MINISTRY OF HEALTH PROTECTION OF UKRAINE

ODESSA NATIONAL MEDICAL UNIVERSITY

Department of General and Clinical Pharmacology and Pharmacognosy

APPROVED

Vice-Rector for Scientific and Pedagogical Work

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METHODOLOGICAL RECOMMENDATIONS FOR INDEPENDENT WORK OF HIGHER EDUCATION STUDENTS ON THE ACADEMIC DISCIPLINE

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CLINICAL PHARMACY AND PHARMACEUTICAL CARE

(Part I)

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TOPIC

INTRODUCTION TO CLINICAL PHARMACY.

SUBJECT, TASKS, MAIN DIRECTIONS OF CLINICAL PHARMACY.

Purpose of the topic.

The strategic direction of the development of health care in the world is the concentration of all medical advances on safe and effective treatment of patients.

These provisions are enshrined in the World Health Organization (WHO). According to this strategy, the role of the pharmacist in the health care system is fundamentally changing.

Pharmacy is one of the oldest sciences in human society and at the same time one of the most dynamic branches of science and production. This is an objective prerequisite for the continuous modernization of pharmaceutical education in order to maximize its approximation to the requirements of today.

In the XV century. for the first time the term “pharmacist” appears - from the Latin provisor - foreseeing, anticipating, predicting, which indicates the important role of the pharmacist in the treatment process. The doctor makes a diagnosis, and the pharmacist predicts the direction of the disease and with the help of drugs determines, corrects its course and further development.

The development of the pharmaceutical industry, the introduction to the market of a huge number of new products and their dosage forms, the emergence and development of the concept of “personal responsibility for their health” brought about a number of problems that pharmacists, doctors and pharmacists from all over the world had to face.

Motivational characteristics of the topic.

Despite the fact that there are currently 30,000 to 40,000 registered drugs on the pharmaceutical market, doctors cannot actively use such an extensive range. The number of new drugs and their forms many times exceeded that which was only 10 years ago and continues to increase. However, the real arsenal of the practitioner rarely exceeds 100 drugs.

Self-treatment has become another significant problem. This is due to the fact that in the current market there are widely represented OTC drugs (OTC drugs). At the second meeting of the advisory group of the World Health Organization (WHO) and the International Pharmaceutical Federation, the concept of “pharmaceutical care” was adopted - the responsibility of a pharmacist and a pharmacist to a specific patient for the result of drug treatment.

In the countries of Western Europe, the specialty “clinical pharmacist” appeared and was formed in the early 1970s. Currently in France, about a quarter of all pharmacists working in the health care system are clinical pharmacists. The scope of such specialists is not limited to work nr

pharmacies. Clinical pharmacists help doctors in the rational selection of drugs based on their pharmacokinetics, pharmacodynamics, interactions with other drugs, as well as the cost of treatment.. The work of a clinical pharmacist in a hospital saves 10–20% of the costs for these purposes. Therefore, it is now being discussed in the United States that a clinical pharmacist

should work in each clinic. The work of a clinical pharmacist in a hospital saves 10–20% of expenses for these purposes. Therefore, it is now being discussed in the USA that a clinical pharmacist should work in each.

In Ukraine, the National Pharmaceutical Academy, the leading pharmaceutical university in Ukraine, which determines the policy and direction of pharmaceutical education, has become the initiator of the development of clinical pharmacy. At the beginning of the 1980s, the NFAU raised the question of the need to introduce into the curricula of the training of highly qualified pharmacists a number of basic medical disciplines. In 1983, the Department of Pathology was opened, in 1985 - pharmacotherapy, in 1993 - the Department of Clinical Pharmacy with a course of laboratory diagnostics. Since 1996, on the basis of the department for students of the 5th year specialization “Clinical Pharmacy” has been conducted. Based on the experience of the Department of Clinical Pharmacy, the specialists of NFAU developed a block of documents necessary for licensing the specialty “Clinical Pharmacy”. In 1998, the Order No. 231 of the Ministry of Health of Ukraine approved the nomenclature of pharmaceutical specialties, among which the specialty “Clinical Pharmacy” and its corresponding specialist - clinical pharmaci. Since 1998, clinical pharmacy has been introduced into the system of continuous postgraduate training at the faculty of advanced training of pharmacists. In 1999, the National Pharmaceutical Academy of Ukraine opened the specialty “Clinical Pharmacy” and carried out the first recruitment of students, future specialists of a new generation - clinical pharmacists.

Preparation of a clinical pharmacist is a promising direction for the development of pharmaceutical education in Ukraine. The discipline “Clinical Pharmacy” is included in the model curriculum for training of pharmacists at all pharmaceutical faculties of Ukraine.

Clinical pharmacy is a science, the subject of which is the study of numerous aspects of the interaction of drugs with the human body care of patients. **. Clinical pharmacy is an integrative applied science that combines the pharmaceutical and clinical aspects of pharmacology, which is the theoretical basis for consulting physicians and the public on rational drug therapy and pharmacists in the care of patients.**
In this regard, as an inevitable consequence of the manifestation of trends occurring in modern health care, the role of the pharmacist and the pharmacist, his responsibility to the patient, has increased.
Participation of the pharmacist in the conduct of drug therapy contributes to the timely bringing to the patient of drugs of optimal quality, setting the most rational ways and modes of administration, preventing the use of incompatible drugs, minimizing the side effects of drugs, as well as reducing polyphragmas
No less important are the clinical trials of new drugs. The answer to the question about their efficacy and safety in comparison with drugs currently used can only be given by clinical studies, during which it is necessary to strictly observe the requirements of the GCP, to take into account the clinical and medical-statistical adequacy of such studies.

Thus, the role of the clinical pharmacist is extremely high. He should be involved in shaping the policy of drug use, cooperate with professionals in the development of guidelines and guidelines for the treatment of certain diseases, participate in the procurement system and distribution of drugs. No less significant is the role of clinical examination as a source of accurate and objective information about them for doctors and patients.
At the same time, an increase in the status and level of responsibility of a clinical pharmacist is unthinkable without changing the system of traini ng pharmacists and pharmacists.
Clinical pharmacy develops in close connection with various fields of medicine and biology. Thus, the disclosure of the etiology and pathogenesis of many diseases allows not only to create

the necessary drug through direct synthesis, but also to develop rational methods for its use. Due to the success of analytical chemistry and the development of highly sensitive equipment, it became possible to determine in medicine and body fluids negligible concentrations of drugs, their biotransformation and excretion from the body, and based on these data, calculate the optimal dose of drugs.

In different countries, the situation of clinical pharmacy as a science is not the same. In some of them, clinical pharmacy is highlighted in a separate discipline, and specially prepared clinical examiners work in their health care system. In others, clinical pharmacy as a science does not exist, and that work, which a clinical pharmacist should perform in the interests of public health, is either very unsatisfactoryly performed by other specialists, or is not carried out at all.

However, now it has become obvious that a doctor, regardless of his qualifications, is not able to fully master all aspects of knowledge about the huge amount of constantly updated medicines. His assistant on all issues of drug therapy is the clinical pharmacist, who should be well aware of the basics of internal diseases and be completely proficient in all issues of clinical pharmacy.

Clinical pharmacy studies the effect of drugs on the patient (pharmacodynamics), the processes of absorption, distribution, biotransformation and release of drugs (pharmacokinetics), adverse reactions, features of the action and influence of various body states (age, pregnancy, disease, etc.) on sensitivity to drugs, the interaction of various drugs in their combined use, the effect of food on the pharmacokinetics and the effect of drugs and a number of other issues related to the effectiveness and tolerability of drugs.

All this information is necessary for the rational, most effective conduct of pharmacotherapy.

The main objectives of clinical pharmacy are:

 clinical trials of new pharmacological agents;

 clinical research and reassessment of old drugs;

 improvement of drug therapy through the development of rational methods for the effective and safe use of drugs;

Organization of drug information services and consulting assistance to various specialists;

 training students and doctors.

In addition, the tasks of the clinical pharmacist include such issues of practical medicine as:

The choice of drugs for the treatment of a particular patient;

 determination of the most suitable for him dosage forms and mode of their use;

 the choice of the route of administration of the drug;

 monitor observation of the effect of the drug;

 prevention and elimination of side effects and undesirable effects of drug interactions;

 research on drug use patterns.

The participation of clinical pharmacists in the work of expert bodies responsible for the testing and use of drugs is also important.

One of the most important tasks of clinical pharmacy is to develop among pharmacy and medicine specialists methodological approaches and practical skills of using drugs for treating a particular patient, taking into account, on the one hand, many factors that characterize his condition and individual characteristics, and on the other hand, properties and features of the action of drugs.

Before you prescribe treatment, you must answer the following questions:

What specifically changes in the patient's condition does he want to achieve?

What drugs can have the desired effect?

What drug is most suitable for this patient?

How best to use the drug in order to obtain the desired concentration of drug substance in a given site of action?

What other effects can the selected drug cause, can it hurt the patient?

How much does the supposed positive effect of the drug and its severity outweigh the probability of occurrence and the severity of the possible damaging effect, what is the ratio of the benefits and risks of using the drug?

To help the doctor answer all these questions can qualified clinical pharmacist, fully mastered the knowledge of clinical pharmacy. In the end, the efficacy and safety of pharmacotherapy depends on the joint work of the doctor and the pharmacist, their ability to correctly evaluate all factors affecting the outcome of drug therapy.

Clinical pharmacist is a specialist who has knowledge of systemic basic and clinical pharmacology and is familiar with the main types of medical documentation, general syndromology and clinical symptomatology, the main methods of clinical, laboratory and instrumental examination of the patient, directions and principles of treatment of diseases.

In treatment-and-prophylactic institutions, the pharmacist plays the role of consulting the doctor on how to increase the effectiveness of pharmacotherapy, reduce the adverse and undesirable effects of drugs, and optimize the cost of treatment.

Due to the fundamental knowledge of chemical disciplines, biochemistry, toxicology and practical skills in working with laboratory and diagnostic equipment, a clinical laboratory assistant can work in clinical and biochemical laboratories.

In pharmacy organizations, a clinical pharmacist provides pharmaceutical care to patients: he advises on the rational use of non-prescription drugs, and selects effective and cheap analogues of expensive and original drugs.

In research organizations of medical and pharmaceutical profiles, a clinical pharmacist takes an active part in preclinical research, in clinical approbation of drugs, in determining their bio-equivalence.

The clinical pharmacist is a valuable employee in the pharmaceutical business. He works on issues of qualified advertising of drugs, marketing research, pharmacoeconomics.

Ultimately, the efficacy and safety of pharmacotherapy depend on correctly assessing all these factors, which should be based on deep knowledge of both clinical medicine and experimental pharmacology.

The drug is a pharmacological agent authorized by the authorized body of the relevant country in the prescribed manner for applications for the treatment, prevention, or diagnosis of a disease in a human or animal. For the designation of drugs not yet approved for use as drugs, the term “pharmacological agent” is used - a substance with established pharmacological activity that is the subject of clinical trials.

Currently, two types of names are used to designate drugs:

1) international non-proprietary names that are approved by official health authorities and are used in national and international pharmacopoeias - collections of standards and regulations that normalize the quality of drugs;

2) trade, or brand names, which are the commercial property of a pharmaceutical company.

The same product, produced by different companies, can have many names. For example, diazepam tranquilizer is produced under the names “Valium”, “Seduxen”, “Sibazon”, etc. Some medicines have more than 100 trade names (for example, vitamin B12). Usually on the packaging of the drug is given both the brand and the international, non-tentative name.

TYPES OF PHARMACOTHERAPY

Etiotropic therapy is aimed at eliminating the cause of the disease, for example, the use of antimicrobial agents for infectious diseases or antidotes for poisoning by toxic substances.

Pathogenetic therapy is aimed at eliminating or suppressing the mechanisms of the disease. Most drugs have exactly pathogenetic action - hypotensive, antiarrhythmic, anti-inflammatory, psychotropic, etc.

Symptomatic therapy is aimed at eliminating or reducing the individual manifestations of the disease. Symptomatic remedies include anti-pain medications that do not affect the cause or mechanism of the disease. However, in some cases (for example, in myocardial infarction), they can significantly affect the course of the pathological process, in effect having a pathogenetic effect.

Replacement therapy is carried out in case of insufficiency of natural biologically active substances. The means of replacement therapy include enzyme preparations, hormones and their analogues, vitamins, which, without eliminating the causes of the disease, can ensure the normal functioning of the body for many years. For example, insulin preparations do not affect insulin production in the islets of the pancreas.
Preventive therapy is carried out to prevent diseases. Some antiviral, disinfecting preparations are referred to prophylactic agents.
The purpose of clinical pharmacy is to prepare professional pharmacists who possess a sufficient amount of theoretical knowledge and practical skills to carry out the most effective and safe drug therapy with a doctor.

Purpose of the lesson: The student should know the main tasks of the clinical pharmacy and the main directions of the clinical pharmacy.

Test questions.

1. When did clinical pharmacy originate as a science, and how did it develop?
2. What does clinical pharmacy study?
3. The definition of the subject - clinical pharmacy.
4. The principal difference between clinical pharmacy from pharmacology, from clinical pharmacology, from pharmacotherapy.
5. The main objectives of clinical pharmacy.
6. The main objectives of clinical pharmacy.
 clinical trial of new pharmacological agents;
 clinical studies and reassessment of old pharmacological agents;
 development of methods for the effective and safe use of drugs;
 organization of information services and advisory assistance to various specialists;
 training students and doctors.
7. Basic concepts in clinical pharmacy.
 Medicinal substance.
 Pharmaceutical drug.
 Drug - brand names, generic names - advantage and non-wealth, requirements for generics;
The concept of "chemical name", "international non-proprietary name", "trade name", "brand name" BOS.
 OTC drug;
8. Drug monitoring: the concept, conditions that determine the need for drug monitoring.
9. The main directions of development of clinical pharmacy, integration with other sciences.
10. To master the course of clinical pharmacy, a student must study the following disciplines:
 Latin - to be able to read and write prescriptions;
 Foreign language - be able to read the annotations of drugs;
 Anatomy - to know the structure of the musculoskeletal, nervous, vascular systems, internal organs;
 Normal physiology;
 Pathology - damage to cells and tissues, impaired microcirculation. Inflammation, pain, extreme conditions, hypoxia, infectious process, fever, hypoxia, pathology of the immune system, blood systems, cardiovascular system, respiratory system, digestive system, endocrine and nervous systems;
 Microbiology - the structure and characteristics of microorganisms (atypical forms, virulence, resistance, dysbacteriosis), the development of resistance of microorganisms;
 Biochemistry: biochemistry of digestion, metabolism of carbohydrates, proteins and fats; biochemistry of blood, liver, nervous tissue, muscles, kidneys; energy assurance of muscle and heart contractility; the characteristic of the main components of urine in normal and pathological conditions; hormones, drug metabolism in the body.

 Pharmaceutical chemistry: patterns of the relationship of the chemical structure of drugs and their physical, chemical and pharmaceutical properties; the dependence of these properties on the structure of chemicals;
 Toxicological chemistry: negative types of drug action; toxic effects.
 Pharmacognosy: the structure of drugs; the importance of the main biologically active components of plants; methods, methods of preparation, drying, storage of medicinal raw materials.
 Pharmacology: medicinal agents (drugs), regulating the function of the digestive system, cardiotonic, antiarrhythmic, antianginal, antihypertensive drugs; metabolism regulating agents, antimicrobial, anti-inflammatory, immunomodulating, antiallergic drugs;
 Pharmacotherapy:

11. Qualification characteristics of a clinical pharmacist:

In accordance with the requirements of the specialty of a clinical pharmacist should know and be able to:

1. General knowledge

- basics of health legislation and policy documents defining the activities of health authorities and institutions;
- General issues of the organization of treatment-and-prophylactic care and the provision of medicines for various groups of the population, including patients in accordance with the nosological forms of the disease;
- The main issues of normal and pathological anatomy and physiology, biology and genetics, medical chemistry and physics, pharmacology and pharmacy, physical and paraclinical diagnostic methods, taking into account their age aspects;
- clinical symptoms and pathogenesis of the main diseases of the internal organs, central and peripheral nervous system, musculoskeletal system, skin, urogenital system, eyes, ENT organs, taking into account age aspects;
- the conditions for carrying out laboratory, biochemical, electrophysiological, radiological, endoscopic and other paraclinical methods of research in medical practice, taking into account the age aspects and the state of the patient;
- features of the main diseases of the internal organs, peripheral and central nervous system, digestive organs, eyes, upper respiratory tract, skin, musculoskeletal system, genitourinary system;
- principles of pharmacotherapy for different course and severity of diseases (urgent, severe, acute, subacute, chronic);
- principles of registration of new domestic and foreign drugs, including laws and regulations governing the conduct of clinical trials in accordance with the requirements of good medical practice (GMP), principles of work

control and licensing system for registration of drugs and medical equipment;

- ethical norms for the use of drugs, both in testing new and registered ones, including narcotic analgesics, psychotropic, drugs interrupting pregnancy, etc .;
- the main requirements governing the use of drugs in the general medical practice, the conditions for their receipt, the delivery to the population in pharmacies and pharmacy kiosks and the provision of hospitals, maternity hospitals and other medical facilities with them. institutions;
- The basic principles of pharmacokinetic and pharmacodynamic studies, used drugs in the clinic to determine their effectiveness and safety;
- forms and methods of work with doctors to increase their knowledge of the rational use of drugs, forms of information about new drugs, taking into account the effectiveness, dosage regimen, interactions and side effects;
- forms and methods of working with the public to increase knowledge about the rational use of drugs prescribed by a doctor and used by patients themselves.

2. General skills

1. Follow the rules of medical and pharmaceutical ethics and deontology; solve a set of tasks related to the relationship of a doctor, a clinical pharmacist and a patient;
2. To be able to evaluate the results of laboratory morphological, biochemical, immunological, microbiological and other research methods;
3. To be able to evaluate the results of the main modern methods of functional diagnostics used in the clinic of internal diseases:
- ECG monitoring,
- BP monitoring,
- rheovasography of the vessels of the head and limbs,
- bicycle ergometry (VEM),
- study of the function of external respiration (respiratory function) - spirography, body plethysmography, PIK-flowmetry,
- Teleradio-pH-metry,
- ultrasonic methods for studying the internal organs of the thyroid gland, heart, kidneys, pelvic organs, blood vessels;
4. To be able to evaluate the results of endoscopic examination methods - bronchoscopy, esophagogastroduodenoscopy, colonoscopy, rectoscopy, laparoscopy;
5. To be able to evaluate the results of radiological methods of research:
   - radiography of the lungs, heart, spine, joints, skull,
   - X-ray of the heart; - X-ray of the lungs;
6. Be able to evaluate the results of radioisotope methods for studying the lungs, heart, kidneys, bones;
7. To be able to conduct independently:
   - consultations on drug therapy (pharmacotherapy and phytotherapy, psi-hofarmacotherapy, psychophytotherapy).
8. To be able to collect complaints of the patient, his history and follow-up history, his medicinal history and follow-up, apply objective examination methods, prescribe and decipher data of paraclinical diagnostic methods, conduct a differential diagnostic search, clarify a detailed diagnosis, determine the direction of therapeutic measures and their sequence and identify damage to the central nervous system, neuroendocrine system, musculoskeletal system, Ko-zh, eyes, an ENT - bodies from medicinal influence;
9. To be able to provide the necessary emergency care and determine the indications for hospitalization of the patient;
10. To be able to diagnose acute syndromes, provide first aid and organize measures for their relief in case of:
   - myocardial infarction,
   - violation of cerebral circulation,
   - bronchial asthma,
   - acute renal colic,
   - pulmonary edema,
   - thromboembolism,
   - “acute abdomen”,
   - internal bleeding,
   - diabetic, hypoglycemic, uremic, cerebral coma;
11. To carry out the necessary anti-epidemic measures in the detection of infectious diseases;
12. Participate in the formation of a range of medicines of medical institutions,
- issue medical documentation provided for by the legislation on AOR;
- be able to organize in a medical institution a system of information on the choice of drugs, their dosage regimen, interactions, predictable side effects;
- assist in the preparation of applications for the needs of drugs, the possibility of their replacement, taking into account the age and nature of the profile of diseases;

- be able to correctly determine the need for medicines;
13. To monitor the use of drugs in a medical institution, their shelf life, compliance with the compatibility, the correctness of the intravenous and intramuscular injections of drugs, compliance with the rules of storage.

3. Special knowledge

General questions of clinical pharmacology:

 pharmacodynamics of drugs,

 principles of the mechanism of action of their specificity and selectivity,

 pharmacokinetics of drugs, introduction, bioavailability, volume of distribution, ad-sorption (absorption), connection with protein, biotransformation, distribution, elimination (elimination); concept of the half-life, its clinical interpretation, equilibrium curve, cumulation of drugs, the interaction of drugs: pharmaceutical, pharmacokinetic, pharmacodynamic, pharmacogenetic, physiological,

 pharmacogenetics and biorhythms (chronopharmacology),

 additional pharmacological effects of drugs and their use in practice;

 side effects of drugs predictable and unpredictable, toxic effects of drugs, iatrogenic; warning and correction paths,

 differential diagnosis of iatrogenic (drug poisoning) and its importance for clinical practice;

 the main antidotes for iatrogeny and emergency pharmacological measures;

 age aspects of clinical pharmacology in pregnant women, fetuses, newborns, children, adults and the elderly and the elderly,

 general principles of pharmacotherapy, drug choice, dose, mode of dosing;

 know the clinical pharmacology of essential drugs used in general medical practice (pharmacodynamics, pharmacokinetics, indications and contraindications, dosing regimen, interaction, side effects):

 psychotropic, antimicrobial, anti-inflammatory drugs, drugs that affect vascular tone and the basic physiological functions of the heart,

 drugs that regulate the secretory and motor function of the gastrointestinal tract,

 drugs acting on the mucous membrane and skin,

 drugs that regulate the function of the broncho-pulmonary system,

 drugs that affect the function of the endocrine glands,

 metabolic drugs,

anesthetics and anesthetics,

 - drugs that affect uterine contractility;

 know drugs that require drug monitoring;

 know the issues of organizing control over the conduct of modern, rational pharmaceutical pharmacology with the principles of identifying and recording side effects and measures for their relief;

Know the indications for the acute drug test.

4. **Special skills**

- be able to organize studies of the main indicators on pharmacodynamics and pharmacokinetics of drugs or to determine and evaluate the equilibrium concentration;
- the study of the oxidative and acetylating functions with the determination of the bio-transformation of drugs in a patient;
- be able to conduct a drug test;
- be able to conduct a search on the issues of clinical pharmacology using information systems;
- be able to organize testing of drugs Crossus ower, double-blind "blind" method or, on the "pilot" system or by alternation; - define the control group and methods for evaluating the data obtained;
- be able to develop a study protocol;

- determine the nature of pharmacotherapy, conduct the choice of drugs, establish the principles of their dosing, choose methods of monitoring their effectiveness and safety;
- to predict the possibility of the development of side effects, to be able to warn them, and to stop them as they develop;
- to predict the possibility of the development of tachyphylaxis, withdrawal syndrome, robbery, rebound, cumulation, paradoxical effect and toxemia;
- be able to assist in the selection of combination therapy in order to eliminate unwanted interactions, enhance PD, reduce the effectiveness of basic drugs;
- be able to assist in the development of tachyphylaxis to the drug used;
- control the accuracy, timeliness of the introduction of the drug to the patient, their registration, especially of the list of drugs A;
- control the correctness of drugs that have a pronounced, rapid pharmacological effect
- to help to carry out pharmacotherapy to physicians of the hospital and clinic, taking into account the severity of the course of the disease, the state of the functional systems, bio-rhythms, genetic background, pharmacokinetics in all age groups.

Pharmaceutical ethics and deontology.

List of practical work:

Homework.

1. To study the main tasks and directions of clinical pharmacy, the fundamentals of pharmacogenetics.
2. To know the definition of the basic concepts: “chemical name”, “international non-proprietary name”, “trade name”, “brand name” of the drug.
3. Know the definition of the concepts: “brand drug” and “generic drug”. Original (brand) drugs and generic drugs - advantages and disadvantages.
4. OTC drug - characteristic.
5. Know the fundamental difference between clinical pharmacy from pharmacology, from clinical pharmacology, from pharmacotherapy.

Control the boundary level of knowledge.

Situational tasks:

1. Give the definitions of the concepts “chemical name of a drug”, “international non-proprietary name”, “firm (trade) name”. Give specific examples of the names of medicines of different pharmacological groups.

Pharmacological group	**Chemical name**	**International title**	**Corporate (trade) name**
Example: beta blockers	1Isopropyl-amino-3- (1-naphthoxy) -2-propanol hydrochloride	Propranolol	Anaprilin, Obzidan, Inderal

2. What are the meanings of the concepts: "pharmacology", "pharmacotherapy", "clinical pharmacology", "clinical pharmacy". Answers cite as a table:

The name of the discipline	**Definition**	**Subject of study**	**Tasks**
1. Pharmacology 2. Pharmacotherapy 3. Clinical pharmacology 4. Clinical Pharmacy			

3.. Define the concepts:

1. Etiological therapy.

2. Pathogenetic therapy.
3. Symptomatic therapy.
4. Replacement therapy.
5. Preventive therapy.
a) Treatment aimed at increasing natural biologically active substances in case of their insufficiency.
b) Treatment aimed at eliminating individual manifestations of the disease, without affecting its cause or mechanism of the disease.
c) Treatment that affects the mechanism of the disease.
d) Treatment aimed at eliminating the cause of the disease.
e) Treatment to prevent the onset of the disease
For each of the marked treatments, give specific examples.

4. What are the meanings of the concepts: „medical monitoring". In what cases is medical monitoring necessary?

A drug	The reason for conducting medical monitoring
1. Theophylline	
2Digitoxin	
3. Aminoglycosides	
4 Propranolol	

5. Fill in the table "Principles of dosage depending on the type of pharmacotherapy":

Types of pharmacotherapy	**Principles of dosing**
1. Replacement therapy 2. Symptomatic therapy 3. Pathogenetic therapy 4. Etiotropic therapy 5. Antidote therapy	

6. The injured patient was diagnosed with a quick medical aid by a quick medical aid unit with a diagnosis of a closed fracture of the middle third of the thigh with displacement. In order to reposition the bone fragments, a patient was injected with 10 ml of a 2% solution of ditilin intravenously, as a result of which a long apnea and myorelaxation developed. What enzyme deficiency caused by side effects?
A. * N-acetyltransferase.
B. Uridinediphosphoglucuron transferase.
C. Glucose-6-phosphate dehydrogenase.
D. Methemoglobin reductase.
E. Pseudocholinesterase.

7. The patient was prescribed the drug A. When you re-take the effect of the use of the drug is significantly reduced and to obtain the initial action you need to increase the dose. What is this phenomenon called?
A. Cumulation.
B. * Tachyphylaxis.

C. Medical addiction.
D. Habituation.
E. Idiosyncrasy.

8. During surgical intervention with the use of muscle relaxants respiratory distortions appeared. Introduction prozerina led to an improvement in the condition. How is this medication interaction determined?
A. Synergism.
B. * Antagonism.
C. Incompatibility.
D. Tachyphylaxis.
E. Cumulation.

9. A patient with epilepsy has been receiving Pheno-Barbital for a long time at a daily dose of 0.2 g. Recently, he has become more prone, he has a suppressed mood. What process leads to the deterioration of the patient?
A. * Induction of monooxygenase enzymes of the liver system.
B. Inhibition of enzymes of the monooxygenase system of the liver.
C. Activation of lipolysis.
D. Activation of gluconeogenesis.
E. Inhibition of glycolysis.

10. In the postoperative period, pro-medol was administered to the patient for a long time. After the drug was discontinued, the patient had severe mental and somatic disorders. What is this phenomenon called?
A. Recoil syndrome
B. Idiosyncrasy.
C. Tachyphylaxis.
D. Robbering syndrome.
E. * Abstinence syndrome.

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
BASIC METHODS OF CLINICAL EXAMINATION OF PATIENTS AND THEIR SIGNIFICANCE FOR PHARMACYST. TYPES OF MEDICAL DOCUMENTATION. MEDICAL ANAMNESIS

Purpose of the topic.
Diagnosis - the science of recognizing various diseases. Only by recognizing the disease can you successfully treat the patient. In ancient times, they said: "Who diagnoses well, he treats well."

Motivational characteristics of the topic.
Familiarization with the main methods of diagnosis, recognition of diseases, is the most important aspect of pharmacotherapy.
Definitions of some concepts.
Clinic - (from the Greek. "Klinike" - healing) is a medical institution or a subdivision of a medical institution (n.p. a department of a hospital, polyclinic), where, in addition to the usual medical and preventive work, medical training theoretical and practical training of students and doctors, as well as research work.
Health is a state of complete physical, mental and social well-being, and not just the absence of symptoms of the disease and physical defects (WHO).
A disease is a violation of the structures and functions of the body due to its insufficient resistance to the constantly changing conditions of the external and internal environment.

Etiology (from the Greek. "Etios" - the reason, "logos" - science) - is the science of the causes and conditions of the disease.
Pathogenesis (from the Greek. "Pathos" - suffering, disease; "genesis" - origin, development) - is the science of the mechanisms of the development of the disease.
Sanogenesis is the study of the mechanisms of protection of the body against the effects of damaging agents aimed at restoring the function of damaged structures.
Internal diseases are one of the largest branches of theoretical and practical medicine, a scientific discipline aimed at studying the recognition of diseases of internal organs in their various clinical forms, the causes of the origin of these diseases, their prevention and treatment.
Tasks
1. Recognition of diseases of internal organs (diagnosis).
2. The study of the etiology and pathogenesis of diseases of internal organs.
3. Development of issues of prevention and treatment of diseases of internal organs.
The main tasks of the department are to train students:
1) the method of clinical examination of patients;
2) symptomatology of diseases;
3) the basics of laboratory and instrumental diagnostic studies for diseases of internal organs;
4) acquaintance of students with the main nosological units (diseases) and syndromes in terms of learning how to apply the data obtained during the examination of the patient to the diagnosis of specific diseases.
Structure (sections) of internal diseases propaedeutics
1. Diagnostics.
2. Private pathology.
Diagnostics (from the Greek. "Diagnosticos" - capable of recognizing) is a branch of medicine, a separate science that studies research methods for recognizing the disease and condition of a patient for the purpose of prescribing necessary treatment and preventive measures.
Structure of diagnostics as a scientific discipline
1. Medical diagnostic equipment (proper diagnostics) is a diagnostic section that studies methods for obtaining information about a patient. It includes the study of methods of questioning and objective examination of the patient.
2. Semiotics or semiology (from the Greek. “Semeion” - a sign) is a section of diagnostics that studies the symptoms revealed in the study of a patient, the study of the diagnostic nature and origin of certain symptoms and syndromes of diseases.
3. The methodology of diagnosis (medical logic) is a section of diagnostics, including the study of the specifics of the doctor’s thinking when establishing a diagnosis and a disease based on the data obtained during the examination of patients.
Medical diagnostic equipment
Methods of research of the patient are divided into 2 groups.
1. Basic.
2. Auxiliary (optional).
The main methods of research of the patient
1. Questioning the patient (lat. "Interrogation") or anamnesis (from the Greek. "Anamnesis" - a memory).
2. Inspection (lat. "Inspection").
3. Feeling (lat. "Palpatio").
4. Percussion (Latin "percussion").
5. Listening (lat. "Auscultation").
Auxiliary research methods
1. Measurements (body temperature, height, weight, chest circumference, daily amount of urine, etc.)
2. Laboratory studies of body fluids and its excretions (blood, cerebrospinal fluid, gastric juice, bile, urine, effusions in the body cavity, sputum, pus, etc.).

3. Morphological studies of organs, tissues, body fluids and its secretions.
4. Instrumental examinations (ECG, X-ray, respiratory function tests, isotope examinations, ultrasound, endoscopic methods, etc.).
According to the method of obtaining information about the patient research methods are divided into:
1) subjective;
2) objective (physical).
The subjective method of examining a patient implies considering the patient as a subject who remembers and tells about those sensations and events that accompanied his disease from the very beginning, which preceded the disease. This is the patient's story about his life and illness, his subjective ideas about the disease he has.
The doctor receives subjective data about the patient by the method of questioning.
Objective (physical) research methods imply the patient, as an object of examination, which the doctor performs, relying on his senses and the ability to manipulate a number of practical actions.
Objective research methods are divided into:
1) the main ones are inspection, palpation (palpation), percussion (percussion) and listening (auscultation);
2) auxiliary - various measurements, laboratory, morphological and instrumental methods.
Semiotics
A symptom (from the Greek. “Symptomos” is a sign, a coincidence) is a sign of a disease, a statistically significant deviation of an indicator from the limits of its normal values, or the appearance of a qualitatively new phenomenon not characteristic of a healthy organism.
Types of symptoms of informative significance
1. Diagnostic (pathognomonic) symptoms are characteristic of only one disease.
2. Specific symptoms are characteristic of a group of diseases of one organ or organs of one system.
3. Nonspecific symptoms are characteristic of many diseases of various organs and organ systems.
4. Symptoms that are not characteristic of this disease are not detected with this disease.
Types of symptoms by their method of detection
1. Subjective symptoms are symptoms, the detection of which is based on the description by the patient of their sensations arising in the course of the development of the disease. They are identified by questioning patients, i.e. subjective method of research.
2. Objective symptoms. These are the symptoms that are revealed by the methods of objective examination of the patient: by inspection, by palpation, by percussion, by auscultation, and by laboratory and instrumental methods.
Types of symptoms at the time of their occurrence
1. Early (initial) - arising in the early, initial stages of development of the disease.
2. Late - occurring during the height of the disease or during the recovery period.
Types of symptoms for their prognostic value
1. Favorable, indicating a mild or normal course of the disease, as well as its resolution.
2. Unfavorable (threatening), indicating a severe form of the disease, the possibility of its adverse outcome.
Syndrome (from the Greek. "Syn" - together, "dromos" - move, run - run together) - these are groups of symptoms that have a common pathogenesis.
A symptom complex is a group of symptoms or syndromes characteristic of the disease, but not united by a common origin.
Methodology of the diagnosis
Diagnosis (from the Greek. "Diagnosis" - recognition) - is a brief medical conclusion about the nature of the disease and the patient's condition, expressed in terms of modern medical science.
Structure of the diagnosis

1. The main disease is the disease that caused the patient to seek medical help, caused him to be hospitalized or a disease that threatens the patient's life, which can cause death or disability on his own or through complications.
2. Complications of the underlying disease are diseases of a different nature and etiology than the main one, but pathogenetically associated with it.
3. Concomitant diseases are diseases found in the patient at the same time as the main one, but not interrelated with it.
Types of diagnoses
I. By nature and content
1. Anatomical.
2. Pathoanatomical.
3. Pathophysiological (functional).
4. Pathogenetic.
5. Nosological.
6. Etiological.
Ii. By way of building and justification
1. Direct diagnosis (or diagnosis by analogy (diagnosis morbi). The diagnosis is established by comparing the clinic of the disease that a patient has with the typical clinical picture characteristic of the disease.
2. Differential diagnosis (diagnosis differentialis). This is a diagnosis by comparing several similar diseases. Here it is necessary to exclude less probable diseases, leaving more likely. This is a diagnosis by exclusion (diagnosis per exclusion).
3. Diagnosis by observation (diagnosis per observatione). It is possible to establish the diagnosis during the observation of the patient when new symptoms of the disease appear or to obtain additional research results.
4. Diagnosis by therapeutic effect (diagnosis ex juvantibus). The diagnosis is established on the basis of a favorable outcome of treatment with drugs specifically acting in this disease.
5. Diagnosis by the result of a harmful action (diagnosis ex nonentibus). This is the use of drugs or other effects that trigger the onset of symptoms of the disease (allergy tests, physical exertion with angina).
6. Diagnosis during surgery (diagnosis sub operatione).
Iii. By the time of detection of the disease
1. Preclinical diagnosis. This is an attempt to recognize and determine the state of the body, the boundary between the norm and pathology. The method of recognition of these states is still being developed (the concept of "pre-illness", "diathesis", etc.).
2. Early diagnosis. The disease is recognized at the very beginning.
3. Late diagnosis. It is installed at the height of the development of the disease or on a sectional table.
4. Retrospective diagnosis. It is established on the basis of data that were previously identified, but for some reason were not taken into account, on the basis of an analysis of medical documentation, etc.
5. Postmortem diagnosis. It is established after the death of the patient and is recorded in a posthumous epicrisis.
Iv. By degree of reliability
1. Indicative diagnosis.
2. Preliminary diagnosis.
3. Clinical diagnosis.
4. The final diagnosis.
5. The diagnosis is hypothetical (questionable).
6. Incomplete or uncertain diagnosis.
7. Misdiagnosis.
Sections of the patient's medical card (inpatient or outpatient)

1. Patient questioning (anamnesis, interrogatio) (passport part, complaints, history of the disease, history of life).
2. Objective research (status praesens obectivus).
3. Diary of medical history (cursus morbi).
4. Treatment (therapia).
5. Data of laboratory and instrumental studies, consultations with specialists.
6. Epicrisis (epicrisis).
Purpose of the lesson: The student should know the general rules for interviewing, examining, palpation, percussion and auscultation. To be able to: interrogate, examine, palpate, repudiate and auscultate the patient, familiarize yourself with the medical documentation

Test questions.
The main methods of clinical examination of patients and their significance for a pharmacist
1. Subjective methods of clinical examination of patients:
a) patient questioning;
b) patient complaints:
o main complaints;
o change in general condition,
o clarification of the features of the state of higher nervous activity;
o determine the type of the nervous system in accordance with the classification of I.P. Pavlova);
c) history of the present disease;
o onset of the disease;
o development of the disease;
o ongoing research and their results;
o treatment and its effectiveness;
d) history of life;
o general biographical information (place and conditions of birth, growth and development);
o living conditions (conditions of life in different periods of life, family situation, diet, etc.);
o working conditions and occupational hazards;
o postponed diseases;
o family history (finding out the health status of relatives - the concept of autosomal dominant and autosomal recessive types of inheritance);
Allergic history.
2. Objective (physical) methods of clinical examination of patients:
a) general inspection:
- the effect of lighting on the inspection;
- inspection technique
- state of consciousness (clear, disturbed: stuporous state, soporous state, coma - types of coma: alcoholic, apoplexic, hypoglycemic, hyperglycemic, hepatic, uremic, epileptic);
- patient's position:
 active;
 passive;
 forced;
- physique (constitution (asthenic, hypersthenic, normostenic types), height and body weight of the patient);
- posture;
- inspection of the head;
- facial expression (puffy face, "Corvizar face", feverish face, acromegalic face, myxedemic face, facies basedovica, "lion face", Parkinson mask, wax-doll face, Hippocrates face, face asymmetry)
-eye examination (eyelid edema, eyelid staining, peep eye asymmetry, eye pupil asymmetry, form of pupils, their reaction to light, color sclera)

- nose (rhinoscleroma);
- mouth (shape, symmetry, lip color, rash, inspection of teeth, tongue);
- skin (moisture, color, turgor, elasticity, rash on the skin - erythema, blisters, herpes rash, purpura, peeling of the skin, brittle nails and their shape);
- development of the subcutaneous fat layer;
- swelling;
- lymph nodes;
- examination of the muscular system;
- examination of the joints (configuration, pain when moving, hyperemia, swelling, etc.);
b) palpation (palpation):
- superficial;
- deep;
c) percussion, basic rules:
- topographic;
- comparative;
d) auscultation (auscultation rules).
3. Laboratory methods of examination of patients:
a) study of the general properties of the material under study:
- physical research - quantity, color, type, smell, presence of impurities, relative density;
- chemical research;
- microscopic examination
b) bacteriological examination;
c) serological examination;
4. Have a clue about instrumental methods of clinical examination of patients:
a) anthropometry (measurement of height, body weight, dynamometry);
b) body thermometry:
- the degree of temperature increase — subfebrile, moderately elevated, high, excessively high, hyperpyretic;
- fever types - persistent fever, laxative fever, intermittent fever, debilitating or hectic fever, reverse fever type, abnormal fever,
- fever - the period of rise of temperature, the period of high temperature, the period of lowering temperature;
- hypothermia;
- concept of temperature curve;
c) X-ray examinations - X-ray, roentgenoscopy, X-ray chemography, tomography, x-ray vision, etc .;
d) endoscopic examinations;
e) cytological examination;
f) radioisotope research methods, the safety of radioisotope research of the patient;
g) modern ultrasound research methods, etc.
5. Types of medical history.
6. Medical documentation: patient history, list of medical values, individual patient outpatient card, prescription forms ...
7. Medical and pharmaceutical ethics and deontology
List of practical work:
Homework.
1. Acquire the methods of examination, survey of a healthy person, palpation, percussion and auscultation of a healthy person.
2. Get acquainted with the main laboratory methods of research of patients.
3. To learn the basic constants of analyzes of the patient's biomaterials.
4. To study the features and advantages of the main instrumental research methods for accurate diagnosis of diseases.

Control the boundary level of knowledge.
Solving situational problems:
1. On examination, the patient discovered fingers in the form of drumsticks. What diseases is this characteristic of?
2. What syndrome is the Parkinson mask typical for?
3. Fill in the table “Types of diseases

Type of diseases	**Definition**
1. Primary disease 2. Concomitant disease 3. Acute illness 4. Chronic disease 5. Complication of the disease 6. relapse	

4. Fill in the table “Types of diagnosis

Diagnosis	**Definition**
1. Preview 2. Differential 3. Final	

5. Fill in the table “Types of anamnesis”.

Types of anamnesis	**Definitions**	**Value for rational drug therapy**
1. Anamnesis of the disease 2. Anamnesis of life 3. Drug history		

6. Fill in the table “Types of comas’’

Types of comas	**Definition, clinical picture**	**For example**
1. Alcohol coma 2. Apoplexic coma 3. Hypoglycemic coma 4. Hyperglycemic coma 5. Hepatic coma 6. Uremic coma 7. Epileptic coma		

7. Give the definition of the concepts “Types of the patient’s position

Types of position of the patient	**Definitions**	**For example**
1. Active position 2. Passive position 3. Forced position		

8. Fill in the table “Constitutional types”.

Constitutional types	**Definitional**
1. Normostenic type 2. Hypersthenic type	

3. Asthenic type	

9. Fill in the table “Methods for examining a patient’’

Methods for examing a patient	**Definitions**
1. Objective: inspection - palpation percussion auscultation 2. Additional: - laboratory - radiological - instrumental: - endoscopy - biopsy ultrasonic methods	

10. Fill in the table “Normal forms of the chest

The forms of the chest	**Clinical definitions**
1. Normostenic 2. Hypersthenic 3. Asthenic	

11. Fill in the table “Pathological forms of the chest”

Types of chest	**Definitions**	**Examples of disease**
1. Emphysematous 2. Rahitic 3. Funnel 4. Scaphoid		

12. Fill in the table “Degrees of body temperature rise”.

Degrees of body temperature rise	**Degrees**
1. Normal 2. Subfebrile 3. Moderately elevated 4. High 5. Overly high 6. Hyperpyretic 7. Hypothermia	

13. Define the concepts of “symptom” and “syndrome”. Give the answers in the form of a table.

Concept	**Definition**	**For example**

1Symptoms		
2. Syndroms		

14. Complete the table “The degree of disorder of consciousness in a patient”.

Degree of disorder ofconsciousness	**Definition**	**Fore exampie**
1. Stuporous condition 2. Soporous state 3. Coma		

15. From the questions below, select those that need to be presented in the case history section: A - “life history” (anamnesis vitae), B - “history of the disease” (anamnesis morbi), C - “objective research data”.
1. When the disease began.
2. The living conditions of the patient in childhood and adolescence.
3. Asthenic body type.
4. Place of birth of the patient.
5. Allergic history.
6. Living and living conditions.
7. Height and weight of the patient.
8. Bad habits.
9. The presence of dyspnea in the patient.
10. Postponed diseases.
11. What was the treatment of the patient before his hospitalization?
12. The presence of fever.
13. Forced position of the patient.
14. Occupational hazards.

16. Fill in the table “Spurious respiratory noise”.

Type of respiratory noise	**Noise generation mechanism**	**Clinical examples**
1. Dry rales 2. Wet wheezing 3. Crepitus 4. Pleural friction noise		

17. Fill in the table “Measurement of respiratory volumes

Name of respiratory volume	**Definition**	**Number in milliliters**
1. Tidal volume 2. Reserve expiratory volume 3. The reserve volume of inspiration 4. Vital capacity of the lungs 5. Residual volume 6. Total maximum lung capacity		

18.Fill in the table “Types of endoscopic fiberglass research’’

Types of endoscopy	Brief description of the method, the object of study	Diagnostic value
1. Esophagoscopy 2. Gastroscopy 3. Duodenoscopy 4. Colonoscopy 5. Bronchoscopy		

19. Fill in the table “Properties of arterial pulse”.

Properties of pulse	Definition and brief description of the concept	Options for impaired pulse properties
1. Symmetry 2. Rhythm 3. Pulse rate 4. Pulse voltage 5. Filling the pulse 6. The value of the pulse 7. Pulse shape		

20. Fill in the table “Blood Pressure Measurement”.

Blood pressure	Definition	Rate
1. Systolic B.P 2. Diastolic B.P 3. Pulse pressure		

21. Fill in the table “Heart Tones”.

Tone	The mechanism of formation	The best listening place
1. First (I) tone 2. Second (II) tone		

22. Fill in the table “Differential diagnosis of jaundice”

ice	Mechanism occurrence	Clinical examples
1. Hemolytic (adhepatic) 2. Parenchymal (hepatic cell) 3. Mechanical (subhepatic)		

23. Fill in the table "Definition of terms in the study of blood".

s		al examples

	pt definition	
1. Leukocytosis 2. . Leukopenia 3. Thrombocytosis 4. Thrombocytopenia 5. Erythrocytosis 6. Anemia		

24. Definition of terms for a urine test. Match the terms.
1. Proteinuria.
2. Microhematuria.
3. Gross hematuria.
4. Glycosuria.
5. Ketonuria.
6. Urobilinuria.
7. Leukocyturia.

A. The appearance of erythrocytes in the urine, identified by macroscopic examination.
B. Increase in the number of leukocytes in the urine.
B. Excretion of urobilinoids with urine in large quantities.
G. The appearance of protein in the urine.
D. The appearance of red blood cells in the urine, detected microscopically.
E. Detection of acetone bodies in urine.
G. The appearance of sugar in the urine

25. Fill in the table "Diagnostic value of radiological methods in pulmonology".

Research method	**Definition, essence, diagnostic capabilities of the method**
Radiography X-ray Tomography Bronchography	

26. From the following diagnoses, select and check the main, concomitant disease and complications. Justify the answers.
- Rheumatism, active phase, activity of the II degree, continuously relapsing course, carditis, mitral heart disease with a predominance of stenosis. Heart failure II-B stage.
- Rheumatoid arthritis: polyarthritis, seropositive, slowly progressive, activity of the II degree, dysfunction of the joints of the II degree. Acute erosive gastritis.
- Chronic glomerulonephritis, hypertensive form, acute phase. Alcoholic cirrhosis of the liver, remission phase.
- Hypertension stage II, left ventricular hypertrophy. Sugar diabet (1st type), severe form. Hypoglycemic coma.
- Acute bronchitis. Diabetes mellitus (type 2), moderate severity, period of compensation.
- Ischemic heart disease: exertional angina (3rd functional class), atrial fibrillation. Heart failure stage II-A. Acute pyelonephritis.

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 PHARMACOLOGY, BASIC PRINCIPLES AND CONDITIONS OF DISCIPLINE

BASES OF CLINICAL BIOFARMATION

Purpose of the topic.

The number of drugs currently available to doctors is measured in tens and even hundreds of thousands. In our country, about 19,000 are registered and entered into the State Register, more than 50,000 drugs are in the Federal Republic of Germany and the United Kingdom, and the total amount of drugs available in different countries and their various combinations exceeds 200,000. years Even 20-30 years ago, 60-80% of the currently used drugs were not known or not used.

Due to such a significant expansion and dynamism of drug therapy, this problem in recent years has attracted increasing attention of the world community in order to make treatment as optimal and safe as possible. At the same time, one should be aware that the processes of creation, study, production, widespread use of drugs should be sufficiently connected, and specialists in each of these areas should understand each other to a sufficient degree. This has led nowadays to the formation of an integrating discipline - pharmaceutical medicine, which is successfully developing.

Motivational characteristics of the topic.

In modern conditions, the field of activity of the pharmacist has changed significantly. This was facilitated by the establishment of market relations, a change in the structure of the pharmaceutical market, a rapid increase in the number of original and reproduced drugs, the registration of a large number of drugs - synonyms that impede their effective use, an increase in over-the-counter distribution of drugs, and falsification of drugs. At the forefront is the information and advisory assistance of the pro-vision to doctors in determining effective and safe pharmacotherapy. It is important to study the main factors affecting the activity of drugs - the basis of biopharmacy.

The selection of an independent direction and development of clinical pharmacy in the second half of the twentieth century was motivated by a number of circumstances, the most important of which were:

Rapid development of the pharmaceutical industry, resulting in the emergence on the pharmaceutical market of tens of thousands of new drugs,

Awareness of the medical community of the need to create principles for the use of medicines, strictly regulated and based on scientifically proven facts.

The main sections of clinical pharmacology are:

 pharmacodynamics;
 pharmacokinetics;
 pharmacotoxicodynamics;
 methods for monitoring the effectiveness and safety of drugs;
 interaction of drugs with their joint use;
 the effect of food on the pharmacokinetics of drugs, etc .;
 study of the peculiarities of the action of medicinal substances in various conditions (advanced age, pregnancy, etc.);
 pharmacogenetics, the subject of which is to determine the genetic basis of the body's reactions to medicinal substances;
 clinical drug testing methods.

TYPES OF PHARMACOTHERAPY

Etiotropic therapy is aimed at eliminating the cause of the disease, for example, the use of antimicrobial agents for infectious diseases or antidotes for poisoning by toxic substances.

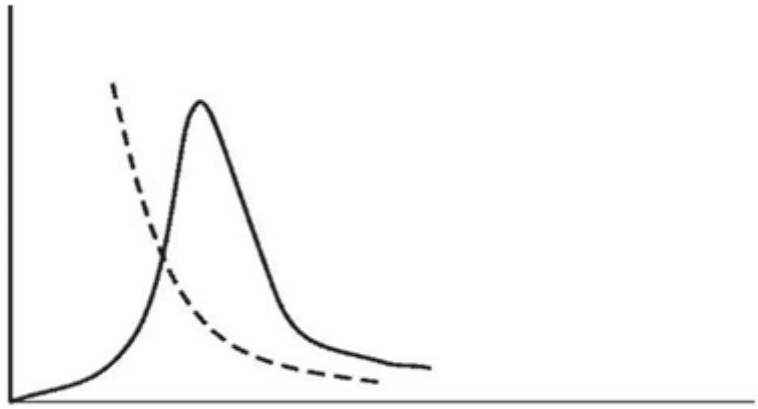
Pathogenetic therapy is aimed at eliminating or suppressing the mechanisms of the disease. Most drugs have exactly pathogenetic action - hypotensive, antiarrhythmic, anti-inflammatory, psychotropic, etc.
Symptomatic therapy is aimed at eliminating or reducing individual manifestations of the disease. Symptomatic remedies include anti-anxiety drugs that do not affect the cause or mechanism of the disease. However, in some cases (for example, in myocardial infarction), they can significantly affect the course of the pathological process, in effect having a pathogenetic effect.
Replacement therapy is carried out in case of insufficiency of natural bi-biologically active substances. Fermenting drugs, hormones and their analogues, vitamins, which, without addressing the causes of the disease, can ensure the normal functioning of the body for many years, are considered as means of replacement therapy. For example, insulin preparations do not affect insulin production in the islets of the pancreas.
Preventive therapy is carried out to prevent diseases. Some of the antiviral and disinfecting drugs are prophylactic agents.

MAIN ISSUES OF PHARMACOKINETICS

Pharmacokinetics - a section of clinical pharmacology, the subject of which is the study of the processes of absorption, distribution, binding to proteins, biotransformation and excretion of drugs. Its development has become possible due to the development and introduction into practice of highly sensitive methods for determining the content of medicinal substances in biological media - gas-liquid chromatography, radio-immune, enzyme-chemical and other methods, as well as through the development of methods for mathematical modeling of pharmacokinetic processes. Pharmacokinetic studies are carried out by experts in the field of analytical chemistry, pharmacists, pharmacists, biologists, but the results can be very useful for the doctor. On the basis of data on the pharmacokinetics of a drug, determine the dose, the optimal route of administration, the mode of use of the drug and the duration of treatment. Regular monitoring of the content of drugs in biological fluids makes it possible to promptly correct treatment.
Pharmacokinetic studies are needed when developing new drugs, their dosage forms, as well as experimental and clinical trials of drugs.
The processes that occur with drugs in the body can be described using a number of parameters.
One of the main indicators determining the pharmacological effect is the concentration of drugs at the receptor level, but it is impossible to establish it under the conditions of the whole organism. The experiment proved that in most cases there is a correlation between the concentration of the drug in the blood and its content in the receptor area. In this regard, to determine the pharmacokinetic parameters, the content of drugs in the blood is studied. In order to obtain a co-appropriate idea of the drug entering the blood and removing it from the body, changes in the concentration of drugs in the blood plasma are monitored for a long time. The content of drugs in the blood plasma is determined by methods of liquid or gas-liquid chromatography, using radioimmunoassay or enzyme immunoassay and other methods.
On the basis of the data obtained build a graph. The time from the beginning of the study is marked on the abscissa, and the drug concentration in the blood plasma (in the corresponding units) is shown on the ordinate axis.

This graph is called the pharmacokinetic curve (Fig. 1).

Drug concentration
Time after administration.



extravascular administration

intravenous

The concentration of a drug substance (C) is its quantity in a certain volume of blood at a specific point in time after administration to the body.

Constants of elimination rate (Kel), absorption (Ka) and excretion (Kex) - characterize, respectively, the rate of disappearance of the drug from the body by biotransformation and excretion, the rate of its receipt from the injection site into the blood and the rate of excretion with urine, feces, saliva, etc. .

The half-life (T1 / 2) - the time required to halve the concentration of the drug in the blood depends on the rate constant of elimination (T1 / 2 = 0.693 / Kel).

$$T_{1/2} = \frac{0{,}693 \times Vd}{CL}$$

where T1 / 2 is the half-life; 0.693 - a coefficient that is the log-rate of 2; Vd is the volume of distribution; CL - total clearance.

The elimination constant (Kel) is the percentage decrease in the concentration of drug in the blood per unit time. The more kel, the faster the drug is removed from the blood. Constant elimination depends on the half-life:

$$K_{el} = \frac{0.693}{T_{1/2}}$$

The period of semi-absorption (T1 / 2a) is the time required for the absorption of one half of the dose of the drug from the injection site into the systemic circulation; proportional to the rate of absorption (T1 / 2a = 0.693 / Ka).

Absorption constant (Ka) - characterizes the rate of absorption of the drug in the human or animal organism. The absorption constant depends on the half-life:

$$K_a = \frac{0.693}{T_{1/2a}}$$

The distribution of the drug in the body is characterized by half-distribution, apparent initial and stationary (equilibrium) concentration, the volume of distribution.

The half-distribution period (T1 / 2, a) is the time required to achieve a drug concentration in the blood equal to 50% of the equilibrium, i.e. in the presence of equilibrium between blood and tissues.

The apparent initial concentration (C0) is the concentration of the drug that would be reached in the blood plasma when administered intravenously and instantaneously distributed

throughout the organs and tissues.

Equilibrium concentration (Css) is the concentration of the drug, which is established in the plasma (serum) of blood when the drug enters the body at a constant rate.

With intermittent administration (intake) of the drug at equal intervals of time in equal doses, the maximum (Cssmax) and minimum (Cssmin) equilibrium concentrations are isolated.

The volume of distribution of the drug (Vd - volume of distribution) characterizes the degree of its capture by the tissues from the plasma (serum) of the blood. Vd (Vd = D / C0) is the conditional volume of fluid in which the entire dose of the drug (D) to be absorbed into the body must be dissolved to obtain a concentration equal to the apparent initial serum concentration (C0).

The total clearance of the drug (Clt) characterizes the rate of "cleansing" of the body from the drug.

$$Cl = \frac{D}{AUC}$$ where CI is the total clearance; D is the dose of the administered drug; AUC - area under the pharmacokinetic curve. Renal (Clr) and extrarenal (Cler) clearances, which reflect the elimination of the drug substance, respectively, with urine and other ways (especially with bile). Total clearance is the sum of the renal and extrarenal clearance.

$$Cl_{renal} + Cl_{hepatic} + Cl_{others} = Cl_{common}$$

The area under the "concentration - time" curve (AUC - area under the curve) is the area of the figure bounded by the pharmacokinetic curve and coordinate axes (AUC = C0 / Kel). The value (AUC) is associated with other pharmacokinetic parameters - the volume of distribution, total clearance. When the kinetics of the drug is linear in the body, the AUC value is proportional to the total amount (dose) of the drug that has entered the systemic circulation. Often, the area under the part of the curve is determined (from zero to some time t); This parameter is designated AUCt, for example, the area under the curve from 0 to 8 h - AUC8.

Absolute bioavailability (f) - part of the drug dose (in%), which reaches the crucible of the systemic blood flow after extravascular administration, is equal to the ratio of AUC after administration by the test method (inside, into muscle, etc.) to AUC after intravenous administration. The relative bioavailability is determined to compare the bio-availability of two dosage forms for extravascular administration. It is equal to the ratio (AUC '/ AUC) (D / D') after the introduction of two compared forms. The total bioavailability is part of the ingested dose of the drug, which has reached the systemic blood flow in an unchanged form and in the form of metabolites formed in the process of absorption as a result of the so-called presystemic metabolism, or the "effect of the primary passage".

$$F = \frac{AUC \ \text{(Extravascular administration)}}{AUC \ \text{(intravascular injection)}} \times 100\%$$

Bioequivalence (comparative bioavailability) is the ratio of the amount of drug entering the blood when administered in various dosage forms (or drugs from different companies). If medicinal preparations demonstrate similar bioavailability, they are regarded as bioequivalent.

SUCTION - the process of intake of a medicinal substance from the injection site into the blood. There are four mechanisms of drug absorption with enteral administration (Fig. 2):

1. passive diffusion;
2. active transport;
3. filtering through the pores;
4. pinocytosis

The passage of most drugs through the mucous membrane of the digestive tract is determined by their solubility in lipids and ionization. When taking drugs inside the speed of their absorption varies in different parts of the gastrointestinal tract.

After passing through the wall of the stomach and / or intestines, the drug enters the liver. Some medicinal substances under the influence of liver enzymes undergo significant changes ("the effect of the primary passage"). That is why, and not because of poor absorption, in order to achieve a sufficient effect, the doses of some drugs (propranolol, aminazine, opiates) when taken orally must be significantly higher than with intravenous administration. The biotransformation of a substance during the initial passage through the liver in the process of absorption is called a first-pass metabolism. The intensity of the presystemic metabolism depends on the speed of blood flow in the liver.

The process of drug absorption in the stomach and intestines is influenced by pH, which is 1-3 in the stomach, in the duodenum - 5-6, and in the small and large intestines - about 8. Acids are more easily absorbed in the stomach, and the bases - in the small or large intestine. colon.

Under the action of the acidic environment of the stomach, some drugs, in particular benzylpenicillin, can be destroyed.

Enzymes of the gastrointestinal tract, which are able to inactivate proteins and polypeptides (ACTH, vasopressin, insulin, etc.), as well as some other substances (progesterone, testosterone, aldosterone) also have an effect on drugs. Bile salts, in turn, can speed up the absorption of drugs or slow it down in the formation of insoluble compounds.

The motility of the gastrointestinal tract, the volume and composition of food, the amount of fluid taken, the interval of time between meals and taking drugs also affect the absorption of drugs. Thus, milk impairs the absorption of tetracyclines, ampicillin, and amoxicillin. It is necessary to take into account the stimulating effect of food on the secretion of gastric juice and hydrochloric acid.

For the transfer of substances in the gastrointestinal tract, a large area of the intestinal surface and the effect of constant blood flow in the mucosa on concentration gradients between the intestinal lumen and blood are of particular importance. By diffusion and osmosis through the mucous membrane of the intestine are transported, in particular, water, $C1^-$, as well as substances such as ascorbic acid, pyridoxine and riboflavin. Because cell membranes contain large amounts of lipids, substances must be somewhat fat soluble to diffuse through the membrane. According to the theory of non-ionic diffusion, the indicated pathway transfers mainly the undissociated salts of weak acids or weak bases. This must be taken into account when prescribing drugs, most of which are absorbed by diffusion. For the transfer of any substance in accordance with the Henderson-Hasselbach equation, the pKa of this substance and the pH in the intestinal lumen is of particular importance:

$$\lg \frac{[A^-]}{[HA]} = pH - pKa \quad \lg \frac{[B]}{[BH+]} = pH - pKa$$

, где

$[A^-]$, $[BH^+]$ – molar concentrations of ionized,

[HA], [B] – non-ionized forms of acid and bases B;

pH – acid-baseline indicator of the environment;

pKa is the logarithm of the dissociation constant of a compound, quantitatively equal to the pH value at which the analyzed compound dissociates by half.

It can be seen from the equation that with an increase in the pH of the medium, the dissociation of acids increases, and that of bases decreases.

Thus, factors affecting the absorption of drugs are diverse: the solubility of a substance in lipids, the degree of ionization of the molecule (the smaller the ionized molecule, the better it is absorbed), intestinal peristalsis, the nature and amount of food mass, features of regional blood flow, connective tissue, aggregative state of substances, combination of drugs.

The main route of administration of drugs.

Enteral path

LS is most often injected into the gastric tract (through the mouth or rectum).

The advantage of this path is the ease of use (does not require the help of medical personnel), as well as comparative safety and the absence of complications characteristic of parenteral administration. Drugs, enterally administered, can have both local (some antimicrobial and anthelmintic agents) and systemic effects.

Oral ingestion (per os). In the treatment of diseases of internal organs, oral drugs should be administered orally, which are well absorbed by the mucous membrane of the stomach or intestines. If you need to create a high concentration of the drug in the gastrointestinal tract, on the contrary, use drugs that are poorly absorbed, which allows to obtain a good effect in the absence of systemic side reactions. In severe cases of certain diseases, such as dysentery, it is desirable that the concentration of drugs be high both in the intestinal lumen and in the blood

The disadvantages of the oral route of drug use, if necessary, to obtain a systemic effect are the following: the relatively slow development of the therapeutic effect; the possibility of large individual differences in the rate and completeness of absorption; the effect of food and other drugs on absorption; the inability to use drugs that are poorly absorbed by the mucous membrane of the stomach and intestines (for example, streptomycin) and degrade in the lumen of the stomach and intestines (insulin, oxytocin, etc.) or when passing through the liver (hormones), as well as substances that have a strong irritant act. The introduction of drugs through the mouth is impossible or very uncomfortable with vomiting and unconsciousness of the patient.

