level of biotransformation. Moreover, as drugs can interfere with the metabolism of ethanol, ethanol itself affects the biotransformation of drugs. Ethanol is metabolized in three directions mainly in the liver. The main pathway for ethanol biotransformation is the oxidation of hepatocytes in the cytosol with alcohol dehydrogenase to acetaldehyde, which then under the influence of acetaldehyde dehydrogenase is converted into acetic acid, which quickly “burns” in the Krebs cycle. This way, 70-80% of ethanol is metabolized. Only 5-10% of ethanol is oxidized in the endoplasmic reticulum of hepatocytes with the participation of the cytochrome P-450 2E1 isoenzyme. Some drugs inhibit acetaldehyde dehydrogenase and cause “acetaldehyde syndrome”, which is manifested by violent vegetative reactions (redness of the skin, feeling of heat, chills, chest tightness, difficulty breathing, head noise, heart palpitations, etc.) and a sense of fear. Such drugs include: metronidazole, chloramphenicol, furazolidone, cephalosporins (cefamandol, cefoperazone), antifungal drugs - imidazole derivatives (clotrimazole, ketoconazole, etc.). When conducting pharmacotherapy with the listed drugs, the patient should be warned about the inadmissibility of taking alcoholic beverages, as well as dosage forms containing ethanol (stand-by, drops, etc.), during the entire treatment period and the next three days after its completion. “Acetaldehyde syndrome” also develops with the use of disulfiram (teturam *, antabuse *) while taking alcohol. This effect of disulfiram is the basis of one of the methods of treating alcoholism (sensitizing therapy method).

The effect of ethanol on biotransformation of drugs is ambiguous. With a single dose of ethanol in large doses, isoenzymes of cytochrome P-450 are inhibited. As a result of a single dose of a large dose of ethanol, the biotransformation of the indirect anticoagulant warfarin is inhibited due to inhibition of the cytochrome P-450 2C9 isoenzyme. This leads to an increase in the concentration of warfarin in blood plasma and an increase in the anticoagulant effect. As a result, the risk of hemorrhagic complications increases.

On the other hand, long-term use of ethanol induces the induction of cytochrome P-450 isoenzymes. In this case, all isoenzymes of cytochrome P-450 can be induced, but the most strongly isoenzyme of cytochrome P-450 2E1. So, due to the induction of the cytochrome P-450 2C9 isoenzyme, the equilibrium concentration of warfarin decreases, which reduces the severity of the anticoagulant effect and requires dose adjustment for this drug. With prolonged use of ethanol, the pharmacokinetics and other drugs similarly change [androgens, anabolic steroids, phenytoin (diphenin *), etc.]. It is known that the hepatotoxic effect of paracetamol is enhanced with chronic use of ethanol. This is explained by the fact that ethanol induces the cytochrome P-450 2E1 isoenzyme, increases the proportion of the oxidative pathway of paracetamol metabolism to the hepatotoxic metabolite of N-acetylbenzoquinonimine

It should be noted that the dose of ethanol necessary for inhibiting the biotransformation of drugs, when taken once, is purely individual and varies widely. The same can be said about the doses of ethanol necessary for the induction of biotransformation of drugs with prolonged use.

Pharmacodynamic interaction of drugs with alcohol

Of greatest clinical significance is the indirect pharmacodynamic interaction of ethanol and drugs, which affects the central nervous system, the functional system for regulating blood pressure, and the hemostatic system.

The effect of the interaction of ethanol with drugs on the central nervous system is manifested by potentiation of the suppressing effect, up to respiratory depression. Such effects on the background of ethanol use can be exerted by narcotic analgesics, tricyclic antidepressants, barbiturates, benzodiazepines, histamine H1 receptor blockers (with a sedative effect), griseofulvin, ketotifen, metoclopramide, antipsychotic and anticonvulsants. Patients using these drugs should completely exclude ethanol consumption during the entire treatment period.

The effect of the interaction of ethanol with drugs on the functional system of blood pressure regulation is manifested in the potentiation of the hypotensive effect, up to collapse. Such an interaction develops with the simultaneous use of clonidine, nifedipine, β-blockers, nitrates with ethanol. Especially dangerous (due to the possibility of collapse and death) is the interaction of ethanol with clonidine. You should warn the patient about the inadmissibility of a co-administration of clonidine with alcoholic beverages.

The interaction of ethanol with drugs may disrupt the functioning of the hemostatic system. Acetylsalicylic acid, ticlopidine and clopidogrel can potentiate the antiplatelet effect and cause hemorrhagic complications.

We should also mention the possibility of hypoglycemia in the interaction of ethanol with disopyramide.

DRUG INTERACTION RISK FACTORS

The risk of the occurrence of dangerous drug interactions depends on many factors: patient age, concomitant diseases, polypharmacy, therapeutic breadth of drugs used, etc.

Age of patient

Undesirable effects of drug interactions more often occur in the “extreme” age groups - in the elderly and newborns. This can be explained by the pharmacokinetics of drugs at this age. The processes of absorption, biotransformation, distribution and excretion of drugs in newborns are still imperfect, while in the elderly they are slowed down due to age-related changes in the functions of the gastrointestinal tract, liver, and kidneys. The central nervous system in the elderly is more sensitive to narcotic analgesics and benzodiazepines, while the intestines and bladder are more sensitive to cholinergic receptor blockers. This group of patients, as a rule, has many concomitant diseases, for the treatment of which they take a larger number of drugs (polypharmacy, see below). In this regard, it is necessary to more carefully select the dosage regimen of drugs and monitor the condition of elderly patients and newborns in order to prevent the development of dangerous effects of drug interactions.

Accompanying illnesses

The risk of developing dangerous drug interactions increases dramatically with some concomitant diseases and conditions. There are several reasons for this:

• with CHF, as well as diseases of the liver and kidneys, the pharmacokinetics of drugs changes, primarily due to damage to the intestinal mucosa, epithelium of the kidneys and liver parenchyma, inhibition of blood protein synthesis;

• in case of epilepsy, diabetes mellitus, systemic diseases of connective tissue, manic-depressive psychosis, tuberculosis and other chronic or long-term illnesses, the patient takes medications for a long time that most often cause undesirable effects of pharmacokinetic interaction (inducers and inhibitors of metabolic enzymes competing for communication with blood proteins drugs, etc.).

Polypharmacy

This is a type of pharmacotherapy in which a large number of drugs are unreasonably prescribed. The risk of developing dangerous drug interactions increases sharply with the appointment of several drugs at once. If a patient is prescribed 2 drugs, then the probability of developing undesirable effects of drug interaction is 3-5%, and if 10 drugs - at least 20%.

For example, if ciprofloxacin (a cytochrome isoenzyme inhibitor P-450 1A2) or cimetidine (a cytochrome P-450 isoenzyme inhibitor P-450 2C9 is inhibited) is unlikely to occur when taking the indirect anticoagulant warfarin (metabolized by isoenzymes of P-450 1A2), then this clinically significant interactions. If all three of the above drugs are prescribed, then the effect of warfarin will sharply increase, and this is fraught with the development of serious hemorrhagic complications.

Therapeutic breadth of drugs

The risk of developing the effects of a dangerous pharmacokinetic interaction of drugs is greater if the drugs have a small therapeutic breadth (narrow therapeutic range). Such drugs include aminoglycosides, indirect anticoagulants, cardiac glycosides, antiepileptic drugs, tricyclic antidepressants, lithium salts, some antiarrhythmic drugs, theophylline. Even a slight increase in the concentration of such drugs in the blood can lead to serious side effects, including intoxication. Especially often, dangerous drug interactions occur when using high therapeutic doses of drugs with a narrow therapeutic range. To increase the safety of pharmacotherapy of drugs with a narrow therapeutic range, their equilibrium concentration in the blood should be constantly monitored (carry out therapeutic drug monitoring).

Pharmacogenetic factors

The existence of interindividual differences in the pharmacological response to certain drugs associated with genetically determined changes in pharmacokinetics and pharmacodynamics is known (see Chapter 7, Clinical Pharmacogenetics). These changes are based on spontaneously occurring and transmitted from generation to generation mutations in the protein genes responsible for the pharmacokinetics and pharmacodynamics of drugs. This phenomenon is called genetic polymorphism. Of greatest clinical importance is the genetic polymorphism of the enzymes of biotransformation of drugs.

Carriers of “slow” alleles of genes encoding cytochrome P-450 isozymes 2D6, 2C9, 2C19 are considered to be “slow metabolizers” of drugs (substrates of the corresponding isoenzymes). It is clearly seen that it is in this category of patients that the highest risk of undesirable effects of drug interaction occurs. To prevent such potentially dangerous drug interactions in the future, genotyping methods (detection of mutant alleles by PCR) will be used.

Knowledge of the main mechanisms of drug interaction, taking into account their risk factors dangerous interactions during pharmacotherapy, as well as a clearly defunct system for reporting clinically significant drug interactions, can increase the effectiveness and safety of pharmacotherapy

Lesson purpose

Know:

I The main types of drug interactions

1. pharmaceutical interaction of drugs;

2. pharmacological interaction of drugs;

pharmacokinetic interaction

at the suction stage,

• the formation of chelated and complex compounds;

• a change in the pH of the gastric or intestinal contents;

• effect on the normal intestinal microflora;

• damage to the intestinal mucosa or effect on its functions;

• change in motility of the digestive tract;

• effect on R. glycoprotein

at the stage of biotransport,

at the distribution stage,

at the stage of biotransformation

at the stage of excretion

Changing glomerular filtration

Change in canalic secretion

Change in canalicium reabsorption

pharmacodynamic interaction

Antagonism - the interaction of drugs that depresses or eliminates part or all of the pharmacological effects of one or more drugs.

Full antagonism

Partial (partial) antagonism

Syneroantagonism

Synergism - the unidirectional effect of drugs, providing a stronger pharmacological effect than the action of each drug in isolation.

sensitizing effect - the result of a synergistic interaction of drugs, in which the pharmacological effect of one drug is enhanced by another that does not have this pharmacological effect;

additive action - the result of a synergistic drug interaction, in which the pharmacological effect of the combination is greater than the action of one of the components, but less than the expected effect of their sum;

summation of action - the result of a synergistic interaction of drugs, in which the pharmacological effect of a combination of drugs is approximately equal to the sum of each of them;

potentiation - the result of a synergistic drug interaction, in which the final pharmacological effect of the combination of drugs is greater than the sum of the effects of each component of the combination.

Pharmacodynamic interaction of drugs with food

Pharmacodynamic interaction of drugs with herbal remedies

Pharmacodynamic interaction of drugs with alcohol

Pharmacodynamic interaction of drugs with ethanol

 pharmacological-dynamic interaction

3. Inductors and inhibits of microsamal liver enzymes,

4. Risk factors for drug interactions

Age of patient

Concomitant diseases

Polypharmacy

Therapeutic breadth of medicines

Pharmacogenetic factors

A) Pharmacological interaction:

1. based on a change in the pharmacokinetics of lek.redstv;

2. based on a change in the pharmacodynamics of lek.redstv;

3. based on the chemical and physico-chemical interaction of lek.redstv in the environment of the body.

Test questions.

1. What are the different types of drug interactions?

2. What is the phenomenon of enhancing the action of one substance called another?

3. What phenomenon is called potentiation of the effect?

4. What are the different types of synergism?

5. What is additive synergism?

6. What is drug antagonism?

7. What are the different types of antagonism?

8. What are antidotes?

9. What is synergoantagonism?

10. What are the types of incompatibility of drugs?

Topics for independent work of students.

1. The principles of interaction of different drugs.

2. Physico-chemical interaction of drugs.

3. Interaction of drugs at the stages of absorption, transport, distribution, biotransformation, excretion (pharmacokinetic type of interaction).

4. Pharmacodynamic interaction of drugs.

5. Pharmaceutical and pharmacological incompatibility of different drugs.

The solution of situational problems.

1. Patient P., 56 years old, was first admitted to treatment at the therapeutic department for arterial hypertension. From the anamnesis it is known that AKD is increased within 3 months. I did not receive treatment. The attending physician appointed: 25 mg capoten 3 times a day, prazosin 1 mg 3 times a day. 30 minutes after the first intake of combination therapy, the patient fell and lost consciousness for several seconds. Objectively: the skin is pale, moist. PE - 100 beats per 1 minute, ABP - 70/30 mm RT. Art.

What complication arose in the patient? Your recommendations for the treatment of this condition, as well as for the prevention of these symptoms in the future.

2. Patient G., 69 years old, regularly (3 times a week) receives 40 mg furosemide for the treatment of heart failure. Currently, the local therapist diagnosed community-acquired pneumonia in the patient and prescribed its combined pharmacotherapy. After 3 days, the patient began to complain of hearing loss.

What antimicrobial drugs and why when interacting with furosemide increase the risk of deafness? Explain the mechanism of this interaction.

3. Patient K., 65 years old with a constant form of atrial fibrillation, was hospitalized in connection with the appearance of signs of decompensation of cardiac insufficiency. Complaints: increased general weakness, shortness of breath at rest, swelling of the legs and feet. In the history of myocardial infarction 15 years ago, the last 5 years have been diagnosed with atrial fibrillation. He constantly took furo-semid 40 mg, veroshpiron 25 mg, enalapril 10 mg, digoxin 0.25-0.50 mg. Deterioration occurred within 2 weeks after ARI. Objectively: the condition is serious, the position is orthopnea, shortness of breath at rest. BH - 28-30 in 1 minute. AKD - 100/60 Hg, heart rate - 104 in 1 minute, state of emergency - 84 in 1 minute, the rhythm is not correct, heart sounds are muffled, in the lower parts of the lungs are moist sonorous rales. The liver is palpated below the costal margin by 5 cm. Free fluid in the abdominal cavity is determined, swelling of the legs, feet, and hips is expressed. ECG: atrial fibrillation with a heart rate of 94 - 106 per 1 minute, cicatricial changes in the anterior septal area. EchoC: dilatation of all chambers of the heart, PV - 28%. Blood flow regurgitation on the mitral valve.

Formulate a diagnosis. Justify the severity of chronic heart failure in a patient. Determine the directions of pharmacotherapy in connection with decompensation of heart failure.

4. Patient Sh., 67 years old, with IHD, atrial fibrillation (tachysystolic form) during treatment with digoxin, heart rate decreased from 126 to 92 in 1 minute. The patient was transferred to a maintenance dose of digoxin, which was 0.37 mg / day. Additionally, verapamil was prescribed (40 mg 3 times a day). After a week, the patient developed symptoms of glycoside intoxication (nausea, vomiting, single ventricular extrasystoles, slowing of atrio-ventricular conduction).

Indicate the possible causes of intoxication with cardiac glycoside. What is the treatment regimen for glycoside intoxication?

5. Hvoriy Z., 50 times, I'll deny gentamycin with a drive for acute bronchitis and isosorbid din with furosemide with a drive for ischemic heart disease and chronic heart failure. Through the december day vidchuv pogir-shennya hearing compassion. In the analysis of the section - protein.

Give an interpretation of the symptoms that have appeared. Your recommendations.

6. The young woman in the pharmacy filed a prescription for tetracycline, almagel, calcium gluconate for treating bronchitis and gastritis in children 10 times.

Give an estimate to the assigned assignments. Your recommendations.

7. In the pharmacy, giving a prescription for enalapril and amiloride.

About a kind of possible ebullient need to get ahead of the sick? Yaka tactics provizora? Your recommendations.

8. In the drugstore ailments, giving a prescription for Adelfan-ezidrex and gipotiazid.

Give an estimate of the given combination of interests. Tactics provizora. Your river-mendatsiї

9. In the drugstore ailments, submitting a prescription to a digoxin and gipotiazide, as a vipisan therapist-therapist.

What can be improved in case of total congestion of these drugs? Your re-commendation for prophylaxis is accelerated.

10. Illness by submitting a prescription to Adelphan-Ezidrex, Celanide, Hypothiazide, Yakip Vipisan therapist.

What can be accelerated in case of total congestion of these problems? Your recommendations are often improved in this sick person. Go ahead.

TESTS

1.Khvoriy N., 50 rokiv, nadiyshov to the state iz ск skargami for the squeezing zagrudn-niy bil, a kind of яв appearing at the hour of fizicheskoy navantazhennya bathe with priyom itroglitserinu. Two rocky ago transference infarct myocardium. In the legends vesicular dyhannya. Tony sertsya muffled, to hear the systolic noise at the top, part of the extrasystole. Pulse - 92 for 1 hvilin. AT - 100/60 mm Hg The stove is not zbi-flawed, typing on dumb homies. ECG - sinus tachycardia, parts of shlunochkov_ extrasystoles. Ailing was prescribed obzidan 160 mg per doba, sustak-forte 19.2 mg per doba, panangin 1 tablet 3 times a day, riboxin intravenously.

What is a secondary effect that is possible for a sick person when given a combined combination of care? Go ahead.

1. Bradycardia.

2. Hypotension, locking.

3. Nausea, bluing, abdominal pain.

4. Nabryaki kintsovok, scum.

5. The grout of ridin.

2.Khvory S., 72 rokiv, on the stretch of 7 rokiv guards є on the message of arterial vise. Nadaє skargs for headache, confined, heartbeat. In the legends - a vesicular dyhannya. Tony sertsya muffled, the rhythm of savings, the emphasis of a different tone over the aorta, to hear the systolic noise above the aorta. Heart rate - 84 for 1 hvilin. Peripheral oznak destruction of hemodynamics nema. AT - 190/85 mm Hg

Enter the option of effective and without antihypertensive therapy for this sick person. Go ahead.

1. Atenolol + nifedipine + triampur.

2. Nifedipin + terazosin.

3. Atenolol + nifedipine + furosemid.

3. Patient R., 35 years old, with gastric ulcer during the period of exacerbation, took almagel, de-nol and famotidine. Recently, insomnia has appeared, for the treatment of which the doctor prescribed phenobarbital at a dose of 0.05 g per day, but no hypnotic effect was observed. How can this be explained?

A. Pharmaceutical interaction.

B. Pharmacokinetic interaction of almagel and phenobarbital at the stage of biotransformation.

C. Pharmacodynamic interaction.

D. Pharmacokinetic interaction of almagel and phenobarbital at the absorption stage.

E. Pharmacokinetic interaction of almagel and phenobarbital at the stage of excretion.

4. Which of the following can weaken the therapeutic effect of iron preparations?

A. Alcohol.

B. Ascorbic acid.

C. Glucose.

D. Methionine.

E. Levomycetin.

5. The anticoagulant effect of heparin is stopped by:

A. Protamine sulfate.

V. Fenilina.

S. Vikasola.

D. Pentoxifylline.

E. Fraxiparine.

6. When releasing the iron preparation for oral administration - ferroplex from the pharmacy, you should warn the patient that this drug should not be washed down with milk and dairy products should be consumed with it, because:

A. The effect of iron preparations is prolonged.

B. Faster absorption of the drug.

C. Accelerated withdrawal of the drug.

D. Poorly soluble chelate complexes form.

E. The activity of the drug is enhanced.

7. Give recommendations to the employee on the selection of a rational combination of drugs for arterial hypertension:

A. Furosemide + potassium orotate.

B. Digoxin + calcium chloride.

S. Veroshpiron + Asparkam.

D. Panangin + potassium chloride.

E. Dichlothiazide + potassium chloride.

8. It is irrational to combine:

A. Rutin with ascorbic acid.

B. Tetracycline with nystatin.

C. Fentanyl with droperidol.

D. Digitoxin with Veroshpiron.

E. Phenylin with vicasol.

9. For urgent surgical intervention, the patient was called to the surgical department by an anesthetist who performed neuroleptanalgesia. Which of the following drug combinations is used for this?

A. Droperidol + fentanyl.

B. Promedol + sibazon.

C. Analgin + diazepam.

D. Haloperidol + fentanyl.

E. Droperidol + sibazon.

10. A patient, 75 years old, with a diagnosis of pneumonia and a concomitant diagnosis of cardiosclerosis, NK IIA art., A course of 40 mg gentamicin was prescribed 3 times a day and furosemide intravenously for a week. Daily diuresis - 1.5 liters. After a few days, the patient's condition worsened, shortness of breath increased, fresh edema appeared, daily diuresis decreased to 200-300 ml, blood creatinine increased. What factors most likely led to a deterioration?

A. Syndrome of dehydration from a diuretic.

B. Overdose of gentamicin.

C. Allergy to furosemide.

D. Toxic interaction with kidney damage.

E. Cortical necrosis of the kidneys from furosemide.

11. The patient, 72 years old, in connection with atrial fibrillation and manifestations of circulatory failure, was prescribed furosemide, digoxin, ACE inhibitors. On the 5th day of treatment, aching abdominal pain, nausea, single vomiting appeared. On the ECG: ventricular bigemia, PQ interval duration - 0.25 s, “trough-like” ST segment shift below the isoline. What complication most likely occurred in the patient?

A. Digital intoxication.

B. Intoxication with furosemide.

C. Hyperkalemia.

D. Myocardial infarction (abdominal variant).

E. Drug gastritis

12. For a patient with a bacterial infection, the doctor prescribed sulfadimezin in tablets, advising him to drink 1.5-2 liters of alkaline mineral water every month. What determines the need for this recommendation?

A. To prolong the action

B. To reduce stomach irritation

C. To neutralize gastric acid

D. To shift the pH of the blood to the alkaline side

E. For the prevention of crystallization of acetyl derivatives of the drug in the renal tubules

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison’s principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod’s clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

PHARMACEUTICAL CARE: GENERAL PRINCIPLES AND PROVISIONS

Relevance of the topic

Medicines benefit only in skilled hands. According to WHO, about 10% of hospitalizations are associated with the wrong prescription of drugs. Sometimes, unfortunately, improper prescribing and use of medications can cause severe, sometimes fatal, complications. The safe and effective use of drugs depends largely on the coordinated activities of the doctor and pharmacist. In the light of the concept of responsible self-medication, the role of the pharmacist is increasing.

Global changes in the field of economics, medicine, consumer psychology, and information technology have led to changes in the relationship between a doctor, a pharmacist, and a patient.

50-70s. In the ranking of the most attractive professions among American youth, the medical profession takes second place after a member of the Supreme Court. Then followed the posts of state governor, minister, etc. The credibility of the doctor was undeniable.

The pharmacist played the role of the “second” plan - he made extemporaneous drugs and released them only on prescription. The prestige of the profession of a pharmacist was not high.

The patient of that time was passive about his health, completely trusted the doctor and practically did not know the medications. His cherished desire was to get a recipe. Moreover, the patient was sure that the medicine should be made only by prescription.

70–90s. the life position of patients becomes more active. They begin to get involved in non-traditional methods of treatment: herbal medicine, homeopathy, eastern medicine. They realize the true value of their health and the harmfulness of bad habits.

Due to the expansion of the range of finished drugs and the emergence of a large group of OTC drugs, the role of the pharmacist is increasing and self-medication is emerging.

At the same time, the doctor does not keep pace with the rapid growth of the range of medicines. Often shows excessive conservatism and ... stops writing recipes.

The beginning of the XXI century. the patient of our time is literate and demanding. He is extremely careful about taking medications. The opportunity appeared to order medicines via the Internet, the struggle of consumers to improve the quality of life (active distribution of vitamins, food additives, mineral complexes) has diametrically changed the role and prestige of the profession of pharmacist and doctor.

Appearing in recent years in the professional vocabulary of pharmacists, the term pharmacopec could not fail to attract the attention of the publisher.

Pharmopeca is a comprehensive program of interaction between a pharmacist and a patient, as well as a pharmacist and a doctor during the entire period of drug therapy - from the time the drug is dispensed to the end of its action.

In other words, pharmopeca is the responsibility to the patient for the results of treatment, a kind of aerobatics of clinical pharmacy. Although the age of this universally recognized world science is already over 30 years old, certain problems still arise in this industry. First of all - mutual relations, or, more precisely, the confrontation between the clinical pharmacist and the doctor. It can be explicit or hidden, but one way or another is aimed at gaining the attention of the patient and determining his place in the treatment of the patient. However, first of all, the pharmacope must defend the interests of the patient. That is why it is advisable to divide it into two parts: a pharmaceutical shop for doctors and a pharmaceutical shop for patients.

This separation is due to the fact that there are drugs that are dispensed by prescription, and there are those that are dispensed without a prescription.

If we are talking about the release of prescription drugs, then the main responsibility of the pharmacy drug is to comply with the doctor's recommendations. In addition, the pharmacist should double-check the dose, the regimen of the drug.

Pharmopeca in relation to the doctor consists in the choice of the best dosage form and brand name of the drug. So, for example, acetylsalicylic acid exists in 10 dosage forms, and there are more than 80 trade names for drugs containing it in the domestic market.

Pharmaceutical care skills for the patient are required when the visitor arrives at the pharmacy without a prescription. In this case, you need to determine the symptoms of the disease, its severity. Depending on the latter, make a decision on referring the patient to the doctor and (or) dispensing the drug to alleviate the symptoms of the disease.

Motivational characteristic of the topic

Pharmaceutical custody is a comprehensive program of interaction between a pharmacist and a patient throughout the entire period of drug therapy, from the time a medicine is dispensed to the end of its action.

Today, the role of the pharmacist is being transformed, he should not worry about increasing the number of drugs (there are more than 350,000 of them on the world pharmaceutical market), he should not just release the drug, the main goal of his professional activity is to increase efficiency and safety drug therapy for a specific patient.

In the modern healthcare system, the pharmacist becomes an indispensable link in the implementation of the main provisions of the concept of responsible self-medication. Based on the level of education, experience and special knowledge, he must not only know, but also actively promote the principles of pharmaceutical guardianship as a means for rational pharmacotherapy, which, in general, will contribute to improving the health of the Ukrainian nation.

In the light of the requirements of Good Pharmaceutical Practice (GPP), the term “pharmaceutical custody” has been established as the name of the ideology of practice that defines the patient and society as the primary users of the pharmacist.

A significant role in enhancing the professional knowledge of the pharmacist belongs to special educational and reference books. To date, the pharmacist of the first table already has practical guidance, a lecture course and the atlas “Pharmaceutical Trusteeship”, a reference book “OTC-preparations”.

The rational use of medicines today is one of the most pressing public health problems, requiring the solution of a number of legislative, organizational, methodological and other issues. The solution to this problem will help preserve the health of the nation, increase the life expectancy of the population and improve the quality of life of patients.

A significant role in improving the effectiveness and safety of drug therapy is given to pharmaceutical care - a comprehensive program of interaction between the pharmacist, doctor and patient throughout the entire period of drug therapy, from the time the drug is dispensed to the end of its action. The formation of a pharmaceutical guardianship system, first of all, implies the adoption by the pharmacist of responsibility to a particular patient for the result of treatment with drugs.

The role of pharmaceutical guardianship significantly increases under the conditions of the development of the self-medication system, when the pharmacist in the pharmacy becomes the main consultant for the patient. It can provide the patient with recommendations for the treatment of other or non-life-threatening symptoms of various diseases and ailments, and can provide significant assistance in recognizing “threatening” symptoms that require a doctor’s consultation.

In order to develop a self-medication system and increase its effectiveness, it is important that for each symptom or ailment that can be treated independently, the pharmacist in the pharmacy should have a clear algorithm of action. The main goal of such an algorithm is to help the pharmacist determine the severity of the symptom, the possibility of its independent treatment, as well as choose the optimal drug and the conditions for its rational use for each specific patient.

Self-medication is an essential part of the modern healthcare system.

1.1 History of pharmaceutical custody

pharmaceutical drug custody self-medication

At the end of the 20th century, the World Health Organization (WHO) defined the strategic direction of global healthcare development in three words: “Focus on the patient.” This provision is a development of the WHO Global Strategy “Health for All by the Year 2000”, adopted by the 34th World Health Assembly, the governing body of WHO, in 1981, and forms the basis of the Action Program on Essential Medicines, approved by the WHO Regional Office for Europe. In 1994, the World Health Assembly adopted a resolution on the role of the pharmacist in implementing the WHO revised drug strategy. In the light of this strategy, the role of the pharmacist in the health system is fundamentally changing. A resolution adopted by WHO noted that the pharmacist could play a key role in public health, and especially in the field of medicines. The Assembly called on pharmacists and their professional associations around the world to “provide informed and objective advice on medicines and their use to the public.” Previously, the effectiveness and safety of drug therapy was determined by three main sets of rules designed to ensure the quality, effectiveness and safety of drugs:

- Good Manufacturing Practice (GMP);
- Good laboratory practice - (Good Laboratory Practice, GLP);
- Good Clinical Practice (GCP).

As a follow-up to the WHO strategy, three existing codes of practice have been supplemented by new ones - good practice in the wholesale distribution of medicines (Good Distribution Practice, GDP) and good pharmacy practice (Good Pharmaceutical Practice, GPP). If the first three codes of professional activity cover preclinical studies, the production process, and clinical trials of drugs, the

GDP rules relate to their wholesale distribution, and GPPs relate to the distribution of drugs, primarily through the pharmacy network. In the light of the provisions of good pharmacy practice (NAP), the main goal of a pharmacist's professional activity is not so much to improve the quality of drugs on the market, but primarily to increase the effectiveness and safety of drug therapy for a particular patient.

The fundamental provisions of pharmaceutical guardianship were further developed in the WHO Special Project on Pharmacy in the Newly Independent States (NIS), together with the WHO Center for Drug Policy and the Development of Pharmaceutical Practice (Copenhagen, 2001), in decisions of the 62nd Gressa International Federation of Pharmacists (Nice, September 2002). Taking into account the peculiarities of socio-economic development, WHO experts have developed and proposed the introduction of a special "Guide for the development and implementation of standards for good pharmacy practice in the New Independent States".

Changes in the professional activities of the pharmacist are closely related to the development of the concept of self-medication. It is activities related to self-medication, according to WHO documents, that are the main element of NAP.

1.2 The concept of self-medication

Self-medication is the use by a consumer of freely available drugs for the prevention and treatment of health problems and symptoms that he recognizes. In practice, the concept of self-treatment also includes the treatment of family members and acquaintances, especially when it comes to treating children.

Such a definition of self-medication is given in WHO documents. A key characteristic of self-medication is the patient's responsibility for their health, therefore in 1994 the European Association of OTC Drug Manufacturers (AEBOR) transformed the term "self-medication" into "responsible self-medication".

It is very important to emphasize that taking medications that are not freely available for sale, on their own responsibility, but without qualified control (on the advice of friends, from the remaining supplies of a home medicine cabinet) can in no way be considered self-medication and should be considered completely unacceptable a phenomenon, although widespread in real life.

The term "self-help" implies those cases when it is necessary to alleviate one's condition with one or another ailment, at the time of an exacerbation of a chronic disease before visiting a doctor, provide first aid before the doctor arrives.

Self-prevention of diseases consists in the adoption by the population of measures to reduce the risk of a disease, identify symptoms of the disease at an early stage to prevent the development of the disease or for its easier course, measures to prevent relapse of the disease, improve the quality of life of a sick person.

Self-help and self-prevention are integral components of the concept of responsible self-medication. They also include a healthy lifestyle, smoking cessation, moderate alcohol consumption, and proper use of medications.

In turn, self-medication is part of the modern healthcare system, aimed at raising citizens' sense of responsibility for their health, their education in this area and the provision of medical and pharmaceutical services that allow them (citizens) to exercise the right to independently protect their health. Responsible self-medication is an objectively existing primary link in the modern healthcare system and does not require the creation of any special organization.

In our country, the whole burden of such expenses falls on the shoulders of the patient. Everyone pays for the treatment. And for 10% of the population, medical care is not available at all. And this is officially published data. Up to 23% of the family budget is spent on the purchase of medicines in Ukraine.

Patients do not want to spend time in clinics and consult doctors.

Out of all the sick people, during the year, 37% of us never went to a doctor, 44% went from 1 to 3 times, 13% visited a doctor 4-7 times, and 6% visited a doctor.

1.3 Objective reasons for the development of the concept of self-treatment in modern conditions

I. Decrease in state participation in the issues of public health protection due to a significant increase in the cost of the healthcare system.

• Advances in the prevention and treatment of diseases lead to increased life expectancy. Most of the population reaches the age when chronic diseases prevail. The proportion of older people in need of support is growing in relation to people of working age. Residential people need more medical care.
• Progress in the field of medical science and the development of medical technology have significantly expanded the range of medical services and the cost of their provision.
• The growth of the general educational and general living standards leads to the fact that people want to use the opportunities in the field of medical services to the fullest extent and also to receive them in the most comfortable conditions.
• Health expenditures, covered directly by the state and social security systems, cannot grow faster than gross national product.
• In the countries of Central and Eastern Europe, the difficulties of the transitional economic period, the restructuring of the economy on a market track, and the reduction of the national budget add to these reasons.
II. Enhancing the role of patients in maintaining their health.
• An increase in the educational level increases the number of people who are inclined to make independent (without the help of a doctor) decisions regarding their health.
• The proliferation of active propaganda of a healthy lifestyle considers improving health not only as a result of the help of a doctor and medication, but also in close connection with good nutrition, gymnastics, the fight against bad habits, the environment, etc.
• A significant increase in the nomenclature of OTC drugs and their active advertising in the media increases the patient's ability to be treated independently.

1.4. Current state of self-treatment concept

Pharmaceutical science and production constantly make available to doctors and patients more and more new drugs. To date, 350 thousand drugs are presented on the world pharmaceutical market, of which more than 14 thousand are registered in Ukraine. The number of drugs based on new substances is growing annually: in 1993 there were 39, in 1994 - 47, in 1995 - 39, in 1996 - 51, in 1997 - 47, in 1998 - 39, in 1999 - 32, 2000 - 43, in 2001 - 36, in 2002 - 30. The growth in the production of drugs is closely related to the increase in their consumption. The volume of drug sales in the 13 leading pharmaceutical markets in the world reached 221.59 billion dollars in 2000, which is 9% more than in 1999. According to forecasts, sales will increase by 8% annually.

Global changes in the field of economics, healthcare, pharmacy, information technology and consumer psychology have led to a change in the relationship of inextricably linked elements in the doctor-patient-pharmacist system. As the European Association of Over-the-Counter Drug Manufacturers (AESGP) notes, in the 1950s and 1960s, the concern for human health was primarily assigned to doctors and other medical professionals. Consumers were patients (in translation from the English. Patient also means "patient"), passively awaiting the help of a doctor or prescribing drugs. People expected to restore their health due to the achievements of medicine, that is, for the majority of the population, a rather passive attitude to their health and complete trust in the unquestioned authority of the doctor were characteristic. At this time, the role of the "second plan" belonged to the pharmacist and the prestige of his profession was low In the 1970s, more attention was paid to risk factors. At the same time, there was a tendency to avoid everything that could damage health: tobacco, smoking, drinking alcohol, sugar, fats and much more.

In the 1980s, an active approach to maintaining one's health was popular. The means of promoting health were jogging, gymnastic exercises, diet food, fruit and vegetable salads, mineral waters, as well as vitamins, minerals, garlic, fish oil, etc.

In the 1990s, there was a tendency to maintain a balance between the impact of adverse factors in everyday life and the use of health measures. In this regard, there is growing interest in preventive medicines and the opportunities that independent treatment provides. Since the late 1990s, there has been a steady tendency to increase patient attention to their health, a passion for alternative methods of treatment, primarily phyto- and homeopathy. The parallel expansion of the range of finished drugs, a decrease in the share of extemporaneous drugs, the emergence of a category of over-the-counter drugs contributed to an increase in the social role and social significance of the pharmacist, to whom patients are increasingly turning to for recommendations. The end of the XX - the

beginning of the XXI century was marked by radical changes in the relationship in the patient-doctor-pharmacist system. On the one hand, the doctor, not having time to master the colossal amount of information associated with the rapid growth of the range of drugs, exhibits excessive "forced" conservatism in matters of pharmacotherapy. On the other hand, the patient is quite competent, demanding of his health, rich in information about drugs from the media, and not having “extra” free time, more and more often turns to a pharmacist, bypassing a doctor. This situation fundamentally changes the role of the pharmaceutical company, which is beginning to occupy a key position in the developing system of self-medication.

The development of the concept of responsible self-medication is called upon to play a positive role in providing the population with more affordable, high-quality and cheap medical services. World practice shows that comprehensive informing the medical community and the population about modern approaches to responsible self-medication and the implementation of relevant standards. for over-the-counter drugs can lead to reduced health costs and an improvement in the general health of the population.

Promoting self-treatment is a real way to reduce the burden of health care costs. It is possible to save funds allocated by the state for health care due to moderate spending of funds for independent treatment. In turn, this encourages the government to pay special attention to the prudent and responsible use of OTC drugs, which, as a result, puts the pharmacist at the forefront of the national health system.

From the point of view of health authorities, the adoption of the concept of self-medication not only satisfies the growing desire of the population to manage their health, but also coincides with the need to keep public spending on health care at a reasonable level.

Self-medication in no way can be considered as an alternative to medical treatment. Moreover, it should have its limits where the picture of the disease and its causes are not understandable to the layman, and the use of drugs at your own peril and risk can be harmful.

The main characteristic of self-medication is the patient’s responsibility for their health. The basis of a responsible approach to self-medication is the availability of complete information. A person needs to be very clearly explained when it is possible to self-medicate, and when it is necessary to consult a doctor. The line between these cases should be clearly understood by the patient. In the presence of even the most minor doubts, it is better to orient the patient to a visit to the doctor.

Of course, if the patient does not manage to eliminate the symptoms of a health disorder within two, at most three days, by self-medication, then contacting a doctor is strictly necessary. The same should be done in case of certain “threatening” symptoms. The patient can obtain information about these symptoms from a pharmacist in a pharmacy by purchasing medicines for self-treatment.

The concept of responsible self-medication recognizes that in some cases it is not always easy for a doctor to draw a line between a serious and non-serious disease, especially since serious pathological conditions can be hidden under the mask of lung diseases. Therefore, people who choose self-medication should be informed in which cases they can self-medicate, and in which they should contact a doctor. In addition, the patient must be informed about effective and safe over-the-counter drugs that can be used for self-medication in certain situations.

1.5 Positive and negative moments of self-medication

Unconditional positive aspects of introducing the concept of self-treatment into the healthcare structure are:

• saving time and money for patients;
• reducing the burden on medical institutions and doctors;
• budget savings;
• the demand for healthcare by a specialist of a new generation - a clinical pharmacist;
• active introduction of pharmaceutical care in the practice of pharmacy institutions;
• increase in profits of drugstores;
• active participation of doctors in the formation of the nomenclature of OTC drugs.

At the same time, as with any phenomenon, the concept of self-treatment has negative aspects, namely: the risk of untimely treatment to the doctor and, as a consequence, a high risk of complicating diseases; high risk of drug complications.

The necessary conditions for introducing the concept of responsible self-treatment and the rational use of OTC drugs are as follows:
1. Creation of a state organizational structure for managing the registration and movement of OTC drugs in Ukraine and determining its functions.
2. Development and approval of regulatory documents regarding self-treatment and dispensing of medicines without a doctor's prescription.
3. Development of the Regulation on over-the-counter dispensing of medicines to the population of Ukraine.
4. Monitoring of the domestic, pharmaceutical market of OTC drugs and responsible self-medication.
Compliance with all of the above conditions will contribute to the implementation of responsible self-medication in the daily practice of protecting the health of the population without the risk of undesirable consequences, which, in turn, will increase the level of health of the nation and cost-effective changes in the structure of budgetary health care costs.
2. OTC drugs
2.1 the Concept of OTC drugs
OTC drugs (OTC drugs - from the English over the counter) are an extensive group of drugs that a patient can buy for self-treatment right at the pharmacy (and some drugs, and not just at the pharmacy) without a doctor's prescription. They come to the patient directly from the hands of the pharmacist, minding the doctor.
OTC drugs are an integral part and at the same time a necessary condition for the successful development of the concept of self-medication.
OTC drugs are represented by various pharmacological groups: analgesics, antipyretics, antacids, antihistamines, antitussive drugs, and others. Among OTC drugs, there are a sufficient number of drugs that can have a pronounced side effect, especially with irrational use.
The list of drugs allowed for self-medication can vary significantly in different countries depending on existing health systems and socio-economic conditions. However, the selection criteria for such drugs should be common to all and based on reliable data, large therapeutic breadth and cost.
In accordance with the provisions of the Council Directive 92/26 / EEC (currently included in the Directive of the European Parliament and of the Council 2001/83 / EC of November 6, 2001 "On the Code of Laws of the European Community on Medicines for person "- Part VI, Articles 70 - 75) all drugs are available for over-the-counter holidays, unless they are:
• may pose a direct or indirect danger, even with proper use, but without the supervision of a doctor;
• are usually prescribed by a doctor for parenteral use;
• are used frequently and in most cases incorrectly, and therefore may be dangerous to human health;
• contain substances or ingredients whose activity or side effects need further study.
The final decision whether a drug belongs to a prescription or OTC discharge is taken by the competent authorities of each state. Nevertheless, on September 29, 1998, the European Commission issued a framework rule - a Guide to changing the category of dispensing of drugs for humans, which describes in more detail the requirements for OTC drugs.
2.2 Criteria on the basis of which drugs belong to the category of prescription or OTC
1. Criterion One
Prescription drugs are subject to prescription, which may pose a direct or indirect threat to the health of the consumer if they are used without medical supervision, even if used correctly.
Before deciding whether this criterion is applicable to a drug, the following factors should be considered.
1.1. Direct health / safety ratio:
a) a direct threat to health, even with the correct use of the drug (in accordance with the instructions for use intended for patients), may be associated with its toxicity, interactions with other substances and adverse reactions. A non-prescription drug should have the following properties:
• low general toxicity, no effect on reproductive function, no genotoxic or carcinogenic effect;
• low risk of severe type A adverse reactions in the general population;
• a very low risk of severe type B adverse reactions;
• lack of interactions with widely used drugs that can lead to severe adverse reactions;

b) assessing the possible threat to the patient's health that this drug may pose, one should take into account the possibility of its prevention. For example, the presence of pronounced adverse reactions of type A is permissible for an over-the-counter drug, if the corresponding risk group can be easily determined and eliminated without even resorting to medical control;
c) the safety of the use of this drug must necessarily be compared with that of alternative drugs.
1.2. Indirect Health / Safety Ratio:
a) an example of an indirect threat to health, even with the correct use of the drug (when used according to the instructions), can be a situation where a decrease in the severity of symptoms can mask the disease itself, in connection with which the patient needs medical help and observation; the use of the drug may lead to a later diagnosis, the appointment of appropriate therapy, as a result of which the opportunity for more successful treatment may be missed; warnings on the use of the medicinal product indicated in the annotation insert and / or on the label may be necessary in order to prevent the "masking" of the symptoms of the development of a serious disease; such warnings should indicate the maximum period after which it is necessary to consult a doctor if the symptoms of the disease still manifest; the authorized body, the use of over-the-counter drugs should initially be allowed only for short-term treatment, for example, in cases where there is a likelihood of "masking" the symptoms of a more serious disease;
b) there is an indirect threat if frequent use of the drug increases the risk of drug resistance, especially among the general population, to such an extent that the benefits of using this drug can be doubtful, or if the symptoms , to reduce the severity of which the drug is used, are usually a manifestation of a number of diseases that the patient cannot diagnose on his own.
1.3. The possibility of self-assessment:
a) it is very important that the patient can objectively assess his condition or symptoms in which an over-the-counter drug is indicated so that it can be used without medical supervision; this means that the consumer must be able to exclude conditions for the treatment of which an over-the-counter drug is not suitable, but similar to those in which the use of this drug is indicated; it is necessary to take into account the availability of appropriate sources of information through which the consumer will be able to distinguish between such conditions (such as printed matter, the ability to take the advice of a pharmacy drug or other medical workers);
it is necessary that the patient can independently correctly evaluate the course of the disease, his condition, the duration of the symptoms, their recovery and the consequences associated with this;
c) contraindications, interactions with other substances, warnings and cautions regarding the use of a medicinal product should be stated in a form accessible to the consumer.
1.4. Risk and consequences of improper use of the drug:
a) a large number of contraindications, warnings and warnings or a high frequency of use by the population of drugs that interact with the drug in question increase the risk of improper use of this drug;
b) it is very important that the risk to the health of consumers is insignificant, even if the consumer does not use the medicine for the indications, uses it for a longer period compared to the recommended one, exceeds the recommended dose or does not take into account warnings and contraindications. Analysis of the consequences of improper use of the drug is an important component in the overall assessment of the safety of the drug, which should be reflected in the information on the package (Art. 2.1, paragraph. Of Council Directive 92/27 / EEC) and / or in the annotation - insert.
1.5. Instructions for the patient:
a) the method of using over-the-counter and similar prescription drugs is different even if the indications for their use are the same or if they are used in the same therapeutic area; it should be taken into account the danger that the consumer may consider that an over-the-counter drug is less dangerous than a similar prescription;
b) the information contained in the annotation insert and on the package should contribute to the safe and effective use of the drug; the instructions should explain how to properly use the drug; the information contained in the instructions should be presented in an accessible form so that patients

can correctly assess the possibility of using this drug; the amount of information should be sufficient so that the drug can be used without medical supervision;
c) in the information materials accompanying the drug, in addition to the control by the pharmacist (if necessary), information should be provided to prevent the risk of the drug if it is contraindicated or not unsafe; contraindications, interactions with other substances, warnings and cautions should be stated in a form accessible to the consumer and in such a way as to attract the attention of the consumer;
d) in order to minimize the risk and maximize the benefit of the use of the drug in the attached annotation insert and on the package, it is necessary to indicate when the drug cannot be used, and this information should be no less detailed than the indications for use, and involve patient attention;
The information should be consistent with the approved summary of the drug.
The consumer needs to know what to do if the drug does not have the desired effect or causes an adverse reaction. Therefore, the annotation insert and the package should contain recommendations on what actions should be taken, for example, consult with your doctor or pharmacist for the time specified in the annotation insert or on the package of the drug.
2. The second criterion
Medication is subject to medical prescription if many consumers often use it improperly, as a result of which medications can pose a direct or indirect threat to human health.
When considering whether this criterion is applicable to the drug, the following factors should be considered.
2.1. There is evidence of improper use of the drug.
The presence of data on the improper use of an over-the-counter drug (for example, use to enhance the effect of alcohol) is the basis for restricting the use of this drug or changing the category of its dispensing to prescription. In this case, the drug cannot be classified as OTC.
3. The third criterion
Medications are subject to a doctor’s prescription if they contain substances whose action and / or side effects require further study.
When considering whether this criterion is applicable to the drug, the following factors should be considered.
3.1. A trade license for a medicinal product has been issued recently / the experience of using the medicinal product is small:
a) further study of the properties of the drug may be required in cases where a commercial license for it has been issued recently or the experience of use is small, for example, due to the small volume of sales; should take into account the experience of using the drug in other EU countries and other countries where a sufficient amount of data on its post-licensed use has been collected;
b) despite the available and encouraging results of clinical trials, the experience of the widespread use of the drug after issuing a trade license is very important, which allows us to obtain evidence of its safe use in those groups of patients who usually do not participate in clinical trials, for example, elderly people, children, certain ethnic groups, groups with a certain phenotype and patients with certain pathological conditions; if the safety or efficacy characteristics of a drug differ when used in different phenotypic or ethnic groups, then special instructions should be provided in the patient instructions.
3.2. Other strength of the drug, dose, route of administration, indication, age group or other combination of substances:
a) additional studies are necessary if an application for dispensing without a prescription of a medicinal product with a different force of action, with a different route of administration, used at a different dose, in a different age group or according to a new indication, especially if indicated, is given not approved for an over-the-counter drug; when using a drug in a lower dose or with a lower force of action, research is not always necessary, however, it should be confirmed that a dose reduction does not affect the effectiveness of this drug;
b) despite the fact that the safety characteristics of a prescription drug are of great importance, a reassessment of the risk / benefit ratio is necessary, however, such an assessment may be difficult due to the lack of experience with the widespread use of the drug in a new dose and according to a

new indication; however, safety data for an existing prescription drug can be extrapolated; it is advisable to use the method if a small amount of adverse reactions has been recorded and / or if the proposed doses for an over-the-counter drug are lower than its prescription analogue, the category of patients who will use this over-the-counter drug is a subgroup of a group of people using a similar prescription drug;
c) a drug containing a combination of two active substances, each of which is part of an over-the-counter drug, cannot be automatically classified as a non-prescription drug; evaluation of a combination drug is carried out in accordance with the "Guidelines for drugs with a fixed combination of active substances".
4. The fourth criterion
Prescription drugs are those that the doctor usually prescribes for parenteral use (e.g., intravenously).
When considering whether this criterion is applicable to the drug, the following factor should be considered: drugs intended for parenteral use are usually classified as prescription drugs, since there is an additional risk and difficulty associated with the administration of the drug the drug.
5. Other criteria
According to the provisions of Article 3.4 Council Directive 92/26 / EEC (Article 70 of the Directive of the European Parliament and of the Council 2001/83 / EC "On the code of laws of the European Community regarding medicinal products for humans"), a medicinal product that meets the criteria on the basis of which it it should be classified as a prescription, it can be classified as over-the-counter if the maximum single dose, maximum daily dose, force of action, dosage form, certain types of packaging and other conditions of use of the drug allow it to be attributed to ATEGORY pharmaceuticals-governmental drugs without prescription.
5.1. The size and shape of the packaging of the drug:
a) the package size of the drug should correspond to the expected duration of treatment; restricting the dispensing of the drug due to the small size of the package can prevent the improper use of the drug, especially its overdose, and facilitate the timely visit of the patient to the doctor;
b) the design of the packaging (container) of OTC drugs should exclude the possibility of children accessing them
5.2. The maximum single dose, the maximum daily dose.
The maximum single dose or maximum daily dose is limited in order to protect the health of the consumer, regardless of whether he is taking the medicine correctly or incorrectly. However, it is necessary to justify that reducing the dose of a drug does not affect its effectiveness.
In some cases, individual ingredients may be licensed both as prescription and as non-prescription. In this case, the main thing is the disease itself and the effect of the drug on the patient. For example, in the United Kingdom, ibuprofen for the treatment of rheumatoid arthritis is licensed as a prescription drug, and as part of complex drugs for the treatment of muscle pain, it can be licensed as non-prescription.
2.3 Prescription of OTC drugs
OTC drugs are the means of symptomatic treatment, since they do not affect the cause and mechanism of the development of the disease. All of them are designed to be taken for a short period of time and are not intended for long-term treatment. OTC drugs are used mainly for the treatment of mild, easily drug-correctable conditions that do not require medical intervention. The main purpose of their application:
• quickly and effectively alleviate the symptoms of diseases that do not require medical advice;
• in the face of financial and personnel difficulties in the public health sector, to enable the patient to relieve minor symptoms on their own when they feel unwell, which will reduce the burden on medical services;
• increase the availability of medical care to people living in remote regions where it is difficult to obtain qualified medical advice.
An analysis of studies on self-medication allows us to identify more than 10 common conditions that are treated with over-the-counter drugs. This is a headache, a cold (cough, rhinitis, sore throat, fever), disorders of the gastrointestinal tract (heartburn, constipation or diarrhea), disorders of the central

nervous system (increased anxiety, emotional lability, insomnia, fatigue) , acne, muscle and joint pain, cuts and abrasions.

From an economic point of view, expanding the range of OTC drugs has very definite benefits.

When converting prescription drugs to over-the-counter drugs, a certain “self-treatment” market appears, and the need for prescriptions for drugs either decreases or remains at the same level. The volume of sales of the drug, as a rule, increases significantly. Patients have a choice - to pay for an over-the-counter drug and save time, or spend time (and in certain situations, money) to visit a doctor and get a prescription for the same drug. In such a situation, it becomes very attractive for the patient to get advice and advice on taking the medicine directly when buying it - in the pharmacy at the pharmacist.

In the 80s, large pharmaceutical companies did not show much interest in the production and sale of OTC drugs, since the profitability of OTC drugs was no more than the profitability of the original prescription drugs

However, in the 90s the situation changed, and large pharmaceutical companies began to pay more and more attention to the market of OTC drugs. This is due to a number of reasons, the main of which are given below.

• Reforms in healthcare systems in the developed countries of the world have caused an increase in the consumption of over-the-counter medicines, which is associated with the encouragement of consumers by the governments of these countries to bear a much greater responsibility for their health.

• Increased ability to transfer prescription drugs to over-the-counter leave categories.

• The assumption that governments will not strictly regulate the prices of over-the-counter medicines, as their cost, in most cases, is not reimbursed by social security systems.

• Reducing the profitability of original drugs in the early 90s.

• The possibility of extending the life cycle of a drug after the expiration of the patent protection period.

• Ability to create brands in the OTC market.

A study of the age of brands and brands of OTC drugs showed that 70% of brands are over 10 years old, and 35% of brands are over 20 years old. Successful over-the-counter drug brands can be 50 years old or more. An example is the Bayer company Aspirin, whose brand is more than 100 years old, the Panadol drug, GlaxoSmithKline, the brand is about 50 years old.

When translating a prescription drug into an over-the-counter holiday category, the pharmaceutical company asks the question: how will this affect its “market fate”?

For a company that has been promoting prescription drugs, it may not be easy to restructure a marketing strategy from moving prescription drugs to doctors and promoting OTC drugs directly to the consumer. In addition, the transfer to the over-the-counter holiday category may even reduce sales for the first time. This phenomenon is not associated with a decrease in consumer demand for the drug, but rather with the fact that previously the drug was prescribed by doctors as an additional one. After the drug is transferred to an over-the-counter vacation category, recipes are no longer written on it, as a result of which consumption is reduced. Sometimes a decrease in sales after transferring the drug to an over-the-counter holiday category can range from 20 to 40%. But this is only the first time.

In most European countries, the transfer of a number of drugs from prescription to the OTC category is accelerating. By the end of 2001, the Western European OTC drug market was estimated at about $ 17.8 billion, and the world - $ 64 billion, with annual growth of about 13%.

OTC drugs are a highly profitable component of pharmaceutical production and marketing. The transfer of one prescription drug to the OTC category brings the pharmaceutical company about $ 150 million in profit annually due to a significant increase in sales.

In the United States, from 1976 to 2000, drugs containing more than 80 active substances acquired OTC status. In 1997, OTC drugs accounted for more than 24% of total sales ($ 20 billion), and their share continues to grow. All new and new preparations containing active substances, which were previously considered strictly prescription, are being transferred to the category of non-prescription

The concept of responsible self-medication is finding more and more supporters in Russia. In 1997, the Ministry of Health of the Russian Federation approved a list of over-the-counter drugs. This indicates an official recognition of the therapeutic advisability of self-care of health through the use of relatively safe drugs. In Russia, the OTC market is practically new compared to the leading European countries. In the late 90s, the total volume of the Russian OTC drug market was approximately 1.2 billion US dollars, which amounted to 40-45% in value and 58-60% in sales. This proportion is much higher than in other countries. So, in Germany it is about 26%, in the USA - 24%, in Japan - 12%. These data once again prove that the modern population of Russia is prone to self-medication. The list of OTC drugs in Russia includes 1,600 trade names, which is 15% of the total number of registered drugs. More than 150 over-the-counter trade names are on the list of essential medicines.

In Ukraine, work to create a legislative framework for licensing and a civilized market for the sale of OTC drugs has been carried out from the first days of the formation of an independent state. The Order of the Ministry of Health of Ukraine No. 233 of July 25, 1997 approved the List of drugs approved for use in Ukraine and dispensed without prescription from pharmacies. Significant changes and additions to the List were made by Order of the Ministry of Health of Ukraine No. 181 dated May 21, 2002. Currently, the List of non-prescription drugs validated by Order of the Ministry of Health of Ukraine No. 441 dated July 2, 2005 is valid.

To bring the pharmaceutical legislation of Ukraine into EU norms, the Ministry of Health of Ukraine issued May 17, 2001 Order No. 185 “On the approval of criteria for determining the categories of dispensing of medicines”, which fully complies with EU Council Directive 92/26 / EEC (currently part VI, Articles 70-75 of the Directive of the European Parliament and of the Council of the European Union 2001/83 / EC of November 6, 2001 “On the Code of Laws of the European Community concerning Medicinal Products for Man”)

According to the order, medicines are divided into two categories:

1. prescription drugs;
2. over-the-counter medicines.

However, far from all the questions about common criteria for including drugs in the OTC category and the mechanism for such inclusion have been resolved, clear rules for selling prescription drugs (with the exception of potent and narcotic drugs) are not implemented. Work in this direction is actively carried out by all interested structures of the health authorities of Ukraine. Currently, over-the-counter drugs in Ukraine account for about 20% of all registered drugs.

The experience of foreign countries shows that putting order in relation to the production and sale of OTC drugs requires a long time, huge costs and joint efforts of all interested parties. However, this work is absolutely necessary and justified in terms of ensuring the health of the nation.

The safe and effective use of over-the-counter drugs is possible only if the patient receives clear and accessible information about the drugs. The consumer must clearly know in which cases of ill health he can be treated without the help of a doctor and what medications in these cases should be used.

2.4 Information on the packaging of the OTC drug

The goal is achieved using the rules by which information should be compiled on the packaging of drugs. The rules were formulated in Directive 92/27 / EEC of March 31, 1992 (currently part V, Articles 54-69 of Directive 2001/83 / EC of the European Parliament and of the Council of November 6, 2001 “On the Code European Community laws on drugs for humans. ”) In accordance with the directive, the presence of an insert leaflet in the packaging of all medicines is mandatory until all necessary information is presented on the packaging.

The package leaflet should be prepared in accordance with the brief characteristics of the preparation and set out in a form accessible to the consumer.

The package insert must contain an exhaustive list of information in accordance with the established procedure.

Information for drug identification:

• name of the drug and its international name (or the name of the active ingredients in complex preparations);

• complete qualitative and quantitative characteristics of the active ingredients using their generally accepted names and qualitative characteristics of the excipients;
• dosage form and composition by volume or number of doses (for each dosage form);
• pharmacotherapeutic group or nature of action in terms (concepts) available to the patient;
• name and address of the manufacturer and trade license holder.
Information about the pharmacotherapeutic properties of the drug:
• indications;
• contraindications;
• precautions for use;
• interaction with other drugs and other interactions (with food, alcohol, etc.);
• special warnings.
All this information should:
• take into account the features of certain categories of consumers (children, drivers of vehicles, pregnant women, breast-feeding, people with concomitant diseases);
• mention the possible effect of the drug on the reaction rate when driving vehicles or other potentially dangerous mechanisms.
Information on the method of administration of drugs should include information on the dosage, method and route of administration, frequency of administration, indicating, if necessary, the time of day when the medicine should be taken; the duration of the course of treatment in cases where it should be limited; actions in case of overdose; actions in the event that the next dose of the drug was missed; cancellation effect warning.
Information about the expiration date must contain a reference to the expiration date; warning not to take the drug after the specified period; if necessary - indications of special storage conditions; warning of visual signs of unsuitability.
However, it is not possible to provide the patient with proper information about drugs only using the instructions in practice for a number of reasons:
• not all instructions meet the proper requirements and for their proper understanding, education is required, at least, of a graduate of a pharmaceutical school;
• reading and perception of the instructions may be difficult in font or color;
• the characterological features of a number of patients adversely affect the installation to read long, detailed instructions.
All these reasons, against the background of the growing popularity of the concept of self-treatment among the population of the absolute majority of countries, necessitate the training of pharmacists as strategic experts in the selection and use of OTC drugs.
Certain categories of patients require increased attention from the pharmacist, since the risk of developing side effects of drugs is significantly higher, and the health consequences can be significantly more severe than for the "average" patient.
2.5 Categories of patients requiring increased attention of the pharmacist
Elderly people - they are in most countries the main consumers of drugs, including OTC. Due to the age-related characteristics of pharmacokinetics, they often have side effects of drugs, and as a result of the use of a significant number of drugs, the problem of drug interaction.
Children - they themselves, in addition to their parents, should be explained both the necessity of using the medicine and the danger associated with its improper use. It is rational to explain to the child (and not just his parents) the importance of taking the medicine in a timely manner, its combination with food, the peculiarities of its taste, etc.
Pregnant women are active over-the-counter drug users. Unfortunately, information on the teratogenic effects of drugs is currently clearly insufficient, so the only guaranteed way to avoid the possible adverse effects of drugs on the fetus is to prevent their unjustified use.
Nursing mothers also require special attention of the pharmacist (pharmaceutical agent), since drugs entering the milk can have an adverse effect on the baby. In addition, a number of drugs can affect milk production. Unfortunately, the data on the penetration of OTC drugs into milk and their ability to affect a child are little known to most pharmacists.
3. Brand and generic drugs

3.1 the Concept of the original drug

In daily practice, when choosing the optimal drug for a patient, the pharmacist must take into account not only the pharmacological properties of the drug, but also its cost. To resolve this issue, the pharmacist must have a clear understanding of the characteristic features of the original (brand) and generic drugs.

An original drug is a drug that is the exclusive property of the company that developed it, or the property of the company that owns the first license to sell it. The active substance of the original medicinal product has a patent obtained in the manner prescribed by law. Until the patent expires, no other pharmaceutical company has the right to synthesize and use this active substance for commercial and non-commercial purposes. Very often, the concept of "original drug" is identified with the concept of "drug - brand."

The concept of "original drug" should not be confused with the concept of "original (trade) name of a drug", which is a proprietary name registered in order to protect the right to its exclusive use only by a company owning a trademark or a patent for this name (and not an active substance). By name, you can identify a specific drug or dosage form that is implemented by its manufacturer. Unlike a patent for an active substance, the ownership of which is limited in time, ownership of the original (trade) name is retained after the expiration of the patent for the active substance. In accordance with the legislative provisions of many countries, the manufacturer is allowed to maintain the trademark when replacing excipients in single-component drugs and even active substances in combination drugs.

Brand drugs are the most studied drugs, since the brand creator company must conduct a number of studies when creating a new drug, and in the future it is interested in collecting as complete information as possible about its use in various categories of patients to improve their "Offspring."

New original drugs are usually brands. The cost of these drugs is high.

3.2 The concept of a generic drug

A generic drug, or a generic drug, is a medicine whose patent protection for the active substance has expired, and it (or rather the active substance), therefore, is not the exclusive property of the pharmaceutical company that developed it or owned the first license on its implementation.

A generic drug may be under the original (brand) or under the common name. The common or international non-proprietary name, unlike the original (trade) name, can be used by any manufacturer after the expiration of the patent for an active substance. In the USA, generally accepted (official) names are contained in the list of Accepted Drug Names in the USA. However, attention should be paid to the fact that the list of generic names may differ from the list of international generic drug names. Thus, generic drugs can be brands - drugs with the brand name patented by the manufacturer.

In recent years, more and more attention has been paid to generic drugs by both pharmacists and doctors. The interest was primarily due to the desire of governments of all industrialized countries to reduce rapidly growing health care costs, while maintaining a high level of quality of treatment.

One of the advantages of the widespread use of generic drugs, which allows immediate economic benefits, is the ability to provide the general population with medicines that are equivalent in effectiveness to the original treatment, but at a significantly lower cost. The use of generics also allows you to direct the savings to finance other pressing health needs. In addition, the presence of competitive generic drugs on the market encourages pharmaceutical companies to improve the quality of their drugs, and stimulates the search for new, more effective drugs.

A generic preparation contains an active drug substance identical to the corresponding active substance of the original drug, but excipients (colorants, flavors, etc.), tablet form, production technology of generic drugs may differ from the original ones.

3.3 Equivalence of generic drugs

The generic medicinal product must meet the following requirements:

• contain the same active substance in the same dose and dosage form as the original drug;
• be identical to the original drug in terms of potency;
• have the same indications for use as the original drug;

• be bioequivalent to the original drug (ie, after oral administration, the same amount of the drug should have the same concentration in the blood as the original drug).
If the preparations are not equivalent in the biological sense due to different manufacturing techniques and / or the presence of unequal auxiliary ingredients and excipients, then a difference (nonequivalence) of their therapeutic effect is possible. Therefore, when comparing preparations of various companies, the concepts of bioequivalence, pharmaceutical equivalence and alternativeness, therapeutic equivalence are the main ones in the pharmacological characteristic.
Pharmaceutically equivalent drugs - drugs in the same dosage form that contain the same active substances in the same amount, meeting the requirements of the same or similar standards. In the United States, drugs are considered pharmaceutically equivalent that contain the same active ingredients in the same dosage form, are for the same route of administration, and are identical in potency or concentration of active substances.
Pharmaceutically alternative drugs are drugs that contain the same drug substance, but differ in the chemical form of this substance (they are different salts, esters or complexes of these substances), dosage form or potency.
Bioequivalent drugs are drugs that give the same concentration of active substances in the blood and tissues of the body when drugs are administered in equal doses in the same way.
In the EU, two drugs are considered bioequivalent if they are pharmaceutically equivalent or alternative and if their bioavailability (rate and degree of absorption) after administration in the same molar dose is similar to such an extent that their efficacy and safety are basically the same.
In the United States, bioequivalent drugs are defined as pharmaceutically equivalent or alternative drugs that have comparable bioavailability when tested under similar experimental conditions.
Bioequivalence means that generic drugs that are bioequivalent to the original provide the same pharmacodynamic effect, the same efficacy and safety of drug therapy.
A bioequivalence study is necessary to confirm the quality of generic drugs and their relevance to the original drug.
It is understood that bioequivalent drugs are therapeutically equivalent.
Therapeutically equivalent drugs are drugs that contain the same active substance or drug substance and, according to the results of clinical trials, have the same effectiveness and safety. In determining therapeutic equivalence, the studied drug is compared with a drug whose efficacy and safety are already established and universally recognized.
Therapeutically equivalent drugs can only be considered if they are pharmaceutically equivalent. In this case, they can be expected to have the same clinical effect and the same safety when they are prescribed to patients.
The concept of bioavailability is closely related to the concept of bioavailability.
Bioavailability is the part of the drug that enters the systemic circulation during the extravascular route of administration.
With intravascular administration, the drug substance completely enters the bloodstream and its bioavailability is 100%. With other routes of administration (even with intramuscular and subcutaneous) bioavailability almost never reaches 100%, since the drug must pass through a number of biological cell membranes (mucous membrane of the stomach, liver, muscles, etc.), and only a part of it enters the systemic circulation. The effect of the drug largely depends on how large this part is.
Factors affecting bioavailability:
• route of administration of the drug;
• individual characteristics of the patient's body;
• condition of the gastrointestinal tract, cardiovascular system, liver, kidneys;
• biopharmaceutical factors (dosage form, composition of excipients, especially the production technology of the drug).
Preparations containing the same medicinal substances, but released by various pharmaceutical companies, can vary significantly in bioavailability. Differences in bioavailability lead to differences in therapeutic efficacy and the different frequency and severity of side effects.
3.4 Rules for the replacement of drugs

Since doctors are responsible for making a diagnosis and treating a patient, including prescribing appropriate drugs, the choice of a prescription drug is the prerogative of the attending physician only. National medical associations of most countries are actively working to strictly comply with drug substitution rules.

A generic substitution is a dispensing of a medicine, the commercial name of which differs from that prescribed by the doctor, and the chemical composition and dosage of the active substance are identical.

There are three main systems for conducting a generic replacement.

• Total generic replacement system - for each prescription written for the original drug (which can be replaced with a generic one), the generic drug is dispensed. When using a total generic substitution, a number of problems may arise, the essence of which is reduced to the problem of liability in case of side effects associated with the replacement of the original drug with a generic one. Especially often, undesirable effects, exacerbation of the disease can occur when replacing the original drug with a generic one from such clinical and pharmacological groups as antiepileptic drugs, P-blockers, anticonvulsants, and calcium antagonists. Complete mandatory generic replacement can cause many problems in the relations of all interested parties, including causing significant damage to the health system. Therefore, a full mandatory generic replacement is not widely used.

• The system of prohibition notes in the prescription - the doctor must make a note in the prescription if he objects to replacing any medication indicated by him in the prescription. In this case, the drug can be replaced if there is no mark, but the doctor is given the opportunity to prevent the replacement.

• The system of permissive notes in the prescription - the doctor must make a special note if he does not mind replacing the medication indicated in the prescription. In this case, replacement with another drug is not obligatory, and the doctor is given the opportunity to decide whether such a replacement is acceptable.

Therapeutic replacement - replacing a medicine prescribed by a doctor with another one that is different in chemical composition. In this case, the replaced medicine, although it belongs to the same pharmacological and / or pharmaco-therapeutic class, however, in chemical composition differs from that prescribed, and therefore can cause a different effect in the patient. An example of a therapeutic substitution is the replacement of an H2 receptor antagonist with an antacid preparation (a drug to reduce stomach acidity) in the treatment of patients with peptic ulcer. However, therapeutic replacement is considered as a violation of the relationship between the doctor and the patient. Therefore, full therapeutic replacement is prohibited in all countries.

Attitudes towards generic substitution are not the same in different countries, which is due to differences in the organization of health systems and differences in the traditions of medical care. In the USA and Canada, the pharmacist is allowed to carry out a generic substitution unless the doctor has forbidden it, which should be indicated on the prescription form. In the UK, a generic substitution by a pharmacist is prohibited. Generic substitution is permitted only in hospitals. In Germany, the doctor must note in the prescription that he agrees to replace the drug or write a prescription immediately with the generic name. In France, doctors are threatened with penalties if they exceed the allowable level of expenses for prescriptions for patients, and the amount of the premium to the fees is calculated on the basis of the cost-saving of prescribing. Despite this, the generic market in France is still underdeveloped.

Before prescribing the drug, the doctor is obliged to make the choice of the medicine, taking into account the individual characteristics of the patient, as well as taking into account the prices of similar drugs, in order to best satisfy the needs of a particular patient. Choosing the best drug is much easier with the advice of a pharmacist. After choosing a drug, it is impossible to carry out a generic replacement without the permission of the patient and his attending physician. It is possible to carry out a therapeutic replacement only after coordinating it with a doctor. When authorizing such a replacement, the doctor should have a clear idea of the features of the pharmacodynamics and pharmacokinetics of analog drugs, the characteristics of the dosage form, and dosage regimens.

When dispensing over-the-counter drugs as part of self-medication, the patient selects the medicine with the help of a pharmacist, and the pharmacist himself can decide on the generic replacement of one or another over-the-counter drug.

Thus, the development of the concept of self-medication, the constant expansion of the nomenclature of OTC drugs create conditions when an increasing number of patients go to the pharmacy, bypassing the doctor. The pharmacist becomes the only qualified consumer interlocutor - the patient.

In this situation, the pharmacist is faced with the task of making recommendations on the symptoms of diseases and pathological conditions, drugs and the conditions for their rational use — the task of ensuring the proper quality of pharmaceutical care for each patient.

conclusions

Currently, in most countries of the world there is a tendency to increase the list of drugs allowed for over-the-counter dispensing, the so-called OTC drugs (from the English over the counter). The very existence of this category of drugs determines the possibility of their use without the recommendation of a doctor, that is, under the responsibility of the patient himself. The World Health Organization has determined that self-medication is the use of freely available drugs by the consumer to prevent and treat well-being and symptoms that he recognizes. In 1994, the European Association of OTC Manufacturers (AESGP) transformed the term “self-medication” into “responsible self-medication”. In this regard, at the end of the twentieth century. The strategic direction of healthcare development worldwide was defined as “focus on the patient”.

The development of the concept of responsible self-medication is called upon to play a positive role in providing the population with more affordable, high-quality and cheap services. World practice shows that comprehensive informing the medical community and the population about modern approaches to responsible self-medication and the introduction of appropriate standards for OTC drugs can lead to a reduction in healthcare costs and an improvement in the general state of public health.

The main characteristic of self-medication is the patient’s responsibility for their health. The basis of a responsible approach to self-medication is the availability of complete information. And it is precisely in such conditions that the role of supervision is significantly increased, which will provide the patient with better care. The pharmacist must find out for the treatment of which ailment a drug is needed, if the patient has symptoms requiring urgent medical advice, he will advise not only the drug, but also choose the optimal dosage form, tell about the rules for taking the drug, warn about possible side effects , the interaction of the drug with food, other drugs, etc., that is, it will carry out full pharmaceutical care. Pharmaceutical custody implies that the pharmacist assumes responsibility to a particular patient for the result of treatment with drugs.

Lesson purpose

Know:

I Pharmaceutical custody - definition of the term

1. Good Pharmaceutical Practice (GPP) Requirements
2. The role of pharmaceutical guardianship in the development of a self-medication system.
3. Algorithm of actions of a pharmacist - The main goal of such an algorithm.

II. Self-medication is an essential part of the modern healthcare system.

1.1 History of pharmaceutical custody

Good Manufacturing Practice (GMP);

good laboratory practice - (Good Laboratory Practice, GLP);

Good Clinical Practice (GCP).

Good practice for the wholesale distribution of medicines (Good Distribution Practice, GDP)

Good Pharmaceutical Practice (GPP).

1.2 The concept of self-medication

Self-medication

“responsible self-treatment”,

"self-help"

definition of terms

Self Prevention

Self-help and self-prevention.
1.3 Objective reasons for the development of the concept of self-treatment in modern conditions
I. Decrease in state participation in public health issues due to a significant increase in the cost of the healthcare system.
II. Enhancing the role of patients in maintaining their health.
o An increase in the educational level increases the number of people who are inclined to make independent (without the help of a doctor) decisions regarding their health.
The spread of active promotion of a healthy lifestyle.
A significant increase in the nomenclature of OTC drugs.
1.4. Current state of self-treatment concept
• Development of the concept of responsible self-medication
• Promotion of self-treatment.
1.5 Positive and negative moments of self-medication
Unconditional positive aspects of introducing the concept of self-treatment into the structure of healthcare:
o saving time and money for patients;
o reducing the burden on medical institutions and doctors;
o saving budget funds;
o the demand for health care specialist of a new generation - a clinical pharmacist;
o the active introduction of pharmaceutical care in the practice of pharmacy institutions;
o increase profits of drugstores;
the active participation of doctors in the formation of the nomenclature of OTC drugs.
The necessary conditions for introducing the concept of responsible self-treatment and the rational use of OTC drugs are as follows:
1. Creation of a state organizational structure for managing the registration and movement of OTC drugs in Ukraine and the definition of its functions.
2. Development and approval of regulatory documents regarding self-medication and dispensing of medicines without a doctor's prescription.
3. Development of the Regulation on over-the-counter dispensing of medicines to the population of Ukraine.
4. Monitoring of the domestic, pharmaceutical market of OTC drugs and responsible self-medication.
2. OTC drugs
2.1 the Concept of OTC drugs
2.2 Criteria on the basis of which drugs are classified as prescription or OTC
1. Criterion One
1.1. Direct health / safety ratio:
a) a direct threat to health, even with the correct use of the drug (in accordance with the instructions for use intended for patients), may be associated with its toxicity, interactions with other substances and adverse reactions.
An over-the-counter drug should have the following properties:
• low general toxicity, no effect on reproductive function, no genotoxic or carcinogenic effect;
• low risk of severe type A adverse reactions in the general population;
• a very low risk of severe type B adverse reactions;
• lack of interactions with widely used drugs that can lead to severe adverse reactions;
b) assessing the possible threat to the patient's health that this drug may pose, one should take into account the possibility of its prevention. For example, the presence of pronounced adverse reactions of type A is permissible for an over-the-counter drug, if the corresponding risk group can be easily determined and eliminated without even resorting to medical control;
c) the safety of the use of this drug must necessarily be compared with that of alternative drugs.
1.2. Indirect Health / Safety Ratio:
1.3. The possibility of self-assessment:
1.4. Risk and consequences of improper use of the drug:
1.5. Instructions for the patient:

2. The second criterion
When considering whether this criterion is applicable to the drug, the following factors should be considered.
2.1. Data on improper use of the drug.
3. The third criterion
Medications are subject to a doctor's prescription if they contain substances whose action and / or side effects require further study.
When considering whether this criterion is applicable to the drug, the following factors should be considered.
3.1. A trade license for a medicinal product has been issued recently / the experience of using the medicinal product is small:
3.2. Other strength of the drug, dose, route of administration, indication, age group or other combination of substances:
4. The fourth criterion
Prescription drugs are those that the doctor usually prescribes for parenteral use (e.g., intravenously).
5. Other criteria
5.1. The size and shape of the packaging of the drug:
5.2. The maximum single dose, the maximum daily dose.
2.3 Prescription of OTC drugs
The main purpose of their application:
o quickly and effectively alleviate the symptoms of diseases that do not require medical advice;
o in the conditions of financial and personnel difficulties in the public health sector, to enable the patient to alleviate minor symptoms on their own when they feel unwell, which will reduce the burden on medical services;
o increase the availability of medical care to populations living in remote regions where obtaining qualified medical advice is difficult.
2.4 Information on the packaging of the OTC drug
Information for drug identification:
o the name of the drug and its international name (or the name of the active ingredients in complex preparations);
o complete qualitative and quantitative characterization of the active ingredients using their generally accepted names and qualitative characteristics of the excipients;
o dosage form and composition by volume or number of doses (for each dosage form);
o pharmacotherapeutic group or nature of action in terms (concepts) available to the patient;
o name and address of the manufacturer and owner of the trade license.
Information about the pharmacotherapeutic properties of the drug:
• indications;
• contraindications;
• precautions for use;
• interaction with other drugs and other interactions (with food, alcohol, etc.);
• special warnings.
2.5 Categories of patients requiring increased attention of the pharmacist
older people
Children.
Pregnant women.
Nursing mothers.
3. Brand and generic drugs
3.1 the Concept of the original drug Brand drugs
3.2 The concept of a generic drug is a generic drug or generic drug.
3.3 Equivalence of generic drugs
The generic medicinal product must meet the following requirements:
contain the same active substance in the same dose and dosage form as the original drug;
be identical to the original drug in terms of potency;

have the same indications for use as the original drug;
be bioequivalent to the original drug (i.e., after oral administration, the same amount of the drug should have the same concentration in the blood as the original drug).
Pharmaceutically equivalent drugs.
Pharmaceutically alternative drugs.
Bioequivalent drugs.
Bioavailability.
Factors affecting bioavailability:
route of administration of the drug;
individual characteristics of the patient;
the condition of the gastrointestinal tract, cardiovascular system, liver, kidneys;
biopharmaceutical factors (dosage form, composition of excipients, especially the production technology of the drug).
3.4 Rules for the replacement of drugs
Generic replacement -
Therapeutic replacement.
The solution of situational problems.
Pharmaceutical custody is a program of complex interaction between a pharmacist and a doctor, a pharmacist and a patient during the entire period of pharmacotherapy from the time the drug is dispensed to the end of its use, in some cases until the pharmacological action of the drugs is completely completed (including manifestations of both basic and side effects).
Pharmaceutical custody includes recommendations for:
- individual dosing of the drug (that is, the calculation of the dose depending on the individual characteristics of the patient);
- interactions of drugs with food, alcohol, nicotine and other drugs;
- features of the use of various dosage forms, and if necessary, and training (briefing) of the patient;
- consultations on the regimen, ways and methods of drug administration;
- prevention or elimination of side effects of drugs;
- informing about storage conditions of medicines, etc.
The final result of pharmacotherapy primarily depends on the patient's "discipline", his willingness to follow the recommendations of a doctor or pro-visor (in modern medical practice this concept is defined as compliance pharmacotherapy from English compliance). Pharmaceutical custody is the key to compliance with the patient.
First of all, pharmaceutical custody should be carried out in cases where the patient acquires drugs without the participation of a doctor, that is, non-prescription drugs.
The share of OTC drugs is 30–70% of total sales. The most common symptoms and health problems for which OTC drugs are prescribed are a cold (cough, fever, runny nose), headache, pain in the joints and muscles, discomfort from the digestive system (heartburn, constipation, diarrhea).
Give an example of a pharmacist interviewing a specific patient during pharmaceutical care. Use the necessary questions and algorithms below.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

PHARMACEUTICAL CARE OF PATIENTS WITH PATHOLOGY OF RESPIRATORY SYSTEM

Relevance of the topic

Respiratory diseases are quite common among all segments of the population. Their prevalence is almost the same as diseases of the circulatory system, and in different age groups ranges from 15 to 20%. High are temporary disability and disability in diseases of the respiratory system. Fortunately, the most common diseases of the respiratory system are short enough to have a significant impact on health status. However, if the treatment is not carried out on time, the probability of the transition of the disease to a chronic form, the development of complications that are dangerous not only for health but also for life, is high.

The most common complaint in respiratory diseases is coughing. Patients who wish to purchase a cough treatment drug make up a significant portion of pharmacy visitors. When dispensing this category of drugs, the pharmacist should remember that among the numerous respiratory diseases, self-medication using over-the-counter drugs is possible only at the first stage of acute respiratory diseases (colds) and acute bronchitis (mild forms). Obligatory participation of a doctor in drug therapy requires acute bronchitis (severe course), exacerbation of chronic bronchitis, pneumonia, asthma, tuberculosis, pleurisy, abscess and lung tumors. In modern conditions, given the significant increase in the incidence of tuberculosis, the pharmacist should be especially careful when dispensing over-the-counter drugs to patients complaining of coughing.