Inside the medicinal substance is administered in the form of solutions, powders, tablets, capsules, pills. To prevent the irritating effect of certain drugs on the gastric mucosa, tablets coated with films resistant to the action of gastric juice but disintegrating in the alkaline environment of the intestine are used. There are dosage forms (tablets with multilayer shells, etc.), providing a gradual, long-term release of the active principle, which allows you to prolong the therapeutic effect of the drug.

It should be remembered that some tablets and capsules, if taken by patients in the prone position, may linger in the esophagus and cause ulceration, especially in elderly people who have impaired peristalsis. To prevent this complication, tablets and capsules should be washed down with plenty of water.

Application under the tongue (sublingual). The mucous membrane of the oral cavity has an abundant blood supply, therefore substances absorbed through it quickly enter the systemic circulation and begin to act after a short time. Sublingual nitroglycerin is used most often. When sublingual drug is not exposed to the action of gastric juice and enters the systemic circulation through the veins of the esophagus, bypassing the liver, thus avoiding its biotransformation.

The drug should be kept under the tongue until completely absorbed. Swallowing its part with saliva reduces the benefits of this way of administering drugs.

Parenteral route

Methods of using drugs in which they are not injected into the gastrointestinal tract are called parenteral. Parenteral methods include various types of injections, inhalations, electrophoresis and superficial application of drugs to the skin and mucous membranes.

Intravenous administration. The introduction of drugs into the vein provides a quick onset and accurate dosing of the effect; rapid termination of the drug in the bloodstream in the event of adverse reactions; the possibility of introducing substances that are not absorbed from the gastrointestinal tract or irritate its mucosa.

With the intravenous administration of drugs should be respected precaution. Before you enter the drug, you must make sure that the needle is in a vein. The ingress of a drug into the near-venous space may be accompanied by severe irritation, even necrosis of the tissues. Some drugs, such as cardiac glycosides, are administered very slowly, as a rapid increase in their concentration in the blood can be dangerous.

The time of blood flow from the veins of the upper extremities to the tongue is 13 ± 3 s. For most drugs, the time of administration, 4-5 such cycles, is enough to evenly dissolve the drug in the blood. With prolonged treatment, venous thrombosis may occur. Intravenous administration is also the main route of infection with hepatitis B viruses and human immunodeficiency.

Intraarterial introduction. For the treatment of diseases of certain organs (liver, limbs), drugs that are rapidly metabolized or bound by tissue are injected into the artery. In this case, a high concentration of the drug is created only in the corresponding organ, and systemic action can be avoided. It should be remembered that possible arterial thrombosis is a much more serious complication than vein thrombosis.

Intramuscular administration. With intramuscular administration of the drug, a relatively rapid onset of effect is ensured (soluble drugs are absorbed within 10-30 minutes). Thus it is possible to use drugs that have a moderate irritant effect, as well as depot preparations. The volume of the entered substance should not exceed 10 ml.

Subcutaneous administration. With subcutaneous administration, absorption of drugs, and hence the manifestation of therapeutic action, occurs more slowly than with intramuscular and intravenous administration. However, the effect lasts longer.

Subcutaneously injected substances are poorly absorbed in case of insufficiency of the peripheral circulation (for example, in shock).

Inhalation. Inhaled drugs are administered in the form of aerosols (b-adrenomimetics), gases (volatile anesthetics), and powders (sodium cromoglycate). Inhalation drugs are rapidly absorbed and have a local and systemic effect. When using gaseous substances, the inhibition of inhalation leads to the rapid cessation of their action (ether for anesthesia, halothane). By inhalation of the aerosol, a high concentration of the drug in the bronchi (beclometa-zones, salbutamol) is achieved with minimal systemic effect. Inhalation is not possible to use annoying drugs. It should be remembered about the possible effect of inhalation drugs, for example, anesthetic agents, on surrounding people. In addition, during inhalation, medicinal substances go directly to the left parts of the heart through the pulmonary veins and can have a cardiotoxic effect.

Intrathecal introduction. For direct action on the central nervous system of drugs introduced into the subarachnoid space. So apply local anesthetics for spinal anesthesia. This path is also used in cases when it is necessary to create a high concentration of a substance (for example, an antibiotic) in the subarachnoid space.

Local application. The application of drugs on the surface of the skin or mucous membranes is used to obtain a local effect. However, some drugs when applied to the mucous membranes of the nose, eyes and even the skin can be absorbed and have a systemic effect. For example, prolonged application of glucocorticoids to the skin leads to the occurrence of adverse reactions in the patient, similar to those in the oral administration of these drugs.

Recently, special dosage forms have been developed, which are fixed with a sticky substance on the skin and provide a slow and long absorption of the drug, thereby increasing its duration of action. In this way, for example, nitroglycerin, scopolamine are introduced.

Electrophoresis. The method is based on the use of galvanic current for the transfer of medicinal substances from the skin to deeply located tissues.

The distribution of medicinal substances in the body is the movement of a substance from the place of absorption to the place of action and, further, to the place of elimination.

The degree of tissue permeability for drugs depends on a number of factors: the concentration of the drug in the blood, the degree of their binding to plasma proteins, the intercellular spaces and the cytoplasm of target cells, the rate of penetration through various biomembranes, the speed of blood flow in the tissues, the presence of certain pathologies that change these indicators (the level or structure of serum and tissue proteins associated with these drugs, membrane permeability, blood flow at the site of infection, etc.). The nature of drug distribution is determined by its solubility in lipids, the degree of binding to plasma proteins, the intensity of regional blood flow and other factors. Most of the drugs in the first minutes after suction gets into those organs and tissues that most actively supply blood - the heart, liver, kidneys. Slower is the saturation of drugs of muscles, mucous membranes, skin and adipose tissue. To achieve therapeutic concentrations of drugs in these tissues take from several minutes to several hours. An important factor determining the distribution of drugs is the rate of its diffusion into various tissues. Diffusion into interstitial tissue occurs easily and quickly. Capillaries are well permeable for both water-soluble and fat-soluble substances, therefore water-soluble drugs (for example, streptomycin), which are poorly absorbed from the intestine, are administered parenterally. They penetrate well into the extracellular areas, but have no effect on the central nervous system and other organs, in which the substance can only get through the membrane barriers. Fat-soluble drugs (eg, gaseous anesthetics) are rapidly distributed throughout the body, penetrating equally well into the extracellular and intracellular regions. The BBBs form a continuous capillary endothelium, the cells of which are connected by extensive tight contacts that almost completely cover the gaps and the very dense basal membrane surrounding the capillaries.

The permeability of the meninges is increased in early childhood and senile age, with an acute inflammatory process, reduced - with the formation of a fibrin capsule around a brain abscess. High concentrations are noted both in the brain tissue and in the purulent contents of the abscesses of the viso-lipophilic drugs poorly bound to serum proteins, as well as low molecular weight drugs (levomycetin, metronidazole, clindamycin, fusidic acid).

Normally, drugs are relatively poorly penetrated into the deeper layers of the eye. Even with topical administration, when the concentration in the eye tissues is higher than with parenteral administration, it is not always possible to determine the drug, for example, in the vitreous.

Different factors play a role in the penetration of drugs through the pleura: binding to blood proteins, the molecular weight of drugs, their lipophilicity, and binding to cell membrane receptors.

As you know, in normal blood of the mother and the fetus does not mix, between them there is the placental barrier. The mechanisms of transplacental transfer are analogous to the mechanisms of penetration through other barriers - passive transport, facilitated diffusion, active transport, endocytosis; some low molecular weight substances can pass through the water pores in the placenta. Hydrophilic and ionized drug molecules very poorly penetrate the placenta. Many neutral substances, weak acids or bases to a greater or lesser extent pass through the placenta, causing embryotoxic or specific pharmacological action in the fetus.

Binding of drugs with proteins in blood and tissues

Many drugs have a pronounced physicochemical affinity for various plasma proteins, primarily albumin. The binding of drugs to plasma proteins leads to a decrease in their concentration in the tissues and the site of action, since only free (unbound) drug passes through the membrane. A substance that is complexed with a protein lacks specific activity. The free and bound parts of a drug are in a state of dynamic equilibrium. Sometimes drugs accumulate in tissues in high concentrations than would be expected, proceeding from diffusion equilibrium. This effect depends on the pH gradient, the binding of drugs to intracellular elements and its distribution in adipose tissue.

Plasma proteins have a specific structure and can bind with drugs through their active groups. The speed, degree and strength of binding depend on the conformation and complementarity of these centers and the nature of the chemical bonds that occur during the interaction. Only unbound substances can diffuse into the tissue, because the protein-drug complex is not able to pass through the cell membrane.

The degree of protein binding to drugs depends on the following factors:

1) the number of different types of binding macromolecules;

2) the concentration of macromolecules of each type;

3) the ability to bind or "kinship" the active center of the protein and the drug preparation;

4) the presence of competing chemical compounds of exogenous nature;

5) physical and chemical state of the blood: pH, temperature, ionic composition, viscosity, osmotic pressure.

A number of tissue structures are able to actively bind certain chemical substances. For example, thyroid tissue accumulates copper compounds, bone tissue — tetracycline, etc.

Violation of drug binding is observed with a decrease in the concentration of albumin in the blood (hypoalbuminemia) and the binding ability of blood proteins in some diseases of the liver and kidneys. Even a decrease in the level of albumin in the blood to 30 g / l (normal 33-55 g / l) can lead to a significant increase in the content of the free fraction of phenytoin. A clinically significant increase in the level of the free fraction of furosemide occurs when the amount of albumin is reduced to 20 g / l.

The main blood proteins that bind drugs are albumin,lipoprotein,acid alfa1-glicoprotein,gamma-globulin,proteins of erythrocytes.

The main indicator of distribution is the volume of distribution (Vd - volume of distribution).

Biotransformation (metabolism) of drugs includes the biochemical processes of the transformation of drugs with a change in their pharmacological properties and the formation of metabolites that can be removed from the body. As a result of biotransformation, therapeutically active, indifferent or toxic products are formed. At the same time, substances get greater polarity and, as a result, high hydrophilicity.

There are two types of drug metabolism reactions in the body: non-synthetic (phase I reactions) and synthetic (phase II reactions). All non-synthetic reactions of drug metabolism can be divided into two groups: reactions catalyzed by endoplasmic reticulum (microsomal) enzymes, and reactions catalyzed by enzymes localized in other places (non-microsomal). Non-synthetic reactions (phase I) cause a specific rearrangement in the substrate molecule to form functional groups with an active hydrogen atom — hydroxy groups, primary or secondary amino groups, and a carboxy group. In synthetic reactions (phase II), functional conjugation occurs conjugation with highly polar acid residues, for example, with residues of glucuronic, sulfuric and other amino acids.

There are several types of redox enzyme reactions. These reactions are catalyzed by enzymes of the cytochrome P450 (or CYP) system, flavin monooxygenase and epoxide hydrolase.

Drugs before systemic circulation can be metabolized in the gastrointestinal epithelium or in the liver. This process, called the effect of the first passage, reduces the biological activity of drugs.

Since drugs that are administered orally pass through the liver before entering the systemic circulation, they can be divided into two groups: the first with high hepatic clearance, and the second with low. The ability of the liver to metabolize drugs of the first group depends on the speed of their delivery to the liver, that is, from the hepatic blood flow. The kinetics of such drugs varies considerably in diseases that violate the hepatic blood flow.

For the second group of drugs, hepatic clearance does not depend on the speed of the hepatic blood flow, but on the capacity of the enzymatic systems of the liver metabolizing these drugs.

The biotransformation of drugs in the body is influenced by many factors - age, gender, external environment, diet, disease.

In the process of aging of the human body, changes in the number and size of the cellular elements of the parenchyma occur, the blood flow through the liver is partially disturbed, its

functions, including protein synthesis and antitoxic, are reduced. Changes in the activity of enzyme systems that metabolize drugs are one of the reasons slowing down the biotransformation of drugs in the body of people of old and old age and increase their concentration in the blood and tissues.

Of particular practical and theoretical interest is the clarification of the nature of changes in the biotransformation of the drug in various pathological conditions. In case of liver diseases, for example, in case of cirrhosis, not only the function of the liver cells is disturbed, but also the hepatic blood flow. Therefore, the pharmacokinetics of drugs with high hepatic clearance is changing

Microsomal Biotransformation

In hepatocytes, the set of enzyme systems that carry out the oxidation of various xenobiotics is most fully represented (Greek "xenos" is alien, "bios" is life), i.e. substances foreign to the human body. These include most medicines. Fat-soluble substances, which easily penetrate through the membrane into the endoplasmic reticulum and bind to one of the cytochromes of the P446-P455 system, are subjected to microsomal transformation primarily through the first enzyme of this system indicated only by cytochrome P450. These cytochromes are the primary components of the oxidative enzyme system. The rate of biotransformation of drugs by the mixed-type oxidase system is determined by the concentration of cytochrome P450, the number of different forms of cytochrome P450 and their affinity for the substrate, the concentration of cytochrome-c-reductase and the recovery rate of the drug-cytochrome P450 complex. The rate of biotransformation may also depend on the competition of endogenous and exogenous substrates.

Further oxidation of drugs occurs under the influence of oxidase and reductase with the obligatory participation of NADP and molecular oxygen. Nonspecific oxidases catalyze the processes of deamination of primary and secondary amines, hydroxylation of side chains and aromatic rings of heterocyclic compounds, the formation of sulfoxides and dealkylation.

Conjugation of drugs with glucuronic acid is also carried out under the influence of microsomal enzymes. This is one of the main ways of biotransformation of carboxylic acids, alcohols, phenols. By conjugation, estrogens, glucocorticoids, progesterone, opium alkaloids and other narcotic analgesics, amidopyrine, salicylates, barbiturates, antibiotics and many other substances are excreted from the body.

Drugs can both increase and decrease the activity of microsomal enzymes. There is a large group of substances involved in hepatic metabolism that activate, suppress, and even destroy cytochrome P450. The latter include lidocaine, sovkain, benkain, inderal, whiskey, araldine, etc. More significant is the group of substances that induce the synthesis of enzymatic liver proteins, apparently with the participation of NADPH.H2-cytochrome P450-reductase, cytochrome P420, N- and O-demethylase microsomes, Mg2 +, Ca2 +, Mn2 +. It geksobarbital, pheno-barbital, pentobarbital, phenylbutazone, caffeine, ethanol, nicotine, phenylbutazone, it-roleptiki, aminopyrine, chlorcyclizine, diphenhydramine, meprobamate, tricyclic en tidepressanty, benzonal, quinine, kordiamin, many chlorinated pesticides.

It has been shown that glucuronyl transferase is involved in the activation of liver enzymes by these substances. This increases the synthesis of RNA and microsomal proteins. Inducers enhance not only the metabolism of drugs in the liver, but also their excretion with bile. Moreover, the metabolism is accelerated not only by the drugs administered with them, but also by the inductors themselves.

Drugs whose biotransformation is accelerated in the body under the influence of enzyme

inducers (phenobarbital, rifampicin, phenytoin)

Non-microsomal biotransformation

Although non-microsomal enzymes are involved in the biotransformation of a small number of drugs, they still play an important role in metabolism. All types of conjugation, excluding glucuronide, recovery and hydrolysis of drugs, are catalyzed by non-microsomal enzymes. Such reactions contribute to the biotransformation of a number of common drugs, including acetylsalicylic acid and sulfonamides. Non-microscopic biotransformation of drugs occurs mainly in the liver, but it is also carried out in blood plasma and other tissues.

With oral administration of drugs, absorbed by the intestinal mucosa, first enter the portal system, and only then into the systemic circulation. Intensive and numerous metabolic reactions take place already in the intestinal wall (almost all known synthetic and non-synthetic reactions). For example, izadrine undergoes conjugation with sulfates, hydralazine - to acetylation. Some medicinal substances are metabolized by non-specific enzymes (penicillins, aminases) or by intestinal bacteria (methotrexate, levodopa), which can be of great practical importance. Thus, in some patients, the absorption of aminazine is reduced to a minimum due to its significant metabolism in the intestine. It is necessary to emphasize nevertheless that the main processes of biotransformation occur in the liver.

Drug metabolism before entering the systemic circulation when passing through the wall of the gastrointestinal tract and the liver is called the “first-pass effect”. The degree of drug metabolism during the first passage is determined by the metabolic capacity of enzymes for this drug, the rate of metabolic reactions and absorption. If the drug is administered orally in a small dose, and the capacity of the enzymes and its metabolic rate are significant, then most of the drug is biotransformed, thereby reducing its bioavailability. With an increase in the dose of drugs, the enzyme systems involved in the metabolism of the first passage can be saturated and the bioavailability of the drug increases.

The main ways of removing drugs from the body

There are several ways of excretion of drugs and their metabolites from the body. The main ones include excretion with feces and urine; excretion with air, sweat, saliva and tear fluid is of less importance.

Urine excretion

To assess the rate of elimination of hp with urine, its renal cle-ren is determined.

Drugs are excreted in the urine by glomerular filtration and tubular secretion. Of great importance is also their reabsorption in the tubules of the kidneys. Blood falling into the kidneys is filtered in the glomeruli. At the same time, drugs penetrate through the wall of capillaries into the lumen of the tubules. Only that part of the drug that is in the free state is filtered. When passing through the canaliculi, part of the HC is reabsorbed and returns to the blood plasma. Many drugs are actively secreted from the capillaries and peritubular fluid into the lumen of the tubules. In case of renal insufficiency, the glomerular filtration decreases, and the elimination of various drugs is disturbed, which leads to an increase in their concentration in the blood. The dose of drugs that are excreted in the urine, with the progression of uremia should be reduced. The canal secretion of organic acids can be blocked by probenecid, which leads to an increase in their half-life. Urine pH affects kidney excretion of some weak acids and bases. The former are more rapidly excreted with the alkaline reaction of urine, and the latter with an acidic one.

Bile excretion

From the liver, drugs in the form of metabolites or unchanged passively or with the help of active transport systems enter the bile. In the future, drugs or their metabolites are eliminated from the body with feces. Under the influence of enzymes of the gastrointestinal tract or bacterial microflora, they can be converted into other compounds that are reabsorbed and re-delivered to the liver, where they undergo a new cycle of metabolic transformations. This cycle is called the enterohepatic circulation. The molecular mass of compounds, their chemical nature, the state of hepatocytes and biliary ducts, the intensity of binding drugs to the liver cells affect the elimination of drugs with bile.

Hepatic clearance of drugs can be determined in the study of duodenal contents obtained using a probe.

Removal with breast milk

Many drugs can be displayed with breast milk. In some cases, the amount of drug absorbed with milk can be dangerous for the child.

Bioavailability of drugs

To provide a therapeutic effect, the drug must be delivered to those organs or tissues in which its specific action takes place (to the biophase). With intravascular administration, the drug immediately and completely enters the bloodstream. For other routes of administration (orally, v / m, s / c, etc.), before entering the bloodstream, the medicinal substance must pass through a number of biological membranes of cells (gastric mucosa, liver cells, muscles, etc.) and only then some part of it will enter the systemic circulation. The effect of the drug depends largely on how much of the injected dose of drug enters the systemic circulation. This indicator characterizes the bioavailability of the agent (F). Thus, essentially, the bioavailability of a drug reflects its concentration at the receptors, that is, in the blood and tissues of the body after absorption.

Naturally, the bioavailability of the same means will be different for each patient. Obviously, with the introduction of a drug, its bioavailability is approximately 100%, and with other routes of administration, bioavailability almost never reaches 100%.

There are absolute and relative bioavailability. Absolute bioavailability is the proportion of the absorbed drug when administered extravascularly in relation to its quantity after intravenous administration.

Relative bioavailability - determines the relative degree of absorption of the medicinal substance from the test drug and from the comparison drugs. In other words, the relative bioavailability is determined for different series of drugs, for drugs with a change in production technology, for drugs manufactured by different manufacturers for different dosage forms. To determine the relative bioavailability can be used data on the level of drug substance in the blood or its excretion in the urine after a single or multiple injections. This term is important when comparing 2 drugs among themselves.

Comparative bioavailability of the same preparations made by different companies (for example: cocarboxinase of the Polish search and made in Dnepropetrovsk) is determined by comparing chemical, biological and therapeutic equivalences.

Chemical equivalence is a coincidence in preparations of not only the chemical formula of drugs, but also the coincidence of isomerism, the spatial configuration of atoms in the molecule of a drug substance.

Biological equivalence means the same, equal to the concentration of the active substance in the blood when taking the drug from different companies.

Therapeutic equivalence implies the same, equivalent therapeutic effect.

If the listed 3 characteristics are the same, they say that drugs have equal bioavailability (bioavailable). Currently, there are many examples of the fact that similar drugs are biologically inequivalent due to differences in bioavailability. A practitioner must remember this, especially when transferring a patient from one drug to a similar drug from another company.

MAIN ISSUES OF PHARMACODYNAMICS

Pharmacodynamics (PD) is a section of pharmacology that studies:

1) mechanisms of action (that is, the essence of the processes of interaction with tissue, cellular or subcellular receptors - specific or non-specific)

2) pharmacological effects (content and changes in the effect of the drug depending on the age, sex of the patient, nature and course of the disease, comorbidities)

3) localization of the action of drugs.

In short, PD can be defined as a section of pharmacology that studies the effect of drugs on the body.

Knowledge of the mechanism of action of drugs allows the doctor to intelligently choose the necessary drug for treatment.

The main mechanisms of drug action include:

□ □ effect on specific receptors (agonists and antagonists);

□ □ effect on enzyme activity (induction and inhibition);

□ □ effect on cell membranes;

□ □ direct chemical interaction of drugs.

The term receptor is applied to a cellular macromolecule with which the drug binds to achieve its effect. The most important group of drug receptors are proteins, which physiologically work as receptors for endogenous regulatory ligands (for example, hormone receptors, neurotransmitters). Many drugs act on such receptors and are often highly selective due to the specificity of physiological receptors. The regulatory activity of the receptor can manifest itself as a result of direct action on cellular targets, effector proteins, or through intermediate cellular signaling molecules (transducer). The interaction of the receptor, cellular target and intermediate molecules is considered as a receptor-effector system.

G-Protein Receptors A large family of receptors for many existing drugs (biogenic amines, eicosanoids, peptide hormones, opioids, amino acids) includes heterotrimeric regulatory proteins associated with guanine triphosphate (G-proteins). G-proteins are signal transducers that transmit information from receptors to effector proteins such as adenylate cyclase, phospholipase C, phosphodiesterase, Ca2 + and K + ion membrane channels.

Enzyme receptors. The group of receptors with intrinsic enzyme activity includes cell-surface kinases that distribute regulatory signals through effector proteins on the inner surface of the cell membrane. Protein phosphorylation may alter the biochemical activity of the effector, or its interaction with other proteins.

Most receptors are protein kinases, phosphorylate tyrosine in the substrate. This group includes insulin receptors, growth factors. Some receptor protein kinases phosphorylate serine and threonine.

For receptors that bind atrial natriuretic peptide, guaniline, and uroguaniline, the intracellular structure is guanylyl cyclase, not protein kinase. Guanilyl cyclase is involved in the secretion of a cyclic guanosine monophosphate (GMP) secondary messenger activating cyclic GMP-dependent protein kinase and activates several nucleotide phosphodiesterases.

Ion channels. Receptors for some neurotransmitters form selective ion channels. This group includes nicotinic cholinergic receptors, GABA receptors, receptors for glutamate, aspartate and glycine.

Transcriptional receptors. The receptors for steroid and thyroid hormones, vitamin D, retinoids are soluble proteins that bind to DNA and regulate the transcription of specific genes.

The selective sensitivity of the drug to the receptor means the fact that the medicinal substance can, firstly, bind to the receptor, that is, has affinity or affinity for it. In other words, affinity or affinity means the ability of a drug to bind to a receptor.

Drugs, the action of which is associated with direct excitation or enhancement of functional capabilities (abilities) of the receptors, are called AGONISTS, and substances that prevent the action of specific agonists are called ANTAGONISTS. In other words, if a medicinal substance has both characteristics (that is, affinity and internal activity), then it is an agonist. Therefore, an agonist is a substance with high affinity for the receptor and high intrinsic activity. If the substance has the ability to only bind to the receptor (that is, it has affinity), but it is not able to cause pharmacological effects, then it causes a receptor blockade and is called an antagonist.

Drugs that have the same affinity for the receptor as an agonist, or a weaker one, but with less pronounced intrinsic activity, are called partial agonists or an antagonist agonist. These drugs, used simultaneously with agonists, reduce the effect of the latter, due to their ability to occupy the receptor.

Example: atropine - has more activity than acetylcholine (endogenous mediator). Atropine interacts with receptors, but since it has no internal activity, it will not cause a physiological effect. Due to its greater affinity for the receptor compared to acetylcholine, it will interfere with the action of the agonist, namely acetylcholine, and therefore be its antagonist.

Medicinal substances can act similarly or oppositely to endogenous mediators. If the medicinal substance acts like a mediator (acetylcholine, noradrenaline, etc.), this substance is called MIMETIC. Mim - root "mime", pantomime, mimicry. Hence the cholinomimetic, adrenergic mimic.

The drug substance that prevents the mediator from interacting with the receptor is called a blocker (holinoblokator, adrenergic blocker, histamine blocker, etc.).

The term "litic" can be found in the literature (lysis - dissolution, physical process). The term is rather old, but sometimes used (anticholinergic, adrenolytic). Thus, the terms "litic" and "blocker" are used as synonyms.

INTERACTION OF MEDICINES

PHARMACOLOGICAL interaction and **PHARMACEUTICAL** interaction are distinguished.

Pharmaceutical interaction is associated with pharmaceutical incompatibility of drugs in the process of their manufacture or storage, as well as when mixed in one syringe. At the same time, the previously existing pharmacological activity of drugs decreases or disappears, and sometimes even new, toxic properties appear.

Pharmacological interaction of drugs is associated with changes in their pharmacokinetics, pharmacodynamics - based on chemical and physico-chemical interaction in the body's environment.

Pharmacokinetic interaction - at any stage of their passage through the patient's body: during absorption, in the transport phase, in the process of meta-bolism, as well as excretion.

Pharmacodynamic interaction reflects the change caused by each drug separately processes associated with the implementation of the effect. In other words, the pharmacodynamic type of interaction is based on the features of changes in the mechanisms and localization of the action of the drugs used, their main effects. If the interaction is carried out at the receptor level, then it mainly concerns agonists and antagonists of various types of receptors. In this case, one medicinal substance may enhance or weaken the effect of another. If medicinal substances act unidirectionally with respect to the effect, these are synergist drugs (syn - together, ergo - work). Thus, synergism is accompanied by an increase in the final effect. As a rule, these medicinal substances act on the same receptors.

There are 2 options for synergism:

1) The effects are the same on the principle of simple sum. Summed (or additive, - Latin. - additio - addition). The effect is observed by simply adding the effects of each of the components. For example, this is how drugs for anesthesia interact (nitrous oxide + halothane). A similar variant of the additive effect with the simultaneous use of aspirin and analgin. If the patient has to take aspirin for a long time, then it should be taken into account that Aspirin acts ulcerogenically, that is, it causes ulceration of the gastrointestinal mucosa, and Analgin has such an undesirable effect as oppression of blood formation. Given the additive analgesic effect, it is possible, without a substantial risk of its occurrence, to reduce, significantly reduce the dosages of both drugs taken by the patient.

2) The second variant of synergism is potentiation or enhancement of the effect. This option arises when, with the introduction of two substances, the total effect exceeds the sum of the effects of both agents. As an example, the interaction of neuroleptics (aminazin) and anesthetics, the interaction of antibiotics and antimicrobial sulfonylamides can be given.

Sometimes a third (3) variant of synergism is identified, - sensitization. Sensitization - when one drug in a minimum dose enhances the effect of another in their combination (the use of small doses of insulin in combination with KCl increases the level of penetration of potassium into the cells).

In addition to synergism, there is the phenomenon of antagonism.

The ability of one substance to one degree or another to reduce the effect of another is called ANTAGONISM, that is, in this case, one drug prevents the action of another.

Allocate physical, chemical and physiological antagonism.

This type of interaction is most often used in overdose or acute drug poisoning. An example of **PHYSICAL** antagonism can be indicated by the ability of adsorbing agents to impede the absorption of substances from the digestive tract (activated carbon, which adsorbs poison on its surface; cholestyramine).

An illustration of **CHEMICAL** interaction can be the formation of complexones (ions of some heavy metals - mercury, lead - binds penicylamine, EDTA), or so the hydrochloric acid of the stomach and sodium bicarbonate (alkali) interact.

PHYSIOLOGICAL antagonism is associated with the interaction of drugs at the receptor level, the nature of which has already been mentioned above.

By analogy with synergism, direct (when both drug compounds act on the same receptors) and **INDIRECT** (different localization of drug action) antagonism are distinguished. In turn, direct antagoism is **COMPETITIVE** and **NON-COMPETITIVE**.

In case of competitive antagonism, drugs enter into competitive relations with natural regulators (mediators) for binding sites in specific receptors. A receptor blockade caused by a competitive antagonist can be removed with large doses of an agonist substance or a natural mediator.

Noncompetitive antagonism is the situation when a drug cannot displace a natural mediator from the receptor, but forms covalent bonds with it (the mediator).

Drug interaction points. The bulk of receptors are located on the outer and inner side of the cell membrane and its organelles. The most frequent points of drug interaction include:

1) mediators and hormonal receptors;

2) ATP phase of Na/K pump, Ca, K and Na - intramembrane channels.

Types of drug action:

1) local action - the action of a substance that occurs at the site of its application. Example: the use of local anesthetics - the introduction of a solution of dikaina in the cavity of the conjunctiva. Using 1% novocaine solution for tooth extraction. This term is somewhat arbitrary, since a truly local effect is observed extremely rarely, due to the fact that since substances can be partially absorbed or have a reflex effect.

2) reflex action - this is when a drug acts on the paths of the reflex, that is, it affects the exteroter or interoreceptors and the effect is manifested by a change in the state of either the corresponding nerve centers or the executive organs. Thus, the use of mustard plasters in the pathology of the respiratory organs improves their trophism reflexively (essential mustard oil stimulates the skin's exteroreceptors). The drug cititon (respiratory analeptic) has a stimulating effect on the carotid glomerulus chemoreceptors and, reflexively stimulating the center of respiration, increases the volume and frequency of respiration. Another example is the use of ammonia when fainting (ammonia), reflexively improving cerebral circulation and tonic vital centers.

3) resorptive action - this is when the effect of a substance develops after its absorption (resorption - absorption; Latin - resorbeo - absorbs), entering the general circulation, then into the tissue. Resorptive action depends on the route of administration of the drug and its ability to penetrate biological barriers. If a substance interacts only with functionally monozyme receptors of a certain localization and does not affect other receptors, the action of such a substance is called ELECTORAL. So, some kurarepodobny substances (muscle relaxants) quite selectively block the cholinergic receptors of the end plates, causing relaxation of skeletal muscles. The action of prazosin is associated with a selective, blocking postsynaptic alpha-one adrenoreceptor effect, which ultimately leads to a decrease in blood pressure. The basis of the selectivity of drugs (selectivity) is the affinity (affinity) of the substance to the receptor, which is determined by the presence of certain functional groups in the molecule of these substances and the general

structural organization of the substance that is most adequate to interact with these receptors, that is, COMPLETENESS.

General characteristics of the effects of drugs on the body

Despite the abundance of drugs, all the changes they cause in the body have a certain commonality and uniformity. Based on the concept of reaction norm, there are 5 types of changes caused by pharmacological agents (N. V. Vershinin):

1) toning (increase function to the norm);

2) arousal (increased function in excess of the norm);

3) sedative effect (sedative), that is, lowering the elevated function to normal;

4) depression (decrease in function below normal);

5) paralysis (cessation of function). The sum of the tonic and aphrodisiac effects is called the rushing action.

The main effects of drugs

First of all, distinguish:

1) physiological effects when drugs cause such changes as an increase or decrease in blood pressure, heart rate, etc .;

2) biochemical (increased levels of enzymes in the blood, glucose, etc.).

In addition, distinguish the main (or main) and

Unsubstantial (minor) effects of drugs. The MAIN EFFECT is the one on which the doctor builds his calculations when treating this (!) Patient (analgesics - for the analgesic effect, hypotensive - for reducing blood pressure, etc.).

NEOBAL, or non-major effects, additional otherwise, those that are inherent in this tool, but the development of which in this patient is not necessary (non-narcotic analgesics - in addition to the analgesic effect, cause a heat-lowering effect, etc.). Among the minor effects may be DESIRABLE and UNDESIRABLE (or ADVERSE) effects.

Example. Atropine - relaxes the smooth muscles of the internal organs. However, at the same time, it simultaneously improves the conductivity in the AV node of the heart (during heart block), increases the diameter of the pupil, etc. All these effects should be considered individually in each particular case.

Factors affecting the magnitude of the effect of drugs

1) Pharmacokinetic factors associated with each drug. This has already been mentioned above, I will only remind you that we are talking about our speed of absorption or absorption, biotransformation, excretion.

2) The second group of factors - physiological.

a) Age. With age, the patient's sensitivity to drugs changes. Stand out in connection with this:

- perinatal pharmacology;

- pediatric pharmacology;

- Geriatric Pharmacology;

- Reproductive pharmacology;

b) Mass of the patient. The greater the mass, the higher the dose. Therefore, the drug is dosed in (mg / kg).

c) Paul. Different sensitivities in men and women to certain substances, for example, to nicotine, alcohol, etc., are revealed, which is explained by the difference in metabolism, the difference in / in the fat layer, and so on.

c) The state of the body. The effect of drugs on the body after a significant physical load will be different than without it.

e) Biological rhythms (daily, monthly, seasonal, annual, and now even population) have the most serious influence on the effect of drugs in the body.

3) Pathological factors. Thus, in case of a goitre's disease, toxic doses of morphine are more easily tolerated, but myocardial sensitivity to adrenaline increases. The effect of cardiac glycosides appears only on the background of cardiac lack of precision. The effect of drugs significantly changes with hypo-and hyperthermia, with infectious diseases, with a change in the functional state of the central nervous system, etc.

4) Genetic factors. It is known that the absence of the enzyme glucose-6-phosphate dehydrogenase (G-6-FDG) during thalassenia makes it impossible to prescribe antimalarial drugs such as primaquine. The lack of the enzyme butyrhyl cholinesterase in the blood, which is found in one of 2500 people, is the reason for the prolonged muscle relaxation to the administration of ditilin. Acyt-transferase deficiency. It was found that the tolerability of tubazid patients is not the same, some patients have severe side effects: headache, vomiting, chest pain, polyneuritis. This phenomenon occurs when a defect in the enzyme, which inactivates isoniazid - acetyltransferase, which must be considered when treating tuberculosis. The enzyme acetylite also sulfonamides, procainamide.

Glucuronyltransferase deficiency. Hereditary non-hemolytic jaundice is based on the deficiency of glucuronyl transferase, an enzyme that ensures the formation of bilirubin glucuronides and many drugs. Some drugs (streptomycin, chloramphenicol, progesterone) inhibit the already sharply reduced enzyme activity, and therefore their use is contraindicated in such patients. The biotransformation of some drugs (cortisone, chlormycetin) is broken: they do not turn into glucuronides and accumulate in the body. Doses of such drugs in this pathology should be significantly reduced.

5) Patients 'comfortiness or placebo effect. In this regard, the antianginal effect of placebo drugs, for example, reaches 40% and up to 81% of the placebo effect arises from the injection route of administration of drugs. This is probably why the use of vitamin preparations, tonics, tranquilizers is largely due to this effect.

6) Dose of medication. The effect of drugs to a large extent determined by their dose. Dose is the amount of drug substance that is intended for a single dose (usually referred to as a single dose). Not only the effectiveness of the treatment, but also the safety of the patient depends on the dose of the drug.

Indicate the dose in grams or in fractions of a gram. For a more accurate dosage of drugs, calculate their amount per 1 kg of body weight (or per 1 sq. M of body area), for example, 1 mg /

kg; 1 mcg / kg, etc. Dose, calculated on a single dose (pro dosi), daily dose (pro die).

The minimum doses in which drugs cause an initial biological (therapeutic) effect are called threshold, or minimally effective (therapeutic) doses.

In practical medicine, average therapeutic doses are most often used, in which drugs have the necessary optimal pharmacotherapeutic effect. If, when they are prescribed to the patient, the effect is not sufficiently pronounced, the dose is increased to the highest therapeutic dose.

Higher therapeutic doses can be single or daily. The highest single dose is the maximum amount of the drug that can be administered once without harm to the patient. These doses are rarely used, in extreme cases (in urgent situations, emergency situations). The average therapeutic dose is usually 1/3-1/2 of the highest single dose. Higher therapeutic doses of poisonous and potent substances are given in the State Pharmacopoeia of the USSR.

In some cases, for example, when using chemotherapeutic agents, the dose of the drug for the course of treatment is indicated (course dose).

If it becomes necessary to quickly create a high concentration of drugs in the body (sepsis, cardiovascular insufficiency), then use the first dose, the so-called strike dose, which exceeds all subsequent ones.

There are also toxic (having dangerous effects) and lethal doses.

The selectivity of the action of drugs

Usually, a drug is intended to treat one or a very limited number of diseases or symptoms. However, it should be remembered that there are practically no drugs that have a completely selective effect on a particular receptor, organ or pathological process. Each drug has a more or less broad spectrum of action and can cause a number of desirable or undesirable reactions. For example, morphine has pronounced analgesic activity and belongs to the group of narcotic analgesics. However, it depresses respiration, suppresses the cough reflex, has a sedative effect, causes constipation, bronchospasm, the release of histamine, has an antidiuretic effect, etc. Obviously, the higher the selectivity of the drug, the better it is.

Substances with low selectivity of action affect many tissues, organs and systems, causing a large number of adverse reactions. Thus, anti-puff agents, acting on rapidly dividing cells, damage not only the tumor tissue, but also the bone marrow, intestinal epithelium.

The selectivity of the drug depends on its dose. The higher the dose of the drug, the less selective it becomes. This applies to synthetic substances, as well as to products of animal and vegetable origin. For example, the antidiuretic hormone of the pituitary gland regulates the fluid content in the body, affecting the reabsorption of water in the kidneys. However, in large doses, vasopressin can cause a spasm of blood vessels, including coronary, and even the death of the patient.

The danger of overdose depends on the therapeutic index or the range of the therapeutic effect, which is determined in experiments on animals.

The increase in the effect of the drug is usually associated with the cumulation of the drug substance, i.e. its accumulation in the body. Cumulation is characteristic of long-acting drugs that are slowly eliminated from the body. These include, for example, cardiac glycosides from the group of digitalis. The accumulation of a medicinal substance with its long-term use can lead to toxic effects. To prevent them, you must gradually reduce the dose, increase the intervals between doses or take breaks in treatment.

Strengthening the action of substances (especially protein nature) with repeated use may be the result of increased sensitivity to them of the body - sensitization.

When using certain drugs (antihypertensives, analgesic, laxatives, etc.), their effectiveness may decrease. An addiction to the action of a medicinal substance may be associated with a decrease in its absorption, an increase in the rate of biotransformation and excretion, as well as a decrease in receptor sensitivity. In the case of the use of antimicrobial agents, addiction develops as a result of the development of microbial resistance. When addictive, the dose of the drug must be increased or one substance replaced by another.

BASES OF BIOPHARMACY

Biopharmacy is a science that studies the dependence of the therapeutic effect of drugs on the body on various factors (pharmaceutical, biological, etc.).

Biopharmacy is a scientific discipline of pharmacy that studies the influence of the physical and physicochemical properties of active and auxiliary substances in medicinal preparations produced in various medicinal forms, but in equal doses on their therapeutic effect.

The emergence of biopharmacy was prepared by the whole course of the progressive development of pharmacy, medicine, chemistry and other sciences. It is at the junction of several branches of knowledge that biopharmacy originates.

It appeared after the establishment of facts of therapeutic nonequivalence of drugs, that is, drugs of the same composition, but prepared by different pharmaceutical companies, differed therapeutic efficacy. This was due to a number of reasons: the degree of fragmentation of medicinal substances, the selection of auxiliary substances and the difference in technological processes, the so-called pharmaceutical factors. The term “pharmaceutical factors” has been widely used in the literature, primarily due to the clinical confirmation of experimental data on the existence of a relationship between drug efficacy and methods for their preparation.

The founders of biopharmacy are American scientists Levi and Wagner, thanks to whose work the term “biopharmacy” was adopted, used in most European countries as the equivalent of the English term “biofarmaceutics”.

The term “biopharmacy” itself appeared for the first time in the US scientific pharmacy in the 60s of the 20th century and soon gained universal international recognition.

The word "pharmaceutics", used in English literature, is not synonymous with "pharmacy", its designation is galenical pharmacy. The literal translation of "biofarmaceutics" and the adjective "biopharmaceutical" formed from it are the terms "biogalenika" and "biogalenic".

The addition of the prefix "bio" to the term "pharmaceutics" does not mean that it is a question of the biological evaluation of galenic pharmacy products, or of biological pharmacy in general.

With this short word, biopharmacy has successfully and sufficiently fully defined the complex of dependencies that bind together the drug substance and the therapeutic effect of the prepared drug.

All pharmaceutical factors that influence the biological effect of drugs can be divided into 5 groups:

- the physical state of the drug substance;

- simple chemical modification of the drug substance;

- excipients (their nature, physical condition and quantity);

- dosage form and the route of its introduction into the body;

- technological process.

A thorough study of the known cases of therapeutic nonequivalence of drugs has shown that the activity of the active substance (drug), its release from the dosage form and absorption are closely dependent on pharmaceutical factors.

Therefore, the study of the latter is mandatory from the point of view of biopharmacy due to their significant effect on the bioavailability of medicinal substances, the stability of drugs during storage and many other indicators.

From the point of view of biopharmacy and pharmacokinetics, the drug will have the necessary bioavailability only if the drug substance is presented in the most favorable state for the resorptive process (ion-molecular or dispersed form).

The physical condition of the drug

The physical state of medicinal substances is understood as:

1. The degree of grinding or dispersion (particle size) of medicinal substances;

2. Polymorphism of medicinal substances;

3. Aggregate state (amorphous, crystallinity, form and nature of crystals), pH, solubility, optical activity, electrical conductivity, melting point.

4. Surface properties of the medicinal substance (surface tension, filicity, etc.).

5. The degree of purity (type and amount of pollution, including the presence of microorganisms, allergens, binders, etc.).

The physical state of medicinal substances affects the stability of the drug during storage, therapeutic efficacy, speed of absorption, distribution and removal from the body.

The degree of grinding and polymorphism of medicinal substances most significantly affect pharmacotherapy.

Grinding of medicinal substances is the most simple, but at the same time one of the most important technological operations performed by a pharmacist in the preparation of various dosage forms. The dispersion of the drug substance affects not only the flowability of powdered materials, bulk mass, mixing homogeneity, dosing accuracy. Especially important is the fact that the speed and completeness of absorption of the medicinal substance, as well as its concentration in biological fluids, mainly in the blood, depends on the particle size, in any of its methods in the form of various dosage forms.

The effect of particle size on therapeutic activity was first proved for sulfanilamide and then steroid preparations, as well as derivatives of furan, salicylic acid, a / b, and now for anticonvulsants, anesthetics, diuretics, anti-tuberculosis, antidiabetic and cardiotonic agents . For example, it was found that when using micronized sulfadiazine, its maximum concentration in the blood of people is reached two hours earlier than when it is prescribed in the form of a powder of the usual degree of grinding. The maximum concentration of sulfadiazine in the blood are 40% higher, and the total amount of the absorbed substance is 20% more. The drug calciferol can be absorbed and have a therapeutic effect only when the particle size is less than 10 microns.

With the reduction of particles of griseofulvin from 10 to 2, 6 microns, its absorption in the gastrointestinal tract increases sharply, which makes it possible to reduce its therapeutic dose by half. By obtaining the molecular degree of dispersion of griseofulvin in polyvinylpyrrolidone, it was possible to increase the bioavailability of this antibiotic in 7–11 times even in comparison with the micronized form of the drug substance. Therefore, the industry produces tablets of micronized griseofulvin, digoxin, acetylsalicylic acid.

The effect of grinding on the process of absorption is particularly pronounced in ointments and suppositories, prepared on the same basis, but using drug fractions, the particle size of which is markedly different.

However, the choice of the degree of grinding of the medicinal substance must be scientifically grounded. It is impossible to consider as correct the desire to obtain in each case micronized powder. Because in some cases, a sharp decrease in the size of the particles of a medicinal substance may cause inactivation of the substance, its rapid elimination from the body, or an undesirable (toxic) effect on the body, and a decrease in the stability of the drug. In particular, with a sharp increase in the degree of dispersion of penicillin and erythromycin, their antimicrobial activity is reduced when taken orally. This is due to the intensification of the processes of their hydrolytic destruction or a decrease in their stability in the presence of digestive juices, as well as an increase in the surface of drug contact with biological fluids.

This led to strict regulation of the particle size of the substance when developing analytical regulatory documentation (AND) for medicinal preparations.

Thus, the medicinal substance in the medicinal product must have an optimal degree of grinding, on which its bioavailability depends.

Polymorphic modifications also have a great influence on the therapeutic activity of drugs.

Polymorphism (from a group of words “poli” - a lot, “morphe” - a form) is a property of a chemical substance to form crystals under different crystallization conditions, differing from each other by the symmetry class or form, physical, and sometimes chemical properties.

As is known, polymorphic modifications form many chemical and, including, medicinal substances. Since the discovery of the Davy (1809) carbon polymorphism (graphite, coal, and diamond), the transitions of some polymorphic modifications to others have been studied in detail. It is emphasized that the chemical composition remains unchanged, which is mainly accepted as an assessment of quality. An overview of the work on the study of polymorphism in medicinal substances is given in the works of A. I. Tentsova, Khaleblein, Bush, Halabala.

Particles of medicinal substances in a powdery solid state have a different structure (crystalline or amorphous), which depends on the particular molecular structure of a particular substance. Electron microscopic studies have shown that medicinal substances in most cases have a crystalline structure, due to the fixed location of atoms in the molecule and the directional growth of crystals under certain conditions during the crystallization process. The amorphous state is less common. Any drug substance in certain conditions (solvent, temperature, pressure, etc.) crystallizes in a certain system and has certain physico-chemical characteristics (solubility, melting point, specific surface, strength, shape and size of particles, etc.) . When conditions change, the substance crystallizes in another system and has other physicochemical characteristics, and, consequently, other indicators of biological availability. Such physical characteristics of powders in the existing AED as “crystalline”, “fine-crystalline”, “amorphous”, “light powder” are sufficient for the technological process, but more precise definitions that crystal chemistry gives to identify their effect on therapeutic activity.

There are seven crystallographic systems (syngonies): monoclinic, diklinnaya, trigonal, tetragonal, hexagonal, rhombic, cubic, they serve to identify medicinal substances. Andronik I. Ya. And Babilev F.V. published an atlas of diffraction patterns of crystalline medicinal substances and developed an information retrieval system for identifying crystalline medicinal substances by their diffraction spectra. The use of atlas and an automated system allows you to speed up the identification of drugs.

The formation of various polymorphic modifications can occur in both liquid and soft dosage forms. This is observed: when replacing solvents; when administered to liquid or soft dosage forms of various excipients; during the drying, cleaning, preparation of medicines and in the course of their storage.

The phenomenon of polymorphism among medicinal substances is especially prevalent among salicylates, barbiturates, sulfonamides, hormonal drugs. For most modifications, there are no special names and they are labeled a, b, etc. or numbers I, II, III, etc.

Accounting and rational use of the phenomena of polymorphism of medicinal substances are of exceptional importance for pharmaceutical and medical practice. Polymorphic modifications of the same substance are characterized by different stability constants, phase transition temperature, solubility, which ultimately determines both the stability of the substance and its pharmacological activity.

In this case, the solubility of various polymorphic modifications is of particular importance, since the absorption (absorption) of medicinal substances depends on it.

The dissolution process also affects the efficacy of drugs.

The solubility of substances depends to a large extent on their surface properties, including the degree of their grinding. Significant differences in the size of the particles of a medicinal substance can lead to unequal absorption rate and content in biological fluids of the same drug, and, consequently, to its possible clinical nonequivalence.

Usually, more soluble substances are released faster from the medicinal form, faster absorbed, more quickly exhibit a therapeutic effect. At the same time, hardly soluble medicinal substances are more suitable for prolonging the action, in order to create such medicinal substances, sometimes they create an environment in which the drug does not dissolve. For example, when prescribing a solution of es-traditionol benzoate in oil, the drug has a therapeutic effect for 3 days, and when administered as an aqueous suspension, it takes about 3 weeks.

The solubility of drugs may vary depending on the methods of their recrystallization, and in the finished drugs - from the presence of the used excipients and technology of dosage forms. The choice of the dosage form also influences the solubility of medicinal substances in dosage forms. So, when using very difficult drug substances in the case of oral administration, the rational drug form is a thin suspension, such drugs are best prescribed in the form of elastic capsules filled with suspension.

Particularly significant impact on the solubility of medicinal substances has a choice of excipients - solubilizers, co-solvents, surfactants, which in turn can increase the effectiveness of the drug. This confirms the need for directional use of both auxiliary substances and the choice of the technological method of obtaining dosage forms.

There are several ways to increase the solubility of sparingly soluble substances and thus bioavailability.

1. Using solubilization. Solubilization is defined as the process of spontaneous transition into a

stable solution with the help of surfactant compounds insoluble or poorly soluble in a given solvent. In the domestic literature, this process is also called colloidal or conjugate solubility.

2. Using individual or mixed solvents (benzyl benzoate, benzyl alcohol, propylene glycol, polyethylene glycol, ethyl cellulose, dimexide, glycerin, etc.).

3. Using hydrotropy, which provides for the production of hydrophilic complexes with organic substances that contain elecro-donor substituents - polar radicals. Examples of hydrotropic substances include sodium salicylate, sodium benzoate, hexamethylenetetramine, novocaine, anti-pyrin, urea, glycerin, amino acids, hydroxy acids, proteins, etc.

4. By the formation of salts and complexes:

a) poorly soluble substances: bases, the acidic form of the compounds in alkali or sodium bicarbonate goes into soluble salt. In this way, phenobarbital, nor-sulphazole, streptocid, osarsol and other substances can be converted into soluble compounds;

b) obtaining aqueous solutions of iodine using easily soluble iodine complexes with alkali metal iodides;

c) to obtain aqueous solutions of polyene antibiotics (nystatin, levorin, etc.) use polyvinylpyrrolidone, with which they form complex compounds, where the water-insoluble substance and the solubilizer are linked by a coordination bond. These complexes are well soluble in water. The scientific research started in this direction allows us to reveal new patterns in relation to the “drug-auxiliary substance” in complex physicochemical systems, such as drugs.

5. The synthetic pathway is the introduction of hydrophilic groups into the structure of the molecule: OH, -COOH, CH2-COOH, -O3H, -CH2O3H. Example: unithiol.

The therapeutic activity of medicinal substances is also significantly affected by their optical properties. Among the optical isomers there is no chemical difference, but each of them rotates the plane of the polarization beam in a certain direction. Despite the fact that chemical analysis fully confirms the presence of the same substance in medicinal preparations with different isomers, they will not be therapeutically equivalent.

When the drug is absorbed in the gastrointestinal tract, a large role is played by the degree of ionization of the substance. Depending on the concentration of hydrogen ions, the substances can be in ionized or non-ionized form. pH also affects solubility, drug distribution coefficient, membrane potential and surface activity.

Anhydrous medicinal substances or crystalline hydrates have different solubilities, which leads to a change in their pharmacological action. For example, anhydrous forms of caffeine, ampicillin, theophylline dissolve faster than their crystalline hydrates, and therefore are absorbed faster.

Simple chemical modification

The term simple chemical modification of drugs means when the same substance can be used as a drug in different chemical compounds (salt, base, acid, ether, complex compound, etc.), in which the pharmacological effect part is completely retained. substance molecules.

For example: Novocain - the base and salt of Novocain hydrochloride; codeine - base and codeine phosphate - salt; caffeine - base and caffeine-sodium benzoate - salt; alginic acid; and sodium and calcium salts of alginic acid.

From the point of view of official standards, the replacement of one substance by another is legal

and should not cause objections and influence therapeutic efficacy, since the substances have a similar pharmacological effect. However, the clinical use of simple modifications of the drug shows different results due to their pharmacokinetics. Thus, the alkaloid quinine - the base can be used in medical practice in the form of various salts: quinine sulfate (solubility 1: 800), quinine chloride (solubility 1:34), quinine bromide (solubility 1:16). These substances have different pharmacokinetics, preserving the main action. When replacing a hydrogen ion in acid Ascorbic to sodium ion, the drug acquires the ability to change the electrolyte balance of the body to a greater degree and to show the characteristics of ascorbic acid that are not characteristic of the acid - to inhibit the function of the insular apparatus in patients with diabetes. Solutions of ethmosine, amphotericin B and partusisten cannot be prepared on an isotonic solution, as the salting out phenomenon occurs. It is not recommended to use glucose solution as a solvent when preparing solutions of alkaline substances. It reduces the activity of aminophylline, hexamitylenetetramine, caffeine sodium benzoate, and other drugs due to changes in the pH of the medium. Cardiac glycosides should also not be diluted with glucose solution, since they are easily hydrolyzed. Essentiale for injection (opalescence) cannot be combined with glucose and sodium chloride solution.

A simple chemical modification (replacement of a drug in the form of a salt with one cation, a chemically similar drug in the form of a salt with another cation, or a preparation in the form of an acid, ether, etc.) often takes place in the initial production.

Based on biopharmaceutical research, it has been proven that the arbitrary replacement of any ion in the molecule of a medicinal substance, based on purely technological or economic considerations, is unacceptable.

Excipients

Auxiliary substances are of natural, synthetic and semi-synthetic origin. When preparing dosage forms, they can perform various functions: solvents, solubilizers, stabilizers, bases, surfactants, thickeners, emulsifiers, preservatives, flavoring agents, dyes, etc.

Such substances include: starch, glucose, purified water, ethanol, petroleum jelly, cocoa butter, talc, bentonites, aerosil, paraffin, wheat flour, polyethylene oxides, various cellulose derivatives, etc.

Throughout the long history of pharmacy, excipients have been considered as indifferent substances in the pharmacological and chemical relations that act as formers. They were added to medicinal substances in order to give them the appropriate form, convenient for use, transportation and storage. In the production of drugs used the most affordable and cheap substances. It did not take into account the influence of the nature and amount of auxiliary substances on the biological activity of medicinal substances.

At the same time, not a single pharmaceutical factor has such a significant and complex influence on the effect of a medicinal product as ancillary substances. Biopharmacy for the first time gave a scientific justification for the use of excipients and showed the utter inconsistency of the empirical attitude towards them, inherited by pharmacy from the distant past. Research in the field of excipients were so significant and revolutionary that it gave grounds for some scientists to define biopharmacy as a science that studies the effect of excipients on the therapeutic efficacy of drugs.

On the basis of biopharmaceutical works, it was found that auxiliary substances are not an indifferent mass used in a purely technological aspect. They have certain physicochemical properties and, depending on the nature of the substance, can enhance, reduce, change the nature of the action of drugs under the influence of various causes and combinations (complexation and

adsorption, molecular reactions, etc.), with the result that change the speed and completeness of absorption of the drug. The interaction between medicinal and auxiliary substances can occur as in the process of preparing medicinalpreparations, and in the course of their storage.

As is known, the degree of interaction is determined by the energy of a physicochemical or chemical bond. If the bond is fragile (van der Waals forces are 1 kcal / mol (4 × 103 J) or hydrogen bond is 7-10 kcal / mol), then the process can be reversible, since the body can cope with this bond, it can break down, modify and will be disposed of.

But if a strong bond is formed, covalent with an energy of 100–140 kcal / mol, the process can become irreversible, since there are no conditions in the body for breaking this bond. Therefore, excipients can reduce to a minima the therapeutic effect of the medicinal substance, enhance it up to the toxic manifestation, or even alter it altogether.

For example, the complex of amphetamine with carboxymethylcellulose is practically not absorbed and, accordingly, does not provide a pharmacological effect.

Phenobarbital is poorly soluble in polyethylene glycol and, as a result, is not absorbed. Theophylline-phenobarbital and tetracycline calcium complexes are poorly soluble compounds and are practically not absorbed.

Excipients can not only reduce the pharmacological effect of drugs, but also form compounds that, conversely, are characterized by a high degree of dissolution and bioavailability (for example, polyvinylpyrrolidone-prednisolone; polyvinylpyrrolidone-griseofulvin; polyvinylpyrrolidone-calcicylamide; acid; norsulfazole-urea). Saponins enhance glucose absorption in the gastrointestinal tract. Sodium lauryl sulfate accelerates the absorption of penicillin, grise-ofulvina, etc.

Selective resorption is also a cause of changes in the biological activity of drugs.

Biological membranes, through which the process of absorption of medicinal substances is carried out, must be considered as a complex receptor mechanism, through which resorption is carried out in accordance with Fick's law on the basis of the diffusion law, but in strict order and with different speed.

The order and speed of resorption is determined by various factors: the time of taking the drug before meals or after meals, the type of food, the amount and nature of the liquid to be washed, the time of day, the physiological condition of the mucous membranes, the chemical and physico-chemical characteristics of the drugs. and etc.

Among these factors, it is necessary to consider the latter under all equal conditions. From the literature it is known that dissociating low-molecular compounds, substances that have a diphilic structure with methyl, ethyl, phenyl and other radicals, substances with high affinity to the biological media of the body have the best resorptive capacity.

Sometimes, with a certain composition, auxiliary substances become active substances, and the active ingredients become auxiliary substances.

It is impossible to put a clear boundary between the active substance and the adjuvant in the dosage form, and therefore modern pharmaceutical science puts a requirement in the development of new drugs: to establish the degree of influence of auxiliary substances on the therapeutic efficacy of drugs. In other words, the auxiliary substance should not be used at all, but specifically with an individual substance. Unreasonable use of an excipient may result in a decrease, an increase, a change in the therapeutic effect, or a complete loss therapeutic action of the drug.

In the literature there are examples of the effect of auxiliary substances on therapeutic efficacy. For example, lactose minimizes the effect of isoniazid, but enhances the effect of testosterone, slows down the effect of barbital. Tween-80 enhances the adsorption of vitamins A, D, E.

Auxiliary substances can not only strengthen but also reduce the therapeutic effect, mechanically blocking the path to the resorption of medicinal substances.

Among the works devoted to the study of the influence of excipients, especially a lot of attention is paid to the ointment and suppository bases. Thus, Professor I.S. Azhgikhin studied the effect of the type of bases on the pharmacokinetics of medicinal substances in suppositories with sodium salicylate, acetylsalicylic acid, norsulfazole, ephedrine hydrochloride, teturam, isoniazid, PAS, fuvazide, furazolidone, butadion, etc. The introduction of even a small amount of dimethyl sulfoxide led to a sharp increase in the rate of adsorption of the active substances.

Ointments prepared on petrolatum have a superficial effect, since petrolatum does not penetrate the skin very well and blocks the access of the medicinal substance to the tissues (ointment of sulfonamides, phenols, antibiotics, etc.).

Replacing the petrolatum-lanolin base with polyethylene glycol in the combined ointment "Levocin" allowed increasing its antimicrobial effect by 20-80 times. In this ointment, the potentiating effect of PEG-400 on levomycetin, discovered by P.S. Bashura and V.I. Bogdanova, was used. It turned out that the dissolution of chloramphenicol in PEO-400 increases the sensitivity of various microorganisms to it (Wood's staphylococcus and hay bacillus 62 times; typhoid, pathogenic E. coli and dysenteric bacteria Grigoriev-Shiga - 8 times).

The antimicrobial spectrum of other antibiotics also increases with the use of such bases, with the exception of penicillin.

The choice of excipients is carried out on a scientific and rational basis (economic, aesthetic, etc.), where their functional purpose, bioavailability, technological characteristics, technological properties, cost-effectiveness and accessibility are provided. Thus, the diversity of properties of medicinal and auxiliary substances and the rapid growth of their range obliges a specialist to abandon attempts to transform any auxiliary material into a universal one, used with any medicinal substance.

Type of dosage form and its route of administration

Numerous studies on the effect of the dosage form on the therapeutic efficacy of drugs have established that the optimal activity of a drug is achieved only when it is prescribed in a rational dosage form. In addition, in this case, you can avoid many of the side effects of drugs on the body.

The dosage form is a rational from a pharmacological point of view, a form of medicinal substance convenient for receiving and storing, providing its optimal therapeutic effect with a minimum of side effects.

According to modern concepts, the dosage form is the material norm for the manifestation of the dialectic unity of the active and auxiliary substances, as well as technological operations that ensure the optimal therapeutic effect of the drug.

Dosage form is a structural unit of both pharmacotherapy and industrial production.

The most important task in the development and is to provide optimal conditions for the release and subsequent absorption of the substance. All other requirements are subject to these conditions, which must meet the dosage form.

Pharmacy considered the dosage form as a means of transporting the drug into the body. In this regard, the convenience of administering medicinal substances through natural routes was mainly taken into account, and therefore it turned out that the oral route of administration constitutes 70-80% of all medicines. Comparative studies of one or another dosage form were not conducted; therefore, from the established practice, it turned out that of all the dosage forms, tablets are the most popular (50% of all GLS). In pediatric practice, up to 70% are liquid medicines. This can be explained by the fact that the oral route is the most convenient, although not always effective. With the introduction of "per os", many medicinal substances undergo enzymatic cleavage, lose their activity, irritate the mucous membrane of the gastrointestinal tract, enter into chemical interaction with different pH from 2 to 8. At the same time, the products

The degree of influence of the dosage form on the processes of absorption is determined by the ability of the active substance to be released from the oral dosage form and the possibility of contact with the mucous membranes of the stomach, intestines and interaction with their secrets. Hence, according to the degree of release and, consequently, the best bioavailability, all oral medicines can be arranged in the following range: –solutions – emulsions – suspensions – powders – granules – tablets.

On the basis of numerous biopharmaceutical studies and the scientific substantiation of the influence of this factor, it is possible to create drugs with specified pharmacokinetic properties that have a certain pharmacological effect: synergism, potentiation, antagonism, prolongation, differentiated or directed action, expansion of the antibacterial spectrum, etc. At the same time, the given therapeutic the effect is provided not so much by the structure of the dosage form, but also by the ability to use physio logical features of the body. Therefore, among modern dosage forms, tablets are widely used: retard, durula, sandwiches, duplex, enteric, perlingual, sublingual, buccal, implant, etc. Or, for example, various rectal forms can be used depending on the situation: rectiols, syringes, tampons, enemas, etc.

New medical forms based on micro- and monocapsulation, spansules, depot preparations, pseudo-powders and pseudosuspensions, as well as liposomes, ionixenes, collagens, etc., which are successfully used in pharmacotherapy, appeared in medical practice.