Motivational characteristic of the topic

Pulmonology (lat. Pulmo - lung; Greek. Logos - teaching) is the section of internal diseases that studies the pathology of the respiratory system and develops methods for the prevention, diagnosis and treatment of diseases of the respiratory system.

Observation of patients with pathology of the respiratory system should be carried out in two directions.

• General events - monitoring and care measures that patients with any diseases of various organs and systems need: monitoring the general condition of the patient, thermometry, monitoring the pulse and blood pressure, filling the temperature sheet, ensuring personal hygiene of the patient, feeding ship, etc.

• Special events - observation and care measures aimed at helping patients with symptoms characteristic of respiratory diseases - shortness of breath, cough, hemoptysis, pain, etc.

PHYSIOLOGY OF THE RESPIRATORY SYSTEM

The main functions of the respiratory system are the supply of oxygen to the body and the removal of carbon dioxide from it. In addition, the respiratory system is involved in complex metabolic processes, inactivation and production of biologically active substances, fatty acids, lipids, etc.

The gas exchange process consists of external and internal (tissue) respiration. External respiration is carried out by gas exchange between pulmonary and atmospheric air and pulmonary air and blood. In an insignificant degree (1-2%), gas exchange occurs through the skin and digestive tract, but mainly occurs in the alveoli. The diameter of each alveoli is 0.2-0.3 mm; in total, there are more than 800 million in the lungs of one person. The total area of the alveoli averages about 100 m2.

Respiration is regulated by humoral * and reflex factors by acting on the respiratory center located in the medulla oblongata at the bottom of the IV ventricle. An immediate irritant of the respiratory center is an increase in the content of carbon dioxide and metabolic products (lactic acid, etc.) in the blood. With hypoxia of the brain (a decrease in the oxygen content in the structures of the brain), the excitability of the respiratory center decreases until its activity ceases **. Reflex stimuli act on the respiratory center through the receptors of the lungs and respiratory tract, skin, abdominal organs and blood vessels. For example, a sharp irritation of the skin with ice water can reflexively cause excitation of the respiratory center.

Pulmonary ventilation is carried out through inhalation and exhalation - the rhythmic movements of the chest.

• Due to the excitation of the respiratory center, motor impulses are transmitted to the muscles of the chest and diaphragm. The muscles of the chest are contracting, the diaphragm is lowering, the chest cavity is expanding; this creates a negative pressure in the pleural cavity. The lungs are stretched, the alveoli expand, and atmospheric air, due to the pressure difference, enters the lungs. Thus, inhalation is an active process that occurs when the respiratory muscles contract.

• When the contraction of the respiratory muscles is replaced by relaxation, the rib cage decreases, the diaphragm rises, and the lungs, due to their elasticity, also decline. The air pressure in the alveoli becomes higher than atmospheric, and the air is displaced from the lungs. Thus, exhalation occurs passively, with relaxation of the respiratory muscles.

* Humoral regulation - regulation of vital functions, carried out through body fluids (blood, lymph, tissue fluid) using biologically active substances secreted by cells, tissues and organs during their functioning.

** In a healthy person, moderate hypoxia causes only a slight increase in pulmonary ventilation, while any increase in it leads to a decrease in the partial pressure of carbon dioxide in arterial blood and, consequently, to a decrease in respiration-stimulating impulses from sensitive chemoreceptors.

In a healthy person, the NPV ranges from 16 to 20 per minute. With calm breathing, a person in one respiratory movement, on average, inhales and exhales 500 cm3 of air.

Respiratory rate depends on age, gender, body position. Increased breathing occurs during physical exertion, nervous excitement. The breathing is reduced in a dream, in a horizontal position of a person.

The calculation of NPV should be carried out unnoticed by the patient. To do this, take the patient’s hand as if in order to determine the pulse and imperceptibly for the patient calculate the NPV. The

results of the calculation of the NPV should be noted daily in the temperature sheet in the form of dots of blue color, which, when connected, form a curve of the respiratory rate. Normally, breathing is rhythmic, of medium depth.

There are three physiological types of breathing.

1. Breast type - breathing is carried out mainly due to the contraction of the intercostal muscles; markedly widening of the chest during inhalation. Breast type of breathing is characteristic mainly for women.

2. Abdominal type - respiratory movements are performed mainly due to the dia-fragment; noticeable displacement of the abdominal wall forward when inhaling. The abdominal type of breath is observed more often in men.

3. A mixed type of breathing is more often observed in the elderly.

SYMPTOMS OF THE RESPIRATORY SYSTEM PATHOLOGY

Dyspnea

Dyspnea, or shortness of breath (Greek dys - difficulty, pnoe - breathing), is a violation of the frequency, rhythm and depth of breathing or increased work of the respiratory muscles, manifested, as a rule, by subjective sensations of lack of air or difficulty breathing. The patient feels a lack of air. It should be remembered that shortness of breath can be either pulmonary or cardiac, neurogenic, or other origin. Two types of dyspnea are distinguished depending on the NPV.

• Tachypnea - rapid shallow breathing (over 20 per minute). Tachypnea is most often observed with lung damage (e.g., pneumonia), fever, blood diseases (e.g., anemia). With hysteria, the respiratory rate can reach 60-80 per minute; this breath is called the "breath of the driven animal."

• Bradypnea - pathological respiratory depression (less than 16 per minute); it is observed in diseases of the brain and its membranes (cerebral hemorrhage, brain tumor), prolonged and severe hypoxia (for example, due to heart failure). The accumulation in the blood of acidic metabolic products (acidosis) in diabetes mellitus, diabetic coma also depresses the respiratory center.

The following types of shortness of breath are distinguished depending on the disturbance of the respiratory phase.

• Respiratory dyspnea - difficulty breathing.

• Expiratory dyspnea - exhalation is difficult.

• Mixed shortness of breath - both phases of breathing are difficult.

Depending on the change in breathing rhythm, the following main forms of shortness of breath are distinguished (the so-called "periodic breathing").

• Cheyne-Stokes breathing * - breathing in which, after a breathing pause, first surface rare breathing appears, which gradually increases in depth and frequency, becomes very noisy, then gradually decreases and ends with a pause during which the patient may be disoriented or lose consciousness. A pause can last from a few to 30 seconds.

• Biota Breathing- rhythmic periods of deep breathing movements alternate at approximately equal intervals with prolonged respiratory pauses. A pause can also last from a few to 30 s.

• Kussmaul breathing- uniform breathing cycles with a deep noisy breath and enhanced exhalation; observed with deep coma.

Suffocation

Asthma, or suffocation (Greek asthma - heavy short breathing), is the common name for acutely developing attacks of shortness of breath of various origins. An attack of suffocation of pulmonary origin due to bronchospasm is called bronchial asthma. With blood stasis in a pulmonary circulation, cardiac asthma develops.

If the patient develops shortness of breath or suffocation, the nurse should immediately inform the doctor of his observations on the nature of shortness of breath, respiratory rate, and take measures to alleviate the patient's condition.

1. Create a rest environment around the patient, calm him and others.

2. Help the patient to take an elevated (semi-sitting) position by lifting the head end of the bed or placing pillows under the head and back.

3. Release from tight clothing and heavy blankets.

4. Ensure access of fresh air to the room (open the window).

5. If there is an appropriate doctor's prescription, give the patient a pocket inhaler and explain how to use it.
Use of a pocket inhaler for asthma (Fig. 1):
1. Remove the protective cap from the mouthpiece of the spray can.
2. Turn the can upside down and shake it well.
3. Ask the patient to take a deep breath.
4. Explain to the patient that he should tightly clasp the mouthpiece with his lips and take a deep breath, while simultaneously pressing the can valve; after inhalation, the patient should hold his breath for several seconds.

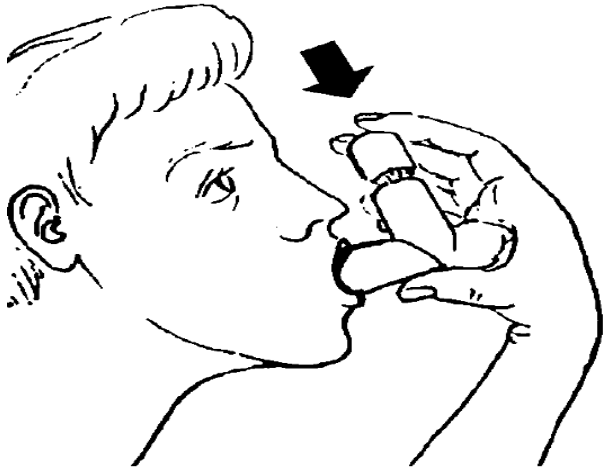

Fig. 1. The use of a pocket inhaler
5. After that, ask the patient to remove the mouthpiece from the mouth and exhale slowly.
The number of doses of aerosol is determined by the doctor. After inhalation of glucocorticoids *, the patient should rinse his mouth with water to prevent the development of oral candidiasis.
Oxygen therapy. With a pronounced degree of respiratory failure, oxygen therapy should be carried out (Latin oxygenium - oxygen; Greek therapeia - treatment) - the use of oxygen for medicinal purposes. The use of oxygen provides tangible help to patients with severe shortness of breath, especially with shortness of breath at rest.
Before using oxygen, make sure that the airways are passable
Indications: acute or chronic respiratory failure, accompanied by cyanosis (bluish tinge of the skin and mucous membranes), tachy-cardia (palpitations), decreased partial pressure of oxygen in the blood.
For treatment, an oxygen mixture containing from 40 to 80% oxygen is used. For carbon monoxide poisoning, carbogen is used (a mixture containing 95% oxygen and 5% carbon dioxide); with pulmonary edema, the oxygen mixture is bubbled through antifoam agents (50-96% solution of ethyl alcohol or 10% alcohol solution of the organosilicon compound antifomsilan).
Pure oxygen should not be used, since it can inhibit the respiratory center, cause burns of the respiratory tract and, in addition, have a toxic effect on the human body, manifested by dry mouth, chest pain, cramps, loss of consciousness.
The following oxygen supply methods are available.
1. The supply of oxygen from an oxygen cushion. This method is more often used at home; in hospitals, it is used in cases where it is not possible to provide the patient with oxygen from the cylinder. The oxygen pillow is a rubberized bag with a capacity of 10 to 75 liters, equipped with a rubber tube with a tap and mouthpiece. The volume of the oxygen-air mixture in a pillow with a capacity of 10-25 liters is enough, as a rule, for only 5-7 minutes. When giving the patient an oxygen pillow, the mouthpiece should be wrapped with 2-3 layers of gauze soaked in water to moisten oxygen.
2. Oxygen supply through nasal catheters - oxygen is supplied from a cylinder with compressed oxygen stored in a special room through a system of metal tubes conducted into the chamber (the so-called centralized oxygen supply). To moisturize, oxygen is passed through water using a Bobrov apparatus.

* Bobrov's apparatus (Russian surgeon Bobrov, Aleksandr Alekseevich, 1850-1904) - an apparatus whose principle of operation is to create a small excess pressure in a graduated vessel with injected fluid by forcing air into it.
Oxygen cylinder with a capacity of 40 liters and a pressure of 150 atm. It is painted in blue color and has an inscription "Medical Oxygen".
Oxygen is supplied to the patient at a pressure of 2-3 atm, so a special reducer is connected to the cylinder with two pressure gauges, one of which shows the pressure in the cylinder, the second shows the oxygen pressure at the outlet of the reducer, i.e. pressure of oxygen supplied to the patient.
3. The supply of oxygen through the mask (Fig. 2). When applied to the face, the mask should cover the mouth and nose.
4. The supply of oxygen through a ventilator. In this case, oxygen is supplied via an endotracheal tube.

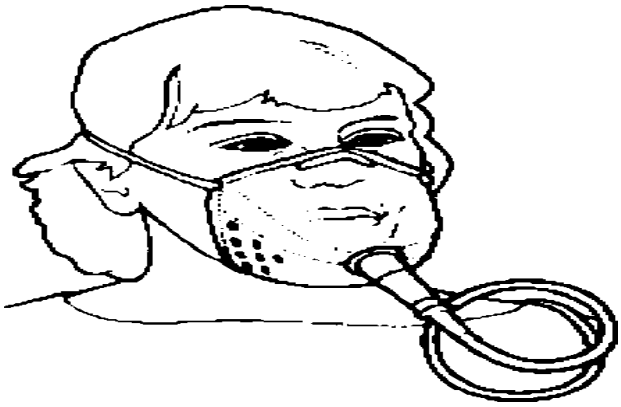

Fig. 2. The supply of oxygen to the patient through the mask

The mask has inhalation and exhalation channels. The tube of the respiratory canal is connected to a breathing bag made of thin rubber, in which oxygen accumulates during exhalation, and when inhaling, oxygen is actively absorbed into the lungs. To moisturize, oxygen is passed through water using a Bobrov apparatus.

5. Hyperbaric oxygenation, or oxygenobarotherapy (Greek barys - heavy), is a therapeutic and prophylactic method of saturating the body with oxygen under high pressure. Hyperbaric oxygenation sessions are carried out in special pressure chambers. The pressure chamber is a hermetically sealed room in which artificially increased air pressure (gases) can be created. The dimensions of the pressure chamber and equipment provide the possibility of a long stay in the pressure chamber of several patients. In pulmonary monology, oxygenobarotherapy is used in the complex treatment of purulent-obstructive pulmonary diseases.

Supply of an oxygen-air mixture from an oxygen pad.

Necessary equipment: oxygen cushion, oxygen cylinder, sterile gauze wipes, water. The procedure for performing the procedure (Fig. 3):

1. Fill the oxygen cushion with oxygen:

- remove the mouthpiece from the rubber tube of the oxygen cushion, open the cushion cock, connect the rubber tube to the cylinder reducer and slowly open the reducer valve;

- fill the oxygen cushion with oxygen from the cylinder.

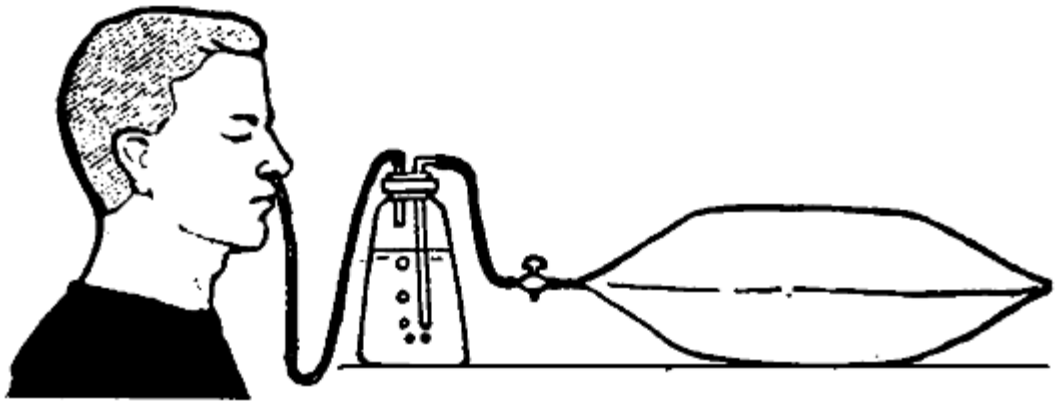

Fig. 3. The supply of oxygen to the patient from an oxygen cushion (scheme)

When filling the oxygen cushion, stand on the side of the balloon so that the oxygen stream does not damage the eyes.

2. Close the gearbox valve and oxygen cushion valve.

3. Treat the mouthpiece of the pillow with a sterile gauze cloth soaked in 70% alcohol solution.

4. Explain to the patient that he should breathe in through his mouth, and exhale through his nose.

5. Wrap the mouthpiece of the oxygen cushion with a 2-3-layer sterile gauze soaked in water.

6. Insert the mouthpiece into the patient's mouth, then slowly open the tap on the rubber tube.

7. The rate of oxygen can be adjusted by pressing the pillow with your hand.

8. As the volume of the mixture decreases, press the pillow with your hand, and then fold it from the angle opposite the mouthpiece until the pillow is empty (it does not fall).

The supply of oxygen-air mixture through nasal catheters. Necessary equipment: oxygen cylinder, sterile nasal catheters, sterile vasulin, rubber or plastic tube, patch.

The procedure for performing the procedure (Fig. 4):

1. Lubricate the sterile nasal catheter with Vaseline.

2. Insert the catheter through the nose along the lower nasal passage to the posterior pharyngeal wall to a depth equal to the distance from the wings of the nose to the patient's earlobe.

3. If the patient is conscious, he can be asked to open his mouth and visually monitor the introduction of a catheter into the nasopharynx; when inserted correctly, the end of the catheter should be visible in the throat.

4. Connect the outer end of the catheter to a rubber or plastic tube connected to a centralized feeding system.

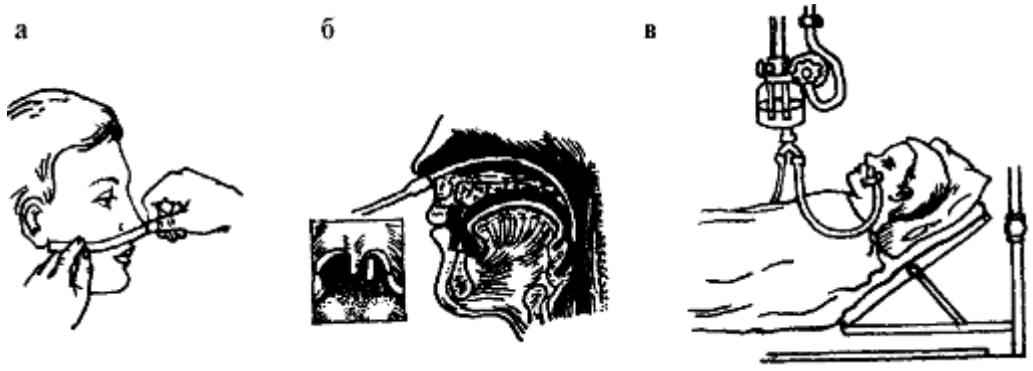

Fig. 4. Supply of oxygen to the patient through the nasal catheter: a - determination of the depth of insertion of the nasal catheter; b - the introduction of a nasal catheter; c - view of the patient who is fed oxygen through nasal catheters

oxygen into the wards, and fix it with a band-aid to the cheek (or to the temple, to the forehead).

5. Open the valve of the cylinder dosimeter (located in the chamber) and supply oxygen at a rate of 2-3 l / min.

6. Every 30-60 minutes to change the position of the catheter in order to prevent progeny and to dry the mucous membrane of the nasal passages.

Oxygen cylinders should be stored only in specially designated premises for which smoking is strictly prohibited. Do not place oxygen cylinders near heat and light sources.

Compressed oxygen in contact with fats and petroleum products ignites and explodes, therefore it is unacceptable to be near oily cylinders of oiled rags, clothing, as well as any objects stained with fresh paint. When working with an oxygen cylinder, do not lubricate your hands with cream.

Sputum

Sputum (Latin sputum) is a pathologically altered secretion of mucous membranes of the trachea, bronchi and lungs with an admixture of saliva and secretion of the mucous membrane of the nasal cavity and paranasal sinuses that is secreted by expectoration.

Sputum characteristics - quantity, color, smell, consistency (liquid, thick, viscous), inclusions (blood, pus and others

impurities) - depend on the disease and, along with the results of other laboratory and instrumental research methods, are of great importance in the diagnosis of diseases of the respiratory system and other organs.

The daily amount of sputum can range from a few milliliters for chronic bronchitis to 1-1.5 liters for bronchiectasis, a breakthrough of the abscess of the lung in the bronchus, lung gangrene.

The following types of sputum are distinguished by nature.

• Mucous sputum (sputum mucosum) - sputum is colorless, transparent, viscous, practically does not contain cellular elements.

• Serous sputum (sputum serosum) - spongy liquid foamy, excreted in pulmonary edema.

• Purulent sputum (sputum purulentum) - sputum contains pus (it is characteristic, in particular, for breaking through a lung abscess into the lumen of the bronchus).

• Putrid sputum (sputum putridum) - purulent sputum with a putrid odor.

• Bloody sputum (sputum sanguinolentum) - sputum contains an admixture of blood (noted, for example, when bleeding from the walls of the respiratory tract in lung cancer).

• “Rusty” sputum (sputum rubiginosum) - bloody sputum, contains inclusions of a rusty color, resulting from the decomposition of hemoglobin (appears, for example, in pneumonia, tuberculosis).

• Pearl sputum - sputum contains rounded opalescent inclusions consisting of atypical cells and detritus * (observed, for example, with squamous cell carcinoma of the bronchi).

• Three-layer sputum - sputum is abundant, purulent, separated upon settling into three layers: the upper is grayish foamy, the middle is watery transparent, the lower is dirty gray-green in color, containing pus and the remains of necrotic tissue (observed with lung gangrene).

If sputum is present, the nurse must ensure that the spittoon is clean and timely. It is necessary to ensure that the patient regularly takes a drainage position, for example, according to Quinck **, which promotes the separation of sputum,

Postural drainage (lat. Positura - position; French drainage - drainage) - drainage by giving the patient a position in which fluid (sputum) flows under the influence of gravity.

Giving the patient a drainage position

Purpose: facilitating sputum discharge in bronchitis, lung abscess, broncho-ectatic disease, etc.

Preparation for the procedure: fill the sputum container (spittoon) with a disinfectant solution (5% chloramine B solution) by one third of its volume and place the spittoon next to the patient so that he can easily reach it.

• Option 1:

- From the initial position of the patient on the back, they gradually turn around the axis of his body by 360 °.

- Turning the patient over 45 °, each time they ask him to take a deep breath and when he coughs, they give him the opportunity to cough well.

- The procedure must be repeated 3-6 times.

• Option 2 (Praying Muslim Pose):

- Ask the patient to kneel and lean forward (to take the knee-elbow position).

- Ask the patient to repeat the slope 6-8 times, pause for 1 min, then again repeat the slope 6-8 times (no more than 6 cycles).

- They make sure that the patient performs this procedure 5-6 times a day.

• Option 3:

- They explain to the patient that he needs 6-8 times in succession (lying on the right or left side) to hang his head and hands from the bed (pose for finding slippers under the bed).

- They make sure that the patient performs this procedure 5-6 times a day.

• Option 4 (Quincke position):

- Raise the foot end of the bed on which the patient lies, 20-30 cm above the level of the head end.

- This procedure is carried out several times for 20-30 minutes with a break of 10-15 minutes.

At the end of the postural drainage procedure, the patient should be helped to take a comfortable position, disinfect sputum and spittoon and make an entry in the medical history about the procedure and the patient's response to it.

If sputum does not go away in any of the drainage positions, their use is ineffective.

To improve blood and lymph circulation in the chest area, patients are shown its massage, and to improve lung ventilation - breathing exercises. It is also necessary to ventilate the room in which the patient is located at least 4 times a day and maintain the air temperature within 18-22 ° C. It is necessary to monitor the patient's compliance with the doctor's prescriptions. The patient should be provided with a sufficient amount of fluid - in order to avoid the formation of kidney stones when taking antibiotics and sulfonamides, you need to give him more to drink.

In order to prevent the infection of others, the nurse must teach the patient how to handle sputum correctly:

• Do not cough in the vicinity of healthy people.

• Cover your mouth with your hand or handkerchief when coughing.

• Do not spit sputum on the floor *, because when it dries, it can turn into particles of dust and infect others.

• Collect sputum in a special spittoon bowl with a tight lid, on the bottom of which a small amount of a 0.5% solution of chloramine B should be poured.

The spittoon must be emptied daily, having previously noted the amount of sputum per day in the temperature sheet, and disinfected with a solution of chloramine B, clarified with a solution of bleach. The sputum of patients with tuberculosis is burned or drained into the sewer after preliminary decontamination for 2 hours with dry bleach at the rate of 20 g per 1 liter of sputum.

Hemoptysis and pulmonary hemorrhage

Hemoptysis (Greek haemoptoe) - the allocation of blood or sputum with an admixture of blood from the respiratory tract when coughing. Blood can be distributed evenly in sputum (for example, sputum in the form of “raspberry jelly” for lung cancer) or in separate streaks. With croupous pneumonia, sputum can be "rusty." The source of bleeding can be vessels of the pulmonary artery system or bronchial vessels. With the so-called false hemoptysis, the sources are bleeding gums, as well as blood flow during nosebleeds.

Hemoptysis can occur with the following diseases.

• Diseases of the lungs, accompanied by the collapse of the lung tissue with involvement in the zone of decomposition of the pulmonary vessels and violation of the integrity of the vascular wall, bronchiectasis, lung abscess, tuberculosis, lung cancer, bronchial adenoma.

• CCC pathology - stenosis of the left atrioventricular opening (mitral stenosis), pulmonary thromboembolism, aortic aneurysm.

• Chest injury.

• Autoimmune diseases.

Hemoptysis is an indication for emergency hospitalization in a hospital, since the appearance of blood in sputum does not exclude the possibility of developing pulmonary hemorrhage.

Pulmonary hemorrhage. The release through the respiratory tract of a significant amount of blood (with a cough or continuous stream) is called pulmonary hemorrhage. Massive is called pulmonary

hemorrhage with a volume of more than 240 ml of extracted blood for 24-48 hours. Massive bleeding is immediate

threat to the patient's life. The most common causes of pulmonary hemorrhage are pulmonary tuberculosis, lung cancer, bronchiectasis, lung abscess, cystic fibrosis, etc. Pulmonary hemorrhage often leads to blood flowing into the lower parts of the lung and the development of aspiration pneumonia.

It is necessary to differentiate pulmonary hemorrhage from gastric. With pulmonary hemorrhage, the blood has a red color, foamy, does not coagulate, has an alkaline reaction, is excreted by coughing. In case of gastric bleeding, the secreted blood, as a rule, is dark, has the appearance of "coffee grounds" due to interaction with acidic gastric juice and the formation of hydrochloric gematin; blood has an acid reaction, mixed with food, excreted by vomiting.

Hemoptysis and pulmonary hemorrhage are very serious symptoms, they require urgent medical intervention, both clinical and instrumental: diagnostic fluoroscopy, tomography, bronchoscopy, etc.

Care for a patient with hemoptysis provides for complete rest. It is necessary to help the patient to take a comfortable position in the semi-sitting bed with a slope to the affected side in order to prevent blood from entering the healthy lung. An ice bladder is placed on the diseased half of the chest. Ice is also allowed to be swallowed, which leads to reflex spasm of the vessels and a decrease in the blood supply to the lungs. With a strong cough that increases bleeding, antitussive drugs are prescribed. Exposure to high temperatures can lead to pulmonary hemorrhage, therefore food is given only in a cold semi-liquid form. Do not take a hot bath or shower. Before examination by a doctor, the patient should not move and talk.

With hemoptysis and the threat of pulmonary hemorrhage, the patient is categorically contraindicated in the setting of cans, mustard plasters, heating pads and hot compresses on the chest.

Chest pain

In diseases of the respiratory system, the pain syndrome is most often associated with involvement of the pleura in the pathological process (pleurisy, pleuropneumonia, pneumothorax, pleural carcinomatosis, etc.).

Pleural pains are provoked by respiratory movements, in connection with which patients try to breathe superficially.

Care for patients with pleural pain consists in giving the patient a comfortable, limiting respiratory movement position (on the sore side), performing the simplest physiotherapeutic procedures as prescribed by the doctor (setting mustard plasters, etc.).

If the patient's body temperature rises above 38 ° C, any physiotherapy procedures are contraindicated.

Cough

Coughing is a complex reflex act that occurs as a protective reaction when mucus, sputum accumulates in the airways, and foreign body enters and allows you to clear the airways of them.

By its nature, a cough can be dry (unproductive) - without sputum production and wet (productive) - with sputum production. A dry, painful cough should be suppressed with the help of drugs. With a wet cough, on the contrary, you should use drugs that facilitate the evacuation of sputum, but do not suppress the cough reflex.

At the first stage of pharmaceutical care, one should try to establish the possible cause of coughing in the patient and to identify the presence (or absence) of "threatening" symptoms.

The most common causes of dry cough

• Cough of heavy smokers.

• Laryngitis (inflammation of the laryngeal mucosa) - dry, sonorous ("barking") cough, sore throat.

• Tracheitis (inflammation of the mucous membrane of the trachea) - a dry, painful cough with a metallic tinge and scanty sputum.

• Acute bronchitis (inflammation of the mucosa of the tracheobronchial tree) in the initial stages of the disease - a deep, painful cough, often against the background of other cold symptoms.

• Pleurisy (inflammation of the pleura) - a dry, extremely painful cough, acute pain in the side is possible.

• Bronchial asthma (a chronic recurrent inflammatory disease of the respiratory system associated with immunopathological mechanisms) at the beginning of the exacerbation period - “spastic” cough, accompanied by wheezing sounds when breathing, shortness of breath.

• Foreign body in the airways - shortness of breath, shortness of breath, pallor, cyanosis.

• Food ingestion (aspiration) - choking, coughing with food (more common in young children and the elderly).

• Whooping cough (acute infectious disease transmitted by airborne droplets and characterized by spasmodic coughing fits), at the end of the illness - a long breath and paroxysmal cough; found mainly in children.

• False croup (laryngeal edema) - paroxysmal, “barking” cough in a child.

• Inhalation of vapors of irritating substances - an attack of dry cough.

• Pulmonary emphysema (increased airiness of the lungs due to overstretching or destruction of the alveoli) - dry, “short” cough on the background of shortness of breath, more common in older people.

• Lung tumors - a dry, long-lasting cough combined with shortness of breath, unmotivated weakness; possible weight loss, hoarseness of the voice.

In cases of laryngitis, tracheitis, in the initial stages of acute bronchitis, with inhalation of irritating vapors (if the general condition is not disturbed), self-medication is possible. Suspicion of one of the other diseases listed above requires the obligatory consultation of a doctor. The slightest suspicion of false croup, a foreign body in the respiratory tract requires emergency medical care (call "03").

The most common causes of wet cough

• Acute respiratory infections (colds) - mucous, sometimes mucous-purulent sputum in combination with other symptoms of a cold (fever, rhinitis, sore throat).

• Flowing mucus from the nasopharynx to the larynx - mainly nocturnal cough.

• Whooping cough - a paroxysmal excruciating cough with an extended inhalation and the discharge of a small amount of light sputum; occurs predominantly in children.

• Pneumonia (acute focal infectious and inflammatory lung disease involving the bronchial tree in the pathological process and the mandatory presence of intra-alveolar inflammatory exudation

- cough with mucopurulent sputum against the background of weakness, sweating, fever; possible chest pain, chills.

• Chronic bronchitis (diffuse, slowly progressive inflammation of the bronchial tree) - a long, persistent cough with mucopurulent or purulent sputum; exacerbations several times a year.

• Bronchial asthma during exacerbation - shortness of breath with an extended expiration, wheezing, copious "vitreous" sputum.

• Bronchiectatic disease (suppurative process in irreversibly changed and functionally defective bronchi) - abundant discharge of mucopurulent or purulent sputum in the morning.

• Pulmonary tuberculosis - profuse sputum, possibly with streaks of blood, sweating, weight loss.

• Tumors of the lung - a long-lasting cough in combination with unmotivated weakness; weight loss, hoarseness of the voice, streaks of blood in the sputum are possible.

With complaints of a wet cough, self-medication is possible for acute respiratory diseases, bronchitis (with a mild course). In other cases, you should definitely consult a doctor.

The "threatening" symptoms that make it possible to suspect a serious illness of the bronchopulmonary system in a patient include:

1. cough, lasting more than a week (especially in those cases when, over time, an increase in cough is noted);

2. cough, accompanied by long-term (weeks) with persisting temperature - 37.5–38C;

3. cough, accompanied by high (above 38 ° C) temperature for 3 or more days;

4. cough, accompanied by shortness of breath, pain in the chest during breathing;

5. cough, accompanied by the separation of thick greenish sputum;

6. cough, accompanied by separation of sputum with streaks of blood;

7. cough with asthma attacks;

8. concomitant cough weakness, weight loss;

9. profuse sweating (especially at night), chills;

10. a sudden attack of severe cough;

11. severe cough for an hour without a break;

12. copious sputum production;

13. voice change.

In all cases, the obligatory consultation of a doctor is required before the use of drugs.

If none of the “threatening symptoms” has been identified by the visitor of the pharmacy, it is possible to carry out the next stage of pharmaceutical care - the choice for this patient of the pharmacological group for the symptomatic treatment of cough.

Directions for symptomatic treatment of patients with coughing complaints

1. With a dry cough - antitussive drugs of central and peripheral action.

2. With a wet cough - expectorant and mucolytic drugs.

General recommendations for patients

• Refrain from smoking, including passive inhalation of tobacco.

• Ventilate the room more often, as clean, cool air reduces the cough reflex.

• Drink as much fluid as possible, which facilitates sputum removal.

OTC drugs used for dry cough and the conditions for their rational use

There are a significant number of over-the-counter drugs for the symptomatic treatment of dry cough. Most of them are complex, containing several active ingredients. Some ingredients in the form of single drugs are allowed only for prescription, but at the same time, as one of the components, they are part of complex over-the-counter products. We give a brief description of the main active ingredients that make up the preparations for the symptomatic treatment of dry and wet cough.

complex preparations containing the specified active substance

Pharmaceutical custody with the use of antitussive drugs

• Antitussive drugs are not prescribed for increased bronchial secretion, profuse sputum removal.

• Antitussive preparations containing codeine, dextromethorphan, buta-mirat are not recommended for children under 2 years of age, during pregnancy and lactation.

• Antitussive preparations containing codeine, dextromethorphan, buta-mirat, when taken in large doses or consumed for a long time, can lead to depression of the central nervous system and breathing.

• Preparations containing oxeladine, butamirate, and especially dextromethorphan, can cause lethargy, drowsiness, and dizziness. These drugs are not recommended for use by drivers and people of other professions that require increased attention.

• Drugs containing oxeladine, butamirate, dextromethorphan, and especially codeine, should not be combined with alcohol because of the high risk of central nervous system depression and respiratory depression.

• When taking large doses, preparations containing butamirate can cause vomiting, diarrhea, a decrease in blood pressure, and in severe cases, severe CNS depression.

• Preparations containing glaucine hydrochloride, when used in children, can lead to a decrease in blood pressure.

• Libexin tablets should be swallowed without chewing - otherwise numbness, loss of sensitivity of the oral mucosa and pharynx are possible.

• When taking Libexin, dry mouth and pharynx may be observed.

• Libexin is not recommended for people with low blood pressure.

OTC drugs used for wet cough and the conditions for their rational use

When coughing, accompanied by sputum separation (wet or productive cough), medications are used that contribute to the separation of liquid sputum - expectorants. With thick, viscous sputum, mucolytic drugs are used - drugs that have the ability to break down disulfide bonds in the mucopolysaccharide molecules of bronchial secretion.

Pharmaceutical custody when using expectorant drugs

• Expectorants cannot be combined with drugs that inhibit the cough reflex (codeine, tusuprex, glaucin, etc.) and with histamineolytics that tighten sputum (diphenhydramine, pipolfen, etc.).

• When taking expectorants, you should not prescribe drugs that dehydrate the patient's body (diuretics, laxatives, etc.).

• Expectorant drugs with a reflex action (thermopsis, terpine hydrate, istod, marshmallow, lycorin) can cause vomiting if the dose is exceeded, it is contraindicated in diseases of the stomach (gastritis, peptic ulcer).

• Expectorant preparations should be washed down with a plentiful alkaline drink. It is recommended to drink in addition to the physiological norm 1.5–2 L of liquid to compensate for physiological losses.

• It is not recommended to prescribe expectorants for bedridden patients.

• The clinical effect of expectorants is usually observed no earlier than 6–7 days of treatment.

• In the first 2–3 days of taking expectorant drugs, cough and sputum separation may intensify: these phenomena indicate the effectiveness of the drug (and not vice versa).

• With an overdose or long-term use of drugs containing iodides (potassium iodide, sodium iodide), iodism may occur: rhinitis, urticaria, Quincke's edema; the occurrence of hyperthyroidism is possible - tachycardia, tremor, irritability, insomnia, diarrhea (in people over 40 years old).

• Preparations containing iodides (potassium iodide, sodium iodide) are contraindicated in pregnancy, acute inflammatory processes, and thyroid diseases.

• In the presence of an acute inflammatory process, expectorant preparations of plant origin are preferred.

• Herbal decoctions and infusions (licorice, marshmallow root, coltsfoot, anise, fennel, thyme) not only have an expectorant effect, but also contribute to the regeneration of damaged bronchial mucosa due to the content of trace elements, vitamins and biogenic stimulants.

Mucolytics

Mucolytic drugs break down the molecules of mucopolysaccharides, polypeptides, mucoproteins that make up the bronchial secretion. They reduce the adhesive properties of sputum (its ability to adhere to the wall of the bronchi). An important feature of mucolytic drugs, especially ambroxol, is the ability to increase the synthesis of pulmonary surfactant - a surfactant of lipid-protein-mucopolysaccharide nature. Surfactant is synthesized by alveolar cells and prevents their decline. With many bronchopulmonary diseases, the synthesis of surfactant is impaired. An increase in the synthesis of surfactant indirectly increases the activity of mucociliary transport. All mucolytic drugs have a mild anti-inflammatory effect.

Pharmaceutical custody with the use of mucolytic drugs

• Bromhexine and ambroxol may increase liver transaminase activity.

• Bromhexine and ambroxol are incompatible with alkaline solutions, with preparations containing codeine, with anticholinergics.

• Ambroxol increases the penetration of antibiotics into the bronchial secret and bronchial mucosa.

• Ambroxol is contraindicated in the first trimester of pregnancy

• Bromhexine is not prescribed for children under 3 years

• Treatment with acetylcysteine should be started with small doses (100-200 mg), since the effect of large doses is unpredictable and can lead to severe hypersecretion.

• Acetylcysteine can cause pulmonary hemorrhage, disrupt the function of the liver and kidneys, in patients with bronchial asthma - provoke bronchospasm.

• Acetylcysteine is contraindicated in the first trimester of pregnancy, in the future it is used only according to strict indications under the supervision of a doctor.

• When taking acetylcysteine orally, antibiotics should be taken two hours after it is taken.

• Carbocysteine is not recommended for persons with erosive and ulcerative lesions of the gastrointestinal tract.

• Mesna is categorically contraindicated in all situations that make it difficult to expectorate (bronchospasm, weakened patient, etc.), as liquid sputum flows down and causes obstruction (blockage) of small bronchi with the development of atelectasis and respiratory failure.

• When taking Mesna in inhalations, cough and bronchospasm are possible.

• Aminoglycoside antibiotics significantly reduce mesna activity.

Lesson purpose

Know:

I. PHYSIOLOGY OF THE RESPIRATORY SYSTEM

The main functions of the respiratory system

II. SYMPTOMS OF THE RESPIRATORY SYSTEM PATHOLOGY

1. Shortness of breath

Depending on respiratory rate:

• Tachypnea

• Bradypnea

The following types of shortness of breath are distinguished depending on the disturbance of the respiratory phase.

• Respiratory dyspnea difficulty breathing.

• Expiratory dyspnea exhalation is difficult.

• Mixed shortness of breath- both phases of breathing are difficult.

Depending on the change in breathing rhythm, the following main forms of shortness of breath are distinguished (the so-called "periodic breathing").

• Cheyne-Stokes breath.

• Biot's breath.

• Kussmaul's breath.

2. Choking

Use of a pocket inhaler for bronchial asthma

Oxygen therapy

Ways to supply oxygen.

1. The supply of oxygen from an oxygen cushion.

2. Oxygen delivery through nasal catheters

3. Hyperbaric oxygenation, or oxygenobarotherapy (Greek barys - severe).

3. Sputum

1) Types of sputum.

• Mucous sputum (sputum mucosum) - sputum is colorless, transparent, viscous, practically does not contain cellular elements.

• Serous sputum (sputum serosum) - spongy liquid foamy, excreted in pulmonary edema.

• Purulent sputum (sputum purulentum) - sputum contains pus (it is characteristic, in particular, for breaking through a lung abscess into the lumen of the bronchus).

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2). Postural drainage (lat. Positura - position; French. Drainage - drainage)

4. Hemoptysis

Hemoptysis can occur with the following diseases.