The choice of a rational dosage form has a positive effect on the therapeutic effect of drugs. Thus, the replacement of tablet forms of theophylline, aminophylline, diprofillin, digoxin, and rectal suppositories significantly increases their biological availability. The use of rectal forms of these drugs can reduce their dose. According to Nagorny V.V., Golovkina V.O., Kechin I.L., suppositories can be replaced with the introduction of these drugs in the form of injections, since the rectal route of administration by bioavailability is equal to the injection route, which allows not to injure the patient. In addition, with the intravenous route of administration, drugs are rapidly excreted from the body, and after rectal administration of certain drugs in the form of a suppository and microclysterism (for example, xantiverin), prolonged action is observed. To achieve the prolonged action of nitroglycerin preparation of dosage formsit is recommended to use the Nitroderm plaster instead of tablets. The well-known anti-ischemic drug "Trinitrolong" is better to enter in the form of plates. This dosage form allows you to individually dose the drugs, providing uninterrupted and maximum therapeutic effect. According to statistics, about 30% of patients experience difficulties in taking tablets and capsules, therefore, crushed tablets and opened the capsules. 23% of patients prefer soluble dosage forms. With this in mind, the industry is setting up the production of soluble forms. So, instead of the usual capsules of Amocillin (bioavailability of 75%), the drug Flekmoksina Solutab (bioavailability of 95%) is produced.

The choice of dosage form at the same time determines the method (way) of introducing the drug into the body.

Each route of administration has its advantages, but not every one of them is effective. For

various reasons, sometimes even intravenous administration of the drug does not provide bioavailability. For example, during therapy with choriogonin in the form of injections, changes in the emotional state of the patient, allergic reactions were observed, and administration of the drug in the form of suppositories had no side effects. In cases of cardiac decompensation, rational medicinal forms of cardiac glycosides should be considered injections and rectal forms, since oral administration causes irritation of the intestines (ulceration, bleeding, pain), which is associated with impaired absorption of the mucous membranes in such patients. Long-term therapy with metindol in suppositories proceeds without complications, with a good therapeutic effect, while the use of the drug in tablets is accompanied by dyspeptic phenomena, disorders of the central nervous system, and other complications.

Thus, the dosage form should be beneficial and rational not only from the economic, aesthetic, convenient for the use of the parties, but above all from the point of view of the pharmacodynamics of the drug and ensure the modern requirements of pharmacotherapy.

Technological process

Technological (production) processes are methods that consist of certain technological methods and operations.

Until the 60s of our century, the method of preparation of medicinal preparations as a factor that influences the effectiveness of the drug, did not attach much importance. This greatly contributed to the alienation of the science of the methods of preparing medicines from clinical disciplines, transforming it into one of the branches of general technology, general commodity research.

With this approach to drugs, it was not taken into account that their behavior in the body may depend on pharmaceutical technology. In pharmacies and factories, medicines were prepared in strict accordance with the provisions of the general technology and evaluated on the basis of merchandising principles on mass, consistency, geometric shape, content of active substances, etc.

At present, it has been proven that the method of obtaining a medicinal preparation largely determines the stability of the medicinal substance, the rate of its release from the dosage form, the intensity of absorption and, ultimately, its therapeutic efficacy.

Depending on the physicochemical, physicomechanical and other characteristics of the dosage forms, specific methods of their preparation and apparatus are used. For example, in the preparation of suppositories, grinding, sieving of medicinal substances, melting of the base, mixing, pouring the suppository mass into molds, cooling, etc .; upon receipt of tablets - grinding, drying, sieving, mixing, granulation, dusting granules, pressing, coating tablets with shells. Among the variety of technological operations of the production process of preparing dosage forms, not all operations are equivalent both in terms of the physicomechanical properties of the dosage forms and in terms of their effect on the pharmacokinetics of the preparations. The significance of medicinal forms in pharmacotherapy, their prevalence, and the degree of knowledge of their production processes are not equal either. Due to the popularity of tablets, their advantage over other dosage forms, tablets became one of the main dosage forms in the middle of the twentieth century, and turned out to be the most studied in the pharmaceutical and biopharmaceutical relation. Moreover, all stages of the preparation of tablets are subjected to extensive research in order to ascertain their influence on the physicomechanical properties of tablets and their pharmacotherapeutic effectiveness. Operations such as granulation, pressing pressure, drying, etc. have been subjected to especially careful experimental study. Theoretically and experimentally, already in the 60s of our century, the necessity of a rational selective approach to the use of tabletting stages in the preparation of tablets was justified.

To a lesser extent, the effect of technological operations on the physico-mechanical and biopharmaceutical characteristics in the preparation of other dosage forms (suspensions, emulsions, liniments, aerosols, etc.) was studied.

In the technological process of preparation of dosage forms, there are also repetitive operations common to a number of stages in the production of drugs. In manufacturing processes for the preparation of medicines in pharmacies or factories, various technological methods are used: grinding, dissolving, drying, filtering, sterilizing, freezing, etc.

Technological stages have their own parameters and modes, which are specified in the process regulations. Non-observance of these parameters leads to a change in medicinal substances during the treatment period, since all types of mechanical, radiation, heat, sound, and other effects cause destruction (mechanocracking) of molecules. Known phenomena of cryolysis, pyrolysis, photolysis, radio-lysis, mechnolysis, causing mechanical transformations in the substance, which are responsible for the inactivation of the active substances or for the toxicity of the compounds obtained.

As a result of the mechanocracking of molecules, free radicals appear, which in a free radical reaction can enter into a chemical bond with oxygen, forming toxic peroxide compounds or between themselves inactive polymers.

Questions of mechanochemical transformations in a substance under various influences on it are dealt with by a new area of science - mechanochemistry.

The quality of the packaging and the shelf life of the drug, the presence of the shell also has a significant impact on the therapeutic activity.

An important role in the preparation of drugs and play subjective factors. This is especially true for small-scale production. For example, in a pharmacy, the choice of technological operations and methods depends on the qualifications and level of knowledge of a specialist, his production experience, analytical thinking, situations, etc., and all these factors can affect the quality of products. A pharmacist must have a high level of preparation in order to take into account various variable factors in the preparation of drugs. The study of biopharmaceuticals is mandatory for the preparation of a highly qualified specialist working in the field of biopharmacy The purpose of the lesson is to know:

A) Clinical aspects of pharmacokinetics.

1. General characteristics of the main kinetic processes in the biological system.

 Simulation of kinetic processes.

 Using chamber models to calculate pharmacokinetic parameters. Single-chamber (single-part), two-chamber (two-part) and their characteristics. Perfusion kinetic models, characteristics, features. The main pharmacokinetic parameters of one-part and two-part models.

2. Structure and types of biological membranes, their characteristics and localization:

 type I membranes (Davenson-Danielly);

 type II membranes, structural features;

 type III membranes, transport features;

 membrane type IV, the distinctive features of the structure, localization.

3. The physical basis of membrane permeability. Diffusion, characteristic, understanding of the resultant flow. Determination of the diffusion rate using the Fick equation. Osmosis. Jacob Vant-Hoff equation.

4. Effect of electric charge on the transmembrane ion flow.

5. Mechanisms of drug transport through membranes.

 Simple diffusion (along the concentration gradient) and its mechanisms. Diffu-zia in the aquatic environment. Lipid diffusion. Factors affecting the rate of diffusion of drugs. Ionization of weak acids and weak bases. The influence of pH and solubility of drugs on the degree of ionization.

 Light diffusion. Mechanisms, characteristic.

 Filtering. Characteristic.

 Mechanisms of active transport through membranes. Primary active transport. Secondary active transport. Simport (contransport). Anti-port (countertransport)

 Transport of drugs through endocytosis and exocytosis.

 Cellular contacts.

 Epithelial transport.

6. Ways of introducing drugs into the human body. Benefits and non-affluence of each.

 Without compromising the integrity of the skin: enteral (sublingual, buccal, duodenal, rectal, per os); parenteral (inhaler, intranasal, transdermal, etc.).

 With violation of the integrity of the skin: subcutaneous; intramuscular; intravascular (intravenous, intraarterial); in the cavity (pleura, peritoneum, joints, endocardial, endosternal); endolyumbalny, in the ventricles of the brain, subdural, etc.

7. Definition of “absorption (absorption)”.

 Factors determining the rate of suction. - The form of drugs. The degree of solubility in fats and water. Dose and concentration of the drug. The intensity of the blood supply to tissues and organs. Ways of introduction.

 Suction in the gastrointestinal tract. Elements of anatomy. Factors affecting the absorbability of drugs with enteral administration - pH in different parts of the gastrointestinal tract. Microbial dissemination of the digestive tract. Enzyme activity. Co-standing motility. The presence of diseases of the gastrointestinal tract and other organs. Intervals between meals and drugs. Features of carbohydrate absorption characteristics, factors affecting the rate of absorption. Absorption of lipids and fat-like substances, localization, characterization. Features of protein absorption. Absorption of fat and water-soluble vitamins. Features of absorption of water and electrolytes. The concept of malabsorption.

 Absorption in parenteral extravascular routes of administration. Features of drug absorption with intramuscular injection. Absorption through the skin. Especially suction in the lungs. Bladder suction. Features of absorption from the uterus. Absorption with other methods of administration.

 Pharmacokinetic parameters characterizing the processes of drug absorption. Absorption rate constant. The period of semi-absorption. The time to reach maximum concentration. The

maximum concentration of drug in the blood. Calculations of the absorption rate constant and the period of semi-absorption. Plotting.

8. Definition of the term “bioavailability”. Absolute and relative biological availability. Characteristic.

9. Effect of physicochemical properties, composition of excipients, dosage form on bioavailability.

10. Biotranspot, its characteristics and value in clinical practice. The main binding serum proteins. The effect of drug binding to blood proteins on their activity. Individual differences affecting the degree of binding to drugs. (The influence of age. The influence of other factors on the degree of binding of drugs). The effect of binding on the dynamics of the level of drugs in the serum. The effect of the connection of drugs with proteins on the penetration of drugs into the organs and tissues of the body.

11. Features of the distribution of related and free drugs in the human body.

12. Characteristics of the distribution of drugs in biological fluids, organs and tissues of the human body.

 Methods to study the distribution of drugs.

 Factors that influence distribution processes.

 Pharmacokinetic constants characterizing the distribution of drugs in biological fluids - Volume of distribution, characterization. The value in clinical practice to calculate the dose of drugs. The specific volume of distribution. The distribution coefficient of the substance. The apparent initial concentration. The area under the pharmacokinetic curve. Bioavailability. Bioequivalence.

 Penetration of drugs through the biological barriers of the body. - Patterns of drug penetration through the blood-brain barrier. Passage of drugs through the hematopoietic barrier, and factors influencing this process. (Physico-chemical properties of drugs - lipid solubility, solubility in water, chemical structure, etc. The condition of the patient's body). Features of drug penetration through the hemato-cerebral barrier. The main characteristics of the penetration of drugs through the hematophthalmic barrier. Barriers created by serous membranes. (Penetration through the pleura, through the pericardium, through the peritoneum). Features of drug penetration through synovial membranes. Factors affecting the penetration of drugs through the placental barrier. The distribution of drugs in the inflamed and tumor tissues. Problems of cellular permeability of drugs.

13. Metabolism of medicinal substances in the human body. Characteristic. The formation of therapeutically active, indifferent or toxic products.

 Types of biotransformation reactions of drugs - Non-synthetic (phase I reactions). Formation of functional groups with an active hydrogen atom - hydroxy groups, carboxy groups, etc. Reactions catalyzed by enzymes endoplasmic reticulum (microsomal). Reactions catalyzed by enzymes localized in other places (non-microsomal). Synthetic (I phase I reactions). Conjugation with highly polar acid residues (with residues of glucuronic, sulfuric, some amino acids, etc.).

 Coenzymes and their functions in the process of biotransformation of drugs: pyridoxal phosphate; thiamine pyrophosphate; coenzyme A (CoA); tetrahydrofolic acid; biotin; NAD +, NADP + FMP, FAD.

 Specific coenzymes catalyzing biological oxidation and their characteristics. Oxidoreductases - succinate dehydrogenase, alcohol dehydrogenase, aldehyde dehydrogenase, cytochrome oxidase, NADH or NADPH dehydrogenase. Hydrolases - peptidases, glycosidhydrolases, esterases, lipases, phosphodiesterase, phosphotases. LiAZ - decarboxylase, aldolase, dehydratase, deaminase, and others. Transferases - phosphotransferase, aminotransferase, acetyltransferase.

 Basic pathways of drug biotransformation. Phase I (oxidation, reduction, hydrolysis). Phase II (conjugation with sulfate, with glucuronic acid, with alpha-amino acid residues, methylation, acetylation).

 Clinically significant aspects of drug metabolism. The effect of the first pass (presystemic metabolism). Metabolic capacity. Medicinal substances with high and low hepatic clearance - definition. Formation of pharmacologically active or toxic metabolites. Induction and inhibition of metabolizing enzymes. Individual variability of metabolic kinetics.

 Factors affecting the metabolism of drugs. The effect of age. Features of bio-transformation in newborns, children and the elderly. Metabolism of drugs in pregnant women. The influence of the genetic factor. Peculiarities of drug metabolism in various diseases: (liver, gastrointestinal tract). The effect of nutritional biotransformation: (increased metabolism of some drugs in a diet with a predominance of proteins over carbohydrates; a decrease in the rate of metabolism in severe eating disorders). The influence of the external environment. The effect of alcohol on the processes of biotransformation: (with a single dose - inhibition of enzymes that metabolize drugs; with chronic consumption - inducing enzyme systems). Increased metabolism of certain drugs during smoking. Influence of the route of administration on the processes of biotransformation. Circadian changes in the metabolism of drugs (depending on the time of administration). Features of biotransformation in the interaction of drugs. Effect of sex and body weight on metabolic processes. Influence of the regime, physical activity and menstrual cycle on the biotransformation of drugs

14. Ways of elimination (excretion, elimination) of drugs from the human body.

 Renal path, characteristic. The main factors affecting renal excretion are: the degree of drug binding to plasma proteins; glomerular filtration rate; the degree of reverse diffusion of drug molecules from the filtrate (which depends on the urine pH); active renal tubular reabsorption and secretion; physico-chemical properties of drugs. Physiological processes that underlie renal excretion: club-barrel filtration, characteristic glomerular filtration rate (GFR) and plasma current through the kidneys (CCI); tubular secretion; tubular reabsorption, tubular fluid / plasma ratio (QOL / P).

 Drugs excreted in faeces: ingested and not absorbed in the intestine; excreted in bile; secreted with a secretpancreas; released from blood plasma into the intestine.

 Exhaled air exhaustion. Drugs secreted by the lungs. Factors determining elimination through the lungs. Physico-chemical properties of drugs. Pulmonary ventilation. Pulmonary blood flow. Solubility of drugs in the blood and in tissues.

 Other selection paths. Excretion with saliva. Selection later. Discharge through the skin. Isolation by lactating mammary glands. Discharge with tear fluid.

 Pharmacokinetic parameters characterizing the processes of excretion and elimination. Definition and calculations of the basic constants.

1. Constant rate of elimination (Kel or Kel, dimension - h-1, min-1).

2. The rate constant of excretion (Ke or Kex, dimension h-1, min-1).

3. The period of semi-elimination of the drug (t1 / 2, dimension - h, min).

4. Total clearance of the drug (Clt or Clт, dimension - ml / min, l / h).

5. Renal (renal) clearance of the drug (Clr, Clpoch or ClR, dimension - ml / min, l / h).

6. Extrarenal (extrarenal) clearance of the drug (Cler, Clv / Poch or ClNR, dimension - ml / min, l / h).

7. Creatinine clearance (Clк, dimension - ml / min, l / h).

B). Clinical aspects of pharmacodynamics.

1. Types of action - local and resorptive: direct and indirect (indirect) and, as a variant of the latter, reflex; specific and non-specific; reversible and irreversible; main and accompanying (side); desirable and undesirable (negative).

2. Types of mechanisms of action of drugs. Concept of medicinal receptors, agonists and antagonists. Metabolism as an object of influence of drugs. Pharmacological effects.

3. Properties of drugs, which determine their action (chemical structure, degree of dissociation, polarity, dose). Types of doses. The breadth of the therapeutic effect of drugs. The concept of biological standardization. The value of dependence “concentration (dose) - effect” in pharmacology.

4. The influence of the state of the body (age, gender, body weight, ethnic factor, the severity of the underlying and associated diseases, pregnancy, lac-tion) on the effect of drugs. The role of genetic factors in the development of the pharmacological effect. The concept of pharmacogenetics. Pharmacogenetic approaches to the prediction of therapeutic efficacy and toxicity of drugs.

5. Dependence of the pharmacological effect on environmental factors (climate, ecology, working conditions), daily and seasonal rhythms. The concept of chronopharmacology.

6. The effect of drugs upon their repeated administration is sensitization; tolerance (addiction), tachyphylaxis; cumulation and its types; dependence (addiction) and its phases (mental, physical). The concept of the Sindroma "cancellation" and "return". Medical and social aspects of the fight against drug addiction.

7. The combined effect of drugs - synergism, antagonism and their types. The concept of polypragmasy.

8. Incompatibility - pharmaceutical (physico-chemical), pharmacological (pharmacokinetic, pharmacodynamic), physiological. Use in medical practice.

C) Clinical aspects of pharmacotoxicodynamics.

1) The concept of safety, undesirable (side) action, reaction, phenomenon

2) The undesirable effect of medicinal substances - organotoxic, allergic reactions, idiosyncrasy, mutagenicity, teratogenicity, embryotoxicity, fetotoxicity, blastomogenicity (carcinogenicity). Examples Overdosing is absolute and relative (toxic effects).

D) Types of drug interaction. The concept of polypragmasy.

D) Basics of clinical biopharmacy. The main factors affecting the effectiveness of

List of practical work:

Homework.

1. To study the basic principles and provisions of clinical pharmacology.

2. Definition of the concept of pharacokinetics “pharmacodynamics”, “clinical effect”, “side effect”.

4. Selective effect of drugs, clinical significance (with specific examples).

5. Types of drug interactions in the combined use (for specific examples).

6. To study the main tasks and directions of clinical biopharmacy.

7. Factors affecting the clinical efficacy of drugs.

Control the boundary level of knowledge.

Solving situational problems:

1. With the simultaneous use of nitroglycerin and digitoxin, the first drug begins to act after 1 min, the other after a day. What caused such a difference in the rate of onset of the effect of drugs?

2. A patient with severe obesity turned to the pharmacist with a question: why did the doctor give him methionine (a lipophilic agent) in a high dose. What is the principle of dosing the drug, based on the characteristics of its distribution in the body?

3. The night pharmacy was called at night with a question: can there be pathological intoxication in a patient taking cytostatics? Explain the peculiarities of the metabolism of substances from the point of view of inhibition of liver microsomal enzymes.

4. Give the definition of the concept of "selectivity of action" drugs. Give examples of high and low selectivity of action

Drugs	**Pharmacological characteristics**	**Benefits**	**disadvantages**
With high selectivity			
low selectivity			

5.Fill in the table “Principles of dosing depending on the type of pharmacotherapy:

Types of Pharmacotherapy	**Dosing principle**
6. Substitution therapy 7. Symptomatic therapy 8. Pathogenetic therapy 9. Etiotropic therapy 10. Antidote drug therapy	

6. Define the terms and give examples of drugs that determine the effects of repeated administration, with combined use, and undesirable effects. Answers cite as a table.

Terms	**Definitions**	**Preparations**
. Addiction . Tachyphylaxis . Drug dependence . Cumulation Drug allergy . Synergism Antagonism Teratogenic and embryotoxic effects Mutagenic effect . Idiosyncrasy Carcinogenic effect		

7.Fill in the table: "Factors affecting drug efficacy in various ways of administration":

Route of administration	**Action start**	**Blood concentration**	**Biological filtration**	**Dosage Forms**
1 Intravenously	Immediately, or after 1 - 2 minutes	High	Absent	Only true solutions (introduction of oil solutions is unacceptable)
2. Intramuscularly				
3. Subcutaneously				
4. Inhalation				
5. Inside				
6. Rectal				

8.Fill in the table "Undesirable drug interactions in the infusion solution:

Interactive drugs		**Incompatibility reason**
Papaverine hydrohloride	euphyllin	
heparin	gentamicin, hydrocortisone, kanamycin	
Group of penicillinum	gentamicin, teyracyclinum	

Interactive drugs		Incompatibility reason
tetracyclinum	Hydrocortisone Natrii hydrocarbonas Calcium sulphate	
Vit.B12	Acidum ascorbinicum, Acidum nicotinicum, Vit.B6 Vit.B2	
Euphillin	Dibazol	

9.Describe the factors that influence the biological activity of drugs. Fill the table:

Groups of factors affecting the biological effect of drugs	Characteristic	Examples
1. The chemical nature of the drug substance 2. The physical condition of the drug substance 3. Aids 4. Type of dosage form and route of administration 5. Pharmaceutical technology		

10. Fill in the table: "Basic concepts of chronobiology and chronomedicine

The concepts	Definitions
1. Biorhythm 2. Chronobiology 3. Chronomedicine 4. Chronopharmacology 5. Chronopharmacokinetics 6. Chronotherapy 7. Chronotoxicology 8. Desynchronosis 9. Chronopathology 10. Circadian rhythms 11. Chronesthesia	

11.Explain what is bioavailability of drugs? The clinical significance of bioavailability. Factors and routes of administration that affect bioavailability

Factors Affecting Bioavailability	Mechanism of influence
I. Related to the features of drugs: 1. ..... 2.	

Factors Affecting Bioavailability	Mechanism of influence
3.	
II. Body-related: 1. ..... 2. ..... 3.	

12. Fill in the table: “Effect of food on drug absorption”:

Drugs	suction	
	Slowdown	Lack of influence
1. Amoxicillin 2. Acetylsalicylic acid 3. Acetampnophen 4. Glibenclamide 5. Digoxin 6. Nitrosorbide 7. Nitrazepam 8. Prednisone 9. Chlorpropamide 10. Cephalosporins 11. Sulfanilamides 12. Phenobarbital 13. Furosemide 14. Theophylline		

13.Fill in the table: “Effects of simultaneous use of alcohol and drugs”:

A drug	Effects
1. Analgesics 2. Anticoagulants 3. Antidepressants 4. Antihistamines 5. Beta-blockers 6. Furazolidone 7. Metronidazole 8. Oral hypoglycemic agents 9. Ethacrylic acid 10. Nitroglycerin	

14.Two patients with AD were prescribed the same dose of prednisone for oral administration according to the following schemes: one - the entire dose in the morning; another - in three doses (morning, afternoon and evening).
Your opinion in terms of chronopharmacology regarding these appointments. Justify the answer.

TESTS

1. The intern doctor prescribed the patient with enterocolitis the simultaneous administration of fluoroquinolone (ciprofloxacin) and the coating preparation (sucralfate). The department head considers the appointment erroneous. What are the consequences of co-administration of these drugs?

A. To enhance the toxicity of fluoroquinolones.
B. To increase the risk of developing kidney failure.
C. * To a significant decrease in the absorption of fluoroquinolones. *
D. To increased allergy to fluoroquinolones.
E. To enhance the ability of sucralfate to cause constipation.

2. A patient, 75 years old, with a diagnosis of pneumonia and a concomitant diagnosis of cardiosclerosis, NK IIA art., Was prescribed a course of gentamicin 40 mg 3 times a day and furosomide 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.

3. For a patient with a bacterial infection, the doctor prescribed Biseptolum in tablets, advising him to drink 1.5-2 liters of alkaline mineral water daily. What is the reason for 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

5. The patient during the course of treatment with nitrofurans consumed a small amount of alcohol, as a result of which severe poisoning developed. Explain the cause of poisoning:

A. Cardiovascular Failure
B. Allergic reaction
C. Neurological disorders
D. * Accumulation of acetaldehyde
E. Impaired renal function

6. In case of an overdose of aspirin, the method of alkalization of urine is used. This method aims to:

A. Inhibit the secretion of acid in the proximal tubule
B. Stimulate acid secretion in the proximal tubule
C. Neutralize blood acid
D. Stimulate tubular acid reabsorption
E. * Inhibit acid reabsorption in the renal tubules

7. Pharmacological incompatibility of drugs, which is detected at the level of a specific effect (for example, the introduction of adrenergic agonists and adrenoblockers), is called:

A. Physical
B. Pharmacokinetic
C. Chemical
D. * Pharmacodynamic
E. Pharmaceutical

8. The patient is shown the use of glucocorticoids inside. How appropriate is it to prescribe

them taking into account the physiological fluctuations in the hormones of the adrenal cortex in the blood?

A. The entire dose in the morning
B. 2/3 in the morning remaining in the afternoon
C. All dose in the evening
D. Evenly throughout the day
E. 2/3 in the evening, the rest in the morning

9. In a man, 36 years old, with a traumatic brain injury, breathing is weakened, the pulse is not shaped, reflexes are absent. Which route of administration of piracetam is most woody in this case?
A. Rectal.
B. Subcutaneous.
C. Oral.
D. * Intravenous.
E. Inhalation.
10. To a man, 22 years old, a medical emergency team was called for an attack of bronchial asthma. Which route of administration of salbutamol is most appropriate in this case?
A. Intravenous
B. Intramuscular
C. * Inhalation.
D. Subcutaneous.
E. Sublingual.
9. A man, 48 years old, had an attack of angina pectoris. The doctor prescribed a nitroglycerin tablet under his tongue. Why did the doctor choose the sublingual method of administering the drug?
A. Poorly absorbed from the intestines.
B. It is destroyed by gastric juice.
C. * Sublingual action cures faster, bypasses the liver.
D. Activated by saliva of the oral void.
E. Through an extremely harmful effect on the liver.
10. To a man, 22 years old, a medical emergency team was called up for bronchial status. Which route of administration of adrenaline hydrochloride is most appropriate in this case?
A. Inhalation.
B. * Intravenous.
C. Intramuscular
D. Subcutaneous.
E. Sublingual.
11. A man, 56 years old, who suffers from insomnia, was assigned phenobarbital. The rhythm of sleep returned to normal. But gradually over the course of 2 months. the effect of the drug decreased and insomnia recovered. What reason caused a decrease in the effect of sleeping pills?
A. Poor solubility.
B. * Tolerance.
C. Poor absorption in the stomach.
D. Fixation in lipoids.
E. Tachyphylaxis
13. In the embryonic period, the metabolism of therapeutic agents is much slower than in adulthood. The indicated pharmacokinetic peculiarity of the fruit is primarily determined by:
A. The functional imperfection of most enzymes or their absence.
B. Great permeability of histohematological barriers.
C. Significant volume of extracellular fluid.
D. The ability of the skin to absorb and excrete water-soluble drugs.

E. "Maturation" of receptors in organs at different times.
14. One of the main indicators of the elimination of therapeutic agents from the human body:
A. Scope of distribution.
B. Bioavailability.
C. Maximum concentration in the blood.
D. Half-life
E. Bioequivalence.
15. What does chronopharmacology study?
A. Principles of dosage of drugs.
B. The dependence of the effectiveness of drugs on their form.
C. Dependence of the effect of drugs on the body on the phase of bio-rhythms.
D. Duration of action of drugs on the body.
E. The rate at which drugs enter the body.
16. What is the reason for the increased toxicity of certain drugs in the elderly?
A. A high-calorie diet.
B. A decrease in the water content in the body and a decrease in cellular metabolism.
C. Drug Interactions.
D. Antagonism of drugs among themselves.
E. Synergistic action of drugs
17. The intern doctor prescribed the patient with enterocolitis the simultaneous administration of fluoroquinolone (ciprofloxacin) and the enveloping drug (sucralfate). The department manager considers the appointment erroneous. What are the consequences of co-administration of these drugs?
A. To enhance the toxicity of fluoroquinolones.
B. To increase the risk of developing kidney failure.
C. To a significant decrease in the absorption of fluoroquinolones. *
D. To increased allergy to fluoroquinolones.
E. To enhance the ability of sucralfate to cause constipation.

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
ADVERSE EFFECTS OF MEDICINES PHARMACOLOGICAL SURVEILLANCE SYSTEM IN UKRAINE

***Purpose of the topic*.**

Medicines accompany a person throughout his life: from birth to death. Statistics say on average in a middle-income family its members can get sick every 3 days. A man aged 20-45 years suffers from one life-threatening disease; in such a family, in addition, 20 diseases leading to temporary disability, 200 diseases without it and 1000 periodically occurring unpleasant symptoms are recorded, which requires taking drugs throughout life. However, neither doctors nor patients can resolve the issue of which drug is most safe and reliable.

Currently, the number of drugs available in the doctor's arsenal is tens and hundreds of thousands. In our country, 8000 items are registered. The number of drugs has increased rapidly in recent years. Only 20-30 years ago, 60-80% of currently used drugs were not known or were not used. The problem of the safety of the use of drugs (PM) is becoming increasingly relevant. This is primarily due to the fact that in medical practice the number of drugs with high biological activity increases, the use of which may be accompanied by the occurrence of adverse reactions (PR), which are different in manifestation and severity. The current situation is so serious that it led to the creation, under the auspices of WHO, of an international program for monitoring adverse reactions / actions of drugs, in which more than

60 countries of the **world** take part, including Ukraine.

Motivational characteristic of the topic.

It is known that drugs used in various diseases, by themselves, can cause severe pathology, as a result of which disability can be lost and sometimes death occurs. It is known that the incidence of PR in hospitalized patients is from 10 to 35%, and the increase in hospitalization due to PR is from 1 to 5.5 days. Mortality from PR takes 5th place in the world after cardiovascular diseases, lung diseases, cancer, injuries. In some countries (for example, the USA), the economic costs associated with the implementation of additional measures for the development of PR are 76.6 million dollars per year. A similar situation is typical for many countries of Europe and Asia, including Ukraine.

The public and professionals first began to pay attention to this problem - toxic drugs in the late 19th century. In the years 1870-1890. committees and commissions were established to investigate the causes of sudden deaths that sometimes occur with chloroform anesthesia. In 1922, a question was raised about jaundice when using salvarsan, an organic arsenic used to treat syphilis. In 1937, 107 people died in the United States as a result of the intake of the sulfonamide elixir, which was diethylene glycol contained as a solvent.

Over the 20th century, there have been a number of tragedies associated with the side effects of drugs, which has changed the professional and social attitude to modern medicines. The largest catastrophe that shook the whole world was the so-called “thalidomide” tragedy. In 1961, an increase in the frequency of phocomelia in newborns (deformation of the limbs) was recorded in West Germany. Subsequently, it was shown that the cause was thalidomide, a non-barbituric dwarf, which, as it turned out, has a teratogenic effect.

The case of thalidomide led to public protests and the establishment of a drug control system around the world with the aim of a deeper preclinical trial and their clinical assessment before being allowed to enter the market, as well as increasing control over side effects of drugs and developing methods for identifying and recording adverse reactions. In 1964, the first WHO program (WHO, 1972) for monitoring PD drugs came into effect. Under the auspices of the EU, structural units are being created (Pharmaceutical Committee, Permanent Committee on Medicinal Products for Human Use) to carry out pharmacological supervision.

Nevertheless, from time to time events occur that become the reason for further improvement of drug control methods. For example, in 1982 a new anti-inflammatory drug benoxaprofen was released. Within 1-2 years, reports appeared that it caused liver damage in the elderly, and in some cases so severe that they caused death. Further studies showed that partly the problem arose due to the fact that the recommended doses were worked out for young people, and it was mainly used in elderly patients who have a different liver metabolism. This observation led to the realization of the need for tests on the necessary contingent of patients. In addition, this increased the tendency of drug manufacturers to withdraw drugs from production at the first evidence of serious side effects. Subsequently, several drugs were discontinued shortly after their introduction into clinical practice at the first reports of PD. Especially often problems arose with NSAIDs. The tragic cases of the use of drugs are associated not only with carelessly and thoroughly conducted tests, but also with the quality of drugs.

The pharmacological surveillance system is a state system of collection, scientific assessment of information on adverse reactions of drugs during their medical use in order to make appropriate regulatory decisions (respectively, part 5A, article 29A of the provisions of the Pharmaceutical legislation of the European Union). Pharmacological supervision also monitors the incidence of adverse reactions in case of incorrect prescribing and / or abuse of drugs.

So, the processes of creation, study, production, widespread medical use of drugs are closely related. The most complete expression of the high appreciation of the importance of all these processes was found in the formation of three well-known codes of practice regarding drugs and adopted by the international community:

GLP - Good laboratory practice - quality laboratory tests (practice) - preclinical studies of drugs.

GCP - Good clinical practice - quality clinical research
GMP - Good manufacturing practice - high-quality production of drugs.
The expert body responsible for all issues of drug testing and use in our country is the State Pharmacological Center of the Ministry of Health of Ukraine.
Preclinical studies are carried out on animals with compulsory study, along with specific activity, acute, chronic toxicity, carcinogenicity, allergenicity, mutagenicity, teratogenicity, embryotoxicity of biologically active substances.
Clinical trials are usually carried out in 4 phases.
Phase I is called "sighting" (pilot) or clinical-pharmacological (a group of 20-50 people, healthy or sick, depending on the class of the drug). The goal is the study of pharmacokinetics, pharmacodynamics, tolerance.
Phase II - clinical examination (60-300 people - patients). The study of pharmacokinetics, pharmacodynamics, development of effective doses. A prerequisite is the presence of a control group. Used random distribution (randomization) in the control and experimental groups. The study can be open (known to both the doctor and the patient). When tested with the "blind" method, the patient does not know what he is taking; when examined with the "double blind", neither the doctor nor the patient knows about this, which increases the reliability of the studies.
Phase III involves official clinical trials (randomized for 250-1000 people or more) to clarify the effectiveness and safety of drugs.
Phase IV includes a post-registration study (after admission to the pharmacy). Held for 2000-10000 people or more. The effect of drugs is studied in a variety of situations in practice.
Clinical trials are usually multicenter, i.e. conducted by at least three independent studies. The total number of patients is usually more than 2500.
The desire of mankind to get rid of suffering and the dream of extending life are forced to look for drugs with therapeutic and minimal unwanted, or side effects. The very idea of creating such tools is contradictory. If the drug can not cause some harm, it is unlikely that it can bring significant benefits. In addition, side reactions sometimes occur against the background of the action of additional factors on the body, or they are due to the very nature of the body. Therefore, the undesirable effects of drugs and their manifestations cannot be represented as a simple list in this complex varying system of relationships, so we will try to analyze them.

TERMINOLOGY, CLASSIFICATIONS

Therefore, before proceeding to the presentation of the activities carried out in Ukraine on pharmacovigilance, it is necessary to dwell on modern terminology and classification of adverse reactions. The main, secondary, undesirable, safety of drugs (lack of serious and unforeseen PR); PD (any undesirable reaction due to the pharmacological properties of drugs and observed exclusively at therapeutic doses); adverse reaction (hazardous reaction undesirable for health, provided that the relationship between the reaction and the use of the drug cannot be ruled out); a side effect (any unfavorable medical manifestation when using drugs in the subject, which does not necessarily have a causal relationship with the use of the drug (change in laboratory data, symptom, disease, which coincided with the use of drugs). the community has adopted a unified approach to the terms used by various doctors and researchers to solve the problems of pharmacological surveillance: possible PR; reliable PR; unintended PR; frivolous PD; anticipated PD; doubtful PR, etc.
There are many classifications of adverse reactions to drugs and complications of pharmacotherapy. However, none of them is perfect. The classification is based on the pathogenetic principle.
1) Dose-dependent, organotoxic (the so-called type A):
A. Associated with pharmacological activity
B. With absolute or relative overdose of drugs
B. In the interaction of drugs
2) not related to the dose (the so-called type B, or unpredictable):
but. Immunological reactions (allergic, impaired immunobiological properties of the body)

b. Pseudo-allergic reactions
at. Pharmacogenetic variability (idiosyncrasy)
d. Topical application
3) With prolonged use:
but. Adaptive changes
b. upon cancellation of drugs (the phenomenon of "bestowal" and "cancellation")
at. organotoxic effect
4) Delayed action:
but. Blastomogenic (carcinogenic)
b. Reproductive Functional Action
1. reduced fertility
2. mutagenicity
3. teratogenicity
4. embryotoxicity
5. Fetotoxicity
6. Drugs in breast milk

Adverse reactions of type A are most common and, as a rule, are organotoxic (nephro, hepato, etc.). They may be due to:

1) the pharmacological properties of the drug, manifested in a therapeutic dose, and are inevitable during therapy (examples: tricyclic antidepressants - dry mouth, double vision, atropine, antipsychotics, etc.). Sometimes an unwanted action can be helpful (example). When developing new drugs, attempts are being made to increase the specificity of drugs.

2) They are usually the result of pharmaceutical, pharmacokinetic or pharmacodynamic deviations that cause a stronger pharmacological effect, which turns into a side effect. Often they are due to the nature of the underlying disease, the pharmacogenetic characteristics of the patient.

- pharmaceutical (change in the ingredients of dosage forms (in Australia in 1961, an outbreak of intoxication with phenytoin due to a change in one of the excipients), drug contamination (pyrogenicity, obsolete drugs;
- pharmacokinetic (change in absorption, biotransformation, elimination): pharmacogenetically determined (the concept of “acetylators” is slow and fast), diseases of the liver, kidneys, heart, thyroid gland (cardiac glycosides increase the effect with hypothyroidism, decreases with hyperthyroidism).
- pharmacodynamic (liver disease, a change in salt-water metabolism - arrhythmogenicity p / arrhythmic with hypokalemia, cardiac glycosides, etc.)

3) Due to the use of large doses or overdose of drugs (hypoglycemia with an overdose of insulin, large doses of penicillin - confusion, epileptiform attacks.

To assess the toxicity of drugs, the concept of therapeutic breadth of action (or therapeutic index) is introduced. Some examples of the most commonly used drugs with a narrow breadth of therapeutic effect:

 anticoagulants (warfarin, heparin);
 hypoglycemic (insulin, sulfonylurea derivatives)
 antiarrhythmic (amiodarone, lidocaine)
 cardiac glycosides (digitoxin, digoxin)
 aminoglycoside antibiotics (gentamicin, neomycin)
 oral contraceptives
 cytotoxic and immunosuppressive drugs (cyclosporine, aza-thioprine, etc.)
 antihypertensive drugs (beta-blockers, angiotensin-converting enzyme inhibitors)

Adverse reactions in the interaction of drugs (pharmaconetic and pharmacodynamic)

Type B adverse reactions include:

1) violations of the immunobiological properties of the body (changes in normal microflora when using antibiotics, isoniazid, etc.; glucocorticoids, immunosuppressants weaken the immune

system, leading to the development of infectious diseases, etc.)
2) immunological (allergy to the drug). Allergy provoking factors can be associated both with the drug (macromolecules, polypeptides (insulin), immunogenic dextranes), and the patient (aggravated allergic history (eczema, asthma, etc.). Various types of immunopathological reactions are distinguished. (anaphylactic shock, etc.). From a clinical point of view, the following syndromes are considered: fever, rash (erythema - antibiotics, thiazides, diuretics, etc., photosensitivity - tetracyclines, sulfonylureas, etc.), combine diseases s-term tissue (novokainamid apressin - lupus erythematosus), blood disorders (ane-mee), respiratory diseases.
3) Conditionally this group includes pseudo-allergic reactions. The term implies reactions similar to manifestations of allergic, but not based on their development and immune changes. For example, asthma and skin rashes caused by aspirin. Ampicillin and amoxicillin cause erythematous skin rashes that resemble toxic erythema with penicillin hypersensitivity. However, they have distinctive features: occur on 10-14 days (penicillin on 7-10), may not be repeated).
4) pharmacogenetically determined changes. These include idiosyncrasy - a genetically determined pathological reaction to a particular drug. As a rule, they are caused by hereditary defects of enzyme systems. Numerous examples are known. When treating patients with glucose-6-phosphate dehydrogenase deficiency with sulfonamides or primaquine, hemolytic anemia; Methemoglobin reductase deficiency in the treatment with nitrates - to methemoglobinemia, malignant hyperthermia under the influence of drugs, etc.
Adverse reactions identified in group 3 can be related both to the dose and the duration of the use of drugs. Chronic diseases require prolonged use of drugs, which naturally affects the effectiveness of therapy.
1) Adaptive changes may occur. So, long-term use of beta-adrenergic agonists with asthma or beta-blockers with hypertension leads to a decrease in the sensitivity of receptors. Long-term use of psychotropic drugs can lead to the development of tolerance and dependence.
2) The formation of the phenomena of “recoil” (hypnotics) and “cancellation” (glucocorticoids) is also associated with this.
3) Other adverse reactions with prolonged use include a number of organo-and systemic toxic effects: chloroquine-keratopathy (1-2 months in 30-70% of patients), retinopathy and blindness; amiodarone - pulmonary fibrosis, neuropathy, corneal damage, etc .; phenacetin - nephrosis, etc.)
The fourth group includes distant adverse reactions: carcinogenicity, mutagenicity, teratogenic, embryotoxic (up to 12 weeks), fetotoxic action. Decreased fertility (potency, infertility).
The degree of reliability of the relationship between PR and the action of drugs has been developed:
Certain, Probable, Possible, Conditional, Doubtful.
Unforeseen.
WHO experts identified the main factors contributing to the occurrence of adverse reactions / actions of drugs:

1. Factors not related to the effect of the drug:
   - features of the patient's body (age, gender, genetic, a tendency to allergic reactions, the specific course of the disease, harmful habits, etc.);
   - external, relatively sick, factors (pharmacotherapy conducted by a doctor, environmental, working conditions, etc.).

2. Factors associated with the action of the drug:
- features of the clinical and pharmacological characteristics of drugs;
- the adequacy of the choice of drug;
- method of using the drug;
- drug interactions with polypharmacy.

3. Factors associated with the quality of the drug:
- substandard drugs;
- falsified;

METHODS OF OBSERVATION AND COLLECTION OF INFORMATION ABOUT

Currently, the main ways to solve the safety problem of using drugs are:

- development of an optimal system for monitoring the safety of using drugs;
- production and launch on the pharmaceutical market of new, better and safer drugs.

Naturally, the latter depends primarily on the effectiveness of preclinical and clinical trials. Thus, pharmacological surveillance is of paramount importance, especially in countries where thousands of drugs are registered.

Currently, there are several methods for collecting and analyzing information about drug PR / PD at both the registration and post-registration stages (D.R. Lawrence, P.N. Bennett (1991):

1. Official clinical trials, allowing to detect only frequently occurring PR / PD, as they are carried out on a limited number of patients (up to 300). The frequency of PR is 1: 200.

   2. Epidemiological studies conducted after the authorization of drugs for widespread use (in groups of patients from 5000 to 20,000 or the assessment of each case of PR). Allow to identify reactions that occur with a frequency of 1: 5000. Unexpected side effects are usually manifested. In England, they use recipe information gathering. Very important.

   3. A system for recording individual reports of side effects. Depends on the intuition and desire of the doctor.

   4. National statistical studies on the basis of which children who are born with developmental defects or cancer patients are registered.

   5. Controlled clinical studies with the studied new drugs.

   Determining the frequency and severity of adverse reactions to drugs is a difficult task. It should be emphasized that the number of patients in clinical trials is limited and sometimes does not allow us to draw final conclusions about the safety of the studied drugs. Therefore, only with mass production and medical use for many years does the actual picture of drug toxicity become clear.

   WHO has developed special observation methods and approaches for objectively identifying adverse drug reactions:

   1. Occasional random messages. Unfortunately, it depends on the doctor's desire. However, thanks to such reports, the toxicity of fluorotone (jaundice), chloramphenicol (anemia) was established.

   2. Voluntary organized communications (in Ukraine - form 137 / o). Each doctor is required to report suspicion of PD. At this stage, it does not matter whether the suspected reaction is fully confirmed, since the system is adapted to refine messages when conclusions are drawn on the accumulation and analysis of messages. Particular attention should be paid to reactions when using new drugs, to all vaccines, and of course, reactions to any drug when a suspected adverse reaction is serious, leading to death or life-threatening patient. This system has a number of disadvantages. For example, it is difficult to identify the PR, the existence of which you do not suspect. Further, of course, the desire to report on the one that you just heard about, and not to communicate known to everyone. The third, unfortunately, is the irregularity of messages due to ordinary laziness. However, you must understand the usefulness and importance of this form of communication.

   3. Other systems for organizing observations at the stages of widespread clinical use of drugs: registration of certain side effects of drugs; prospective studies (in patient groups); retrospective studies (case studies); population statistics; generalization of information from all sources of registration of side effects of drugs (medical records).

   Advantages and disadvantages of various post-marketing types of drug observations (table)

   Methods for receiving reports of side effects of drugs are classified:

   1.Spontaneous messages allow you to control side effects of all drugs authorized for clinical use in the country. At the same time, the timing of the study of adverse reactions is not limited, there is the possibility of distributing patients to the necessary groups, which requires low research costs.

2. Active monitoring of hospitals is based on the fact that demographic, social and medical data are collected on all patients entering the hospital.

3. Prescription monitoring is based on the systematic collection and analysis of prescriptions for new drugs. In this case, contact is made with a doctor who personally reports on the side effects of the drugs.

4. The study in groups is carried out in certain groups of patients using the appropriate drugs; at the same time, a comparative analysis of the effectiveness and safety of pharmacotherapy with a control group of people is carried out.

5. A comparative study is based on the selection of patients who are characterized by a certain negative reaction when prescribing drugs, as well as the selection of patients who do not have a certain negative reaction when using the corresponding drugs.

1. According to the WHO international program, the data of each country on undesirable reactions to drugs are sent to its Information Center in Uppsala (Sweden). Currently, it already contains about 2 million such messages.
2. In our country, the state system of pharmacological supervision is regulated by the Law of Ukraine "On the Likes" (1996). Given the importance and magnitude of the problem of the safety of the use of drugs and with the aim of organizing a constant and timely receipt of information about PR, on the basis of the Law of Ukraine "On Polics" in 2000-2001. normative documents of the Ministry of Health of Ukraine were adopted - orders: No. 347 of 12/19/2000, No. 51 of 02/28/2001, and No. 292 of July 16, 2001, which oblige medical personnel to inspect state health structures about manifest and suspected cases of OL / PD drugs.
3. Monitoring the side effects of drugs and conducting a scientific assessment of the data received is assigned to the State Pharmacological Center of the Ministry of Health of Ukraine (HFC). A special unit has been created in its composition - the Department of Pharmacological Supervision, where all information on adverse reactions of drugs from:
4. doctors, pharmacists and medical workers, regardless of departmental subordination and ownership;
5. manufacturers / owners of a registration certificate or their authorized representatives;
6. authorized international organizations (WHO, EU, etc.);
7. medical information sources and scientific publications;
8. public organizations representing the interests of drug users, as well as citizens;
9. bioethics commissions (including during clinical trials of drugs);
10. regional branches of the State Pharmacological Center.
11. Information is sent monthly in the form of special forms developed by the Ministry of Health of Ukraine separately: for researchers conducting clinical trials;
12. doctors (form 137 / o);
13. drug manufacturers.
14. For a clear and timely collection of information about adverse reactions of drugs by the order of the Director of the State Pharmacological Center in each region of the country, inspectors have been appointed to carry out this work. Their responsibilities include providing organizational and methodological assistance to health departments of regional administrations, medical institutions, etc.
15. The provision and collection of data on side effects of drugs to the State Pharmacological Center from healthcare institutions is entrusted to regional therapists (Order of the Ministry of Health of Ukraine No. 51 dated 08.02.2001).
16. To improve control over the side effects of drugs, the form No. 69-healthy of industry-specific statistical reporting has been approved, which medical and preventive institutions of all profiles submit to the State Pharmacological Center no later than January 20, and the oblast health management body no later than January 30 of each year (Order of the Ministry of Health of Ukraine No. 292 dated July 16, 2001). Additions on side effects of drugs have

been made by the Ministry of Health of Ukraine also in the accounting and reporting documentation of medical institutions.

17. The State Pharmacological Center analyzes the information received in accordance with the specified deadlines, prepares informational reports, analytical reviews, express information, methodological recommendations, proposals of the Ministry of Health of Ukraine regarding changes in instructions for medical use and drug circulation, etc. Reports on suspected serious adverse reactions of the State Pharmacological Center submitted to WHO, and copies to the EU Agency.
18. For the period 1996-2001 The Department of Pharmaceutical Supervision received 822 cards of spontaneous messages, among them 52% of cases of suspected PR / PD in domestic drugs and 48% in overseas production. The most frequent cases were observed with PR when using CVS drugs (26%) and antimicrobial agents (21%). Among the manifestations of PR drugs, allergic reactions from the skin (33%), symptoms of gastrointestinal diseases (23%) and CVS (17%) predominated. 47% of PRs were recorded with the use of complex pharmacotherapy (up to three drugs).

    What you need to report:

    It is necessary to report on the PR / PD of drugs registered in Ukraine, their undesirable effect on the fetus and newborns during pregnancy and lactation, as well as on the complications resulting from drug abuse and the formation of dependence on them.

    Messages should contain information about:

    □ unknown and unforeseen PR drugs (the nature or degree of which does not meet the available information about drugs in the package leaflet and / or instructions for the medical use of drugs);

    □ serious PR / PD (any adverse, life-threatening PR that occurs during the medical use of drugs and leads to hospitalization or an increase in the duration of hospitalization, disability, death, cause fetal development abnormalities)

    □ the results of observations in which there is clear evidence that the drug will cause anticipated PR (for example, the development of an allergic reaction to the second appointment of the drug);

    □ adverse events in the interaction of drugs.

    In addition to informing about the clinical manifestations of PR, you should also report changes in laboratory parameters, complications of the course of the disease, which may be associated with taking drugs.

    2. How to report:

    To provide information, they use a special form of card message No. 137o, which contains information about the patient, a description of the suspected PR / PD (time of occurrence, course of treatment, examination results, investigation), data on the suspected drug, all other appointments Drugs (including self-medication), risk factors, name and addresses of the person who can be contacted in case of need to clarify messages. Confidentiality of information is guaranteed.

    It must be emphasized that the provision of a message about suspected undesirable PR / PD drugs will not only not cause any administrative negative measures, but, on the contrary, indicate a high professionalism of the doctor.

    3. Who should report:

    With the widespread medical use of LZ, doctors of all specialties should report suspected PR / PD. Annual information (summary report) on cases of PR / PD can also come from the hospital.

    4. Deadlines for submitting messages about unwanted PD LZ:

    Information about all serious unwanted, as well as unintended PR / PD drugs should be provided for two days (48 hours) to the State Pharmacological Center of the Ministry of Health of Ukraine by any means of communication (letter, fax, telegram, e-mail). Information about all other cases of PR / PD drugs - no later than 15 days from their

detection.

5. Where should the information go:

In the Odessa region, the following scheme was developed - in the Regional Information and Analytical Center for Medical Statistics of the UZ of the Odessa Regional State Administration until the 3rd Thursday of every month at the address: 65117, metro Odessa, vul. Ak. Zabolotnogo, 32; tel. (8048) 711-93-96, E-mail: medstat@tm.odessa.ua. Then all information should be sent to the State Pharmacological Center of the Ministry of Health of Ukraine at the address: 01042 Kiev, st. Chigorina, 18; backgrounds / fax (044) 268 2500; e-mail: vigilance@pharma-center.kiev.ua

However, it should be noted that it is not enough to record the frequency of adverse reactions, the type of their manifestations and severity, although careful collection is very important. It is necessary to try to analyze which of the PRs are inevitable and caused by the characteristics of the drug itself or the patient's body, and which of them can be avoided with a reasonable choice and expert use.

To summarize the foregoing, I would like to note that the first steps in organizing pharmacological supervision in Ukraine have already been taken, and they have brought significant results both in terms of the use of this information by doctors, drug manufacturers, and pharmacists. Everyone understands that the process of organizing a pharmacological surveillance system is not easy. But the longer we put off his decision, the more difficulties we have in treating our patients, our children, and ultimately ourselves.

The purpose of the lesson: The student must know the classification and the main manifestations of the side effects of drugs, know the processes of creation, study, production, medical use of drugs, know the basic codes of rules for drugs adopted by the international community:

Test questions.

I. **TERMINOLOGY.**

 The main action,

 Side effect (PD) /, possible PR; reliable PR; unforeseen PR; frivolous PD; anticipated PD; doubtful PR and others.

 Adverse Reactions (OL)

 Side effect The concept is the breadth of the therapeutic effect (or the therapeutic index).

 Unwanted action,

 The degree of reliability of the relationship of PR with the action of drugs:

 Certain

 Probable

 Possible

 Conditional,

 Doubtful.

 Unexpected.

II. **Classification of adverse reactions**. The classification is based on the pathogenetic principle.

1) Dose-dependent, organotoxic (the so-called type A):

but. Associated with pharmacological activity

b. With an absolute or relative overdose of drugs

at. With the interaction of drugs

2) Not dose-related (so-called type B, or unpredictable):

but. Immunological reactions (allergic, impaired immunobiological properties of the body)

b. Pseudo-allergic reactions

at. Pharmacogenetic variability (idiosyncrasy)

d. Topical application

3) With prolonged use:

but. Adaptive changes
b. When canceling drugs (the phenomenon of "bestowal" and "cancellation")
at. Organotoxic effect
4) Delayed action:
but. Blastomogenic (carcinogenic)
b. Reproductive function action:
1. reduced fertility
2. mutagenicity
3. teratogenicity
4. embryotoxicity
5. Fetotoxicity
6. Drugs in breast milk
Adverse Reactions Type A
Adverse Reactions Type B
the formation of the phenomena of "bestowal" (sleeping pills) and "cancellation" (GCS).
III. **The main factors contributing to the occurrence of adverse reactions to drugs:**
1. Factors not related to the effect of the drug:
 body features (age, gender, genetic, a tendency to allergic reactions, the specific course of the disease, harmful habits ...);
 external, relatively sick, factors (pharmacotherapy carried out by a doctor, environmental, working conditions, etc.).
2. Factors associated with the action of the drug:
 features of the clinical and pharmacological characteristics of drugs;
 the adequacy of the choice of drug;
 method of using the drug;
 drug interactions with polypharmacy.
3. Factors associated with the quality of the drug:
 substandard drugs;
 falsified;
III. **Organization of a pharmacological surveillance system**.
1. The expert body responsible for testing and using drugs in Ukraine is the State Pharmacological Center of the Ministry of Health of Ukraine.
2. The main legislative documents of the Pharmaceutical legislation of the European Union.
3. Codes of medicine regulations adopted by the international community:
 GLP - Good laboratory practice
 GCP - Good clinical practice
 GMP - Good manufacturing practice
a. Preclinical Studies
b. Clinical trials - 4 phases.
A. The main ways to solve the safety problem of using drugs:
 development of an optimal system for monitoring the safety of drug use;
 production and launch on the pharmaceutical market of new, better and safer drugs.
B. Methods for collecting and analyzing information about adverse reactions / side effects (PR / PD) of drugs:
 at the registration,
 at the post-registration stages.
5. Epidemiological studies,
6. System for registering individual messages
7. Nationwide statistical studies,
8. Controlled clinical trials
B. Special monitoring methods and approaches for the objective identification of adverse drug reactions developed by WHO:

2. Occasional random messages.
3. Voluntary organized communications (in Ukraine - form 137 / o).
4. Other systems for organizing observations at the stages of wide clinical use of drugs:
G. The methods for receiving reports of side effects of drugs are classified:
6. Spontaneous messages
7. Active monitoring of hospitals
8. Prescription monitoring
9. Study in groups
10. Comparative study
D. Monitoring the side effects of drugs and conducting a scientific assessment of the data received -
E. Information sent monthly in the form of special forms developed by the Ministry of Health of Ukraine:
 for researchers conducting clinical trials;
 doctors (form 137 / o);
 drug manufacturers.
1. What you need to report:
2. Messages should contain information about:
3. How to report:
4. Who should report:
5. Deadlines for submitting messages about unwanted drugs:
6. Where should the information go:

The list of practical works:

Homework.
1. To study the main adverse effects, classification.
1. To study the main provisions and organization of the Pharmaceutical Supervision system in Ukraine.
2. Be able to fill out form No. 137o. (see Attachment).
Independent practical work in class
1. Clinical manifestations of the negative effect of drugs.
2. Fill No. 137o.
Control of the intermediate level of knowledge.
The solution of situational tasks:

TESTS

1. What is the irreversible complication that may occur with the appointment of glucocorticoids:
   A. Arterial hypertension
   B. Propensity for thrombosis
   C. Glaucoma
   D. * Growth retardation
   E. Silent Sores
2. Choose a factor that increases the risk of developing unwanted effects of natural glucocorticoids:
   A. Hyponatremia
   B. Administration of glucocorticoids in physiological doses
   C. * Joint appointment with antihypertensive drugs
   D. Co-administration with histamine 2 blockers
   E. Prescription of glucocorticoids in the morning
3. What is the drug prescribed for prophylactic or therapeutic purposes, the patient with gastropathy that occurred when using NSAIDs:
   A. Cimetidine
   B. * Omeprazole
   S. de nol

D. Sucralfate
E. Carbenoxolone (biogastron)

4. The undesirable effects of sodium cromoglycate do not include:
A. Bronchospasm
B. Decrease in acidity of gastric juice, gastroenteritis
C. Candidiasis of the oral cavity
D. Persecution, cough, hoarseness
E. * Dry throat

5. The undesirable effects of M-anticholinergics do not include:
A. Disturbance of swallowing, hoarseness
B. * Bradycardia, lowering body temperature
C. Increased intraocular pressure
D. Atony of the intestine, decreased secretion of gastric juice
E. Mydriasis, paralysis of accommodation

7. The undesirable effects of beta-blockers do not include:
A. Bradycardia
B. Bronchospasm
C. Impotence
D. Intermittent claudication, Raynaud's disease
E. * Decrease in tone of a pregnant uterus

8. For the treatment of urticaria with the aim of eliminating an itchy rash 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. The doctor prescribed the patient the drug streptokinase, which has serious undesirable effects. What does not relate to the characteristic adverse effects of this drug?
A. Hematuria
B. Thrombosis
C. Nasal hemorrhages
D. Allergic reactions
E. Pyrogenic reactions

10. In a patient who takes neodicumarin in connection with thrombophlebitis, intestinal bleeding has opened. What drug should be prescribed?
A. Dichlothiazide
B. Protamine sulfate
C. Acetylsalicylic acid
D. Trental
E. * Vikasol

11. In a patient who had been taking glucocorticoids for a long time, as a result of drug withdrawal, an exacerbation of an existing disease, a decrease in blood pressure, and weakness appeared. These phenomena can be associated with:
A. Sensitization
B. * The occurrence of adrenal insufficiency
C. Addiction to the drug
D. Hyperproduction of ACTH
E. Cumulation

12. The patient was prescribed a water-soluble cardiac glycoside. What concomitant pathology can contribute to the accumulation of water-soluble cardiac glycosides?

A. Hyperacid gastritis
B. * Renal failure
C. Hepatic failure
D. Hypoacid gastritis
E. Hypertension

13. Addicts after the end of the drug have 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

14. For the treatment of chronic rheumatoid arthritis, the patient took a therapeutic agent for a long time. After some time, general weakness, malaise, necrotic tonsillitis developed. In the blood test, there is a sharp decrease in granulocytes. What drug could cause this complication?

A. * Analgin
B. Dimexide
C. Piroxicam
D. Mefenamic acid
E. Paracetamol

15. A patient with a hypertensive crisis was given a ganglion blocker - benzohexonium. What phenomena should be feared after drug administration?

A. Depressing effect on the central nervous system.
B. Recoil Syndrome
*C. * Orthostatic hypotension*
D. Impairment of taste
E. Diarrhea

The patient read the instructions for the prescribed antibiotic, where the possibility of muscle relaxant, ototoxic, teratogenic, mutagenic effects was noted in the section of undesirable effects. What drug was prescribed?

A. Chloramphenicol
B. Penicillin
C. * Streptomycin
D. Chloramphenicol
E. Dicloxacillin

17. A man, 40 years old, with hypertension was prescribed a drug that in 3 days improved the patient's condition and normalized blood pressure. After a while, the patient turned to the doctor complaining of unproductive cough, which was not removed after the use of antitussive drugs and caused the patient's sleep disturbance. There is no history of obstructive pulmonary disease. What drug was most likely taken by the patient?

A. Anaprilin
B. * Enalapril
S. Klofelin
D. Verapamil
E. Reserpin

18. A man, 60 years old, complains of shortness of breath with difficulty breathing out, dry cough. For 30 years he has been suffering from chronic obstructive bronchitis. Deterioration noted 3 weeks ago, often uses berotek. Smokes up to 1.5 packs of cigarettes per day. The last month is being treated for angina pectoris taking phenigidine, nitroglycerin, anaprilin. Objectively: body temperature - 36.40 ° C, BH - 28 rpm, heart rate - 98 rpm, BP - 120/80 mm Hg. In the lungs, vesicular breathing, scattered dry wheezing mainly during exhalation. Heart sounds are muffled, the rhythm is correct. What is most likely the cause of the deterioration?

A. Smoking.
B. * Reception of anaprilin.
C. Administration of phenygidine.
D. Abuse of berotek.
E. Exacerbation of chronic bronchitis.
19. 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 its implementation, the patient's hearing deteriorated. What drug, when combined with furosemide, led to hearing loss?
A. Mukaltin.
B. Linex.
C. Nystatin.
D. Tavegil.
E. * Amikacin.
20 A patient with infiltrative pulmonary tuberculosis was prescribed: streptomycin, rifampicin, isoniazid, pyrazinamide, vitamin C. After 1 month from the start of treatment, the patient began to complain of hearing loss, tinnitus. Which of the prescribed drugs has such a side effect?
A. Pyrazinamide.
B. Rifampicin.
C. Isoniazid.
D. * Streptomycin.
E. Vitamin C.
21. A patient with pneumonia is injected with benzylpenicillin sodium salt at a dose of 500,000 units 6 times a day. After the next administration of the medicinal product, there was a fever, convulsions, a woman lost consciousness. What developed in the patient?
A. * Anaphylactic shock.
B. Idiosyncrasy.
C. Tachyphylaxis.
D. Cumulation.
E. Tolerance.
22. In the postoperative period, the patient was administered pro-medol for a long time. After distinguishing the drug, severe mental and somatic disorders occurred in the patient. What is the name of this phenomenon?
A. Recoil Syndrome
B. Idiosyncrasy.
C. Tachyphylaxis.
D. Theft syndrome.
E. * Withdrawal syndrome.
23. A patient with hypertension has been taking an antihypertensive drug for a long time, but suddenly stopped taking it. After this, the patient's condition worsened, hypertensive crisis developed. What kind of side effect developed in the patient?
A. Cumulation.
B. * Cancellation syndrome.
C. Tolerance.
D. Sensitization.
E. Dependence.
24. A patient with chronic heart failure for several months took digoxin in therapeutic doses on an outpatient basis. At a certain stage of treatment, he developed symptoms of an overdose. What phenomenon underlies the development of this complication?
A. Sensitization.
B. Addiction.
C. * Material cumulation.

D. Functional cumulation.
E. Tachyphylaxis.

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 BRONCHOLYTICS

Purpose of the topic.

Bronchial obstruction syndrome is a serious medical and social problem. According to epidemiological studies, 5% of the adult population and 15% of children have bronchopulmonary pathology with this syndrome. The syndrome of bronchial obstruction occurs at a fairly early age and accompanies the patient all his life, significantly worsening its quality, in our region is the main cause of death in pulmonology.

Motivational characteristic of the topic.

The importance of the topic under study is determined by the ability to effectively treat and prevent the development of bronchial obstruction syndrome (SBO) in patients with chronic specific and non-specific obstructive pulmonary diseases (COPD), bronchial asthma (BA), acute allergic reactions, the pathogenesis of this syndrome in each specific case has special characteristic features, without which effective medical correction of the patient's condition, struggle for his life, recovery and rehabilitation are impossible.

Classification

Bronchial asthma is classified depending on the origin, severity of the disease, and special forms of bronchial asthma are also distinguished.

Etiological classification

Depending on the causes of the attacks, there are:

 exogenous bronchial asthma - seizures are caused by exposure to the respiratory tract of an allergen from the external environment (plant pollen, molds, animal hair, tiny mites found in house dust). A special option is atopic bronchial asthma, caused by a hereditary-related predisposition to allergic reactions;

 endogenous bronchial asthma - an attack is caused by such factors as infection, physical activity, cold air, psycho-emotional irritants;

 bronchial asthma of mixed genesis - seizures can occur both when exposed to the respiratory tract of an allergen, and when exposed to the factors listed above.

Gravity stratification

When assessing the severity of the disease, take into account:

- the number of nightly symptoms per month, week, day;
- the number of daily symptoms per week, day;
- the severity of violations of physical activity and sleep;
- the best indicators of FEV1 and PSV per day;
- daily fluctuations of FEV1 and PSV.

In the stratification of asthma by severity, there is the concept of a step corresponding to certain gradations of symptoms of the asthma symptom complex. Four steps are distinguished, if the patient does not take basic drugs, then each of these steps corresponds to one of four degrees of severity:

Step 1. Intermittent Asthma

Attacks rarely occur (less than once a week)

Short exacerbations

Nighttime attacks of the disease rarely occur (no more than twice a month)

FEV1 or PSV more than 80% of the norm

PSV spread less than 20%

Step 2. Mild persistent asthma

Symptoms of the disease occur more often 1 time per week, but less than 1 time per day

Exacerbations can disrupt the patient's sleep, inhibit physical activity

Nocturnal attacks of the disease occur at least 2 times a month

FEV1 or PSV more than 80% of the norm

Scatter PSV 20-30%
Stage 3. Persistent moderate asthma
Asthma attacks occur almost daily
Exacerbations disturb the patient's sleep, reduce physical activity
Nighttime attacks of the disease happen very often (usually 1 time per week)
FEV1 or PSV are reduced to indicators from 60% to 80% of the normal value
PSV spread more than 30%
Stage 4. Severe persistent asthma
Bouts of illness occur daily
Nighttime asthma attacks happen very often.
Limitation of physical activity
FEV1 or PSV account for about 60% of the norm
PSV spread more than 30%
Classification of severity of exacerbation of asthma
Exacerbations of bronchial asthma are episodes of a progressive increase in shortness of breath, cough, wheezing, wheezing. At this time, the lumen of the bronchi is narrowing, which is accompanied by a decrease in peak expiratory flow rate (PSV), forced expiratory volume in 1 second (FEV1), and forced lung vital capacity (FVC). To assess the severity of an exacerbation, a physical examination is performed, a study of the function of external respiration, a study of arterial blood gases, an ECG, and chest x-ray.
Bronchodilators are a pharmacological group of symptomatic drugs that directly relieve bronchospasm and are used in the treatment of bronchial asthma and chronic obstructive pulmonary disease and some other diseases. This group does not include drugs that affect the causes of bronchospasm, such as antihistamines, corticosteroids, antiviral, antimicrobial and others.
These include drugs that block bronchospasm in various ways:
• β2-adrenergic agonists
• Nonspecific β-agonists (beta-agonists, β-adrenergic agonists, BDA)
• Orciprenaline, Isoprenaline
• Specific β2-agonists (beta-two-agonists, β2-adrenergic agonists, β2-adrenergic receptor agonists):
• short-acting (BDAC): salbutamol, fenoterol, terbutaline, hexoprenaline, clenbuterol
• long-term (prolonged) action (BDAP): salmeterol, formoterol
• for oral administration (BDAV): saltos
• M-anticholinergic antagonists (M-anticholinergics, anticholinergics, anticholinergics) - ipratropium bromide, tiotropium bromide and glycopyrronium bromide
• Xanthine derivatives - myotropic antispasmodics
Bronchodilators are available in the form of inhalers, tablets, syrups and solutions for injection. Inhalers (and their subspecies, nebulizers) are the most popular.
Beta 2 – agonists (BDA)
They occupy a central place among the means of symptomatic control of AD, since they have pronounced bronchodilator activity and, when used correctly, cause a minimal number of side effects.
Since 1970 In clinical practice, selective beta-two-agonists (BDAs) are used. The first drug from this group was salbutamol, which rightfully acquired the status of the "gold standard" in the series of BDA. Salbutamol was followed by the introduction into clinical practice of other beta-two agonists, in particular phenoterol (berotek). Significantly expanded the possibilities of AD therapy the emergence of prolonged inhaled beta-two agonists (salmeterol, formo-terol). V1990g. An aerosol formoterol preparation appeared, and since 1994. a powder inhaler is used. There was a possibility of taking individual BDA (sal-tos) inside.
Inhalation is recognized as the most effective route of administration of BDA. Its important advantage is the possibility of direct delivery of the drug to the target organ, as a result of which

the therapeutic effect of broncholytic quickly sets in with minimal side effects.
Among currently known delivery vehicles for BDA:
- most often (almost 70% of cases) they use metered-dose aerosol inhalers - DAI;
- less commonly used metering powder inhalers - DPI;
- even less commonly, nebulizers.
Pharmacodynamics
- Stimulation of beta-adrenergic receptors leads to activation of adenylate cyclase, resulting in an increase in the content of intracellular cAMP. Further, there is a decrease in intracellular calcium concentration, which leads to the weakening of the smooth muscles of the bronchial tree. BDA are universal bronchodilators, since they eliminate bronchoconstriction, regardless of its genesis and mechanisms.
- BDA apparently have a modest broncho-protective effect, which is manifested by a slight decrease in remodeling of the bronchial tree in obstructive pulmonary diseases.
- In addition, BDA inhibit the release of mediators from inflammatory cells, limit the permeability of capillaries, and prevent the development of edema of the bronchial mucosa.
- Reduce cholinergic reflex bronchoconstriction.
- Modulate mucus production and optimize mucociliary clearance.
- Long term use of saltos significantly improves the passage of the entire bronchial tree. The maximum bronchodilator effect at the level of small bronchi develops by the end of the second week of therapy. Along with a pronounced bronchodilator effect, only saltos among all BDA has a reliable bronchoprotective effect.
- Frequent regular use of inhaled DBA can lead to the development of tolerance (desensitization) to them, which, unlike tachyphylaxis, develops gradually, over several days or weeks, and is associated with the transition of receptors to an inactive state.
- It should be remembered that the selectivity of BDA is always relative and dose-dependent. It was found that selectivity clinically significantly decreases with increasing dose or frequency of administration during the day. This should be taken into account during treatment of exacerbated asthma, especially when stopping asthmatic status, when the patient inhales 5-10 or more admissible daily doses of the drug for several hours.
- Clinically important is the question of whether the BDA has an anti-inflammatory effect. So far, this question remains open. In addition, regular use of BDA can mask a growing exacerbation, thereby delaying the onset or intensification of true anti-inflammatory therapy by HA.
- A relationship has been established between the increased risk of death in patients with AD and the use of high doses of inhaled ADS. It is believed that patients receiving high doses of BDA (more than 1.4 aerosol cans per month), of course, and, above all, need to strengthen anti-inflammatory therapy.
BDA short-acting (BDAK)
Salbutamol (salben. Salgim, saltos)
Currently the most popular bronchodilator. This is a classic short-acting BDA.
F.v. - for salbutamol-DAI, containing 200 doses of 100 μg each.
- for salbena - DPI Cyclohaler complete with a capsule containing 200 doses of the drug, 200 μg of active substance each
- salgim in vials containing 5 or 10 ml of a 0.1% salbutamol solution for inhalation through a nebulizer.
Pharmacodynamics of salbutamol preparations
- Salbutamol is a selective beta-two agonist, due to which it has a pronounced bronchodilator effect. A short-acting drug stops and prevents bronchospasm, that is, it is the drug of choice for situational symptomatic control of asthma.
- Reduces the release of histamine and other biologically active substances from mast cells.
- Increases excitability, frequency and strength of heartbeat.
Pharmacokinetics

The therapeutic effect of short-acting salbutamol after inhalation from the DAI begins in 1 to 3 minutes and lasts up to 3 to 4 hours. The bronchodilator effect of salbene appears in 4 to 5 minutes; the maximum is reached by 40-60 minutes, and the duration of the drug is 4-5 hours. The response to salgim inhalation through a nebulizer is usually observed after 10-15 minutes, and the action lasts 4-6 hours.

Indications for appointment

-Kupirovanie ("on demand") and prevention of bronchospasm. Usually, bronchodilatory therapy of patients with AD begins with the appointment of salbutamol. The drug is less effective for COPD and COPD.

Dosage regimen

Salbutamol preparations, with the exception of saltos, are used only on demand.

Adults take 1-2 inhalations of salbutamol no more than 3-4 times a day.

For children over 2 years of age, 1 inhalation of salbutamol from 1 to 3 times a day.

Salben is used in 1 - 2 inhalation doses per dose from 1 to 4 times a day.

When using salgim, the starting dose = 2.5 mg every 4 to 6 hours during the first 2 days of treatment or until the clinical picture stabilizes.

If control over AD is not achieved with the use of the above doses of salbutamol preparations, it is necessary to strengthen anti-inflammatory therapy.

Side effects and effects of overdose

Heart rhythm disturbances, lowering blood pressure, headache, anxiety, anxiety, muscle tremor.

Fenoterol (berotek, berotek N)

F.v. - for berotek - freon DAI containing 200 doses of 100 μg each.

- for Berotek N - freon-free DAI containing 200 doses of 100 μg each. The product contains small amounts of ethanol and citrates, which give it a light alcoholic and lemon flavor.

Pharmacodynamics

“Similar to salbutamol.” It surpasses salbutamol in therapeutic efficacy. Therefore, with an insufficient effect of salbutamol, the patient is transferred to berotek. However, a return to salbutamol for such patients is practically excluded.

- Successfully combined with ipratropium bromide. There is a combined drug called berodual.

Results of Comparative Controlled Studies

As a result of the studies, it was found that berotek in both forms - freon and freon-free DAI - had almost the same effect on the HPF parameters in patients with AD. At the same time, berotek N was 2 times more effective than a simple berotek.

Indications for appointment

- Stopping and prevention of bronchospasm, especially in patients with AD

Dosage regimen

To stop attacks of bronchospasm, 1 dose is prescribed. If necessary, after 5 minutes, inhalation can be repeated.

Side effects

In this regard, berotek is more active than salbutamol.

From the side of the central nervous system: small tremor, dizziness, headache, nervousness.

From the side of the cardiovascular system: tachycardia and other abnormalities of the heart rhythm, angina attacks, increased systolic blood pressure.

Also possible: cough, nausea, vomiting, weakness, muscle pain.

Long-acting BDA (BDAP)

Currently available inhaled BDAP (formoterol, salmeterol) exert their effect for 12 hours with almost the same bronchodilator effect.

Clinical studies indicate the feasibility of an earlier on-going IBDAP.

When using formoterol more often than 2 times a week, “on demand”, IHC should be added to the treatment. Currently, it is recommended to use IB-DAP only in patients who are simultaneously receiving IHC.

Salmeterol (Serevent)

F.v. - DAI containing 60 or 120 doses of 25 μg of salmeterol in each
- DPI with rotadisks, each of which contains 4 doses of 50 μg of active substance.
Pharmacodynamics
- This is a highly selective extended-release BDA.
- Provides long-term AD control in patients with daily symptoms.
- Improves the quality of life, in particular, improves the quality of sleep in patients with AD
- In therapeutic doses, does not affect the cardiovascular system.
Pharmacokinetics
The onset of action is noted 5-10 minutes after inhalation. The oncholytic effect lasts for 12 hours after a single inhalation.
Indications for appointment
- Regular long-term treatment of patients with clinically significant reversible bronchial obstruction.
- Night asthma.
Mode of application
For adults, the contents of one rotadisk or 2 inhalations 2 times a day
For children aged 4 years and older, 1 to 2 inhalations 2 times a day.
Side effects
Rarely tremor, usually transient and diminishing during treatment
Overdose symptoms
Tremor, headache and palpitations, heart rhythm disturbances are possible
Formoterol (Foradil Aerolizer, Oxis Turbuhaler)
F.v. - Turbuhaler inhaler containing 60 doses of 4.5 or 9 mcg.
- capsules, each of which contains 12 mcg of powder for inhalation, complete with DPI "Aerolizer".
Pharmacodynamics
- It is a powerful selective BDA with a pronounced bronchodilator effect
- The rapid onset of bronchodilator action (within 1-3 minutes) allows you to effectively stop acute bronchial obstruction. In this regard, formo-terol does not tolerate salbutamol.
- The effect of the drug lasts up to 12 hours
- Does not affect the effects of short-acting BDA, which allows them to be additionally used against the background of basic therapy with formoterol. This is confirmed by the results of numerous clinical studies.
- In comparative studies with salbutamol, there were no significant differences in the frequency of side effects.
- Side effects of formoterol are dose-dependent and reach a clinically significant level only in doses significantly higher than therapeutic, which indicates a high safety of the drug.
- When using therapeutic doses, the drug does not cumulate.
- In patients with COPD, on the basis of FEV 1, Foradil in doses of 12 and 24 mcg 2 times a day significantly exceeds the effect of ipratropium bromide.
Moreover, unlike anticholinergic, formoterol in both doses causes a statistically significant improvement in the quality of life. In addition, against the background of treatment with fora-dil, the percentage of "dysfunctional days" is significantly lower than with ipratropium bromide. The frequency of adverse events was comparable in all examined groups.
- It should be emphasized that formoterol, like other IBDAP, potentiates the effects of HA. The results of clinical studies have shown that the addition of formoterol to the basic treatment of AD has a greater effect compared to theophylline with a significantly lower risk of side effects.
Indications for appointment
- Stopping and prevention of attacks of bronchospasm, including with night asthma. In fact, formoterol is necessary for every BA patient in any situation.
- Formoterol is indicated for BA patients of moderate severity and severe form as a basic anti-asthma therapy in combination with inhaled and / or systemic GC.

- In COPD, formoterol improves lung function, reduces the frequency and severity of exacerbations.

Application mode

Adults inhaled through Turbuhaler 4.5-9 mcg 1-2 times a day

Adults are inhaled through an aerolizer 12-24 mcg (contents of 1-2 capsules) 1-2 r / s

Side effects

Caution should be used for coronary heart disease, cardiac arrhythmias, thyrotoxicosis, diabetes mellitus.

After starting treatment with formoterol, patients with asthma should continue anti-inflammatory therapy of HA without changing the dosage regimen of the latter.

Saltos

F.v. - Osmogenic tablets, each of which contains 7.23 mg of the active substance.

Pharmacodynamics

The prolonged salbutamol preparation is used mainly for the prevention of episodes of bronchospasm, especially at night.

Combined BDA (BDA + IHC)

Seretide Multidisk (salmeterol + fluticasone propionate)

It contains two active components: salmeterol xinafoate (SC) and fluticasone propionate (AF)

F.v. - DPI "Multidisk", inside of which there is a foil tape with 60 uniformly spaced cells, each of which contains one dose of the drug in the form of a powder for inhalation.

Seretide Multidisk is available in the following dosages:

. 50 μg SK + 100 μg AF in a single dose; 60 doses.

- 50 μg SK + 250 μg AF in a single dose, 60 doses. 'f
- 50 μg SK + 500 μg AF in a single dose; 60 doses.

Pharmacodynamics

- Effective BA control with a single inhaler.
- Reducing the severity of the symptoms of the disease from the first day of treatment.
- Ability to control asthma with lower doses of IHC.

-High security profile.

- A unique delivery system with an accurate dose counter.
- Convenient dosage regimen: 1 inhalation 2 times a day.
- Improving the compliance of patients with AD.
- Improving the quality of life of patients with AD.
- Reducing the cost of treatment compared with the simultaneous use of salmeterol and fluticasone in individual inhalers.

Indications for appointment

- Patients receiving maintenance therapy BDAP and IHC.
- Patients who have symptoms of the disease during treatment with IHC.
- Patients who regularly use bronchodilators, who are additionally shown therapy for IHC.

Dosage regimen

The starting dose of Seretide Multidisk is determined on the basis of the dose of fluticasone propionate, which is recommended for AD of this severity.

Adults and adolescents 12 years of age and older: one inhalation (50 μg of salmeterol + 100/250/500 fluticasone) 2 times a day.

Children 4 years of age and older: one inhalation (50 μg of salmeterol + 100 μg of fluticasone) 2 times a day.

Side effects

Similar to those of salmeterol and fluticasone.

Symbicort (formoterol + budesonide)

This combination is in one inhaler Turbuhaler IHC budesonide and prolonged BDA formoterol.

F.v. - DPI Turbuhaler containing 60 doses, in each of which 4.5 micrograms of formoterol + 80 or 160 micrograms of budesonide.

Pharmacodynamics
- Quick relief of AD symptoms, occurring within 1 to 3 minutes, after inhalation.
- Long-term disease control.
- The possibility of a single dose during the day.
- Dosing flexibility with the same inhaler.
- An increase in compliance, as patients note an immediate relief from the inhalation of symbicort, which prompts them to systematically continue treatment.
- Turbuhaler - an effective and convenient system for the delivery of drugs to the BLS.
Indications for appointment
- Patients who are simultaneously receiving maintenance therapy BDAP and IHC.
- Patients who have a symptom of the disease during therapy with HI.
- Patients who regularly use bronchodilators, who are additionally shown therapy for IHC.
Clinical efficacy
Symbicort has passed a number of clinical trials abroad. It has been established that, compared with IHC, symbicort significantly reduces asthma symptoms, the frequency and duration of exacerbations, and improves HPF. Compared with budesonide, Symbicort gives the patient 2 additional months of the year, not only without daytime, but even without nighttime symptoms of AD. Symbicort treatment compared with treatment with budesonide and formoterol via separate inhalers leads to a more rapid increase and stabilization of peak flow metrics.
In terms of speed of onset and severity of the bronchodilator effect, symbicort is superior to the combination of salmeterol 50 mcg + fluticasone 250 mcg.
Dosing mode
Adults, including PAP, and adolescents 12 years of age and older at 1-2 inhalations (based on 1 dose = 160 / 4.5 μg) 2 times a day. After achieving optimal control of AD symptoms, a dose reduction is possible, up to the minimum effective = 1 inhalation 1 time per day.
Side effects. Similar to those of budesonide and formoterol. The most common tremors and tachycardia. These symptoms are usually mild and disappear after a few days of treatment. Less common are headache, tremor, candidiasis of the oral part of the pharynx, cough, hoarseness of the voice.
Biasten (salbutamol + budesonide)
F.v. - DPI Cyclohaler containing 100 or 200 doses of the drug, each of which includes 200 μg of salbutamol and 100 μg of budesonide.
This is a combined drug that has anti-inflammatory and bronchodilator effects in the treatment of AD patients. This allows you to reduce the severity of symptoms, as well as the frequency and severity of exacerbations of the disease. Bronchodilator action occurs rapidly, within 1 to 3 minutes. after inhalation, and persists for 5-7 hours after taking a single dose.
Biasten is indicated for basic treatment of AD. It goes well with virtually any anti-asthma medication. Particular caution is required in individuals with cardiac arrhythmias and hypokalemia.
Using the drug allows you to achieve high compliance, as well as reduce the cost of basic therapy compared to the separate use of two inhalers.

The drug is recommended to be used 1 inhalation 3 times a day or 2 inhalations 2 times a day. After achieving optimal control of asthma symptoms, a dose reduction is possible, up to 1 dose 1 time per day

Xanthines

1. Short acting drugs:
• Theophylline (Eufillin).
2. Long-acting drugs: I generation:
• Theopec.
• Theodur.
• Theotard.
• Systire.

• Theobiolong.
• Retafil.
• Ventax.
• Durofillin.

II generation:

• Dilatran.
• Theodur-24.
• Eufilong.
• Unifil.
• Retafil retard.
• Filocontin.
• Diffumal-24.
• Theo-24.

Currently, short-acting theophylline preparations are used to relieve bronchospasm, while long-acting TFs are used for the systematic treatment of AD. As monotherapy, long-acting TFs are not very effective and, obviously, are not suitable for long-term maintenance therapy. At the same time, in those patients in whom control over AD was not achieved only with the help of IHC, a combination of the latter with prolonged theophyllines can improve treatment outcomes. It should be borne in mind that the combination of IHC with prolonged-release TF is less effective than the combination of IHC with β2-AM, but much cheaper.

The mechanism of action of xanthines has not yet been fully disclosed. It has been shown that methylxanthines nonselectively inhibit the III and IV isoforms of phosphodiesterase (PDE), which contributes to the accumulation of cAMP in cells. PDE III prevails in the smooth muscles of the bronchi, while the IV isoform of the enzyme plays the greatest role in inflammatory cells (mast cells, eosinophils, T-lymphocytes). As a result, myosin light chain kinase phosphorylation occurs, followed by bronchodilation (see Scheme 5.4), as well as suppression of the release of inflammatory mediators.

In addition, drugs of this group are capable of non-selectively blocking all subtypes of adenosine receptors. Adenosine, being an endogenous purine nucleotide, is considered as a natural ligand that specifically interacts with adenosine receptors (A1, A2A, A2B, A3). Activation of type 1 adenosine receptors in the bronchi leads to an increase in bronchial tone, while bronchodilator action is realized through type 2 receptors (see Scheme 5.4). In AD, there is a change in the density of adenosine receptors in the bronchi with a predominance of A1 receptors and a significant decrease in the number of A2 adenosine receptors. Thus, the bronchodilator effect of xanthines is due to blockade of A1-adenosine receptors and inhibition of PDE.

At the same time, when xanthines are treated for more than 3 weeks in the bronchi, the density and activity of A2-adenosine receptors increases.

Blockade of adenosine receptors (especially types A2B and A3) on the surface of mast cells leads to a decrease in the release of inflammatory mediators. A certain role in the mechanism of action of xanthines can play their antagonism with TNF-α, which is of great importance in severe asthma. These components of the mechanism of action of theophylline, apparently, mediate its slight anti-inflammatory effect (in low doses).

Currently, it is believed that with the systematic use of theophylline, its ability to prevent the release of allergy mediators prevails over a direct bronchodilator effect.

TF is metabolized in the liver to caffeine and 3-methylxanthine, which also have pharmacological activity. The kinetics of this process is non-linear, which does not allow us to accurately predict the dependence of the drug metabolism on the administered dose.

The therapeutic effect of TF is manifested in a narrow dose range (from 10 to 20 μg / ml), the excess of which leads to the development of side effects. A stable serum concentration of TF is determined by the dose, interval of administration and clearance of the drug. Even in one patient, pharmacokinetics may vary depending on the severity of the condition, the duration of the

previous therapy with methylxanthines, etc., which requires pharmacokinetic monitoring based on serum TF concentration (
For the treatment of AD, sustained release TF preparations that slowly release theophylline from the dosage form can be used. In the latter, theophylline can be either in the form of microcapsules or layered on a carrier (soluble film). The initial dose of TF drugs of prolonged action is 16 mg / kg per day or 400 mg / day (a lower dose is preferred). The therapeutic concentration of TF in the blood in this case is maintained at a constant level up to 12-24 hours (depending on the generation of the drug), which allows them to be taken 1 time (II generation) or 2 times (I generation) per day. From the standpoint of chronopharmacology, the promoted forms of TF of the second generation should be taken in the evening (at 18-19 hours), since the metabolism of xanthines is significantly slowed at night.
When stopping asthma attacks, theophylline is not completely defined. It can be administered in the form of a 2.4% solution of aminophylline in 10 ml intravenously, slowly or drip. If it is not possible to administer aminophylline intravenously, it is administered intramuscularly (1 ml of a 24% solution). However, it should be borne in mind that the addition of short-acting theophylline to adequate doses of β2-AM short (fast) action may not give an additional bronchodilator effect, although it stimulates the act of breathing. In addition, it was shown that, according to the severity of the bronchodilator effect, intravenously administered aminophylline is inferior to both β2-AM short (fast) action, administered with a nebulizer, and magnesium sulfate (intravenously 2 g (or 25 mg / kg) for 20 min).
Side effects, as a rule, are manifested with a serum TF concentration of more than 20 μg / ml:
 - from the nervous system - insomnia (usually disappears after 5-6 days), headache, tremors, fainting. The most formidable complication is convulsions, in the event of which lethality can reach 40% or more;
 - from the gastrointestinal tract - nausea, vomiting, abdominal pain, diarrhea;
 - from the cardiovascular system - tachycardia, cardiac arrhythmias, hypotension;
 - from the urinary system - polyuria. The creation of selective PDE IV inhibitors, cilomilast (ariflo) and roflumilast, has become a new approach in pharmacotherapy of bronchial obstructive diseases. Their feature is the high selectivity for certain types of immunocompetent cells involved in the formation of inflammation in the respiratory tract and smooth muscles of the bronchi. In addition, the drugs contribute to the relaxation of the smooth muscles of the bronchi, suppress the excessive activation of nerve endings in the bronchopulmonary tissue, reducing the effects of bronchospasm.
The use of drugs that change the state of the bronchial tree has a multi-functional purpose, due to their impact on the pathophysiological mechanisms of vascular tone disorders, edematous syndrome, heart rhythm and conduction disturbance syndromes, etc. The use of these drugs in case of combined pathology with syndromic disorders.

The purpose of the lesson. To master the classification of antimicrobial bronchodilators, the characteristics of the main groups, pharmacokinetics, pharmacodynamics of the main representatives, undesirable effects, drug interchangeability, pharmacosafety, their use. To learn the basic principles of the use of bronchodilators.
Test questions.
I. Classification of bronchodilators by the mechanism of action.
 Adrenergic stimulants.
 α- and β-adrenorenostimulants - epinephrine (adrenaline), efetonin (ephedrine),
 β1- and β2-adrenorenostimulants (non-selective) - isoprenaline, orciprenaline (alupent, astmopent), isadrine (euspiran, novodrin),
 short-acting β-adrenorenostimulants (selective) - terbutamine (brikanil), salbutamol (ventolin, salamol), fenoterol (berotek),
Длительного β2-adrenorenostimulants (selective), long-acting - maple-buterol, formoterol (foradil), salmeterol (Serevent).

 M-anticholinergics: Quaternary derivatives of atropine - bronchodilators: ipratropium bromide (atrovent, traventol), tiotropium bromide (spiriva).
 Phosphodiesterase inhibitors (methylxanthines) - theophylline, aminophylline (aminofillin, aminophylline, theopec).
II. The mechanism of action and the main pharmacological effects of adrenoreceptor stimulants.
 According to the effectiveness of the bronchodilating effect, β-adrenorenostimulants are arranged in the following order: formoterol> salmoterol> isoprenaline> salbutamol.
 By the ability to block the transport of proteins through endothelial cells and thereby prevent the development of pulmonary edema, β-adrenorenostimulants can be positioned: salmoterol> formoterol> salbutamol> short-acting β-adrenorenostimulants.
 Selectivity of the action of β-adrenorenostimulants (comparison).
 Pharmacokinet of β-adrenorenostimulants (absorption, protein binding, bioavailability, rate and nature of metabolism), microkinetics of β-adrenorenostimulants.
 Indications for use. Dosage regimen of β-adrenorenostimulants.
 Side effects and contraindications of β-adrenorenostimulants.
 Drug interaction, drug selection.
III. The mechanism of action and the main pharmacological effects of m-anticholinergics.
 Basic pharmacodynamic effects and pharmacokinetics.
 Indications for use and dosage regimen of m-anticholinergics.
 Side effects and contraindications of m-anticholinergics.
IV. The mechanism of action and the main pharmacological effects of phosphodiesterase inhibitors (methylxanthines). The main pharmacodynamic effects and pharmacokinetics. Indications for use and dosage regimen. Side effects and contraindications.
V. Algorithm for choosing bronchodilators.
VI. Combined preparations containing bronchodilators Indications for use. Side effects and contraindications.
VII. Monitoring the effectiveness and safety of bronchodilators.
1. The main pathogenetic mechanisms of SBO, which are the object of drug exposure, causing the development and course of bronchial obstruction syndrome.

2. Diseases and clinical syndromes, the development of which is accompanied by a violation of bronchial obstruction.

3. Diagnostic criteria, clinical classification and treatment depending on the severity of asthma and COPD in the light of the instructions for the diagnosis, clinical classification and treatment of asthma and COPD of March 19, 07 No. 128.

A. Criteria for the diagnosis and treatment of intermittent AD:
 short-acting β2-agonists are inhaled.
b. Criteria for the diagnosis and treatment of mild persistent AD:
 anti-inflammatory drugs - inhaled short-acting glucocorticosteroids (beclomethasone - 200-300 mcg, fluticasone - 100-250 mcg);
 β2-agonists of prolonged action (salmeterol - 25 μg);
 combined drugs - (Seretide 25/50 1-2 r per day);
 xanthines (theophylline);
 crowns (intal);
 leukotriene modifiers (montelukast, zafirlukast).
at. Criteria for the diagnosis and treatment of moderate severity of persistent AD:
 anti-inflammatory drugs - short-acting inhaled glucocorticosteroids (beclomethasone - 400-1000 mcg, fluticasone - 250-500 mcg);
 β2-agonists of prolonged action (salmeterol - 50-100 mcg);
 combined drugs - (Seretide 25/125 1-2 r per day);
 xanthines (theophylline);
 leukotriene modifiers.
The criteria for the diagnosis and treatment of severe persistent AD:

 anti-inflammatory drugs - short-acting inhaled glucocorticosteroids (beclomethasone - 1000-2000 mcg, fluticasone - 500-1000 mcg), glucocorticoids orally;
 β2-agonists of prolonged action (salmeterol - 50-100 mcg);
 combined drugs - (Seretide 25/250 1-2 r per day);
 xanthines (theophylline);
 leukotriene modifiers.

Basic principles of pharmacological treatment of COPD.

but. The principles underlying the classification of drugs affecting bronchial patency.

b. Individual treatment regimen of a patient with COPD, depending on the severity of symptoms, the degree of impairment of the internal respiratory function, the frequency and severity of exacerbations, the presence of complications, the presence and severity of concomitant pathology: (bronchodilators, glucorticosteroids).

at. Treatment of AD depending on the severity of an exacerbation of AD (mild, moderate, severe, threatened respiratory arrest).

The role of glucocorticoids in the treatment of patients with SBO, the rules for their appointment and cancellation, taking into account the pharmacodynamic and pharmacokinetic features.

The list of practical works:

Homework.

1. To study - pharmacokinetics, pharmacodynamics, indications, contraindications for use, undesirable effects of the medicines listed in the previous section.
2. The student must be able to:

a) select the necessary drug for a particular patient, select the dose, regimen and route of administration of the drug;

b) identify criteria for evaluating the therapeutic efficacy and safety of the drugs used;

c) provide differential medical assistance for: BA and COPD.

3. Know the drugs used in the syndrome of bronchial obstruction, principles and features of use, undesirable effects.

Control of the intermediate level of knowledge.

The solution of situational tasks:

1. A patient, 23 years old, was admitted to the department with a diagnosis of right-side lower-non-lobar bronchopneumonia. From the anamnesis it is known that a patient from 8 years old suffers from infectious-allergic bronchial asthma. Attacks are provoked by book and house dust. To stop attacks, he uses theophedrine, which takes 10 tablets. in a day. Against the background of the clinic of the underlying disease, the patient has signs of severe syndrome of bronchial obstruction and an overdose of theofedrine.

Offer a treatment plan for the underlying and concomitant diseases indicating specific drugs, their doses, route of administration.

2. A patient, 53 years old, has been suffering from bronchial asthma of infection-allergic genesis, chronic bronchitis for 10 years. Celebrates annual exacerbations in the autumn-winter period. She was admitted to the department in a state of asthmatic status. Objectively: breathing is frequent (40 in 1 min.), Noisy, wheezing. Above the lungs, multiple dry, wheezing and buzzing rales are heard. Percussion - boxed sound. Rhythmic cardiac activity, heart rate and emergency - 110 in 1 min., AKD - 140/80 mm Hg, heart sounds are muffled. The mucous membranes are cyanotic, the tibia of the paste.

Offer a specific treatment plan for this patient, indicating the drugs, their doses, route and route of administration.

3. A 45-year-old patient has persistent recurrent syndrome of bronchial obstruction with reduced sensitivity to cholinergic and adrenotropic drugs. Bronchial asthma suffers for more than 10 years. What can be prescribed to reduce the frequency and severity of asthma attacks?

4. The patient is 48 years old with bronchial asthma. In connection with asthma attacks, uses isadrine inhalation. The drug caused a patient's heartbeat.

Note the stimulation of which receptors caused tachycardia and palpitations in the patient, list the undesirable effects, what are the tactics for further patient management?
5. A 62-year-old patient suffers from non-atopic bronchial asthma, which is accompanied by severe bronchorrhea. After the appointment of atropine for therapeutic purposes, the patient initially showed improvement - bronchorrhea decreased sharply. However, after 10 days the condition worsened again: there was a fever (up to 38 ° C), shortness of breath, cough with sputum difficult to separate, heart rate - 90 strokes in 1 min.
What are the causes of such changes in the patient's condition. List all the undesirable effects of the drug that caused this condition? Prevention of complications, first aid.
6.56-year-old patient is hospitalized in the therapeutic department with an exacerbation of the course of bronchial asthma. Combination therapy includes intravenous jet administration of 10 ml of 2.4% aminophylline at 10 a.m. What are the safety criteria for aminophylline therapy.
7. Two patients with AD were prescribed the same dose of prednisone for oral use according to the following schemes: one - the entire dose in the morning; another - in three doses (morning, afternoon and evening).
Your opinion in terms of chronopharmacology regarding these appointments. Justify the answer.

TESTS

1. A 68-year-old patient with persistent bronchial asthma regularly uses astmopent (inhalation). The drug causes tachycardia, palpitations in a patient. What is the mechanism of this side effect?
   A. * Excitation of beta1-adrenergic receptors.
   B. Excitation of beta2-adrenergic receptors.
   C. Excitation of alpha2-adrenergic receptors.
   D. Excitation of alpha1-adrenergic receptors.
   E. Excitation of M-cholinergic receptors.
2. Indicate a short-acting selective beta2 agonist for relief of suffocation gag:
   A. Salmeterol.
   B. Clenbuterol.
   C. * Fenoterol.
   D. Thiotropium bromide.
   E. Atrovent.
3. What is a long-acting selective beta2-agonist for continuous therapy of bronchial asthma:
   A. Salbutamol.
   B. Ipratropium bromide.
   C. Fluticasone.
   D. beclomethasone.
   E. * Salmeterol.
4. A 46-year-old patient with bronchial asthma, persistent course, 3 degrees. Additional studies have revealed a decreased sensitivity of the adrenergic and cholinergic receptors of the bronchi to drugs. What drugs are the drugs of choice for treating a patient?
   A. Salbutamol inhalation.
   B. * beclomethasone inhalation.
   C. Berodual inhalation.
   D. Spiriva inhalation.
   E. Formoterol inhaled.
5. A 62-year-old patient with combined pathology: coronary artery disease, angina pectoris, W f.c., chronic obstructive pulmonary disease, sought help with the aim of correcting pharmacotherapy. As a result of the measures taken, the patient had an asthma attack, expiratory dyspnea. What drug could cause these complications?
   A. Salbutamol.
   B. Ambroxol.
   C. Nifedipine Retard.

D. * Propranolol.
E. Eufilong.

6. In the intensive care unit, a patient with asthmatic status is treated. The drug of first choice is:
A. Lazolvan intravenously.
B. * Hydrocortisone intravenously.
C. Sodium bicarbonate intravenously.
D. Eufillin intravenously.
E. Beclomethasone inhalation.

7. For the treatment of bronchial obstructive syndrome, a patient with bronchial asthma is prescribed a drug that reduces the activity of phosphodiesterase. Specify a drug that meets these conditions:
A. Izadrin.
B. * Eufillin.
C. Salbutamol.
D. Spiriva.
E. Salmeterol.

8. As a bronchodilator, a 49-year-old patient with bronchial asthma prescribed berotek. The mechanism of action of the drug is associated with an increase in the enzymatic activity of the receptor apparatus. Indicate the name of the enzyme:
A. Phospholipase A2.
B. Phosphodiesterase.
C. * Adenylate cyclase.
D. Cyclic oxygenase 1.
E. Cyclic oxygenase 2.

9. For the treatment of persistent bronchial asthma P degree of severity, glucocorticosteroids are prescribed. What route of administration of these funds is used in this case?
A. Transdermal.
B. Rectal.
C. Intravenous.
D. Oral.
E. * Inhalation.

10. For long-term therapy of bronchial asthma, the patient is recommended oral administration of aminophylline. What safety criteria for the drug will you control in the first place?
A. palpitations, tachycardia.
B. Mental agitation.
C. Tremor of the hands.
D. * Anorexia, nausea, epigastric pain.
E. Insomnia.

11. A patient with bronchial asthma against the background of prolonged bronchodilator therapy developed oral candidiasis. Which of the following drugs can cause this side effect in the first place?
A. * Bekonase.
V. Berotek.
S. Theopec.
D. Berodual.
E. Salamol.

12. When performing physical work on a personal plot in a patient with bronchial asthma, shortness of breath intensified, breathing worsened, a cough and dry wheezing appeared. What group of drugs do you recommend for stopping such attacks?
A. Beta2-blockers.
B. Methylxanthines.
C. * Beta2-adrenoagonists.

D. Oral glucocorticoids.
E. Mast cell membrane stabilizers.

13. A 54-year-old patient with a severe attack of expiratory dyspnea, palpitations, arterial hypertension, dry cough, distance rales. Indicate emergency medicine:

A. * Salbutamol.
B. Strofantin.
S. Lazolvan.
D. Atrovent.
E. Furosemide.

14. A woman has asthma. Over the past month, rhythm disturbances (extrasystole), anginal pain, and increased blood pressure appeared. Which drug is contraindicated in the patient?

A. Sustak.
V. Rhythmilen.
S. Isoket.
D. * Reviewed.
E. Diltiazem.

15. A woman was brought to the admission department with complaints of prolonged asthma, the inefficiency of the previously used alupent, palpitations, and a sense of fear. A history of chronic bronchitis. Objectively: severe condition, forced sitting position, pale cyanosis, noisy breathing, scattered dry wheezing. What drugs are used in the first place?

A. Anticholinergics.
B. * Glucocorticoids.
C. Antihistamines.
D. Adrenomimetics.
E. Mast cell membrane stabilizers.

16. A young man, 23 years old, after taking 1 g of aspirin as an antipyretic for influenza, complained of a severe attack of suffocation with difficulty exhaling, which was stopped by the intravenous administration of aminophylline. A history of recurrent nasal polyposis. Specify the expected diagnosis:

A. Infectious-allergic bronchial asthma.
B. Asthma of physical stress.
C. Symptomatic bronchospasm.
D. * Aspirin asthma.
E. Atopic bronchial asthma.

17.A woman of 44 years old has been suffering from bronchial asthma for 18 years. Recently: asthma attacks up to 5 times a week, nightly symptoms up to 3 times a month, BH - 20 in 1 minute, heart rate - 76 in 1 minute, blood pressure - 130/80 mm Hg, vesicular breathing. For relief of attacks uses salbutamol. What do you designate for seizure prophylaxis?

A. Regular use of salbutamol.
B. Glucocorticoids orally.
S. * Int.
D. Glucocorticoids for injection.
E. Glucocorticoids inhaled.

18. A 48-year-old man has 18 years of bronchial asthma. Attacks of suffocation occur up to 3 times a week. It is used by intal, ventolin if necessary. If the patient has a night attack, what do you recommend?

A. Additionally use the intal.
B. * Corticosteroids inhaled.
C. Go to the atrovent.
D. Continue routine therapy.

E. Take prednisone inside.

19. A 50-year-old patient suffers from chronic obstructive pulmonary disease for 10 years. At the moment, complaints of coughing, shortness of breath on exertion, weakness, aching heart pain, dry wheezing, pulmonary artery pressure 50 mm Hg For treatment, the patient must be prescribed:

A. * Eufillin.
V. Atropin.
C. Prednisolone.
D. Bromhexine.
E. Cordiamine.

20. A 17-year-old patient was diagnosed with persistent bronchial asthma. Your recommendations for the prevention of asthma attacks:

A. Use of aminophylline.
B. Use of atrovent.
C. Use of salbutamol.
D. * Use of nedocromil sodium.
E. Use of diphenhydramine.

Recommended literature:

Basic:

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

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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 ANTIBACTERIAL DRUGS IN PHARMACOTHERAPY OF RESPIRATORY SYSTEM DISEASES

Purpose of the topic.

The general level of respiratory diseases is gradually increasing throughout the world, including in Ukraine. More than half of visits to doctors are associated with respiratory diseases. In predisposed individuals, sequential and closely interconnected structural changes in the airways and lung tissue, rheology of the bronchial secretion, and local immunological defense of the bronchi occur. This naturally leads to inhibition of anti-infection protection, i.e. to create conditions favorable for the attachment of a respiratory infection, colonization of the pathogen and its adhesion on the surface of the respiratory tract. In the following, repeated episodes of respiratory infection in a significant number of patients act as the leading cause of respiratory diseases. Therefore, antibiotic therapy, along with the appointment of mucolytic, anti-histamine, antitussive drugs, is one of the key areas of the complex treatment of patients with diseases of the respiratory system.

In all countries of the world, including Ukraine, the number of patients with tuberculosis, and atypical forms, is steadily increasing. Today we can talk about the tuberculosis pandemic. Every year in the world 10 million people get tuberculosis, 3 million of them die, 8 thousand people die every day. According to WHO, 1/3 of the world's population contains tubercle bacillus in the body.

Motivational characteristic of the topic.

Etiotropic pharmacotherapy is the main direction in the treatment of patients with respiratory diseases. This is, first of all, antimicrobial therapy.

Objectives of antimicrobial therapy

1. Complete elimination of the pathogen and recovery of the patient.
2. Ensuring the abortive course of the disease with the delimitation of the territory of the inflammatory process and a rapid reduction in intoxication.
3. Prevention of a protracted course and complications of the disease.

Basic principles of antimicrobial therapy

1. It is necessary to know the etiological structure of modern pneumonia, ideally the list of pneumotropic pathogens that dominate in a given region or medical institution, the prevalence of drug-resistant strains of the most relevant pathogens.
2. Initial antibiotic therapy should be focused on the clinical and radiological features of the course of the disease and the specific epidemic situation.

3. Begin treatment as soon as possible, without waiting for the isolation and identification of the pathogen.

4. Antibacterial agents should be used in such doses and with such intervals that a therapeutic concentration of the drug is created and maintained in the blood and lung tissue; small dose tactics are a way to chronic the process.

5. It is necessary to monitor the effectiveness of treatment by clinical observation and, if possible, bacteriologically.

6. It is advisable to combine antibacterial therapy with pathogenetic treatment agents aimed at improving the drainage function of the bronchi.

7. At the stage of resolving the infectious process, the use of non-drug therapy aimed at strengthening the nonspecific resistance of the body is justified.

Clinical and pharmacological characteristics of drugs used in pulmonology

Classification of antimicrobial drugs

I. Means of advanced therapy

1. Betalactam antibiotics.
2. Amipoglycosides.
3. Macrolides.
4. Tetracyclines.
5. Fluoroquinolones.
6. Sulfanilamides.

Requirements for antibacterial drugs used in pulmonology

1. Rapid penetration into the tissues and fluids of the respiratory tract.
2. The predominant accumulation of the drug in the respiratory tract compared with its content in the blood serum.
3. Creation at the locus of infection of concentrations exceeding the minimum inhibitory for a given pathogen by tens and hundreds of times, and for intracellular pathogens (chlamydia, legionella, mycoplasma) - high concentrations inside the cell.
4. A long period of elimination from lung tissue, significantly exceeding the half-life in serum.
5. A wide therapeutic range of drug concentrations.

Betalactam antibiotics (UAVs)

1. Penicillins.

• Natural penicillins: Benzylpenicillin Na / K-salt, Phenoxymethylpenicillin.
• Semi-systemic penicillins:
- penicillin-stable: Methicillin, Oxacillin, Dicloxacillin, Nifcillin;
- aminopenicillins: Ampicillium, Amoxicillin,
- carboxypenicillins: Carbenicillin, Carfecillin, Ticarcillin;
- ureidopenicillins: Azlocillin, Meslocillin, Piperacillin;
- combinations of two penicillins: Ampicillin / oxacillin, Ampicillin-lin / klokssschillin
Amoxicillin / Cloxacillin.

2. Cephalosporins.

A. First-generation drugs:
- parenteral: cephalotin, cephaloridin, cefazolin,
- oral: cephalexin, cefradin, cefadroxil.

B. Second-generation drugs:
- parenteral; Cefoxitin, cefuroxime, cefamandol, cefotetan, cefmetazole;
- oral: cefaclor, cefuroxime.

B. Third generation drugs:
- parenteral: cefataxime, ceftriaxone, cefodizim, ceftizoxime, cefoperazone, cefpiramide, ceftazidime, moxalactam;
- oral: cefixime,

G. Drugs of the fourth generation:
- parenteral; Cefpir, cefipim.

Carbapenems: Imipinem, Meropenem.
Myobactam: Aztreonam.
3 protective beta-lactams: Ampicillin / sulbactam, Amoxicillin / clavunalate, Ticarcillin / clavulalate, piperacillin / tazobactam, Cefopera-zones / sulbactam.
UAVs are the basis of modern pneumonia chemotherapy. A common fragment in their chemical structure is the betalactam ring, with the presence of which the antimicrobial activity is associated. The target of UAVs in a microbial cell are trans- and carboxypeptidase enzymes, or "nonpicillin-binding proteins", which are involved in the synthesis of the main component of the cell wall - penti-doglican, both gram-positive and gram-negative microorganisms. The nature of the antimicrobial action of UAVs is usually bactericidal. Combining with penicillin-binding proteins and inactivating them, the antibiotic ensures the cessation of growth and death of the microbial cell. Penicillin-binding proteins of microorganisms are localized in the cytoplasmic membrane of the bacterial cell, and to connect with them, the drug must penetrate through the external structures of the bacterium. In gram-positive microorganisms, the capsule and peptidoglycan are not a significant obstacle to the diffusion of UAVs, while the lipopolysaccharide layer of gram-negative bacteria presents an almost insurmountable obstacle for them. The only way for UAVs to penetrate in this case is through the porin channels of the outer membrane of the microorganism. The size of molecules capable of penetrating the lipopolysaccharide layer is limited by the diameter of the channels.
This determines the natural resistance of gram-negative microorganisms to UAVs. The lack of clinical efficacy in infections caused by obligate and optional intracellular parasites (rickettsia, chlamydia, legionella, brunella, etc.) and mycoplasma is associated with the limited ability of UAVs to penetrate the cells of a macroorganism, primarily phagocytes, where the pathogen is localized.
The selectivity of the action of various UAVs on individual microorganisms is not the same.
Natural penicillins, a number of semisynthetic penicillins (methicillin, oxacillin) and 1st generation cephalosporin are predominantly active against gram-positive flora. 2nd generation cephalosporins are active mainly against gram-negative flora. Ticarcillin and azlocillin are active against Pseudomonas aeruginosa. Finally, ampicillin, amoxicillin, cephalosporins of the latest generations and monobactams are characterized by the widest spectrum of action. The diversity and heterogeneity of UAVs are also due to the fairly rapid growth rates of the acquired resistance of microorganisms to them.
The most famous mechanisms for the formation of resistance to these antibiotics are mutations in genes encoding proteins of porin channels, as well as inactivation of the drug molecule as a result of hydrolysis of the beta-lactam ring by specific microbial enzymes beta-lactamases. The fundamentally important properties of the latter include the ability to predominantly hydrolyze certain UAVs, for example, penicillins or cephalosporins, or both. The wide distribution of beta-lactamases among various microorganisms is due to interspecific gene transfer.
A number of UAVs (methicillin, oxacillin, cephalosiorins 3-4 generations, carbapenems), due to the peculiarities of the chemical structure, are able to overcome the resistance of most microorganisms. There are also protected UAVs - dosage forms that combine antibiotics and beta-lactamase inhibitors (clavulapic acid, sulbactam, tazobactam). They have the ability to protect antibiotics from hydrolysis.
UAVs are eliminated primarily through the kidneys and liver.
Adverse reactions and complications associated with the use of UAVs are manifested by allergic reactions such as urticaria, Quincke's edema and anaphylaxis, dyspeptic disorders, less commonly hemolytic anemia, interstitial nephritis, and coagulopathy.
Benzylpenicillin
The first natural antibiotic continues to be one of the most important antibacterial drugs. Its advantages include a powerful bactericidal effect against a number of clinically significant microorganisms (streptococci, meningococci, etc.), a post-antibiotic effect against gram-positive cocci, low toxicity and low cost. The disadvantages are high allergenicity, cross with all

penipillins, and secondary resistance of staphylococci. It is used in oil and iv in 3-6 million units / day for 6 injections. In severe pneumonia - 20-60 million units / day or more.

Phenoxymethylpenicillin

Compared to penicillin, it is more acid resistant. Absorbed in the gastrointestinal tract when taken on an empty stomach by 35-40%. High concentrations of the drug in the blood are not created (ingestion of 0.5 g is equivalent to the administration of 300 thousand units of penicillin / m), therefore, it can not be used to treat severe infections. The half-life is 1 hour.

It is applied orally 1 hour before meals, 0.5-1.25 g / day for 4-6 doses before meals.

Methicillin

The first antistaphylococcal penicillin. Its main significance is that it is resistant to the action of peninylinase, which is produced by more than 90% of S. aureus strains and a number of S. epidermidis strains that are resistant to natural penicillins, amino, carboxy, and ureidopenicillins. It is used in oil but 1.0-4.0 g / day for 4 injections.

The drug has no advantages over newer analogues (nafcillin, oxacillin, cloc-sacillia, dicloxacillin, fluloxacillin), it has nephro-toxicity.

Oxacillin (Prostaflin)

The main antistaphylococcal penicillin, unlike methicillin, is acid-stable, therefore it is used not only parenterally at 2-6 g / day for 4-6 injections, but also orally at 2-3 g / day for 4-6 doses 1 hour before food.

Dicloxacillin

Compared to oxacillin, it is more resistant to penicillinase. It is administered orally but 2 g / day for 4 doses 1 hour before meals and parenterally for 1-2 g / day for 4 doses.

Ampicillin (pentrixil, roscillin, campicillin, ampicide)

Along with amoxipillin, it belongs to the extended-spectrum group of penicillins, retains activity (at the level of penicillin) against gram-positive cocci, acts on some aerobic gram-negative bacteria (Escherichia coli, Salmonella, Shigella, hemophilic bacillus). The drug is destroyed by staphylococcus beta-lactamases. It is administered orally for 2-4 1 / day for 4 doses and parenterally but 1-3 g / day for 4-6 administration, with severe pneumonia up to 10 g / day or more.

Amoxicillin (gonoform, amoxil, amoxy, hiconcil)

According to the antimicrobial spectrum, it is close to ampicillin, more active against pneumococci, has improved pharmacokinetic properties, requires a lower frequency of administration. is a leading oral penicillin with an extended spectrum of action.

It is applied orally at 0.75-2.25 g / day for 3 doses.

Carbenicillin (Geopen)

Less active than ampicillin against gram-positive cocci. Its main advantage is anti-pseudomonas activity. In addition, the drug acts on some ampicillin-resistant gram-negative bacteria (enterobacter, proteus, morganella, and providence). It is used parenterally at 4-8 g / cit for 4-6 injections, and in severe pneumonia up to 20-30 g / day. Undesirable drug reactions - hypernatremia, hypokalemia, thrombocytopenia.

Azlozzillin (securopen)

It refers to ureidopenicillins. In relation to P. aeruqinosa is more active than carbenicillin, but less toxic. It is used parenterally at 4-8 g / day for 4-6 injections, with severe pneumonia up to 20-30 g / day.

Meslocillin (bipen)

It is applied parenterally at 0.8-0.15 g / kg / day for 3 administrations, with severe pneumonia up to 0.2-0.3 g / kg / day.

Piperacillin (pipril, piprcil, piprax, isipen)

In the group of anti-pseudomonas penicillins is the strongest. It is applied parenterally at 4-8 g / day for 4-6 injections, with severe pneumonia up to 20-24 g / day.

Ampicillin / Oxycillin

The combination of ampicillin and oxacillin in a ratio of 1: 1 (for oral administration) and 2: 1

(for parenteral administration). It combines an extended antimicrobial spectrum of action of ampicillin and antistaphylococcal activity of oxacillin, but there is no synergy between the components. The drug should not be used to treat hospital infections, since most hospital strains of Gram-negative flora are resistant to it, and the antistaphylococcal activity of the drug is low due to the low oxacillin content. It is used for moderate infections of the respiratory tract inside but 0.5-1 g 4 times a day 1 hour before meals; parenterally but 2-8 g / day for 4 injections.

Cephalosporins, unlike penicillins, are resistant to beta-lactamases.

In clinical practice, about 60 cephalosporins are used, conditionally divided into four generations. Each subsequent one differs from the previous one with a wider spectrum of antibacterial activity and greater resistance to beta-lactamases.

The first generation includes drugs that are highly active against gram-positive cocci, including S.aureus, coagulase-negative staphylococci, beta-hemolytic streptococcus, pneumococcus and green streptococcus, they are usually resistant to staphylococcal beta-lactamase, but hydrolyzed by bacteria .

Second-generation drugs are highly active against enterobacteriacerebacteria (Escherichia coli, Proteus, Klebsiella, Enterobacter) and act on H. influenzae and several other bacteria.

The third generation includes antibiotics with the highest activity against Pseudomonas aeruginosa and Acinetobacter, some of which are resistant to gram-negative bacteria beta-lactamases.

The fourth generation of cephalosporins is also active against bacteroids and other anaerobes, has a very pronounced resistance to beta-lactamases.

The main indications for the use of cephalosporins are upper respiratory tract infections. Parenteral forms are usually used for severe and moderate pneumonia, and oral forms for outpatient lung infections of moderate severity. A promising direction for the use of oral cephalosporins is their use in the therapy of “switching” the administration of oral drugs after 3-4 days of treatment with parenteral antibiotics when a clinical effect appears.

Cephalotin (Keflin)

It is applied parenterally at 2-6 g / day for 4 injections. The level of antibiotic in pleural exudate is 50-100% of the level of its concentration in the blood. It is metabolized in the liver with the formation of inactive metabolites, up to 65% of the drug is excreted by the kidneys in a biologically active form, and has nephrotoxicity.

Cefazolin (lysolin, cesolin, cefamezin, kefzol, reflin)

Less active than cephalotin, but is the least nephrotoxic of group 1 cephalosporins. It is applied parenterally but 2-6 g / day for 2-3 injections.

Cephalexin (Kefexin, Keflex, Chorex, Sporidex)

Quickly absorbed by ingestion, oral absorption leaves 90%, but hu, than other oral cephalosporins, penetrates the hematobronchoalveolar barrier.

About 70% of the drug is excreted at night for 12 hours. It is used for 1-2 g / day (up to 4.0 g / cit for 3-4 doses.

Cefadroxil (cefradur)

Quickly absorbed after oral administration, bioavailability - 95%, mainly excreted by the kidneys. It is applied at 1.5-2 g / day (up to 4 g / cyt for 2-3 doses.

Cefuroxime (zinacef, zinnat) Resistant to beta-lactamases of gram-negative bacteria, active against gram-positive and gram-negative microorganisms. Effective against Staphylococcus aureus resistant to penicillin. The drug is not utilized in the body and is almost completely excreted by the kidneys unchanged.

It is applied parenterally at 1.5-4 g / day for 3-4 injections.

Cefimandol (mandol)

It has a pronounced resistance to beta-lactamases, excreted in the urine.

The highest concentration in the blood is achieved after 30-120 minutes after the / m and 10 minutes after the / in the introduction. It is applied parenterally at 1.5-6 g / day for 3-4 injections.

Cefaclor (alpha acetate, ceclor)

It is well absorbed when taken orally, eating reduces the absorption of the drug. Excreted in urine, basically, unchanged. It is used but 0.75-2.0 g / day (up to 4 g / day) for 3-4 doses.

Cefotaxime (claforan, oritaxim)

It has a wide range of antimicrobial effects. It is most active in relation to streptococci, surpasses ampicillin and its analogues in efficiency. It is excreted by the kidneys, without nephrotoxicity. It is used parenterally at 2-4 g / day for 2-3 injections, with severe pneumonia - up to 12.0 g / day.

Cefotriaxone (Lendacin, Rocefin, Longacef)

Highly active against streptococci, effective against 90% of strains of enterobacteria and most other gram-negative bacteria. Up to 10% of the drug is excreted in the bile and up to 67% in the urine. 27 h after the i / m administration of 1 g of the drug, its concentration in the lungs exceeds many times the minimum inhibitory (MPC) for respiratory pathogens. It is applied 2-4 g / day after 12-24 hours.

Cefodizim (modivid)

It is comparable in antibacterial activity with cefotaxime, but it has a higher activity against enterobacteria and Klebsiella. In an open multicenter study, the clinical effect of cefosidime in bronchopulmonary infection occurred in 88% of cases, with pneumococcal pneumonia - 94%, and in infections caused by hemophilic bacillus 95.5%. The drug is used for 1 g / m or / in twice a day.

Ceftizoxime (epocesin)

It is highly effective for pneumonia caused by Klebsiella, and the concentration of antibiotic in sputum is 40 times higher than the MPC for this pathogen. It is applied parenterally at 0.5-2 g / day for 2-4 injections, with severe pneumonia - up to 4.0 g / day.

Moxalactam

It is applied parenterally but 1–9 g / day for 2–4 administrations, with severe pneumonia up to 12 g / day.

Cefixime (cefspan)

Third generation cephalosporin for oral use. Bioavailability is 40-50%, the maximum absorption is observed 0.8 hours after administration. A high level of concentration in the blood lasts for 5 hours. About 10% of the drug is excreted unchanged in the bile, up to 50% in the urine. It is applied orally at 0.1-0.2 g / day (up to 0.4 g) in 2 doses.

Cefpir

It has a pronounced activity against gram-negative bacteria, including Pseudomonas aeruginosa and enterobacter, as well as against staphylococci and enterococci. The drug quickly penetrates into the bacterial cell and firmly binds to the penncillin-binding protein, has a high affinity for beta-lactamases. In the presence of a mixed aerobic and anaerobic infection, it is advisable to combine cefpir with metronidazole or tazobactam. The drug is not metabolized and is mainly excreted by the kidneys. Apply 1-2 g twice a day in / in or in / m for severe intrahospital infections in patients with neutropenia, sepsis and bacteremia.

Imipepem-cilostatin (thiepam, primaxin)

The combination (1: 1) of a thienamycin antibiotic (carbanenem _____) and a renal dehydropeptidase inhibitor, sodium cilastatna, for intravenous and intravenous administration. It has a pronounced resistance to the action of beta-lactamases (peninylinases and cephalosiornases) produced by gram-negative and gram-positive bacteria. The drug is indicated for severe infections caused by multiple-resistant and intrahospital bacterial strains. Its concentration in plasma, lung tissue, sputum, pleural fluid, even after a single injection, exceeds the BMD for the main causative agents of bronchopulmonary infection. Imipenem is a drug of the 2nd reserve with the ineffectiveness of other antibiotics.

It is applied parenterally at 1-4 g / day for 4 injections.

Side effects: thrombophlebitis, agranulocytosis and pancytopenia, dyspeptic disorders.

Aztreonam (azactam)

Refers to monobactam antibiotics, stable to the action of beta-lactamases. The drug acts mainly on gram-negative aerobes, multiresistant (to the main penicillins, cephalos-porins and

aminoglycosides) strains of Escherichia coli, Proteus, Klebsiella, enterobacter, siphegnous bacillus are highly sensitive to it. The elimination pathway is predominantly renal. In renal failure and in the elderly, a dose or regimen adjustment is necessary. It is applied parenterally at 1.5-6 g / day for 2-3 administrations, with severe pneumonia up to 8 g / day.
Side effects are similar to those of imipenem and do not exceed 1.5%.
The destruction of the beta-lactam ring, the most important structural element of UAVs providing their bactericidal effect, is one of the leading protective mechanisms for such clinically important pathogens as S.aureus, H.influcnzae, M. catarrhalis, S. pneumoniae, B .fragilis and several others.
Combined preparations containing a beta-lactam antibiotic and one of the beta-lactamase inhibitors (clavulanic acid, sulbactam and tazobactam) prevent the enzymatic degradation of the beta-lactam ring of the antibiotic by specific bacterial enzymes.
Amoxicillin / clavulanate (co-amoxiclav, augmentin, clavocin)
It acts on all microorganisms sensitive to amoxicillin. It has a higher antistaphylococcal activity, surpasses amoxicillin in action on enterococcus. It is active against gram-negative flora producing beta-lactamases (Proteus, Klebsiella, Escherichia coli, Moraxella cataris, Haemophilus influenzae), has a high antianerobic activity. The drug does not act on gram-negative bacteria resistant to aminopenicillins: Pseudomonas aeruginosa, Enterobacter, nitrobacter, serration, Providence, Morganella. It is applied orally at 0.75-2.25 g / day for 3 doses. iv 3.6 g / day for 3 administrations (up to 4, S g / day for 4 administrations).
Ampicillin // sulbactam (unazin, sultamycillin)
It has almost the same spectrum of activity as in the combination of clavulanic acid, but it inhibits microbial beta-lactamases to a somewhat weaker degree. In parenteral form it is used: for mild infections - 1.5 3 g / day, for moderate infections - up to 6 g / day, for severe infections - up to 12 g / day for 3-4 injections / m or iv for 10-15 minutes, inside - 0.375-0.75 g 2 times a day.
Aminoglycosides
• First-generation drugs: Streptomycin, Neomycin, Kanamycin.
• Second-generation drugs: Gentamicin, Tobramiin, Sisomycin, Neomycin.
• Third-generation drugs: Amikacin, Isepamycin
The group includes antibiotics, the common chemical structure of which is the presence of amino sugars connected by a glycosidic bond. They have a powerful bactericidal effect, and it develops more rapidly than UAVs. The advantages of the group include the absence of an “ipoculum” effect, the slow development of microflora resistance (excluding streptomycin), the dependence of action on blood concentration, synergism with UAVs (a different mechanism of bactericidal action), rare cases of allergies and idiosyncrasy, the possibility of use in patients with an allergy to UAVs.
The main clinical significance of aminoglncosides is their high activity against aerobic gram-negative bacteria, they act moderately on gram-positive cocci, and are completely inactive against anaerobic flora. The resistance of microorganisms to these antibiotics is due to the ability to produce specific inactivating enzymes - aminoglycoside-acetyltransferase, etc. Microorganisms that are resistant to first-generation drugs are sensitive to gentaminin, third-generation agents are active against microorganisms that are resistant to gentamicin.
The disadvantages of the drugs are a relatively narrow antimicrobial spectrum, poor penetration into sputum, decreased activity during hypoxia and acidosis, rather high oto- and nephrotoxicity, and in rare cases neuromuscular blockade up to respiratory paralysis. Hearing impairment is usually irreversible, while kidney function is gradually restored.
Aminoglycosides are not metabolized in the liver and excreted by the kidneys unchanged. Given the dependence of their action on the concentration in the blood, as well as high toxicity, a number of important points should be taken into account when choosing the dose of the drug.
The daily dose of aminoglycosides for parenteral administration to adults and / children over 1 month. depends on body weight: for drugs of the first generation (except for non-omicin and

amikacin) - 15 mg / kg, for drugs of the second generation - 3-5 mg / kg, for netilm-ntsnna - 4-6.6 mg / kg. This dose can be administered by dividing into 2-3 injections (after 8-12 hours), or once, as a rule, in / in a drip. The advantages of the second option are a high peak concentration of the drug, less toxicity, and convenience for the patient;
- Since amioglycosides are not distributed into adipose tissue, the dose in patients with obesity (if the ideal body weight is exceeded by more than 25%) should be reduced. The most rationally calculated dose for actual body weight should be reduced by 25%. Her very thin patients. on the contrary, it should be increased by 25%;
- In severe pneumonia, the maximum doses of aminoglycosides are prescribed;
- The determination of serum creatinine must be carried out every 2-3 days - an increase of more than 25%) from the initial level indicates a possible onset of the nephrotoxic effect of aminoglycosides, and more than 50% - serves as an indication for its abolition.
- The maximum duration of the course of treatment is 7-10 days, in rare cases - up to 14 days.