• Diseases of the lungs, accompanied by the collapse of the lung tissue with involvement in the zone of decomposition of the pulmonary vessels and violation of the integrity of the vascular wall, bronchiectasis, lung abscess, tuberculosis, lung cancer, bronchial adenoma.

• CVS pathology - stenosis of the left atrioventricular opening (mitral stenosis), pulmonary thromboembolism, aortic aneurysm.

• Chest injury.

• Autoimmune diseases.

5. Pulmonary hemorrhage.

6. Pain in the chest

7. Cough

1). The most common causes of dry cough

• Cough of heavy smokers.

• Laryngitis (inflammation of the laryngeal mucosa) - dry, sonorous ("barking") cough, sore throat.

• Tracheitis (inflammation of the mucous membrane of the trachea) - a dry, painful cough with a metallic tinge and scanty sputum.

• Acute bronchitis (inflammation of the mucosa of the tracheobronchial tree) in the initial stages of the disease - a deep, painful cough, often against the background of other cold symptoms.

• Pleurisy (inflammation of the pleura) - a dry, extremely painful cough, acute pain in the side is possible.

• Bronchial asthma (a chronic recurrent inflammatory disease of the respiratory system associated with immunopathological mechanisms) at the beginning of the exacerbation period - “spastic” cough, accompanied by wheezing sounds when breathing, shortness of breath.

• Foreign body in the airways - shortness of breath, shortness of breath, pallor, cyanosis.

• Food ingestion (aspiration) - choking, coughing with food (more common in young children and the elderly).

• Whooping cough (acute infectious disease transmitted by airborne droplets and characterized by spasmodic coughing fits), at the end of the illness - a long breath and paroxysmal cough; found mainly in children.

• False croup (laryngeal edema) - paroxysmal, “barking” cough in a child.

• Inhalation of vapors of irritating substances - an attack of dry cough.

• Pulmonary emphysema (increased airiness of the lungs due to overstretching or destruction of the alveoli) - dry, “short” cough on the background of shortness of breath, more common in older people.

• Lung tumors - a dry, long-lasting cough combined with shortness of breath, unmotivated weakness; possible weight loss, hoarseness of the voice.

2). The most common causes of wet cough

• Acute respiratory infections (colds) - mucous, sometimes mucous-purulent sputum in combination with other symptoms of a cold (fever, rhinitis, sore throat).

• Flowing mucus from the nasopharynx to the larynx - mainly nocturnal cough.

• Whooping cough - a paroxysmal excruciating cough with an extended inhalation and the discharge of a small amount of light sputum; occurs predominantly in children.

• Pneumonia (acute focal infectious and inflammatory lung disease involving the bronchial tree in the pathological process and the obligatory presence of intra-alveolar inflammatory exudation) - cough with mucopurulent sputum against the background of weakness, sweating, and fever; possible chest pain, chills.

• Chronic bronchitis (diffuse, slowly progressive inflammation of the bronchial tree) - a long, persistent cough with mucopurulent or purulent sputum; exacerbations several times a year.

• Bronchial asthma during exacerbation - shortness of breath with an extended expiration, wheezing, copious "vitreous" sputum.

• Bronchiectatic disease (suppurative process in irreversibly changed and functionally defective bronchi) - abundant discharge of mucopurulent or purulent sputum in the morning.

• Pulmonary tuberculosis - profuse sputum, possibly with streaks of blood, sweating, weight loss.

• Tumors of the lung - a long-lasting cough in combination with unmotivated weakness; weight loss, hoarseness of the voice, streaks of blood in the sputum are possible.

3). The "threatening" symptoms that make it possible to suspect a patient with a serious illness of the bronchopulmonary system include:

cough that lasts more than a week (especially in those cases when a cough intensifies over time);

cough, accompanied by long-term (weeks) with persisting temperature - 37.5–38 ° C;

cough, accompanied by a high (above 38 ° C) temperature for 3 or more days;

cough, accompanied by shortness of breath, chest pain with breathing;

cough, accompanied by the separation of thick greenish sputum;

cough, accompanied by separation of sputum with streaks of blood;

cough with asthma attacks;

concomitant cough weakness, weight loss;

profuse sweating (especially at night), chills;

sudden attack of severe cough;

severe cough for an hour without a break;

abundant sputum;

voice change.

III. DIRECTIONS OF SYMPTOMATIC TREATMENT OF PATIENTS WITH A COMPLAINT FOR Cough

With dry cough - antitussive drugs of central and peripheral action.

With a wet cough - expectorant and mucolytic drugs.

1). General recommendations for patients

• Refrain from smoking, including passive inhalation of tobacco.

• Ventilate the room more often, as clean, cool air reduces the cough reflex.

• Drink as much fluid as possible, which facilitates sputum removal.

2). OTC drugs used for dry cough and the conditions for their rational use

1. Central action antitussive (narcotic)

Methylmorphine (codeine) Preparations: Kaffetin *, Kodipront *, Codterpin *, Neoco-dion *, Paracodamol *, Solpadein *

Dextromethorphan Preparations: Akodin, Atussin *, Robitussin, Coldrex-night *, Flux *, Coldran *, Mucodex *, Tussin-plus *

2. Central antitussive drugs (non-narcotic)

Glaucine hydrochloride Preparations: Glauvent, Broncholitin

Oxeladine Drugs: Tusuprex, Pakseladin

Butamirate citrate Preparations: Sinecode, Stoptussin *

3. Antitussive drugs of peripheral action (non-narcotic)

Prenoxidiazine Drugs: Libexin, Glibeksin

3). OTC drugs used for wet cough and the conditions for their rational use

1. Expectorant

a. Expectorant Expectorants

Terpinghydrate Preparations: Coldrex *

b. Expectorants for the reflex action of plant origin

Grass Thermopsis

Guaifenesin Preparations: Tussin *, Coldrex, Coldrex-broncho *, Brosolin *, Bron-hotussin *

Licorice root Preparations: Breast elixir *, Collection of chest *, Licorice root extract dry, thick

Althea root Preparations: Mukaltin; Dry marshmallow root extract; syrup altein; Breast collection No. 1, 2, 3; Dry cough syrup for children

Essential oils of medicinal plants

Eucalyptus leaf Drugs: Pectussin, Eumenol, Eucabal

Thyme herb Preparations: Bronchicum *, Liquid extract, Pertussin *

Shoots of Ledum marsh Preparations: Ledin

Elecampane Root Drugs: Pectosol

Other plants Oregano herb Violet grass Sage leaf Peppermint leaf Pine buds

Expectorant means of a resorptive (direct) action

Sodium iodide

Potassium iodide

Sodium bicarbonate

4). Pharmaceutical custody when using expectorant drugs

• Expectorants cannot be combined with drugs that inhibit the cough reflex (codeine, tusuprex, glaucin, etc.) and with histamineolytics that tighten sputum (diphenhydramine, pipolfen, etc.).

• When taking expectorants, you should not prescribe drugs that dehydrate the patient's body (diuretics, laxatives, etc.).

• Expectorant drugs with a reflex action (thermopsis, terpine hydrate, istod, marshmallow, lycorin) can cause vomiting if the dose is exceeded, it is contraindicated in diseases of the stomach (gastritis, peptic ulcer).

• Expectorant preparations should be washed down with a plentiful alkaline drink. It is recommended to drink in addition to the physiological norm 1.5–2 L of liquid to compensate for physiological losses.

• It is not recommended to prescribe expectorants for bedridden patients.

• The clinical effect of expectorants is usually observed no earlier than 6–7 days of treatment.

• In the first 2–3 days of taking expectorant drugs, cough and sputum separation may intensify: these phenomena indicate the effectiveness of the drug (and not vice versa).

• With an overdose or long-term use of drugs containing iodides (potassium iodide, sodium iodide), iodism may occur: rhinitis, urticaria, Quincke's edema; the occurrence of hyperthyroidism is possible - tachycardia, tremor, irritability, insomnia, diarrhea (in people over 40 years old).

• Preparations containing iodides (potassium iodide, sodium iodide) are contraindicated in pregnancy, acute inflammatory processes, and thyroid diseases.

• In the presence of an acute inflammatory process, expectorant preparations of plant origin are preferred.

• Herbal decoctions and infusions (licorice, marshmallow root, coltsfoot, anise, fennel, thyme) not only have an expectorant effect, but also contribute to the regeneration of damaged bronchial mucosa due to the content of trace elements, vitamins and biogenic stimulants.

5). Mucolytics

Bromhexine Preparations: Bizolvon, Bronchosan, Diamelitus, Paxirazole, Solvin, Phlegamine, Flekoksin

Ambroxol hydrochloride Preparations: Ambrobene, Ambrohexal, Ambroxol, Ambrolan, Ambrosan, Ambrosol, Bronhovern, Deflegmin, Dignobroxol, drops of La Zolvan, Medovent, Mukosolvan, Mukolvan, Halixol

Mesna Preparations: Mistabron, Uromitexan

Acetylcysteine Preparations: ACC, ACC injection, ACC long, Mucobene, Mukomist, Muko sanigen, Tussikom, Fluimucil, Exomyuk

Carbocysteine Preparations: Bronkatar, Drill expectorant, Carbocysteine, Mu-codine, Mucopront, Mucosol, Fluifort, Fluvik, Fluditec, Estival

6). Pharmaceutical custody with the use of mucolytic drugs

• Bromhexine and ambroxol may increase liver transaminase activity.

• Bromhexine and ambroxol are incompatible with alkaline solutions, with preparations containing codeine, with anticholinergics.

• Ambroxol increases the penetration of antibiotics into the bronchial secret and bronchial mucosa.

• Ambroxol is contraindicated in the first trimester of pregnancy

• Bromhexine is not prescribed for children under 3 years

• Treatment with acetylcysteine should be started with small doses (100-200 mg), since the effect of large doses is unpredictable and can lead to severe hypersecretion.

• Acetylcysteine can cause pulmonary hemorrhage, disrupt the function of the liver and kidneys, in patients with bronchial asthma - provoke bronchospasm.

• Acetylcysteine is contraindicated in the first trimester of pregnancy, in the future it is used only according to strict indications under the supervision of a doctor.

• When taking acetylcysteine orally, antibiotics should be taken two hours after it is taken.

• Carbocysteine is not recommended for persons with erosive and ulcerative lesions of the gastrointestinal tract.

• Mesna is categorically contraindicated in all situations that make it difficult to expectorate (bronchospasm, weakened patient, etc.), as liquid sputum flows down and causes obstruction (blockage) of small bronchi with the development of atelectasis and respiratory failure.

• When taking Mesna in inhalations, cough and bronchospasm are possible.

• Aminoglycoside antibiotics significantly reduce mesna activity.

The solution of situational problems.

TASK № 1.

Select and dispense the drug to relieve symptoms of the common cold (fever).

A. A pregnant woman is 25 years old.

B. A sick child is 3 years old.

B. A 34-year-old man with a history of gastric ulcer.

To do this, complete the following tasks:

1. Give a brief definition of the term “fever”.

2. Give an algorithm for interviewing a pharmacist with a patient with an emphasis on the elements of pharmaceutical care, using these key questions:

What body temperature is observed?

Are there temperature fluctuations during the day?

What other symptoms accompany a cold?

3. What OTC drugs are used to normalize the temperature for colds? Give the nomenclature of drugs.

4. What are the features of using antipyretic drugs in:

Pregnant women?

children?

In patients with concomitant pathology?

5. What combination drugs are used to relieve the symptoms of a cold? What pharmacological phenomena are the basis of such combinations?

6. What are the criteria for the effectiveness of cold medicines?

7. Give recommendations to the patient on the conditions of rational use of the drug you have chosen (dosing regimen, interaction with food, alcohol, and other medicines).

TASK № 2.

Select and dispense the medicine to eliminate the common cold.

A. A child 2 years old.

B. A 56-year-old man with hypertension.

C. A 32-year-old woman with seasonal allergic rhinitis.

To do this, complete the following tasks:

1. Give a brief definition of runny nose.

2. Give an algorithm for interviewing a pharmacist with a patient with an emphasis on the elements of pharmaceutical care, using these key questions:

When did a runny nose appear?

Is discharge observed from one or both nasal passages?

What is the nature of discharge from the nose?

What other symptoms are accompanied by a runny nose (sneezing, shortness of breath, fever, skin rash)?

3. What are the medications for easing nasal breathing with a runny nose? What pharmacological groups do they belong to?

4. What are the features of the use of drugs against the common cold in children?

5. Give recommendations to the patient (mother) on the conditions of rational use of the drug you have chosen (dosing regimen, appropriate technique and conditions for the procedure for using the drug).

TASK № 3.

Select and dispense the cough remedy.

A. The child is 5 years old.

B. The man is 52 years old.

V. The student is 19 years old.

To do this, complete the following tasks:

1. Give a brief definition of cough.

2. Give an algorithm for interviewing a pharmacist with a patient with an emphasis on the elements of pharmaceutical care, using these key questions:

When did the cough appear?

What other symptoms accompany a cough?

Give a description of the cough (dry or wet, night or day, the nature of sputum, etc.)?

Do you smoke? How long ago? How intense?

How many cigarettes per day?

3. What are the medicines to relieve cough. What pharmacological groups do they belong to?

4. Give recommendations to the patient on the conditions of rational use of the drug you have chosen (dosing regimen, interaction with food, alcohol, and other medicines).

5. What phytochemicals of ectemporal manufacture should be prescribed to a patient?

6. Consult him on the manufacturing technology and the use of the selected herbal medicine

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

PHARMACEUTICAL CARE OF PATIENTS WITH PATHOLOGY OF THE CARDIOVASCULAR SYSTEM

Relevance of the topic

Cardiovascular pathology ranks first in terms of morbidity and mortality in almost all countries of the world. This sad leadership is due to many factors, among which are poor nutrition, poor ecology, and the wrong lifestyle. No wonder many cardiovascular disorders are called diseases of civilization.

Motivational characteristic of the topic.

The circulatory system is one of the integrating systems of the body. Normally, it optimally meets the needs of organs and tissues in the blood supply. In this case, the level of systemic circulation is determined:

• activity of the heart;

• vascular tone;

• blood condition - the value of its total and circulating mass, as well as rheological properties.

Dysfunctions of the heart, vascular tone, or changes in the blood system can lead to circulatory failure - a condition in which the circulatory system does not meet the needs of tissues and organs for the delivery of oxygen and metabolic substrates to them with blood, as well as transport of carbon dioxide and metabolites from tissues

The main causes of circulatory failure:

• heart pathology;

• violation of the tone of the walls of blood vessels;

• changes in the mass of circulating blood and / or its rheological properties.

According to the severity of development and nature of the course, acute and chronic circulatory failure is distinguished.

Acute circulatory failure develops within hours or days. The most common causes of it may be:

• acute myocardial infarction;

• some types of arrhythmias;

• shock;

• acute blood loss.

Chronic circulatory failure develops over the course of several months or years and its causes are:

• chronic inflammatory heart disease;

• cardiosclerosis;

• heart defects

• hyper- and hypotensive conditions;

• anemia.

According to the severity of signs of circulatory failure, 3 stages are distinguished. At stage I, signs of circulatory failure (shortness of breath, palpitations, venous congestion) are absent at rest and are detected only with physical exertion. In stage II, these and other signs of circulatory failure are found both at rest, and especially with physical exertion. At stage III, significant disturbances in cardiac activity and hemodynamics at rest are observed, as well as the development of pronounced dystrophic and structural changes in organs and tissues.

PATHOLOGY OF CARDIAC ACTIVITY

The main part of various pathological processes affecting the heart are three groups of typical forms of pathology: coronary insufficiency, arrhythmias and heart failure.

1. Coronary insufficiency is characterized by an excess of myocardial demand for oxygen and metabolic substrates over their inflow through the coronary arteries.

Types of coronary insufficiency:

• reversible (transient) coronary blood flow disorders; they include angina pectoris, characterized by severe compressive pain in the sternum, resulting from myocardial ischemia;

• irreversible cessation of blood flow or a long-term significant decrease in blood flow through the coronary arteries, which ends, as a rule, with myocardial infarction.

The mechanisms of heart damage in coronary insufficiency.

The lack of oxygen and metabolic substrates in the myocardium with coronary insufficiency (angina pectoris, myocardial infarction) determines the development of a number of common, typical mechanisms of myocardial damage:

• disorder of the processes of energy supply of cardiomyocytes;

• damage to their membranes and enzymes;

• imbalance of ions and liquids;

• disorder of the mechanisms of regulation of cardiac activity.

Changes in the basic functions of the heart in coronary insufficiency primarily consist in violations of its contractile activity, an indicator of which is a decrease in stroke and cardiac output.

2. Arrhythmias - a pathological condition caused by a violation of the heart rhythm. They are characterized by a change in the frequency and periodicity of the generation of excitation pulses or the sequence of excitation of the atria and ventricles. Arrhythmias are a complication of many diseases of the cardiovascular system and the main cause of sudden death in cardiac pathology.

Types of arrhythmias, their etiology and pathogenesis. Arrhythmias are the result of a violation of one, two or three basic properties of the heart muscle: automatism, conduction and excitability.

Arrhythmias as a result of a violation of automatism, that is, the ability of heart tissue to generate an action potential (“stimulation pulse”). These arrhythmias are manifested by a change in the frequency and regularity of the generation of pulses by the heart, and can occur in the form of tachycardia and bradycardia.

Arrhythmias as a result of a violation of the ability of heart cells to conduct an excitation pulse.

The following types of conduction disturbances are distinguished:

• slowdown or blockade of conduct;

• acceleration of conduct.

Arrhythmias as a result of disturbances in the excitability of cardiac tissue.

Excitability is the property of cells to perceive the action of an irritant and to react to it with an excitation reaction.

Such arrhythmias include extrasystole. paroxysmal tachycardia and atrial or ventricular fibrillation (flickering).

Extrasystole is an extraordinary, premature impulse that causes contraction of the whole heart or its departments. In this case, the correct sequence of heart contractions is violated.

Paroxysmal tachycardia is a paroxysmal, sudden increase in the frequency of impulses of the correct rhythm. The frequency of ectopic pulses is from 160 to 220 per minute.

Atrial or ventricular fibrillation (flickering) is an irregular, erratic electrical activity of the atria and ventricles, accompanied by the cessation of the effective pumping function of the heart.

3. Heart failure - a syndrome that develops with many diseases that affect various organs and tissues. Moreover, the heart does not provide for their need for blood supply adequate to their function.

The etiology of heart failure is mainly associated with two groups of causes: direct damage to the heart - trauma, inflammation of the membranes of the heart, prolonged ischemia, myocardial infarction, toxic damage to the heart muscle, etc., or functional overload of the heart as a result of:

• an increase in the volume of blood flowing to the heart and increasing the pressure in its ventricles with hypervolemia, polycythemia, heart defects;

• resistance to the expulsion of blood from the ventricles to the aorta and pulmonary artery, which occurs with arterial hypertension of any genesis and some heart defects.

Types of heart failure

In the predominantly affected part of the heart:

• left ventricular, which develops as a result of damage or overload of the left ventricular myocardium;

• right ventricular, which is usually the result of overload of myocardium of the right ventricle, for example, with chronic obstructive pulmonary diseases - bronchiectasis, bronchial asthma, emphysema, pneumosclerosis, etc.

By development speed:

Acute (minutes, hours). It is the result of heart wounds, acute myocardial infarction, pulmonary embolism, hypertensive crisis, acute toxic myocarditis, etc.

Chronic (months, years). It is a consequence of chronic arterial hypertension, chronic respiratory failure, prolonged anemia, chronic heart defects.

Dysfunctions of the heart and central hemodynamics. A decrease in the strength and speed of contraction, as well as myocardial relaxation in case of cardiac insufficiency, is manifested by a change in indicators of heart function, central and peripheral hemodynamics.

Among the main ones are:

• reduction of shock and cardiac output, which develops as a result of depression of myocardial contractile function;

• an increase in the residual systolic blood volume in the cavities of the ventricles of the heart, which is a consequence of incomplete systole;

DISEASES OF THE CARDIOVASCULAR SYSTEM

A group of diseases of the cardiovascular system consists of such common diseases as atherosclerosis, hypertension, coronary heart disease, inflammatory heart diseases and its defects, as well. also vascular disease. At the same time, atherosclerosis, hypertension, and coronary heart disease (CHD) are characterized by the highest morbidity and mortality worldwide, although these are relatively “young” diseases and they acquired their significance only at the beginning of the 20th century. I. V. Davydovsky called them “diseases of civilization”, caused by a person’s inability to adapt to rapidly progressing urbanization and the changes in people's lifestyle associated with it, constant stressful influences, environmental disruptions and other features of a “civilized society”.

The etiology and pathogenesis of atherosclerosis and hypertension have much in common. However, coronary heart disease. which: is now regarded as an independent disease, is essentially a cardiac form of atherosclerosis and hypertension. However, due to the fact that the main mortality is associated with myocardial infarction, which is the essence of IHD. by decision of WHO, it acquired the status of an independent nosological unit.

ATHEROSCLEROSIS

Atherosclerosis is a chronic disease of the large and medium arteries (elastic and muscular-elastic type), associated with a violation in the main fat and protein metabolism.

This disease is extremely widespread throughout the world, as the signs of atherosclerosis are found in all people over 30-35 years old, although they are expressed to varying degrees. Atherosclerosis is characterized by focal deposits in the walls of large arteries of lipids and proteins, around which connective tissue grows, resulting in the formation of atherosclerotic plaque.

The etiology of atherosclerosis is not fully disclosed, although it is generally recognized that this is a polyetiological disease caused by a combination of changes in fat-protein metabolism and damage to the endothelium of the intima of the arteries. The causes of metabolic disorders, as well as factors damaging the endothelium, can be different, but extensive epidemiological studies of atherosclerosis have allowed us to identify the most significant effects, which are called risk factors.

These include:

• age, since an increase in the frequency and severity of atherosclerosis with age is not in doubt;

• gender - in men, the disease develops earlier than in women, and proceeds harder, more often complications arise;

• heredity - the existence of genetically determined forms of the disease has been proven;

• hyperlipidemia (hypercholesterolemia) - a leading risk factor, due to the predominance in the blood of low density lipoproteins over lipoproteins and high density, which is primarily associated with eating habits;

• arterial hypertension, which leads to an increase in the permeability of the vascular walls, including for lipoproteins, as well as damage to the intima endothelium;

• stressful situations are the most important risk factor, since they lead to psychoemotional overstrain, which causes neuroendocrine regulation of fat-protein metabolism and vasomotor disorders;

• smoking - atherosclerosis in smokers develops 2 times more intensively and occurs 2 times more often than non-smokers;

• hormonal factors, since most hormones affect the violation of fat-protein metabolism, which is especially manifested in diabetes mellitus and hypothyroidism. Oral contraceptives are close to these risk factors, provided they have been used for more than 5 years;

• obesity and lack of exercise contribute to the violation of fat-protein metabolism and the accumulation of low density lipoproteins in the blood.

The patho- and morphogenesis of atherosclerosis consists of several stages

The dolipid stage is characterized by the appearance in the intima of the arteries of the fat-protein complexes in amounts that are still not visible to the naked eye and there are no atherosclerotic plaques.

The stage of ltoidosis reflects the accumulation in the intima of the vessels of fat-protein complexes, which become visible in the form of fat spots and yellow stripes. Under the microscope, structureless fat-protein masses are determined, around which macrophages, fibroblasts and lymphocytes are located.

The stage of liposclerosis develops as a result of proliferation of connective tissue around the fat-protein masses and a fibrous plaque forms, which begins to rise above the surface of the intima. An intima is sclerosed above the plaque - a plaque tire is formed, which can be hyalinized. Fibrous plaques are the main form of atherosclerotic vascular disease. They are located in places of the greatest hemodynamic effect on the artery wall - in the area of branching and bending of blood vessels.

The stage of complicated lesions includes three processes: atheromatosis, ulceration, and calcification.

Atheromatosis is characterized by the breakdown of fat-protein masses in the center of the plaque with the formation of amorphous gruel-like detritus containing residues of collagen and elastic fibers of the vessel wall, cholesterol crystals, saponified fats, and coagulated proteins. The middle shell of the vessel under the plaque often atrophies.

An ulceration is often preceded by a hemorrhage in a plaque. At the same time, the lid of the plaque ruptures and the atheromatous masses fall into the lumen of the vessel. A plaque is an atheromatous ulcer that is covered by thrombotic masses.

Calcification completes the morphogenesis of the atherosclerotic plaque and is characterized by the precipitation of calcium salts in it. Calcification, or petrification, of plaque occurs, which acquires a stony density

The course of atherosclerosis is undulating. With the progression of the disease, intimal lipoidosis increases, with the disease subsiding around the plaques, the proliferation of connective tissue and the deposition of calcium salts increase in them.

Clinical and morphological forms of atherosclerosis. Manifestations of atherosclerosis depend on which large arteries are affected. For clinical practice, atherosclerotic lesions of the aorta, coronary arteries of the heart, cerebral arteries and limb arteries are of the greatest importance.

Aortic atherosclerosis is the most frequent localization of atherosclerotic changes, which are most pronounced here.

Typically, plaques form in the area of discharge from the aorta of smaller vessels. The arc and abdominal aorta, where large and small plaques are located, are more affected. When plaques reach the stages of ulceration and athero-calcification, blood flow disturbances occur at their locations and parietal thrombi form. When they come off, they turn into thrombotic emboli, clog the arteries of the spleen, kidneys and other organs, causing heart attacks. The ulceration of the atherosclerotic plaque and the destruction of the elastic fibers of the aortic wall in this regard can contribute to the formation of aneurysm, a saccular protrusion of the vessel wall filled with blood and thrombotic masses. Aneurysm rupture leads to rapid massive blood loss and sudden death.

Atherosclerosis of the arteries of the brain, or cerebral form, is characteristic of elderly and old patients. With significant stenosis of the lumen of the arteries with atherosclerotic plaques, the brain constantly experiences oxygen starvation; and gradually atrophies. Such patients develop atherosclerotic dementia. If the lumen of one of the cerebral arteries is completely closed by a thrombus, ischemic heart attack occurs in the form of foci of its gray softening. Atherosclerosis-afflicted cerebral arteries become fragile and can rupture. A hemorrhage occurs - a hemorrhagic stroke, in which the corresponding area of brain tissue dies. The course of hemorrhagic stroke depends on its location and massiveness. If hemorrhage occurred in the bottom of the IV ventricle or the spilled blood broke into the lateral ventricles of the brain, then quick death occurs. With ischemic infarction, as well as with small hemorrhagic strokes that did not lead the patient to death, the dead brain tissue gradually dissolves and a cavity containing liquid forms in its place - a brain cyst. Ischemic infarction and hemorrhagic brain stroke are accompanied by neurological disorders. Surviving patients develop paralysis, speech often suffers, and other dyspepsia appear. When

appropriate treatment over time, it is possible to restore part of the lost functions of the central nervous system.

Atherosclerosis of the vessels of the lower extremities is also more common in old age. With a significant narrowing of the lumen of the arteries of the legs or feet with atherosclerotic plaques, the tissues of the lower extremities undergo ischemia. With an increase in the load on the muscles of the limbs, for example when walking, pain appears in them, and patients are forced to stop. This symptom is called intermittent claudication. In addition, cooling and atrophy of limb tissues are noted. If the lumen of stenotic arteries is completely closed by a plaque, thrombus or embolus, patients develop atherosclerotic gangrene.

In the clinical picture of atherosclerosis, the defeat of the renal and intestinal arteries can most clearly appear, however, these forms of the disease are less common.

HYPERTONIC DISEASE

Hypertension is a chronic disease characterized by a prolonged and persistent increase in blood pressure (BP) - systolic above 140 mm Hg. Art. and diastolic - above 90 mm RT. Art.

Men get sick more often than women. The disease usually begins at 35–45 years and progresses to 55–58 years, after which blood pressure often stabilizes at elevated values. Sometimes a persistent and rapidly increasing increase in blood pressure develops in young people.

Etiology.

The basis of hypertension is a combination of 3 factors:

• chronic psycho-emotional overstrain;

• a hereditary defect in cell membranes, leading to disruption of the exchange of Ca2 + and Na2 + ions;

• a genetically determined defect in the renal volumetric mechanism of blood pressure regulation.

Risk factors:

• genetic factors are not in doubt, since hypertensive disease is often family-related;

• repeated emotional stress;

• diet with high consumption of table salt;

• hormonal factors - increased pressor influences of the hypothalamic-pituitary system, excessive secretion of catecholamines and activation of the renin-angiotensin system;

• renal factor;

• obesity;

• smoking;

• physical inactivity, sedentary lifestyle.

Patho- and morphogenesis.

Hypertension is characterized by staged development.

The transient, or preclinical, stage is characterized by periodic rises in blood pressure. They are caused by a spasm of arterioles, during which the wall of the vessel itself experiences oxygen starvation, causing dystrophic changes in it. As a result, the permeability of the walls of the arterioles increases. They are impregnated with blood plasma (plasmorrhagia), which also extends beyond the vessels, causing perivascular edema.

After normalizing the blood pressure level and restoring microcirculation, blood plasma from the walls of arterioles and perivascular spaces is removed into the lymphatic system, and the blood proteins that get into the walls of the vessels together with the plasma precipitate. Due to the repeated increase in the load on the heart, moderate compensatory hypertrophy of the left ventricle develops. If the conditions causing psycho-emotional overstrain are eliminated in the transient stage and appropriate treatment is performed, the onset of hypertension can be cured, since irreversible morphological changes are still absent in this stage.

The vascular stage is clinically characterized by a persistent increase in blood pressure. This is due to deep dysregulation of the vascular system and its morphological changes. The transition from a transient increase in blood pressure to a stable one is associated with the action of several neuroendocrine mechanisms, among which the most important are reflex, renal, vascular, membrane and endocrine. Often repeated rises in blood pressure lead to a decrease in the sensitivity of the baroreceptors of the aortic arch, which normally provide a weakening of the activity of the sympathetic-adrenal system and a decrease in blood pressure. The increased influence of this regulatory system and spasm of the renal arterioles stimulate the production of the renin enzyme. The latter leads to the formation of angiotensin in blood plasma, which stabilizes blood pressure at a high level. In addition, angiotensin enhances the formation and release of mineralocorticoids from the adrenal cortex, which further increase blood pressure and also contribute to its stabilization at a high level.

Repeated with increasing frequency of arterioles spasms, increasing plasmorrhagia and an increasing number of precipitated protein masses in their walls lead to hyalinosis, or parteriosclerosis. The walls of arterioles become denser, lose their elasticity, their thickness increases significantly and the lumen of the vessels decreases accordingly.

Constant high blood pressure significantly increases the load falling on the heart, as a result of which its compensatory hypertrophy develops (Fig. 48, b). Moreover, the heart weight reaches 600-800 g. A constant high blood pressure increases the load on large arteries, as a result of which muscle cells atrophy and the elastic fibers of their walls lose their elasticity. In combination with changes in the biochemical composition of blood, the accumulation of cholesterol and large molecular proteins in it, the prerequisites for the development of atherosclerotic lesions of large arteries are created. Moreover, the severity of these changes is much greater than with atherosclerosis, which is not accompanied by an increase in blood pressure.

Stage of organ changes.

Changes in the organs are secondary. Their severity, as well as clinical manifestations, depend on the degree of damage to the arterioles and arteries, as well as on the complications associated with these changes. The basis of chronic organ changes is not their circulatory disturbance, increasing oxygen starvation and caused by they have organ sclerosis with decreased function.

During the course of hypertension, a hypertensive crisis, that is, a sharp and prolonged increase in blood pressure due to spasm of the arterioles, is of utmost importance. The hypertensive crisis has its morphological expression: spasm of arterioles, plasmorrhagia and fibrinoid necrosis of their walls, perivascular diapedetic hemorrhages. These changes that occur in organs such as the brain, heart, and kidneys often lead patients to death. A crisis can occur at any stage of the development of hypertension. Frequent crises characterize the malignant course of the disease, which is usually found in young people.

Complications of hypertension, manifested by spasm, thrombosis of arterioles and arteries or their rupture, lead to heart attacks or hemorrhages in organs, which are usually the cause of death.

Clinical and morphological forms of hypertension.

Depending on the prevalence of damage to bodies or other organs, cardiac, cerebral and renal clinical and morphological forms of hypertension are distinguished.

The heart form, like the heart form of atherosclerosis, is the essence of coronary heart disease and is considered as an independent disease.

The cerebral or cerebral form is one of the most common forms of hypertension.

Usually it is associated with the rupture of a hyalinized vessel and the development of massive hemorrhage in the brain (hemorrhagic stroke) as a hematoma. A breakthrough of blood into the ventricles of the brain always ends with the death of the patient. Ischemic cerebral infarction can also occur with hypertension, although much less frequently than with atherosclerosis. Their development is associated with thrombosis or spasm of atherosclerotic altered middle cerebral arteries or arteries of the base of the brain.

Renal form. In the chronic course of hypertension, arteriolosclerotic nephrosclerosis develops, associated with hyalinosis that brings arterioles. A decrease in blood flow leads to atrophy and hyalinosis of the corresponding clubs. Their function is performed by preserved glomeruli, which undergo hypertrophy.

Therefore, the surface of the kidneys acquires a granular appearance: hyalinized glomeruli and atrophied, sclerotic, nephrons sink, and hypertrophic glomeruli protrude above the surface of the kidneys (Fig. 48, c, 49). Gradually sclerotic processes begin to prevail and primary shriveled kidneys develop. At the same time, chronic renal failure is increasing, which culminates in uremia.

Symptomatic hypertension (hypertension). Hypertension is called an increase in blood pressure of a secondary nature - a symptom in various diseases of the kidney, endocrine glands, blood vessels. If it is possible to eliminate the underlying disease, hypertension also disappears. So, after removal of a

tumor of the adrenal gland - pheochromocytoma. accompanied by significant hypertension, BP normalizes as well. Therefore, hypertension should be distinguished from symptomatic hypertension.

ISCHEMIC HEART DISEASE (CHD)

Coronary or coronary heart disease is a group of diseases caused by absolute or relative insufficiency of coronary blood circulation, which is manifested by a mismatch between the oxygen demand of the myocardium and its delivery to the heart muscle. In 95% of cases, IHD is caused by atherosclerosis of the coronary arteries. It is coronary heart disease that acts as the main cause of mortality. Latent (preclinical) coronary heart disease is found in 4-6% of people over 35 years of age. More than 5 million patients are registered annually in the world. And BS and more than 500 thousand of them die. Men get sick earlier than women, however, after 70 years, men and women suffer from ischemic heart disease equally often.

Forms of coronary heart disease. There are 4 forms of the disease:

• sudden coronary death occurring due to cardiac arrest in a person 6 hours before that did not show heart complaints;

• angina pectoris - a form of ischemic heart disease, characterized by bouts of sternal pain with ECG changes, but without the appearance of characteristic enzymes in the blood;

• myocardial infarction - acute focal ischemic (circulatory) necrosis of the heart muscle, developing as a result of a sudden violation of the coronary circulation;

• cardiosclerosis - chronic coronary heart disease (CHD) - the outcome of angina pectoris or myocardial infarction; based on cardiosclerosis, a chronic aneurysm of the heart can form.

The course of coronary disease can be acute and chronic. Therefore, acute IHD (angina pectoris, sudden coronary death, myocardial infarction) and ihronic IHD (cardiosclerosis in all its manifestations) are distinguished.

Risk factors are the same as for atherosclerosis and hypertension.

The etiology of ischemic heart disease is fundamentally the same as the etiology of atherosclerosis and hypertension. More than 90% of IHD patients suffer from stenosing atherosclerosis of the coronary arteries with a degree of narrowing of at least one of them to 75% and higher. In this case, blood flow adequate even to a small physical load cannot be provided.

The pathogenesis of various forms of ischemic heart disease

The development of various types of acute coronary heart disease is associated with acute disturbance of coronary circulation, which leads to ischemic damage to the heart muscle.

The extent of these lesions depends on the duration of ischemia.

1. Angina pectoris is characterized by reversible myocardial ischemia associated with stenosing coronary sclerosis, and is a clinical form of all types of coronary heart disease. It is characterized by attacks of constricting pain and a burning sensation in the left half of the chest with radiation to the left arm, the region of the scapula, neck, and lower jaw. Attacks occur during physical exertion, emotional stress, etc., and are stopped by the use of vasodilators. If death occurs during an attack of angina pectoris, lasting 3-5 or even 30 minutes, morphological changes in the myocardium can be detected only using special techniques, since the heart is not macroscopically changed.

2. Sudden coronary death is due to the fact that in case of acute ischemia in the myocardium 5-10 minutes after the attack arshmogenic substances can be formed - substances that cause electrical instability of the heart and create the preconditions for fibrillation of its ventricles. At the autopsy of

the dead due to myocardial fibrillation, the heart is flabby, with an expanded cavity of the left ventricle. Microscopically expressed fragmentation of muscle fibers.

3. Myocardial infarction.

The etiology of acute myocardial infarction is associated with a sudden cessation of coronary blood flow, either due to obstruction of the coronary artery by a thrombus or embolus, or as a result of a prolonged spasm of an atherosclerotic altered coronary artery.

The pathogenesis of myocardial infarction is largely determined by that. that the preserved lumens of the three coronary arteries in total amount to only 34% of the average norm, while the "critical amount" of these lumens should be at least 35%, because even then the total blood flow in the coronary arteries drops to the minimum acceptable level.

Three stages are distinguished in the dynamics of myocardial infarction, each of which is characterized by its morphological features.

The ischemic stage, or stage of ischemic dystrophy, develops in the first 18-24 hours after clogging of the coronary artery with a thrombus. Macroscopic changes in the myocardium at this stage are not visible. Microscopic examination shows dystrophic changes in muscle fibers in the form of fragmentation, loss of transverse striation, and myocardial stroma. Microcirculatory disorders are expressed in the form of stasis and sludge in capillaries and venules, there are diapedemic hemorrhages. In areas of ischemia, glycogen and redox enzymes are absent. An electron microscopic study of cardiomyocytes from the site of myocardial ischemia reveals swelling and destruction of mitochondria, the disappearance of glycogen granules, sarcoplasma edema, myofilament overexposure These changes are associated with hypoxia, electrolyte imbalance and metabolic termination in areas of myocardial ischemia. During this period, microcirculatory disturbances and stromal edema develop in myocardial areas unaffected by ischemia.

Death in the ischemic stage occurs from cardiogenic shock, ventricular fibrillation, or cardiac arrest (asystole).

Necrotic stage of myocardial infarction develops at the end of the first day after an attack of angina pectoris. At autopsy, in the area of a heart attack, fibrinous pericarditis is often observed. On the section of the heart muscle, yellowish, irregular foci of myocardial necrosis are clearly visible, surrounded by a red strip of hyperemic vessels and hemorrhages - ischemic infarction with a hemorrhagic corolla. Histological examination reveals foci of muscle tissue necrosis, limited from the unaffected myocardium with the demarcation (border) line of the line, presented infiltration and hyperemic vessels

Outside of the infarction sites during this period, microcirculation disorders, marked dystrophic changes in cardiomyocytes, and destruction of many mitochondria simultaneously with an increase in their number and volume develop.

The stage of organization of myocardial infarction begins immediately after the development of necrosis. White blood cells and macrophages clear the field of inflammation from necrotic masses. Fibroblasts appear in the demarcation zone. producing collagen. The focus of necrosis is initially replaced by granulation tissue, which matures in about 4 weeks into coarse-fibrous connective tissue. Myocardial infarction is organized, and a scar remains in its place. Large-focal cardiosclerosis occurs. During this period, the myocardium around the scar and the myocardium of all other parts of the heart, especially the left ventricle, undergoes regenerative hypertrophy. This allows you to gradually normalize the function of the heart.

Thus, acute myocardial infarction lasts 4 weeks. If during this period a patient develops a new myocardial infarction, then it is called recurrent. If a new myocardial infarction develops after 4 weeks or more after the first heart attack, then it is called repeated.

Complications can occur already in the necrotic stage. So, the necrosis site undergoes melting - myomalacia, as a result of which the myocardial wall can rupture in the area of myocardial infarction, filling the pericardial cavity with blood - cardiac tamponade, leading to sudden death.

Myomalacia can lead to swelling of the ventricular wall and the formation of acute cardiac aneurysm. In case of rupture of the aneurysm, cardiac tamponade also occurs. If an acute aneurysm does not burst, blood clots form in its cavity, which can become a source of thromboembolism of the vessels of the brain, spleen, kidneys and coronary arteries themselves. Gradually, in an acute aneurysm of the heart, blood clots are replaced by connective tissue, however, thrombotic masses persist or form in the formed cavity of the aneurysm. Aneurysm becomes chronic. Thrombotic embolism can be a source of thrombotic overlay on the endocardium in the area of a heart attack. Death in the necrotic stage can also occur from ventricular fibrillation of the heart.

Outcomes. Acute myocardial infarction can result in acute heart failure, often with the development of pulmonary edema and swelling of the substance of the brain. The outcome is also large focal cardiosclerosis and chronic ischemic heart disease.

4. Chronic coronary heart disease

The morphological expression of chronic coronary heart disease are:

• severe atherosclerotic small focal cardiosclerosis;

• postinfarction macrofocal cardiosclerosis;

• chronic heart aneurysm in combination with atherosclerosis of coronary arteries. It occurs in cases when, after an extensive myocardial infarction, the resulting scar tissue begins to swell under blood pressure, thinns and a saccular protrusion forms. Due to the turbulence in the aneurysm, blood clots appear, which can become a source of thromboembolism. Chronic heart aneurysm in most cases is the cause of increasing chronic heart failure.

All these changes are accompanied by a moderately pronounced regenerative myocardial hypertrophy.

Clinically, chronic coronary heart disease is manifested by angina pectoris and the gradual development of chronic cardiovascular failure, resulting in the death of the patient. At any stage of chronic coronary heart disease, acute or repeated myocardial infarction may occur.

Causes of heart inflammation are various infections and intoxications. The inflammatory process can affect one of the membranes of the heart or its entire wall. Endocardial inflammation is endocarditis, myocardial inflammation is myocarditis, pericardium is pericarditis, and inflammation of all heart membranes is pancreatitis.

Endocarditis.

Inflammation of the endocardium usually extends only to a certain part of it, covering either the valves of the heart, or their chords, or the walls of the stripes of the heart. With endocarditis, a combination of processes characteristic of inflammation is observed - alteration, exudation and proliferation. Clinical endocarditis is of the greatest importance in the clinic. More often than others, a bicuspid valve is affected, somewhat less often - an aortic valve, quite rarely there is inflammation of the valves of the right half of the heart. Alterations are either only the surface layers of the valve, or it is affected entirely, to the full depth. Often, alteration of the valve leads to ulceration and even perforation. In the area of valve destruction, thrombotic masses (thromboendocarditis) are usually formed in the form of warts or polyps. Exudative changes consist in impregnating the valve with blood plasma and infiltrating it with exudate cells. In this case, the valve swells and becomes thicker. The productive phase of inflammation ends with sclerosis, thickening, deformation and fusion of the valve cusps, which leads to heart disease.

Endocarditis dramatically complicates the course of the disease in which it developed, since heart function is severely affected. In addition, thrombotic overlay on the valves can become a source of thromboembolism.

Valvular endocarditis results in heart defects and heart failure.

Myocarditis.

Inflammation of the heart muscle usually complicates various diseases, not being an independent disease. In the development of myocarditis, an infectious lesion of the heart muscle with viruses, rickettsia, and bacteria that reach the myocardium with a blood stream, i.e., through the hematogenous route, is important. Myocarditis is acute or chronic. Depending on the prevalence of a particular phase, myocardial inflammation can be alternative, exudative, productive (proliferative).

The acute course of exudative and productive myocarditis can cause acute heart failure. In a chronic course, they lead to diffuse cardiosclerosis, which in turn can lead to the development of chronic heart failure.

Pericarditis.

Inflammation of the outer lining of the heart occurs as a complication of other diseases and occurs either in the form of exudative or chronic adhesive pericarditis.

Exudative pericarditis, depending on the nature of the exudate, can be serous, fibrinous, purulent, hemorrhagic and mixed.

Serous pericarditis is characterized by the accumulation of serous exudate in the pericardial cavity, which often resolves without any particular consequences in the event of a favorable outcome of the underlying disease.

Fibrinous pericarditis develops more often with intoxication, for example, with uremia, as well as with myocardial infarction, rheumatism, tuberculosis and a number of other diseases. Fibrinous exudate accumulates in the pericardial cavity and fibrin bundles appear in the form of hairs on the surface of its leaves (“hairy heart”). With the organization of fibrinous exudate, dense adhesions form between the pericardial leaves.

Purulent pericarditis most often occurs as a complication of inflammatory processes in nearby organs - the lungs, pleura, mediastinum, lymph nodes of the mediastinum, from which the inflammation spreads to the pericardium.

Hemorrhagic pericarditis develops with cancer metastases in the heart.

Acute exudative pericarditis may result in cardiac arrest.

Chronic adhesive pericarditis is characterized by exudative-productive inflammation, often developing with tuberculosis and rheumatism. In this type of pericarditis, the exudate does not dissolve, but undergoes organization. As a result, commissures form between the leaves of the pericardium, then the pericardial cavity is completely overgrown, sclerosed. squeezing the heart. Often calcium salts are deposited in the scar tissue and a “shell-like heart” develops.

The outcome of such pericarditis is chronic heart failure.

FAULTS OF THE HEART

Heart defects are a frequent pathology, usually only subject to surgical treatment. The essence of heart defects is to change the structure of its individual parts or large vessels departing from the heart. This is accompanied by impaired cardiac function and general circulatory disorders. Heart defects can be congenital and acquired.

Congenital heart thresholds are the result of embryonic development disorders associated either with genetic changes in embryogenesis or with diseases carried by the fetus during this period. Most often among this group of heart defects, there is a non-closure of the oval window, arterial duct, interventricular septum and Fallot tetrad.

Non-oval window. Through this hole in the atrial septum, blood from the left atrium enters the right, then into the right ventricle and into the pulmonary circulation. In this case, the right departments of the heart are filled with blood, and in order to remove it from the right ventricle to the pulmonary trunk, a constant increase in the work of the myocardium is necessary. This leads to hypertrophy of the right ventricle, which allows the heart to cope with circulatory disorders in it for some time. However, if the oval window is not closed operatively, then decompensation of the myocardium of the right heart department will develop. If the defect in the atrial septum is very large, then venous blood from the right atrium, bypassing the small circle of blood circulation, can enter the left atrium and here mix with arterial blood. As a result of this, mixed blood, poor in oxygen, circulates in a large circle of blood circulation. The patient develops hypoxia and cyanosis.

Non-proliferation of the arterial (botallic) duct In the fetus, the lungs do not function, and therefore blood flows through the tall duct from the pulmonary trunk directly into the aorta, bypassing the pulmonary circulation. Normally, the arterial duct overgrows 15-20 days after the birth of the baby. If this does not happen, then blood from the aorta, in which high blood pressure, through the botalls, the duct enters the pulmonary trunk. The amount of blood and blood pressure in it increase, in the pulmonary circulation increases the amount of blood that enters the left heart. The load on the myocardium increases and hypertrophy of the left ventricle and left atrium develops. Gradually, sclerotic changes develop in the lungs, contributing to an increase in pressure in the pulmonary circulation. This makes the right ventricle work more intensively, as a result of which its hypertrophy also develops. With far-reaching changes in the pulmonary circulation in the pulmonary trunk, the pressure may become higher than in the aorta, in which case venous blood from the pulmonary trunk through the arterial duct partially passes into the aorta. Mixed blood enters the large circle of blood circulation, the patient develops hypoxia and cyanosis.

Ventricular septal defect. In this defect, blood from the left ventricle enters the right ventricle, causing it to overload and hypertrophy (Fig. 54, C, D). Sometimes the interventricular septum may be completely absent (three-chambered heart). Such a vice is incompatible with life, although for some time newborns with a three-chambered heart can live.

The FALLO tetrad is a ventricular septal defect that is combined with other abnormalities in the development of the heart: narrowing of the pulmonary trunk, aortic discharge from the left and right ventricles at the same time as right ventricular hypertrophy. This defect occurs in 40-50% of all heart defects in newborns. With a defect such as tetralogy of Fallot, blood flows from the right parts of the heart to the left. At the same time, less blood enters the small circle of blood circulation than necessary, and mixed blood enters the large circle of blood circulation. The patient develops hypoxia and cyanosis.

Acquired heart defects in the vast majority of cases are the result of inflammatory diseases of the heart and its valves. The most common cause of acquired heart defects is rheumatism, and sometimes they are associated with endocarditis of a different etiology.

Pathogenesis.

As a result of inflammatory changes and sclerosis of the valve cusps, the valves are deformed, become dense, lose their elasticity and cannot completely close the atrioventricular openings or the mouth of the aorta and pulmonary trunk. In this case, a heart defect is formed, which can have various options.

Valve insufficiency develops with incomplete closure of the atrioventricular opening. In case of insufficiency of bicuspid or tricuspid valves, blood during systole enters not only the aorta or

pulmonary trunk, but also back to the atria. If there is insufficiency of the valves of the aorta or pulmonary artery, then during diastole the blood partially enters the ventricles of the heart.

Stenosis, or narrowing of the openings, between the atrium and ventricles develops not only with inflammation and sclerosis of the heart valves, but also with partial fusion of their valves. In this case, the atrioventricular opening or the mouth of the pulmonary artery or the opening of the aortic cone becomes smaller.

Combined heart disease occurs with a combination of stenosis of the atrioventricular opening and valve insufficiency. This is the most common type of acquired heart disease. With a combined malformation of a bicuspid or tricuspid valve, an increased blood volume during diastole cannot enter the ventricle without the additional efforts of the myocardium of the atrium, and during systole, the blood partially returns from the ventricle to the atrium, which is full of blood. In order to prevent overstretching of the atrial cavity, as well as to ensure that the necessary volume of blood enters the vascular bed, the force of contraction of the myocardium of the atrium and ventricle is compensated, as a result of which its hypertrophy develops. However, the constant overflow of blood, for example, of the left atrium with stenosis of the atrioventricular opening and bicuspid valve insufficiency leads to the fact that blood from the pulmonary veins cannot completely enter the left atrium. There is stagnation of blood in the pulmonary circulation, and this complicates the flow of venous blood from the right ventricle into the pulmonary artery. To overcome high blood pressure in the pulmonary circulation, the force of contraction of the myocardium of the right ventricle rises and the heart muscle also hypertrophies. Compensatory (working) hypertrophy of the heart develops.

Chronic heart failure and decompensation of the heart, which develops after a certain time, usually counted for years or decades, is the outcome of acquired heart defects, if the valve defect is not eliminated surgically.

VASCULAR DISEASES

Vascular diseases can be congenital and acquired.

CONGENITAL VASCULAR DISEASES

Congenital vascular diseases are characterized by malformations, among which congenital aneurysms, coarctation of the aorta, arterial hypoplasia and atresia of the veins are of the greatest importance.

Congenital aneurysms are focal protrusions of the vascular wall caused by a defect in its structure and hemodynamic load.

Aneurysms have the appearance of small saccular formations, sometimes multiple, up to 1.5 cm in size. Among them, aneurysms of the intracerebral arteries are especially dangerous, since their rupture leads to subarachnoid or intracerebral hemorrhage. The causes of aneurysms are congenital absence of smooth muscle cells in the vessel wall and a defect in elastic membranes. Arterial hypertension contributes to the formation of aneurysms.

Coarctation of the aorta is a congenital narrowing of the aorta, usually in the area of transition of the arch to the descending part. The defect is manifested by a sharp increase in arterial pressure on the upper extremities and its decrease on the lower extremities with weakening of the pulsation there. In this case, hypertrophy of the left half of the heart and collateral circulation through the systems of the internal thoracic and intercostal arteries develop

Arterial hypoplasia is characterized by underdevelopment of these vessels, including the aorta, while coronary artery hypoplasia may underlie sudden cardiac death.

Atresia of the veins is a rare malformation, consisting in the congenital absence of certain veins. The atresia of the hepatic veins is of greatest importance, which is manifested by severe violations of the structure and function of the liver (Budd-Chiari syndrome).

Acquired vascular disease is very common, especially with atherosclerosis and hypertension. Obliterating endarteritis, acquired aneurysms, vasculitis are also of clinical importance.

Obliterating endarteritis is a disease of arteries, mainly of the lower extremities, characterized by a thickening of intima with a narrowing of the lumen of the vessels up to its obliteration. This condition is manifested by severe, progressive tissue hypoxia with an outcome in gangrene. The cause of the disease has not been established, but among the risk factors, smoking and arterial hypertension are critical. In the pathogenesis of suffering, a certain role is played by an increase in the activity of the sympathetic-adrenal system and autoimmune processes.

ACQUIRED ANEURISMS

Acquired aneurysms - local expansion of the lumen of blood vessels due to pathological changes in the vascular wall. They can be bag-shaped or cylindrical in shape. The causes of these aneurysms may be damage to the vascular wall of an atherosclerotic, syphilitic or traumatic nature. More often, aneurysms are found in the aorta, less often in other arteries.

Atherosclerotic aneurysms, as a rule, develop in a damaged atherosclerotic aortic process with a predominance of complicated changes, usually after 65-75 years, more often in men. The cause is the destruction of the muscular-elastic skeleton of the aortic heart membrane with atheromatous plaques. Typical localization is the abdominal aorta. In an aneurysm, thrombotic masses are formed, which serve as a source of thromboembolism.

Complications - rupture of the aneurysm with the development of fatal bleeding, as well as thromboembolism of the arteries of the lower extremities, followed by gangrene.

Syphilitic aneurysms are a consequence of syphilitic mesenteritis, characterized by the destruction of the muscular-elastic skeleton of the middle membrane of the aortic wall, as a rule, in the region of the ascending part of the arch and its thoracic part.

Most often, these aneurysms are observed in men, can reach 15-20 cm in diameter. With prolonged existence, the aneurysm puts pressure on the adjacent vertebral bodies and ribs, causing their atrophy. Clinical symptoms are associated with compression of the adjacent organs and are manifested by respiratory failure, dysphagia due to compression of the esophagus, persistent cough due to compression of the return nerve, pain syndrome, decompensation of cardiac activity.

Vasculitis is a large and heterogeneous group of inflammatory diseases of blood vessels.

Vasculitis is characterized by the formation of infiltrate in the vessel wall and in the perivascular tissue, damage and desquamation of the endothelium, loss of tonus by the vessels and hyperemia in the acute period, wall sclerosis and often obliteration of the lumen in a chronic course.

Vasculitis is divided into systemic, or primary, and secondary. Primary vasculitis constitutes a large group of diseases, are widespread and have independent significance. Secondary vasculitis develops in many diseases and will be described in the relevant chapters.

Vein diseases are represented mainly by phlebitis - inflammation of the veins, thrombophlebitis - phlebitis complicated by thrombosis, phlebothrombosis - thrombosis of the veins without their previous inflammation, and varicose veins.

Phlebitis, thrombophlebitis and phlebothrombosis.

Phlebitis is usually a consequence of infection of the venous wall, it can complicate acute infectious diseases. Sometimes phlebitis develops as a result of a vein injury or its chemical damage. With inflammation of the vein, the endothelium is usually damaged, which leads to the loss of its fibrinolytic function and the formation of a blood clot in this area. Thrombophlebitis occurs. It manifests itself as a pain symptom, tissue edema distal to occlusion, cyanosis and redness of the skin. In the acute period, thrombophlebitis can be complicated by thromboembolism. With a long chronic course, thrombotic masses undergo organization, however, thrombophlebitis and phlebotrombosis of the main veins can cause the development of trophic ulcers, usually lower limbs.

Varicose veins - an abnormal expansion, tortuosity and lengthening of the veins that occurs under conditions of increased intravenous pressure.

A predisposing factor is congenital or acquired inferiority of the venous wall and its thinning. At the same time, foci of hypertrophy of smooth muscle cells and sclerosis appear nearby in a compensatory manner. More often, the veins of the lower extremities, hemorrhoidal veins and veins of the lower esophagus are affected when the venous outflow is blocked in them. The areas of vein expansion can have a nodular, aneurysm-like, fusiform shape. Varicose veins are often combined with vein thrombosis.

Varicose veins of the lower extremities are the most common form of venous pathology. It occurs mainly in women after 50 years.

An increase in intravenous pressure may be associated with professional activities and lifestyle (with pregnancy, standing work, weight transfer, etc.). Mostly superficial veins are affected, clinically the disease is manifested by swelling of the limbs, trophic skin disorders with the development of dermatitis and ulcers.

Varicose hemorrhoidal veins are also a common form of pathology. Predisposing factors are constipation, pregnancy, and sometimes portal hypertension.

Varicose veins develop in the lower hemorrhoid plexus with the formation of external nodes or in the upper plexus with the formation of internal nodes. The nodes are usually thrombosed, swell into the lumen of the intestine, are injured, undergo inflammation and ulceration with the development of bleeding.

Esophageal varicose veins develop with portal hypertension, usually associated with cirrhosis of the liver, or with tumor compression of the portal tract. This is due to the fact that the veins of the esophagus shunt blood from the portal system into the caval system. Thinning of the wall, inflammation and erosion occur in varicose veins. Rupture of the wall of the esophagus varicose vein leads to severe, often fatal, bleeding

Pharmaceutical custody: symptomatic treatment of headache

How often, in order to emphasize the importance of a problem, we say: this is my headache. Although a person can have any organ, any part of the body, it is the headache that has become synonymous with things that cannot be put off, which cannot be forgotten even for a minute.

Headache is one of the most common complaints with which patients turn to a doctor. It can be the leading, and sometimes the only complaint in more than 45 different diseases: neurosis, depression, hypertension, arterial hypotension, renal and endocrine pathology, diseases of the nervous system, ENT organs and eyes, and as one of Symptoms can accompany almost any pathological process. The problem of chronic headaches has become particularly relevant in recent years. According to epidemiological studies in Europe, 78% of women and 64% of men experience headaches at least once a year, and 36% of women and 19% of men suffer from chronic pain syndrome of this localization. Not only adults, but also children are subject to this suffering - by the age of 7, headache occurs at least once in 40% of children, and by 15 years - in 75% of children. However, these figures

do not reflect the true state of things, because many patients do not go to doctors, self-medicating. At least 90% of the population periodically experience headaches, more than half of them take over-the-counter analgesics, often abusing the drugs of this group, not observing the conditions for their rational use, which leads to the development of side effects of the drugs.

Headache

Headache - a painful or simply unpleasant sensation arising upward from the eyebrows and to the cervical-occipital region.

Headache occurs with irritation of pain receptors in the skin, subcutaneous tissue, in the vessels of the soft integument of the head, periosteum of the skull, membranes of the brain, intracranial arteries, veins and venous sinuses. Chep bones and brain substance of the pain receptor are deprived.

Headache occurs when stretching or squeezing structures containing pain receptors.

Depending on the cause and taking into account the characteristic signs, several pathogenetic types of headache are distinguished. The determination of the pathogenetic type of headache is of practical importance for its drug therapy.

Pathogenetic types of headache

Vascular type of headache - a pain breaking, dull, accompanied by a feeling of compression, nausea, darkening in the eyes, flickering of "flies" in front of the eyes; possible pain of a pulsating nature, a feeling of heaviness in the head, a feeling of blunt bursting. Vascular pain intensifies in the lay position, when working with the head down.

This type of headache occurs when there is a violation of the tone of the vessels of the brain.

A headache of muscle tension occurs when the muscles of the soft integuments of the head are stretched or squeezed as a result of an increase in the tone of the sympathetic nervous system (stress, neurosis, infectious-toxic diseases, hormonal changes, hypertension), pathological painful impulse in local processes (diseases of the eyes, ears, sinuses, cervical osteochondrosis). It is characterized by a sensation of "tightening the head with a hoop", increased sensitivity to loud sounds, bright light, and increased irritability.

The liquorodynamic type of headache occurs when there is a disturbance in the dynamic balance between secretion and outflow of cerebrospinal fluid, resulting in either an increase in intracranial pressure (swelling, brain abscess, cerebral edema as a result of trauma, inflammation, cerebrovascular accident), or its decrease (a decrease in cerebrospinal fluid production after a traumatic brain injury or inflammatory process).

The characteristic signs of a headache of this type are its bursting nature, the feeling of “pressure from the inside out”, increased pain when straining, coughing, changing the position of the head, increased pain in an upright position, when walking. Focal neurological symptoms, meningial syndromes, impaired consciousness are possible.

With the neuralgic type of headache, the focus of pathological pain impulse is located in the central structures (most often, the trigeminal nerve). The paroxysmal nature of pain (paroxysms of pain), the presence of trigger (trigger) zones, the irritation of which provokes an attack, the irradiation of pain to neighboring or distant areas are characteristic. Pain is described by patients as “piercing,” “shooting,” “like current,” or “like lightning.”

Hallucinatory headache (psychalgia) occurs at any age.

In this case, the formation of a pathological focus occurs in the system of central structures of pain reception, structures of the central psycho-emotional perception of pain. It is characterized by the

absence of specific physical characteristics when describing a headache (for example, pulsating, constricting), its certain metaphorical characteristics (for example, “how a snake nibbles”, etc.). Psychogenic headache, as a rule, is bilateral, occurs daily, lasts several hours, and is observed against the background of psycho-emotional stress (although patients often deny this). With instrumental methods for the study of patients with psychogenic headache, there are no pathological deviations.

The same pathogenetic type of headache can occur in different diseases, and, conversely, in the same disease there can be different types of headache.

Taking into account that a headache can occur in a variety of diseases, including those posing a serious threat to the patient’s health and even life, first of all, one should try to establish a possible cause of the headache in the patient and to identify the presence (or absence) of “threatening” "Symptoms.

The most common causes of headache

• Emotional stress, stress.

• Infectious diseases, especially accompanied by intoxication (influenza, foodborne diseases, etc.).

• Inflammation of the sinuses (sinusitis).

• Diseases of the organ of vision - glaucoma, a high degree of myopia.

•Hypertensive crisis.

• Diseases of the brain:

o brain tumors;

o increased intracranial pressure;

o inflammatory diseases (meningitis, encephalitis, arachnoiditis);

o impaired blood supply to the brain.

• Diseases of the sensory nerves (neuralgia, most often the trigeminal nerve).

• Hormonal disorders (premenstrual syndrome, hypoglycemia).

Iron-deficiency anemia.

• Migraine, in which pain occurs as a result of a violation of the tone of the cerebral arteries.

• Psychogenic headaches.

• Headaches of tension (do not have a specific reason, are associated with a number of contributing factors leading to tension of the muscles of the scalp).

• Irrational medication.

Unfortunately, not only adults, but also kids suffer from headaches. Their complaints can be very diverse, which greatly complicates the diagnosis and treatment. Children complain of visual impairment, nausea, sudden and passing abdominal pains and very rarely headaches themselves, which makes it difficult for parents and doctors to make a diagnosis. Of all types of headaches in children, two of its types are most often found: migraine and tension headaches. With migraines, headache attacks in children can last from two hours to two days. The pain on one side of the head, pulsating, very strong, practically deprives the child of the ability to behave normally, that is, to run, jump, have fun. Sometimes there is nausea (vomiting), abdominal pain, a sharp "non-perception" of

bright light and odors. Children may complain of visual impairment, causeless fear, and sometimes sensory impairment in their arms and legs. Tension headaches occur sporadically and last from half an hour to a week. The headache is bilateral, constant, but does not affect the motor activity of the child. No vomiting, nausea, or other signs characteristic of migraine are noted.

The most common causes of headaches in school children

• Emotional stress, stress.

• Short or, on the contrary, too long sleep.

• Prolonged watching TV or playing on a computer.

• Stress in the family.

• Stress and failure at school (fear of tests or poor grades, etc.).

• A sharp change in the weather.

• Disappointments, unfulfilled dreams and hopes (especially among girls).

• Excessively intense exercise.

• Irregular nutrition (in some cases - just a missed meal).

• Intolerance to certain products, such as cheese, chocolate, milk, etc.

It should be noted once again that for certain age groups, the most common are various causes of headache, which requires fundamentally different approaches to treatment - both drug and non-drug.

The main causes of headache in various age groups

Children

• Various infections (in children the first 6 months. When a headache occurs, the probability of meningitis is high).

• Mental disorders.

• Migraine.

• Traumatic brain injury.

Middle-aged

• Migraine.

• Mental disorders.

• Violation of blood pressure (both increase and decrease in blood pressure).

• Diseases of the cervical spine.

• Subarachnoid hemorrhage.

• Nonspecific headache (sinusitis, trigeminal neuralgia, carious tooth, smoking, alcohol abuse, etc.).

• Acceptance and / or withdrawal of drugs.

Elderly people

• Diseases of the cervical spine.

• Brain tumors.

• Neuralgia.

• Glaucoma (increased intraocular pressure).

• Subdural hematoma.

• Acceptance and / or withdrawal of drugs.

It should be emphasized that the cause of headaches is often taking medications of various groups. For the diagnosis of such a headache, a thorough medical history is necessary. An effective method of its prevention is the rational choice of drugs, as well as the gradual withdrawal of drugs, which are characterized by "rebound syndrome" (deterioration against the background of a sharp drug withdrawal).

Medicines most commonly causing headache:

• ergot alkaloids (rebound syndrome)

• analgesics and non-steroidal anti-inflammatory drugs (especially aspirin, indomethacin, codeine) - rebound syndrome

• antimicrobial agents

• H2 blockers (ranitidine, cimetidine)

• nitrates

• antihypertensive drugs (calcium, methyldopa, reserpine antagonists)

• dipyridamole

• MAO inhibitors

• nitrazepam

• oral contraceptives

• sympathomimetics (including vasoconstrictor drugs for the treatment of rhinitis, complex drugs for the relief of cold symptoms)

• theophylline

Factors contributing to the development of a headache attack

• Emotional stress, stress.

• A sharp change in mood (excitement, fear).

• Significant physical overwork.

• Stay in a stuffy, hot, smoky room.

• For migraines - a number of foods (nuts, chocolate, cheese, smoked meats, drinks containing caffeine, alcohol).

“Threatening” headache symptoms

• The occurrence of pain is associated with a head injury (especially dangerous if loss of consciousness has occurred).

• Headache appeared suddenly, its intensity is much stronger than usual.

• Headache lasts 2-3 days and intensifies.

• Headache occurred in the course of the disease, accompanied by high fever.

• Headache accompanied by stiff neck

• The pain is accompanied by a feeling of compression, nausea, darkening in the eyes, "flies" in front of the eyes.

Pain is accompanied by increased sensitivity to loud sounds, bright light, and increased irritability.

• Pain of a bursting nature, a feeling of “pressure from the inside out”, increased pain when straining, coughing, changing the position of the head.

• Headache combined with pain in the heart.

• Headache combined with redness of the eyes, decreased vision.

• A headache of a pulsating nature.

• Headache is accompanied by loss (decrease) of sensitivity in the limbs.

• Headache appeared after taking (canceling) the drug.

Situations requiring emergency diagnosis and treatment

• The nature and frequency of chronic headache attacks suddenly changed and / or they became much more intense.

• Headache is combined with the sudden development of neurological symptoms (difficulty speaking, movement, etc.) or depression of consciousness.

• A headache develops a few days or weeks after the herbs of the head.

• According to the patient, this is the most severe headache he has ever experienced in life (typical of spontaneous subarachnoid hemorrhage).

If none of the “threatening symptoms” is detected in a pharmacy visitor, you can take one of the OTC drugs to relieve headaches.

If a headache recurs regularly, a mandatory medical consultation and a full examination are required before using the medications to make an accurate diagnosis, since a serious illness can underlie such a headache. It is impossible to properly treat a patient without making a correct diagnosis. The best specialists in the field of headache are neuropathologists.

Directions for the symptomatic treatment of patients with headache

1. The use of medications - analgesics, antipyretics, drugs for the treatment of migraine.

2. Non-drug methods of treatment, including psychotherapy, massage, reflexology.

General recommendations for patients

• The most common cause of a short-term headache is acute respiratory infections, in this case measure the temperature, take an analgesic-antipyretic.

• During an acute attack, relieve headache in a quiet place without bright light.

• For the treatment of regular headaches that do not have a migraine character and are not associated with common diseases (see “Causes”), it is recommended:

o regular nutrition, intake of B vitamins, calcium and magnesium preparations;

o normalize sleep and wakefulness, regularly sleep well;

o refrain from smoking, including from the passive inhalation of ta-bak;

o avoid stuffy, polluted rooms;

o try to determine the relationship of headache attacks with the intake of certain foods; if there is such a relationship, exclude certain foods from the diet

Tips for Parents

• Young children do not know how to complain of a headache, but become restless and irritable.

• In case of frequent headaches in children, it is imperative to establish their cause with the help of a doctor.

• In schoolchildren, headaches are most often caused by overwork.

• It is necessary to plan the day of the child so that he has free time for rest (playing on the computer does not count), and also that physical and mental stress does not exceed his capabilities.

• Whenever you are in pain, be close to the child whenever possible. However, one should not allow the child to turn into a domestic “deity” because of headaches, this helps to consolidate the pathological pain reflex, especially in the case of psychogenic pain.

Medicines used for headaches and conditions for their rational use

For the symptomatic treatment of headaches, the pharmaceutical industry offers a significant number of over-the-counter drugs from the group of antipyretic analgesics, including complex ones, which include codeine and / or caffeine.

Antipyretic analgesics (acetylsalicylic acid, paracetamol, metamizole) along with an analgesic effect have a mild anti-inflammatory effect, which in turn also helps to reduce pain.

Codeine is a fairly effective central analgesic. When it is used together with antipyretic analgesics, pharmacological potentiation occurs when the total analgesic effect is greater than the simple arithmetic sum of the effects of the two drugs.

Caffeine regulates the processes of excitation in the brain, enhances positive reflexes, and normalizes the tone of cerebral vessels. There is a point of view that caffeine increases the permeability of the blood-brain barrier to drugs used with it.

In addition to analgesics, antipyretics, drugs containing ergot alkaloid - dihydroergotamine - are used to relieve headaches. It causes the expansion of spasm vessels, improves blood supply to the brain, has a sedative effect.

In recent years, in the treatment of migraine, drugs acting on specific brain serotonin receptors, sumatriptan group drugs, have proven themselves well.

Sumatriptan is a specific selective agonist of 5HT1-serotonin receptors. Selectively narrows the vascular lumen of the carotid artery system without affecting cerebral blood flow. It is believed that

the expansion of precisely the vessels of the carotid artery system that supply the meninges is the main reason for the development of a migraine attack in humans.

Sumatriptan should be taken as early as possible from the onset of a migraine attack, but it is equally effective at any stage of the attack. For the prevention of seizures, the drug is not used.

It should be remembered that the drugs of the sumatriptan group are shown only with the established diagnosis of migraine - after consulting a doctor and conducting the necessary examination for the diagnosis.

Pharmaceutical custody when using drugs for the symptomatic treatment of headache

• A headache can be a symptom of serious illness, so be sure to consult a doctor to exclude conditions dangerous to life and health

• Analgesic drugs for headache do not take more than two days without consulting a doctor.

• Analgesic drugs for headaches should not be taken more than 2 times a week - otherwise it is possible to lower the threshold of pain sensitivity and increase the frequency and strength of headache attacks.

• If the pain during migraine does not go away within 12 hours, it is imperative to consult a doctor, since there is a threat of a violation of cerebral circulation.

• Soluble dosage forms and dosage forms in the form of aerosols provide a faster onset of therapeutic effect, reduce the effect of the active substances contained in the preparation on the gastric mucosa.

• Combined drugs from the group of analgesic antipyretics containing caffeine should not be combined with the intake of coffee or tea in large quantities to avoid overdose.

• Preparations containing paracetamol should be used with caution in persons with severely impaired liver function.

• With prolonged use of drugs containing paracetamol with a low degree of purification, the composition of peripheral blood should be monitored.

• Preparations containing acetylsalicylic acid are recommended to be taken after meals.

• Drugs containing acetylsalicylic acid should not be taken with anticoagulants.

• Preparations containing acetylsalicylic acid should not be combined with alcohol (the risk of ulcerogenic action, gastric bleeding increases sharply).

• With prolonged use of drugs containing acetylsalicylic acid, a study of feces for occult blood is recommended.

• Drugs containing acetylsalicylic acid should not be taken during pregnancy and lactation.

• Medications of the sumatriptan group can only be used after a doctor has diagnosed a migraine.

• Medications of the sumatriptan group should not be used during pregnancy and lactation, in young children.

• Medicines containing sumatriptan should not be used in patients with diseases of the heart, blood vessels, or with hypertension.

• Medicines containing sumatriptan are not used to prevent a migraine attack.

• With prolonged use of codeine-containing preparations, addiction may develop.

• Sumatriptan should not be combined with ergot drugs - severe vasospasm may develop.

• After taking drugs containing ergot alkaloids (dihydroergotamine), sumatriptan drugs can be taken no earlier than after a 24-hour break

• After taking the drugs of the sumatriptan group, preparations containing ergot alkaloids (dihydroergotamine) can be taken only after a break of 6 hours or more

• The interval between taking various drugs of the sumatriptan group is at least 12 hours.

• If taking one dose of a drug of the sumatriptan group did not have an effect, taking a repeated dose is possible no earlier than 3 hours later.

Lesson purpose

Know:

I. MAJOR REASONS FOR BLOOD CIRCULATION INSUFFICIENCY:

• heart pathology;

• violation of the tone of the walls of blood vessels;

• changes in the mass of circulating blood and / or its rheological properties.

According to the severity of development and nature of the course, acute and chronic circulatory failure is distinguished.

1. Acute circulatory failure develops within hours or days. The most common causes of it may be:

• acute myocardial infarction;

• some types of arrhythmias;

• shock;

• acute blood loss.

2. Chronic circulatory failure develops over several months or years and its causes are:

• chronic inflammatory heart disease;

• cardiosclerosis;

• heart defects;

• hyper- and hypotensive conditions;

• anemia.

II. PATHOLOGY OF CARDIAC ACTIVITY

A. Coronary insufficiency,

• reversible (transient) coronary blood flow disorders; they include angina pectoris, characterized by severe compressive pain in the sternum, resulting from myocardial ischemia;

• irreversible cessation of blood flow or a long-term significant decrease in blood flow through the coronary arteries, which ends, as a rule, with myocardial infarction.

B. Arrhythmias

a. Arrhythmias as a result of a violation of automatism.

bradycardia

tachycardia

b. Arrhythmias due to conduction disturbances:

• slowdown or blockade of conduct;

• acceleration of conduct.

Arrhythmias due to disturbance of excitability

Extrasystole.

Paroxysmal tachycardia.

Atrial or ventricular fibrillation (flickering)

B. Heart failure.

1.Ethiology:

2. Types of heart failure

A. According to the mainly affected part of the heart:

• left ventricular;

• right ventricular.

b. By development speed:

Acute (minutes, hours).

Chronic (months, years).

III. DISEASES OF THE CARDIOVASCULAR SYSTEM

1. Atherosclerosis

a. Risk factors.

• age;

• gender;

• heredity;

• hyperlipidemia;

•arterial hypertension;

• stressful situations;

• smoking;

• hormonal factors;

• obesity and physical inactivity

b. Patho and morphogenesis of atherosclerosis

Dolipid stage

Stage of ltoidosis.

Stage of liposclerosis.

Stage of complicated lesions

2. Hypertension.

a. Risk factors

• chronic psycho-emotional overstrain;

• a hereditary defect in cell membranes, leading to a violation of the exchange of Ca2 + and Na2 + ions;

• a genetically determined defect in the renal volumetric mechanism for regulating blood pressure.

• diet with high consumption of table salt;

• hormonal factors - increased pressor influences of the hypothalamic-pituitary system, excessive secretion of catecholamines and activation of the renin-angiotensin system;

• renal factor;

• obesity;

• smoking;

• physical inactivity, sedentary lifestyle.

b. Complications

3. Ischemic, or coronary, heart disease.

a.Forms of coronary heart disease.

sudden coronary death;

angina pectoris;

myocardial infarction;

cardiosclerosis.

b.Current coronary disease

sharp

chronic

IV. PHARMACEUTICAL CARE: SYMPTOMATIC TREATMENT OF HEAD PAIN

1. Headache

2. Pathogenetic types of headache

a. Vascular type of head

b. Muscle tension headache

c. Liquorodynamic type of headache

d. With the neuralgic type of headache, the focus of pathological pain impulse is located in the central structures (most often, the trigeminal nerve).

e. Hallucinatory headache (psychalgia) occurs in any age.

f. Psychogenic headache

3. The most common causes of headache

• Emotional stress, stress.

• Infectious diseases, especially accompanied by intoxication (influenza, foodborne diseases, etc.).

• Inflammation of the sinuses (sinusitis).

• Diseases of the organ of vision - glaucoma, a high degree of myopia.

•Hypertensive crisis.

• Diseases of the brain:

brain tumors;

increased intracranial pressure;

inflammatory diseases (meningitis, encephalitis, arachnoiditis);

impaired blood supply to the brain.

• Diseases of the sensory nerves (neuralgia, most often the trigeminal nerve).

• Hormonal disorders (premenstrual syndrome, hypoglycemia).

•Iron-deficiency anemia.

• Migraine, in which pain occurs as a result of a violation of the tone of the cerebral arteries.

• Psychogenic headaches.

• Headaches of tension (do not have a specific reason, are associated with a number of contributing factors leading to tension of the muscles of the scalp).

• Irrational medication

4. The most common causes of headache in school children

• Emotional stress, stress.

• Short or, on the contrary, too long sleep.

• Prolonged watching TV or playing on a computer.

• Stress in the family.

• Stress and failure at school (fear of tests or poor grades, etc.).

• A sharp change in the weather.

• Disappointments, unfulfilled dreams and hopes (especially among girls).

• Excessively intense exercise.

• Irregular nutrition (in some cases - just a missed meal).

• Intolerance to certain products, such as cheese, chocolate, milk, etc.

5. The main causes of headache in various age groups

a.Children

• Various infections (in children the first 6 months. When a headache occurs, the probability of meningitis is high).

• Mental disorders.

• Migraine.

• Traumatic brain injury.

b. Middle-aged

• Migraine.

• Mental disorders.

• Violation of blood pressure (both increase and decrease in blood pressure).

• Diseases of the cervical spine.

• Subarachnoid hemorrhage.

• Nonspecific headache (sinusitis, trigeminal neuralgia, carious tooth, smoking, alcohol abuse, etc.).

• Acceptance and / or withdrawal of drugs.

c. Elderly

• Diseases of the cervical spine.

• Brain tumors.

• Neuralgia.

• Glaucoma (increased intraocular pressure).

• Subdural hematoma.

• Acceptance and / or withdrawal of drugs.

6. Medicines most commonly causing headache:

• ergot alkaloids (rebound syndrome)

• analgesics and non-steroidal anti-inflammatory drugs (especially aspirin, indomethacin, codeine) - rebound syndrome

• antimicrobial agents

• H2 blockers (ranitidine, cimetidine)

• nitrates

• antihypertensive drugs (calcium, methyldopa, reserpine antagonists)

• dipyridamole

• MAO inhibitors

• nitrazepam

• oral contraceptives

• sympathomimetics (including vasoconstrictor drugs for the treatment of rhinitis, complex drugs for the relief of cold symptoms)

• theophylline

7. Factors contributing to the development of a headache attack

• Emotional stress, stress.

• A sharp change in mood (excitement, fear).

• Significant physical overwork.

• Stay in a stuffy, hot, smoky room.

• For migraines - a number of foods (nuts, chocolate, cheese, smoked meats, drinks containing caffeine, alcohol).

8. "Threatening" symptoms with a headache

• The occurrence of pain is associated with a head injury (especially dangerous if loss of consciousness has occurred).

• Headache appeared suddenly, its intensity is much stronger than usual.

• Headache lasts 2-3 days and intensifies.

• Headache occurred in the course of the disease, accompanied by high fever.

• Headache accompanied by stiff neck

• The pain is accompanied by a feeling of compression, nausea, darkening in the eyes, "flies" in front of the eyes.

• Pain is accompanied by increased sensitivity to loud sounds, bright light, and increased irritability.

• Pain of a bursting nature, a feeling of “pressure from the inside out”, increased pain when straining, coughing, changing the position of the head.

• Headache combined with pain in the heart.

• Headache combined with redness of the eyes, decreased vision.

• A headache of a pulsating nature.

• Headache is accompanied by loss (decrease) of sensitivity in the limbs.

• Headache appeared after taking (canceling) the drug.

a. Situations requiring emergency diagnosis and treatment

• The nature and frequency of chronic headache attacks suddenly changed and / or they became much more intense.