Kanamycin

It yields to aminoglycosides of the II and III generation in activity against pneumococcus, enterococcus and hospital strains of gram-negative flora, does not act on Pseudomonas aeruginosa. It is applied orally at 0.25 0.6 g / day for 2-3 doses and i / m for 1-1.5 g / day for 23 injections.

Gentamicin (Garamycin, Genzin)

More active than kanamice, acts on Pseudomonas aeruginosa. Most active among aminoglycosides against enterococcus. It is applied parenterally but 0.0008 - 0.0032 g / kg / day for 2-3 injections.

Tobramycin (brullomycin, nebcin)

Less active against serrania and enterococcus, less nephrotoxic. It is applied parenterally at 0.002-0.003 g / kg / day (up to 0.005 g / kg / day) for 2 3 injections.

Sizomycin

According to antimicrobial activity, it practically does not differ from gentamicin, but is less nephrotoxic. It is applied parenterally at 0.002-0.004 g / kg / day for 2-4 injections.

Netilmicin (guardocine)

It is able to act on certain microflora strains that are resistant to drugs of the II and III generations (more resistant to the action of microbial enzymes that destroy aminoglycosides). It is applied parenterally at 0.0045-0.007 g / kg / day for 2-3 injections.

Amikacin (amikin, amicositis)

The group’s most powerful drug, strains resistant to it, are completely resistant to aminoglycosides. It is applied parenterally at 0.01 to 0.015 g / kg / day for 2-3 injections.

Macrolides (ML)

Fourteen-membered macrolides: erythromycin, oleandomycin, clarithromycin. Fifteen-membered macrolides: Azithromycin.

Sixteen-membered macrolides: Cnupamycin, Josamycin, Rovamycin.

The basis of the chemical structure of antibiotics of this group is the macrocyclic lactone ring. Depending on the number of carbon atoms in the lactone ring, they are divided into 14, 15 and 16 membered, respectively. The mechanism of action of ML is associated with inhibition of protein synthesis in cells of sensitive microorganisms due to binding to the catalytic peptidyl transferase center of the ribosomal 50S subunit. Their peculiarity is the ability to accumulate in tissues, including macrophages, monocytes, polymorphonuclear cells. The high activity of ML in respiratory infections is due to their active diffusion into the bronchial mucosa and bronchial secretion.

The concentration of the antibiotic inside the cell is 17-25 times higher than in extracellular fluid. For most bronchopulmonary pathogens, with the exception of H.inllueiizae, it is many times higher than their BMD. ML have the same antimicrobial spectrum of action as natural penicillins. However, unlike the latter, they are active against pathogens of SARS (Legionella and C. Tilamydia spp.), Bacteroids and enterobacteria. ML act on the microorganism at the stage

of reproduction.
The nature of the antimicrobial action is usually bacteriostatic. Bactericidal action is manifested, as a rule, against beta-hemolytic group A streptococcus, pneumococcus and intracellular located bronchopulmonary pathogens. Staphylococci and other gram-positive microorganisms resistant to penicillin, tetracycline and chloramphenicol remain sensitive to ML. Viruses, fungi, nocardia, and brucella are resistant to them.
ML resistance develops due to a violation of the ability of an antibiotic to bind to ribosomes, active elimination of the drug from the microbial cell, and its inactivation by cleavage of the lactone ring.
ML is metabolized in the liver with the formation of compounds with antibacterial properties. Metabolites are predominantly excreted with bile and further with feces. Renal excretion is 5-10%. In case of impaired renal function, the rate of excretion of ML (with the exception of clarithromycin and roxithromycip) does not change, therefore, dosage regimen adjustment is not required. With cirrhosis of the liver, the half-life of erythromycip and josamycin can significantly increase.
Adverse reactions: nausea, vomiting, diarrhea; with prolonged use - jaundice, reversible ototoxic reactions, manifested by impaired hearing and ringing in the ears. In general, ML is one of the safest groups of antibiotics; hypersensitivity to HIM is very rare.
Erythromycin
Used for pneumonia caused by Staphylococcus aureus. The greening streptococcus, enterococcus. mycoplasma. I / O is used at 0.4-1 g / day for 2-3 injections and inside but 1-2 g / day for 4-6 doses, after oral administration, its therapeutic concentration in the pleural fluid remains for three days.
Roxithromycin (Rulide)
It has a spectrum of antimicrobial activity similar to erythromycin, it is applied orally before meals at 0.3 g / day for 2 doses.
Azithromycin (sumamed)
Unlike other ML in therapeutic concentrations, it has bactericidal effect on S. pyogenes, H. Irifkienzae, M. catarrhalis. Beta-hemolytic streptococcus, pneumococcus are also sensitive to it, Staphylococcus aureus is moderately sensitive. The drug is highly active against chlamydia and mycoplasmas. It is completely absorbed from the gastrointestinal tract, metabolized in the liver, and excreted in the bile and, to a lesser extent, in the urine. It is applied inside on the first day of 0.5 g. From 2 but 5 days but 0.25 g.
Spiramycin (Rovamstscin)
It has an antibacterial spectrum, including gram-positive and negative-negative cocci, legionella, chlamydia, mycoplasma and a number of other microorganisms, and is not active against gram-negative bacteria. It has a long stantibiotic effect (suppression of bacterial growth that goes beyond the time of their interaction with the drug). It is used internally at 69 million ME for 2 3 doses.

Dlosamycin (vilnrafen)

The antibacterial spectrum is similar to spirampcin. It is applied orally before meals but 0.8-2.0 g / day for 3 doses.

Lincosamides (LS) Linkomycin, Clindamycin.

The group is similar in spectrum of action to ML (erythromycin, oleandomycin), although it differs from them in chemical structure. Their mechanism of action is associated with impaired synthesis of microbial wall proteins. The drugs are characterized by a narrow spectrum of activity and a predominantly bacteriostatic effect. They are most active against gram-positive microorganisms, anaerobes and staphylococci resistant to other antibiotics. The resistance of microorganisms to drugs develops slowly and, as a rule, is cross-linked. In the treatment of pneumonia, they are reserve drugs.
Adverse reactions of drugs include a decrease in blood pressure with rapid iv administration, dyspeptic disorders when taken orally, and in some cases, leuko- and thrombocytopenia.

Lincomycin (Lerolen, Linkocin)
It is administered orally at 1.5-2 g / day for 3-4 doses, parenterally at 0.6-1.8 g / day for 2-3 doses.
Clindamycin (menopause, dalacin C)
It is administered orally at 0.6-1.8 g / day for 34 doses, parenterally at 0.6-2.7 g / day for 24 administration, with severe infections up to 4.8 g / day.
Tetracyclines (TC)
Natural: Tetracycline, Oxetetracycline,
Semisynthetic: Metacyclin, Doxycycil, Monocycline.
These are antibiotics in which the molecule is based on a polyfunctional hydronaphthacene compound with the generic name “tetracyclines”. This group is characterized by an effect on intracellularly located microorganisms.
Their common properties are bacteriostatic action, a wide spectrum of activity, cross-resistance of microorganisms to all drugs of this class, and a high frequency of adverse reactions.
TCs are active against the entire gram-positive flora, gram-negative cocci, Escherichia coli, enterobacter, Klebsiella, mycoplasma, chlamydia. The strains of microorganisms producing beta-lactamases, Pseudomonas aeruginosa, most fungi, viruses and bacteroids are resistant to them. When TC is combined with bactericidal antibiotics, an additive effect is observed, in combination with ML synergism.
Adverse reactions and complications: dyspeptic disorders, dysbiosis and superinfection (including oral and other types of candidiasis), bone and dental tissue formation disorders, photodermatitis, hepatotoxicity, nephrotoxicity.
Tetracycline (tetrimig)
It is well absorbed in the gastrointestinal tract when taken on an empty stomach, significantly reduces the bioavailability of the drug. Side effects are more frequent than with the appointment of semi-synthetic tetracyclines. It is applied orally after a meal of 0.8-1 g / day for 3-4 doses.
Oxytetracycline
Oxytetracycline is worse than tetracycline, absorbed in the gastrointestinal tract.
It is used orally after a meal of 0.75-1 g / day for 3–4 doses; it is a component of the combined preparation Erycycline, which also includes erythromycin.
Metacycline (rondomycin)
It is applied orally after a meal of 0.3-0.6 g / day for 2-4 doses, with severe pneumonia - up to 0.015 g / kg / day.
Doxycycine (vibramycin, doxybeche)
The best antibiotic of the tetracycline group today is well absorbed in the gastrointestinal tract, and food has little effect on its bioavailability, it penetrates well into the bronchial secretion, and is better tolerated by other drugs in this group. It is applied orally but 0.1-0.2 g once a day after meals, in / in drops, but 0.2 g once a day.
Ftirkhipolona (FH)
Pefloxacin, Tsinofloksatsin. Ofloxacin, Lomefloxanin. Amifloc-Sacin, 'Groafloxacin. Moxifloxacin. Rufloxacin and others.
The group is represented by derivatives of 4-hydroxyquinolone, the antimicrobial mechanism of which is mainly associated with inhibition of the DNA gyrase enzyme, which controls the structure and function of the microorganism's DNA.
PFs have a wide spectrum of action. Their highest efficiency against gram-negative bacteria, in particular, multi-resistant enterobacteria. Ciprofloxacin and ofloxacin have the maximum activity for streptococci, including pneumococci. New PF (sparfloxacin, tro-wafloxacin, grefafloxacin, moxifloxation) are also active against anaerobes, chlamydia and mycoplasmas. The mechanisms of formation of resistance of microorganisms to these drugs are similar to those for other antimicrobial agents. Plasmid resistance to them is absent. In the treatment of pneumonia, PF are reserve drugs or alternative means of choice.
PF excreted mainly by the kidneys.

Adverse reactions in the form of dyspeptic disorders, leukopenia, agranulocytosis and photosensitivity are relatively rare.

Pefloxacin (abactal, peflacin)

It shows a very high activity against intracellular bacteria (chlamydia, legionella, mycoplasmas), enterobacteria, and gram-negative cocci. Staphilo and streptococci are less sensitive to it. The drug accumulates well in bronchial secretions (up to 70-120%). It is applied orally at 0.8-1.2 g / day for 2 doses and iv drip at 0.4-0.8 g / day.

Ciprofloxacin (ciprobay, ciplox, ciproxin, tsifran, ciprolet)

One of the most active drugs of the group, has a wide spectrum of action both against gram-positive cocci and gram-negative bacteria, highly active against Klebsiella, enterococci, hemophilic bacillus. It penetrates well into sputum (up to 100%) and pleural fluid (90-80%.). It is used orally at 0.25 1.0 g / day (up to 1.5 g / day) for 1-2 doses, iv in a drop of 0.2-0.4 g / day for 2 injections.

Ofloxacin (tarid)

By antimicrobial activity it is close to ciprofloxacin, more active against Staphylococcus aureus. It is applied orally at 0.4-0.8 g / day for 2 doses.

Sulfonamides

Cotrimoxazole

The group includes antibacterial drugs - structural analogues of para-aminobenzoic acid, which act as competitive inhibitors of dihydroperoate synthetase, which is necessary for folate biosynthesis in prokaryotes. By activity, they are significantly inferior to antibiotics. Of greatest clinical importance is cotrimoxazole - a tool with the best antibacterial properties.

Cotrimoxazole (centrin, bactrim, biseptol, oriprim)

The combined preparation consisting of sulfamethoxazole and trimethonrim (5: 1). The advantages of the combination are the synergism of the components and the bactericidal effect against many gram-positive cocci and gram-negative rods, as well as the relatively slow development of resistance. In the pathogen Pneumocystis carinii, resistance to cotrimoxazole does not occur at all. The use of the drug is limited by the risk of developing serious adverse reactions (Lyell toxic toxic epidermal necrolysis syndrome, anemia, neutropepia, thrombocytopenia).

In pulmonology, the use of cotrimoxazole is indicated for the treatment and prevention of pneumocystis pneumonia in patients with AIDS and other immunodeficiencies, and for the treatment of pulmonary infections caused by pathogens that are resistant to UAVs, PX, and aminoglycosides. The drug contains 400 mg of sulfamethoxazole and 80 mg of trimethoprim.

Elimination by it is carried out mainly through the kidneys. Dosage 1600 mg / day, divided into 2 doses or 5 ml iv twice a day

The purpose of the lesson.

To know the classification of antimicrobial drugs used in respiratory diseases, the characteristics of the main groups, pharmacokinetics, pharmacodynamics of the main representatives, undesirable effects, drug interchangeability, pharmacosafety, their use in various respiratory diseases. Learn the basic principles of tuberculosis pharmacotherapy, classification of anti-TB drugs, characteristics of the main groups, pharmacokinetics, pharmacodynamics of the main representatives, undesirable effects, drug interchangeability, pharmacosafety,

Test questions.

1. The role of infection in the development of respiratory diseases.

2. Acute respiratory diseases - determination, etiology, pathogenesis, use of antimicrobial drugs, characteristics of the main groups, pharmacokinetics, pharmacodynamics, main representatives, undesirable effects, choice of route of administration.

3. Acute bronchitis - definition, etiology, pathogenesis, choice of antimicrobial drugs depending on the form, severity of the course and stage of the disease.

 characteristics of the main groups of antimicrobial drugs, pharmacokinetics, pharmacodynamics, key representatives;

 undesirable effects of animikrobic drugs, the choice of route of administration.
4. Pneumonia. Definition, diagnostic criteria, clinical classification and treatment depending on the type of pneumonia in the light of the instructions for the diagnosis, clinical classification and treatment of pneumonia dated March 19, 2007 No. 128.
 Classification:
 community-acquired pneumonia,
 nosocomial pneumonia (hospital),
 suction
 pneumonia in people with severely impaired immunity (congenital immunodeficiency, HIV infection, iatrogenic immunosuppression).
 Risk classes (PORT, RSI).
 Class I-II - place of treatment: outpatient.
 Class III - place of treatment: outpatient or inpatient.
 Class IV-V - place of treatment: inpatient or in the AIT department.
 Risk groups (CRS).
 Group I - place of treatment: outpatient.
 Group II - place of treatment: hospital.
 Group III - place of treatment: in the AIT department.
 Criteria for the severity of pneumonia.
 Antibacterial therapy for patients with community-acquired pneumonia:
 community-acquired pneumonia of the risk group I (mild course, does not require state hospitalization, without concomitant pathology) - semisynthetic penicillins (amoxicillin - amoxil, hikontsil), generation II macrolides (azithromycin - azimed, clarithramycin - clerimed, mimedename , spiramycin), as an alternative - antibiotics with a wide spectrum of action - doxycycline, fluoroquinolones of the III-IV generation (levofloxacin III pok. - flocium, IV p. - gatifloxacin, moxifloxacin).
 community-acquired pneumonia of the risk group II (mild course, does not require hospitalization, with concomitant pathology) - aminopenicillins protected from beta-lactomases - (ampicillin / sulbactam (ampisulbin), amoxicillin / clavulonic acid (medoclave), amoxicillin /), cephalosporins of the second generation - (cefuroxime - aksetin, kimacef), macrolides of the second generation - azithramycin (azimed), clarithramycin clerimed, (fromilide), midecamycin - (macropen), spiramycin, as an alternative - fluoroquinolones III-IV generation (levofofin III p.- phloxium, IV p.- gati loksatsin, moxifloxacin); 3rd generation cephalosporins - cefoperazone (hepaceph, medocef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime.
 community-acquired pneumonia of the risk group III (mild course, requires state hospitalization, with concomitant pathology) - aminopenicillins, protected from beta-lactomases - (ampicillin / sulbactam (ampisulbin), amoxicillin / clavulonic acid (medoclave), amoxicillin / sulbactam), II-III generation cephalosporins - II p. (cefuroxime - aksetin, kimacef), III pok. cefoperazone (hepatacef, medocef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime in combination with second-generation macrolides (azithromycin - azimed, clarithramycin - clerimed, midecamycin - macropen, spiramycin III generation (alternin fluorine), as alternative levofloxacin III p.- phloxium, IV p.- gatifloxacin, moxifloxacin)
 community-acquired pneumonia of the risk group IV (severe course, requires hospitalization in the intensive care unit) - aminopenicillins protected from beta-lactomas - (ampicillin / sulbactam (ampisulbin), amoxicillin / clavulonic acid (medoclave), amoxicillin / sulbactam), cef-losporins of the II-III generation - II pok. (cefuroxime - aksetin, kimacef), III pok. cefoperazone (hepatacef, medocef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime in combination with second generation macrolides (azithromycin - azimed, clarithramycin - clerimed, midecamycin - macropen, generation spiramycinol levon III, fluorine III fluorine, fluorine pok. - phloxium, IV p. - gatifloxacin, moxifloxacin), in the presence of Pseudomonas aeruginosa - anti-pseudomonas cephalosporins III-IV generation - III pok. cefoperazone (hepaceph, medocef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime, IV generation - cefepime in

combination with aminoglycosides of the third generation amikacin (amicyl) and fluoroquinolone II-IV generation - (II p. honey cyprin, cyprinol), (levofloxacin III poc. - phloxium, IV poc. - gatifloxacin, moxifloxacin), in reserve - carbopenems (meropenem, ronem), teicoplanin, linezolid in combination with fluconozole, amphotericin B, itraconazole.

 Antibacterial therapy for patients with nosocomial pneumonia:

 nosocomial pneumonia of the risk group I (occurs in the first 5 days of hospitalization) - cephalosporins of the III-IV generation - III pok. cefoperazone (hepaceph, medocef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime, IV generation - cefepime or aminopenicillins protected from beta-lactomases - (ampicillin / sulbactam (ampisulbin), amoxiclavinum), amoxicillin / sulbactam), in combination with third-generation aminoglycosides amikacin (amicyl):

 nosocomial pneumonia of the risk group II (occurs after 5 days of hospitalization) - cephalosporins of the III-IV generation - III pok. cefoperazone (hepaceph, honeycef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime, IV generation - cefepime in combination with aminoglycosides of the third generation amikacin (amicyl): or fluoroquinolones of the III-IV generation (levofloxacin III pok. - phoxy .- gatifloxacin, moxifloxacin), carbopenems (meropenem, ronem), clindamycin in combination with fluconosole, amphotericin B, itraconazole.

 nosocomial pneumonia of the risk group III (48 hours after mechanical ventilation) - cephalosporins of the III-IV generation - III pok. cefoperazone (hepaceph, honeycef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime, IV generation - cefepime in combination with aminoglycosides of the third generation amikacin (amicyl): or fluoroquinolones of the III-IV generation (levofloxacin III pok. - phoxy . - gatifloxacin, moxifloxacin), carbopenems (meropenem, ronem), clindamycin, teicoplanin, linezolid in combination with fluconozole, amphotericin B, itraconazole.

 Antibacterial therapy for patients with aspiration pneumonia:

 aspiration community-acquired pneumonia (risk group I) -beta-lactomase-protected aminopenicillins - (ampicillin / sulbactam (Ampisulbin), amoxicillin / clavulonic acid (medoclave), 3rd generation cephalosporins - 3rd form. cefoperazone (hepaceph, honeycef), ceftazidime (ceftum), ceftri), ceftri with metronidazole (ornidazole, ornisole) clindamycin,

 aspiration nosocomial pneumonia (risk group II) - IV generation cephalosporins - cefepime in combination with III generation aminoglycosides amikacin (amicyl): or III-IV generation fluoroquinolones (levofloxacin III generation. - phloxium, IV generation. - gatifloxacin, moxifloxacin), carbo-penems (meropenem, ronem), in combination with metronidazole (ornidazole, ornizol) clindamycin,

 Antibacterial therapy in patients with severe immunodeficiency: fourth-generation cephalosporins - cefepime in combination with third-generation aminoglycosides amikacin (amicyl): or third-fourth-generation fluoroquinolones (levofloxacin III pok. - phloxium, IV pok. - gatifloxacin, moxifoxacin, moxifoxacin), carbopenems (meropenem, ronem), in combination with metronidazole (ornidazole, ornisole) clindamycin, antifungal fluconosole, amphotericin B, itraconazole, naramycin, sulfonamides - trimethaprim.

5. Pharmacotherapy of pneumonia complications.

 Lung abscess - cephalosporins III-IV generation - III pok. cefoperazone (hepaceph, honeycef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime, IV generation - cefepime, aminopenicillins protected from beta-lactomases - (ampicillin / sulbactam (ampisulbin), amoxlavicillin / clavicillin / amoxicillin / amoxicillin / sulbactam), in combination with metronidazole (ornidazole, ornizole), the alternative is lincosamides (lincomycin, clindomycin), aminoglycides of the third generation amikacin (amicyl): or fluoroquinolones of the III-IV generation (levofloxacin III pok. - phloxium, gatifloxacin, moxifloxacin), carbopenems (meropenem, ronem)

 Pleural empyema - cephalosporins III-IV generation - III pok. cefoperazone (hepaceph, medocef), ceftazidime (ceftum), ceftriaxone (medaxone), cefotoxime, 4th generation - cefepime,

aminopenicillins protected from beta-lactomases - (ampicillin / sulbactam (ampisulbin), amoxlavicillin (clavicillin / amlavicillin) amoxicillin / sulbactam), in combination with metronidazole (ornidazole, ornizole), the alternative is lincosamides (lincomycin, clindomycin), aminoglycides of the third generation amikacin (amicyl): or fluoroquinolones of the III-IV generation (levofloxacin III pok. - phloxium, gatifloxacin, moxifloxacin), carbopenems (meropenem, dropping it).

6. Features of the use of antibiotics in diseases of the respiratory tract:

 When prescribing antibiotics, one should take into account: route of administration, single and daily dose, frequency of doses, choice of combination - synergy of action.

 Antibiotic therapy should not be prolonged if only residual radiological signs of pneumonia are present.

 In the treatment of pregnant women with pneumonia - semisynthetic penicillins (amoxicillin - amoxil, hikontsil), protected from beta-lactomas - (ampi-cillin / sulbactam (ampisulbin), amoxicillin / clavulonic acid (meclavlid), amoxicillamine / c generations (azithromycin - azimed, clarithramycin - clerimed, midecamycin - macropen, spiramycin), II generation cephalosporins - (cefuroxime - aksetin, kimacef), III generations of cefoperazone (hepaceph, honeycef), ceftazidime (ceftum) cefotoxime, according to absolute indications - lincosis ides from antifungal - metamycin.

 Aminoglycosides are not indicated for the treatment of community-acquired pneumonia, they are administered iv once a day, they are not used as monotherapy, like carbopenems and fluoroquinolones

 Nitroimidazoles are not indicated for the treatment of both community-acquired and nosocomial pneumonia.

 effective against intracellular pathogens: chlamydia, legionella, mycoplasmas - macrolides, fluoroquinolones, doxycycline, rifampicin.

 Drug therapy of pneumonia in patients with severe immunodeficiency is carried out in a hospital with parenteral administration of the maximum permissible doses of antimicrobial agents, in combination with antifungal agents and the use of interferons (laferobion) and iv immunoglobulins, immunomodulators (amexin).

 In case of liver failure - penicillins, cephalosporins, except cefoperazone.

 With renal failure - penicillins, cephalosporins, chloramphenicol, fluoroquinolones, macrolides, lincosamides.

 For the prevention of pseudomembranous colitis - probiotics (lactobacterin, linex, etc.).

The list of practical works:

Homework.

1. To study - pharmacokinetics, pharmacodynamics, indications, contraindications to the use of drugs listed in the previous section.

2. The student must be able to:

a) select the necessary drug for a particular patient, select the dose, regimen and route of administration of the drug;

b) identify criteria for evaluating the therapeutic efficacy and safety of the drugs used;

c) provide differential medical assistance with:

 ostomy bronchitis,

 pneumonia.

3. Know the drugs used in pneumonia, taking into account risk groups and classes, undesirable effects, and performance criteria.

Control of the intermediate level of knowledge.

The solution of situational tasks:

1. To improve the drainage function of the bronchi, sputum discharge, a 52-year-old patient who suffers from bronchial asthma is prescribed a drug. 24 hours after the start of the drug, the patient

had a sore throat, runny nose, lacrimation. Note which drug the patient received?

2. Fill in the table “Biological effect of antibacterial drugs”:

Biological action	Definition, developmental mechanisms, clinical manifestations, examples
1. Superinfection 2. Hypovitaminosis 3. The reaction of massive bacteriolysis 4. Pseudomembranous colitis	

3. Fill in the table „Undesirable effects of some antibiotics

Drug	**Unwanted effects**	
	often	**seldom**
1. Benzylpenicillin 2. Ampicillin 3. Amoxiclav 4. Methicillin 5. Gentamicin 6. Cefazolin 7. Cefuroxime 8. Ceftazidime 9. Azithromycin 10. Clarithromycin 11. Erythromycin		

A patient who received treatment at the intensive care unit for nosocomial pneumonia experienced a complication after the first injections of cefotaxime, his blood pressure sharply decreased, and respiratory arrhythmia appeared. An allergic history is not burdened.

Explain the possible mechanism of the developed complication. Offer emergency care activities.

4. Fill in the table “Phenomena of antagonism and synergism between antibiotics

Antibiotic combination	**Synergism**	**Antagonism**
• Ampicillin + aminoglycosides • Penicillini + chloramphenicol • Amoxiclav + vancomycin • Fluoroquinoloni + rifampicin • Penicillini + tetracycline • Cephalosporins + aminoglycosides • Clarithromycin + cephalosporini		

5. Patient Z., 50 years old, takes gentamicin for exacerbation of chronic bronchitis and isosorbide dinitrate with furosemide for IHD and chronic heart failure. A few days later I felt a hearing impairment. In urine tests, proteinuria.
6. Give an interpretation of the symptoms. Your recommendations.
7. . A patient with mild community-acquired pneumonia is prescribed amoxicillin-clavulanate (amoxiclav). After 10 days of therapy, pneumonia was completed, which was confirmed by radiology (absence of inflammatory-infiltrative shadows), then the body temperature began to rise to 380C. Objective surveys did not provide additional information. In the hemogram - accelerated ESR, eosinophilia, anemia. In the urogram, there are no pathological changes.

8. Explain the possible mechanism for increasing the patient's body temperature.
9. . Patient L., 20 years old, with acute respiratory viral infections (pharyngitis, rhinitis) with elevated body temperature up to 39 ° C was prescribed biseptol for the prevention of bacterial complications.
   Assess the correctness of medical tactics. Your recommendations.
   Your recommendations.

TESTS

1. A patient, 19 years old, complains of a dry cough, muscle pain, fever up 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. Chest x-ray data: increased pulmonary pattern, focal shadows of low 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.

2. A patient with infiltrative pulmonary tuberculosis is prescribed: streptomycin, rifampicin, isoniazid, pyrazinamide, vitamin C. After 1 month from the start of treatment, the patient began to complain of hearing loss, tinnitus. Which of the prescribed drugs has such a side effect?

A. Pyrazinamide.

B.Rifampicin.

C. Isoniazid.

D. Streptomycin.

E. Vitamin C.

3. A man, 60 years old, who for a long time suffers from chronic obstructive bronchitis and smokes a lot, has a dry cough, increased body temperature to 37.5 ° C, 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.

4. After a clinical, radiological and laboratory examination of the patient, 35 years old, a preliminary diagnosis was made: atypical pneumonia of mycoplasma etiology, moderate severity, DN I st. With which group of drugs is it advisable to start treatment?

A. Fluoroquinolones.

B. Cephalosporin.

C. β-lactam antibiotics.

D. Macrolides.

E. Aminoglycosides.

5. 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.

6. The child, 5 years old, is ill on the 2nd day. The premorbid background is not burdened. There is a slight general weakness, fever up to 37.3 ° C, a decrease in ap-petit, frequent wet cough, significant discharge from the nose. Objectively: BH - 25 per min. Percussion - pulmonary sound. Auscultation on both sides is heard medium and large bubbling rales, after coughing, the nature of wheezing changes. Diagnosed with acute respiratory viral infections, acute bronchitis. What type of treatment is the most optimal?

A. Sulfanilamides.

B. Aminoglycosides.

C. Antihistamines.

D. Cephalosporins.

E. Expectorant drugs + vitamins.

7. For a woman of 46 years old, for the treatment of acute bronchitis, the doctor prescribed a combination drug from the group of sulfonamides with a high bactericidal effect. Name this drug.

A. Phthalazole

B. Clarithromycin

C. Co-trimoxazole

D. Salazopyridazine

E. Ethambutol

8.In a 56-year-old patient with acute pneumonia, penicillin-producing staphylococcus strain was detected. For treatment, a drug from the penicillin group was prescribed
Name this drug.

- A. Benizlpenicillin sodium salt
- B. Oxacillin

- C. Ampicillin
- D. Ticarcillin
- E. Meslocillin
- 9. Name the fluoroquinolone with the highest activity against pneumococci:
- A. Ciprofloxacin

B. Levofloxacin
C. Ofloxacin
D. Norfloxacin
E. Pefloxacin
10. For infections of the respiratory system with Pseudomonas aeruginosa, the use of the following drugs is indicated:
A. Kefzol
B. Brulomycin
C. * Polymyxin
D. Levorina
E. Erythromycin
11. A 32-year-old patient was diagnosed with bilateral interstitial pneumonia caused by pulmonary mycoplasma. What antibacterial agents should be included in the treatment regimen?
A. Cephalosporins.
B. Tetracyclines.
C. Penicillins.
D. Sulfanilamides.
E. Aminoglycosides.
12. What is the drug of choice for the treatment of SARS:
A. Ampicillin.
B. Cefoperazone.
C. Rovamycin.
D. Gentamicin.
E. Oxacillin.
13. A pregnant woman fell ill with pneumonia. Which of the following antibacterial drugs should be prescribed to her?
A. Ofloxacin.
B. Biseptol.
C. Cefotaxime.
D. Gentamicin sulfate.
E. Tetracycline hydrochloride.
14. The patient, 36 years old, revealed atypical out-of-hospital pneumonia, which is caused by chlamydia. What antibacterial agent is advisable in this case?
A. Ampicillin.
B. Roxithromycin.
C. Penicillin.
D. cefuroxime.
E. Vancomycin.
15. The patient, 36 years old. revealed atypical community-acquired pneumonia, which is caused by chlamydial infection. What antibacterial agent should be recommended in this case?
A. Roxithromycin.
B. Ampicillin.
C. Penicillin.
D. cefuroxime.
E. Vancomycin.
16. A patient of advanced age is diagnosed with hospital pneumonia. Treated with gentamicin. What side effect is most common when using antibiotics in this group?

A. Hematotoxic effect.
B. Damage to the liver.
C. Pseudomembranous colitis.
D. Thrombophlebitis.
E. Ototoxic effect.
17. 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. What drugs should be prescribed?
A. Aminoglycosides.
B. Macrolides.
C. Penicillin antibiotics.
D. Cephalosporins II or III generation.
E. Sulfanilamides.
18. A patient with infiltrative pulmonary tuberculosis is prescribed: streptomycin, rifampicin, isoniazid, pyrazinamide, vitamin C. After 1 month from the start of treatment, the patient began to complain of hearing loss, tinnitus. Which of the prescribed drugs has such a side effect?
A. Pyrazinamide.
B. Rifampicin.
C. Isoniazid.
D. Streptomycin.
E. Vitamin C.
19. A man, 27 years old, complains of a cough with the release of rusty sputum, pain in the chest during breathing, fever up to 39 ° C. He became ill acutely after hypothermia. Objectively: BH-30 per minute, heart rate - 92 per minute, blood pressure - 130/80 mm RT. Art. In the lungs to the right of the IV rib downward - increased voice trembling, dullness of percussion sound, bronchial breathing. What activities should start treatment with?
A. With pleural puncture.
B. With the appointment of aminopenicillins.
C. With the appointment of gentamicin.
D. With the appointment of aminocaproic acid.
E. With the appointment of biseptol.
20. A man, 60 years old, who for a long time suffers from chronic obstructive bronchitis and smokes a lot, has a dry cough, increased body temperature to 37.5 ° C, 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.
B. Claforan.
C. chloramphenicol.
D. Tetracycline.
E. Benzylpenicillin.
21. 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.

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.

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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

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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 MUKOLITIC, ANTIHISTAMINE, ANTICOTITIC D

Purpose of the topic.

The problem of rational therapy of bronchopulmonary pathology remains very relevant. Despite the improvement of antibacterial agents, an increase in the number and worsening of the outcomes of this group of diseases is everywhere observed. Over 2.5 million people are observed annually in the United States about pneumonia, more than 750 thousand in Great Britain, and about 2 million people in Russia. In Ukraine, the incidence of pneumonia in recent years is constantly growing, and hospital lethality, from pneumonia, is also increasing. The use of mucolytic, antitussive antihistamines is highly relevant.

Motivational characteristic of the topic.

Of the pathogenetic drugs, first-line drugs should be considered drugs that improve the drainage function of the bronchi and normalize mucociliary clearance (bronchodilators and mucolytic drugs),

Cough is the main symptom of the main symptom of respiratory diseases. A cough is a complex reflex reaction of the respiratory tract, the main function of which is to restore their normal patency.

The onset of coughing may be due to irritation of the cough receptors of the nose, ears, back wall of the pharynx, trachea, bronchi, pleura, diaphragm, pericardium, and esophagus. External and internal factors (foreign bodies, cold and dry air, airborne pollutants, tobacco smoke, nasal mucus, sputum, inflammation of the mucous membranes of the respiratory tract, etc.) excite cough receptors, which are subdivided into irritant, quickly reacting to mechanical, thermal, chemical irritants, and C-receptors, mainly stimulated by inflammatory mediators (prostaglandins, kinins, substance P, etc.). The impulse arising from this is transmitted through the afferent fibers of the vagus nerve to the cough center located in the medulla oblongata. The reflex arc is closed by the efferent fibers of the vagus, phrenic and spinal nerves that go to the muscles of the chest, diaphragm and abdominal press, the reduction of which leads to the closure of the glottis with its subsequent opening and pushing out with a high speed of air, which is manifested by a cough.

In addition, a cough can be triggered or suppressed arbitrarily, since the formation of a cough reflex is controlled by the cerebral cortex.

Cough is classified by nature (unproductive, or dry, and productive, or wet cough), by intensity (cough, mild and severe cough), by duration (episodic, paroxysmal and persistent cough), with the course (acute - up to 3 weeks, lingering) - more than 3 weeks and chronic - 3 months or more).

In some cases, a cough loses its physiological feasibility and not only does not contribute to the resolution of the pathological process in the respiratory system, but also leads to the development of complications.

The cough reflex reflex arc includes receptors, the cough center, afferent and efferent nerve fibers, and the executive link is the respiratory muscles. Cough is most effectively suppressed at two levels - the receptor level and the level of the cough center. In this regard, antitussive drugs are divided into 2 groups: central and peripheral action. In turn, centrally acting drugs can be divided into narcotic and non-narcotic drugs.

EXPECTORANT DRUGS

a) secretomotor (stimulating expectoration):

 reflex action - thermopsis grass, thyme grass, marshmallow root, licorin hydrochloride, source root, licorice, ipecacuanh, cyanosis rhizome, sodium benzoate, terpinghydrate, essential oils (eucalyptus, etc.),

 local reagents of resorptive action - ammonium chloride, potassium iodide, sodium iodide;

 stimulators of bronchial glands (potassium iodide, sodium iodide);

 medicinal expectorant fees.

b) mucolytic (bronchosecretolytic):

 proteolytic enzymes - trypsin, chymotrypsin, chymopsin, ribonuclease,

 cysteine derivatives, thiol-containing preparations: acetylcysteine (ACC), mesna, N-acetylcysteine (fluimucil);

 preparations of the carbocysteine group: flooditech, fluifort, bronkatar, muco-pront, mucodin)

 flour regulators, derivatives of vizitsin: bromhexine / bisolvon /, ambrok-sol / lazolvan /.

 stimulators of mucociliary function (bsta-2 agonists, theophyllines):

Of the large number of expectorant drugs, the most effective is the use of acetylcysteine derivatives (acetylcysteine, carbocysteine, mesna) and drugs that normalize the intracellular formation of bronchial secretion (bromhexine, ambroxol). The main mechanism of their action is the cleavage of the peptide bonds of glycoproteins, depolymerization and destruction of mucopolysaccharides and, thereby, a decrease in the viscosity of sputum. In addition to the mucolytic effect, their ability to stimulate mucociliary clearance in patients with a verified decrease in it, a detoxifying effect (binding of free radicals, reactive oxygen metabolites due to potentiation of glutathione synthesis) was established.

Side effects are rare. Sometimes nausea, vomiting, heartburn and other dyspeptic disorders can be observed. With renal and hepatic insufficiency, the dosage of the drugs should be reduced.

Acetylcysteine

M-derivative of the natural amino acid cysteine. The effect of the drug is associated with the presence of a free sulfhydryl group in the structure of the molecule, which breaks down disulfide bonds of macromolecules, mucus glycoprotein by the reaction of sulfhydryl-disulfide substitution; as a result, M-acetylcysteine disulfides are formed having a significantly lower molecular weight, and sputum viscosity decreases.

Acetylcysteine:

• has a stimulating effect on mucous cells, the secret of which has the ability to lyse fibrin and blood clots,

• able to increase the synthesis of glutathione, which is important for detoxification, in particular, with poisoning with paracetamol and pale grebe,

• protective properties have been identified that are directed against such factors as free radicals, reactive oxygen metabolites responsible for the development of acute and chronic inflammation

in the lung tissue.

Long-term use of acetylcysteine is not practical, since it suppresses mucociliary transport and secretory IgA production. In some cases, the mucolytic effect of acetylcysteine is undesirable, because the state of mucociliary transport is negatively affected by both an increase and an excessive decrease in the viscosity of the secretion. Acetylcysteine is sometimes able to exert an excessive diluting effect, which can cause the syndrome of the so-called “flooding” of the lungs and require the use of a suction to remove the accumulated secretion, especially in young children. Therefore, conditions must be provided for adequate sputum removal: postural drainage, vibration massage, bronchoscopy.

Pharmacokinetics and pharmacodynamics

When administered, the drug is rapidly and well absorbed, in the liver it is metabolized (hydrolyzed) to the active metabolite - cysteine. Due to the “first pass” effect, the bioavailability of the drug is low (about 10%). The maximum plasma concentration is reached after 1-3 hours. T1 / 2 is 1 hour, the elimination pathway is predominantly hepatic.

Indications and contraindications

Acetylcysteine is indicated as an adjunct in various bronchopulmonary diseases with the presence of thick, viscous, difficult to separate sputum of mucous or mucopurulent nature: chronic obstructive bronchitis, bronchiolitis, bronchopneumonia, bronchiectasis, bronchial asthma, cystic fibrosis. It should be used with caution in prescribing the drug to patients with broncho-obstructive syndrome, since in 1/3 of the cases, bronchospasm intensifies. Do not prescribe the drug for an attack of bronchial asthma and bronchial asthma with normal discharge of sputum. In otolaryngology, the mucolytic effect of the drug is also widely used for purulent sinusitis, inflammation of the middle ear. The use of this mucolytic in acute bronchitis requires caution, since the drug is able to reduce the production of lysozyme and IgA and increase bronchial hyperreactivity. Acetylcysteine is well tolerated, sometimes when taking the drug, nausea, vomiting, heartburn can be observed; liquefaction of mucus eliminates its protective effect, which can lead, for example, to an exacerbation of peptic ulcer. In such cases, these funds are recommended to be used in lower doses and mainly in the form of inhalations.

Dosage regimens

Acetylcysteine in adults is used 200 mg 3 times a day or 600 mg 1 time a day in acute conditions for 5-10 days or 2 times a day for up to 6 months for chronic diseases. In newborns, acetylcysteine is used only for health reasons at a dose of 10 mg / kg body weight, an average of 50-100 mg 2 times a day. With cystic fibrosis, the drug is used in the same single doses 3 times a day. In surgical and endoscopic practice, acetylcysteine is also used. endotracheally, by slow instillations and, if necessary, parenterally - intramuscularly or intravenously. The action of the drug begins after 30-60 minutes and lasts for 4 hours. The endobronchial route of administration makes it possible to avoid undesirable effects. Perhaps the combined administration of drugs - inhalation + oral. Broncho obstructive syndrome can be avoided by first using a bronchodilator.

Mesna

It has a similar effect to acetylcysteine, but it is more effective. Mesna as a mucolytic is usually used by inhalation and intratracheal. It is also used to prevent hemorrhagic cystitis in the treatment of cyclophosphamide (iv and orally). In children, not applicable.

Pharmacokinetics and pharmacodynamics

The drug is easily absorbed and quickly excreted from the body in an unchanged form. Used for

inhalation in conditions after neurosurgical and thoracic operations, after resuscitation, and with chest injuries to improve sputum discharge; with cystic fibrosis, bronchial asthma with difficult discharge of sputum, with chronic bronchitis, emphysema and bronchiectasis, atelectasis due to obstruction of the bronchi with mucus. Drop infusions are indicated when it is necessary to prevent the formation of a mucous plug and to facilitate the suction of the secretion from the bronchi during anesthesia or under intensive treatment, as well as for drainage with sinusitis or otitis media.

Dosage regimens

Inhalation is carried out 2-4 times a day for 2-24 days. To do this, use the contents of 1-2 ampoules without dilution or in a 1: 1 dilution with distilled water. Drip infusion is carried out through an intratracheal tube, 1-2 ml of the drug diluted with the same volume of water; instill every hour until the moment of liquefaction and secretion. In asthmatic conditions, the drug is used only in a hospital. With inhalation use of mesna, cough and bronchospasm are possible (especially in patients with bronchial asthma, poorly tolerating aerosols), when using a 20% solution, burning pain may occur (in these cases, the drug is diluted with distilled water in a ratio of 1: 2) . Mesna is combined with almost all antibiotics, except aminoglycosides.

Fluimucil

The mechanism of action is similar to acetylcysteine, but more active. It also has the least pronounced side effects: practically does not irritate the gastrointestinal tract. The advantages of fluimucil are the ability to use its solution during nebulizer therapy in patients with COPD, as well as its antioxidant and anti-inflammatory activity.

Rinofluimucil

Used for acute and chronic rhinosinusitis, exudative and recurrent otitis media. In otolaryngology, acetylcysteines, used in short courses, topically intranasally (rinofluimucil) in combination with the introduction of an antibiotic (in particular, chloramphenicol) into the sinuses, gave preliminary good results in patients with exacerbations of chronic rhinosinusitis with increased secretion viscosity and with prolonged subacute rhinosinitis. A rapid mucolytic effect was noted, but there was not only a dilution of purulent exudate, but also an increase in its volume. Therefore, the introduction of acetylcysteine into the sinuses requires active drainage, aspiration of the intra-sinus secretion in the next 5-6 hours after administration of the drug; 2-3 receptions are enough for a course of treatment. However, with inadequate use of acetylcysteines and in the absence of proper active aspiration of the secret in the conditions of impaired mucociliary activity observed with subacute and chronic rhinosinusitis, a deterioration of the rhinoscopic picture may be noted.

Interactions

Antibacterial therapy significantly increases the viscosity of sputum due to the release of DNA during the lysis of microbial bodies and white blood cells. In this regard, it is necessary to take measures to improve the rheological properties of sputum and facilitate its discharge. Such a measure is the appointment of mucolytics in combination with antibiotics. With their simultaneous administration, their compatibility should be taken into account: acetylcysteine reduces the absorption of penicillins, cephalosporins, tetracycline, erythromycin (the interval between doses is 2 hours). Mesna cannot be used together with aminoglycosides. Acetylcysteine preparations during inhalations or installations should not be mixed with antibiotics, as this causes their mutual inactivation. The exception is fluimucil, for which a special form has even been created: fluimucil + IT antibiotic (thiamphenicol glycinate acetylcysteinate). It is available for inhalation, parenteral, endobronchial and topical use. Thiamphenicol has a wide spectrum of

antibacterial action. Once in the respiratory tract, it is hydrolyzed to N-acetylcysteine and thiamphenicol. It is effective against bacteria that most commonly cause respiratory infections. Fluimucil effectively dilutes sputum and facilitates the penetration of thiamphenicol into the area of inflammation, inhibits the adhesion of bacteria on the epithelium of the respiratory tract.

Acetylcysteine enhances the effect of nitroglycerin, and therefore an interval is necessary between the doses of the drug. You can not combine acetylcysteine with antitussive agents (stagnation due to suppression of the cough reflex is possible). In patients with bronchial obstructive syndrome, acetylcysteines can be combined with bronchodilators β2-agonists, theophyllines), a combination with m-anticholinergics is undesirable, since they thicken sputum.

Combined cough medicine.

This group of drugs, usually over-the-counter or prescribed by doctors, contains two or more components. A number of combination drugs include a centrally acting antitussive drug, antihistamine, expectorant and decongestant (broncholitin, stoptussin, synecode, hexapnevmin, lorraine). Often they also include a bronchodilator (solutan, trisolvin) and / or an antipyretic component, antibacterial agents (hexapnevmin, lorraine). They facilitate coughing with bronchospasm, acute respiratory viral infections or bacterial infection, but they should be prescribed according to appropriate indications. Often, such drugs are not indicated or even contraindicated in young children, especially the first months of life. In addition, combined preparations, in particular those prescribed by doctors, may combine medications that are opposite in their effect or may contain suboptimal or low concentrations of drugs, which reduces their effectiveness.

Carbocysteine group preparations (fluditec, fluifort, bronkatar, muco-pront, mucodin)

The mechanism of action of carbocysteine is associated with the activation of sialic transferase, an enzyme of goblet cells of the bronchial mucosa, under the influence of which the production of acidic mucins slows down. In this case, the ratio of neutral or acidic mucin of mucus is normalized, as a result of which the elasticity and regeneration of the mucous membrane are normalized, its structure is restored, the number of goblet cells is reduced (this effect is observed throughout all mucous membranes of the body) and, as a result, the amount of mucus produced is reduced. In addition to the above, the secretion of immunologically active IgA (specific protection) and the number of sgroups (non-specific protection), mucociliary clearance improves (activity of ciliary cells is potentiated). Thus, carbocysteine, unlike acetylcysteine, bromhexine and ambroxol, also has a mucoregulatory effect. In this case, the action of carbocysteine extends to the upper and lower respiratory tract, as well as the paranasal sinuses, middle and inner ear. Carbocysteine is active only when taken orally. Using the flooditech as an example, it was shown that as a result of optimizing the ratio of acidic and neutral sialomucins between the layer of pathological mucus and the mucous membrane of the respiratory tract, a new layer of mucus with normal rheological properties is formed. It is she who contacts the cilia of the ciliated epithelium, pushing up the old mucus.

Indications and contraindications

The drug is indicated primarily in the initial stage of an acute inflammatory process in the respiratory system, when there is a significant increase in the secretion of liquid mucus and a characteristic increase in the formation of goblet cells, as well as chronic inflammation, accompanied by increased production of mucus with altered physico-chemical characteristics, but not purulent. Since the effect of the drug is manifested at all levels of the respiratory tract: both at the level of the mucous membrane of the bronchial tree and at the level of the mucous membranes of the nasopharynx, paranasal sinuses and mucous membranes of the middle ear, carbocysteine is widely used not only in pulmonology, but also in otorhinolaryngology. Positive

results with the inclusion of mucolytics with a mucus-regulating effect (fluiford, carbocysteine lysine salt) were also obtained in the group of patients with acute and chronic exudative otitis media, as well as with rediding otitis media. Special indications for the use of carbocysteine in children of the first year of life may include the following: “wet” bronchitis, occurring with an abundance of low-viscosity liquid sputum and the danger of “swelling of the bronchi”; bronchopulmonary diseases with a violation of the cough reflex (against the background of organic and functional lesions of the central nervous system, traumatic brain injuries, after surgical interventions on the central nervous system, etc.); congestive bronchitis against congenital heart defects; bronchitis against the background of the “motionless cilia” syndrome, Sievert-Kartagener syndrome, after intubation, in the postoperative period; prevention of chronic bronchitis with bronchopulmonary diplasia in order to prevent glandular degeneration of the mucous membrane. Side effects rarely develop, mainly in the form of dyspeptic symptoms and allergic reactions. Do not use the drug for exacerbation of peptic ulcer of the stomach and duodenum, as well as conditions in which there is pulmonary bleeding. The simultaneous use of antitussive and mucolytic drugs is completely unacceptable. Carbocysteine is not recommended for pregnant and lactating mothers.

Pharmacokinetics and pharmacodynamics

The maximum concentration in the blood serum and mucous membrane of the respiratory tract is reached after 2-3 hours and remains in the mucous membrane for 8 hours. It is excreted mainly in urine.

Dosage regimens

Carbocysteine preparations are available only for oral administration (in the form of capsules, granules and syrups). Use the drug orally at 750 mg 3 times a day. Duration of admission is 8-10 days. Long-term administration (up to 6 months 2 times a day) in patients with COPD is possible.

Interactions

Carbocysteine is the drug of choice as a mucolytic in bronchial asthma, not only because of the mucoregulatory effect, but also due toulfhydryl are rest ability to potentiate the effects of β2-adrenergic agonists, antibacterial drugs, xanthines and glucorticoids. A combination of carbocysteine with other drugs that suppress the secretory function of bronchial glands is undesirable (centrally acting antitussive drugs, macrolide antibiotics, first generation antihistamines, etc.), its purpose is not justified in case of poor secretion. With the simultaneous use of carbocysteine with atropine-like agents, a weakening of the therapeutic effect is possible.

Proteolytic enzymes (trypsin, chymotrypsin, ribonuclease, deoxyribonuclease)

Reduce both the viscosity and elasticity of sputum, have anti-edematous and anti-inflammatory effects. However, drugs of this group are practically not used in pulmonology, since they can provoke damage to the pulmonary matrix, bronchospasm, hemoptysis, allergic reactions [3]. The exception is recombinant a-DNase (pulmozyme). The accumulation of viscous purulent secretion in the respiratory tract plays a role in reducing the functional ability of the lungs and in exacerbations of the infectious process. The purulent secretion contains very high concentrations of extracellular DNA - a viscous polyanion released from the decaying white blood cells that accumulate as a result of infection. Alpha-DNase (pulmozyme) has the ability to specifically cleave high molecular weight nucleic acids and nucleoproteins into small and soluble molecules, which helps to reduce the viscosity of sputum, and also have anti-inflammatory properties. The anti-inflammatory effect of Alpha DNase (pulmozyme) and its ability to delay the reproduction of some RNA-containing viruses (herpes virus, adenoviruses) are shown.

Pharmacokinetics and pharmacodynamics

Alpha DNase is a genetically engineered version of a natural human enzyme that breaks down extracellular DNA. Normally, DNase is present in human serum. Inhalation of alpha-DNase in doses up to 40 mg for 6 days did not lead to an increase in serum DNase concentration compared to normal enogenous levels. Serum DNase concentration did not exceed 10 ng / ml. After the administration of alpha-DNase at 2500 IU (2.5 mg) twice a day for 24 weeks, the average serum concentrations of DNase did not differ from the average values before treatment, equal to 3.5 ± 0.1 ng / ml, which indicates low systemic absorption or low cumulation.

The activity of the drug is determined by the biological method according to the amount of acid-soluble substances as a result of DNA hydrolysis under certain conditions. One unit of activity (EA) corresponds to 1 mg of the drug.

Indications and contraindications

Recombinant human deoxyribonuclease (pulmozyme) is used in the treatment of cystic fibrosis, purulent pleurisy, resolution of recurrent atelectasis in patients with spinal cord injury, bronchiectasis, lung abscesses, pneumonia; in the preoperative and postoperative periods in patients with purulent lung diseases.

Dosage regimens

Apply topically, in the form of aerosols for inhalation, intrapleural, intramuscularly. For inhalation use a fine aerosol; dose - 0.025 mg per procedure; the drug is dissolved in 3-4 ml of an isotonic sodium chloride solution or in a 0.5% solution of novocaine. A solution containing 0.025-0.05 g of the drug is administered endobronchially with the help of a laryngeal syringe or catheter. The same dose is administered intrapleurally in 5-10 ml of an isotonic sodium chloride solution or 0.25% novocaine solution. With cystic fibrosis through a nebulizer, in addition to bronchodilators, glucocorticoids and recombinant DNase, antibiotics that are active against P. aeruginosa (colimycin, tobramycin, etc.) are also used. The maximum single dose for intramuscular injection is 0.01 g. Before treatment, tests are carried out for sensitivity to the drug: 0.1 ml of the solution is injected intracutaneously into the flexion surface of the forearm. In the absence of a local and general reaction, the drug is treated. As shown by recently completed multicenter studies, daily two-time inhalations of 2.5 mg of the drug reduce the number of exacerbations, improve the patient’s well-being, functional indicators and, as a result, the patient’s quality of life. In the treatment of cystic fibrosis, the following recommendations are made: at the beginning of therapy (usually within 2 weeks), it is necessary to conduct a trial appointment of pulmozyme when, possibly, undesirable phenomena requiring withdrawal of the drug are detected. In the next 3 months, it is necessary to monitor functional tests to determine the effectiveness of pulmozyme therapy. If there is no increase in FVD indicators, but the patient feels subjective improvement, easier breathing and coughing, therapy should be continued. If there is no reaction to the introduction of pulmozyme, you can extend the therapy for another 3 months and evaluate the effect of pulmozyme on the frequency of respiratory episodes. If this indicator has improved, therapy with pulmozyme is recommended to continue. Pulmozyme should be prescribed during the period of the patient’s stable state, when it is possible to more objectively assess the effect of therapy on the state of the bronchopulmonary system and track possible adverse events. When prescribing pulmozyme, one should not immediately cancel the standard mucolytic therapy that the patient had received before. Only when it becomes clear that the patient responded well to pulmozyme therapy can other mucolytic drugs be gradually withdrawn. Children, starting from 2 years of age, can be prescribed pulmozyme if they have a good command of inhalation technique through the mouthpiece or are calm about inhalation through a mask.

One should not strive for the complete abolition of other mucolytic therapy in severe patients, since all known groups of mucolytics act on different links in the pathogenesis of the formation of viscous sputum and its accumulation in the respiratory tract. It is more advisable to inhale the pulmozyme after kinesitherapy, reaching its maximum penetration into the lungs. Carrying out kinesotherapy after inhalation of pulmozyme should be attributed to the time of the onset of the maximum mucolytic effect in each individual patient. With manifestations of pharyngitis or laryngitis in the first days of prescribing pulmozyme, do not immediately discontinue the drug. Most likely, these phenomena will pass over time. When hemoptysis, you should immediately consult a doctor, since, perhaps, this is not a reaction to pulmo-winters, but the first signs of an exacerbation of the bronchopulmonary process. And only when pulmonary hemorrhage does not disappear with the use of antibacterial and hemostatic therapy, the pulmozyme should be temporarily canceled in order to conduct a new trial prescription of the drug some time after the condition has stabilized. With repeated episodes of hemoptysis, coinciding with the beginning of the use of bulimozyme, the drug should not be prescribed. If the condition worsens, shortness of breath increases, the appearance of dry coughing attacks, and a decrease in the HPF indices, the drug should be immediately canceled. The early appointment of pulmozyme helps to improve lung function, prevent respiratory episodes, and reduce inflammatory activity in the lungs.

Drug interactions

Drug interactions are not known. In a nebulizer, pulmozyme should not be mixed with other drugs or solutions. Pulmozyme can be effectively and safely used simultaneously with standard drugs for the treatment of cystic fibrosis, such as antibiotics, bronchodilating, food-processing enzymes, vitamins, inhaled and systemic glucocorticoids an analgesics.

Vasicinoids: Bromhexine (Bisolvan), Ambroxol (Ambrobene, Lasolvan)

Bromhexine has a mucolytic (secretolytic) and expectorant effect, which is associated with the depolymerization and destruction of mucoproteins and mucopolysaccharides that are part of sputum, has a slight antitussive effect. However, the availability of bromhexine, its relatively low cost, and the absence of side effects explain the rather wide use of the drug. Almost all researchers note a lower pharmacological effect of bromhexine compared with the new generation of the drug, which is an active metabolite of bromhexine, Ambroxol hydrochloride.

Pharmacokinetics and pharmacodynamics

The oral bioavailability of bromhexine is low - 80% due to the effect of "first passage through the liver", the drug is rapidly metabolized with the formation of active compounds. When taken orally in tablets or in the form of a solution, bromhexine is completely absorbed within 30 minutes, is 99% bound to proteins in blood plasma, and the distribution volume at a stationary concentration is 400 liters. In addition, bromhexine binds to the erythrocyte membrane. The drug crosses the blood-brain and placental barrier. It is eliminated mainly in the form of metabolites, an unchanged drug is eliminated by the kidneys only in the amount of 1%, metabolites are also excreted by the kidneys. In severe liver failure, the clearance of bromhexine decreases, and in chronic renal failure - the clearance of its metabolites. The pharmacokinetics of bromhexine is dose-dependent, the drug can cumulate with repeated use.

Indications and contraindications

In cystic fibrosis and bronchial asthma, the drug is used with caution, preferably against the background of bronchodilators, since it is able to provoke a cough reflex itself, it is also used for acute and chronic bronchopulmonary diseases, but it is not recommended for pregnancy and lactating mothers. Side effects: gastrointestinal upsets, skin reactions are rare. In severe chronic renal failure, dose adjustment and dosing regimen are necessary.

Dosage regimens

Bromhexine is used mainly inside, but inhalation of its solution through a nebulizer is also possible, and in surgery, parenteral administration intramuscularly or intravenously. After inhalation

2 ml of bromhexine solution occurs after 20 minutes and lasts for 4-8 hours. In tablets, adults are prescribed 8-16 mg 2-

3 times a day, and for children from 6 to 14 years old, 8 mg three times a day, younger than 6 years -

4 mg 3 times a day. A solution for intravenous administration of 16 mg (2 ampoules) 2-3 times a day is also used, and for children under 6 years of age - 4-8 mg once. There is a combined form - Ascoril, which includes salbutamol sulfate, bromhexine hydrochloride, guaifenesin and menthol as components.

The clinical effect of ambroxol hydrochloride is significantly superior to bromhexine, especially with regard to the ability to increase the level of surfactant, since, in addition to stimulating the synthesis of surfactant, it blocks its decomposition. This is based on its more pronounced ability compared with bromhexine to increase mucociliary clearance. Being a hydrophobic boundary layer, surfactant facilitates the exchange of non-polar gases, has an anti-edematous effect on the membranes of the alveoli. He is involved in ensuring the transport of foreign particles from the alveoli to the bronchial section, where mucociliary transport begins. By exerting a positive effect on surfactant, ambroxol hydrochloride indirectly increases mucociliary transport and, in combination with increased secretion of glycoproteins (mucokinetic effect), gives a pronounced expectorant Effect. The mechanism of action of ambroxol is not completely clear. It is known that it stimulates the formation of a lower viscosity tracheobronchial secretion due to a change in mucopolysaccharides in sputum. The drug improves mucociliary transport, stimulating the activity of the ciliary system. It is very important that ambroxol does not provoke bronchial obstruction. The literature data indicate the anti-inflammatory and immunomodulating effect of ambroxol: it enhances local immunity by activating tissue macrophages and increasing secretory IgA production, and also has an inhibitory effect on the production of interleukin-1 and tumor necrosis factor mononuclear cells, which are some of the mediators of inflammation. It is suggested that inhibition of the synthesis of pro-inflammatory cytokinesis can improve the course of leukocyte-related pulmonary damage. The antioxidant properties of ambroxol are also proved, which can be explained by its effect on the release of oxygen radicals and interference with the metabolism of arachidonic acid in the focus of inflammation; the drug protects it from bleomycin-induced pulmonary toxin and fibrosis, and inhibits neutrophil chemotaxis in vitro.

Pharmacokinetics and pharmacodynamics

After ingestion, the drug is rapidly and completely absorbed, but 20-30% of it undergoes rapid hepatic metabolism due to the “first pass” phenomenon. The duration of action after taking one dose is 6-12 hours. Ambroxol passes through the placental and blood-brain barrier, as well as into breast milk, is metabolized in the liver: dibromanthranilic acid and glucuronic conjugates are formed.

Dosage regimens and methods

Ambroxol hydrochloride has a wide selection of dosage forms: tablets, oral solution, syrup, retard capsules, solution for inhalation and endobronchial administration, injection. The dose of the drug for children under 5 years old is 7.5 mg 2-3 times a day, for children over 5 years old - 15 mg 3 times a day. For patients over 12 years of age, Ambroxol is prescribed 30 mg 3

times a day or 1 capsule of retard per day. The duration of treatment is from 1 to 3-4 weeks, depending on the effect and nature of the process [13, 14]. Adults and children over 12 years of age are prescribed 30 mg in tablets 3 times a day for the first 3 days, and then twice a day; children aged 6-12 years - 15 mg 2-3 times, under 6 years - 15 mg once, from 2 to 5 years, 7.5 mg 2-3 times a day. The total volume of inhaled substance should be 3-4 ml (if necessary, the drug is diluted with saline), the inhalation time is 5-7 minutes. It should be remembered that drug particles almost do not precipitate in places of atelectasis and emphysema. Obstructive syndrome also significantly reduces the penetration of aerosol into the respiratory tract, therefore, it is better to carry out inhalation of mucolytic drugs in patients with bronchial obstruction 15-20 minutes after inhalation of bronchodilators. It must be borne in mind that when using a mask, mucolytic helps to improve the rheological properties of sputum, but at the same time, the use of a mask reduces the dose of a substance inhaled in the bronchi. Therefore, young children need to use a mask of the appropriate size, and after 3 years it is better to use not a mask, but a mouthpiece. The combined use of the inhaled form of the mucolytic drug with the administration of it parenterally (intramuscularly or intravenously) significantly improves the effectiveness of therapy, especially in patients with complicated and chronic bronchopulmonary diseases. The parenteral method of administration of a mucolytic ensures the rapid penetration of the drug, including in the presence of severe inflammatory edema, bronchial obstruction and atelectasis. However, if there is a lot of mucus in the lungs, the drug does not affect the parietal layer of the secretion, which does not allow to achieve the maximum effective expectorant action. In such cases, it is better to combine the endobronchial and inhalation delivery method with the administration of retard capsules, the purpose of which once a day is quite effective.

Indications and contraindications

Ambroxol hydrochloride is used for acute and chronic diseases of the respiratory system, including bronchial asthma, bronchiectasis, and respiratory distress syndrome in newborns. You can use the drug in children of any age, even in premature infants. Perhaps the use of women in the II and III trimester of pregnancy. Side effects are rare; these are nausea, abdominal pain and allergic reactions, sometimes dry mouth and nasopharynx.

Interactions

The combination of ambroxol with antibiotics, of course, has advantages over the use of a single antibiotic, even if the effectiveness of an antibacterial drug is proven. Ambroxol helps to increase the concentration of antibiotic in the alveoli and the mucous membrane of the bronchi, which improves the course of the disease with bacterial infections of the lungs. When used together with antibiotics, the drug increases the penetration into the bronchial secretion of amoxicillin, cefuroxime, erythromycin and doxycycline, which can be a significant factor affecting the effectiveness of antibiotic therapy. A statistically significant improvement in the parameters of external respiration functions in patients with bronchial obstruction and a decrease in hypoxemia while taking Ambroxol are shown.

Lazolvan can be used together with β2-adrenergic agonists in the same nebulizer chamber. Side effects during its use are rare and occur in the form of nausea, abdominal pain, allergic reactions, dry mouth and nasopharynx [8].

Evidence base for use of expectorant drugs

Opinions on the use of mucolytics (mucoregulators) in the treatment of patients with COPD are mixed. The mucolytic properties of these drugs, their ability to reduce adhesion and activate mucociliary clearance are successfully realized in patients with COPD with dyskrinia and hypersecretion. In the same place where bronchial obstruction is associated with

bronchospasm or irreversible phenomena, mucolytics do not find a point of application. An analysis of 15 randomized, double-blind, placebo-controlled studies on the use of oral mucolytic drugs for 2 months revealed a slight decrease in the average number of days of disability and the number of exacerbations after treatment, which indicates an insignificant role of mucolytics in the treatment of exacerbation of COPD. This did not allow the inclusion of these drugs in the number of basic therapies for patients with COPD (level of evidence D). The GOLD program discussed the antioxidant effect of N-acetylcysteine derivatives and it was shown that, like N-acetylcysteine, they reduce the frequency of exacerbations of COPD. This is important for patients with frequent exacerbations (level of evidence: B). A well-known National mucolytic study conducted in the United States in stable patients with COPD showed that mucoregulators (iodinated glycerol-organidin was studied) can bring subjective relief to patients, but objective evidence of the effectiveness of the drugs was not obtained. A study of oral N-acetylcysteine by the Swedish Society of Pulmonary Diseases showed that mucolytic drugs can reduce the number of exacerbations in patients with chronic bronchitis. It was shown that, despite the weak relationship between the amount of tracheobronchial secretion and the severity of bronchial obstruction, there is a reliable correlation between the overproduction of the secretion, the number of hospital admissions to the hospital, and even the risk of death in patients with severe impaired ventilation functions. Received in the study, the results did not reveal a significant increase in FEV1 in the general group of COPD, but patients' scoring of their health and dyskrinia shows significant positive dynamics, however, in the presence of dyskrinia syndrome, FEV1 is the most objective criterion for the effectiveness of mucolytic in the treatment of COPD. Thus, when choosing therapy for patients with COPD, one should focus on a specific nosological form, taking into account the severity of one or another pathogenetic mechanism: dyskrinia, bronchospasm, obstruction.

It is not recommended to prescribe cough suppressing drugs to patients with bronchial asthma: this disrupts bronchial drainage, aggravates bronchial obstruction and, as a result, worsens the patient's condition. This applies to codeine and non-codeine drugs, for example, libexin, synecode, etc.

Most severe cases of asthma that do not respond to bronchodilator drugs are associated with widespread obstruction of the airways with mucous plugs, which leads to a progression of the obstruction process, and as a result, asthmatic status may develop. This is confirmed by the fact that in most of those who died from asthma, the lumen of the bronchi is clogged with thick and viscous sputum. This happens in cases where the rate of mucus accumulation exceeds the rate of its evacuation from the respiratory tract and elimination of mucus congestion in the lungs is possible only with the help of various expectorants. Mucolytics are widely used in Russia in patients with COPD, but in the European and American guidelines they play a modest role because of their unproven effectiveness.

The choice of drugs, monitoring their effectiveness and safety

Along with expectorant drugs, β2-adrenergic agonists and theophylline are enhanced by mucociliary transport, which, due to the expansion of the bronchi, reduction of spasm of the bronchial muscles, and reduction of mucosal edema, accelerate the movement of ciliated epithelium and increase mucus secretion.

During pharmacotherapy with expectorant drugs, a stable clinical effect is observed on the 2nd-4th day, depending on the nature and severity of the course of the disease. In patients with acute bronchospastic syndrome, the effect is observed with the appointment of beta2-adrenergic agonists, theophylline in combination with acetylcysteine or drugs that stimulate expectoration. It should be borne in mind that in a number of patients with COPD after the first day of expectorant therapy, an increase in adhesion and viscosity of sputum was noted; this, apparently,

was due to the separation of sputum accumulated in the bronchi and containing a large amount of detritus, inflammatory elements, proteins, etc. In the following days, the rheological properties of sputum improve, its quantity significantly increases, viscosity and adhesion decrease (usually by the 4th day of use of expectorant drugs), which indicates the correctness of their choice. The stabilization of the clinical effect was observed on the 6-8th day and was characterized by a decrease in the level of adhesion when used in patients with COPD with lazolvan by 49.8%, bromhexine - by 46.5%, potassium iodide - by 38.7%, bromhexine in combination with chymotrypsin - by 48.4%. Less significant changes were noted in patients taking chymotrypsin (30.0%) and mucaltin (21.3%).

In cases where there is a diffuse lesion of the bronchial tree, significant changes in the rheological properties of sputum and a decrease in mucociliary transport, it is necessary to use complex drugs that stimulate expectoration, and bromhexine; it is also logical to combine proteolytic enzymes or acetylcysteine with bromhexine.

In patients with chronic bronchospastic and inflammatory β2-adrenergic agonist syndrome, theophylline is best combined with ambroxol hydrochloride or acetylcysteine. In patients with chronic obstructive pulmonary disease (COPD), the effect of mucolytics on reducing the average number of days has not been proven the effect of mucolytics on reducing the average number of days of disability and the number of exacerbations after treatment, which indicates an insignificant role of mucolytics in the treatment of exacerbation of COPD. This did not allow the inclusion of these drugs in the number of basic therapies for patients with COPD (level of evidence D). It has been proven that N-acetylcysteine reduces the frequency of exacerbations of COPD. This is important for patients with frequent exacerbations. Despite the absence of a relationship between the amount of tracheobronchial secretion and the severity of bronchial obstruction, a significant correlation was revealed between overproduction of the secretion, the number of hospital admissions to the hospital, and even the risk of death in patients with severely impaired ventilation functions. In the presence of discriminatory syndrome, the most objective criterion for the effectiveness of mucolytic in the treatment of COPD is FEV1. When choosing therapy in patients with COPD, one should focus on a specific nosological form, taking into account the severity of one or another pathogenetic mechanism: dyskrinia, bronchospasm, obstruction.

A sharp decrease in viscosity and adhesion and a significant increase in the amount of sputum excreted cause a deterioration in the general condition, increased coughing and the appearance of dyspnea in some patients, due to bronchorrhea. With the development of these symptoms, it is necessary to cancel expectorant drugs, it is possible to attach M-anticholinergics such as ipratropium bromide (atrovent) or tiotropium bromide (spiriva).

It is not recommended to prescribe cough suppressing drugs to patients with bronchial asthma: this disrupts bronchial drainage, aggravates bronchial obstruction and, as a result, worsens the patient's condition. Most severe cases of asthma that do not respond to bronchodilator drugs are associated with widespread airway obstruction with mucous plugs, which requires the appointment of mucolytics. Mucolytics are widely used in Russia in patients with COPD, but in the European and American guidelines they play a modest role due to the lack of evidence of their effectiveness.

ANTITUSSIVE DRUGS

The drugs with antitussive effects include the following.

1. Medicines, central action

o Narcotic antitussive drugs (codeine, dextromethorphan, dionine, morphine) suppress the cough reflex, inhibiting the cough center in the medulla oblongata. With prolonged use, physical dependence develops. These drugs inhibit the respiratory center.

 Non-narcotic antitussive drugs (glaucin, oxeladine, pe-toxiverin, synecode, tussuprex, broncholitin) have an antitussive, hypotensive and antispasmodic effect, do not depress respiration, do not inhibit intestinal motility, do not cause addiction and drug dependence.

2. Drugs of peripheral action

o Libexin. The drug with an afferent effect acts as a mild analgesic or anesthetic on the mucous membrane of the respiratory tract, reduces reflex stimulation of the cough reflex, it also changes the secretion formation and viscosity, increases its mobility, and relaxes the smooth muscles of the bronchi.

o Enveloping and local anesthetics. Enveloping agents are used for coughing, which occurs with irritation of the mucosa of the upper epiglottis of the respiratory tract. Their action is based on the creation of a protective layer for the mucous membrane of the nose and oropharynx. Typically, these are lozenges or syrups of plant origin (eucalyptus, acacia, licorice, etc.), glycerin, honey, etc. Locally anesthetizing drugs (benzocaine, cyclaine, tetracaine) are used only in a hospital according to indications, in particular for the inhibition of the cough reflex during bronchoscopy or bronchography.

A group of centrally acting non-narcotic antitussives is indicated for coughing associated with irritation of the mucous membranes of the upper (epiglottis) airways due to infectious or irritative inflammation (ARVI, tonsillitis, laryngitis, pharyngitis, etc.), as well as with a dry, intrusive cough accompanied by pain and / or impairing the patient's quality of life (aspiration, foreign body, oncological process), children with whooping cough. Apply before meals 1-3 times a day (according to indications). In patients with dry cough with acute bronchitis, ingestion of foreign particles, the use of libexin, glaucin is not effective enough. In these cases, the appointment of codeine or dionine at night (within 2-3 days) is justified. With pleurisy, stagnation in the pulmonary circulation, the development of cough aggravates the course of the underlying disease and requires the use of codeine.

With the development of a cough reflex due to factors that are not associated with bronchopulmonary diseases, the use of both non-narcotic and narcotic antitussive drugs is indicated, depending on the severity of the syndrome.

The mechanism of action and pharmacological effects Narcotic antitussive drugs of central action.

These include morphine-like compounds such as codeine, ethyl morphine and dextromethorphan, which inhibit the function of the cough center of the medulla oblongata. The most famous antitussive drug of narcotic action is codeine, which is a natural narcotic analgesic from the group of opiate receptor agonists. Medicines from the codeine group are very effective, but have significant drawbacks. Their antitussive effect is not selective, they simultaneously inhibit the respiratory center. Dextromethorphan is a synthetic antitussive drug, similar in chemical structure and activity to opiates (codeine); It has a central effect, increasing the cough threshold.

Non-narcotic antitussive drugs of central action.

These include oxeladine, butamirate, glaucin, pentoxiverin, ledin and fol-codine, which have a selective central effect. They partially suppress the cough center, without having a pronounced inhibitory effect on the respiratory center. Not inferior in strength to the action of

codeine, they do not cause addiction and addiction, do not depress breathing and do not affect intestinal motility (do not cause constipation). Some antitussive drugs have additional effects that improve their effect. So, for oxeladine, butamirate and ice floes, a certain bronchodilator effect is characteristic. Butamirate also has expectorant and anti-inflammatory effects.

Non-narcotic antitussive drugs of peripheral action

This group of drugs includes prenoxdiazine, levodropropisin, benpropirin and biodiodine, which affect the afferent component of the cough reflex, acting on the mucous membrane of the respiratory tract as an anesthetic and reducing the reflex stimulation of the cough reflex. In addition, they have a local anti-inflammatory effect, contribute to the relaxation of the smooth muscles of the bronchi.

Envelope drugs also belong to the peripheral antitussive drug of afferent action. Their action is based on the creation of a protective layer on the mucous membrane of the nasopharynx and oropharynx They are oral lozenges or syrups and teas containing plant extracts of eucalyptus, acacia, licorice, wild cherry, linden, etc., glycerin, honey, etc.

One of the ways to influence the afferent part of the reflex arc is also the use of aerosols and steam inhalations to moisten the mucous membranes of the respiratory tract. Inhalation of water vapor, alone or with the addition of sodium chloride or herbal decoctions or extracts, is the most affordable method of moisturizing. Along with inhalation, a plentiful drink can be used.

Antitussive drugs with local anesthetic activity reduce the feeling of perspiration and irritation in the throat, reduce sensitivity to various irritating factors, weakening the cough reflex. The drugs are used in the form of drugs for resorption in the oral cavity.

Local anesthetics (benzocaine, cyclaine, tetracaine) are also anti-enzyme drugs, but are used only in a hospital for special indications.

Pharmacokinetics

Most drugs are well absorbed after oral administration. The maximum concentration in the blood plasma of codeine is reached after 1 h, butyrate citrate - after 1.5 hours. In the latter case, it is 6.4 μg / ml, communication with proteins is 95%. Both drugs undergo biotransformation in the liver and are almost completely excreted in the urine as metabolites and unchanged. T1 / 2 of codeine - 3-4 hours, butyrate citrate - 6 hours. The pharmacokinetics of most other drugs and their components were not studied.

Tactics for choosing cough medicines

If the reason for prescribing drugs is actually a cough, it is better to use drugs that act on a specific cause of the cough. Antitussive drugs are symptomatic therapy. To ease the cough associated with the phenomena of acute respiratory infection, moisturizing inhalations and drugs with an enveloping peripheral effect or their combination with non-narcotic central-action drugs such as prenoxdiazine are indicated. In the presence of sputum, it is advisable to prescribe expectorant drugs or mucolytics. When coughing in a patient with bronchospasm, along with hydration, it is advisable to prescribe bronchodilators and anti-inflammatory drugs, however, narcotic antitussive drugs and mucolytics are contraindicated, with the exception of bromhexine and ambroxol. For targeted suppression of unproductive cough caused by irritation of the mucous membrane of the respiratory tract (for example, with whooping cough), in children it is possible to use antitussive non-narcotic drugs of central action.

Place in therapy

Antitussive drugs are used to suppress frequent dry cough that violates the patient's condition. When coughing associated with irritation of the upper respiratory tract, the use of antitussive drugs with local anesthetic activity is indicated. They are drugs of symptomatic therapy in the treatment of inflammatory processes in the pharynx (tonsillitis, pharyngitis) and larynx (laryngitis). Actually local anesthetics are used to afferently inhibit the cough reflex during bronchoscopy or bronchography.

Contraindications and Cautions

The administration of antitussive drugs to a patient with a wet cough leads to stagnation of sputum in the airways, which worsens bronchial obstruction and may contribute to the development of pneumonia. Narcotic antitussive drugs can cause respiratory depression.

Antihistamines drugs

Historically, the term “antihistamines” means drugs that block H1-histamine receptors, and drugs that act on H2-histamine receptors (cimetidine, ranitidine, famotidine, etc.) are called H2-histamine blockers. The former are used to treat allergic diseases, the latter are used as antisecretory drugs.

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 receptors in the body for histamine was proved and their three subtypes were distinguished: H1, H2 and H3, which differ in structure, localization and physiological effects that arise during their activation and blockade. From this time, the active period of synthesis and clinical testing of various antihistamines begins.

Numerous studies have shown that 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 with drugs have a number of specific pharmacological properties that characterize them as a separate group. These include the following effects: antipruritic, decongestant, antispasmodic, 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.

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 the amino group by means of 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, although none of them are generally accepted. 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, show the generations of cardiotoxicity

In addition, according to the chemical structure (depending on the X-bond), antihistamines are divided into several groups (ethanolamines, ethylenediamines, alkylamines, derivatives of alfacarbolin, quinuclidine, phenothiazine, piperazine and piperidine).

First generation antihistamines (sedatives).

All of them are highly 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 dissolving 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 moderate 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, mono-amino oxidase inhibitors and alcohol.

• The anxiolytic effect characteristic of hydroxysine 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 increase 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 possess absence of a sedative effect and a characteristic of the second drugs 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 available in parenteral forms. All of the above, as well as low cost, determine the widespread use of antihistamines today.

Moreover, many of the qualities that were discussed, made it possible for the "old" antihistamines to occupy their niche in the treatment of certain pathologies (migraine, sleep disturbances, extrapyramidal disorders, anxiety, motion sickness, etc.) that are not related to allergies. A lot of first-generation antihistamines are part of the combined preparations used for colds, as sedatives, sleeping pills and other components.

The most commonly used are chloropyramine, diphenhydramine, clemastine, cyproheptadine, promethazine, phencarol, and hydroxyzine.

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 perennial allergic rhinoconjunctivitis, Quincke edema, urticaria, atopic dermatitis, eczema, pruritus 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) effect. At the same time, 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 injection ones, and low cost.

Diphenhydramine, the most famous in our country under the name di-medrol, is one of the first synthesized H1-blockers. It has a sufficiently 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. Di-medrol is presented in various dosage forms, including for parenteral use, which 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 means.

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 others is known antihistamines with a similar chemical structure.

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 an anxiolytic, sedative, muscle relaxant and antipruritic agent.

Thus, first-generation antihistamines that 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 drowsiness, which is rarely the cause of drug discontinuation.

• Lack of tachyphylaxis with prolonged use.

• The ability to block potassium channels of the heart muscle, which is associated with lengthening of the QT interval and heart rhythm disturbance. The risk of this side effect increases with the combination of antihistamines with antifungal (ketoconazole and intraconazole), macrolides (erythromycin and clarithromycin), antidepressants (fluoxetine,

sertraline and paroxetine), with grapefruit juice and patients with severe impaired liver function.

• Lack of parenteral forms, however, some of them (azelastine, left-cabastine, bamipine) are available as topical forms.

Below are the second generation antihistamines with the most characteristic properties.

Terfenadine - the first antihistamine, deprived of depressing

actions on the central nervous system. Its creation in 1977 was the result of a study of both the types of histamine receptors and the structural features and effects of the available H1-blockers, and laid the foundation for 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, but may 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.

Acrivastin (Semprex) is a drug with high antihistamine activity with minimally pronounced sedative and anticholinergic effects. A feature of its pharmacokinetics is a low metabolic rate and the lack 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, but differs from them by a significantly lower severity 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 aspemisole 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 are local drugs and are intended to relieve local manifestations of allergies.

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 a negligible amount 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 antihistamines of the previous generation. 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. Characteristic of him feature is the high penetration into 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 area of practical use of metabolite drugs and determined the creation of a new drug - fexofenadine.

Fexofenadine (telfast) is an active metabolite of terphe-nadine. Fexofenadine is not subjected to transformations in the body and its kinetics does 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 long-term 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, the peculiarities of pharmacokinetics, a safety profile and high clinical efficacy make fexofenadine the most promising antihistamine in the present.

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.

Three generations of antihistamines (in brackets are trade names)

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,	• 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)

pipolfen) • Trimeprazine (teralen) • Oxomazine • Alimemazine • Cyclizine • Hydroxyzine (atarax) • Meclizine (Bonin)		

Criteria for choosing antihistamines

1. The feasibility of choosing a drug with an additional anti-allergic effect:

o year-round allergic rhinitis;

o seasonal allergic rhinitis (conjunctivitis) with a duration of seasonal exacerbations> 2 weeks;

o chronic urticaria;

o atopic dermatitis;

o allergic contact dermatitis;

o early atopic syndrome in children.

2. The patient has specific problems:

o children under 12 years old:

 loratadine (Claritine)

 cetirizine (Zyrtec)

 terfenadine (Trexyl)

 astemizole (Hismanal)

 dimetinden (Fenistil)

o children 1-4 years old with early atopic syndrome:

 cetirizine (Zyrtec)

 loratadine (Claritine)

o pregnant women:

 loratadine (Claritine)

 fexofenadine (Telfast)

 astemizole (Hismanal)

o women during lactation:

 clemastine (Tavegyl)

 pheniramine (Avil)

o patients with renal failure:

 loratadine (Claritine)

 astemizole (Hismanal)

 terfenadine (Trexyl)

o patients with impaired liver function:

 loratadine (Claritine)

 cetirizine (Zytrec), fexofenadine (Telfast)

The purpose of the lesson.

To know the classification of mucolytic, antihistamines, antitussive drugs, pharmacokinetics, pharmacodynamics of the main representatives, undesirable effects, drug interchangeability, pharmacosafety

Test questions.

4. The role of infection in the development of respiratory diseases.

3. Acute respiratory diseases - definition, etiology, pathogenesis, pharmacotherapy, characteristics of the main groups, pharmacokinetics, pharmacodynamics, main representatives, undesirable effects, choice of route of administration.

4. Acute bronchitis - definition, etiology, pathogenesis, choice of drugs depending on the form, severity and stage of the disease.

5. Pneumonia. Definition, diagnostic criteria, clinical classification and treatment depending on the type of pneumonia in the light of the instructions for the diagnosis, clinical classification and treatment of pneumonia of 03.19.07 No. 128.

 Classification:

 community-acquired pneumonia,

 nosocomial pneumonia (hospital),

 suction,

 pneumonia in people with severely impaired immunity (congenital immunodeficiency, HIV infection, iatrogenic immunosuppression).

 Risk classes (PORT, RSI).

 Class I-II - place of treatment: outpatient.

 Class III - place of treatment: outpatient or inpatient.

 Class IV-V - place of treatment: inpatient or in the AIT department.

 Risk groups (CRS).

 Group I - place of treatment: outpatient.

 Group II - place of treatment: hospital.

 Group III - place of treatment: in the AIT department.

 Criteria for the severity of pneumonia.

ANTIHISTAMINE MEDICINES.

but. The concept of allergies, types of allergic reactions. Modern ideas about the etiopathogenesis of allergic diseases, stages of the allergic process. General principles for the treatment of allergic diseases (etiotropic, pathogenetic, symptomatic therapy).

b. The concept of histamine receptors, their localization and stimulation effects.

at. Classification of antihistamines.

1) glucocorticoids - prednisone, triamcinolone, betamethasone, etc .;

2) antihistamines:

 drugs that prevent the production and release of histamine and other mediators of allergy - ketotifen / zaditen /, cromolin sodium (intal, lomodal, ifiral), nedocromil (tiled mint), oxatomide / tinset /, fenspiride;

 H1-histamine blockers:

 I generation - diphenhydramine, diprazine, promethazine, clemastine, chloropyramide, chifenadine, mebhydroline, bikrafen.

 2nd generation - cetirizine, loratadine / clarithin /, ebastine, cyproheptadine, azelastine, acrivastine.mebhydroline, dimethindene, levocabastine / histimetin / terfenadine / histadine, traksil /.

 III generation - fexofenadine, desloratidine

 histamine binding agents - histaglobulin.

Anxiolytic, atropine-like, anti-emetic and anti-agonizing, anti-serotonin, local anesthetizing, protoparkinsonian, alpha-adrenergic blocking effects, as well as the development of tolerance in first-generation drugs.

D. Pharmacological and comparative characteristics of H1-histamine blockers of the 1st generation and 2nd generation, as well as the 3rd generation, the benefits of drugs of the 2nd generation of the 3rd generation. Undesirable effects.

EXPECTORANT. Classification:

a) secretomotor (stimulating expectoration):

 reflex action - thermopsis grass, thyme grass, marshmallow root, licorin hydrochloride, source root, licorice, ipecacuanh, cyanosis rhizome, sodium benzoate, terpinghydrate, essential oils (eucalyptus, etc.),

 local rehydrants of resorptive action - ammonium chloride, potassium iodide, sodium iodide;

 stimulators of bronchial glands (potassium iodide, sodium iodide);

 medicinal expectorant fees.

b) mucolytic (bronchosecretolytic):

 proteolytic enzymes - trypsin, chymotrypsin, chymopsin, ribo-nuclease,

 cysteine derivatives, thiol-containing preparations: acetylcysteine (ACC), mesna, N-acetylcysteine (fluimucil);

 preparations of the carbocysteine group: fluditec, fluifort, broncatar, mu-copront, mucodine)

 flour regulators, derivatives of vizitsin: bromhexine / bisolvon /, am-broxol / lazolvan /.

 stimulators of mucociliary function (bsta-2 agonists, theophyllines):

Mechanisms of action. Indications, contraindications for use. The choice of drug, effectiveness control. Undesirable effects. The concept of pulmonary surfactants (kurosurf, exosurf, beractant).

Antitussive drugs. Classification.

a) Preparations of central action.

 Narcotic antitussive drugs - codeine phosphate, morphine hydrochloride, ethyl morphine hydrochloride.

 Non-narcotic antitussive drugs - gluacin.

 Antitussive drugs of a peripheral effect, which have an anesthetic effect - prenoxdiazine.

Mechanisms of action. Indications, contraindications for use. The choice of drug, control of effectiveness. Undesirable effects.

The list of practical works:

Homework.

1. To study - pharmacokinetics, pharmacodynamics, indications, contraindications for the use of drugs listed in the previous section.

2. The student must be able to:

a) select the necessary drug for a particular patient, select the dose, regimen and route of administration of the drug;

b) identify criteria for evaluating the therapeutic efficacy and safety of the drugs used;

c) provide differential medical assistance with:

 ostomy bronchitis,

 pneumonia.

3. Know the drugs used in pneumonia, taking into account risk groups and classes, undesirable effects, and performance criteria.

Control of the intermediate level of knowledge.

Solving situational tasks:

1. To improve the drainage function of the bronchi, sputum discharge, a 52-year-old patient who suffers from bronchial asthma is prescribed a drug. 24 hours after the start of the drug, the patient had a sore throat, runny nose, lacrimation. Note which drug the patient received?

2 .. In a patient who was admitted for treatment to the intensive care unit for nosocomial pneumonia, complications arose after the first injections of cefotaxime, blood pressure sharply decreased, and respiratory arrhythmia appeared. An allergic history is not burdened.

Explain the possible mechanism of the developed complication. Offer emergency care activities.

3.Fill in the table on the mechanism of action of the main expectorant and mucolytic agents

Mechanism of action	**Drugs**
Stomach receptors are irritated, bronchial motility and reflex activity of bronchial ciliary epithelium are reflexively enhanced, facilitating the discharge of sputum.	
Absorbed by ingestion, stimulate the bronchial glands and enhance liquefaction of sputum, enhance the production of liquid sputum and the activity of ciliated epithelium of the bronchi	
Reduce the viscous secretion, affect its chemical and physical properties.	
Absorbed after inhalation, they are secreted by the mucous membrane of the respiratory tract, cause a rupture of disulfide bonds between mucoprotein complexes of mucus, and thus reduce the viscosity of bronchial secretions	

1. Althea root	6. Thermopsis	11. ACC
2. Licorice root	7. Sodium benzoate	12. Sodium bicarbonate
3. Elecampane	8. Ammonium chloride	13. Bromhexine
4. Plantain leaves	9. Terpinghydrate	14. Carbocysteine
5. Ledum grass	10. Potassium iodide	15. Ambroxol

1. 4. Patient N., 45 years old, complains of a dry cough, fever up to 38.50C, malaise, headache. He subsequently became ill acutely subsequently with hypothermia. it is sick 2 days. Objectively: percussion above the lungs, a clear pulmonary sound, auscultation of the breathing, dry wheezing.

What disease can be assumed in this patient? Prescribe drugs that can be recommended to a doctor for treating a patient:

1. Penicillin 6. Analgin 11. Vitamin C

2. Ampioks 7. Aspirin 12. Mukaltin

3. Gentamicin 8. Voltaren 13. Prednisone

4. Tetracycline 9. Eufillin 14. Trypsin

5. Streptomycin 10. Theophylline 15. Potassium iodide

TESTS

1. 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

2. An expectorant was prescribed for a patient with acute bronchitis, after taking which vomiting occurred. Which of the following drugs could cause a similar effect?

A. Potassium iodide

B. Bromhexine

C. Infusion of Thermopsis Herb

D. Sodium bicarbonate

E. Acetylcysteine

3. A patient with chronic bronchitis for a long time took an expectorant medicine. However, over time, he developed a runny nose, lacrimation, and itchy skin. Which component of the medicine could cause these side effects?

A. Terpinghydrate

B. Acetylcysteine

C. Infusion of Thermopsis Herb

D. Potassium iodide

E. Sodium bicarbonate

4. A woman, 32 years old, suffering from bronchial asthma, is scheduled for surgery cholecystectomy. Which of the following drugs should be included in premedication for the prevention of allergic conditions?

A. Seduxen.

B. droperidol.

C. Pipolfen.

D. Aminazine.

E. Promedol

5. When using expectorant drugs, the patient should be recommended:

A. Increase salt intake.

B. Increase the intake of plant foods.

C. Increase your intake of protein foods.

D. Increase vitamin intake.

E. Increase fluid intake.

6. In case of an overdose of expectorant drugs of reflex action, the possible occurrence in a patient is:

A. Vomiting.

B. Diarrhea.

C. Runny nose.

D. Skin rashes.

E. Hoarseness of voice.

7. A patient with exacerbation of chronic bronchitis takes lazolvan (ambroxol hydrochloride), potassium iodide, ascorutin, theophylline, biseptol. After 8 days, he developed acne-like skin rashes, acute rhinitis and swelling of the salivary glands. Consult a doctor who of the drugs could cause the indicated phenomena:

A. Potassium iodide.

B. Ambroxol hydrochloride.

S. Biseptol.

D. Ascorutin.

E. Theophylline.

8. A patient with a strong dry cough came to the pharmacy. What kind of remedy do you recommend to use for the patient in order to suppress the unproductive cough reflex?

A. Trypsin.

B. Potassium iodide.

S. Libexin.

D. Acetylcysteine.

E. Sodium bicarbonate.

9. A patient with pneumonia has a dry cough that causes sharp pain in chest cavity. What drug should be included in the complex treatment of pneumonia to suppress cough?

A. Camphor.

B. Infusion of thermopsis herb.

C. Salbutamol.

D. Codeine phosphate.

E. Metacin.

10. What drug should be prescribed for chronic bronchitis with dense sputum of a purulent nature?

A. Salbutamol

B. Codeine Phosphate

C. Ipratropium

D. Glaucine hydrochloride

E. Bromhexine

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. 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.

13. 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

14. Select a condition that is not necessary when prescribing expectorant drugs:

A. Additionally, drink 15-20% of the fluid due to pathological losses

B. Limit the use of diuretics

C. Limit the use of drugs that inhibit the cough reflex (codeine, glaucin)

D. Limit the appointment of 1st generation histamine-lithics

E. * Limit antibiotic use

15. II generation antihistamines differ from I generation antihistamines in that:

A. They cause dry mouth

B. They cause ataxia, tinnitus

C. They cannot be administered parenterally

D. * They are active substances. E. They affect the late phase of the allergic response.

16. 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.

17. 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

18. 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

19. 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

20. 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

21. A patient with chronic bronchitis took an expectorant medicine for a long time. However, over time, he developed a runny nose, lacrimation, and itchy skin. Which component of the medicine could cause these side effects?

A. Terpinghydrate

B. Acetylcysteine

C. Infusion of Thermopsis Herb

D. * Potassium iodide

E. Sodium bicarbonate

22. 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 in anaphylactic shock?

A. Suprastin.

B. * Prednisolone.

C. Calcium chloride.

D. Diphenhydramine.

E. Ephedrine hydrochloride.

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 INFLUENCING THE VOLUME OF VESSELS AND BRAIN BLOOD

Purpose of the topic.

Among the main causes of death in our country in recent years, mortality from diseases of the circulatory system is almost 61%. Severe vascular lesions lead to disability of the population. In recent years, there has been an increase in the incidence associated with damage to not only coronary, but also peripheral vessels, especially the brain and lower extremities. Smoking, alcohol, metabolic disorders, injuries, emotional stress, infection, autoimmune disorders lead to diseases of the lower extremity vessels such as obliterating endarteritis, atherosclerosis, Raynaud's disease, thrombophlebitis and others. Pharmacological regulation of cerebral circulation is one of the most important problems of medicine. This is due to the fact that acute and chronic disorders of the blood supply to the brain are one of the main causes of mortality and disability of the population. To acute brain disorders blood circulation can lead to cerebral arteriosclerosis, spasm, thrombosis, hypertension and others. Depending on the cause and type of pathology, various cerebrovascular agents are used. Therefore, an urgent problem is the study of pharmacological agents used in cases of cerebrovascular circulation in the extremities. Medicines that affect vascular tone are widely used in many diseases.

Motivational characteristic of the topic.

Drug regulation of vascular tone is the most important area of activity of a practitioner, which allows saving a patient’s life in emergency situations (shock, collapse, impaired coronary circulation, etc.), and conducting effective secondary prophylaxis of a number of widespread diseases (IHD, primary hypotension, etc.). Knowledge of the main groups of drugs that affect systemic vascular tone, the ability to rationally use them in a particular patient, conduct combination therapy and prevent side effects determine the importance of this topic

MEANS AFFECTING VASCULAR TONUS

Drugs that increase vascular tone

I drugs of central action.

1. Psychostimulants,

2. Analeptics,

3. Toning drugs.

II *drugs stimulating the peripheral nervous system*

1. Stimulants of alpha and beta adrenergic receptors (adrenaline, ephedrine)

2. Stimulants primarily alpha-adrenergic receptors (norepinephrine, mesa tone).

3. Stimulants of dopamine, alpha and beta adrenergic receptors (dopamine).

III. Drugs mainly of myotropic action: angiotensinamide.

PSYCHOSTIMULATORS - psychotropic substances that activate the mental and, to a lesser extent, physical activity of the body. They stimulate higher mental functions, quickly relieve fatigue, drowsiness, and lethargy, increase efficiency. Many of the drugs in this group are addictive and addictive. The group of psychostimulants can include both drugs and commonly

available drugs (tea, coffee, tobacco), as well as illegal drugs.

Drugs of other pharmacological groups (for example, some antidepressants, nootropics, adaptogens, etc.) can also have a psychostimulating effect.

The classification of psychostimulants is based on their chemical structure.

The main representatives of psychostimulants and drugs with psychostimulating effects

Amphetamine sulfate (phenamine) derivatives of phenylalkylamine	Derivatives of phenylalkyl sidnonimine Sydnocarb, Sydnophen
Derivatives of piperidine Methylphenidate (Meridil, Ritalin, Centedrine)	
Chemical structure Drugs	Xanthine derivatives Caffeine, caffeine-sodium benzoate
Amphetamine sulfate (phenamine) derivatives of phenylalkylamine	Derivatives of phenylalkyl sidnonimine Sydnocarb, Sydnophen

Currently, for medical reasons, psychostimulants are used for nonpsychotic disorders of various etiologies with a predominance of anergic disorders, asthenic and apathetic symptoms, with narcolepsy (increased drowsiness), and torpid forms of mental retardation in children. The use of drugs of this group is becoming increasingly important -benno sydnocarb and methylphenidate, in children with attention deficit hyperactivity disorder (over the age of 6 years).

In addition, in healthy people, drugs of this group can be used for fatigue in order to increase mental and muscle performance. At the same time, psychostimulants only mobilize the body's reserves and do not eliminate the need for normal rest and restoration of strength.

Caffeine, in addition to the indications considered, is used for migraines, and as a drug with pronounced analeptic properties, for arterial hypotension and respiratory depression

In the 30s and 40s of the 20th century, psychostimulants were used not only to increase efficiency, but also to treat bronchial asthma. Then attempts were made to prescribe phenamine as an anorexigenic in obese patients. Data on the property of these drugs to cause drug dependence appeared a long time after their introduction into medical practice - only in 1947.Today, there is a widespread use of psychostimulants around the world without medical indications - as narcotic drugs - in connection with euphoric properties. First of all, we are talking about phenamine and several more legally produced and more than 50 illegally synthesized analogues of it. Caffeine abuse is often found. This important fact increases the relevance of the analysis of side effects of this group of drugs.

According to the mechanism of therapeutic action and the development of side effects, there are significant differences between individual psychostimulants.

Caffeine, which combines a psychostimulating effect with a pronounced analeptic effect, is a competitive blocker of adenosine receptors of types A1 and A2. Adenosine, stimulating these receptors, inhibits the release of catechol-mines, causes CNS depression, reduces strength and

heart rate, as well as renal blood flow and renin release, reduces lipolysis in adipose tissue, and enhances the release of histamine from mast cells. Caffeine, an antagonist of adenosine, has the opposite effect. It also enhances the release of norepinephrine from the presynaptic membrane, sensitizes dopaminergic systems, and contributes to an increase in intracellular calcium content. In addition, caffeine inhibits the enzyme phosphodiesterase, which leads to a decrease in destruction and the accumulation in the cells of cyclic adenosine monophosphate (cAMP). This link of the mechanism of action, most pronounced in the brain and in the myocardium, is realized mainly when using high doses of caffeine.

Phenylalkylamines are characterized by a different mechanism of action. These substances are indirect adrenomimetics (sympathomimetics), i.e., they promote the release of norepinephrine, dopamine and serotonin from the presynaptic device and disrupt the return of these mediators to the presynaptic end. Inhibition of the enzyme monoamine oxidase (MAO), which destroys mediator monoamines, is also important. As a result, the concentration of norepinephrine, dopamine, and especially serotonin in the synaptic cleft increases. In addition, direct excitation of α- and β-adrenergic receptors is possible, but this link in the mechanism of action plays a secondary role. Sympathomimetic effects are realized both in the central nervous system and on the periphery, especially in the cardiovascular system. This determines a significant part of the side effects and contraindications to the use of phenamine, which will be discussed in detail below. A similar mechanism of action is also characteristic of phenylalkylsidnonimine derivatives and piperidine, but they mainly enhance noradrenergic processes, and the main target of these drugs is the central nervous system. The peripheral sympathomimetic effects for them are less characteristic than for phenamine, therefore, side effects from the cardiovascular system are less frequent and less pronounced.

Before analyzing the side effects of psychostimulants, it is necessary to note that the drugs in this group, especially phenamine, act quite harshly on the body. They can cause uneconomical, depleting expenditure of energy resources of the body, and in extreme conditions (hypoxia, fever, etc.) the psychostimulating effect is reduced and even perverted, and the quality of complex activity is reduced. In this regard, it is important to observe the conditions for the effective and safe use of psychostimulants. The condition for their effectiveness is the use against the background of fatigue (but not overwork) and in uncomplicated conditions of activity. A safety condition should be considered a short intake of drugs in order to increase mental and muscle performance during fatigue, which reduces the likelihood of dependence formation with subsequent proper rest and nutrition to restore the body’s energy resources. In children with attention deficit hyperactivity disorder, treatment with psychostimulants lasts a long time - up to 2-3 years, which increases the risk of side effects. In addition, psychostimulants can not be taken before bedtime, since these drugs often cause its disturbance.

Characterization of side effects of psychostimulants

The most typical for all drugs are anxiety, psychomotor agitation, insomnia, the ability to cause drug dependence (especially in phenamine and other phenylalkylamines, to a lesser extent in other drugs), and infrequent allergic reactions (skin rash).

Caffeine can cause not only side effects from the central nervous system, but also tachycardia, arrhythmias, chest pains, increased blood pressure, and nausea. Pain in the epigastrium is sometimes noted, especially when using Natochak, which is associated with a stimulating effect on the secretion of gastric juice.

With prolonged use of large amounts of caffeine, its side effects are most pronounced. These include anxiety syndrome, hypochondriacal disorders with complaints of general weakness, pain of various localization. These phenomena can be observed in individuals consuming 250-750 mg of caffeine (3-6 cups of coffee) per day. In addition, sleep disturbances with difficulty falling

asleep, an increase in the duration of the paradoxical phase, increased motor activity in sleep, and morning headache are typical; depressive states (more often with more than 750 mg of caffeine per day). Often there are tremors, paresthesias, tinnitus, rapid urination. Diarrhea associated with increased secretion of the small intestine, which stimulates the motility of the colon, and reflux esophagitis as a result of dysfunction of the lower esophageal sphincter are also possible. Metabolic disorders are often noted - an increase in the level of glucose and lipids in the blood due to increased glycogenolysis, gluconeogenesis and lipolysis, as well as glucosuria and ketonuria.

Addiction develops to caffeine. The weakening of the psychostimulating effect is apparently associated with the formation of new adenosine receptors in the brain cells.

A rather dangerous side effect of caffeine is the formation of dependence. The term “caffeineism” is sometimes used to denote this dependence, and in the case of abuse of hard-brewed tea, “theism”. Manifestations of withdrawal symptoms are headache, yawning, nausea, vomiting,

, runny nose, increased irritability, mental depression.

Of particular note is the effect of caffeine on the fetus and the body of the newborn. In high doses, this substance can cause fetotoxic and teratogenic effects, partly due to excessive release of catecholamines.

Phenamine causes agitation, speech arousal, tremors, sleep disorders, which is associated with the activation of the reticular formation of the brain. The appearance of ticks and their strengthening is possible if they took place before the appointment of the drug. Often, taking phenamine is accompanied by a headache, depressive symptoms, acute delusional disorders are possible. A characteristic side effect is an increase in body temperature.

As a result of the activation of peripheral adrenergic receptors, phenamine more often than other psychostimulants causes tachycardia, arterial hypertension, dilated pupils, increased uterine tone, inhibition of peristalsis of the gastrointestinal tract, increased tone of the sphincter of the bladder with difficulty urinating.

Sometimes, due to a decrease in appetite, a decrease in body weight is noted. Possible decrease in sexual desire and potency. Side effects are also known as accommodation disturbances, dry mouth.

Cases of severe nervous exhaustion with severe somatic pathology are described: the development of dilated cardiomyopathy, aneurysms, keratopathy, purulent-septic complications

There may be paradoxical reactions to phenamine - drowsiness and apathy instead of arousal, decreased performance. Apparently, they arise in cases where the influence of the drug on the cerebral cortex predominates, since the stimulating effects are due to the activation of subcortical structures - the reticular formation, neostriatum.

Addiction quickly develops to phenamine, requiring a dose increase to achieve stimulating effects, but due to the small breadth of the therapeutic effect, increasing the dose threatens the development of poisoning.

Phenylalkylamines are characterized by the ability to cause euphoria and the easy development of addiction. Discontinuation of phenamine causes symptoms of abstinence - a psychotic state, depression, which may be accompanied by suicidal attempts, a long period of increased drowsiness (sleep normalizes only after 2-3 months). Patients after prolonged use of phenamine require observation and treatment by a psychiatrist.

Phenamine causes pronounced metabolic disorders of neurotransmitters (norepinephrine, serotonin, GABA, and others) in the fetal brain, which leads to the so-called behavioral teratogenesis. The experiment revealed a decrease in motor activity in the offspring of animals that received phe-namine during pregnancy. Cases of phenamine interference in the human CNS morphogenesis are known, which leads to the birth of children with spina bifida and exencephaly

Sydnocarb and Sydnophen in comparison with phenamine are characterized by better tolerance. Sydnocarb is used more often, which surpasses phenamine in the strength and duration of the psychostimulating effect. Among its side effects are sleep disturbances, irritability, aggravation of productive symptoms in mentally ill patients (therefore, patients with psychotic disorders of sydnocarb are prescribed only in a hospital), and appetite deterioration. Possible increase in depressive symptoms. Since sydnocarb has little effect on the cardiovascular system, only in rare cases is there a moderate increase in blood pressure. The ability to cause addiction is weakly expressed, and some authors even deny it. Side effects occur with dose reduction or temporary discontinuation of the drug. Sidnofen is used relatively rarely, differs from sydnocarb in a less pronounced psychostimulating effect and a slight antidepressant effect.

According to the spectrum of side effects, methylphenidate is generally close to phenylalkyl sidononyms. The most common sleep disturbances, irritability, loss of appetite, weight loss, less commonly, abdominal pain, nausea, constipation, headaches. The main differences between methylpheniadate and Sydnocarb and Sydnophene are that it can cause anxiety and dyspeptic symptoms, and it has practically no effect on the cardiovascular system. In addition, there is evidence of the ability of methylphenidate to delay physical development - stunted children. The mechanism of this side effect is associated with a violation of the natural daily rhythm of secretion of growth hormone with a maximum at night: increased hormone secretion during the day.

Contraindications to the use of psychostimulants

The state of psychomotor agitation, anxiety and anxiety disorders, severe atherosclerosis and cardiovascular diseases, drug abuse and drug dependence in history, alcoholism, arterial hypertension, hyperthyroidism, psychosis, epilepsy and other convulsive disorders, impaired renal and liver function, tics, Tourette syndrome and other hyperkinetic disorders, cross-sensitivity to psychostimulants and other adreno-and sympathomimetic drugs, sleep disturbances, as well as children (up to 6 years old) and senile age.

Caffeine, in addition, is contraindicated in case of high sensitivity to other xanthine derivatives (theophylline, aminophylline, theobromine), glaucoma.

Pregnancy and lactation are also contraindications to the appointment of most psychostimulants, and the use of caffeine and drinks containing it should be limited, especially in the first trimester of pregnancy

The interaction of psychostimulants with other drugs, enhancing side effects

Psychostimulants can not be prescribed simultaneously with antidepressants, adrenergic agonists, ephedrine, since the risk of a sharp increase in blood pressure increases.

With the combination of psychostimulants with tricyclic antidepressants (amitriptyline, imipramine, etc.), it is possible to increase sympathomimetic effects, which is manifested by the development of cardiac arrhythmias, tachycardia, arterial hypertension and hyperthermia. Monoamine oxidase (MAO) inhibitors, including nialamide, furazolidone, procarbazine, selegiline, can enhance the stimulation of the heart and the pressure effects of amphetamines. Therefore, phenamine and related drugs should not be prescribed earlier than 14 days after the

cancellation of MAO inhibitors.

The use of sympathomimetics and levodopa together with phenylalkylamines and their analogues can lead to the development of severe psychomotor agitation, insomnia, convulsive syndrome, and also to increase the effect of sympathomimetics on blood vessels and the heart.

Psychostimulants cannot be combined with M-anticholinergics (atropine, platifillin, metacin, etc.), since the latter, by inhibiting parasympathetic influences, contribute to the predominance of sympathetic, which in turn are amplified by the influence of psychostimulants. As a result, potentiation of the side effects of the latter, in particular, from the cardiovascular system, is possible.

With the simultaneous administration of phenamine with β-blockers the likelihood of developing excessive bradycardia and atrioventricular block is increased. When combined with cardiac glycosides, the risk of developing arrhythmias increases.

Amphetamines can potentiate the side effects of thyroid hormones on the heart. In particular, the risk of developing coronary insufficiency increases. Large doses of propoxyphene can enhance the central stimulatory effect of amphetamines, with a fatal convulsive syndrome.

Agents for inhalation anesthesia (fluorotan and, to a lesser extent, en-fluran) can increase the sensitivity of the myocardium to the action of sympathomimetic drugs, including phenamine, thereby increasing the risk of developing severe ventricular arrhythmias.

Means that alkalinize urine (sodium bicarbonate, diacarb carbonic anhydrase inhibitor) enhance the effect of phenamine due to a slowdown in its elimination from the organism. Against the background of ammonium chloride and other drugs that acidify urine, the effects of phenamine, on the contrary, are weakened due to accelerated excretion from the body.

The combination of caffeine with other xanthine derivatives (aminophylline, theophylline, theobromine), as well as bronchodilators from the group of adrenergic agonists may increase the risk of side effects. Cimetidine, macrolide antibiotics, ciprofloxacin, enoxacin, oral contraceptives, disulfiram inhibit caffeine metabolism and increase its overall clearance.

The antiarrhythmic drug mexiletine is able to significantly reduce the excretion of caffeine and enhance its stimulating effects.

ANALEPTICS (from the Greek. Analēptikos - restoring) - drugs that have a strong stimulating effect on the respiratory and vasomotor centers of the medulla oblongata [1] directly (caffeine, camphor, bemegrid), or by increasing their sensitivity (strychnine), which stimulates vital important respiratory and circulatory functions. Some analeptics can, in addition, stimulate other parts of the central nervous system, which in case of an overdose causes seizures.

They are used to reduce vascular tone, respiratory depression (in particular, poisoning) and cardiac activity, shock, and for the general stimulating effect on the body in infectious diseases, in the postoperative period, etc. Previously, analeptics (corazole, camphor) were widely used for asphyxiation, but after the advent of modern equipment for artificial ventilation of the lungs, “chemical” respiratory stimulators practically lost their significance, with the exception of some cases of emergency care. Bemegrid, being a specific antagonist of barbiturates, is used in case of poisoning by them.

Drugs that lower vascular tone.

I. Classification of drugs that lower vascular tone.

1. Central action drugs.

 Antagonists of central α1-adrenergic receptors and

I1-imidazoline receptors.

2. Drugs affecting the peripheral nervous system.

 Ganglion blockers.

 Cute.

 α-blockers (non-selective α-blockers and selective α1-blockers).

 β-blockers (non-selective β-blockers and selective β1-blockers).

 α- and β- adrenergic blockers.

1. Drugs, myotropic effects (vasodilators).
2. Venous vasodilators (organic nitrates and nitrites, sydnimines).
3. Mixed action vasodilators (sodium nitroprusside).
4. Arterial vasodilators (potassium channel activators, hydralazine).
5. Slow calcium channel blockers (phenylalkylamines, dihydropyridines, benzotazepines, diphenylpiperazines).

4. Reducing the activity of the renin-angiotensin-aldosterone system.

 ACE inhibitors.

 Antagonists of receptors of the first type of angiotensin II.

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF MEDICINES AFFECTING THE BRAIN BLOOD

The brain receives from 15 to 20% of the minute volume of blood. The constancy of blood flow with changes in systemic blood pressure is due to a change in resistance in the system of the main arteries, mainly the internal carotid and vertebral. Regulation of adequate blood supply to the brain tissue in accordance with its metabolic needs and functional redistribution of local blood flow occurs due to changes in the resistance of small vessels. The mismatch between the oxygen demand of the brain tissue and its delivery leads to the development of various forms of cerebrovascular accident. These can be (according to the classification of E.V. Schmidt): 1) the initial manifestations of a lack of cerebral circulation; 2) transient cerebrovascular accidents (transient ischemic attacks, cerebral crises); 3) strokes; 4) discirculatory encephalopathy.

In the pathogenesis of ischemic disorders of cerebral circulation, inadequate changes in the tone of the vascular wall in the form of spasm or pathological vasodilation are of great importance. Therefore, for the correction of cerebral discirculatory disorders, drugs are used that affect vascular tone - vasoactive drugs. The mechanism of their action is associated with a direct effect on smooth muscle (cinnarizine, flunarizine, derivatives of nicotinic acid, papaverine), a-adrenergic blocking action (dihydroergotoxin, dihydroergocristine, nicergoline), and inhibition of the central nervous system vasomotor centers (dihydrohydroergyrrhydroergide).

In acute ischemic cerebrovascular accident, cerebral vasodilators are used to normalize cerebral circulation in the ischemic and peri-infarction zone, which helps to restore the activity of viable neurons. However, the action of vasodilators may be accompanied by a decrease in systemic

blood pressure, a decrease in perfusion pressure and a deepening of cerebral ischemia. Reducing the tone of not only arteries, but also veins can disrupt the venous outflow, increase intracranial hypertension and provoke cerebral edema. In addition, the brain after the development of a stroke is a complex mosaic of areas with different levels of blood flow, from areas with reduced perfusion to areas of hyperperfusion. Local autoregulation in the lesion is impaired. Resistive cerebral vessels are compensatory dilated and do not respond well to pharmacological agents. Therefore, vessels of non-ischemic zones of the brain are primarily responsible for administering vasoactive drugs, causing redistribution of blood flow in their favor (robbery syndrome).

The use of vasodilators for the treatment of chronic forms of cerebrovascular disorders is pathogenetically more justified. In patients with dyscirculatory encephalopathy (regardless of its etiology), significant changes in cerebral blood flow. Vasoactive drugs, reducing the resistance of cerebral vessels, cause an increase in both total hemispheric and regional blood flow. This contributes to better oxygenation of brain tissue, normalization of metabolic processes and improvement of the clinical condition of patients. The correct choice of drug is of great importance. Vascular-active agents, especially in large doses, along with the expansion of the cerebral vessels, can significantly reduce the total peripheral resistance, reduce systemic blood pressure, which in conditions of chronic cerebrovascular insufficiency can lead to the progression of ischemic damage to the brain tissue. Such complications are described for papaverine, no-shpa, nicotinic acid and its derivatives. Therefore, for the correction of cerebral vascular disorders, it is desirable to use selective vasoactive drugs, in therapeutic doses that do not affect the indicators of central hemodynamics.

A certain place in the pathogenesis of ischemic disorders of cerebral circulation is occupied by changes in the physicochemical properties of blood, an increase in the functional activity of its shaped elements, which leads to a slowdown of blood flow, disturbance of microcirculation, and a change in metabolism. Many clinical manifestations of cerebral vascular insufficiency (symptoms of cerebral stenosis, extrapyramidal disorders, mental changes) are caused by imbalance of neurotransmitters in the central nervous system. In this regard, drugs that affect various parts of the pathogenesis of discirculatory disorders are the means of choice for the treatment of cerebrovascular disorders

1. Classification of cerebrovascular agents.

I. Agents affecting blood aggregation and coagulation:

1) ANTI-AGGREGANTS: acetylsalicylic acid, ticlopidine.

2) ANTICOAGULANTS: heparin, warfarin, syncumar, phenyline.

II. Means that increase cerebral blood flow:

1) MYOTROPIC PRODUCTS:

1. Derivatives of vincamic acid to-you: vincamine (devinkan, minorin), vinpocetine (cavinton), vincanor (vincapan, vincaton).

2. Derivatives of xanthine and purine: pentoxifylline (trental), xanthinolum nicotinate (compliment, theonicol), aminophylline (aminophylline).

3. Myotropic antispasmodics: • derivatives of isoquinoline - papaverine hydrochloride, drotaverine hydrochloride (no-spa), benzimidazole derivatives - bendazole hydrochloride (dibazole).

4. Drugs of other groups: nicotinic acid, picamilon

2) ALPHA-ADRENOLYTICS (from ergot alkaloids derivatives): dihydroergot-min mesylate (ditamine), dihydroergotoxin methanesulfonate (redergin), dihydroergocristine, nicergoline (sermion).

3) SEROTONIN ANTAGONISTS: pisotifen maleate (sandomigran), metisergide (deseryl), cyproheptadine hydrochloride (peritol), iprazochrome (divaskan).

4) CALCIUM ANTAGONISTS: prod. 1,4-dihydropyridine - nimodipine (nimotope), others - cinnarizine (stugeron), flunarizine hydrochloride (sibelium).

5) COMBINED DRUGS: papazol (papaverine + dibazole), nicoverin (papaverine + nicotinic acid), instenon (hexobendin + ethamivan + etofillin), baralgin (analgin, pitofenon, fenpiveronium) - trigan, spazgang, spazgang, spazgang, spazgang, spazgang, spazgang, spazgan baralgan), bishpan (isopropamide + no-spa), nicoshpan (nicotinic acid + no-spa), papazol (papaverine + dibazole), andipal (analgin + dibazole + papaverine + phenobarbital), bepasal (phenyl salicylate + papaverine belladonna extract), tefafillin (platifillin + papaverine + phenobarbital + theobromine), palyufin (platifillin + pap averin + phenobarbital), teoverin(theobromine + papaverine + barbamil), theodibaverin (theobromine + papaverine + dibazole), amazole (amidopyrine + dibazole), teminal (theobromine + amidopyrine + phenobarbital), theofedrine (theophylline, theobromine, caffeine, phenedin, amidephedrine belladonna extract, cytisine), theo-astachalin (theophylline + salbutamol).

There are acute and chronic disorders of cerebral circulation.

Acute cerebrovascular accidents can occur due to spasm, thrombosis or embolism of the brain vessels (ischemic stroke), for example, against the background of atherosclerotic vascular lesions (especially stenosis of the carotid and vertebral arteries). Another form of acute cerebrovascular accident is cerebral hemorrhage (hemorrhagic stroke), which can be caused by arterial hypertension, rupture of aneurysm, etc. With prolonged and severe ischemia, brain tissue necrosis develops.

Chronic disorders of cerebral circulation are usually associated with age-related changes, including vascular atherosclerosis, arterial hypertension, and metabolic disorders in the brain tissue. At the same time, gradual memory impairment, intellectual impairment, other changes in the mental sphere, and motor disorders are observed.

One of the main methods for the prevention and treatment of chronic ischemic cerebrovascular accidents is the use of drugs that expand the blood vessels of the brain (increase cerebral blood flow), to a lesser extent affecting systemic hemodynamics. These drugs can also be used to treat residual symptoms after acute cerebrovascular accidents (mainly after ischemic strokes). Such drugs include certain calcium channel blockers (nimodipine, cinnarizine), derivatives of vinca alkaloids (vinpocetine), GABA derivatives (nicotinoyl-GABA), some ergot alkaloids derivatives (nicergoline), nicotinic acid derivatives (xanthine and nicotine nickel Of these drugs, nimodipine, vinpocetine, and GABA derivatives exert a predominant (more selective) effect on the vessels of the brain. Nicergoline, xanthinol nicotinate, cinnarizine also dilate peripheral vessels, they are used for peripheral circulation disorders (Raynaud's disease, diabetic angiopathy, etc.).

Some drugs can improve cerebral circulation, not only due to the expansion of blood vessels, but also by improving the rheological properties of blood, such as cinnarizine, vinpocetine, pentoxifylline, etc.

CALCIUM CHANNEL BLOCKERS

Nimodipine (nimotope *), cinnarizine (Stugeron *). Nimodipine and cinnarizine block the entry

of Ca2 + ions into the smooth muscle cells of brain vessels, which leads to a decrease in vascular tone.

Nimodipine is a calcium channel blocker, a derivative of 1,4-dihydropyridine, mainly expands the arterioles of the brain and increases cerebral blood flow without a significant decrease in systemic blood pressure. May prevent or eliminate cerebrovascular spasm.

Nimodipine is used for the prevention and treatment of cerebrovascular accidents (after acute cerebral ischemia, in chronic cerebral ischemia). Nimodipine is the only drug in this group that can be used to reduce neurological disorders after a sub-arachnoid hemorrhage. The drug is prescribed orally (quickly and completely absorbed from the gastrointestinal tract, the maximum concentration in the blood is reached after 0.5-1 hours), and with acute ischemia of the brain intravenously.

The most common side effects of nimodipine are a decrease in systemic blood pressure (with intravenous administration), reflex tachycardia. Less commonly noted are feelings of heat and flushing of the face, gastrointestinal upsets, increased liver transaminases and decreased renal function. The drug has virtually no effect on myocardial contractility.

Cinnarizine - a calcium channel blocker that has a tropic approach to the arterioles of the brain, reduces the response of vascular smooth muscle cells to endogenous vasoconstrictors

(catecholamines, bradykinin, angiotensin, vasopressin, etc.), moderately dilates peripheral vessels. The rheological effects of cinnarizine are to increase the ability of red blood cells to deform and reduce the increased viscosity of blood. This leads to improved microcirculation in ischemic areas of the brain.

Cinnarizine is used in cases of residual effects after a stroke and traumatic brain injury, for the prevention and treatment of peripheral blood circulation disorders. In addition to affecting cerebral blood flow, cinnarizine exhibits moderate antihistamine activity. The drug reduces the excitability of the vestibular apparatus, as a result of which it is used to prevent sea and air sickness (motion sickness), 25 mg is prescribed 30 minutes before the upcoming trip, if necessary again after 6 hours.

Side effects: dry mouth, drowsiness, dyspeptic symptoms. With prolonged use, a control study of liver, kidney, and peripheral blood picture is recommended.

Derivatives of alkaloids

Vinpocetine (Cavinton *) - a semisynthetic derivative of the vinca min alkaloid contained in the periwinkle plant (Vinca minor L. and Vinca erecta), mainly dilates the blood vessels of the brain. The myotropic antispasmodic effect of the drug is associated with inhibition of phosphodiesterase, which contributes to the accumulation of cAMP in smooth muscle cells. Vinpocetine does not cause the "robbery" phenomenon; without affecting the blood supply to intact areas, it enhances the blood supply to ischemic areas of the brain. Vinpocetine improves cerebral circulation (microcirculation) not only due to the expansion of the blood vessels of the brain, but also by increasing the ability of red blood cells to deform, which leads to a decrease in increased blood viscosity, since platelet aggregation is reduced. In addition, vinpocetine increases the resistance of the brain to hypoxia, increases oxygen utilization, enhances the absorption and metabolism of glucose with a switch to an energetically more favorable, aerobic oxidation pathway.

Vinpocetine is indicated for chronic cerebrovascular insufficiency, conditions after a stroke, neurological and mental disorders in patients with cerebrovascular insufficiency, for vascular diseases of the eyes and decreased hearing acuity of vascular or toxic genesis. Assign inside for a

long time. If necessary, administered intravenously.

Side effects: decreased blood pressure, nausea and dizziness. With rapid intravenous administration, tachycardia, extrasystole, and slowing of intraventricular conduction are possible.

ERKIN ALKALOID DERIVATIVES

Nicergoline (sermion *) is a synthetic derivative of ergot alkaloids, with an attached bromo-substituted nicotinic acid residue. The vasodilating effect of the drug is associated with α-adrenergic blocking and direct myotropic action. Expands the arterioles of the brain and peripheral vessels. Improves cerebral, pulmonary, renal blood flow and blood supply to the limbs.

It is used for cerebrovascular accidents against the background of atherosclerosis and thromboembolism, for peripheral circulatory disorders, etc. It is administered orally and parenterally. When taken orally in therapeutic doses, it does not affect blood pressure, after intravenous administration a hypotensive effect is possible. Of the side effects, dizziness, itching, and dyspeptic disorders are also possible.