• Headache is combined with the sudden development of neurological symptoms (difficulty speaking, movement, etc.) or depression of consciousness.

• A headache develops a few days or weeks after the herbs of the head.

• According to the patient, this is the most severe headache he has ever experienced in life (typical of spontaneous subarachnoid hemorrhage).

9. Directions for the symptomatic treatment of patients with headache

The use of medications - analgesics, antipyretics, drugs for the treatment of migraine.

Non-drug methods of treatment, including psychotherapy, massage, reflexology.

a.General recommendations for patients

• The most common cause of a short-term headache is acute respiratory infections, in this case measure the temperature, take an analgesic-antipyretic.

• During an acute attack, relieve headache in a quiet place without bright light.

• For the treatment of regular headaches that do not have a migraine character and are not associated with common diseases (see “Causes”), it is recommended:

regular nutrition, intake of B vitamins, calcium and magnesium preparations;

normalize sleep and wakefulness, regularly sleep well;

refrain from smoking, including from the passive inhalation of ta-bak;

avoid stuffy, polluted rooms;

try to determine the relationship of headache attacks with the intake of certain foods; if there is such a relationship, exclude certain foods from the diet.

b. Tips for parents

• Young children do not know how to complain of a headache, but become restless and irritable.

• In case of frequent headaches in children, it is imperative to establish their cause with the help of a doctor.

• In schoolchildren, headaches are most often caused by overwork.

• It is necessary to plan the day of the child so that he has free time for rest (playing on the computer does not count), and also that physical and mental stress does not exceed his capabilities.

• Whenever you are in pain, be close to the child whenever possible. However, one should not allow the child to turn into a domestic “deity” because of headaches, this helps to consolidate the pathological pain reflex, especially in the case of psychogenic pain.

10. Medicines used for headaches and the conditions for their rational use

11. Pharmaceutical custody when using drugs for the symptomatic treatment of headache

• A headache can be a symptom of serious illness, so be sure to consult a doctor to exclude dangerous conditions for life and health.

• Analgesic drugs for headache do not take more than two days without consulting a doctor.

• Analgesic drugs for headaches should not be taken more than 2 times a week - otherwise it is possible to lower the threshold of pain sensitivity and increase the frequency and strength of headache attacks.

• If the pain during migraine does not go away within 12 hours, it is imperative to consult a doctor, since there is a threat of a violation of cerebral circulation.

• Soluble dosage forms and dosage forms in the form of aerosols provide a faster onset of therapeutic effect, reduce the effect of the active substances contained in the preparation on the gastric mucosa.

• Combined drugs from the group of analgesic antipyretics containing caffeine should not be combined with the intake of coffee or tea in large quantities to avoid overdose.

• Preparations containing paracetamol should be used with caution in persons with severely impaired liver function.

• With prolonged use of drugs containing paracetamol with a low degree of purification, the composition of peripheral blood should be monitored.

• Preparations containing acetylsalicylic acid are recommended to be taken after meals.

• Drugs containing acetylsalicylic acid should not be taken with anticoagulants.

• Preparations containing acetylsalicylic acid should not be combined with alcohol (the risk of ulcerogenic action, gastric bleeding increases sharply).

• With prolonged use of drugs containing acetylsalicylic acid, a study of feces for occult blood is recommended.

• Drugs containing acetylsalicylic acid should not be taken during pregnancy and lactation.

• Medications of the sumatriptan group can only be used after a doctor has diagnosed a migraine.

• Medications of the sumatriptan group should not be used during pregnancy and lactation, in young children.

• Medicines containing sumatriptan should not be used in patients with diseases of the heart, blood vessels, or with hypertension.

• Medicines containing sumatriptan are not used to prevent a migraine attack.

• With prolonged use of codeine-containing preparations, addiction may develop.

• Sumatriptan should not be combined with ergot drugs - severe vasospasm may develop.

• After taking drugs containing ergot alkaloids (dihydroergotamine), sumatriptan drugs can be taken no earlier than after a 24-hour break

• After taking the drugs of the sumatriptan group, preparations containing ergot alkaloids (dihydroergotamine) can be taken only after a break of 6 hours or more

• The interval between taking various drugs of the sumatriptan group is at least 12 hours.

• If taking one dose of a drug of the sumatriptan group did not have an effect, taking a repeated dose is possible no earlier than 3 hours later.

The solution of situational problems.

TASK № 1.

Select and dispense a medication to treat headaches.

A. A 37-year-old woman with a migraine patient.

B. A man of 62 years with hypertension.

B. The student is 23 years old and passed a difficult exam.

To do this, complete the following tasks:

1. Give a brief definition of the pathology (disease, syndrome).

2. Give an algorithm for interviewing a pharmacist with a patient with an emphasis on the elements of pharmaceutical care, using these key questions:

How often do you experience a headache?

- What are the reasons for the appearance of the headache?

- Give a detailed description of the headache (nature, intensity, localization).

- What accompanying symptoms accompany pain (nausea, vomiting, fever, fainting, etc.)?

- Recently, a head injury?

- When was the last time you measured your blood pressure? What blood pressure indicators were observed?

- Is a headache related to physical or mental stress?

- Your work is associated with a long or uncomfortable position, prolonged work at the computer, contact with chemicals, etc.?

- Are you taking any medications now? What kind?

- In your opinion, is there a connection between the appearance of a headache and the phases of the menstrual cycle?

- Have you tried to take any medicine? Did it bring relief?

3. What complaints or manifestations should the pharmacist pay attention to and strongly recommend consulting a doctor?

4. What are the medicines to treat or relieve headaches? What pharmacotherapeutic groups do they belong to?

5. Give recommendations to the patient on the conditions of rational use of the drug chosen by you (dosing regimen, interaction with food, alcohol, other drugs)

TASK № 2.

Select and dispense the medicine to eliminate the common cold.

A. A child 2 years old.

B. A 56-year-old man with hypertension.

C. A 32-year-old woman with seasonal allergic rhinitis.

To do this, complete the following tasks:

1. Give a brief definition of runny nose.

2. Give an algorithm for interviewing a pharmacist with a patient with an emphasis on the elements of pharmaceutical care, using these key questions:

When did a runny nose appear?

Is discharge observed from one or both nasal passages?

What is the nature of discharge from the nose?

What other symptoms are accompanied by a runny nose (sneezing, shortness of breath, fever, skin rash)?

3. What are the medications for easing nasal breathing with a runny nose? What pharmacological groups do they belong to?

4. What are the features of the use of drugs against the common cold in children?

5. Give recommendations to the patient (mother) on the conditions of rational use of the drug you have chosen (dosing regimen, appropriate technique and conditions for the procedure for using the drug).

Task 3

Select and dispense a medication to relieve constipation.

A. Woman 43 years old, accountant.

B. A 57-year-old man with hemorrhoids.

C. The woman is 82 years old and has been taking antianginal and antihypertensive drugs for a long time.

To do this, complete the following tasks:

1. Give a concise definition of constipation.

2. Place an algorithm for interviewing a pharmacist with a patient with an emphasis on the elements of pharmaceutical care, using the following key questions:

• Have you always suffered from constipation?

• When did you first notice constipation?

• Have you noticed that along with constipation, bowel movements became painful?

• What other symptoms (abdominal pain, rumbling, heartburn) do you feel?

• Do you use any medications at this time?

• Do you have a disease of the gastrointestinal tract?

• Is your work unrelated to prolonged sitting?

3. What are the medications for constipation? What pharmacological groups do they belong to?

4. Give recommendations to the patient under conditions of rational use of the drug chosen by you (dosing regimen, interaction with food, alcohol, other drugs).

5. What herbal preparations of extemporaneous preparation should be prescribed to the patient? Consult him on the technology of preparation and use of your chosen herbal remedy.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

PHARMACEUTICAL CARE OF PATIENTS WITH PATHOLOGY OF THE DOIGESTIVE SYSTEM

Relevance of the topic.

Digestive diseases are widespread among all segments of the population and in different age groups make up from 18 to 37%. Such a high frequency of the pathology of the gastrointestinal tract is due to many reasons, primarily, poor nutrition, adverse environmental conditions, low physical activity, decreased immune defense of the body, and high infection with Helicobacter pylori.

Gastroenterological patients comprise a significant percentage of all patients in therapeutic hospitals and outpatients in outpatient clinics. This is associated with a high frequency of patients' visits to the pharmacy in order to purchase medicines for the symptomatic treatment of various disorders of the gastrointestinal tract.

Often in a pharmacy, patients are asked by the pharmacist to recommend a drug for the treatment of heaviness in the stomach, feelings of overflow, nausea. This symptom complex is defined by the term "dyspepsia". Experts from an international working group (Roman Criteria II, 1999) proposed defining dyspepsia as a sensation of pain and discomfort (heaviness in the stomach, feeling of fullness, early satiety, bloating in the epigastric region, nausea) localized in the epigastric region closer to the midline.

The prevalence of dyspeptic complaints among the population occurs from 19 to 41%, and more than two-thirds (75%) of patients who see a doctor have no organic pathology, and complaints are caused by disorders of the motor activity of the stomach.

Dyspepsia can be either one of the symptoms of another disease, or act as a separate disease (functional dyspepsia).

The participation of a pharmacist in the treatment of dyspepsia patients using over-the-counter drugs is advisable only if it is functional in nature.

Motivational characteristic of the topic

Symptomatic treatment of impaired gastrointestinal function.

CONSTIPATION

Constipation (obstipatio) - a violation of the intestinal function, expressed in increasing the intervals between acts of defecation (more than 48 hours) in comparison with the individual physiological norm or in a systematic insufficient bowel movement. Regular bowel movement once every 2-3 days is a possible variant of the physiological norm, therefore such a delay in stool does not pose a threat to the body and is not constipation.

In patients suffering from constipation, appetite is often reduced, belching, an unpleasant aftertaste in the mouth are noted. Feelings of heaviness, overflow in the abdomen are characteristic. Many patients have observed changes in the skin: pallor with an earthy tint, dryness, increased peeling, and dermatitis. The nails are flaked, dandruff appears, and the hair easily falls out and splits. Due to constant intoxication, weakness, headaches develop, mood and performance are reduced (in severe cases - depression), sleep disturbance, complaints of memory loss are frequent. Chronic constipation contributes to the development of secondary enterocolitis, hemorrhoids, anal fissures. They are usually accompanied by dysbiosis, disorders of the immune system, metabolic disorders. Slow bowel movement leads to an increase in the concentration of various toxins in the blood and lymph, including carcinogens. Strong straining for constipation can provoke complications of diseases of the

cardiovascular system, especially in the elderly (strokes, heart attacks, thromboembolism). Therefore, chronic constipation requires compulsory treatment.

The most common causes of constipation

Constipation is a symptom of various pathological processes that occur both in the intestine itself and in other organs. The diverse causes of constipation can be divided into several groups:

• pathology of the large intestine - colitis, intestinal atony, spasm of the large intestine, megacolon, polyposis of the colon;

• metabolic disorders - dehydration, hypothyroidism, hypofunction of the adrenal glands;

• nutritional features - a sharp change in diet, lack of dietary fiber (dietary fiber), excess fat in the diet, insufficient fluid intake, excess iron in food, folic acid deficiency;

• painful bowel movements - anal fissures, hemorrhoids;

• use of drugs - antacids containing aluminum salts; antihistamines; codeine-containing preparations; cho linolytics; antihypertensive drugs (calcium channel blockers); iron, calcium preparations; antidepressants, antipsychotics; psychotropic drugs and a number of other drugs.

Factors contributing to the occurrence of constipation:

• systemic diseases of the connective tissue (rheumatism, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, etc.);

• the predominance of protein foods, fatty foods in the diet;

• lack of physical activity;

• prolonged use of laxatives;

• frequent use of enemas.

"Threatening" symptoms that make it possible to suspect a serious illness in a patient that requires the mandatory intervention of a doctor for constipation are:

• temperature rise;

• traces of blood in the stool;

• severe abdominal pain;

• sharp bloating;

• vomiting;

• weight loss;

• the relationship of constipation with the use of a particular drug.

Common approaches to treating constipation

Before recommending a drug, it is necessary to find out the possible causes that contribute to the development of constipation. Often, eliminating the cause leads to normalization of the stool.

Treatment of constipation is aimed at restoring the normal function of the intestine with minimal use of laxatives and cleansing enemas. Therefore, before using medications aimed at normalizing bowel

function, a number of non-medicamentous measures that promote stool normalization should be recommended.

General recommendations for patients on non-drug methods for normalizing bowel function

1. Eat foods rich in dietary fiber, primarily pectin, soluble dietary fiber (beets, apples, plums, oatmeal and other cereals from whole grains, as well as leafy vegetables, cabbage, wholemeal bread, bran).

2. Reduce animal fat intake.

3. Drinking fluids at least 8 glasses a day.

4. If it is necessary to take iron or calcium preparations, give preference to vitamin-mineral complexes.

5. Increase physical activity.

6. To defecate slowly, in a calm, conducive to relaxation environment.

7. Treat hemorrhoids or anal fissures (hygiene of the anus, use of emollients and creams).

8. Do not abuse cleansing enemas and laxatives that stimulate peristalsis.

If the measures to normalize the motor-evacuation function of the intestine are unsuccessful by physiological non-pharmacological methods, laxatives are included in the treatment of constipation.

The success of constipation therapy consists of three components:

• the degree of identification and completeness of elimination of the causes that caused stool retention;

• the patient's readiness to change lifestyle, eating habits, follow the recommendations of the doctor and pharmacist (patient compliance for treatment);

• the willingness of the doctor and pharmacist to conduct a comprehensive, individualized therapy for each patient.

Violations of the motor function of the colon are possible according to the hypertonic (increased tonus of the smooth muscles of the intestines) and atonic (decreased tonus of the smooth muscles of the intestines) type. Therapeutic measures have significant differences depending on the prevailing disorders of the motor function of the colon.

The basis of the action of laxatives is mechanical or chemical irritation of the receptors of the intestinal mucosa. In the main focus of the action, the means are distinguished:

• stimulating the motor function of the intestine;

• softening feces;

• increasing the volume of intestinal contents.

Clinical and pharmaceutical characteristics of the main groups of laxatives

1. Means inhibiting the absorption of water and enhancing intestinal motility (contact laxatives)

Means that stimulate the intestinal motor function make up the largest group of laxatives. A significant part of this group is represented by herbal preparations, which include anthraglycosides.

1.1. Preparations containing anthraglycosides irritate the chemoreceptors of the mucous membrane of the large intestine, which in turn excites peristalsis. They practically do not affect the muscles of the

small intestine; therefore, they do not interfere with digestion and absorption. Laxatives of this group act 8-12 hours after administration.

1.2. Preparations - diphenylmethane derivatives stimulate the receptors of the colon wall by direct contact with the intestinal mucosa. As a result, the secretion of mucus in the colon increases, its peristalsis accelerates and intensifies.

1.3. Synthetic preparations of other groups (sodium picosulfate) are activated in the colon under the influence of bacterial sulfatases, and the resulting substance stimulates the nerve endings of the intestinal mucosa, enhancing its motility. In infants, the drug is ineffective due to the small amount of bacterial flora and, accordingly, sulfatases.

1.4. Osmotic laxatives - saline laxatives act throughout the intestine. Salts contain anions and cations, which are poorly absorbed from the intestine and create increased osmotic pressure. The latter prevents the reverse absorption of water from the intestine. An increase in volume leads to stretching and reflex stimulation of peristalsis, as well as to an increase in the amount of cholecystokinin released from the mucous membrane of the small intestine, which enhances peristalsis. Against the background of prolonged intake of saline laxatives, atrophic and inflammatory changes in the intestinal mucosa may develop due to local irritating effect.

Lactulose is a synthetic disaccharide that after oral administration is not destroyed by disaccharidase of the small intestine, is not absorbed in the small intestine, reaches the colon, where it decomposes into short chain fatty acids (lactic, acetic, propionic and butyric acid) during bacterial decomposition. This lowers the pH of the colon and stimulates peristalsis. In addition, decomposition into short chain fatty acids increases the osmotic pressure in the intestinal lumen.

Forlax is an osmotic laxative that acts throughout the intestine. It causes an increase in the volume of intestinal contents and its softening due to the formation of additional hydrogen bonds with water molecules, its retention and accumulation in the intestinal lumen, increasing intracellular osmotic pressure. In terms of chemical composition, forlax is a macrogol 4000, which, due to its high molecular weight, is not absorbed and metabolized in the gastrointestinal tract.

1.5. Castor oil in the small intestine is broken down by lipase with the formation of ricinoleic acid and glycerol, which irritate the intestinal receptors throughout and strengthen its peristalsis reflexively. These substances simultaneously inhibit the processes of absorption of water and electrolytes, disrupting the activity of the surface epithelium of the intestine, contribute to an increase in the volume of intestinal contents. Castor oil, in addition to the above effects, is partially excreted in an unchanged state and in the form of glycerin, softening the stool. The laxative effect develops after 5-6 hours.

2. Means that increase the volume of intestinal contents "fillers"

A large group of laxatives that increase the intestinal content include plant fibers and hydrophilic colloids (osmotic laxatives). Their laxative effect is associated with the ability of high molecular weight polysaccharides of plant materials to swell in the gastrointestinal tract due to binding to water and, increasing in volume, irritate the intestinal mucosa receptors, promoting its emptying.

3. Means that lubricate the intestinal mucosa, soften feces

Vegetable oils mechanically facilitate the passage of feces and cause their loosening.

Vaseline oil (liquid paraffin) is a mineral oil that is not absorbed in the intestines and is not broken down. It reduces fluid absorption, accelerating the promotion of contents in both the small and large intestines. With prolonged use, the absorption of fat-soluble vitamins is reduced.

Softening laxatives are used mainly when it is necessary to achieve a quick effect, for example, in case of poisoning, in patients in the postoperative period, in preparation for a diagnostic examination of the intestine

Pharmaceutical custody when using drugs for the symptomatic treatment of constipation (laxatives)

• Laxatives should be given on an empty stomach.

• With prolonged use of laxatives, hypokalemia develops, so it is recommended that laxatives be taken with potassium preparations.

• Laxatives containing anthraglycosides act 8-12 hours after administration, therefore it is recommended to take them in the evening, before going to bed.

• Laxatives containing antraglycosides are not used for spastic constipation, as they can cause pain in the colon.

• Anthraquinone glycosides pass into mother's milk, therefore, preparations containing them should not be prescribed to nursing mothers.

• Laxatives from the antraglycoside group are not recommended for long-term use.

• Laxatives from the group of derivatives of anthraquinone with an acidic reaction of urine can stain it intensely yellow, with alkaline - in red.

• Sodium picosulfate in infants is ineffective.

• With prolonged use of liquid paraffin, the absorption of fat-soluble vitamins (A and D) is reduced and the risk of malignant tumors in the gastrointestinal tract is increased.

• Lactulose laxatives can be given to young and middle-aged children.

• Lactulose should not be taken in patients with acute inflammatory bowel disease.

• Castor oil has a laxative effect after 5-6 hours.

• Castor oil should not be prescribed to pregnant women.

• Castor oil is contraindicated in cases of poisoning with fat-soluble poisons.

• Saline laxatives have an effect after 4-6 hours.

• Saline laxatives are contraindicated during pregnancy, as violent peristalsis can stimulate uterine contractility.

• When taking laxatives containing plant fibers, you should drink at least 1.5 liters of fluid per day

Pharmaceutical custody for dyspepsia

Functional dyspepsia is based on various disorders of the motor-evacuation function of the stomach: its weakening, the absence of synchronous peristalsis of the output (antrum) section of the stomach with the opening of the pyloric sphincter (antroduodenal coordination), decreased tonus of the lower esophageal sphincter and reflux of the stomach into the esophagus (gastroesophageal reflux) decreased tone of the pyloric sphincter and casting of the contents of the duodenum into the stomach (duodenogastric reflux), etc.

For the treatment of functional dyspepsia, a group of drugs is used - peristalsis stimulants (prokinetics).

The representative of the group of prokinetics Motilium® (domperidone), which normalizes the motor activity of the stomach and duodenum, is the drug of choice for the treatment of functional dyspepsia. According to the mechanism of action, he is an antagonist of dopamine receptors. The gastrokinetic effect is due to the blockade of peripheral dopamine receptors, as well as the effect on the hypothalamus and parasympathetic nerves. As a result, the duration of peristaltic contractions of the antrum of the stomach and duodenum increases, and the tone of the lower food-water sphincter increases. The drug has an antiemetic and anti-nausea effect, associated with both gastrokinetic action and inhibition of the receptors of the trigger zone of the brain stem, which decreases the sensitivity of nerves that transmit impulses from the stomach and duodenum to the vomiting center. Motilium® has no effect on gastric secretion.

Pharmaceutical custody when using Motilium®

• Motilium® is available over-the-counter.

• The drug should be taken in 15-30 minutes. before eating.

• During pregnancy and lactation, Motilium® should be prescribed only in cases where its use is justified by the expected therapeutic effect.

• Since the pituitary gland is outside the blood-brain barrier, Motilium® can induce an increase in plasma prolactin levels.

• Motilium® in therapeutic doses does not affect the speed of psychomotor reactions, therefore it can be used by vehicle drivers.

• Extrapyramidal phenomena were rarely observed in children and are an exception in adults, their spontaneous and complete reversibility occurs immediately after treatment is discontinued

• It is inappropriate to use anticholinergics with the drug, due to their neutralizing effect.

• When combined in the therapy complex of Motilium® with antacids or antisecretory drugs, the latter should be taken after a meal.

HEARTBURN

Diseases of the gastrointestinal tract are among the most common. Often they take a chronic nature, force to onerous diets, which worsens the quality of life. Currently, the structure of diseases of the gastrointestinal tract is dominated by functional dyspepsia - a symptom complex, accompanied by pain in the stomach, heartburn, belching, nausea, vomiting, a feeling of heaviness in the stomach and other unpleasant subjective sensations. Complaints about dyspeptic symptoms are presented by 30–40% of the population of industrialized countries. These complaints are the cause of 5% of visits to general practitioners and 40-50% of visits to gastro-enterologists. Among people with dyspepsia, young and middle-aged people, the most active and able-bodied, predominate. One of the manifestations of dyspepsia is heartburn.

Heartburn (pyrosis)- a burning sensation in the epigastric region and behind the chest, accompanied by a sour taste in the mouth.

The appearance of heartburn is associated with an increase in the acidity of the gastric contents and its entry into the lower esophagus.

Heartburn can be either a sign of specific, serious diseases of the gastrointestinal tract, one of the manifestations of dyspepsia, or an independent symptom.

The most common causes of heartburn

When identifying the causes of heartburn, two groups of patients should be distinguished.

Heartburn in patients with diseases of the gastrointestinal tract:

• chronic gastritis with high acidity (type B gastritis);

• peptic ulcer of the stomach and duodenum;

•chronic cholecystitis;

• gastroesophageal reflux.

Heartburn in healthy individuals:

• malnutrition

overeating;

fast food "on the go", in a stressful environment;

abuse of butter and fatty foods;

consumption of a large number of sweets and products containing caffeine (coffee, tea, chocolate);

abuse of spicy and spicy food;

• individual hypersensitivity to food products - citrus fruits, onions, garlic, tomato products (juices, pastes, sauces);

• first half of pregnancy;

• taking medications (NSAIDs, steroid hormones, cholinomimetics and some other drugs).

Factors contributing to the occurrence of heartburn:

• alcohol abuse;

• smoking;

• sleep or rest lying immediately after eating;

• wearing tight clothes;

• lack of exercise;

• obesity.

“Threatening” symptoms that make it possible to suspect a serious illness in a patient requiring compulsory intervention of a doctor in case of heartburn are:

• heartburn, accompanied by vomiting the color of "coffee grounds" or blood;

• the presence of black (tarry) stools;

• constant heartburn for 3 days or more;

• heartburn, accompanied by shortness of breath, sweating, difficulty swallowing;

• heartburn combined with abdominal pain;

• progressive weight loss;

• Heartburn is associated with taking certain medications.

Common approaches to treat heartburn

Treatment of heartburn is based on identifying its cause. In gastritis, peptic ulcer, under the supervision of a doctor, a long-term (4–8 weeks or more) treatment is performed with agents that reduce gastric secretion (H2-histamine receptor blockers, proton pump inhibitors, etc.). At the same time, anti-Helicobacter therapy is carried out, gastroprotective agents (protecting the gastric mucosa) are used.

With heartburn, the cause of which is gastroesophageal reflux, also agents that reduce gastric secretion in combination with antacids and prokinetics, drugs that accelerate the evacuation of the gastric contents (metoclopramide, cisapride, domperidone), are also used.

To prevent heartburn in healthy individuals (without organic diseases of the gastrointestinal tract), you should eat regularly, avoid spicy and fatty foods, stop smoking, monitor your weight. These measures will help eliminate stomach problems. However, in real life, adhering to all these rules is difficult, and often not even possible. Therefore, with heartburn in a number of cases, you have to resort to the help of drugs.

General recommendations for patients on non-drug methods of treating heartburn:

• do not abuse products that stimulate acid formation in the stomach: spicy, spicy foods, citrus fruits, pastes and juice from tomatoes, onions, garlic;

• prevent overeating, fast food;

• eliminate or reduce smoking;

• avoid lying down after eating;

• limit the consumption of products containing gases (pastries, soufflés, whipped cream, carbonated drinks);

• drugs that enhance acidity, taken with food or milk;

• in case of heartburn during sleep, raise the head of the bed;

• reduce body weight.

The most common group of over-the-counter drugs used for heartburn are antacids.

Antacids are a group of drugs that reduce the aggressiveness of the contents of the stomach and duodenum due to direct chemical interaction. This group of drugs does not affect the physiological mechanisms of gastric secretion.

Most antacids gradually reduce the acidity of the gastric environment, while forming a uniform protective layer in the stomach that prevents the gastric juice from touching the inflamed parts of the stomach wall.

1. Absorbable antacids

Sodium bicarbonate (soda). An irreversible one-way interaction with hydrochloric acid occurs in the stomach.

$NaHCO3 + HCl = NaCl + H2O + CO2$

The main advantage of the drug is the instant neutralization of hydrochloric acid. For this quality, soda is figuratively called "nitroglycerin heartburn." However, sodium bicarbonate has a short duration of action. In 15–20 minutes a sharp alkalization of the medium occurs (up to pH = 7 and higher), which in combination with the extension of the stomach walls with carbon dioxide causes a

secondary increase in secretion (recoil syndrome). In the presence of a peptic ulcer deeply penetrating the wall of the stomach, stretching the wall with carbon dioxide is dangerous - perforation is possible.

Unlike hydrochloric acid, the chloride formed in the stomach of sodium does not interact with bicarbonate of intestinal and pancreatic juice. Therefore, an excess of endogenous alkali, as well as the unreacted amount of sodium bicarbonate taken by the patient, is easily absorbed and increases the alkaline reserve of plasma, which is the reason for the systemic effect of this antacid. It can occur especially quickly in people with impaired renal function. Systemic alkalosis is accompanied by a deterioration in appetite, nausea, vomiting, weakness, abdominal pain, muscle cramps, and sometimes cramps.

Excretion of an additional amount of sodium bicarbonate with urine leads to its alkalization, which contributes to the formation of phosphate stones in the urinary tract.

With prolonged use of sodium bicarbonate in the body, sodium ions accumulate, which is accompanied by an increase in blood pressure and the development of edema.

Calcium carbonate precipitated. The following reaction occurs in the stomach.

$CaCO3 + 2HCl = CaCl2 + H2O + CO2$

A suspension of calcium bicarbonate reacts with hydrochloric acid rather slowly.

It is believed that calcium carbonate is stronger than all other antacids, stimulates the secondary secretion of hydrochloric acid, which is associated with a direct stimulating effect of calcium on gastrin secretion by the cells of the mucous membrane of the stomach.

About 10% of calcium chloride is absorbed, which with constant intake of calcium carbonate can lead to hypercalcemia, especially with impaired renal function.

Long-term intake of calcium carbonate may be accompanied by the development of nephro-calcinosis and constipation.

2. Non-absorbable antacids

Aluminum hydroxide. It has an enveloping and adsorbing effect. Able to bind pepsin. The effect develops slowly.

Even an excess of the drug does not completely neutralize HCl, which is very important for maintaining the activity of pepsin, which digests proteins. It adsorbs bile salts, which reduces their damaging effect on the gastric mucosa. It increases the synthesis of prostaglandins in the gastric mucosa, due to which the blood supply to the mucous membrane improves and the secretion of protective mucus increases. Does not disturb the acid-base balance.

Long-term administration in renal failure can lead to the accumulation of aluminum in the tissues (bones, muscles, brain), which leads to pain in the bones and muscles, and Alzheimer's type of encephalopathy. It causes hypophosphatemia (weakness, malaise, impaired thinking, decreased appetite), hypophosphaturia, hypercalciuria and calcium nephrolithiasis. Osteoporosis is possible due to decreased absorption of calcium in the intestines and leaching of calcium from bones. It inhibits gastrointestinal motility, promotes the development of constipation

Aluminum phosphate. It has buffered antacid and adsorption properties. Thanks to the buffering action, it helps to reduce the increased acidity to normal and does not cause an acid "rebound". The adsorption properties of aluminum phosphate micelles allow the binding of bacteria, endogenous and exogenous toxic substances, as well as gases formed due to pathological fermentation and decay in

the large intestine. It does not cause constipation, displacement of acid-base balance, does not violate the absorption of phosphates.

Magnesium oxide. It does not cause secondary hypersecretion of gastric juice (phenomemen "recoil"). Does not violate the acid-base state. The effect develops slowly.

Accelerates gastrointestinal motility, due to which it has a laxative effect. This is due to the osmotic ability of magnesium ions, as well as their ability to enhance the secretion of cholecystokinin, which stimulates intestinal motility.

With renal failure, neurological and cardiovascular disorders are possible.

Bismuth nitrate basic. It has an astringent and anti-inflammatory effect. Does not violate the acid-base state. When using preparations containing bismuth, dark (black) stool color is possible, which is important to consider when diagnosing gastric bleeding.

In addition to single products, the combined antacid agents (second generation) combining the positive effect of several active substances are widely represented on the pharmaceutical market.

The complex composition of the "third generation" includes alginic acid. It has a pronounced antiseptic effect by binding of acidic gastric proteases and has a cytoprotective effect, forming, together with magnesium salts, a floating layer in the stomach cavity.

Pharmaceutical custody when using drugs for the symptomatic treatment of heartburn (antacids)

• All antacids are taken only orally - in case of heartburn or 1 hour after eating.

• To avoid drug interactions, antacids should be used 2 hours before or 2 hours after taking other drugs.

• Antacids containing aluminum are indicated for diarrhea, and magnesium is indicated for constipation.

• Antacids based on aluminum salt of first-generation phosphoric acid (phosphalugel, compensated, pensionamar) have a therapeutic effect slowly.

• All aluminum-containing antacids interfere with the absorption of phosphorus, forming insoluble salts of aluminum phosphate. Clinically, this is manifested by muscle weakness, malaise, osteoporosis.

• An increase in the aluminum content in the body, due to excessive use of drugs, can cause encephalopathy (speech impairment, muscle twitching, cramps), and later dementia.

• Excess aluminum, when using non-absorbable antacids, accumulates in the renal glomeruli, which can lead to the development of renal failure.

• Non-absorbable antacids inhibit the absorption of certain drugs: tetracycline, norfloxacin, cardiac glycosides, corticosteroids.

• Acceptance of absorbed antacids is often accompanied by the phenomenon of “ri-kosh” - a repeated increase in the secretion of hydrochloric acid after the initial neutralizing effect.

• Absorbable antacids in large doses can cause systemic metabolic reactions - alkalosis and lactic acid syndrome.

• Patients with hypertension, heart and kidney failure, liver cirrhosis are contraindicated in antacids containing sodium bicarbonate. As a result of a chemical reaction with hydrochloric acid, they form sodium chloride, which is well absorbed and causes water retention in the body.

• Patients with urolithiasis should not take antacids containing silicon (in the form of magnesium trisilicate) - excreted in the urine, it contributes to the formation of stones in the urinary tract.

• With prolonged use of antacids, there is a tendency to infections of the gastrointestinal tract as a result of a decrease in the protective role of hydrochloric acid.

• Antacids cannot be combined with de-nol and sucralfate (pharmacodynamic incompatibility).

FLATULENCE. Dysbacteriosis

Flatulence

Flatulence - bloating due to increased gas formation in the digestive tract (stomach and intestines), which may be accompanied by abdominal pain, belching, shortness of breath.

The main causes of flatulence

The most common cause of flatulence is the decomposition of food containing proteins and carbohydrates or the ingestion of air during chewing while eating and when using chewing gum.

In addition, the causes of flatulence can be:

• intolerance to certain types of food (dairy products and carbohydrates of certain types of food products (mushrooms, soybeans, sweets, legumes, nuts, cabbage, plums, some cereals, fruit juices, etc.);

•binge eating;

• Unaccustomed food or a change in the nature of nutrition (business trips, holidays, vegetarianism, etc.);

• smoking;

• gastritis and peptic ulcers;

•holelithiasis;

• dysbiosis;

• abnormal peristalsis (contraction of the muscles of the colon)

• premenstrual period;

• postoperative period.

"Threatening" symptoms in flatulence requiring compulsory medical attention

• intense abdominal pain;

•nausea and vomiting;

• yellowness of skin color and sclera of the eyes;

• sharp and pronounced weight loss;

• bloating after taking medication.

Recommendations for non-pharmacological relief of flatulence

• identification and exclusion (restriction) from the diet of foods that cause flatulence;

• restriction of consumption of products containing sugar substitutes, causing bloating and pain from gas congestion;

• increase in physical activity;

• rejection of chewing gum;

• smoking cessation or reduction;

• food intake in small portions 4-5 times a day;

• the use of products containing acidophilic cultures.

Drug treatment of flatulence

For the symptomatic treatment of flatulence, the use of drugs of the following pharmacotherapeutic groups is currently recommended.

1. Enterosorbents - effectively adsorb various toxic metabolites from the intestine. Detoxification of the body against the background of the use of enterosorbents prepares organs and tissues and improves the interaction of biologically active compounds, in particular herbal products with the receptor apparatus of the body. Enterosorbents contribute to a decrease in flatulence and other dyspeptic disorders. They can be successfully used as part of complex therapy, in particular in combination with herbal preparations.

For symptomatic treatment of flatulence, enterosgel, caopektate, attapulgite, polyphepan are recommended.

A comparative description of these drugs is given in the article “Pharmaceutical care: symptomatic treatment of impaired function of the gastrointestinal tract. Diarrhea ”(Pharmacist, 2002, No. 15).

Silicones are chemically inert surfactants derived from silicon. According to the mechanism of action, they are defoamers: they reduce the surface tension of gas bubbles formed in the intestine. Bubbles burst and / or are resorbed and removed naturally. Silicones act exclusively on the surface of gas bubbles and do not affect the intestinal mucosa, are not absorbed in the intestine. Preparations of this group are practically non-toxic. They can be prescribed to pregnant and lactating women, children.
3. From this group two medicinal substances are currently used - dimethicone (zeolate) and simethicone (dysflatil, espumisan).
4. Enzyme preparations. In symptomatic treatment of flatulence, the purpose of prescribing enzyme preparations is not substitution therapy due to lack of function, but the creation of a “functional rest” of excessively spurred abundant pancreatic food. It is advisable to use drugs with a moderate content of lipolytic enzymes and a sufficient content of proteolytic. One of the most preferred drugs in this situation is Festal.
5. Carminative products of plant origin: ukro-pa preparations (odorous dill fruits, dill water), fennel fruits, caraway seeds, chamomile flowers.
6. Probiotics. Drugs of this group inhibit vital activity in the intestine of putrefactive and gas-forming microorganisms, which helps to eliminate flatulence, normalize digestion and absorption in the stomach. A more detailed description of the drugs is given below.
7. Domperidone. A synthetic dopamine antagonist, poorly penetrating the blood-brain barrier, and therefore does not have central effects. It has a gastrokinetic and antiemetic effect. When taken orally, domperidone improves gastric emptying without affecting gastric secretion. In Ukraine, the drug Motilium is presented on the basis of domperidone.
The use of the drug is not recommended for gastrointestinal hemorrhage, intestinal obstruction, in children under 1 year old, when breast milk is fed. With an overdose, drowsiness and symptoms of disorientation are possible, especially in children.

Currently, Motilium refers to prescription drugs, therefore, it can only be prescribed by a doctor.
Pharmaceutical custody when using drugs for the symptomatic treatment of flatulence
• Due to the adsorption properties, preparations of the sorbent group are capable of decreasing the effectiveness of simultaneously prescribed oral drugs.
• It is recommended that the interval between the intake of adsorbents and other drugs be observed.
• With prolonged use of adsorbents, the body becomes depleted of vitamins, proteins, fats, etc.
• Adsorbents, due to moderate fixing action during prolonged use (and / or use in high doses), can contribute to constipation.
• Activated charcoal stains black feces.
• Attapulgite is contraindicated in high temperature.
• Attapulgite is contraindicated in the first trimester of pregnancy and with lactation.
• Attapulgite in the form of tablets can be prescribed to children only after 6 years, in the form of a suspension after 3 years.
• Silicones (simethicone, dimethicone) are recommended to be taken with a small amount of liquid after each meal and at bedtime.
• Domperidone is used only as directed by your doctor!
• Herbal carminative agents are used in the form of infusions or decoctions.
• Infusions from dill, fennel and caraway seeds stimulate milk production in nursing mothers.
• Infusions and decoctions are stored in the refrigerator for no more than 3 days.
• Plantex tea cannot be sweetened!
• Enzyme preparations should be taken during or immediately after a meal.
• Tablets containing enzyme preparations should not be chewed.
INTESTINAL DYSBACTERIOSIS
Dysbacteriosis is a quantitative (decrease in the content of beneficial and increase of pathogenic microflora) and qualitative (change in the biological properties of the intestinal flora, weakening of the performance of useful functions and increased toxicity) change in the intestinal microflora.
According to modern epidemiological studies, intestinal dysbiosis to one degree or another affects 90% of the world's population. This is primarily due to poor nutrition, stress, decreased immunological reactivity of the body, environmental and physico-chemical environmental factors, unjustified and uncontrolled use of drugs that affect the microflora of the body. It was found that after acute intestinal infection in the absence of adequate therapy, dysbiotic changes in the intestine persist for at least 2-3 years.
Especially often intestinal dysbiosis is observed in children of the first year of life (70–80%) and newborns (80–100%). At the age of over 1 year, dysbacteriosis is found in 60–70% of children, in healthy children older than 3 years - in 30–50% of cases. However, most children do not have any clinical manifestations of the disease.
The main composition and functions of normal intestinal microflora
The human digestive tract is the habitat of a large number of microorganisms, the quantitative and qualitative composition of which differs in different sections of the gastrointestinal tract. The greatest number of microflora is observed in the large intestine, where three groups of microorganisms are normally found: bifidobacteria and bacteroids (main group), lactic acid bacteria and E. coli strains (concomitant group), staphylococcus, fungi, protea (residual group). Normally, the composition of microflora in an adult is quite stable and is characterized by certain ratios between its individual representatives.
Temporary disturbances of microflora can occur depending on the characteristics of nutrition, human conditions.
The microflora of the digestive tract refers to factors of nonspecific defense of the body.
The main functions of intestinal microflora are normal
• Detoxification (inactivation of enterokinase, alkaline phosphatase).
• Enzymatic (hydrolysis of metabolic products of proteins, lipids, carbohydrates).
• Synthetic (synthesis of vitamins, antibiotic and other biologically active substances).
• Digestive (increase the physiological activity of the digestive tract).
• Antianemic (promotes absorption of iron).