NICOTIC ACID DERIVATIVES

Niacin has a pronounced vasodilating effect on both peripheral vessels and cerebral vessels. Nicotinic acid is poorly tolerated (see the chapter "Means used for atherosclerosis"), therefore, for cerebrovascular disorders, its derivatives with less pronounced side effects are used.

Xantinol nicotinate (Complamin *) in its structure has elements of nicotinic acid and theophylline. The drug dilates the peripheral vessels and vessels of the brain, improves both peripheral and cerebral blood circulation, reduces the effects of brain hypoxia, and somewhat reduces platelet aggregation. The drug is used for disorders of peripheral and cerebral blood circulation associated with atherosclerosis of the cerebral vessels.

Nicotinoyl-GABA (Picamilon *) belongs to the group of GABA derivatives, combines the structure of GABA and nicotinic acid, and predominantly dilates the blood vessels of the brain.

Xanthine derivatives

Pentoxifylline (trental *, agapurin *) is similar in chemical structure to theophylline, blocks adenosine receptors and, being an inhibitor of phosphodiesterase, increases the content of cAMP in vascular smooth muscle cells, which is associated with its moderate vasodilator (up to 18 years old) and old (over 65 years old) age.

For the relief of migraine attacks, ergot alkaloids (ergotamine) and their dihydrogenated derivatives (dihydroergotamine) are used. Dihydroergotamine (dihydergot *) stimulates 5-HT receptors, in particular 5-HTID receptors, and is used as a nasal spray to quickly stop a migraine attack. To eliminate vomiting that occurs with migraines, antiemetics (metoclopramide) are prescribed. For the prevention of migraine attacks, an antagonist of 5-HT2 receptor metisergide *, as well as β-blockers (propranolol), tricyclic antidepressants (amitriptyline), antiepileptic drugs (carbamazepine, clonazepam) are used.

The purpose of the lesson.

Know the classification of drugs that affect vascular tone, use, characteristics of the main groups, undesirable effects, drug interchangeability, pharmacosafety. To know the classification of drugs used for circulatory disorders in the extremities, the characteristics of the main groups, undesirable effects, the interchangeability of drugs.

Test questions.

Drugs affecting vascular tone (Kukes V.G. 2006)

A. Drugs that increase vascular tone.

I drugs of central action.

4. Psychostimulants,

5. Analeptics,

6. Toning drugs.

II drugs stimulating the peripheral nervous system

1. Stimulants of alpha and beta adrenergic receptors (adrenaline, ephedrine)

a) Localization of alpha and beta adrenoreceptors.

b) Mechanism of action, pharmacodynamic effects, pharmacokinetics.

c) Indications for use - immediate allergic reactions, anti-shock therapy, hypoglycemic coma, SBO.

d) Pharmacotoxicodynamics, contraindications.

e) Drug Interactions.

2. Stimulants primarily alpha-adrenergic receptors (norepinephrine, mesa tone).

a. The mechanism of action, pharmacodynamic effects, pharmacokinetics.

b. Indications for use, dosing regimen - acute arterial hypotension, antishock therapy, overdose of ganglion blockers and other hypotensive drugs.

c. Pharmacotoxicodynamics, contraindications.

3. Stimulants of dopamine, alpha and beta adrenergic receptors (dopamine).

 Mechanism of action, pharmacodynamic effects, pharmacokinetics.

 Indications for use, dosing regimen - arterial hypotension, anti-shock therapy, heart failure, etc.

 Pharmacotoxicodynamics, contraindications.

 Drug interaction.

III. Drugs mainly of myotropic action: angiotensinamide.

 Mechanism of action, pharmacodynamic effects, pharmacokinetics.

 Indications for use, dosage regimen.

 Pharmacotoxicodynamics, contraindications.

 Drug interaction.

IV. The principles of choosing drugs that increase vascular tone.

V. Methods for assessing the effectiveness and safety of drugs that increase vascular tone.

B. Drugs that lower vascular tone.

I. Classification of drugs that lower vascular tone.

2. Central action drugs.

 Antagonists of central α1-adrenergic receptors and

I1-imidazoline receptors.

3. Drugs affecting the peripheral nervous system.

 Ganglion blockers.

 Cute.

 α-blockers (non-selective α-blockers and selective α1-blockers).

 β-blockers (non-selective β-blockers and selective β1-blockers).

 α- and β- adrenergic blockers.

3. Drugs, myotropic effects (vasodilators).

 Venous vasodilators (organic nitrates and nitrites, sydnimines).

 Mixed action vasodilators (sodium nitroprusside).

 Arterial vasodilators (potassium channel activators, hydralazine).

 Slow calcium channel blockers (phenylalkylamines, dihydropyridines, benzotazepines, diphenylpiperazines).

4. Reducing the activity of the renin-angiotensin-aldosterone system.

 ACE inhibitors.

 Antagonists of receptors of the first type of angiotensin II.

II. Pharmacokinetics, pharmacodynamics, interaction, indication for use, side effects and contraindications.

III. The principles of choosing drugs that lower vascular tone.

2. Etiopathogenetic factors of cerebrovascular pathology.

3. Classification of cerebrovascular agents.

I. Agents affecting blood aggregation and coagulation:

1) ANTI-AGGREGANTS: acetylsalicylic acid, ticlopidine.

2) ANTICOAGULANTS: heparin, warfarin, syncumar, phenyline.

II. Means that increase cerebral blood flow:

6) MIOTROPIC MEANS:

1. Derivatives of vincamic acid to-you: vincamine (devinkan, minorin), vinpocetine (cavinton), vincanor (vincapan, vincaton).

2. Derivatives of xanthine and purine: pentoxifylline (trental), xanthinolum nicotinate (compliment, theonicol), aminophylline (aminophylline).

3. Myotropic antispasmodics: • derivatives of isoquinoline - papaverine hydrochloride, drotaverine hydrochloride (no-spa), benzimidazole derivatives - bendazole hydrochloride (dibazole).

4. Drugs of other groups: nicotinic acid, picamilon

7) ALPHA-ADRENOLYTICS (from ergot alkaloids derivatives): dihydroergot-min mesylate (ditamine), dihydroergotoxin methanesulfonate (redergin), dihydroergocristine, nicergoline (sermion).

8) SEROTONIN ANTAGONISTS: pisotifen maleate (sandomigran), metisergide (deseryl), cyproheptadine hydrochloride (peritol), iprazochrome (divaskan).

9) CALCIUM ANTAGONISTS: prod. 1,4-dihydropyridine - nimodipine (nimotope), others - cinnarizine (stugeron), flunarizine hydrochloride (sibelium).

10) COMBINED DRUGS: papazol (papaverine + dibazole), nicoverin (papaverine + nicotinic acid), instenon (hexobendin + ethamivan + etofillin), baralgin (analgin, pitophenone, fenpiveronium) - trigan, spazgan, spazmalgin, spazmolgon, maksigan, baralgan), bishpan (isopropamide + no-spa), nikoshpan (nicotinic acid + no-spa), papazol (papaverol + dib), andipal (analgin + dibazole + papaverine + phenobarbital), bepasal (phenyl salicylate + papaverine + belladonna extract), tefafillin (platyphyllin + papaverine + phenobarbital + theobromine), palyufin (platyphyllin + papaverine + phenobarbine + theobarbamin + phenobarbine + phenobarbine +), theodibaverine (theobromine + papaverine + dibazole), amazole (amidopyrine + dibazole), those Ending (theobromine Amidopyrine + + phenobarbital), Teofedrin (theophylline, theobromine, caffeine, aminopyrine, Feng atsetin, ephedrine, phenobarbital, belladonna extract cytisine), Theo Astahalin (theophylline + salbutamol).

Characterization of drugs, mechanisms of action, undesirable effects. Indications and contraindications for use. Interchangeability and pharmacosafety.

3. Drugs for the treatment of migraine. Classification:

I. Ergot alkaloids: ergotamine hydrotartrate (cornutamine);

II. SEROTONINOLYTICS: iprachrome (divascan), metisergide (deseryl);

III. CALCIUM ANTAGONISTS: cinnarizine (stugeron);

IV. H1-HISTAMIN BLOCKERS: diphenhydramine hydrochloride (diphenhydramine), chloropyramine hydrochloride (suprastin);

V. Beta-adrenergic blockers: propranolol hydrochloride (anaprilin, obzidan, inderal).

VI. OTHER: clonidine hydrochloride (clonidine, hemiton, catapresan).

Characterization of drugs, mechanisms of action, undesirable effects. Indications and contraindications for use. Interchangeability and pharmacobesafety.

1. Etiopathogenetic factors and forms of circulatory disorders in the limbs.

2. Classification of drugs used for circulatory disorders in the extremities.

I. ALPHA-ADRENOLYTICS: phentolamine hydrochloride (regitin), tropodiphene hydrochloride (tropafen), dihydroergotamine mesylate (ditamine), dihydroergotoksin methanesulfonate (redergin), dihydroergocroxanane (pyroxane), proprooxane, proprooxane.

II. MYOTROPIC SPASMOLITICS: (phosphodiesterase inhibitors and adenosine receptor blockers);

1. Derivatives of purine and xanthine - theobromine, theophylline, aminophylline (aminophylline), diprofillin, xanthinol nicotinate (compliment, theonicol), pentoxifylline (trental, agapurin), etofillin - as part of instenon.

2. Derivatives of isoquinoline - papaverine hydrochloride, drotaverine hydrochloride (no-spa).

3. Derivatives of benzofuran - phenicaberan.

4. Imidazole derivatives - bendazole hydrochloride (dibazole).

5. Plant and animal origin - andekalin (depot-padutin), dil-minal, phloverin.

6. Other groups - diprofen, naftidrofuril oxalate (duzodril), benziclan fumarate (halidor), pitophenone - as a part of baralgin, nicotinic acid.

III. ANGIOPROTECTORS - pyridinol carbamate (parmidin, prodectin, anginin), ethamylate (dicinone), calcium dobesylate (doxium, doxylex), alprostadil (vasoprostane, PG E1), esculin (escusan), troxerutin (troxrovasonazole, adeno, adeno, aveno, adeno) .

IV. ANTIHYPERCHOLESTERINEMIC MEANS: 1. Anion-exchange resins - cholestyramine (questran), colestipol, guarem.

2. Fibrates (derivatives of fibroic acid) - clofibrate (miskleron), bezafibrate (beamidine, sedur), fenofibrate (lipantil), gemfibrozil (hevilon).

3. Derivatives of nicotinic acid - nicotinic acid, acipimox.

4. Statins - lovastatin (mevacor), simvastatin, pravastatin.

5. Preparations of unsaturated fatty acids - linetol, arachiden, lipostabil.

6. Drugs of other groups - polysponin, tribusponin, neomycin sulfate, probucol (lipomal).

V. VENOTONIZING AGENTS: dihydroergotamine mesylate (ditamine), dihydroergotoxin methanesulfonate (redergin), dihydroergocristine. ethylephrine (fetanol), troxerutin (troxevasin, venoruton), escin (reparil), esculin, escusan (esflazide), tribenoside (glivenol), combined preparations: anavenol (esculin + dihydroergocristine + rutin), repsilyl gel .

VI. SPASMOLITIC MEDICINES:

neurotropic drugs:

1. Cholinolytic drugs: •

 M-cholinolytics of the atropine group - atropine sulfate, hyoscine hydrobromide (scopolamine), homatropine hydrobromide, platifillin hydrotartrate, hyoscia min, radobellin (belladonna preparations);

 synthetic M-anticholinergics - metacinium iodide (metacin), chlorosyl, propantheline bromide

(pro-bantine), ipratropium bromide (atrovent);

 M-H-anticholinergics - aprofen, arpenal, antispasmodic, gastrikson, fubroman;

 H-anticholinergics (rarely) - ganglefin hydrochloride (gangleron), benzohexonium.

myotropic effects (phosphodiesterase inhibitors and adenosine receptor blockers):

1. Derivatives of purine and xanthine - theobromine, theophylline and its prolonged products (theopec, theobiolong), aminophylline (aminophylline), diprofillin, xanthinol nicotinate (compliment, theonicol), pentoxifylline (trental, agapurin-vaphenone), etofilin;

2. Derivatives of isoquinoline - papaverine hydrochloride, drotaverine hydrochloride (no-spa);

3. Derivatives of benzofuran - phenicaberan;

4. Imidazole derivatives - bendazole hydrochloride (dibazole);

5. Plant and animal origin - andekalin (depot-padutin), dilmiln, kellin, phloverin, linden flower decoction, raspberry fruit decoction, tea

elderberry black flowers, hawthorn fruit extract, tincture;

6. Other groups - diprofen, naftidrofuril oxalate (duzodril), benziclan fu-marat (halidor), pitophenone - as part of baralgin, nicotinic acid.

combined preparations: baralgin (analgin, pitophenone, fenpiveronium) - trigan, spazgan, spazmalgin, spasmolgon, maxigan, baralgan), bishpan (iso-propamide + no-spa), nicoshpan (nicotinic acid + nicpa), nicoverin (nicotine n-ta + papaverine), bapazol (papaverine + dibazole), andipal (analgin + dibazol + papaverine + phenobarbital), bepasal (phenyl salicylate + papaverine + belladonna extract), tefapillin (platifillin + papaverine + phenobarbin) (platifillin + papaverine + phenobarbital), teoverin (theobromine + papaverine + barbamil), theodibava rin (theobromine + papaverine + dibazole), amazole (amidopyrine + dibazole), teminal (theobromine + amidopyrine + phenobarbital).

The mechanisms of action of each group. Pharmacological effects Comparative characteristics of drugs. Indications and contraindications. Undesirable effects. Pharmacosafe, interchangeability.

The list of practical works:

Homework.

1. To study - pharmacokinetics, pharmacodynamics, indications, contraindications, adverse effects

2. The student must be able to:

a) select the necessary drug for a particular patient, select the dose, regimen and route of administration of the drug;

b) identify criteria for evaluating the therapeutic efficacy and safety of the drugs used;

c) provide differential medical assistance with:

 discirculatory encephalopathy,

 acute and chronic cerebrovascular accident,

 migraine

 obliterating endarteritis,

 obliterating atherosclerosis of the lower extremities,

Рей Raynaud's syndrome,

 venous insufficiency of vessels of the lower extremities.

3. Know the drugs used in cerebrovascular diseases, principles and features of use, undesirable effects, know the main drugs used for circulatory disorders in the extremities, indications for use, undesirable effects.

4. Indicate which medicines are part of the following combined preparations and justify the appropriateness of their use in case of circulatory disorders in the extremities: baralgin, nicoshpan, tefafillin, theofedrine, nicoverin

Control of the intermediate level of knowledge.

Solving situational tasks:

1. For the treatment of migraine, the doctor prescribed a remedy from the group of sporinium alkaloids. Name the drug, indications for use and undesirable effects.

2. In the complex treatment of transient cerebrovascular accident, a combination agent was prescribed consisting of myotropic spas-prayer and a vitamin preparation. Name the medicine and indicate which combination preparations containing antispasmodics do you know? Place examples, indicate indications for use.

3. Advantages and disadvantages of alpha adrenolytics, calcium antagonists, serotonin. What undesirable effects do they show when used in large doses? Justify the answer.

4. What derivatives of xanthine and purine do you know? Indicate the indications for use and undesirable effects.

5. What drugs are recommended for use with vascular thrombosis? Justify the answer.

6. What drugs are recommended for cerebrovascular spasms? Justify the answer.

7. Myotropic antispasmodics and alpha adrenolytics, compare them, indicate the features of the application, pharmacological safety.

8. A patient with a spasm of peripheral vessels is prescribed a drug - a xanthine derivative. Prescribe the drug, indicate undesirable effects. . Regarding atherosclerosis, the patient receives a drug from the group of anion-exchange resins. Specify a drug, explain the mechanism of action.

10. A patient suffering from varicose veins is prescribed a venotonic agent, which reduces capillary permeability, has an anti-edematous effect. It is administered orally, parenterally, externally. Prescribe the drug, indicate the undesirable effects.

11. In the complex treatment of hemorrhoids, the patient was prescribed a drug, which is an introductory alcohol extract of horse chestnut and has a tonic, anti-thrombotic and anti-inflammatory effect. Prescribe the drug, indicate the features of use.

12. The patient is prescribed a drug derived from vincamic acid, indicate which drug is prescribed.

13. Tell about“Types of adrenergic receptors”:

Recommend a combination remedy for a migraine patient.

15. In the complex treatment of cerebrovascular spasms, a combination drug was prescribed containing an analgesic, anticholinergic and ganglion blocker. Prescribe a drug for oral and parenteral use, indicate undesirable effects. Write out a prescription and justify the choice of the drug, taking into account undesirable effects.

16. Patients came to the pharmacy with prescriptions for the following drugs. Indicate which drugs were prescribed:

 refers to serotonin antagonists, is a derivative of lysergic acid, is prescribed for the prevention of migraine attacks, causes undesirable effects such as dyspepsia, insomnia, euphoria;

 belongs to the group of calcium antagonists, is a peripheral vasodilator, is used for migraine, hypertension, ischemic heart disease, can cause facial redness, drowsiness, hypotension;

 an analogue of ergot alkaloids, has an alpha adrenergic blocking effect, has myotropic antispasmodic activity, is used for migraines, early cerebrovascular disorders.

TESTS

1. A patient, 52 years old, consulted a doctor with complaints of recurrent headache, dizziness, numbness of limbs. History: chronic obstructive bronchitis. Objectively: pulse - 78 beats per 1 min, rhythmic, blood pressure - 160/95 mm RT. Art. Percussion: the left border of the heart is 1 cm outwards from the midclavicular line. Heart sounds are rhythmic, accent II tone over the aorta. The liver is not enlarged. No swelling. What drug is most appropriate for a patient as monotherapy?

A. Dopegit.

B. Propranolol.

C. Clonidine.

D. Hypothiazide.

E. Raunatin.

2. Under what conditions are dihydropyridine calcium antagonists contraindicated?

A. Arterial hypertension.

B. Bronchospasm.

C. Tachycardia.

D. Bradycardia.

E. Hyperglycemia.

3. For the treatment of arterial hypertension, the doctor considers it appropriate to

prescribe a patient from the group of calcium channel blockers of the second-generation dihydropyridine derivative to the patient. From the following therapeutic agents, choose such a drug:

A. Verapamil.

B. Cordaron.

C. Diltiazem.

D. Nifedipine.

E. Amlodipine.

4. Which of the following drug groups can cause "stealing syndrome"?

A. Myotropic antispasmodics.

B. Nitrates.

C. Anticoagulants.

D. β-blockers.

E. Diuretics.

5. The following side effects are possible with enalapril treatment:

A. Hypokalemia.

B. Drooling.

C. Constipation.

D. Cough.

E. Swelling of the legs.

6. Which of the following medicinal products should be used by patients with collapse and shock in order to increase blood pressure?

A. Korglikon.

B. Propranolol.

C. Mesaton.

D. Dobutamine.

E. Eufillin.

7. Select the effect that occurs when using ACE inhibitors:

A. Increased arterial vascular tone

B. Increased venous vascular tone

C. Decreased urine output

D. Reduction of heart muscle hypertrophy

E. Increased vascular hypertrophy

8 .. Simultaneously with ACE inhibitors, you can not prescribe:

A. Beta blockers

B. Calcium channel blockers

C. Potassium preparations

D. Thiazide diuretics

E. Prazosin

9. The undesirable effects of ACE inhibitors do not include:

A. Allergic reactions

B. Micro and Macropsy

S. Cough

D. Antihypertensive effect

E. Hyperkalemia

10. Beta-adrenolytics can be combined with:

A. Klofelin

V. Reserpine

C. Pilocarpine

D. losartan

E. Verapamil

11. The undesirable effects of beta-blockers do not include:

A. Bradycardia

B. Bronchospasm

C. Impotence

D. Intermittent claudication, Raynaud's disease

E. Decrease in tone of a pregnant uterus

12. What is the pharmacological effect characteristic of calcium channel blockers:

A. Slow down the automatism of p-cells of the sinus node

B. Increase platelet aggregation

C. Increase myocardial contractility

D. Increase the tone of smooth muscle of cerebral vessels

E. Contribute to the dissociation of oxyhemoglobin

13. An increase in peripheral vascular resistance is associated with the excitation of postsynaptic:

A. N-cholinergic receptors.

B. M-cholinergic receptors.

C. Beta-1-adrenergic receptors.

D. * Alpha-1-adrenergic receptors.

E. Beta-2-adrenergic receptors.

14. The introduction of which adrenomimetic increases blood glucose and is contraindicated in diabetes?

A. * Adrenaline hydrochloride.

B. Norepinephrine hydrotartrate.

C. Izadrin.

D. Mesaton.

E. Angiotensinamide.

15. The mechanism of the hypertensive effect of adrenaline hydrochloride is associated with:

A. Non-selective stimulation of M-cholinergic receptors.

B. Stimulation of the central nervous system.

C. Analeptic effect.

D. * Activation of alpha-1 and beta-1-adrenergic receptors.

E. An increase in circulating blood volume.

16. The mechanism of the hypertensive effect of caffeine is due to:

A. Stimulation of alpha-1-adrenergic receptors.

B. Stimulation of alpha-2 adrenergic receptors.

C. Stimulation of beta-1 adrenergic receptors.

D. Stimulation of beta-2 adrenergic receptors.

E. * Excitation of the vasomotor center of the medulla oblongata.

17. A 39-year-old patient with chronic arterial hypotension. What therapeutic measures do you recommend?

A. Introduction of ephedrine.

B. * Dosed exercise, hardening, taking adaptogens.

C. Introduction of diazepam.

D. The use of immunostimulants of animal origin.

E. Introduction of cordiamine.

18. What hypertensive drug is used for fainting?

A. Adrenaline.

B. * Cordiamine.

C. Prednisolone.

D. Hydrocortisone.

E. Dobutamine.

Recommended literature:

Basic:

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

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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.

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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.

13. 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 ANTI-HYPERTENSIVE MEDICINES

Purpose of the topic.

Arterial hypertension affects 20-30% of the adult population and 50-65% of people over 65 years of age. In Ukraine, hypertension affects 8.5 million people. Of these, 57% are aware of their disease, 17% receive treatment, and only 8% of people with hypertension receive adequate pharmacotherapy.

Hypertension drug therapy is the most important area of activity of a practical doctor, which allows saving a patient's life in case of emergency conditions - hypertensive crisis, eclampsia, shock, collapse, impaired coronary and cerebral circulation, lead to effective secondary prevention of hypertension, symptomatic arterial hypertension, pregnant women and others.

Motivational characteristic of the topic.

Knowledge of the main groups of drugs that affect the systemic and local vascular tone, the ability to rationally use them in a particular patient, to conduct combination therapy and prevent side effects determine the importance of this topic for the pharmacist. The drugs used in hypertension have a multifunctional purpose, as they act on the pathological mechanisms underlying the heart rhythm and conduction disturbance syndrome, acute and chronic heart failure, etc. Their use in combination with other drugs leading to this pathology. The ability to navigate in the world of drug action mechanisms, to use them scientifically for controlling the etiology and pathogenesis of diseases, to apply drug therapy as a method for verifying the diagnosis - forms the clinical thinking of a future pharmacist.

DRUG THERAPY OF ARTERIAL HYPERTENSION

In 90-95% of cases, hypertension is a sign of hypertension (GB), a pathological state of multiple etiology and complex pathogenesis, manifested by persistent prolonged systolodiastolic hypertension.

To date, quite effective approaches to the treatment of hypertension have been developed

. **ETIOLOGY AND PATHOGENESIS OF HYPERTENSIVE DISEASE**

The increase in blood pressure (BP) is due to a violation of the factors that regulate the activity of the cardiovascular system.

The primary factor is hereditary predisposition. According to the concept of Yu.V. Postnova, it consists in common violations of the ion transport function and structure of the cytoplasmic membrane of cells. Under these conditions, the preservation of the specific function of cells is ensured by the mechanism of cellular adaptation associated with the regulation of calcium metabolism, with a change in hormonal-cell relationships, with an increase in the activity of neurohumoral systems (hypothalamic-pituitary-adrenal, renin-angiotensin-aldosterone, insular).

Calcium cell overload increases the contractile potential of vascular smooth muscle and activates cellular growth factors (proto-oncogenes). The hypertrophy and hyperplasia of the ugly muscles of blood vessels and the heart that occurs leads to the reconstruction of the heart (hypertrophy) and blood vessels (increased contractility, wall thickening and narrowing of the lumen), which, being adaptive, simultaneously support hypertension. Increased blood pressure leads to an increase in left ventricular synglastic pressure, an increase in ventricular tension (and hypertrophy), and an increase in the degree of myocardial damage by free radical oxidation.

Hemodynamic disorders are realized through the pathology of neurohumoral factors in the system of short-term action (adaptive) and in the system of long-term action (integral). The first are the distortion of the baroreceptor relationships in the chain: large arteries - centers of the brain - sympathetic nerves - resistive vessels - capacitive vessels - heart. and also in the activation of the renal endocrine circuit, including the renin-angiotensin mechanism and resistive vessels. Violations in the integral regulation system are represented by excessive secretion of aldosterone, sodium and water retention, as well as depletion of the depressor mechanisms of the kidneys (prostaglandin E2, kallikrein, bradykinin), blood vessels (prostacyclin, kallikrein-kinin and dopaminergic vascular systems, endothelial editing factor and nitrogen - heart (atrial sodium-urethic factor).

Important pathogenetic factors of hypertension are tissue insulin resistance associated with increased sodium reabsorption, sympathetic nervous system activity, expression of proto-oncogenes and weakening of vasodilator stimuli, as well as an increase in the density of the receptors of the vascular bed and myocardium and their sensitivity to adrenergic effects under the influence of excessive secretion and secretion . A significant role belongs to violations of the biological rhythm of the neuroendocrine systems and hormones that regulate the rhythms of the cardiovascular system. The pathogenetic significance of reducing the production of sex hormones and their protective effect on the vascular bed, the effect on the hemodynamics of local neurohumoral systems (renal, brain, cardiac, vascular), vascular reconstruction and utilization of vasoactive hormones is discussed. Reconstruction of the heart and blood vessels, long periods of hypertension lead to impaired diastolic and systolic functions of the myocardium, as well as cerebral, coronary and peripheral hemodynamics with the formation of typical complications of arterial hypertension (stroke, heart attack, heart and kidney failure).

CRITERIA FOR ARTERIAL HYPERTENSION

The normal level of blood pressure depends on age, gender, individual characteristics of the person and other factors. Recently, the usual norms of blood pressure have been substantially revised. According to the recommendations of WHO experts (1999) AH in the range from 139/89 to 130/85 mm rg. Art., previously considered normal, is now considered to be “high normal”, and the interval from 140/90 to 159/94 mm RT. Art., a former borderline hypertension, went into the category of mild hypertension. Blood pressure is considered normal in the range from 130/85 to 120/80 mm Hg, and lower values are defined as “optimal”, since they are associated with a correspondingly lower risk of cardiovascular catastrophes.

AD classification

International Society for Hypertension, WHO (1999)

Categories	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mmHg)
Optimum <120 <80	Normal blood pressure <130 <85	High Normal 130 - 139 85 - 89

Apertial hypertension	I degree of hypertension (mild) subgroup 140 - 159 90 - 99	Borderline AG 140--149 90-94
II degree of hypertension (moderate) 160 - 179 100 - 109	III degree of hypertension (severe)> 180> 110	Isolated systolic hypertension subgroup:> 140
<90		
Optimum <120 <80	Normal blood pressure <130 <85	High Normal 130 - 139 85 - 89
Apertial hypertension	I degree of hypertension (mild) subgroup 140 - 159 90 - 99	Borderline AG 140--149 90-94
II degree of hypertension (moderate) 160 - 179 100 - 109	III degree of hypertension (severe)> 180> 110	Isolated systolic hypertension subgroup:> 140
<90	Edge AG 140--149 <90	
Optimum <120 <80	Normal blood pressure <130 <85	High Normal 130 - 139 85 - 89
Apertial hypertension	I degree of hypertension (mild) subgroup 140 - 159 90 - 99	Borderline AG 140--149 90-94

To establish a diagnosis of hypertension, confirmation of an increase in blood pressure by repeated measurements for several weeks is necessary, and if mild hypertension is detected, it should be confirmed within 2 months.

It was established that the level of blood pressure is directly related to the risk of cardiovascular complication, and this HOCIT relationship is independent, continuous and stable. So, a decrease in diastolic pressure in hypertensive patients to 90-105 mm RT. Art., and systolic up to 140-180 mm RT. Art. reduces the risk of stroke by 35-40%, and coronary heart disease (CHD) by 15-20%.

In the analysis of the daily profile of blood pressure, critical indicators are 140/90 mm Hg. Art. and night 120/80 mm Hg To quantify the magnitude of the “pressure load” exerted on the target organs, the time index (SI) is determined, which is a percentage of the time when blood pressure values exceed the critical (“safe”) level during the day.

The daily rhythm of blood pressure is estimated on the basis of the degree of its nightly decrease (SADAD), which is defined as the difference between the average blood pressure per day and per night, expressed as a percentage of the average blood pressure per day: SADAD = (ADden-ADN / ADden * 100% .

The optimum is recognized as SNSAD from 10 to 20%. At the same time, low and high indices, as well as steady nocturnal elevations in blood pressure, are potentially dangerous as factors of damage to target organs, myocardial and cerebral catastrophes. Based on SNSAD, a classification scheme for patients is used: "dippers" - 10% <SNSAD <20%>; “nondippers - 0 <SNICAD <l0%;“ hyperdippers u1084 ”- 20%, <SNAD:“ night pickers ”- SNSAD <0.

Insufficient SNAD is observed in a number of patients with hypertension (including carotid arteriosclerosis), it is also characteristic of malignant and vasorenal hypertension, chronic renal failure, Cushing's syndrome, congestive heart failure.

Increased blood pressure variability is associated with changes in target organs (retinal angiopathy, left ventricular hypertrophy of the heart) and an increase in the frequency of carotid arteriosclerosis. Critical Variability Standards for mild and moderate hypertension are: for systolic blood pressure - 15/15 mm Hg (day / night), for diastolic 14/12 mm Hg (day Night). Patients belong to the group of increased variability when exceeding at least one of the four critical values.

OBJECTIVES OF ANTI-HYPERGENERIC THERAPY

1. The main goal is to reduce and maintain blood pressure on a patient safe for health

(within age or individual norms) level.

2. Reducing the severity and progression of structural changes in the heart and

vessels - a substrate of cardiac and cerebral complications of the disease.

3. Reducing the concentration of low and very low density lipoproteins for the prevention of atherosclerosis, aggravating vascular lesions due to hypertension.

4. Decrease in insulin resistance, which contributes to hypersympathicotonia, sodium and water retention, increased blood coagulation potential, increased concentration of atherogenic fractions of lipoproteins and activation of insulin-like growth factors that accelerate the development of atherosclerosis.

BASIC PRINCIPLES OF TREATMENT OF GB

Treatment of a patient with hypertension requires compliance with a number of fundamental principles.

1. The patient should know the prospects and goals of treatment, the need to spend it for many years or all his life, clearly understand that only a long and stable normalization of blood pressure can improve the condition of his heart and blood vessels, reduce the risk of serious complications.

3. A systematic monitoring of blood pressure by the patient is required.

4. It should strive to lower blood pressure to the level of “optimal” or “normal” (below 130/85 mm Hg) in young people, middle-aged people, and also in patients with diabetes mellitus. In elderly patients, maintaining blood pressure at a “high normal” level (below 140/90 mmHg) is acceptable. The higher the overall cardiovascular risk in this patient, the more persistent and persistent the treatment of hypertension should be.

5. The treatment of people with PAG and patients with stage I GB is usually carried out by non-drug methods - a rational diet, reducing body overweight, controlling physical inactivity, smoking, autogenous training, reducing psycho-emotional stress (only if there is no effect through 1 to 3 months. Medicines are prescribed).

6. With stage II and stage III GB, continuous pharmacotherapy is carried out against the background of non-drug treatment.

7. It is advisable to start drug treatment with a moderate dosage of the drug, increasing it, if

necessary, to the full dose, which is prescribed immediately only in severe cases of the disease. At the beginning of treatment, a skillfully selected drug or a combination of them can “loosen” even the most stable hypertension.

8. It should not be aimed at a rapid decrease in blood pressure over the next 4-10 days, especially in the elderly with cerebral atherosclerosis. Next, the phase of effective control of blood pressure begins with the help of sufficiently large doses of drugs.

9. In the third phase of treatment, patients for many years can do with small maintenance doses of drugs, however, their complete withdrawal leads to relapse of hypertension.

10. The patient should be aware of the possible side effects of the prescribed drugs, if they occur, you should consult a doctor for correction therapy.

11. When prescribing drugs, it is necessary to take into account the clip-pathogenetic forms of GB and concomitant pathology (IHD, diabetes mellitus, etc.), an individual reaction

patient on antihypertensive drugs.

12. The use of a combination of drugs should be based on knowledge of the pharmacokinetics and pharmacodynamics of antihypertensive drugs. The use of fixed (patented) medicinal mixtures is rational after practicing the dosages of each component.

13. Frequently recurring hypertensive crises - an indication of the need for adjustments in the treatment of the patient, isolated crises against a background of well-controlled hypertension are not an indicator of treatment failure.

14. Against the background of the use of long-acting drugs for episodes of a small increase in blood pressure, it is permissible for patients to use fast and short-acting drugs.

CLINICAL AND PHARMACOLOGICAL CHARACTERISTICS OF DRUGS

Classification of antihypertensive agents

/. Neurotropic drugs

1. Affecting the vasomotor center

2. Sympatolytics

3. Ganglion blockers

4. Alpha adrenoreceptor blockers

5. Beta-blockers

//. Means acting on smooth muscle elements of blood vessels

1. Myotropic antispasmodics

2. Calcium antagonists

3. Activators of potassium channels

///. Means acting on the renin-angiotensin system

V. Diuretics

V /. Drugs of other groups

1. Serotonin receptor blockers

2. Prostaglandins

3. Other means

VI /. Combination drugs

1. Reserpip-containing

2. Containing beta blockers

3. Containing anti-angiotensin agents

Among the currently used antihypertensive drugs, the main ones are 4 groups: diuretics, beta-adrenoblockers (BAB), calcium antagonists (AK) and angiotensin-converting enzyme inhibitors (ILPF)

In addition to the drugs indicated in the classification, sedatives and lipid-lowering drugs, antiaggregants, antihypoxants, and antioxidants are also used in the treatment of hypertension.

Diuretics

1. Loopback: Furasemide, Ethacrinic acid, Bumetanid, Pyretanid, Torso mid.

2. Acting on the proximal tubule:

 Osmotic diuretics - Mannitol, Urea, Isosorbitol, Potassium acetate.

 Carbonic anhydrase inhibitors - Acetazolamide, Ethoxosolamide

3. Acting on the initial part of the distal tubule:

 thiazide sulfonamides - hydrochlorothiazide, polythiazide Cyclopentiazide;

 non-thiazide sulfonamides Clopamide, Chlortalidone, Indanamide, Xi-pamide.

4. Acting on the final part of the distal tubule:

 competitive aldosterone antagonists - spironolactone, potassium canreonate;

 Na - Tpu amteren transport blockers, Amiloride;

5. Combined dnuretics: Triampur, Moduretik.

Diuretics have long been widely used in the treatment of hypertension, however, as a means of monotherapy, they are inferior to drugs of other groups and are more often used in combination.

The effect of diuretics at the beginning of therapy is due to a decrease in the volume of circulating blood (BCC) due to the excretion of sodium and water, then (after 3-4 weeks) due to a decrease in vascular reactivity to sympathetic stimulation and peripheral vascular resistance as a result of a decrease in edema of their wall .

Diuretics are indicated primarily for volume-dependent forms of GB. Their use is desirable against the background of a low-salt diet with a rich potassium content.

With hypokalemia, potassium preparations (up to 5-6 g / day) and magnesium are prescribed or

potassium-sparing diuretics are added.

To determine the feasibility of using a diuretic in a particular patient, a test with furosemide is used. In cases where the increase in the activity of the sympathoadrenal and renin-angnotensin-aldosterone systems prevails over the hypotensive effect of diuretics, which is manifested by a predominant decrease in systolic blood pressure with stable diastolic, thirst, craving for salty foods, tachycardia, and the dose of the drug is reduced and add AK, ILPF or BAB.

Diuretics are contraindicated in severe renal and hepatic insufficiency, intolerance to sulphonamides, and breast-feeding.

Side effects: hypovolemia and hyponatremia, hypokalemia and hypomagnesemia (hence cardiotoxicity and the threat of arrhythmia), ginerlipidemia, hyperuricemia, impaired carbohydrate tolerance, nephro- and hepatotoxicity. Other adverse reactions: weakness, drowsiness, dizziness, constipation, nausea, decreased potency, headache, cramps. With cancellation, recoil syndrome is often expressed (a rapid increase in bcc and sodium content). Hypokalemia is especially dangerous when using drugs that extend QT (cardiac glycosides, antiarrhythmic drugs of the 1st group).

The main groups of diuretics used have a number of features.

Loop diuretics, blocking the co-transport of Na +, K + and 2 Cl- in the thick section of the ascending knee of the Henle loop, increase diuresis, reduce the volume of circulating blood, return blood to the heart, reduce cardiac output and, consequently, blood pressure.

By increasing the synthesis of vasodilating prostaglandins, loop diuretics expand arterioles and veins, and reduce pre- and afterload. Moreover, this effect is most pronounced when administered intravenously and is manifested before the onset of the diuretic effect.

Loop diuretics are the most powerful diuretics with a quick and short effect, more often used for hypertensive crises, with resistance to thiazide diuretics and with impaired renal function due to the property of increasing renal blood flow and effectiveness in renal failure.

Thiazide 'diuretics (the most widely used group) block the electrically neutral transport of sodium and chlorine through the distal convoluted tubule the luminal membrane, thereby increasing diuresis and reducing the volume of circulating blood, the return of blood to the heart and, secondly, cardiac output. Blood pressure decreases. With prolonged use of thiazide diuretics (one month or more), the diuretic effect decreases. In this case, the following mechanisms are the basis for lowering blood pressure.

1. Increased excretion of Na and water from the vascular wall, which leads to a decrease

reactions to pressor influences.

2. Decreased sensitivity of adrenoreceptors to vasoconstrictor action

catecholamines.

3. Increased synthesis of vasodilating prostaglandins.

Thiazides more often than loop diuretics cause hyponatremia, in large doses can reduce renal blood flow, and are ineffective in renal failure.

Used in combination with potassium-sparing diuretics, NAPF, sim-patholytics and beta-blockers. May cause hypercalcemia, thrombocytopenia, rarely neutropenia.

Potassium-sparingly weak diuretics, effective in primary and secondary hyperaldosteronism, capable of causing hyperkalemia. Most often used in combination with other diuretics.

The osmotic acting on the proximal tubule is sometimes used for some hypertensive crises (it is dangerous to increase the BCC in the first phase of action), carbonic anhydrase inhibitors are used only in the absence of other diuretics (due to the acidosis caused by them).

Hydrochlorothiazide (hypothiazide, dichlithiiside, nephrix, ezidrex) is one of the main diuretics for the treatment of hypertension. Depending on the severity of hypertension

used in doses of 25-150 (up to 200) mg / day in 1-3 doses, usually or 25 mg 1 time in the morning up to 150 mg in 3 doses in the first half of the day, a maintenance dose of 12.5-50 mg 1 time per day in the morning You can 1-3 times a week. The onset of action is 2 hours; peak is 4 hours; duration is 6-12 hours.

Other thiazides: polythiazide, longer-acting methicothiazide (up to 24-48 hours), but are generally similar to hydrochlorothiazide.

Chlortalidone (oxodoline, hygrotone)

It is used in doses of 25-100 mg in the morning before meals. Maintenance dose 12.5-50 mg 1 time per day. The onset of action is 2 hours peak - 2-6 hours, duration - 48-72 hours. The duration of action is longer than that of hydrochlorothiazide, more often causes hypokalemia.

Clopamide (Brinaldix)

It is used in doses of 10-40 MG in the morning, a maintenance dose of 10-20 MG once a day or every other day. The onset of action is 1-3 hours, the duration is 8-20 hours, and the difference from other thiazide and thiazide-like diuretics increases venous tone (indicated for patients with orthostatic reactions).

Indapamide (Arifon, Lescopride, Natrilix)

It has an additional vasodilating effect, has little effect on the excretion of potassium, the level of glucose, lipids and uric acid in the blood, has an anti-aggregate effect.

It is used in doses of 1.25-5 mg in the morning, a maintenance dose of 1.25-2.5 mg once a day. The onset of action is 1-3 hours, the duration is up to 38 hours, the onset of antihypertensive action after 1-2 weeks, a maximum of 8 weeks.

Furosemide (Lasiks)

It causes a quick, powerful, but short-lasting diuretic effect. Cancellation syndrome is quite pronounced. Furosemide enhances the diuresis of phosphates, calcium and magnesium, without affecting the glomerular filtration rate, unlike ethacrylic acid increases the excretion of bicarbonates and increases the pH of urine, but, like ethacrylic acid, it has ototoxicity. It is indicated for renal failure. The onset of action is 15-30 minutes, the peak of action is 1-2 hours, the duration is 6-8 hours, the maximum antihypertensive effect is 3-4 days.

Ethacrinic acid (uregitis)

Somewhat less active than furosemide. The onset of action is after 30 minutes, the peak of action is after 2 hours, the duration is 6-8 hours.

TPuamteren (pterophene, in the form of fixed combinations with hydrochlorothiiside - triampur comnositum, diazide, maxzid)

It has a weak hypotensive effect, but effectively reduces the loss of potassium in combination with hydrochlorothiazide or furosemide. In older people, it increases the risk of developing hyperkalemia and hyponatremia, with diabetes - hyperglycemia. It is used at 25-100 mg / day, with a further individual selection of doses (no more than 300 mg / day in 2 divided doses). With arterial hypertension, complex preparations of the triampur type are often used for 1-2 tablets. at the reception 1-2 times a day. The onset of action is 2-4 hours, the peak of action is 6-8 hours, duration 7-9 hours.

Spironolactone (Veroshpiron)

It has a diuretic effect on the level of aldosterone in the blood. In hypertension, the drug is prescribed together with hydrochlorothiazide or furosemide. The onset of action after 24-48 hours, the peak of action for 2-3 days, the duration is 4-6 days. Apply 50-100 mg / day in 1-2 doses, but not more than 400 mg / day.

Beta blockers

1. Non-selective without their own sympathomimetic activity - Proprano-lol,

Timolol, Nadolol, Sotalol, Chlorinolol.

2. Non-selective with their own sympathomimetic activity - Oxpreno-lol,

Pindolol, Penbutolol, Bopinbolol.

3. Non-selective with vasodilating properties Karteolol, Carvedilol.

4. Cardioselective without its own sympathomimetic activity - Atenolol,

Metoprolol, Betaxolol, Bisoprolol, Esmolol.

5. Cardioselective with its own sympathomimetic activity - Acebu-tolol.

6. Cardioselective with vasodilating properties - Celiprolol, Bevanto-lol.

7. New different mechanism of action - Nebivolol, Flestolol.

8. Alpha-beta-blockers - Libetilol, Kirvedilol, Proxodolol.

The hypothetical effect of BAB is realized through the following mechanisms.

1. Blockade of beta1-adrenergic receptors of the heart, resulting in a decrease in heart rate, heart rate and cardiac output.

2. Blockade of beta1-adrenergic receptors of the juxta-glomerular apparatus of the night, decreased release of renin, angiotensin II (the most powerful vasoconstrictor factor), aldosterone.

3. Blockade of inhibitory presynaptic beta2-adrenergic receptors, resulting in a decrease in the release of catecholamines and the implementation of their vasoconstrictor effect.

4. Reducing the degree of left ventricular myocardial hypertrophy with prolonged use (except for drugs with sympathomimetic activity).

The most significant mechanism of the hypotensive effect of BAB is considered to be a decrease in cardiac output, which over time leads to a decrease in vascular resistance. BAB are quite effective in monotherapy. Drugs on their own properties differ significantly within the group.

Cardioselective beta-blockers cause fewer side effects from blood vessels (impaired blood

circulation in the extremities), bronchi (bronchosi-azm), kidneys (impaired function) and pancreas (impaired tolerance to carbohydrates), although these differences are leveled out.

Drugs with their own sympathomimetic activity do not cause bradycardia, to a lesser extent provoke heart failure, withdrawal syndrome, impaired blood supply to the kidneys and impaired lipid metabolism, but they have a weak cardioprotective effect.

BAB do not cause orthostatic reactions; they prevent an increase in blood pressure and heart rate caused by stress and stress. They combine well with dihydropyridine AKs, peripheral vasodilators, IANF, but are not prescribed together with clonidine, sympatholytics, phenylalkylamine AKs.

BAB is indicated primarily in patients with high activity of the sympathoadrenal system (increased cardiac output and tachycardia). Their purpose in the volume-dependent form of GB, with low cardiac output (circulatory failure), bradycardia, impaired renal function.

BAB is contraindicated in severe bradycardia, hypotheisia, AV blockade of the II-III degrees, heart failure without tachycardia, bronchospastic conditions, intermittent claudication.

Side effects: bronchospasm, bradycardia, hypotension, muscle weakness,

impotence, depression.

Propranolol (Apaprilin, Obzidan, Inderal)

It is a reference non-cardioselective beta-blocker without internal activity, has membrane-stabilizing activity. Use in doses of 20-320 (up to 640) mg / day, usually begin with small doses (20-60 mg / day in 2 doses), then increase the dose by 40-80 mg every 3-4 days, the maintenance dose is 80-240 mg / day.

Pindolol (Wisken)

The drug with the most pronounced sympathomimetic activity. Practically does not affect the lipid spectrum of the blood. Assigned to 10 mg / day in 2 divided doses, the dose can be gradually increased to a maximum of 60 mg / day.

Nadolol (korgard)

The drug is a prolonged action (24 hours), which allows you to prescribe it 1 time and day. The onset of action is in 1-2 hours, its peak in 3-4 hours. Its properties are close to propranolol, differs from it in more pronounced negative chronotropic effect and less negative inotropic effect, almost does not reduce renal blood flow and glomerular filtration rate , and even has a direct vasodilating effect on the renal vessels. With LH, the initial dose of the drug is 40 mg / day (with increased sensitivity - 20 mg). With an interval of 1 week, the dose can be increased by 40-80 mg / day, up to a maximum of 240- 320 mg. Combination therapy with a lower dose of nadolol is possible.

Atenolol (menormine)

Reference cardioselective BAB without its own sympathomimetic activity. With arterial hypertension, an initial dose of 25-50 mg / day is prescribed, after 2 weeks it can be increased to 50-100 mg / day. The drug is often combined with diuretics. The onset of action after 1 hour, its peak after 2-4 hours, the duration is 24 hours.

Acebutolol (sectral)

It practically does not cause withdrawal syndrome and does not affect the lipid spectrum of the blood, it has membrane-stabilizing activity. The beginning of the action is through 1-3 hours, its peak after 3-8 hours, duration 12-24 hours. It is prescribed 200 mg / day in 1 dose, after 1 week the dose can be increased to 400-800 mg / day in 2 doses.

Libetalol (Tradate)

Blocks alpha and beta receptors in a ratio of 1: 3. Blood pressure decreases due to a decrease in peripheral vascular resistance with unchanged cardiac output. Increases the concentration of potassium in the plasma. It is mainly used for relief of crises, with pheochromocytoma. The onset of action after 1 hour, its peak after 2-4 hours, duration 8-12 hours. Assign 200 mg / day in 2 doses, every 3-4 days the dose can be increased by 100 mg, not more than 2400 mg / day. .

Calcium antagonists

1. Dihydropyridine derivatives - Nifedipine, Nitrepdipine, Nicardipine,

Isradipine, Amlodipine, Felodipine, Nisoldipine.

2. Derivatives of benzothiazepine - Diltiazem.

3. Derivatives of phenylalkylamine Verapamil, Bepridil, Tiapamil, Anipamil,

Gallopamil, Fallipamil.

The drugs are powerful specific arteriolar vasodilators due to their ability to reduce the transmembrane current of calcium ions into smooth muscle cells. The mechanisms of the hypotensive effect of AK are as follows.

1. Blockade of slow calcium channels and calcium intake into smooth muscle cells, due to which the arteries relax, the total peripheral resistance decreases and blood pressure decreases (more typical for dihydropyridine derivatives).

2. Blockade of the slow calcium channels of the cardiomyocyte and a decrease in the absorption of calcium into the cell, resulting in a decrease in heart rate, heart rate, cardiac output and blood pressure (more typical for dihydropyridine derivatives).

3. Reducing the degree of left ventricular myocardial hypertrophy with prolonged use. When taking the first doses of AK, a decrease in blood pressure leads to a reflex increase in sympathetic activation in patients with hypertension, which is manifested by an increase in heart rate, cardiac output, concentration of norepinephrine and plasma renin activity. This reaction is especially pronounced in patients with normally functioning baroreceptors. In individuals with high hypertension or advanced age, the sensitivity of arterial baroreflexes is reduced, therefore, sympathetic activation when taking AK is less pronounced.

Unlike direct vasodilators (hydralazine, etc.), AKs do not cause fluid retention in the body. On the contrary, when taking the first doses of drugs in connection with an increase in renal blood flow for several weeks, the loss of sodium and water increases without the development of hypokalemia.

AK do not alter the lipid profile of plasma, reduce platelet aggregation and blood viscosity, inhibit platelet-related growth factors, block the vasoconstrictor effect of endothelin, and do not cause bronchoconstriction. They have no adverse effect on patients with peripheral atherosclerosis, bronchial obstructive diseases, and gout. Due to a possible decrease in carbohydrate tolerance, they should be used with caution in diabetes.

Side effects: headache and dizziness, hypotension, facial flushing, pasty skin of the ankles and legs (sometimes significant swelling), nausea, blurred vision, rapid and painful urination, hyperplasia of the mucous membrane of the gums, sweating, muscle cramps, palpitations, tachycardia, unusual tiredness and weakness. Long-term administration of first-generation AK leads to an increase in the concentration of aldosterone and renin with a delay in sodium and water, which exacerbates the course of heart failure and reduces the hypotensive effect To enhance the antihypertensive effect, AK is combined with thiazide diuretics, NAPF, and dihydropyridine drugs also with BAB. Combination with alpha-adrenergic blockers requires caution because of the possibility of severe hypotension.

Unlike dihydropyridine AK (nifedipine) phenylalkylamine derivatives (verapamil) have negative inotropic (decreased contractility), chronotropic (rhythm reduction) and dromotropic (AV inhibition) effects. Diltiazem and its group have an intermediate (between verapamil and nifedipine) action.

Second-generation AKs, which are more suitable for prophylactic use, include derivatives of dihydropyridines and phenylalkylamines of prolonged action (verapamil SR or isoptin SR and nifedipine GITS), new compounds chemically associated with prototypes of the first generation phenylalkylamines (gallopamil, anipamil, falipamil), dihydropyridiai (isra-dipine, amlodipine, felodipine, etc.), benzothiazepine (clentiazem), as well as new compounds that are fundamentally different from the first-generation drugs and have additional their properties (fluospirylene, HOE-166, etc.), such as antiaggregation and antiserotonin activity. The duration of their action is increased to 12 hours or more (for amlodipine - 36-40 hours), which allows to reduce the severity of side effects due to a slower increase in the concentration of the drug in the blood and its greater constancy, achieving milder vasodilation.

Nifedipine (adalat, corinfarum, kordafen)

In the form of prolonged forms (adalat retard, corinfar retard, procardia, nifedipine GITS) is the strongest short-acting AK, effective in monotherapy or combined treatment with thiaznd diuretics or BAB. The drug is of particular importance for the relief of hypertensive crises, since, quickly reducing blood pressure, it simultaneously slightly increases cardiac output and blood flow, including in cerebral vessels. The latter is important for ischemic stroke and “local robbery” syndrome.

With sublingual administration of nifedipine, the onset of the antihypertensive effect occurs after 1-5 minutes, the peak of action is after 20-30 minutes, its duration is 2-4 hours. When the drug is taken orally, the effect occurs after 0.5-1 hours (10 mg capsules)

. For regular treatment of hypertension with a drug of the usual duration of action, they start with a dose of 10-20 mg 3 times a day, then the dose is gradually increased with an interval of 7-14 days to a maximum of 40 mg 3 times a day. To enhance the effect, nifedipine is combined with thiazide diuretics, BAB or NAPF. Treatment with a prolonged-acting drug is carried out at 20-30 mg once a day.

The dose can be gradually increased with an interval of 7-14 days to 90-120 mg once a day.

Dosage forms of prolonged release should be swallowed whole, they can not be broken, crushed or chewed.

To stop the hypertensive crisis, nifedipine is used sublingually, but at 5-10 mg (rarely 20 mg), while the tablet should be chewed. In severe crisis and a persistent increase in blood pressure, the drug is taken orally again at 20 mg in tablets or 10 mg in capsules every 4-6 hours until the effect is obtained.

Verapamil (isoptin, isoptin SR, finoptin)

With normal myocardial contractility, it does not lead to a decrease in cardiac output during exertion, it slows down AV conduction, can contribute to the development of bradycardia, does not have a bronchoconstrictor effect, and can be cumulated in the body. In hypertension, the drug is prescribed 80 mg 3 times a day. In elderly people, increase with bradycardia, low body weight and risk of occurrence AV blockade begins with a dose of 40 mg 3 times a day. During the first weeks up to 3 months. the effect of the drug may increase. The maximum daily dose for hypertension is 360-480 MG.

Prolonged dosage forms are initially prescribed 120-180 mg 1 time and day, after 1 week. the dose can be increased to 240 mg 1 time in the morning. Further, the drug is taken 180 MI 2 times a day, or 240 mg in the morning and 120 mg in the evening, or 240 mg every 12 hours. And due to the danger of cumulation of the drug in the body, it is necessary to monitor the state of AV conduction.

Diltiazem (diltzem, cardyl, cardtem; prolonged forms: cardizem retard, cortiasm retard, diltiazem CD, diltiazem SR, diltiazem XR)

Reduces blood pressure, while increasing stroke volume. Postural hypotension is rare. With prolonged use, it does not cause reflex tachycardia, it increases the glomerular filtration rate, diuresis and natriuresis, without causing hypokalemia, and does not affect the blood lipid spectrum. It lengthens the AV conductivity, and with a weak sinus node can increase the sinus cycle by 50%. Tolerance does not develop to the drug.

As a hypotensive agent, the usual dosage forms of diltiazem are prescribed at 90 mg / day in 3 divided doses with a gradual increase to 360 mg in 3 divided doses.

Dosage forms of sustained release are used starting from 120 mg / day in 2 doses and increasing the dose to 360 mg in 2 doses. Very prolonged dosage forms are prescribed 180 mg once a day with a gradual increase in dose to 360 mg.

Felodipine (captive)

It is highly selective for vessels of AK. It has a pronounced vasodilating effect both in relation to peripheral vessels and coronary arteries. With prolonged treatment, a regression of already developed myocardial hypertrophy is observed. The drug, unlike other dihydropyridine derivatives, does not affect myocardial conductivity and contractility, is characterized by the absence of orthostatic hypotension and significantly higher vascular selectivity.

Felodinin has the unique property of sustained release, which provides clear advantages over nifedi-pin retard forms. At the same time, it is effective in various ranges of increasing diastolic blood pressure and is not inferior in hypotensive effect to combinations of BAB, diuretics and NAPF. A decrease in blood pressure occurs 2 hours after taking the first dose and lasts 24 hours. The maintenance dose is 5-10 mg / day, in elderly patients up to 2.5 mg. No evidence of cumulation.

Means acting on the renin-angiotensin system

1. Inhibitors of the angiotensin-converting enzyme –Kapmonpil, Enalopril,

Ramipril, Perindopril, Lisinopril, Quinapril, Fosinopril.

2. Antagonists of angiotensin receptors - losartan, valzartan.

The mechanisms of the antihypertensive effect of ACE inhibitors and antagonists of A-II

receptors

• inhibition of the conversion of angiotensin I into a powerful angiotensin II vasoconstrictor:

• a decrease in the secretion of aldosterone, stimulating natriuresis;

• specific vasodilation of the renal vessels (at the level of both afferent and efferent glomerular arterioles), promoting natriuresis;

• reduced inactivation of the vasodilator bradykinin;

• inhibition of local formation of angiotensin II;

• increase in the formation of prostaglandins stimulated by a phospholipase membrane cells;

• a decrease in insulin resistance due to local accumulation of bradykinin;

• reverse development of hypertrophy of the walls of the myocardium and blood vessels with prolonged use.

Acting through the blockade of the formation of angiotensin II, ACE inhibitors affect the blood pressure regulation system and ultimately lead to a decrease in the negative aspects associated with activation of subtype angiotensin II receptors: they eliminate pathological vasoconstriction, inhibit cell growth and proliferation of myocardium and smooth muscle cells blood vessels, weaken sympathetic activation, reduce the retention of sodium and water. In addition, in addition to acting on pressor systems for regulating blood pressure, they also act on depressor systems, increasing their activity by slowing down the degradation of vasodepressor peptides - bradykinin and prostaglandin E2, which cause relaxation of vascular smooth muscles and promote the production of vasodilating lay-ups and the release of the endothelium-relaxing factor.

These pathophysiological mechanisms provide the main pharmacotherapeutic effects of ACE inhibitors: antihypertensive and organoprotective effects, the absence of a significant effect on carbohydrate, lipid and purine metabolism, a decrease in the production of aldosterone by the adrenal cortex, a decrease in the production of adrenaline and norepinephrine, a decrease in the activity of ACE, and an increase in angiotensin II the content of bradykinin and prostaglandins in blood plasma.

The initial effect of ACE inhibitors is due to their effect on the RAAS of systemic blood flow, which is manifested by a suppression of ACE activity, a decrease in the formation of angiotensin II and leads to vasodilation, a decrease in the production of aldosterone, natriuresis and a slight increase in plasma potassium.

To date, 3 generations of ACE inhibitors have already been introduced into clinical practice.

Depending on the nature of the chemical group in the drug molecule, responsible for the interaction with the active center of ACE, distinguish:

 1st generation ACE inhibitors containing sulfhydryl group: captopril, pivalopril, zofenopril.

 ACE inhibitors of the 2nd generation containing a carboxyl group: enala-pril, lisinopril, cilazapril, ramipril, perindopril, benazepril, moexi-adj.

 3rd generation ACE inhibitors (phosphorus-containing ACE inhibitors): fosinopril.

A significant difference in the chemical formulas of modern ACE inhibitors is the presence or absence of a sulfhydryl group. This group, which is an active zinc ligand, can enhance the activity of the inhibitor, i.e., the degree of its binding to the ACE active center. At the same time,

the development of certain undesirable side effects of captopril, such as taste impairment, rash, is associated with the sulfhydryl group. The same sulfhydryl group, due to mild oxidation, may be responsible for the shorter duration of action of the drug.

In order to improve absorption, most modern ACE inhibitors are available as prodrugs. ACE inhibitors in the form of prodrugs differ from unesterified drugs in a somewhat more delayed onset of action and an increase in the duration of the effect.

All ACE inhibitors can be divided into active drug forms and prodrugs.

 First class - lipophilic ACE inhibitors with pharmacological activity and metabolized in the liver (captopril);

 The second class is lipophilic prodrugs that become active after metabolic transformation (hydrolysis) in the liver and other organs (enalapril, moexipril, trandolapril, fosinopril);

 The third class - hydrophilic drugs with pharmacological activity and not metabolized in the body (excreted by the kidneys in an unchanged form) (lisinopril).

By the duration of the clinical effect:

 short-acting drugs that need to be prescribed 2-3 times a day (captopril);

 drugs with an average duration of action that must be taken at least 2 times a day (enalapril);

Длительного long-acting drugs, which in most cases can be taken once a day (quinapril, lisinopril, perindopril, ramipril, spiral-adj, trandolapril, fosinopril, etc.).

On the basis of rational combinations of ACE inhibitors with diuretics, new drugs are created, such as caposide (captopril 50 mg + hydrochlorothiazide 25 mg), angiopril DU (captopril 25 mg + hydrochlorothiazide 25 mg), enap HL (enalapril 20 mg + hydrochlorothiazide 25 mg).

The combination of ACE inhibitors with potassium-sparing diuretics (amiloride, triamteren) is not justified due to the likelihood of hyperkalemia.

Long-term use of ACE inhibitors is most indicated for patients with GB with:

 initially reduced indicators of contractile function of the left ventricular myocardium (with / without clinical signs of heart failure);

Л left ventricular myocardial hypertrophy (myocardial mass index according to Echocardiography for men is more than 134 g / m2, for women - 110 g / m2).

Organoprotective effects of ACE inhibitors:

 Cardioprotective effect (regression of myocardial hypertrophy, prevention of cardiac remodeling processes, anti-ischemic action, antiarrhythmic action)

 Vasoprotective effect (increased endothelium-dependent vasodilation, inhibition of proliferation of smooth muscle of arteries, cytoprotective effect)

 Nephroprotective effect (increase in sodium urea and decrease in potassium urea, decrease in intracubule pressure, inhibition of proliferation and hypertrophy of mesangial cells, renal tubule epithelial cells and fibroblasts)

 Metabolic effects (improved glucose metabolism, increased peripheral tissue sensitivity to insulin, anti-atherogenic effects, anti-inflammatory effects)

The complex of cardiac changes in hypertension, including left ventricular myocardial hypertrophy (LVM) and a change in its structure and function, is called "hypertensive heart."

In addition to hemodynamic factors, neurohumoral factors also influence the formation of LVHM and cardiac remodeling in hypertension. In this case, the main role is played by the RAAS, the sympathoadrenal system (CAS) and the mineralocorticoid function of the adrenal cortex. Angiotensin II has a direct trophic effect on myocardial cells, causes activation of myocardial cell proto-oncogenes, enhances adrenergic effects, and causes vasoconstriction of coronary arteries.

Being initially compensatory, LVHM during its progression carries a number of negative consequences, which is referred to as “overlap” of compensation. Among these consequences, the leading ones are recognized as violations of diastolic and systolic functions, disturbances in coronary circulation (acceleration of atherogenesis in large and medium-sized coronary vessels, pathology of small coronary arteries, changes in coronary vasodilator reserve and autoregulation of coronary perfusion) and an increase in ventricular ectopic activity.

ACE inhibitors are original drugs that can not only interfere with the existing balance of the pressor and depressor neurohumoral systems of the body, but also have the ability to influence the processes of remodeling of the left ventricle, causing regression of LVM and preventing ischemic and reperfusion damage to the myocardium. The cardioprotective properties of ACE inhibitors are due to the elimination of the trophic effect of angiotensin II on the myocardium and a decrease in the sympathetic effect on the heart and blood vessels. It is important to note that ACE inhibitors affect only hypertrophied myocardium.

A decrease in LVM can be expected no earlier than after 4–6 months of continuous treatment.