• Antirachitic (promotes the absorption of calcium and vitamin D).
• Immune (activation of the immune system, synthesis of immunoglobulins, interferon).
• Intermicrobial antagonism.
Factors leading to disruption of the normal intestinal microflora are many and varied.
The main factors for the development of dysbiosis
Exogenous:
• industrial poisons;
• violation of sanitary standards in everyday life and at work;
• ionizing radiation;
• climatic and geographical factors;
• surgical interventions on the organs of the gastrointestinal tract.
Endogenous:
• immune disorders;
• stressful conditions;
• non-infectious diseases of the gastrointestinal tract (pathology of the intestine and gall bladder, gastric ulcer, etc.);
•infectious diseases;
•diabetes;
• rheumatic diseases;
• starvation;
• poor nutrition;
• old and senile age;
• irrational medication.
In addition to the above, in children, dysbacteriosis development factors can also be:
• anatomical disorders;
• food allergy;
• errors in nutrition;
• antibiotic therapy (including rational).
The clinical manifestations of dysbiosis are diverse and are largely determined by the degree of violation of the normal intestinal biocenosis. In some patients, any manifestations of dysbiosis may be absent, but most often there are the following characteristic complaints:
• unstable stools (constipation, diarrhea or alternating constipation and diarrhea);
• bloating and rumbling of the abdomen;
• pain in the lower abdomen, decreasing after the discharge of gases;
• nausea, belching, bitterness in the mouth.
In addition, as a result of a long-lasting dysbiosis, a number of pathological conditions arise a second time, namely:
• asthenoneurotic syndrome (due to hypovitaminosis and intoxication);
• anemia;
• hypoproteinemia;
• osteomalacia;
• weight loss;
• hypovitaminosis (mainly fat-soluble vitamins).
In young children with the development of dysbiosis, regurgitation, vomiting, a decrease in the rate of increase in body weight, anxiety, and sleep disturbance are observed. The stool can be plentiful, liquid or mushy, frothy, greenish with an acidic or putrid odor. Abdominal pains are paroxysmal, appear 2–3 hours after eating and are accompanied by bloating, urges to defecate.
Clinically distinguish three degrees of severity of violations of the microbial landscape of the intestine.
1 degree
compensated (latent dysbiosis) - is characterized by a change in the quantitative composition of aerobic microorganisms with a normal ratio of bifidobacteria and lactobacilli. No clinical signs
2 degree

subcompensated (or localized) dysbiosis - manifests itself along with a decrease in the qualitative and quantitative composition of Escherichia, a moderate decrease in the content of bifidobacteria with a simultaneous increase in opportunistic microorganisms. At the same time, a moderately pronounced inflammatory process (enteritis, co-lithitis) takes place in the intestine.

3 degree -

widespread dysbiosis - characterized by significant changes in the qualitative and quantitative composition of normal microflora. Clinically manifested by intestinal dysfunction of varying severity.

4 degree -

generalized (decompensated dysbiosis) along with a significant increase in the content of Escherichia coli, it is characterized by an almost complete absence of bifidobacteria and a sharp decrease in lactic acid bacteria. It is clinically manifested by severe intestinal dysfunction, bacteremia, septic complications, dystrophic changes from the internal organs.

The basic principles of the treatment of intestinal dysbiosis

The treatment of intestinal dysbiosis is complex. It is aimed at eliminating the cause of dysbiosis, elimination of pathogenic and conditionally pathogenic microorganisms and the restoration of normal colon microflora. The latter is achieved using drugs called “probiotics”.

Outpatient treatment is possible only with latent (compensated) form of intestinal dysbiosis. You should not start it yourself - it is necessary to conduct a microbiological examination of feces and be sure to consult a doctor.

Non-drug treatment of intestinal dysbiosis

Based on rational diet therapy. Diet therapy for intestinal dysbiosis should be complete, chemically, mechanically and thermally sparing and aimed at:

• providing good nutrition;
• improving the functional state of the intestine and other organs of the digestive system;
• stimulation of regeneration processes and increase immunity.

With dysbacteriosis, lean boiled meat, fish, cereals (buckwheat, oatmeal, rice), low-fat cottage cheese, white stale bread, fruits and vegetables in large quantities (as products containing dietary fiber) are indicated.

In case of diarrhea, it is recommended that patients with dysbiosis temporarily exclude black bread, whole milk, raw vegetables and fruits, and fatty and spicy seasonings. It is rational to use mucous rice and oat soups, cereals, jelly, sautéed pecans made from boiled vegetables, jelly and juices from carrots, black currants, quinces, pomegranates.

In case of constipation, the diet of patients with dysbiosis should include foods rich in dietary fiber and having a laxative effect - bread with bran, vegetable vinaigrettes, buckwheat porridge, kefir, raw vegetables and juices, sour fruits, highly mineralized mineral waters.

With severe flatulence, the use of legumes, cabbage, and foods with a high glucose content is limited - honey, jam, sweets, grapes. It is recommended to increase the content of cooked meat and fish in the diet

For children, it is advisable to use traditional fermented milk products and special adapted fermented milk mixtures that are close to human milk in chemical composition - “ASU-1”, “ASU-2”, acidophilic “Malyut-ka”, “Bifilin”. For older children, non-adapted lactic acid mixtures are intended - Acidolact, Biolokt, Narine, Bifilin-M, Lactobacterin, Tonus, Vita, Biokefir, Bifidokefir, Beef Dock, yoghurts.

Drug treatment of intestinal dysbiosis

In compensated dysbiosis, probiotics are used to normalize microflora and suppress the growth of pathogenic and conditionally pathogenic microbes, which contain components or waste products of more than 20 types of microorganisms.

Probiotics (eubiotics) - freeze-dried live attenuated strains of normal intestinal microflora, which, after ingestion, colonize the intestines. Bacteria that have come to life in the intestines produce acetic and lactic acids, creating an acidic environment in it that inhibits putrefactive and gas-forming microorganisms (clostridia, protea, bacteroids); produce antibacterial substances that inhibit the

division of various opportunistic bacteria and pathogens of intestinal infections (salmonella, shigella, etc.).
Probiotics are prescribed not as replacement therapy, but as means providing conditions for the restoration of normal microflora.
Eubiotics suppresses the processes of decay and fermentation eliminates flatulence, normalizes the processes of digestion and absorption in the intestine. Restoring normal microflora, in turn, contributes to the immunization of the body, increases its resistance to infection.
Eubiotics are used both for treatment and for the prevention of dysbiosis, especially in children.
For the prevention and treatment of dysbiosis, along with probiotics, functional food products are used. This is a special form of probiotics, which is a food product that contains substances of natural origin intended for daily use and that have a regulatory effect on the physiological functions and biochemical reactions of the human body.
In our country, functional food products include lactic acid products containing bifidobacteria and lactobacilli - “Biokefir”, “Bifilife”, “Narine”, “Gerolact”, “Streptosan”, “Yogurt”, the above products for children.
The regular use of products containing lactic acid, bifidobacteria, dietary fiber and natural antioxidants helps to maintain health, softens the effects of adverse environmental factors, and helps to increase life expectancy.
Pharmaceutical custody with the use of probiotic preparations
• Before taking probiotics, you should always consult your doctor.
• A complex multicomponent preparation “Linex” is a means of choice for the correction of dysbacteriosis of the small and large intestines
• When used in young children, you can open the Linex capsule and mix its contents with a teaspoon of liquid (tea, water, juice). The resulting mixture is a suspension of white powder in water. Not subject to storage.
• Against the background of antimicrobial therapy, probiotics or linex or bifi-form preparations are possible, since they include antibiotic-resistant strains of the intestinal flora.
• Hilak and Hilak forte are not recommended for use with milk and other dairy products.
• Simultaneous administration of Hilak and Hilak forte preparations with antacids is inadmissible.
• Preparations lactobacterin and lactobacillus acidophilus are recommended to drink milk.
• Any probiotics are not recommended for drinking hot drinks.
• Any probiotics are not recommended to be taken along with alcohol.
• For the prevention of dysbiosis, functional food products are indicated.
Symptomatic treatment for functional pathology of the digestive system, accompanied by pain, includes the following complex of drugs:
• for the relief of pain, the use of antispasmodics with analgesics is indicated;
• with signs of digestive disorders (nausea, flatulence, belching, heartburn, etc.), aggravated after eating, the use of enzyme preparations is indicated;
• for flatulence, the use of antifoam agents and wind-chasing is indicated; for heartburn, antacid preparations;
• for constipation or diarrhea, the use of laxatives or anti-diarrheal drugs is indicated, respectively;
• with the phenomena of biliary dyskinesia, the use of drugs that eliminate the phenomena of stagnation of bile is indicated.
In acute abdominal pain, it is unacceptable to use preparations with an analgesic effect, including non-narcotic analgesics. They can mask the true causes of pain, which in some cases contributes to the progression of the disease, since the treatment of the underlying disease is not carried out.
• The most common side effects when using antispasmodics in combination with analgesics (sodium metamizole) are allergic reactions, decreased blood pressure, decreased daily urine output, interstitial nephritis, bronchospastic syndrome.
• With long-term use of drugs containing metamizole sodium, a monthly clinical blood test is necessary to timely detect possible changes in the composition of peripheral blood (agranulocytosis, leukopenia, thrombocytopenia).

• Antispasmodics in combination with analgesics with special caution are used in patients with arterial hypertension, a history of kidney disease, myocardial infarction, and multiple injuries.
• Patients with atonic bronchial asthma and hay fever have an increased risk of developing hypersensitivity reactions to antispasmodic drugs in combination with sodium metamizole.
• Antispasmodic drugs in combination with analgesics enhance the effects of ethanol.
• Caution should be exercised in the simultaneous use of drugs containing metamizole sodium, with oral hypoglycemic drugs, anticoagulants, gricyclic antidepressants, hormonal contraceptives, sedatives, and other non-narcotic analgesics.
• In case of an overdose of oral antispasmodic drugs in combination with analgesics, gastric lavage is performed, 30 g of sodium sulfate dissolved in 250 ml of water, activated charcoal are prescribed as a laxative.

Lesson purpose

Know:

I. Pharmaceutical care for constipation

1. The most common causes of constipation

• pathology of the large intestine - colitis, intestinal atony, spasm of the large intestine, megacolon, polyposis of the colon;
• metabolic disorders - dehydration, hypothyroidism, hypofunction of the adrenal glands;
• nutritional features - a sharp change in diet, lack of dietary fiber (dietary fiber), excess fat in the diet, insufficient fluid intake, excess iron in food, folic acid deficiency;
• painful bowel movements - anal fissures, hemorrhoids;
• use of drugs - antacids containing aluminum salts; antihistamines; codeine-containing preparations; cho linolytics; antihypertensive drugs (calcium channel blockers); iron, calcium preparations; antidepressants, antipsychotics; psychotropic drugs and a number of other drugs.

3. Factors contributing to the occurrence of constipation:

• systemic diseases of the connective tissue (rheumatism, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, etc.);
• the predominance of protein foods, fatty foods in the diet;
• lack of physical activity;
• prolonged use of laxatives;
• frequent use of enemas.

4. "Threatening" symptoms that allow suspecting a serious illness in a patient requiring compulsory medical intervention:

•temperature rise;
• traces of blood in the stool;
• severe abdominal pain;
• sharp bloating;
• vomiting;
•weight loss;
• the relationship of constipation with the use of a particular drug.

5. General approaches and recommendations for patients on non-drug methods for normalizing bowel function

6. Classification of laxatives

By the main focus of action, laxatives are distinguished:

• stimulating the motor function of the intestine;
• softening feces;
• increasing the volume of intestinal contents.

a. Agents inhibiting water absorption and enhancing intestinal motility (contact laxatives)

1.1. Preparations containing anthraglycosides.
1.2. Preparations are derivatives of diphenylmethane.
1.3. Synthetic preparations of other groups (sodium picosulfate).
1.4. Osmotic laxatives.
1.5. Castor oil

b. Means that increase the volume of intestinal contents, - "fillers"
in. Means that lubricate the intestinal mucosa, soften stool. Petroleum jelly (liquid paraffin)
7. Pharmaceutical custody when using drugs for the symptomatic treatment of constipation (laxatives)
• Laxatives should be given on an empty stomach.
• With prolonged use of laxatives, hypokalemia develops, so it is recommended that laxatives be taken with potassium preparations.
• Laxatives containing anthraglycosides act 8-12 hours after administration, therefore it is recommended to take them in the evening, before going to bed.
• Laxatives containing antraglycosides are not used for spastic constipation, as they can cause pain in the colon.
• Anthraquinone glycosides pass into mother's milk, therefore, preparations containing them should not be prescribed to nursing mothers.
• Laxatives from the antraglycoside group are not recommended for long-term use.
• Laxatives from the group of derivatives of anthraquinone with an acidic reaction of urine can stain it intensely yellow, with alkaline - in red.
• Sodium picosulfate in infants is ineffective.
• With prolonged use of liquid paraffin, the absorption of fat-soluble vitamins (A and D) is reduced and the risk of malignant tumors in the gastrointestinal tract is increased.
• Lactulose laxatives can be given to young and middle-aged children.
• Lactulose should not be taken in patients with acute inflammatory bowel disease.
• Castor oil has a laxative effect after 5-6 hours.
• Castor oil should not be prescribed to pregnant women.
• Castor oil is contraindicated in cases of poisoning with fat-soluble poisons.
• Saline laxatives have an effect after 4-6 hours
• Saline laxatives are contraindicated during pregnancy, as violent peristalsis can stimulate uterine contractility.
• When taking laxatives containing plant fibers, you should drink at least 1.5 liters of fluid per day
II. Pharmaceutical custody when using Motilium®
• Motilium® is available over-the-counter.
• The drug should be taken in 15-30 minutes. before eating.
• During pregnancy and lactation, Motilium® should be prescribed only in cases where its use is justified by the expected therapeutic effect.
• Since the pituitary gland is outside the blood-brain barrier, Motilium® can induce an increase in plasma prolactin levels.
• Motilium® in therapeutic doses does not affect the speed of psychomotor reactions, therefore it can be used by vehicle drivers.
• Extrapyramidal phenomena were rarely observed in children and are an exception in adults, their spontaneous and complete reversibility occurs immediately after treatment is discontinued.
• It is inappropriate to use anticholinergics with the drug, due to their neutralizing effect.
• When combined in the complex of therapy of the drug Motilium® with antacids or antisecretory drugs, the latter should be taken after a meal.
III. Pharmaceutical care for heartburn
1. The most common causes of heartburn
A. Heartburn in patients with diseases of the gastrointestinal tract:
• chronic gastritis with high acidity (type B gastritis);
• peptic ulcer of the stomach and duodenum;
•chronic cholecystitis;
• gastroesophageal reflux.
b. Heartburn in healthy individuals:
• malnutrition
overeating;
fast food "on the go", in a stressful environment;

abuse of butter and fatty foods;
o consumption of a large number of sweets and products containing caffeine (coffee, tea, chocolate);
abuse of spicy and spicy food;
• individual hypersensitivity to food products - citrus fruits, onions, garlic, tomato products (juices, pastes, sauces);
• first half of pregnancy;
• taking medications (NSAIDs, steroid hormones, cholinomimetics and some other drugs).
c. Factors contributing to the occurrence of heartburn:
• alcohol abuse;
• smoking;
• sleep or rest lying immediately after eating;
• wearing tight clothes;
• lack of exercise;
• obesity.
d. "Threatening" symptoms that make it possible to suspect a patient of a serious illness that requires the mandatory intervention of a doctor, with heartburn are:
• heartburn, accompanied by vomiting the color of "coffee grounds" or blood;
• the presence of black (tarry) stools;
• constant heartburn for 3 days or more;
• heartburn, accompanied by shortness of breath, sweating, difficulty swallowing;
• heartburn combined with abdominal pain;
• progressive weight loss;
• Heartburn is associated with taking certain medications.
2. General recommendations for patients on non-drug methods of treating heartburn:
• do not abuse products that stimulate acid formation in the stomach: spicy, spicy foods, citrus fruits, pastes and juice from tomatoes, onions, garlic;
• prevent overeating, fast food;
• eliminate or reduce smoking;
• avoid lying down after eating;
• limit the consumption of products containing gases (pastries, soufflés, whipped cream, carbonated drinks);
• drugs that enhance acidity, taken with food or milk;
• in case of heartburn during sleep, raise the head of the bed;
• reduce body weight.
3. Modern classification of antacids
a. Absorbable sodium antacids bicarbonate (soda). Calcium carbonate precipitated.
b. Non-absorbable antacids Aluminum hydroxide. Aluminum phosphate. Magnesium oxide. Bismuth nitrate basic.
4. Pharmaceutical custody when using drugs for the symptomatic treatment of heartburn (antacids)
• All antacids are taken only orally - in case of heartburn or 1 hour after eating.
• To avoid drug interactions, antacids should be used 2 hours before or 2 hours after taking other drugs.
• Antacids containing aluminum are indicated for diarrhea, and magnesium is indicated for constipation.
• Antacids based on aluminum salt of first-generation phosphoric acid (phosphalugel, compensated, pensionamar) have a therapeutic effect slowly.
• All aluminum-containing antacids interfere with the absorption of phosphorus, forming insoluble salts of aluminum phosphate. Clinically, this is manifested by muscle weakness, malaise, osteoporosis.
• An increase in the aluminum content in the body, due to excessive use of drugs, can cause encephalopathy (speech impairment, muscle twitching, cramps), and later dementia.
• Excess aluminum, when using non-absorbable antacids, accumulates in the renal glomeruli, which can lead to the development of renal failure.

• Non-absorbable antacids inhibit the absorption of certain drugs: tetracycline, norfloxacin, cardiac glycosides, corticosteroids.
• Acceptance of absorbed antacids is often accompanied by the phenomenon of “ri-kosh” - a repeated increase in the secretion of hydrochloric acid after the initial neutralizing effect.
• Absorbable antacids in large doses can cause systemic metabolic reactions - alkalosis and lactic acid syndrome.
• Patients with hypertension, heart and kidney failure, liver cirrhosis are contraindicated in antacids containing sodium bicarbonate. As a result of a chemical reaction with hydrochloric acid, they form sodium chloride, which is well absorbed and causes water retention in the body.
• Patients with urolithiasis should not take antacids containing silicon (in the form of magnesium trisilicate) - excreted in the urine, it contributes to the formation of stones in the urinary tract.
• With prolonged use of antacids, there is a tendency to infections of the gastrointestinal tract as a result of a decrease in the protective role of hydrochloric acid.
• Antacids cannot be combined with de-nol and sucralfate (pharmacodynamic incompatibility).
IV. Pharmaceutical custody during flatulence
1. The main causes of flatulence
• intolerance to certain types of food (dairy products and carbohydrates of certain types of food products (mushrooms, soybeans, sweets, legumes, nuts, cabbage, plums, some cereals, fruit juices, etc.);
• binge eating;
• Unaccustomed food or a change in the nature of nutrition (business trips, holidays, vegetarianism, etc.);
• smoking;
• gastritis and peptic ulcers;
•cholelithiasis;
• dysbiosis;
• abnormal peristalsis (contraction of the muscles of the colon)
• premenstrual period;
• postoperative period.
2. "Threatening" symptoms in flatulence, requiring mandatory medical intervention
• intense abdominal pain;
•nausea and vomiting;
• yellowness of skin color and sclera of the eyes;
• sharp and pronounced weight loss;
• bloating after taking medication.
3. Recommendations for non-drug relief of flatulence
• identification and exclusion (restriction) from the diet of foods that cause flatulence;
• restriction of consumption of products containing sugar substitutes, causing bloating and pain from gas congestion;
• increase in physical activity;
• rejection of chewing gum;
• smoking cessation or reduction;
• food intake in small portions 4-5 times a day;
• the use of products containing acidophilic cultures.
4. Medication for flatulence
Enterosorbents - enterosgel, caopectate, attapulgite, polyphepan
Silicones - dimethicone (zeolate) and simethicone (disflatil, espumisan).
Enzyme preparations. "Festal".
Carminative products of plant origin: ukro-pa preparations (odorous dill fruits, dill water), fennel fruits, caraway seeds, chamomile flowers.
Probiotics.
Domperidon - “Motilium”.
5. Pharmaceutical custody when using drugs for the symptomatic treatment of flatulence

• Due to the adsorption properties, preparations of the sorbent group are capable of decreasing the effectiveness of simultaneously prescribed oral drugs.
• It is recommended that the interval between the intake of adsorbents and other drugs be observed.
• With prolonged use of adsorbents, the body becomes depleted of vitamins, proteins, fats, etc.
• Adsorbents, due to moderate fixing action during prolonged use (and / or use in high doses), can contribute to constipation.
• Activated charcoal stains black feces.
• Attapulgite is contraindicated in high temperature.
• Attapulgite is contraindicated in the first trimester of pregnancy and with lactation.
• Attapulgite in the form of tablets can be prescribed to children only after 6 years, in the form of a suspension after 3 years.
• Silicones (simethicone, dimethicone) are recommended to be taken with a small amount of liquid after each meal and at bedtime.
• Domperidone is used only as directed by your doctor!
• Herbal carminative agents are used in the form of infusions or decoctions.
• Infusions from dill, fennel and caraway seeds stimulate milk production in nursing mothers.
• Infusions and decoctions are stored in the refrigerator for no more than 3 days.
• Plantex tea cannot be sweetened!
• Enzyme preparations should be taken during or immediately after a meal.
• Tablets containing enzyme preparations should not be chewed.
V. Pharmaceutical custody for dysbiosis
1. The main composition and functions of normal intestinal microflora
2. The main functions of intestinal microflora are normal
• Detoxification (inactivation of enterokinase, alkaline phosphatase).
• Enzymatic (hydrolysis of metabolic products of proteins, lipids, carbohydrates).
• Synthetic (synthesis of vitamins, antibiotic and other biologically active substances).
• Digestive (increase the physiological activity of the digestive tract).
• Antianemic (promotes absorption of iron).
• Antirachitic (promotes the absorption of calcium and vitamin D).
• Immune (activation of the immune system, synthesis of immunoglobulins, interferon).
• Intermicrobial antagonism.
3. The main factors for the development of dysbiosis
Exogenous:
• industrial poisons;
• violation of sanitary standards in everyday life and at work;
• ionizing radiation;
• climatic and geographical factors;
• surgical interventions on the organs of the gastrointestinal tract.
Endogenous:
• immune disorders;
• stressful conditions;
• non-infectious diseases of the gastrointestinal tract (pathology of the intestine and gall bladder, gastric ulcer, etc.);
•infectious diseases;
•diabetes;
• rheumatic diseases;
• starvation;
• poor nutrition;
• old and senile age;
• irrational medication.
In addition to the above, in children, dysbacteriosis development factors can also be:
• anatomical disorders;
• food allergy;

• errors in nutrition;
• antibiotic therapy (including rational).
5. Clinical manifestations of dysbiosis:
• unstable stools (constipation, diarrhea or alternating constipation and diarrhea);
• bloating and rumbling of the abdomen;
• pain in the lower abdomen, decreasing after the discharge of gases;
• nausea, belching, bitterness in the mouth.
• asthenoneurotic syndrome (due to hypovitaminosis and intoxication);
• anemia;
• hypoproteinemia;
• osteomalacia;
• weight loss;
• hypovitaminosis (mainly fat-soluble vitamins).
4. Classification of dysbiosis.
1 degree - compensated (latent dysbiosis)
2 degree - subcompensated (or localized) dysbiosis
Grade 3 - common dysbiosis.
Grade 4 - generalized (decompensated dysbiosis)
5. The basic principles of the treatment of intestinal dysbiosis
A. Non-drug treatment of intestinal dysbiosis
• providing good nutrition;
• improving the functional state of the intestine and other organs of the digestive system;
• stimulation of regeneration processes and increase immunity.
B. Drug treatment of intestinal dysbiosis
5. Pharmaceutical custody with the use of probiotic preparations
• Before taking probiotics, you should always consult your doctor.
• A complex multicomponent preparation “Linex” is a means of choice for the correction of dysbacteriosis of the small and large intestines
• When used in young children, you can open the Linex capsule and mix its contents with a teaspoon of liquid (tea, water, juice). The resulting mixture is a suspension of white powder in water. Not subject to storage.
• Against the background of antimicrobial therapy, probiotics or linex or bifi-form preparations are possible, since they include antibiotic-resistant strains of the intestinal flora.
• Hilak and Hilak forte are not recommended for use with milk and other dairy products.
• Simultaneous administration of Hilak and Hilak forte preparations with antacids is inadmissible.
• Preparations lactobacterin and lactobacillus acidophilus are recommended to drink milk.
• Any probiotics are not recommended for drinking hot drinks.
• Any probiotics are not recommended to be taken along with alcohol.
• For the prevention of dysbiosis, functional food products are indicated.
VI. Pharmaceutical custody for functional pathology of the digestive system, accompanied by pain:
• for the relief of pain, the use of antispasmodics with analgesics is indicated;
• with signs of digestive disorders (nausea, flatulence, belching, heartburn, etc.), aggravated after eating, the use of enzyme preparations is indicated;
• for flatulence, the use of antifoam agents and wind-chasing is indicated; for heartburn, antacid preparations;
• for constipation or diarrhea, the use of laxatives or anti-diarrheal drugs is indicated, respectively;
• with the phenomena of biliary dyskinesia, the use of drugs that eliminate the phenomena of stagnation of bile is indicated.
The decision of situational problems
Exercise 1
Select and dispense a medication to relieve constipation.
A. Woman 43 years old, accountant.
B. A 57-year-old man with hemorrhoids.

C. The woman is 82 years old and has been taking antianginal and antihypertensive drugs for a long time.
To do this, complete the following tasks:
1. Give a concise definition of constipation.
2. Place an algorithm for interviewing a pharmacist with a patient with an emphasis on the elements of pharmaceutical care, using the following key questions:
• Have you always suffered from constipation?
• When did you first notice constipation?
• Have you noticed that along with constipation, bowel movements became painful?
• What other symptoms (abdominal pain, rumbling, heartburn) do you feel?
• Do you use any medications at this time?
• Do you have a disease of the gastrointestinal tract?
• Is your work unrelated to prolonged sitting?
What are the medications for constipation? What pharmacological groups do they belong to?
4. Give recommendations to the patient under conditions of rational use of the drug chosen by you (dosing regimen, interaction with food, alcohol, other drugs).
5. What herbal preparations of extemporaneous preparation should be prescribed to the patient? Consult him on the technology of preparation and use of your chosen herbal remedy.
What is OTC drug:
A. Phosphalugel.
B Analgin.
C. Klofelin.
D. Digoxin.
E. Amiodarone.

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
PHARMACEUTICAL CARE OF PATIENTS WITH PATHOLOGY OF THE URINARY SYSTEM

Relevance of the topic.

Disorders of the kidneys and other organs of the urinary system
manifested by a wide variety of symptoms, often disguised as those of other diseases.

That is why a person who first encountered manifestations of nephro- or uropathology does not always attach serious importance to them and begins to use various treatment methods at his own discretion (the opposite of responsible self-medication). The danger of this situation is that, turning to the pharmacy, the client focuses on the symptom that bothers him most (mainly pain in the lower back, lower abdomen; fever) and does not attach importance to other indicator manifestations of the pathology.

In the framework of pharmaceutical custody, the primary task of the pharmacist is to correctly assess the state of the visitor to the pharmacy, taking into account both the nature and the totality of the complaints.

Motivational characteristic of the topic.

The urinary system is one of the systems responsible for maintaining homeostasis (constancy of the internal environment).

Brief anatomical and physiological data

The role of the kidneys is to remove from the body the toxins that are formed during the course of life and to regulate a number of functions (in particular, blood pressure).

Urine is formed in the kidneys. From there, through thin elastic tubes - urinary tracts, it enters the bladder and is secreted out through the urethra.

The kidneys (two of them) are located to the right and left of the lumbar-thoracic spine, outside the abdominal cavity. There is a liver above the right kidney, and the spleen above the left. The shape of a kidney resembles a bean. Its length is 10-12 cm, weight 150-170 g. The kidney is surrounded by a thin connective tissue capsule, a large layer of adipose tissue.

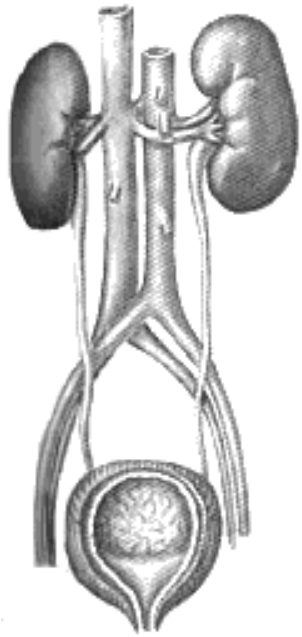
The kidney is well supplied with blood and innervated (renal artery, renal nerves). On the section of the kidney, the outer cortical and inner cerebral layer is visible. In the cortical layer are glomeruli (glomeruli) formed from branches of the renal artery. Each glomerulus is surrounded by a special capsule, named after the researchers who first described it, the Shumlyansky-Bowman capsule.

This capsule can be compared with a kind of filter: here the substances accumulated in the blood that are unnecessary for the body come from the glomeruli into the tubules, which depart from the capsule.

Distinguish tubules of the first and second order. They are located in the cortex and medulla of the kidney. Ultimately, the tubules flow into the renal pelvis, where urine is collected through the ureters.

According to modern concepts, the process of urine formation goes through two stages: the first is filtration in the glomeruli (primary urine) and the second is the absorption of certain components of water by the tubules from the primary urine - water, sodium chloride and other substances, resulting in the formation of real urine.

Blood continuously (about 1 l / min) passes through the kidneys, due to which the body is cleansed of toxins. Typically, a healthy person excretes no more than 2 liters of urine per day, but with large amounts of fluid, this amount increases, and with dry eating, it decreases.



Kidney and bladder

The activity of the kidneys is influenced by the central nervous system. Urination may be impaired with certain neuropsychiatric stresses, severe excitement can cause involuntary urination.

The complete absence of urine is called anuria (cessation of urination in severe kidney damage, for example, with poisoning).

A decrease in the amount of urine (oliguria) and an increase (polyuria) can be a result of both physiological abnormalities and diseases of the kidneys and other organs and systems (for example, sugar disease).

The relative density of the urine of a healthy person ranges from 1017 to 1024.

A constant decrease in the relative density of urine (hypostenuria) occurs with impaired renal function. Diseases of the kidneys and urinary tract are diverse, but are mainly divided into local (nephritis, nephrosis) diseases (tuberculosis, cancer, kidney stones, pyelonephritis).

Along with the symptoms that are characteristic of only one disease, there are symptoms specific to a number of diseases of the urinary organs.

When questioning a patient, they pay attention to pain in the lumbar region (inflammatory processes, stones, malignant neoplasms, etc.). The pains are acute (an attack of renal colic) or aching, persistent (chronic inflammatory process). The patient may complain of frequent urination, pain during urination, the appearance of impurities in the urine, for example, blood (hematuria), which is typical for nephritis.

When examining a patient, edema, puffiness of the face, pallor can be established.

For an objective assessment of puffiness, there is a special Aldrich test. Intradermally, 0.1 ml of an isotonic sodium chloride solution is injected into the inner surface of the forearm. The resulting small blister in healthy people resolves in 45-50 minutes; with a tendency to edema, this blister resolves faster (10-15 minutes).

As mentioned above, in the urine there may be pathological impurities. In addition to hematuria, there is pyuria (the appearance of pus in the urine), albuminuria (protein in the urine). The last symptom is determined by a laboratory method in the study of urine.

Functional tests are of great importance for the diagnosis of kidney diseases. An example is the sample proposed by a major domestic clinician Zimnitsky. In the morning, a portion of urine is collected every 3 hours from the patient. Take into account daily diuresis - the amount of urine

excreted from 8 a.m. to 8 p.m. and night diuresis - from 20 p.m. to 8 a.m. the next day. Urine is collected in 8 glass vessels. In each portion, the quantity and relative density of urine are determined.
Normally, nocturnal diuresis should account for about 30% of total diuresis (the amount of urine excreted per day). The amount of urine corresponds approximately to the amount of liquid drunk per day. The relative density of urine in different portions varies.
Violation of these indicators (monotonous or low relative density of urine, the prevalence of nocturnal diuresis over daytime, etc.) is a consequence of kidney disease.
Objective clinical methods for studying the kidneys present certain difficulties, since healthy, normal in size and shape of the kidneys cannot be examined, palpated or palpated (the kidneys are located deep behind the peritoneum, covered with a thick muscle layer in the back, and the intestines are in front). Pathological changes during examination can be detected only in cases where the kidney is significantly enlarged (for example, with a malignant tumor) and protrudes either from the side of the anterior abdominal wall, or in the lumbar region on the right or left.
Palpation (palpation) of the kidneys also becomes possible only in case of enlargement of the organ or its displacement (omission).
Feeling (palpation) of the kidneys is carried out in the position of the patient lying and standing.
When palpating the kidneys in the supine position (in this case, the abdominal muscles relax, which facilitates palpation), the examiner sits to the right of the patient. The patient lies with outstretched legs and makes deep, even breathing movements in the stomach.
The kidneys are palpated with both hands. To recognize kidney prolapse, the best data can be obtained when the patient is standing. In the study of the kidneys, a peculiar tapping or striking method is also used: the doctor puts the left palm on the lower back in the region of the right or left kidney, and strikes with moderate force with the edge of the palm or fingertips (less often with the fist). If such striking is painful, they speak of a positive symptom of Pasternatsky, which happens with the inflammatory process in the renal pelvis, kidney stone disease.
Other symptoms of kidney disease include an increase in blood pressure (hypertension), which is observed in acute and chronic nephritis, as well as changes in vision. In patients with chronic nephritis due to hypertension, spasm of the vessels of the retina of the eye first occurs, and later vascular sclerosis develops.
The term "urinary tract infection" combines a number of diseases. The inflammatory process can be localized in the urethra, urinary bladder, renal pelvis. Depending on this, the patient is diagnosed with ureitis, cystitis, pyelonephritis, respectively.
Glomerulonephritis (nephritis) is an inflammation of the kidneys with a predominant lesion of the renal glomeruli. With the course, acute, subacute (malignant, progressive) and chronic nephritis are distinguished.
Acute glomerulonephritis - an infectious-allergic disease occurs after tonsillitis, flu, scarlet fever and other diseases as a result of allergic reactions to the introduction of infection into the body. The development of the disease contributes to cooling.
In acute glomerulonephritis, patients complain of headaches, lower back pain, shortness of breath. The most characteristic symptoms of the disease are swelling, increased blood pressure, changes in the urine (protein, red blood cells). The amount of urine decreases, renal failure may occur, and sometimes even anuria. The disease in some cases causes left ventricular heart failure. Treatment: bed rest, dairy and vegetable diet with restriction of salt and liquid, antibiotics, hormone therapy, cardiac drugs.
Chronic glomerulonephritis develops as a result of uncured acute inflammation of the kidneys. In the absence of characteristic symptoms, the acute period of the disease often cannot be diagnosed. It proceeds for a long time, with repeated exacerbations, which are characterized by the same symptoms as for an acute disease. In the interval between exacerbations (remission period), the patient may feel well and not show any stitches. Treatment: elimination of foci of chronic infection, diet, medication, spa treatment (resorts with a dry and hot climate).
In etiology, streptococcal (tonsillitis, upper respiratory tract diseases, streptoderma) and other infections (pneumococci, diphtheria, typhoid, brucellosis, etc.) play a role. Along with this, factors that change the reactivity of the body, especially hypothermia, microtrauma of the kidneys, are

important. In this case, reflex disorders of the blood supply to the kidneys and changes in immunological reactions occur. Immunoallergic theory predominates in pathogenesis. Against the background of infection, under the influence of factors that change the reactivity of the immune system, sensitivity to the pathogen increases, antibodies are produced. They do not perform a protective function, on the contrary, their complex with antigen (pathogen) is fixed in the glomeruli.
The production of anti-renal autoantibodies begins. As a result, damage to the glomerular basement membrane develops. In the reaction of allergic inflammation, complement, the kinnova system, are involved. Enzymes of lysosomes are activated, as well as inflammatory mediators (opiate, serotonin, etc.). The processes of blood coagulation in glomerular vessels are disturbed (complement activation, platelet aggregation, increased serum kallikreins and kinins).
This leads to the deposition of fibrin in the walls of the renal capillaries. As a result, the structure of the basement membranes and their permeability are violated. In the primary urine, blood cells, plasma proteins begin to be filtered. As proliferation and deposition of fibrin increase, a delay in the body of fluid and metabolites begins to prevail. Edema is caused by a decrease in glomerular filtration, a decrease in plasma oncotic pressure (hypoproteinemia with proteinuria), increased sodium reabsorption (increased aldosterone secretion due to activation of RAAS), and impaired vascular permeability.
The treatment of glomerulonephritis is one of the most acute and controversial problems of nephrology. The variety of causes of the disease involves polytiotropic treatment, but it is difficult to determine its direction, and in some patients with chronic forms it is impossible. The pathogenesis of glomerulonephritis has been studied deeply, but in a specific case, immunological studies and biopsies are not always available to clarify it. Finally, the choice of treatment method is very responsible. On the one hand, the probability of spontaneous recovery is quite high, especially with a benign course in children (up to 30-40%, Papayan A.V., 1994).
On the other hand, universally recognized immunosuppressive ("active", and more correctly "aggressive") therapy poses a real threat to the health, and often the life of the patient, especially the child (see table). Therefore, the main principle should be caution in choosing a treatment strategy and tactics. In our opinion, glomerulonephritis should not be treated "according to the scheme", the more dangerous is the formal approach when glucocorticoid therapy is thoughtlessly prescribed, prolonged use of which deprives the patient of a chance for recovery.
In acute forms of the disease, hospitalization is indicated. At the same time, it is very important to create a favorable social and psychological environment; children need unhindered contact with their parents.
Strict bed rest provides a decrease in metabolic load on the kidneys. But prolonged physical inactivity can exacerbate microcirculation disorders and contributes to thrombosis. Therefore, the restriction of the regimen is shown in the first to second weeks of the disease and should be strict in case of malignant course and the threat of acute renal failure (ARF). Sudden movements, heavy lifting, hypothermia of the lumbar region are unacceptable; a warm bed is needed.
Diet therapy is prescribed taking into account the severity of the process. With urinary syndrome, protein is limited to 50-60 g / day, sodium (salt) to 3-4 g / day. In the nephrotic variant, the protein is given in an amount equal to the sum of its daily loss in urine and the daily norm; sodium is sharply limited (up to 2 g per day), the fluid should not exceed diuresis by more than 300-400 ml). If hypertension predominates, limit salt (1-3 g / day) and fluid. In the acute period, extractives, strong broths, ear, jellied meat are not given; meat and fish are fried after preliminary boiling. In severe nephrotic variant with hypertension, "hunger and thirst" are shown for the first two days. As the clinical manifestations subside, the diet is gradually expanding. According to and during the period of remission, it is preferable to avoid salty and spicy dishes, canned food, smoked meats, refractory animal fats. Vegetable proteins, juices, vegetables with an alkalizing reserve (cucumbers, zucchini, pumpkin), non-acidic varieties of berries, as well as fruits and mineral waters are useful.
Among all clinical forms of glomerulonephritis, the fastest progressing glomerulonephritis (subacute, malignant glomerulonephritis) proceeds most severely.
Pyelitis is an inflammation of the renal pelvis of an infectious nature. Microorganisms enter the kidney either through the ascending ureters, or are carried with blood or lymph. The course of the

disease is acute or chronic. In the acute course, the temperature suddenly rises to 39–40 ° (not uncommonly with chills), lower back pain appears, and the heart rate increases. Urine becomes cloudy, with lots of white blood cells. Chronic pyelitis can occur without pronounced symptoms, manifested by subfebrile temperature, a feeling of weakness. The diagnosis is made on the basis of a urological study. An exacerbation proceeds as an acute disease. In chronic pyelitis, inflammation seizes the kidney tissue (pyelonephritis) and can lead to the development of renal failure.

Treatment: bed rest, dairy and vegetable diet, plentiful drink, antimicrobial agents, antibiotics.

Pyelonephritis is an infectious and inflammatory kidney disease with a predominant lesion of the interstitial tissue of the tubules, pelvis, chalice, and, in most cases, the urinary tract.

In etiology, the leading ones are urodynamic disorders, decreased immunity and infection.

Congenital malformations of the urinary tract, constitutional features predisposing to the omission of internal organs, including nephroptosis, contribute to impaired passage of urine. Hereditary predisposition can also occur in dyskinesia of the urinary tract due to neurosis. Disorders of urine outflow occur during pregnancy, hemorrhoids, constipation, prostate adenoma, nephrolithiasis, as a result of adhesions after surgery (secondary pyelonephritis).

Infection usually enters the kidneys in an ascending (urinogenous) way from the mucous membranes of the genitourinary organs through the urethra, bladder, and urinary tract. Pathogens from any focus of infection (caries, sinusitis, sinusitis, tosillitis, cholecystitis, adnexitis, enterocolitis, etc.) can enter the lymphogenous pathway. For viruses, the hematogenous pathway is very likely. The most common pathogens are gram-negative bacteria and cocci (Escherichin, staphylococci, enterococci, Proteus, Pseudomonas aeruginosa), as well as viruses, leptospira, fungi.

Bacterial endotoxins inhibit peristalsis of the ureters, cause adhesion (adhesion to the urinary tract epithelium) of pathogens. Adherence of saprophytic microorganisms (komensals or “defenders”) is also facilitated by receptors present in the mucous membrane, the density of which is higher in patients predisposed to pyelonephritis. Along with the decline in local immunity, factors that violate the functions of the immune system and reduce the overall resistance of the body provoke the disease: overwork, hypovitaminosis, adverse environmental conditions, regular use of antibiotics, nmmunosuppressants, hormonal contraceptives, etc.

Violation of the outflow of urine causes an increase in pressure in the pelvis. Detained toxins in the tubules activate the peroxide oxidation of lipids. This leads to disorganization of cell membranes, cessation of the formation of protective mucus, acidosis and a violation of the colloidal structure of urine. Adhesion of pathogens contributes to the development of inflammation, in which neutrophils and immunoreactive kallikrein are involved. With a combination of hereditarily fixed defects of local protection and violations of the T-system of immunity, the formation of an autoimmune process with the involvement of glomeruli and subsequent nephrosclerosis is possible. Chronization is facilitated by anatomical abnormalities, as well as the formation of non-shell forms of pathogens (L-forms and protoplasts), which is often associated with irrational antimicrobial therapy. Inflammation disrupts the excretory function of the kidneys. Intoxication develops, which exacerbates urodynamic disorders and immunodeficiency.

More often, women under the age of 40 get sick (60-70% of the total number of patients), and in old age men get sick more often. About 10% of patients get sick before the age of 10 years.

Acute pyelonephritis is characterized by a sudden onset, high fever, back pain, pyuria (leukocyturia, bacteriuria, prinsinuria). Dysuric disorders are not infrequently observed. Often a high relative density of urine is found, sometimes - a pylindrurna (epithelial cylinders).

Chronic pyelonephritis is characterized by poverty of clinical manifestations. Complaints of fatigue, headaches, epigastric pain, dysuria, low-grade fever prevail. Pain in the lumbar region is dull, often - just a feeling of heaviness, discomfort. It is usually possible to detect soreness when striking the lumbar region (a positive symptom of Pasternatsky) and with bimanual palpation of the kidney area.

To clarify the diagnosis, a bacterial urine test (an antibiotiogram is desirable) and an ultrasound scan are necessary. Leukocytosis with a neutrophilic shift and accelerated ESR are detected in the blood. In severe cases, azotemia is possible. Gynecological examination is shown to women. Complications of pyelonephritis can be renal failure and bacterial shock.

With pyelonephritis, bed rest is necessary only at the height of famously (usually 1-3 days). Hypodynamia contributes to stagnation of urine, therefore, the motor regimen is expanded as the clinical manifestations subside, physiotherapy is desirable.
Nutrition for pyelonephritis should be complete. Salt restriction is necessary only in severe cases. It is undesirable to use foods that destroy the parenchyma of the kidneys. With excessive excretion of salts with urine, a more strict diet is required. It is desirable to increase fluid intake, preferably in the form of mineral waters and juices with a diuretic effect (apricot, watermelon, birch, grape, cherry, pear, cucumber, peach, pumpkin, blueberry, apple). In this case, it is important to control the pH of the urine, avoiding excessive acidification and alkalization, as sharp fluctuations increase the risk of crystallization. In elderly people, a sharp decrease in potassium and sodium in the body is dangerous, cardiovascular complications are frequent, so the amount of fluid consumed in them is determined individually.
Until recently, the prevailing direction (and not rarely, the only one) in the treatment of pyelonephritis was the fight against infection. However, modern ideas about the etiopathogenesis of the disease suggest a shift in emphasis and normalization of urodynamics and immune correction become priority.
Restoring normal outflow of urine can only be achieved by a phytotherapeutic way. The use of diuretics of synthetic origin for this purpose is unacceptable, since all of them are actively secreted in the canals. In the best case, the inflamed tubules will not react in any way to the diuretic, and in the worst case, such therapy will strengthen the inflammatory process.
The choice of herbal remedies for uncomplicated pyelonephritis is very simple - extracts from plants - any medicinal plants with diuretic properties can be used. However, those types of medicinal plants that, in addition to diuretic action, possess immunotropic properties and a wide range of effects on pathogens, are more preferable. The restoration of the broken links of immunity should be carried out in accordance with the results of an immunological study. Given the real possibility of the participation of autoimmune mechanisms in the pathogenesis of pyelonephritis, uncontrolled administration of immunosuppressants, immunomulators and immuno-modulators of synthetic and natural origin is unacceptable.
The fight against infection must begin as early as possible. The drug must meet the following requirements: ensuring a sufficient antimicrobial (antiviral, antistocidal, fungicidal) concentration in the kidneys and urinary tract, a wide spectrum of action, the absence of nephrotoxicity, eubioticity against saprophytic microorganisms of the genitourinary system.
• Drugs for pyelonephritis
The most common complication of chronic pyelonephritis is hypertensive syndrome. With the development of renal hypertension, RAAS antagonists (angiotensin converting enzyme inhibitors) are prescribed: benazepril (lotensic), captopril (alkadil, acetene, capoten, cardopril, catopril, systopril, tenziomin, etc.), perindopril (prestarium), ramipril (tritride) (apo-enal, vazolapril, renitec, enam).
A very important aspect is the prevention of nephrolithiasis. In chronic forms, monitoring of urine pH and sediment composition is necessary. With an increase in the content of poorly soluble salts, changes in the diet and the appointment of litholytic drugs are necessary.
When the acute manifestations of inflammation subside, physiotherapy (paraffino, ozokeritotherapy, ultrasound, etc.) and spa treatment are indicated.
In the absence of organic defects (congenital malformations, nephroptosis, etc.), the prognosis is favorable. Fatal causes and untimely irrational therapy can contribute to the formation of renal failure and other complications.
Urolithiasis (kidney stones)
Renal stone disease (PCB) - (urolithiasis, nephrolithiasis) is a polyetiological disease with impaired passage of urine and accumulation of insoluble salts in the cups, pelvis and urinary tract.
Kidney stone disease develops in violation of metabolic processes (mainly mineral), as a result of infection, trauma and is characterized by the formation of kidney stones. The formation of stones is facilitated by the nature of nutrition (a large amount of meat food, a lack of vitamin A), the

composition of drinking water (hard water), impaired urine outflow, impaired colloidal state of urine, prolonged bed rest.

Until now, the etiology of PCB is not completely clear, but it has been established that the following factors have a significant impact on its development:

1. Hypoxia
2. Hypodynamia
3. Reception of a small amount of liquid.
4. Violation of the regular passage of urine.
5. Oversaturation of urine with salts.
6. Changes in the pH of urine, contributing to the appearance of hardly soluble salts.
7. Urinary tract infection.
8. Eating foods with an excess of substances that contribute to stone formation.

Stone formation is based on a decrease in the content of protective colloids in the urine. Under these conditions, a group of molecules is formed - a “micelle”, which can become the nucleus of a future stone. Fibrin, blood cells, bacteria, residues of epithelial cells, and, finally, hardly soluble salts with their excessive content in the urine join it. Calculi form in the collecting tubules. If the urine is oversaturated with salts and the pH changes (to the acid side for urates, oxalates; to the alkaline side for phosphates), then crystallization and retention of calculi at the mouth of the tubules with incrustation of the papillae increase. Violation of urodynamics will contribute to the formation of large stones - single and multiple. With sharp and frequent fluctuations in pH, uncontrolled administration of litholytic drugs, complex so-called coral-shaped stones are formed.

It is possible to start treatment of urolithiasis (kidney stone) only after establishing the nature of the accumulating salts, since inadequate dietary and therapeutic measures can contribute to the formation of complex stones. Etiotropic therapy is very important, which is all the more successful, the more fully the causes of the resulting metabolic disorders are identified. In our opinion, the complex etiopathogenesis of the disease and the leading role of metabolic disorders are defined as priority conservative therapy.

Surgical removal of stones, as well as distance lithotripsy, which differs little from it, do not essentially provide healing and do not eliminate the causes and conditions of stone formation. At the same time, these methods of treatment are very traumatic and can themselves be the causes of serious complications. Therefore, they are applicable only in life-threatening situations, for example, in acute blockage of the ureter with a large calculus, which cannot be eliminated by emergency conservative therapy and threatening the development of hydronephrosis and anuria.

Treatment of urolithiasis should be comprehensive, individual. The regimen should help restore the tone of the smooth muscles of the urinary tract. Needed morning exercises, walks; quiet games, swimming, skiing (avoid hypothermia). The patient should pay attention to the importance of regular emptying of the bladder.

Alcoholic beverages and canned foods are contraindicated. It is very important to normalize the diet and increase the amount of fluid consumed (in the absence of contraindications from the CCC, endocrine and other body systems).

Pharmacotherapy and herbal medicine should be focused on a specific form of nephrolithiasis and include the following main areas:

Change in urine pH: alkalization with urate and oxalaturia, acidification with phosphaturia.

2. Lithological therapy provides increased solubility of salts, loosening and destruction of stones.
3. Reducing the formation of insoluble salts by reducing their synthesis and normalizing metabolic processes in the body.
4. Elimination of oxygen deficiency and improvement of metabolic processes in the kidneys (nephroprotectors).
5. Restoration of the colloidal structure of urine is provided by plants with a high content of silicic acids: knotweed (grass), nettle and stinging nettle (grass, especially roots), medunica medicinal (grass), common fireweed (rhizome), common burdock (grass), horsetail field (grass).
6. The fight against infection
7. Elimination of hypovitaminosis and immunodeficiency.

8. At the stage of excretion of destroyed calculi, it is necessary to prescribe antispasmodics: Avisan, Pin-bin, Rovachol, Rovatin, Spaz-mo-urgenin, Urolesan, phytolysin, flavoxate (urispas), pistenal, and medicinal plants that relax the smooth muscles of the urinary tract: Ammi tooth (fruits), mint (grass), lemon balm (grass), parsley (grass, seeds), dill (seeds), fennel (seeds), etc.
9. The restoration of urodynamics is carried out the more carefully, the larger the stones are detected.
Treatment of urolithiasis should be comprehensive. However, preference should be given to herbal medicine. It has several advantages, since it allows you to take into account the etiology and pathogenesis of the disease in a particular patient, can be quickly reoriented depending on changes in metabolic processes and the patient's condition. Small-component formulations are preferred, including herbal remedies of various therapeutic directions.
Components with bactericidal, antihypoxic and normalizing colloidal structure of urine properties must be included in collections. Our experience shows the need for regular monitoring of the composition of urine sediment once every 2 days in the 1st week, then once every 10-15 days, and repeated ultrasound examinations (once every 2-3 months). It is highly advisable to teach the patient "monitor-mu" control of urine pH using paper indicators. Careful observation allows you to make timely changes to the diet and the composition of fees, to appoint additional funds to prevent the formation of mixed stones.
Identifying a patient with coral stones poses a very serious problem for the doctor. With large stones, the use of intensive diuretic therapy is extremely dangerous, they carry out anti-infection and anti-inflammatory treatment with collections with weak diuretic activity. In the absence of effect for 2-3 months of such treatment, it is possible to resolve the issue of non-operative removal of stones. For this purpose, endoscopic methods (urethronyeloscopy nephroscopy) are widely used and, since 1980, remote lithotripsy (stone crushing), the destruction of the calculus by exposure to focused shock waves obtained electrohydraulically using an alternating magnetic field or piezoelectric crystals and high current voltage (piezoelectric principle).
It is safer to use these methods for stones of not very large size, so early detection and timely treatment of nephrolithiasis is extremely important.

• Treatment of nephrolithiasis

Renal colic requires emergency treatment. After clarification of the diagnosis, heat is assigned to the lumbar region and to the stomach (heating pad, compress, preferably a hot bath). Bed mode. Drug therapy begins with the introduction of antispasmodics (subcutaneously or intramuscularly): platifilln, papaverine, no-spa, baralgin. In the absence of effect, lytic mixtures are introduced:

1. No-spa 2 ml of 2% solution + platifillin hydrotartrate 1 ml of 0.2% solution + pro-medol 1 ml of 1% solution + diphenhydramine 1 ml of 1% solution.

2. Papaverine hydrochloride 2 ml 2% solution + promedol 1 ml 1% solution + analgin 2 ml 50% solution + pentamine 0.5 ml 5% solution.

3. Halidor 2 ml 2.5% solution + papaverine hydrochloride 2 ml 2% solution + -f di-medrol 1 ml 1% solution + chlorpromazine 1 ml 2.5% solution.

If the effect is not achieved by intramuscular administration, they are administered iv. In this case, it is necessary to monitor the state of the cardiovascular system, especially in patients with concomitant coronary heart disease, hypertension, atherosclerosis. In the hospital, novocaine blockade is performed (the area of the seminal canal in men, the uterine ligament in women).

In severe cases (with large stones, frequent bouts of renal colic, severe hematuria, the threat of hydronephrosis with blockage of the ureter, a stone of a single kidney), surgical treatment is indicated.

In conclusion, I want to emphasize that the underestimation of conservative treatment and especially the phytotherapy of nephrolithiasis, passion for stone crushing do not contribute to the outcome of the disease favorable for the patient, and often expose his life to unjustified risk.

Symptoms that may signal kidney and urinary tract diseases:

- changes in the amount of urine excreted (increase, decrease in urine output, frequent nightly urination, frequent urination);

- dysuric disorders (pain during urination, discoloration and transparency of urine);

- pain in the lumbar spine (dull, intense, pain during urination, unilateral, symmetrical);

- increase in body temperature, chills; - changes in the appearance of the patient (pallor of the skin);

- dry mouth, thirst;

- edema (mainly faces in the morning);

- increase in blood pressure;

- general complaints (weakness, fatigue, drowsiness, irritability), etc.

It should be noted that there are predisposing factors for the development of the pathology of the urinary system that trigger the pathological process (of a different nature depending on the disease).

So, in the case of pyelonephritis, predisposing factors are

abnormalities of the urinary tract,

the presence of calculi in them, prostate adenoma, etc.,

pathological refluxes (pelvis-ureteric, vesicoureteral and vesicourethral), leading to a violation of urodynamics.

Also leads to pyelonephritis

a number of common diseases (diabetes mellitus (diabetes), tuberculosis, hypovitaminosis, liver disease, etc.),

in women - pregnancy, prolonged use of oral contraceptives.

The likelihood of developing autoimmune inflammation (glomerulonephritis) increase

the effect of low temperatures on the body,

alcohol abuse,

the use of immune preparations (vaccines, serums, immunoglobulins),

transferred streptococcal infection (tonsillitis, rheumatism, scarlet fever, etc.).

In the occurrence of cystitis, a certain role is assigned

hypothermia, the presence of chronic foci of infection,

non-observance of personal hygiene rules,

circulatory disorders in the pelvis,

violation of the biocenosis of the vagina or intestines,

the effects of chemicals on the mucous membrane of the bladder, etc.

With urolithiasis (ICD), you must consider

diet features (animal proteins and refined sahar, lack of vitamins),

quality and quantity (dehydration) of water consumed,

the presence of metabolic diseases, such as gout,

pathology of the musculoskeletal system (osteomyelitis, osteoporosis),

gastrointestinal tract (chronic enteritis and pancreatitis), kidneys and organs of the genitourinary system (pyelonephritis, cystitis, prostate adenoma, prostatitis, etc.). !

The presence of risk factors and the corresponding clinical manifestations gives reason to suspect the presence of a certain disease, and, therefore, this complex of complaints should be regarded as a threatening symptomatology and recommend that the patient immediately consult a doctor!

The course of the disease is classified into acute and chronic.

Acute glomerulonephritis is characteristic

the appearance of urine the color of "meat slops",

fever

edematous syndrome,

increased blood pressure and, as a consequence, a headache.

In patients with pyelonephritis with exacerbation of the disease, the pain is often one-sided,

increase in body temperature,

severe weakness,

positive symptom of Pasternatsky.

With cystitis, patients are usually

complain of frequent urination,

pulling pain in the lower abdomen.

The main clinical manifestation of ICD is an attack of renal colic.

An important aspect is the differentiation of the first condition and relapse of the disease.

With the recurrent nature of the disease, preventive metaphylaxis is relevant.

In the case of a chronic course of the disease, patients are aware of it, are under constant medical supervision and can carry out metaphylaxis.

Metaphylaxis (from Lat. Meta - for, behind, after, for anything; filasso - to guard, set sentries) - a complex of medical preventive measures aimed at preventing relapse of the disease.

Despite the ever-expanding range of synthetic drugs, herbal preparations, which have undeniable advantages, occupy a significant place in metaphylaxis.

So, for example, various combined herbal preparations for metaphylaxis of the ICD are presented on the domestic pharmaceutical market, the effect of which is due to the presence of a polytropic pharmacodynamic potential:

antispasmodic,

antiseptic,

anti-inflammatory

diuretic effects.

contribute to the removal of stones and their dissolution

has a direct impact on the process of stone formation,

stabilization of the ionic composition of urine and stone formation inhibitors,

acceleration of the passage of stones, their fragments and sand after successful destruction using the method of remote lithotripsy,

the possibility of prolonged use without pronounced side effects.

One of such agents is the combined herbal preparation Kanefron® N (Bionorika SE, Germany), which includes a standardized extract of three medicinal plants:

root lovage,

centaury grass,

rosemary leaves.

Their components have a complex effect on the urinary system:

• antispasmodic (essential oil and phthalides, lovage, bitterness, phenolcarboxylic acids of centaury, rosemary leaves of rosemary eliminate reflex spasms of the urinary tract, improve urinary passage and blood flow in the kidney tissue due to dilatation of the renal arterioles);

• anti-inflammatory (rosmarinic acid inhibits the non-specific activation of the complement system and lipoxygenase and, as a result, inhibits the synthesis of leukotrienes, in combination with other phenols, breaks the chain of radical reactions);

• antimicrobial (all plant components that make up the preparation contain active substances with antimicrobial effects (phenolcarboxylic acids, essential oils, etc.); potentiation of the effect of antibacterial therapy also occurs while taking the drug);

• a diuretic (the indirect effect of lovage essential oils on the reabsorption function of the epithelium by improving blood supply to the renal tubules and direct - by increasing the osmotic pressure of phenolcarboxylic acids in the renal tubules);

• nephroprotective (due to a decrease in the permeability of the capillaries of the kidneys, which has an antiproteinuric effect with prolonged use).

The presented range of pharmacodynamic properties determines the therapeutic efficacy and tolerability of the drug, proven in numerous clinical studies, because 21st century medicine is evidence-based medicine! In a study involving 138 patients with ICD conducted by co-workers of the Institute of Urology Institute of Urology of the National Academy of Medical Sciences of Ukraine, after an 8-week course of metaphylactic treatment with the drug Kanefron® N, it was found that urine pH normalizes to 6.2 6.35 under the influence of the studied drug ; an increase in daily urine output by an average of 33.8% and a change in the concentration of uric acid in urine from 8 to 13%. ! It has been shown that the addition of the phytopreparation Kanefron® N to metaphylactic therapy contributes to a more rapid and stably effective improvement of the functional parameters of the state of the kidneys after removal of the calculus and to reduce the possibility of stone formation recurrence. When choosing a drug for metaphylaxis of nephrophysiology and uropathology, a

responsible medical and the pharmaceutical specialist should be guided by evidence-based medicine as the highest determining category in the process of rational pharmacotherapy, and motive consumer - choose the drug with the highest degree of trust (brand recognition, determined including constant high quality

One of the most common urological ailments is cystitis.

The disease can occur acutely or have a chronic form, recurring at the slightest hypothermia. That is why this problem is especially relevant in the cold season, i.e. in winter and in the offseason.

The treatment of cystitis is the prerogative of the doctor, as it requires the appointment of anti-biotic therapy.

Normally, the urinary tract is sterile, with the exception of the anterior section of the urethra. But the multiplication of microorganisms and their spread up the urinary tract is constrained by several mechanisms. Firstly, the urethra is periodically washed with a stream of urine, which moves in only one direction, i.e. outward (its reverse current is simply impossible due to the characteristics of the anatomy of the urinary system). Due to this, on the one hand, microorganisms are excreted from the urethra, and on the other hand, their adhesion to the mucous membrane is restrained and entry into the overlying urinary tract is prevented. Secondly, urine has an acidic pH reaction (its pH = 5.5), which is unacceptable for the vital functions of bacteria, since they require a more alkaline environment (pH from 6 to 8). With pathology, these important protective mechanisms are violated, as a result of which bacteria spread unhindered through the urinary tract, causing inflammation of certain departments. Thus, tumors, stones, anatomical abnormalities, injuries, as well as neuropathy of the bladder, observed in diabetes mellitus, can contribute to stagnation of urine. In turn, the cause of changes in the pH and composition of urine can be metabolic diseases or malnutrition.

What are the symptoms of cystitis?

Inflammation of the mucous membrane of the bladder, as a rule, manifests itself:

- pain in the lower abdomen;

- frequent urination;

- burning and pain during urination;

- the appearance of blood in the urine and the presence of a sharp unpleasant smell of urine.

These symptoms significantly reduce the patient's quality of life, limit communication and disrupt his usual activity.

Most susceptible to urinary tract infections:

- women. This is due to the anatomical and physiological features. The fact is that the cause of infection in 70-95% of cases is E. coli (Escherichiacoli), which enters the urinary tract from the intestine. In women, the urethra is shorter and wider than in men and due to the proximity of the source of this microorganism (anus), the risk of it entering the urinary tract increases. In addition, hormonal "changes" observed during puberty, pregnancy, and menopause can contribute to the onset of cystitis;

- aged people. In women in the postmenopausal period, urinary tract infections occur due to estrogen deficiency, which leads to dystrophy, thinning and increased trauma to the epithelium. In older men, the prerequisites for infection are reduced mobility, urinary incontinence, prostate dysfunction, and other disorders;

- people with a urinary catheter (for example, after surgery);

- infants and young children - especially those who have a congenital malformation of the urinary tract;

- patients with diabetes. They are less able to resist infection due to a weakened immune system. In addition, their process of growth and reproduction of bacteria is accelerated due to the high sugar content in the urine and stagnation of urine resulting from neuropathy of the bladder;

- pregnant, which is associated with hormonal changes;

- Patients with urolithiasis.

Risk factors for the occurrence of the disease include:

- active sex life;

- subcooling;

- weakening of the immune system;

- the presence in the body of foci of chronic infection.

The onset of cystitis symptoms requires medical attention, immediate - if along with the above symptoms are observed:

- nausea and vomiting;

- fever and chills;

- pain in the lumbar region, which is felt just below the chest and above the waist from the back;

- the presence of blood or pus in the urine;

- relapse of the disease;

- lack of improvement after antibiotic treatment.

Emergency medical attention is also necessary if symptoms of cystitis are observed in a pregnant woman and a patient with diabetes mellitus.

General recommendations for urinary tract infections include:

- peace, warmth and bed rest;

- regular emptying of the bladder;

- drink more liquid, preferably just water, because with each urination, bacteria that cause the disease are washed out. You should use at least one and a half to two liters of fluid per day (urine should have a light yellow color). Cranberry, carrot, apple and beetroot juices, which should be drunk warm and not sweet, are especially useful. It is not recommended to use tomato and citrus juices;

- exclude tea, coffee, alcohol. They have an irritating effect on the bladder;

- Avoid the use of acidic, spicy, salty, pickled foods and carbonated drinks. They can aggravate a burning sensation during urination;

- Guidelines for the treatment of urinary tract infections, including cystitis, recommend supplementing complex therapy with herbal remedies containing cranberry and bearberry extracts. Cranberries are very rich in type A proanthocyanidynamics (or PAC-A), which have anti-adhesive activity against bacterial agents, i.e. do not allow them to attach to epithelial cells lining the urinary tract - a feature of infection with Escherichia coli. Due to this, E. coli bacteria cannot be fixed on the

walls of the bladder and are excreted with the flow of urine. In addition, these substances have the ability to damage the cell membrane of pathogenic bacteria, thereby preventing their further reproduction. Bearberry leaf extract due to the high content of phenolic glycosides and tannins has a pronounced diuretic, anti-inflammatory and antimicrobial effects.

Zicibon® combines North American clove extract (Vaccinium Macrocarpon) and bearberry leaf extract.

In addition to the above components, it contains orthosiphon (Javanese tea) and vitamin C, which further enhance its beneficial effect on cystitis. So, orthosiphon increases glomerular filtration, improves renal tubule function, has a pronounced diuretic, potassium-sparing and anti-inflammatory effect, and vitamin C reduces the incidence of cystitis during pregnancy, enhances the anti-adhesive properties of PAC-

Tsitsibon® is used to prevent relapse, as well as an adjunct in the treatment of urinary tract infections. Enhances the effect of antibiotics. It contributes to the normalization of urination, reduces the risk of repeated exacerbations of chronic cystitis, improves the functional state of the kidneys and urinary tract. The complex of biologically active substances that make up Tsitsibona® has an antimicrobial, anti-inflammatory and diuretic effect. The systematic use of Cicibone® for cystitis allows you to achieve longer and better remissions (recoveries) with rare exacerbations (in case of a chronic disease) or to prevent re-illness with cured acute cystitis.

The method of use of Cicibone® is very convenient: 2 capsules 1 time per day, drinking with a glass of water. Cicibone® should be taken for at least 1 month. In case of acute urinary tract infection, combine with antibiotics and continue taking Cicibone® for at least 3 weeks after completing the course of antibiotic therapy.

According to statistics, every woman suffers from cystitis at least once in her life. In 20-25% of the disease becomes chronic, exacerbating 4-5 times a year.

It is important to remember the measures for the prevention of cystitis:

- the use of a sufficient amount of liquid;

- elimination of spicy, sour, fried foods, spices, pickles, pickled products from the diet;

- avoidance of hypothermia at any time of the year;

- proper general and genital hygiene (should: wash hands after using the toilet; wash the genital area twice a day with a shower from front to back, wipe the genitals in the same direction after emptying; completely wash the soap; avoid using antibacterial detergents and douching with antiseptics, as they eliminate the normal microflora that protects us from pathogenic bacteria; use detergents of a certain pH; wash the genitals before sex and induce the partner to do this; empty to bladder and drink a glass of water after intimacy);

- regular change of sanitary pads during menstruation;

- preference for cotton underwear, synthetic underwear does not absorb moisture and prevents its evaporation, as a result of which conditions are created favorable for the reproduction of microorganisms;

- to exclude narrow tight underwear - thongs, in the process of wearing which friction is observed and the spread of bacteria and fungal infections is possible;

- timely treatment of vaginal infections;

- a ban on the use of spermicides;

- prevention of constipation.

Careful adherence to all of the above recommendations will help the patient cope with cystitis and quickly return to the usual rhythm of life.

Remember! In case of urinary tract infections, self-medication is unacceptable.

The purpose of the lesson:

Know:

I. The main syndromes signaling diseases of the kidneys and urinary system:

- changes in the amount of urine excreted (increase, decrease in urine output, frequent nightly urination, frequent urination);

- dysuric disorders (pain during urination, discoloration and transparency of urine);

- pain in the lumbar spine (dull, intense, pain during urination, unilateral, symmetrical);

- increase in body temperature, chills; - changes in the appearance of the patient (pallor of the skin);

- dry mouth, thirst;

- edema (mainly faces in the morning);

- increase in blood pressure;

- general complaints (weakness, fatigue, drowsiness, irritability), etc.

II. The main syndromes and nosoforms of the urinary tract

1. Glomerulonephritis (nephritis) classification

Acute glomerulonephritis -

Chronic glomerulonephritis

Treatment of glomerulonephritis

2. Pyelitis

3. Pyelonephritis clinic, treatment Drugs for pyelonephritis

4. Urolithiasis (nephrolithiasis)

5. Factors of development of urolithiasis

violation of metabolic processes (mainly mineral),

violation of the colloidal state of urine,

hypoxia

lack of exercise, prolonged bed rest

intake of a small amount of liquid, the composition of drinking water (hard water),

violation of the regular passage of urine.

glut of urine with salts.

changes in the pH of urine, contributing to the appearance of hardly soluble salts.

infections, injuries of the urinary tract.

the nature of the diet (a large amount of meat food, lack of vit. A), the use of food with an excess of substances that contribute to stone formation.

6. Directions of pharmacotherapy and phytotherapy of nephrolithiasis:

Change in urine pH: alkalization with urate and oxalaturia, acidification with phosphaturia.

Lithological therapy provides increased solubility of salts, loosening and destruction of stones.

Reducing the formation of sparingly soluble salts by reducing their synthesis and normalizing metabolic processes in the body.

Elimination of oxygen deficiency and improvement of metabolic processes in the kidneys (nephroprotectors).

Растения The restoration of the colloidal structure of urine is provided by plants with a high content of silicic acids: knotweed (grass), nettle and stinging nettle (grass, especially roots), medunica medicinal (grass), common fireweed (rhizome), common burdock (grass), horsetail (grass).

fight against infection

Elimination of hypovitaminosis and immunodeficiency.

At the stage of excretion of destroyed calculi, it is necessary to prescribe antispasmodic drugs: Avisan, Pin-bin, Rovachol, Rovatin, Spaz-mo-urgenin, Urolesan, phytolysin, flavoxate (urispas), pistenal, and medicinal plants that relax the smooth muscles of the urinary tract: Ammi dental (fruits), mint (grass), lemon balm (grass), parsley (grass, seeds), dill (seeds), fennel (seeds), etc.

The restoration of urodynamics is carried out the more carefully, the larger the stones are detected.

7. Treatment of renal colic with antispasmodics (subcutaneously, or intramuscularly, or iv): platifilln, papaverine, no-spa, baralgin

8. Cystitis.

a. Risk factors for cystitis:

- active sex life;

- subcooling;

- weakening of the immune system;

- the presence in the body of foci of chronic infection.

b. Symptoms of cystitis requiring immediate medical attention:

- nausea and vomiting;

- fever and chills;

- pain in the lumbar region, which is felt just below the chest and above the waist from the back;

- the presence of blood or pus in the urine;

- relapse of the disease;

- lack of improvement after antibiotic treatment.

- cystitis of pregnant women and a patient with diabetes.

in. General recommendations for urinary tract infections include:

- peace, warmth and bed rest;

- regular emptying of the bladder;

- drink more liquid, preferably just water, because with each urination, bacteria that cause the disease are washed out. You should use at least one and a half to two liters of fluid per day (urine should have a light yellow color). Cranberry, carrot, apple and beetroot juices, which should be drunk warm and not sweet, are especially useful. It is not recommended to use tomato and citrus juices;

- exclude tea, coffee, alcohol. They have an irritating effect on the bladder;

- Avoid the use of acidic, spicy, salty, pickled foods and carbonated drinks. They can aggravate a burning sensation during urination;

Remember! In case of urinary tract infections, self-medication is unacceptable.

9. Metaphylaxis - definition of the term

10. Herbal preparations for metaphylaxis

The solution of situational problems.

TASK № 1.

Diagnosis: Chronic bilateral pyelonephritis, exacerbation phase, hypertonic form. CRF 1 tbsp.

1. Tab. Ampicillini 0.25 for 2 tab. 4 times a day

2. Tab. Furadonini 0.05 Po 2 tab. 4 times a day

3. Streptomycini sulfatis 0.5 0.5 0.5 2 times a day IM

4. Dragee Nitroxolini 0.1 For 1 tablet 4 times a day

5. Tab. Dimedroli 0.05 1 tab. 2 times a day

6. Dragee Panangini 1 tablet 2 times a day

7. Sol. Curantili 0.5% - 2 ml 2 ml 2 times a day intramuscularly

8. Tab. Verospironi 0.025 1 tab. 2 times a day

9. Tab. Prednisoloni 0.005 to 4 tab. 2 times a day

10. Sol. Dibazoli 0.5% - 2 ml 1 ml 2 times a day

Question to the appointment sheet:

Define the concept of chronic renal failure 1 degree.

List the diagnostic criteria for chronic pyelonephritis.

What clinical forms of chronic pyelonephritis are known to you?

What are the main and additional research methods (laboratory, instrumental) used in the examination of patients with chronic pyelonephritis?

Give a pathogenetic justification for the use in a patient of those medications that you think is advisable to leave in the list of medical prescriptions (explain what purpose they are used in this patient and what link in the pathogenesis of the disease affects).

Correct the incorrectly prescribed drugs, doses, routes of administration.

How can the patient leave the drugs you left on the prescription sheet with this patient? What is the difference between your replacement drugs?

What suggestions under the conditions of rational use of medicines left by you on the prescription list could you give the doctor (combination with food, time of day, duration of use, combination with other drugs, route of administration, etc.)? Motivate your suggestions.

Does this patient have any specific pharmacokinetics of drugs? If so, which ones? What are they due to?

What are the criteria for the effectiveness of the use of medicines for this patient that you left in the list of medical appointments.

What complications are possible with prolonged use of veroshpiron? What are they caused by?

TASK №2. Diagnosis: Chronic diffuse glomerulonephritis, exacerbation phase, nephrotic form, CRF -0.

1. Amriokhi 0.25 1.0 4 times a day IM

2. Tab. Furadordni 0.05 for 2 tab. 4 times a day

3. Tab. Furosemidi 0.04 1 tab. 1 time in 3 days

4. Tab. Prednisoloni 0.005 to 4 tab. 2 times a day

5. Tab. Indometacini 0,025 1 tab. 4 times a day

6. Sol. Curantili 0.5% - 2 ml 2 ml 2 times a day intramuscularly

7. Non-rape 5 ml. For 20 000 OD once a day in oil

8. Sol. Droperidoli 0.25% 5 ml 2 times a day iv

9. Sol. Dibazoli 0.5% - 2 ml 1 ml po / cutaneous 2 times a day

10. Sol. Retabolili 5% - 1 ml 1 ml 2 times for 2 weeks

Question to the appointment sheet:

Define the concept of chronic diffuse glomerulonephritis, nephrotic form.

List the pathogenesis factors of chronic glomerulonephritis.

What history data are relevant in the occurrence of chronic glomerulonephritis?

What complaints are characteristic for a patient with chronic glomerulonephritis?

Give a pathogenetic justification for the use in a patient of those medications that you think is advisable to leave in the list of medical prescriptions (explain what purpose they are used in this patient and what link in the pathogenesis of the disease affects).

Correct the incorrectly prescribed drugs, doses, routes of administration.

How can the patient leave the drugs you left on the prescription sheet with this patient? What is the difference between your replacement drugs?

Does this patient have any specific pharmacokinetics of drugs? If so, which ones? What are they due to?

Are there synergists in the prescription list? If so, what kind of synergism takes place, its significance for the patient?

Can the drugs you leave on the prescription list cause changes in the clinical analysis of urine? If so, which ones?

What type of pharmacotherapy with glucocorticosteroids is used for glomerulonephritis? What are the conditions for the rational use of corticosteroids?

TASK №3. Diagnosis: Acute left-sided pyelonephritis. Acute pneumonia of the lower lobe of the right lung.

1. Gentamycini sulfas 0.08 At 0.04 in \ m 2 times a day. Dissolve in 1 ml of water for injection

2. Cephazolini 0.5. 0.04 in \ m 2 times a day

3. Tab. Bromhexmi 0.008 to 1 tab. 2 times a day

4. Tab. Biseptoli-480 1 tab. 2 times a day

5. Dragee Nitroxolini 0.1 For 1 tablet 4 times a day

6. Tab. Urosulfani 0.5 to 2 tab. 4 times a day

7. Sol. Papaverini hydrochloridi 2% - 2 ml 2 ml 2 times a day

8. Non-Ragini 5 ml For 20 000 OD 1 time a day in / in

9. Tab. Dimedroli 0.05 1 tab. 2 times a day

10. Tab. Ace. Acetylsalicylici 0.5 to 1 tab. 2 times a day

Question to the appointment sheet:

Define acute pneumonia.

What complaints are typical for a patient with acute focal pneumonia?

What complaints are typical for a patient with acute pyelonephritis?

What complications is possible in a patient with acute pyelonephritis? Motivate the answer.

Give a pathogenetic justification for the use in a patient of those medications that you think is advisable to leave in the list of medical prescriptions (explain what purpose they are used in this patient and what link in the pathogenesis of the disease affects).

Correct the incorrectly prescribed drugs, doses, routes of administration.

Explain why you excluded certain drugs from the prescription list.

What suggestions under the conditions of rational use of medicines left by you on the prescription list could you give the doctor (combination with food, time of day, duration of use, combination with other drugs, route of administration, etc.)? Motivate your suggestions.

What diseases is nitroxoline used for? What kind of analogs do you know?

Are there antagonist drugs in the prescription list? Synergists? If so, what kind of antagonism (synergism) takes place, its significance for the patient?

What complications are possible when using drugs that you have left on the prescription list? What are they caused by?

TASK №4. Diagnosis: Chronic left-sided recurrent pyelonephritis, exacerbation phase. HNN of 1 degree. Chronic persistent hepatitis, remission phase.

1. Amriokhi 0.25 1.0 4 times a day IM

2. Tab.Sulfadimethoxini 0.5 1.0 1.0 2 times a day

3. Tab. Verospironi 0.025 1 tab. 2 times a day

4. Tab. Furosemidi 0.04 1 tab. 1 time in 3 days

5. Tab. Prednisoloni 0.005 to 4 tab. 2 times a day

6. Tab. Indometacini 0,025 1 tab. 4 times a day

7. Essentiale 5 ml 5 ml 2 times a day IM

8. Non-rape 5 ml. For 20 000 OD once a day, iv.

9. Sol. Droperidoli 0.25% 5 ml 2 times a day iv

10. Sol. Retabolili 5% - 1 ml 1 ml 2 times a week

Question to the appointment sheet:

Define the term “acute glomerulonephritis, nephrotic form”.

List the etiological factors of acute glomerulonephritis.

List the diagnostic criteria for acute glomerulonephritis.

Which disease in this patient is the main, and which is concomitant? Motivate the answer.

Give a pathogenetic justification for the use in a patient of those medications that you think is advisable to leave in the list of medical prescriptions (explain what purpose they are used in this patient and what link in the pathogenesis of the disease affects).

Correct the incorrectly prescribed drugs, doses, routes of administration.

Explain why you excluded certain drugs from the prescription list.

How can the patient leave the drugs you left on the prescription sheet with this patient? What is the difference between your replacement drugs?

What suggestions under the conditions of rational use of medicines left by you on the prescription list could you give your doctor (combination with food, time of day, duration of use, combination with other drugs, route of administration)?

Does this patient have any specific pharmacokinetics of drugs? If so, which ones? What are they due to?

What, in your opinion, adverse consequences are possible for this patient if the correction proposed by you is not included in the appointment list (development of complications, ineffective therapy, unreasonable high cost of treatment, worsening of the course of the disease, etc.)? Why?

Recommended literature:
Basic:

1) Betram G Katzung Basic and Clinical Pharmacology, 14th Edition. - McGraw-Hill Medical, 2018.- 1235 p.
2) Pharmacology in rehabilitation. – 4-th edition / Charles D. Ciccone, PT. – USA, 2007. – 653 p.

3) Clinical pharmacology: Manual for practical classes. – 2-nd edition / Edited by O.V.Kraydashenko. – Vinnytsya: Nova Khyna Publishers, 2010. – 192 p.

4) T.R.Harrison and others Harrison's principles of internal medicine,

19 th edition (Vols 1&2). – McGraw Hill education, 2015. – 3983 p.

5) Craham Douglas, Fiona Nicol, Colin Robertson Macleod's clinical

Examination, 13 th edition. – Churchill Livingstone, 2013. – 471 p.

Additional:

1) Emergency management of internal diseases / Edited by O.Babak and O.Bilovol. – Kyiv: AUS Medicine Publishing, 2010. – 448 p.

2) Godovan V.V. Pharmacology in pictures and schemes. – Nova Knyha, 2021. - 464 p.

3) Клініко-фармакологічний глосарій: навч.посібник / В.Й.Кресюн,

В.В.Годован, С.Б.Стречень. – Одеса: ОНМедУ, 2015. – 328 с.

Electronic information resources:

1. Resources for predicting inter-drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

2. Resource-Directory of Medicines and Forecasting of Intercurricular Interactions (in English). URL: http://www.medscape.org

3. Interregional Society of Evidence-Based Medicine: http://www.osdm.org/index.php

4. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ru

5. European Society of Clinical Pharmacologists and Pharmacists: http://www.eacpt.org

6. Resources for drug interactions: http://medicine.iupui.edu/flockart/