Among the target organs in hypertension, the kidneys occupy a special place, since they play an important role in maintaining the activity of RAAS, in the excretion of kallikrein with urine, in the synthesis of prostaglandins, in the regulation of water-electrolyte homeostasis by means of sodium modulating hormones, in controlling the level of antidiuretic hormone.

The development of vascular changes in the kidneys characteristic of GB, with the addition of a secondary tubulointerstitial component, can cause a progressive decrease in the functional activity of the renal parenchyma, the development of sclerotic changes in them and renal failure. An important mechanism for the progression of nephropathy is impaired intrarenal hemodynamics with the development of intracubular hypertension and hyperfiltration, which lead to an increase in the permeability of the basement membranes of the glomerular capillaries and glomerulosclerosis.

Markers of kidney involvement in the pathological process and indicators intracubic hypertension is proteinuria (PU), glomerular filtration rate (GFR), reabsorption, as well as the state of intracubular hemodynamics, which is determined in the clinic by the filtration fraction (ratio of GFR to the amount of renal plasma flow) or renal functional reserve (PFR) - an increase in GFR after oral administration protein load. With an increase in intracubule pressure, the filtration fraction increases, and there is no renal reserve.

ACE inhibitors are superior to other antihypertensive drugs in nephroprotective activity, which, at least partially, does not depend on their antihypertensive effect.

By blocking the formation of angiotensin II, including in the tissue of the kidneys themselves, ACE inhibitors expand the glomerular efferent arteriole and thereby reduce intracranial hypertension. In addition, angiotensin II has a direct effect on the kidneys, accelerating the development of sclerosis due to the blockade of stimulation of the growth of mesangial cells,

stimulation of their production of collagen and epidermal growth factor of the renal tubules. In addition, ACE inhibitors have pronounced antiproteinuric activity, regardless of their antihypertensive effect.

ACE inhibitors have the most pronounced positive effect on the basic parameters of quality of life compared with other treatments for hypertension.

The antihypertensive effect of monotherapy can be enhanced by a combination with a thiazide diuretic or with other vasodilators, in particular with AK, and (caution) with BAB. ACE inhibitors, although they differ in chemical structure, practically do not differ in magnitude of the hypotensive effect.

Captopril (Capoten)

The severity of the antihypertensive effect is similar to propranolol, hydrochlorothiazide, but inferior to nifedipine. The drug has a cardioprotective effect in patients after acute myocardial infarction, with a left ventricular ejection fraction of less than 40%.

When ingested 50 mg of captopril, the onset of the hypotensive effect is noted after 30-60 minutes, the peak of action is after 1-2 hours, its duration is 6-12 hours. Sublingual administration of 50 mg of the drug causes a hypotensive effect after 10 minutes, after 20 minutes Blood pressure decreases by 15%, after an hour - by 20% ”from the initial level (excessive hypotension is not observed). Complex preparations - caposide-25 and caposide-50 (captopril and hydrochlorothiazide 25 and 50 mg, respectively) have a more pronounced hypotensive effect.

Enaptril (Renitec)

It shows antihypertensive effect after 2-4 hours. Its peak - after 8-12 hours, duration - 24 hours. In case of hypertension, it is prescribed in an initial dose of 5 mg / day 1 time a day, a maintenance dose of 10-20 mg / day, maximum - 40 mg / day in 1 or 2 doses, In older people, with severe renal failure, with renovascular hypertension or with diuretics, the initial dose is halved. To enhance the antihypertensive effect, combined with hypertension and heart failure, combined drugs are used: eiap-N (10 mg enalapril and 25 mg hydrochlorothiazide) and eiap-H L (10 mg enalapril and 12.5 mg hydrochlorothiazide).

Undesirable effects of ACE inhibitors

When taking, specific (dry cough, first-dose hypotension, impaired renal function, hyperkalemia and angioedema), and non-specific (taste impairment, leukopenia, skin rash and dyspepsia) side effects can be observed.

 Dry cough is one of the most specific PE ACE inhibitors. The development frequency varies from 0.2 to 33%. Cough may occur not only in early treatment, but also at a later date. The mechanism of coughing is associated with inhibition of the breakdown of bradykinin and the accumulation of kinins, which, on the one hand, leads to vascular laryngeal edema, and on the other, to bronchoconstriction. Inhibition of the breakdown of bradykinin causes an increase in the synthesis of prostaglandins, especially PGE2, which in turn can lead to the stimulation of afferent C-fibers and the appearance of an excruciating dry cough.

 Arterial hypotension as an excessive manifestation of the main pharmacodynamic effect of ACE inhibitors usually develops after taking the first dose (first-dose hypotension).

 Impaired renal function. During prolonged therapy with ACE inhibitors, it is advisable to periodically monitor the level of creatinine and proteinuria.

 Angioneurotic edema is much less common than dry cough (0.1–0.5% of cases).

Contraindications to the appointment of ACE inhibitors

o Increased individual sensitivity to the drug (intolerance)

o Pregnancy and lactation

o History of angioedema in the history of any other ACE inhibitor

o Bilateral hemodynamically significant renal artery stenosis or single kidney renal artery stenosis

o Severe CRF (serum creatinine above 300 mmol / L) or severe hyperkalemia (above 5.5 mmol / L)

o HCMP with obstruction of the exit tract of the left ventricle, hemodynamically significant stenosis of the aortic or mitral valves, constrictive pericarditis

o Leukopenia (neutrophil count less than 1000 in 1 mm3), severe anemia (hemoglobin less than 70 g / l)

Angiotensin II receptor antagonists (ARBs): mechanism of action.

The action of ARBs is based on the inhibition of RAAS activity at the level of angiotensin II receptor subtype II. Angiotensin II receptor antagonists neutralize the effect of angiotensin II on the cardiovascular system by selective blocking of AII receptors.

The direct mechanism of the antihypertensive effect of AII receptor antagonists is associated with a weakening of the effects of angiotensin II (and angiotensin III), which are mediated by AT1-angiotensin receptors. By blocking AT1 receptors, antagonists of AII receptors reduce vasoconstriction, reduce increased hydraulic pressure in the renal glomeruli, and also decrease the secretion of aldosterone, endothelin-1, and norepinephrine. With prolonged use, antagonists of AII receptors weaken the proliferative effects of angiotensin II in relation to cardiomyocytes and smooth muscle cells of the vascular wall, as well as mesangial cells and fibroblasts.

Antagonists of AII receptors are able to penetrate the blood-brain barrier and inhibit the activity of presynaptic AT1 receptors of sympathetic neurons, which regulate the release of norepinephrine. Therefore, it is also impossible to exclude the central mechanisms of the antihypertensive action of antagonists of AII receptors.

A direct mechanism of the antihypertensive action of AII receptor antagonists is associated with blockade of AT1 receptors, and indirect mechanisms are associated with stimulation of AT2 receptors and ATx receptors.

These pathophysiological mechanisms provide the main pharmacotherapeutic effects of AII receptor antagonists, which have much in common with the effects of ACE inhibitors.

Common for these classes of drugs are antihypertensive and organo-protective effects, the absence of a significant effect on carbohydrate, lipid and purine metabolism, a decrease in aldosterone production by the adrenal cortex, and a decrease in the production of adrenaline and norepinephrine.

Classification

According to the chemical structure of ARBs can be divided into three groups:

 biphenyl derivatives of tetrazole: losartan, irbesartan, candesartan, tazosartan;

 non-biphenyl non-tetrazole compounds: eprosartan, telmisartan;

 non-heterocyclic compounds: valsartan.

Losartan, valsartan and irbesartan are active drug forms. Candesartan is a prodrug and becomes active after a series of metabolic transformations in the liver. Losartan and tazosartan have active metabolites that have a stronger and longer lasting effect than the drugs themselves.

Pharmacologically, antagonists of AII receptors also differ in the nature of binding to receptors. Thus, eprosartan and the active metabolite of tazosartan enoltazosartan are competitive antagonists of angiotensin II. In contrast, valsartan, irbesartan, candesartan, telmisartan, as well as the active metabolite of losartan EXP-3174, act as noncompetitive angiotensin II antagonists.

Eprosartan has an additional mechanism of vasodilating action that is not characteristic of other antagonists of II receptors - it blocks presynaptic AT1 receptors in the sympathetic nervous system. Due to this property, eprosartan inhibits the release of norepinephrine from the ends of the sympathetic nerve fibers and thereby reduces the stimulation of adrenoreceptors of the smooth muscles of blood vessels.

AII receptor antagonists have a number of important advantages over ACE inhibitors, which make their use promising in the treatment of hypertension patients.

First, AII receptor antagonists provide a more complete and more selective blocking of RAAS than ACE inhibitors.

Secondly, the action of AII receptor antagonists is more specific than the action of ACE inhibitors. Unlike ACE inhibitors, they do not affect the activity of other neurohumoral systems, which are associated with side effects characteristic of ACE inhibitors, such as dry cough and angioedema. The greater selectivity and specificity of the blockade of RAAS explain the better tolerance of antagonists of AII receptors in comparison with ACE inhibitors.

The maximum antihypertensive effect of antagonists of AII receptors is achieved no earlier than 4-8 weeks after the start of therapy. Hypotension after taking the first dose for these drugs is uncharacteristic. The sudden withdrawal of AT1-angiotensin receptor blockers is not accompanied by the development of rebound hypertension.

With prolonged use, antagonists of AII receptors cause the reverse development of left ventricular hypertrophy in patients with GB, increase renal plasma flow, without significantly affecting GFR. They reduce urinary albumin excretion in patients with hypertension with diabetic nephropathy. AII receptor antagonists do not adversely affect purine metabolism, glucose metabolism and blood lipid composition.

Side effects and contraindications to the appointment of antagonists of receptors AII.

AII receptor antagonist drugs have good security and portability profile. The most common side effects - weakness, dizziness, headache and dyspeptic symptoms (feeling of bitterness in the mouth, nausea) - occur in 13 - 15% of patients. Dry cough when using receptor antagonists A II occurs only in 0.5 - 0.8% of cases. Contraindications to the appointment of AII receptor antagonists are considered individual hypersensitivity to drugs, pregnancy and breastfeeding. They are not recommended for severe renal and hepatic insufficiency, as well as for obstruction of the biliary tract. In severe renal failure, renal function is maintained due to the activation of the renin-angiogensin system, and under these conditions, inhibition of RAAS activity may cause further deterioration of renal function.

Losartan (cozaar)

A non-peptide angiotensin receptor antagonist with specificity for the AT1 receptor subtype. Its advantage is a direct effect on angiotensin II receptors in the absence of an effect on the degradation of kinins: unlike NAPP, losartan does not suppress kininase-2, which destroys bradykinin, and therefore does not cause coughing. The hemodynamic effects of the drug include a mild decrease in blood pressure, mainly due to a decrease in peripheral vascular resistance, a decrease in left ventricular hypertrophy, a decrease in pressure in the pulmonary circulation, and prevention of congestive heart failure. Its neurohumoral effects are caused by a decrease in blood aldosterone and norepinephrine levels: itatriuretic and diuretic effects, especially with a diet low in sodium chloride, a decrease in the concentration of uric acid and blood creatinine, a decrease in proteinuria.

The advantage of losartan is the absence of the effect of withdrawal after stopping its administration. It does not affect lipid and carbohydrate metabolism, has high tolerance and safety, and the specific mechanisms of action of the drug allow it to be prescribed for the treatment of patients with hypertension in the presence of many concomitant diseases.

The average daily dose is 50 mg, the maximum is 100 mg. Multiplicity of admission - 1 time per day. The maximum hypotensive effect develops after 3-6 weeks.

Side effects: headache, dizziness, asthenic reactions, hypersensitivity to respiratory infection. A slight and short-term increase in hepatic cytolytic enzymes and an increase in potassium levels are possible. However, the total frequency of its side effects is comparable with placebo, they are. as a rule, they are not a reason for drug withdrawal.

Sympatholytic drugs

SYMPTOMATIC presynaptic agents affect the mediator processes in various parts of the sympathetic nervous system. They reduce the amount of norepinephrine in the neuron, deplete the central depot of ca-teholamines, and inhibit the central nervous system. Both in terms of efficacy and tolerability, sympatholytics are inferior to the four main groups of antihypertensive drugs.

Reserpine (serpazil, rusedil)

It is the sum of the alkaloids of the rauwolfia plant. The antihypertensive effect after oral administration develops within a few pedals, after parenteral administration - within 2-4 hours. The drug is administered orally, starting with a dose of 0.1 - 0.25 mg / day after meals; if necessary, increasing it to 0.3-0.5 mg / day.

There are combination preparations containing reserpine. Adelfan contains reserpine (0.1 mg) + hydralazine (10 mg), adelfan ezidrex and trireside in addition, they contain hydrochlorothiazide (10 mg), and potassium chloride is additionally included in adelfan-esidrex-K and trresid-K.

Treatment with these agents provides a smooth decrease in blood pressure. The combination of reserpine and alpha-adresiomimetics can cause severe hypertensive crisis due to sensitization of receptors to adrenergic agonists due to depletion of catecholamine stores in adrenergic neurons.

Contraindications: stage III circulatory failure, bradycardia, nephrosclerosis, peptic ulcer, epilepsy, parkinsonism, depression.

Side effects: hyperemia of the mucous membranes of the eyes, skin rash, dry mouth, nausea, vomiting, stomach pain, diarrhea, bradycardia, drowsiness, dizziness, depression, parkinsonism, bronchospasm, sodium and water retention.

Riunatin (Rauwazan)

To a lesser extent than reserpine, it acts on the central nervous system, is administered orally 2-4 mg 2-3 times a day, usually used in combination with thiazide diuretics and vasodilators. The antihypertensive effect develops after 2 weeks from the start of therapy. Side effects are much less pronounced than with reserpine.

Drugs affecting the vasomotor center

Clonidine (clonidine, catapresan)

Releasing the "false mediator", it stimulates postsynaptic central alpha receptors and inhibits sympathetic impulse to the vasomotor center, which determines a predominant decrease in peripheral vascular resistance and a slight decrease in cardiac output, as well as reduction in heart rate.

The combination of the drug with BAB is dangerous due to the potentiation of bradycardia, withdrawal syndrome, as well as possible severe hypotension. Reserpine and guanethidine, depleting the reserves of catecholamines in the sympathetic nerves, are competitive inhibitors of clonidine. At the same time, vasodilator drugs enhance the hypotensive effect of central alpha agonists. Clonidine is able to reduce plasma cholesterol, in high doses it potentiates the central effects of alcohol, sedatives and tranquilizers, in combination with cardiac glycosides enhances AV block, has withdrawal syndrome (hypertension, tachycardia, sweating, anxiety).

When clonidine is taken orally, the onset of the antihypertensive effect is noted after 30-60 minutes. action Inc. after 2-4 hours, its duration is 6-12 hours. With sublingual administration of the drug, the effect begins after 15-30 MIIH. duration of action - several hours. With iv administration, the effect develops in 3-5 minutes. peak action - after 15-30 minutes, its duration is 4-8 hours

In hypertension, clonidine is prescribed orally at a dose of 0.075-0.1 mg 2 times a day with an interval of 2-4 days, the dose is increased by 0.075-0.1 mg / day. The maintenance dose is usually 0.15-0.2 mg / day. In severe hypertension in urgent cases, treatment can be started with 0.15-0.2 mg, then but 0.075-0.1 mg every hour until the desired effect is achieved - while the maximum dose should not be more than 0.8 mg / day.

To stop the hypertensive crisis, you can take 0.075 MG of clonidine sublingually. It is administered parenterally in the form of 0.01% solution of 0.5-1 ml iv (after preliminary dilution in 10 ml of isotonic solution for 3-5 minutes (danger of increasing blood pressure in the first minutes of rapid administration). In order to avoid orthostatic hypotension after administration of the drug, the patient should be in bed for 1.5-2 hours.

Contraindications: depression, acute myocardial infarction, alcoholism.

Side effects are consistent with those in the treatment of sympatholytics, especially dry patients with dry mouth Methyldopa (dopegit, aldomet)

After ingestion of a single dose, it gives a hypotensive effect in 4-6 hours, its duration is up to 24 hours, the maximum effect with regular intake is achieved for 2-3 days.

Contraindications: acute hepatitis, cirrhosis, pheochromocytoma, pregnancy.

Side effects: activates autoimmune mechanisms, which limits its use in patients with liver pathology.

Gunfacin (estulik)

Provides after oral administration of a single dose, the maximum hypotensive effect after 8-12 hours with regular intake - after 1-3 months.

Contraindications and side effects are common to the group.

Moxonidine (physiotens, zinc)

It is a selective agonist of the imidazolone receptors of the central nervous system. It weakly binds to alpha2-adrenergic receptors, therefore, it provides suppression of sympathetic effects and a decrease in blood pressure with a minimum of side effects. It is prescribed 1 time per day after meals, preferably in the morning. The initial dose of the drug is 0.2 mg. The drug is well tolerated, caution is required in the treatment of patients with impaired night function.

Alpha adrenergic blockers

Selective - Prazosin, Terazosin, Doxizosin, Urapidol, Non-selective -

Phentolamine, Tropodifec, Butyroxan, Pyroxane, Dihydroergotamine, Di-hydroergotoxin, Dihydroergocristine.

Prazosin (vasoflex, minress)

By blocking alpha-1-adrenergic receptors at the level of peripheral arterioles, it has a pronounced antihypertensive effect without a significant effect on heart rate, causes dilatation of bulky and resistive vessels, and reduces their peripheral resistance.

The effect of the first dose was noted - orthostatic hypotension - especially severe with diuretics. After discontinuation of the drug and its reappointment within 1 week, this effect is not observed. Prazosin reduces myocardial oxygen demand, increases stroke volume during exercise, and can cause regression of left ventricular myocardial hypertrophy. The drug does not change the glomerular filtration rate and renal blood flow, reduces the resistance of the renal vessels, does not retain fluid and the body.

The onset of the antihypertensive effect of a single dose of prazosin is observed within 2 hours, its peak after 2-4 hours, duration up to 10 hours. By the 12th month of mono-therapy, tolerance to the drug may develop. The first dose (0.5-1 mg) is administered at bedtime (danger of orthostatic hypotension), after canceling diuretics after a few days. Then they switch to taking 1 mg 2-3 times a day. With an interval of 3-5 days, the dose can be gradually increased to 6-15 mg / day. The maximum dose is 20 mg / day, extremely rarely - 40 mg / day. The question of its further increase should be solved after the addition of thiazide diuretics.

The maximum effect occurs after 4-6 weeks. The gynotensive effect of the drug persists for several days after its withdrawal.

Prazosin potentiates the antihypertensive effect of BAB and diuretics, which, in turn, enhance its effect. Unlike BAB and diuretics, it reduces the level of total cholesterol, triglycerides and atherogenic fractions of lipoproteins while increasing the level of cholesterol in high density lipoproteins and apoprotein A-1 without changing the level of apoprotein B. The drug does not affect carbohydrate tolerance and urinary metabolism acid, which allows you to prescribe it to patients with diabetes and those in need in chronic hemodialysis.

Phentolamine

Expands mainly small blood vessels - arterioles and pre-capillaries. It has a direct stimulating effect on the heart with an increase in cardiac output, enhances the secretion and motility of the gastrointestinal tract. It is used for pheochromocytoma and due to a very short-term effect - with

hypertensive crises. The onset of the effect is immediate after iv administration, its peak in 2-5 minutes, duration - 5-10 minutes.

Ganglion-blocking drugs

 Short-acting - Trepirius, Arfonad.

 Medium duration - Pentamine, Dimecolin, Benzohexonium, Kwacheron.

 Long-acting - Pupulen, Camphony, Temekhin.

The antihypertensive effect of ganglioblocking drugs is due to blockade of the sympathetic ganglia, leading to a pronounced decrease in peripheral vascular resistance and cardiac output. This group is not used for long-term treatment of patients with GB, only drugs with short and medium duration of action are used to stop hypertensive crises.

Contraindications: myocardial infarction, cerebral artery thrombosis, pheochromocytoma.

Side effects: orthostatic hypotension, decreased glomerular filtration, as well as paralytic ileus, paresis of the gallbladder, disorders of akomodation, impotence (associated with blockade of the parasympathetic ganglia of atony of smooth muscle organs).

Pentamine

0.2-0.75 ml of 5% solution is injected into a vein in isotonic solution or 5% glucose.

Harfonade

It is indicated for hypertensive encephalopathy, cerebral edema, stratified aortic aneurysm, is administered iv 30-50 drops per minute in a solution of 500 mg arfonade per 500 ml of 5% glucose.

Myotropic antispasmodics

Drugs of this group cause relaxation of blood vessels, primarily arterial, or arterial and venous.

Hydralazine (apressin)

A peripheral vasodilator that has a direct pronounced effect on arterioles and a slight effect on veins. It increases renal blood flow with a decrease in glomerular filtration rate, has a hypotensive effect. The drug has a pacemaking effect, although it is not able to cause regression of left ventricular hypertrophy in patients with hypertension, increases the average pressure in the pulmonary artery, which is undesirable for patients with hypertension in combination with stenocardia and mitral defects. With a decrease in blood pressure, it simultaneously (through baro-reflexes) activates sympathetic nerve impulses to the heart, blood vessels, kidneys, increases the release of catecholamines, histamine, increases the activity of plasma renin, and increases the excretion of kallikrein. With prolonged use of hydralazine, tolerance develops to it.

The antihypertensive effect when taking the drug inside begins after 45 minutes, with the / m introduction of 10-40 mg - after 20-30 minutes, after the / in the introduction - after 10-20 minutes. The peak of action is observed after 1 hour (ingestion) or after 15-30 minutes (iv), its duration is 2-6 hours. The effect is achieved 4 times more often with mild than with moderate hypertension.

Use hydralazine, mainly in combination with BAB and diuretics. AT fixed combination preparations (adelfan, adelfan ezidrex and adelfan ezidrex K, trireside K) contain 10 mg of hydralazine.

Side effects of hydralazine (tachycardia, facial flushing, headache, lupus-like syndrome) are directly associated with vasodilation and reflex stimulation of the heart and kidneys, as well as with autoimmune reactions that manifest clinically after 6-24 months. treatment.

Contraindications: systemic lupus erythematosus, gastric ulcer. Autoimmune processes, sharp atherosclerosis.

Sodium nitroprusside) (niprid, naniprus)

Refers to mixed vasodilators. It reduces peripheral resistance by reducing vascular tone, widens the lumen of arteries and veins, reducing pre- and afterload. It is used only iv with a dilution of 500 ml of dextrose solution in case of hypertensive crises,

The purpose of the lesson.

1. To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of anti-hypertensive drugs:

but. affecting the central nervous system: anxiolytics - diazepam (re-lanium, seduxen, valium); dehydrobenzperidol (droperidol, droleptan); clonidine (clonidine, hemiton);

b. slow calcium channel blockers: dihydroperidin - amlodipine (norvax), isradipine (lomir), lacidipine (lacipil), nislodipine (siskor), felodipine, nitrendipine (bypass), long-acting nifedipine (adalat); non-dihydroperidines - verapamil, diltiazem, mibefradil (zikor);

at. β-blockers: non-selective - nadolol (korgard), propranolol (ana-prilin, obzidan, etc.), timolol (blockard), chloranolol (tobanum), bopin-dolol (sandonorm); β1-selective: atenolol (tenormine, betacard, atenobene, atenosan), betaxolol (lockren), bisprolol (concor), metoprolol (metoprol ratard, spesicor, betalok, vazocardine, corvitol), talinolol (cordanum), celiprolol (with partial sympathomimetic activity - albetol, acebutolol (sectral), dilevalol (cartrol),

ACE inhibitors: benazepril, captopril, (tenziomin, kapoten), enalapril (enap, renitec, berlipril), moexipril (moex), perindopril (carpeterex, pre-oldium), spirapril (renpres), trandolapril (licopardis, Dapril, Lysir, Prinivil, Sinopril), Fisinopril (Monopril), Ramipril (Tritace);

D. antagonists of angiotensin II receptors: losortan (cozaar), valsartan (diovan), irbesartan (aprovel), telmisartan (mycardis),

e. diuretics;

g. α-blockers: phentolamine, prazosin, doxazosin;

h. peripheral vasodilators: apressin, etc.

and. ganglil blockers (pentamine, pachycarpin, hygronium, arfonad)

2. To know the main pathogenetic mechanisms that are the object of drug exposure for: arterial hypertension, hypertensive crises;

3. Be able to:

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

b. prescribe combination therapy;

at. substantiate and provide urgent differential medical assistance for: hypertensive crisis.

Control questions of the studied topic.

1. List the clinical and pharmacological principles of drug selection and selection for arterial hypertension.

2. What principles are the basis for the classification of antihypertensive drugs?

3. Justify the appointment of diazepam for hypertensive crisis and specify criteria for evaluating the effectiveness and safety of its use.

4. What changes in hemodynamics occur in the body against the background of the action of propranolol? What are the drugs, the combined use of which is impractical, and explain why?

5. List drugs and the main mechanisms that cause vasodilation.

6. What changes in hemodynamics occur in the body against the background of the action of slow calcium channel blockers? Indications and contraindications for their use.

7. Explain the mechanism of the hypotensive effect of drugs that affect the humoral links in blood pressure regulation. Formulate indications and contraindications to their purpose.

8. What are the main undesirable effects of clonidine and the mechanisms of their occurrence, which must be taken into account in urgent and planned therapy of arterial hypertension.

9. Explain why in case of hypertensive crisis caused by pheochromocytoma, the patient must first administer phentolamine, then beta-blockers and you can not enter isobarin (sympatholytic), antipsychotics?

10. Name and explain the mechanisms of hemodynamic changes in the body after the introduction of pentamine and other ganglioblockotors.

11. What are the undesirable effects of ganglion blockers?

Control of the intermediate level of knowledge.

The solution of situational problems.

1. A man, 33 years old, complains of a heartbeat, ineffective breath, heaviness in the heart region of moderate intensity, a pulsating headache, flushing of the face, trembling gel, sweating, nervous tension. The condition worsened sharply after psycho-emotional stress. History: hypertension stage I. Drug therapy is episodic. Objectively, facial skin is hyperemic. Normostenik, a little increased nutrition. Pulse - 94 beats. in 1 min, rhythmic, AKD - 198/96 mm Hg. Art. The left border of the heart is shifted outwardly by 1.5 cm. An accent of the II tone above the pulmonary artery is heard.

Specify the nature of the crisis. Select a drug to stop it. Explain their mechanism of action.

2. In a man, 58 years old, two days ago, headaches, nausea, arose and increase, three times there was vomiting, which does not bring relief. Concerned about weakness, instability of gait, dizziness, periodically difficulty speaking. The condition worsened after a nervous strain. History: has been suffering from arterial hypertension over the past 25 years. Regularly, over the past 2 years, takes 1 table. (0.000075 g) of clonidine before bedtime. The maximum AKD is 230/130 mm Hg. Art., working - 170/100 mm RT. Art. Mother suffered from a hypertensive disease, died due to cerebrovascular stroke. Objectively: the patient is drowsy, lethargic. Hypersthenic. Obesity II tbsp. Xanthelasma in the upper eyelid of the right eye. Pulse - 54 beats.

in 1 min, rhythmic. AKD - 220/154 mm RT. Art. Left ventricular hypertrophy. Accent II tone over the aorta. On the ECG, a decrease in the amplitude of the T wave in the lead \ / 3 - \ / e.

Formulate a diagnosis. Indicate the drugs needed to stop this painful process, justify their choice.

3. A woman, 44 years old, complains of a sharp headache, blurred vision, nausea, repeated vomiting, weakness in the right arm and leg, periodically blurring of consciousness. The condition deteriorated sharply 50 minutes ago. In the anamnesis: for 10 years suffers from hypertension. The maximum AKD is 220/130 mm Hg. Art., working -170 / 110-115 mm RT. Art. The last 1.5 years often calls emergency doctors due to high blood pressure. Objectively: the general condition is serious. Consciousness is periodically clouded. Convulsive twitching in limbs. Pulse - 82 beats. in 1 min, rhythmic. AKD - 240/140 mm Hg. Art. Left ventricular hypertrophy. Accent II tone and systolic murmur over the aorta.

Formulate a diagnosis. Specify the nature of the attack. Justify the choice of drugs to stop existing violations.

4. A man, 60 years old, complains of headaches, dizziness, noise in the head, lack of night sleep, nausea in the morning, blurred vision, paroxysmal pains in the heart area of angina character after 50-100 m walk, when lifting 2- floor, shortness of breath during physical exertion, interruptions in the activity of the heart. He has a history of hypertension for 30 years. The maximum AKD is 200/140 mm Hg. Art., working - 160/120 mm RT. Art. Five years ago he suffered a myocardial infarction, two years - acute cerebrovascular accident in the pool of the right middle cerebral artery. Objectively: general state of moderate severity. Cyanosis of the lips. Left-sided pyramidal insufficiency Pulse 84 beats per 1 min, arrhythmic as extrasystolic arrhythmia (6-10 in 1 min), solid. AKD - 84/136 mm RT. Art. Left ventricular hypertrophy. Accent II tone and systolic murmur over the aorta. Vesicular breathing over the lungs, marginal crepitus. The abdomen is soft, painless. The 2 cm liver protrudes from under the edge of the costal arch along the right midclavicular line. No swelling.

Formulate a diagnosis. Make a selection of drugs. Make a combination therapy program. Give her a clinical and pharmacological rationale.

5. A 44-year-old patient suffering from hypertension developed a headache, “internal” trembling, palpitations, and a sense of fear. Objectively: pulse - 100 beats. in 1 min, blood pressure - 200/100 mm RT. Art., the left border of cardiac dullness is 1.5 cm shifted to the left of the left mid-clavicular line, heart sounds are sonic, vesicular breathing. On an ECG: sinus tachycardia, signs of left ventricular hypertrophy.

Formulate a diagnosis. Make a combination therapy program. Give her a clinical and pharmacological rationale.

6. A woman, 42 years old, complains of a severe headache of a pulsating nature in the frontoparietal region, a feeling of palpitations. He has hypertension for 3 years. A significant increase in blood pressure is noted 2-3 times a month lasting 3-8 hours. The attack ends with excessive urination. The left ventricle is enlarged, heart sounds are clean, pulse is 105 beats per 1 min, blood pressure is 225/115 mm Hg. Art. The shock and minute volume of the heart is increased. Total peripheral vascular resistance is moderately elevated. On an ECG: signs of left ventricular hypertrophy. In the fundus: a symptom of Salus-Hun.

Formulate a diagnosis. Make a combination therapy program. Give her a clinical and pharmacological rationale.

7. A patient, 62 years old, has been suffering from hypertension for 10 years. 2 years ago, chronic obstructive bronchitis was diagnosed. Objectively: pulse - 64 beats per 1 min, blood

pressure - 210/130 mm RT. Art., the left border of relative cardiac dullness is shifted to the left by 2.5 cm from the midclavicular line, I tone above the apex is weakened, the accent of II tone above the aorta. ECG: left ventricular hypertrophy.

Formulate a diagnosis. Indicate the drugs needed to stop this painful process, justify their choice, taking into account the accompanying pathology.

8. A patient, 52 years old, suffers from hypertension of the II Art. Smokes. Not regularly treated. Objectively: HELL - 175/105 mm RT. Art., heart rate - 92 beats per 1 min, in the lungs scattered dry rales against a background of weakened vesicular breathing. The liver protrudes 2 cm from under the edge of the costal arch, edema in the ankle joints.

State the main and concomitant diagnosis. Make a combination therapy program taking into account the concomitant disease. Give her a wedge-co-pharmacological rationale.

9. The patient, 56 years old, is in the hospital for a hypertensive disease. He took medications: Kapoten 25 mg three times a day, Adversuten - 1 mg 3 times a day. 30 minutes after taking the drugs, the patient fell and lost consciousness for several seconds. Objectively: the skin is pale, moist. Pulse - 100 in 1 min, rhythmic. HELL 60/20 mm RT. Art.

What complication arose in the patient? Indicate the drugs necessary for the purchase of this painful process.

10. Patient A., 33 years old, complains of a feeling of palpitations, frequent ineffective breathing, heaviness in the heart, a pulsating headache, trembling body, sweating, nervous tension. The condition worsened after a stressful situation. History: hypertension stage I. Drug therapy is episodic. Objectively: the skin of the face, neck hyperemic. Heart rate - 104 beats per 1 minute, AKD - 195/95 mm Hg, accent 2 tones above the aorta, the left border of the heart is shifted outward by 1.5 cm.

Your preliminary diagnosis. Clarify the nature of the hypertensive crisis. Make a selection of medicines for its stopping with the indication of doses and routes of administration. Briefly explain their mechanism of action.

11. Patient Z., 54 years old, complains of a sharp headache, nausea, vomiting, blurred vision, weakness, lethargy, and impaired movement in the right arm and leg. The condition worsened within an hour. In the anamnesis: for 15 years - hypertensive disease with maximum numbers of AKD - 220/120 mm RT. Art. The treatment is episodic. Objectively: the state is serious, consciousness is periodically clouded. Impaired speech. Violation of motor activity and sensitivity of the right half of the body. State of emergency - 82 beats per 1 minute; AKD - 240/140 mm Hg. Art. Left ventricular hypertrophy, 2 tone accent and systolic murmur over the aorta.

Formulate a preliminary diagnosis. Specify the nature of the crisis. Justify the plan of additional examination and the choice of drugs to stop the existing violations.

12. Patient M., 62 years old, has been suffering from hypertension and chronic obstructive pulmonary disease for 10 years. Objectively: heart rate - 64 beats per 1 minute, AKD - 190/120 mm RT. Art., increased nutrition, the left border of the heart is shifted 2.5 cm from the midclavicular line, 1 tone above the apex is weakened, ac-cent2 tone above the aorta.

Formulate a diagnosis indicating the underlying and concomitant diseases. Make a differentiated choice of drugs taking into account the existing pathology in the patient. Explain their mechanism of action.

12. Patient P., 56 years old, was first admitted for treatment to 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 was 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, AKD - 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.

13. Patient B., 64 years old, at the doctor's appointment developed an acute glaucoma attack with severe pain in the right eye with radiation to the head. Nausea, vomiting, shortness of breath appeared. PE - 62 strokes per 1 minute, AKD - 200/120 mm Hg Identified signs of hypertensive crisis. For many years, the patient suffers from arterial hypertension. In the lungs, a large number of wet small bubbling rales, forced orthopnea.

Determine the nature of the hypertensive crisis. What diuretics are indicated for the patient to provide urgent care and for the further treatment of glaucoma? Explain their mechanism of action and indicate the leading side effects of their use.

TESTS

3. For the treatment of stage 1 hypertension, an appointment is necessary:

A. Combinations of 3 drugs.

B. Combinations of 2 drugs.

C. Non-drug treatment.

D. * 1 antihypertensive agent.

E. No treatment required.

4. In which concomitant diseases are beta-blockers contraindicated in patients with hypertension?

A. Chronic colitis.

B. * Bronchial asthma.

C. Coronary heart disease.

D. Chronic pancreatitis.

E. Urolithiasis.

5. The mechanism of action of propranolol in hypertension is associated with:

A. * Reduced cardiac output.

B. Dilation of peripheral vessels.

C. Weakening of vagal influences.

D. Antiarrhythmic action.

E. Reducing the volume of circulating blood.

6. What drugs are ACE inhibitors?

A. Lokren.

V. Liprimar.

C. Metoprolol.

D. Amlodipine.

E. * Lisinopril.

7. The patient was diagnosed with Cohn syndrome, accompanied by arterial hypertension. Specify a medicine for conservative symptomatic therapy:

A. Verapamil.

B. * Veroshpiron.

C. Propranolol.

D. Furosemide.

E. Clonidine.

8. Indicate the combination of drugs contraindicated for use in a patient with stage 2 hypertension:

A. Captopril + hypothiazide.

B. Nifedipine + metoprolol.

C. Amlodipine + indapamide.

D. * Anaprilin + verapamil.

E. Lisinopril + indapamide.

9. The safety criterion for using beta-blockers for arterial hypertension is:

A. Decrease in heart rate not lower than 40 in 1 minute.

B. The reduction in heart rate is not lower than 50 in 1 minute.

* Decrease in heart rate not lower than 60 in 1 minute.

D. Decrease in heart rate not lower than 80 in 1 minute.

E. Decrease in heart rate not lower than 90 in 1 minute.

10. A patient 30 years after emotional stress complains of a headache, palpitations, arousal. Objectively: facial flushing, skin moisture, PE - 100 in 1 minute, blood pressure - 180/90 mm Hg; has been suffering from hypertensive illness for 2 years. What should be prescribed to the patient?

A. * Anaprilin.

B. Dibazole.

S. Furosemide.

D. Apressin.

E. Clonidine.

11. In a 52-year-old patient, blood pressure rises for 15 years. Objectively: HELL - 175/100 - 180/110 mm Hg; left ventricular hypertrophy, activation of the renin-aldosterone system was detected. Specify the drug for treatment:

A. * Enalapril.

B. Verapamil.

S. Veroshpiron.

D. Lasix.

E. Atenolol.

12. The patient was admitted to the department with a complicated hypertensive crisis (cardiac asthma). The drug of choice for urgent care is:

A. Clonidine sublingually.

B. Clonidine intravenously.

S. Anaprilin sublingually.

D. Adelfan orally.

E. * Furosemide intravenously.

13. The patient has a diencephalic sympathoadrenal uncomplicated hypertensive crisis. The drug of choice for treatment is:

A. Furosemide intravenously.

B. * Diazepam intravenously.

S. Eufillin intravenously.

D. Nitroglycerin sublingual.

E. Verapamil intravenously.

14. A 52-year-old patient with hypertension after stress noted a headache, dizziness, palpitations, anxiety, fear, cardialgia. State of emergency - 120 in 1 minute, HELL - 210/100 mm Hg Which group of drugs should be prescribed?

A. ACE inhibitors.

B. Myotropic antispasmodics.

C. Diuretics.

D. * Beta-blockers.

E. Calcium channel blockers.

15. A 56-year-old man with headache complaints. A history of chronic obstructive pulmonary disease. PE - 78 in 1 minute, blood pressure - 160/98 mm RT. Art., hypertrophy of the left ventricle, no edema. What drug is advisable to assign:

A. Raunatin.

B. Aldomet.

C. * Indapamide.

D. Anaprilin.

E. Adelfan

. 16. For conservative symptomatic treatment of arterial hypertension in a patient with pheochromocytoma, the following is indicated:

A. Central alpha blockers.

B. Calcium channel blockers.

C. * Peripheral alpha-blockers.

D. Diuretics.

E. Beta-blockers.

17. During the treatment of high blood pressure, a woman developed a dry, unproductive cough. Clinical manifestations of the disease of the respiratory tract and cardiovascular system have not been identified. The doctor suggested a side effect of the drug. Which group can the drug belong to?

A. * ACE inhibitors.

B. Ganglion blockers.

C. Diuretics.

D. Calcium channel blockers.

E. Rauwolfia preparations.

18. The patient has stage I hypertension, coronary heart disease, supraventricular extrasystole. For treatment, a drug from the group is appropriate:

A. Nitratov.

V. Sympatolitikov.

C. Diuretics.

D. Ganglion blockers.

E. * Beta-blockers.

19. A 44-year-old patient with stage P hypertension and ventricular extrasystole, state of emergency - 80 in 1 minute, blood pressure - 170/100 mm Hg. Complaints of pain by the type of angina pectoris. Choose a drug for treatment:

A. Nifedipine.

B. Captopril.

C. Verapamil.

D. * Bisoprolol.

E. Isoket.

20. Against the background of long-term therapy of arterial hypertension, the patient complained to the attending physician about swelling in the legs by the evening. What side effect of the drug may be associated with?

A. Atenolol.

B. * Nifedipine.

C. Hypothiazide.

D. Indapamide.

E. Captopril.

21. A patient, 61 years old, for 2 years took adelfan for the treatment of hypertension. In the last six months, blood pressure has remained constantly elevated, shortness of breath and palpitations appeared during walking. A year ago, diabetes was detected. The patient takes manin. Objectively: increased nutrition, BH - 20 in 1 min, pulse - 80 bpm, BP - 180/105 mm Hg. Art. Heart sounds are muffled, emphasis II tone over the aorta. The liver is not enlarged, there is no edema. What is the most appropriate way to prescribe a patient for the treatment of hypertension?

A. Central-acting drugs.

B. ACE inhibitors.

C. Diuretics.

D. Beta-blockers.

E. Ganglion blockers.

22. A patient, 59 years old, who has been suffering from hypertension for 15 years, developed acute left ventricular failure amid hypertensive crisis. What drug is most appropriate for this patient?

A. Anaprilin.

B. Nifedipine.

C. Sodium nitroprusside.

D. Veroshpiron.

E. Captopril.

23. A patient, 62 years old, has been suffering from hypertension for 10 years. 2 years ago, chronic obstructive bronchitis was diagnosed. Objectively: pulse - 64 beats per 1 min, blood

pressure - 210/130 mm RT. Art., the left border of relative cardiac dullness is shifted to the left by 2.5 cm from the midclavicular line, I tone above the apex is weakened, the accent of II tone above the aorta. ECG: left ventricular hypertrophy. What drug is most appropriate in this case?

A. Amlodipine.

B. Observed.

C. Atenolol.

D. Furosemide.

E. Reserpine.

24. A patient, 58 years old, suffers from hypertension of the II art., Which was complicated by HF IIA art. What drug is most appropriate for the patient?

A. Propranolol.

V. Klofelin.

S. Raunatin.

D. Calcium antagonists.

E. ACE inhibitors.

25. The patient is in the dispensary for hypertension. Has concomitant diseases: atrial fibrillation, angina pectoris, bronchial asthma. The patient must be prescribed a drug from the group of beta-blockers. What drug will be shown to the patient, taking into account concomitant diseases?

A. Timolol

B. Anaprilin

C. Bisoprolol

D. Salbutamol

E. Pyroxan

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.

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

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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 HYPERTENSIVE MEDICINES

Purpose of the topic.

Arterial hypotension is one of the most significant risk factors for cardiovascular complications. In connection with convincing evidence of the close relationship between hypertension and mortality obtained in population studies, the review of normal blood pressure (BP) values has been ongoing for many years. Modern classifications and standards are defined as the "optimal" systolic blood pressure below 120 mm Hg. Art., and diastolic - below 80 mm RT. Art. But to what level "the lower the better" there is ample evidence bimodal dependence of blood pressure and mortality in the population, since an excessive decrease in blood pressure - arterial hypotension - is also associated with an increased risk of developing cardiovascular complications.

Criteria for arterial hypotension

Arterial hypotension is diagnosed with blood pressure below 100/60 mm RT. Art. in men and 95/65 mm RT. Art. among women. Blood pressure below 100/60 mm RT. Art. in people aged 25 years or younger and below 105/65 mm Hg. Art. in people over 30 years old. Arterial hypotension should be diagnosed with a simultaneous decrease in systolic and diastolic blood pressure, and with a decrease in one of these indicators.

Motivational characteristic of the topic.

Arterial hypotension (from other Greek. Ὑπό - under, below and Latin tensio - stress) - lowering blood pressure by more than 20% of the initial / usual values or in absolute figures - below 90 mm RT. Art. systolic pressure or 60 mm Hg average blood pressure. An isolated decrease in diastolic pressure, for example, with insufficiency of lunar aortic valves or with thyrotoxicosis, is not commonly called arterial hypotension (hypotension). A decrease in blood pressure on only one arm (as, for example, in Takayasu's disease) should also not be attributed to arterial hypotension, since the latter involves a general decrease in blood pressure, or rather, a decrease in central blood pressure.

• I95.0 Idiopathic hypotension

• I95.1 Orthostatic hypotension

• I95.2 Drug-induced hypotension

• I95.8 Other types of hypotension

• I95.9 Hypotension, unspecified

Arterial hypotension (Hypotension) can be the result of nervous overstrain, it often develops as a result of infectious and other diseases and with insufficient or erratic nutrition, restrictive diets, an imbalance in the ratio of hours of rest and work.

Mean arterial pressure = diastolic arterial pressure + one third of the pulse. Pulse blood pressure = systolic - diastolic.

Classification of arterial hypotension

The following types of arterial hypotension are distinguished:

• Acute arterial hypotension

• Chronic arterial hypotension

• Primary chronic arterial hypotension

• Secondary chronic arterial hypotension

Acute symptomatic hypotension (a sharp drop in pressure). For example, very low blood pressure is often accompanied by acute myocardial infarction, pulmonary embolism, severe arrhythmias, intracardiac blockade, allergic reactions, blood loss, etc. Emergency medical care is required.

Physiological (chronic) hypotension manifests itself in trained athletes and as a hereditary predisposition to low blood pressure that does not go beyond the norm.

Primary (otherwise - idiopathic or essential) hypotension is an independent disease.

According to one theory, primary hypotension is a special form of a neurosis-like disease of the vasomotor centers of the brain, since long-term psychoemotional overstrain and stress can play a very large role in its development. Secondary arterial hypotension occurs against the background of other diseases (for example, osteochondrosis of the cervical spine, stomach ulcers, anemia, hepatitis, pancreatitis, cystitis, tuberculosis, rheumatism), arrhythmias, alcoholism, diabetes mellitus, diseases of the endocrine system or respiratory organs, tumors, shock, brain injuries, cirrhosis of the liver, mental trauma, circulatory disorders, heart failure, intoxication, as a side effect of certain medications (for example, their overdose in the treatment of gi pertension), etc.

Hypotension can also develop due to starvation and lack of vitamin E, C, B and pantothenic acid (B5).

Hypotension can also occur in healthy people, for example, athletes with constant physical activity. This is the so-called "hypotension of training." In this case, low blood pressure acts as a kind of precautionary measure of the body. It turns out that with constant overloads, the body begins to work in the "economical" mode, the heart rate becomes less frequent and the pressure decreases.

Pressure also decreases when a person adapts to a sharp change in climatic or weather conditions. In addition, the pressure level is affected by: increased humidity, the influence of electromagnetic fields, radiation, etc.

Most often, low blood pressure is associated with a violation of vascular tone. Normally, the vessels should, if necessary, quickly narrow and expand, but in hypotensive patients this reaction is slowed down. So it turns out that because of this, the blood ceases to flow in sufficient quantities to organs and tissues. As a result, body systems and organs, in particular, the brain and heart, experience oxygen starvation and are not able to work in optimal mode.

Some doctors explain the reduced tone of the venous vessels as an inborn predisposition of the body to hypotensive reactions.

Causes of Arterial Hypotension

Depending on the form, arterial hypotension can be caused by the following reasons:

• In trained athletes (physiological hypotension)

• Adaptation to high altitude conditions (physiological hypotension), as well as hot shops, tropics and subtropics (in these cases, it may be associated with excessive sweating)

• A sharp decrease in the volume of circulating blood (blood loss, burns)

• Heart failure

• Reducing the tone of blood vessels (anaphylactic shock, septic shock)

• Injuries to the brain and spinal cord

• neurosis, psychological trauma, chronic lack of sleep, chronic fatigue due to an imbalance in the ratio of hours of rest and work, stress, depression and other lethargic and depressed conditions.

• Orthostatic hypotension - a sudden decrease in blood pressure, manifested when a person gets up after prolonged squatting or lying down.

Fluctuations in resting blood pressure up to hypotension levels are usually considered as a

separate hypotonic type of somatoform autonomic dysfunction of the heart and the cardiovascular system (a disorder in which the autonomic regulation of arterial vascular tone is disturbed), but can also be a manifestation of panic disorder and other neuroses and mental disorders. Secondary chronic arterial hypotension occurs against the background of diseases such as brain injury, decreased thyroid function adrenal glands, pheochromocytoma, etc., intracranial hypertension (may be the result of not only head injuries, but also rotational subluxation or dislocation of the cervical vertebra C1 (with (old) birth, obstetric injuries due to accidents in children and adults, including somersaults, sometimes - just a careless sharp turn of the head)). Arterial hypotension can occur during pregnancy, characterized by a low tone of the arteries.

Symptoms

• weakness, drowsiness;

• irritability;

• sensitivity to weather changes;

• emotional instability, apathy;

• distraction, memory impairment;

• lethargy in the morning;

• increased sweating;

• violation of thermoregulation (cold hands and feet);

• sensitivity to changing climatic conditions;

• shortness of breath and a strong heartbeat during physical exertion;

• pallor;

• headache, usually dull, constricting, bursting or pulsating more often in the frontotemporal or frontotoparietal region;

• dizziness;

• tendency to motion sickness, nausea.

In addition, with hypotension, fainting is possible. Most often they happen in stuffy and hot rooms, as well as when driving in public transport [1], especially when the hypotonic is in an upright position. With dizziness and a premonition of fainting, hypotension must either take a horizontal position or sit so that your head rests on your knees.

Hypotension leads to daytime sleepiness and disturbances in night sleep (disorder of falling asleep and sleep rhythm), which makes fatigue and weakness only intensify. Hypotonic patients need more time to sleep than is usually recommended, not 6-8, but already 8-12 hours. They hardly wake up in the morning, but even after a long sleep, there is usually no sense of vigor and freshness.

Distinguish between physiological hypotension (which is a variant of the norm characteristic of trained athletes, people in highlands and in hot climates) and pathological hypotension (including neurocirculatory, primary or essential hypotension, whose persistent or chronic form is called hypotonic disease, and idiopathic orthostatic hypotension and symptom forms of the disease).

The decrease in blood pressure during hypotension is usually due to a mismatch in the co-relationship between peripheral vascular resistance and minute volume of blood circulation. A decrease in peripheral vascular resistance during the expansion of resistive vessels, capacitive vessels, a decrease in cardiac output, a violation of regulatory autonomic influences can be caused by many reasons:

 diseases of the cardiovascular system (myocardial infarction, arrhythmias, heart failure, heart defects, pericarditis, etc.);

 the influence of drugs (both an excessive decrease in blood pressure and orthostatic hypotension may occur when using centrally acting antihypertensive drugs, tricyclic antidepressants, α- and β-blockers, peripheral vasodilators, diuretics, antipsychotics, anesthetics and drugs of other groups), medical procedures anesthesia;

 endocrine pathology (adrenal insufficiency, hypothyroidism diabetes mellitus - autonomous diabetic neuropathy, etc.);

 neurological pathology (spinal cord, syringomyelia, brain tumors, consequences of traumatic brain injury, etc.);

 hypovolemia (due to dehydration with diarrhea, violation of the drinking regime; with loss of blood, redistribution of blood within the body, etc.);

 infections, intoxication (the effect of toxins on vascular tone);

 neurogenic syncope (vasodepressor and mixed type);

 allergic reactions (anaphylaxis).

Clinical varieties of hypotensive syndrome

Since arterial hypotension, as a rule, does not have nosological independence, it is important to recognize and characterize it at the syndromic level in a timely manner.

Arterial hypotension is relatively rarely stable, more often low blood pressure and the associated symptoms are transient (the most severe hypotension attacks are usually accompanied by fainting).

Orthostatic hypotension (OG) is the most common form of arterial hypotension. There are several criteria for exhaust gas:

1) any decrease in blood pressure that occurs in the patient when moving from a horizontal position to a vertical one and causing the appearance of symptoms, presumably indicating a decrease in blood supply to the brain;

2) a decrease in systolic blood pressure by 20 mm RT. Art. and / or diastolic blood pressure per 10 mm RT. Art. regardless of the appearance of clinical symptoms.

The most significant risk factors for exhaustive hypertension are old age, diabetes mellitus, hypertension, and common atherosclerosis. The symptoms of hypertension are diverse - from asymptomatic forms to the appearance in the orthostasis of weakness, dizziness, instability, visual impairment, palpitations, tremors, and fainting.

Postprandial hypotension (PPG) - hypotension associated with food intake is diagnosed if, within 2 hours after starting a meal, systolic blood pressure decreases by 20 mmHg. Art. and more or if it as a result of eating is below 90 mm RT. Art., and initially it was above 100 mm RT. Art. (in

this case, clinical symptoms may be absent), or, finally, if the decrease in systolic blood pressure associated with food does not exceed 20 mm Hg. Art. (or its level remains above 90 mm Hg), but is accompanied by the appearance of malaise. The most significant risk factors for PPH also include old age, diabetes mellitus, systolic hypertension, organic diseases of the nervous system (stroke, parkinsonism, Alzheimer's disease, etc.). Postprandial decrease in blood pressure, sometimes even pronounced significantly, may not be accompanied by clinical symptoms, while moderate PPH may lead to the development of weakness, nausea, angina pectoris, dizziness

Antihypertensive conditions associated with physical stress are subdivided into physical loads developing at the height and after their completion. The former require the exclusion of organic pathology of the heart (primarily coronary insufficiency and arrhythmias) as the causes of hypotension, the latter are usually associated with insufficiency of the autonomic regulation of blood circulation and are interpreted as “vasovagal”.

Antihypertensive conditions during psycho-emotional stress are also associated with defects in the autonomic regulation of blood circulation, as well as neurogenic frenzy due to the reflex effect of the autonomic nervous system on the regulation of vascular tone (its weakening and development of hypotension) and / or heart rhythm (its slowdown and the development of bradycardia)

Primary arterial hypotension, or hypotonic disease – these terms are commonly used for chronic essential hypotension. They mean a decrease in blood pressure characteristic of this individual of unknown etiology, during which clinical symptoms are determined that limit daily activity and worsen the patient's quality of life. Among these symptoms are dizziness, headaches, weakness, fatigue, decreased performance, irritability, often arising immediately after sleep. Blood pressure in patients with hypotension can be subject to significant fluctuations, against the background of lowered levels, its significant rises can be observed.

Classification of hypertensive drugs

 Adrenomimetics - phenylephrine (adrenaline), ephedrine, norepinephrine, mesatone, dobutamine, midodrine;

 Dopaminomimetics - dopamine;

 Glucocorticosteroids - hydrocortisone, prednisone, triamsinolone, dexamethasone;

 Mineralocorticoids - DOXA, Fludrocortisone acetate;

 Analeptics - caffeine, cordiamine, camphor, sulfocamphocaine;

 Agents affecting the angiotensin system - angiotensinamide;

 Adaptogens - preparations of Eleutherococcus, Ginseng, Leuzea, Rhodiola rosea, Zamaniha, Echinacea, Aralia, Schisandra.

Treatment of hypotensive conditions

For targeted treatment of patients with hypotension, it is important to establish a basic diagnosis.

In general, therapeutic tactics in individuals prone to antihypertensive conditions are as follows:

• The cautious use of drugs that can cause orthostatic disorders, especially in elderly patients (diuretics, vasodilators). The selection of antihypertensive drugs should be carried out taking into account the reactions of blood pressure in orthostasis, the characteristics of the blood pressure profile, determined by 24-hour monitoring. In patients with transient hypotensive conditions,

preference should be given to short-acting or medium-acting drugs.

• The exclusion of factors and triggers of antihypertensive conditions (to avoid a sharp rise and prolonged standing, as well as prolonged horizontal position during the daytime, stay in stuffy rooms, at high ambient temperature, avoid sharp straining, hyperventilation overvoltage, etc.). After breakfast, patients with BCP are recommended a short rest for 15-30 minutes in the supine or reclining position.

• Treatment of the underlying disease in primary and secondary autonomous insufficiency, hypovolemia.

• Increased intake of salt and liquid (up to 2–2.5 liters of liquid, at least 8 g of salt per day). It is important to prevent dehydration, especially on hot days or in diseases accompanied by increased fluid loss.

• Meals should be taken in small portions (preferably in 4–5 meals). Refusal of hot food and limiting the amount of carbohydrates in the diet significantly reduce the severity of PPG and the likelihood of its occurrence. Avoid overeating, exclude alcohol.

Additionally, you can use:

• sleep with a raised head of the bed (20-30 cm or up to 15 °);

• abdominal bandages, compression knitwear;

• portable seats if you need a long stay in orthostasis;

• special exercises with crossing legs, leg extension, activation of the calf, gluteus muscles, with forward inclinations and performed "squatting";

• special “maneuvers” - exercises for the arms (tension of the arms in the shoulder girdle), legs and abdominals;

• physical training (both dynamic loads and tilt training - special training for orthostatic stability), the regularity of physical training is a major factor in improving the endurance and tolerance of orthostasis.

In the case of ineffectiveness of non-drug methods of correction of hypotensive states, pharmacotherapy can be used.

Midodrin is an adrenergic agonist that causes arterial and venous vaso-constriction with increased peripheral vascular resistance and redistribution of blood volume, recommended for all types of hypotension in the form of monotherapy or in combination with fludrocortisone. Midodrin was used in an individual dosage depending on the severity of the clinical manifestations - usually 2.5 mg (1 tablet or 7 drops) 2-3 times a day. The dose can be increased with an interval of 1 week up to 30 mg / day. Midodrin can aggravate the patient’s arterial hypertension (noted in a horizontal position), therefore, its last dose is recommended to be taken at least 4 hours before bedtime. The use of midodrine in a dose of 3–7 drops (7 drops is equivalent to 2.5 mg) 10–15 minutes before meals provides a prendial pressor effect, reducing the degree of postprandial decrease in blood pressure.

Fludrocortisone acetate, a mineralocorticoid, has been used for many years to treat all types of GO in a dose of 0.1-0.2 mg / day. Its main therapeutic effect is sodium and fluid retention due to a decrease in al-dosterone secretion. Potential complications of long-term therapy are hypokalemia, hypomagnesemia, progression of heart failure, arterial hypertension.

Sympathomimetic direct amines (phenylephrine, norepinephrine) can be used for hypotensive conditions with an endogenous deficiency of catecholamines (in particular, for idiopathic GO, Shay-Drajger's syndrome). These drugs are rapidly inactivated when administered orally and can be used in short courses as single appointments the need to activate patients.

Emergency treatment

In urgent conditions associated with the development of arterial hypotension against the background of severe hypovolemia, emergency replenishment of the circulating blood volume is necessary. In combination with heavy drinking, intravenous (iv) administration of sodium bicarbonate, sodium chloride / potassium chloride 400–1200 ml and / or sodium acetate / sodium chloride / potassium chloride 400–1200 ml can be used. In acute blood loss, iv administration of dextran 400–1200 ml is indicated once and / or an isotonic 0.9% sodium chloride solution 400–1200 ml. The reason for stopping rapid fluid infusion is an increase in systolic blood pressure to 100 mmHg. Art. and the absence of severe tachycardia (heart rate of not more than 100 beats / min).

With drug-induced arterial hypotension, the introduction of 1% phenylephrine (1.0 ml in 100 ml of physiological saline) or 5% intravenous glucose solution is recommended. In combination with phenylephrine or on its own, midodrine may be used.

In case of arterial hypotension of unclear origin, potentially life-threatening, the administration of colloidal solutions of at least 400 ml iv can be used once in combination with dopamine iv in a dose of 2 to 15 μg / kg / min to increase blood pressure and / or norepinephrine in / c, starting at 10 mcg / min with a gradual increase doses.

In urgent hypotensive conditions caused by adrenal insufficiency, substitution therapy with glucocorticoids - hydrocortisone at a dose of 100 mg iv is used, followed by a prolonged hydrocortisone infusion.

Lesson purpose

1. To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of hypertensive drugs:

 Adrenomimetics - phenylephrine (adrenaline), ephedrine, mesatone, dobutamine, midodrine;

 Dopaminomimetics - dopamine.

 Glucocorticosteroids - hydrocortisone, prednisone.

 Mineralocorticoids - DOXA;

 Analeptics - caffeine, cordiamine, camphor, sulfocamphocaine;

 Agents affecting the angiotensin system - angiotensinamide;

 Adaptogens - preparations of Eleutherococcus, Ginseng, Leuzea, Rhodiola rosea, Zamaniha, Echinacea, Aralia, Schisandra.

2. To know the main pathogenetic mechanisms that are the object of a mediocamenous effect in case of: arterial hypertension, hypertensive crises, in hypotensive conditions and in shock, collapse

3. Be able to:

 select the necessary drugs for a particular patient with the indicated pathology, highlight the

criteria for therapeutic efficacy and safety;

 prescribe combination therapy;

 substantiate and provide urgent differentiated medication for complicated and unmalted hypertensive crisis, with shock and collapse.

The task for self-checking the initial level.

1. Etiology, pathogenesis, classification of arterial hypotension, hypotensive conditions.

2. State the significance of the leading pharmacokinetic characteristics (T1 / 2el, association with plasma proteins, \ / d) in the individual selection of antihypertensive drugs.

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

4. Explain the mechanism of the hypotensive effect of drugs that affect the humoral links in blood pressure regulation. Formulate indications and contraindications to their purpose.

5. What undesirable effects are inherent in antihypertensive drugs?

Control of the intermediate level of knowledge.

The solution of situational problems.

1. The patient, 56 years old, is in the hospital due to hypertension. He took medications: Kapoten 25 mg three times a day, Adversuten - 1 mg 3 times a day. 30 minutes after taking the drugs, the patient fell and lost consciousness for several seconds. Objectively: the skin is pale, moist. Pulse - 100 in 1 min, rhythmic. HELL 60/20 mm RT. Art.

What complication arose in the patient? Indicate the drugs necessary for the purchase of this painful process.

2. In a woman, 34 years old, with acute bronchopneumonia, after an intradermal test for penicillin, after 5 minutes, a cough, shortness of breath, fear, anxiety suddenly appeared headache, dizziness, tinnitus, nausea, vomiting, abdominal pain. Objectively: the general condition is serious. Consciousness is blurred. Foam, cramps, involuntary bowel movements and urination. The skin is pale with a cyanotic hue. Pulse 120 beats. in 1 min, rhythmic, small filling, filiform. AKD - 60/20 mm RT. Art. Heart sounds are deaf. In the lungs, hard vesicular breathing, scattered dry rales.

Formulate a diagnosis. Make an intensive care program, justify its purpose.

3. 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 following were prescribed by the attending physician: 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 down and lost consciousness for several seconds. Objectively: the skin is pale, moist. PE - 100 beats per 1 minute, AKD - 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.

4. 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 following were prescribed by the attending physician: 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 down and lost consciousness for several seconds. Objectively: the skin is pale, moist. PE - 100 beats per 1 minute, AKD - 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.

5. Patient T., 48 years old, manager, asked for help with complaints of episodes of general weakness, sweating, shortness of breath, palpitations, paroxysmal cough. These attacks are accompanied by a decrease in AKD to 95/50 mm RT. Art. In the anamnesis - NCD by hypotensive type, smokes (1 pack per day), has been taking oral contraceptives for the last 7 years. The described symptoms appeared 2 months ago after a long flight. Objectively: increased nutrition, varicose veins of the lower extremities, displacement of the right and upper borders of the heart, vesicular breathing over the lungs, pastes of the legs. Additional studies: prothrombin index - 104%, fibrinogen - 4.4 g / l; Echocardiography: a significant expansion of the right heart, signs of pulmonary hypertension; radiologically in the lungs - there are no focal and infiltrative changes.

Justify and give a preliminary diagnosis. What is the treatment tactic in this case? Indicate the criteria for the effectiveness and safety of the use of the proposed drugs.

TESTS

1. 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 medication is needed for emergency treatment?

A. Unitiol.

B. * Bemegrid.

C. Dipiroxim.

D. Atropine sulfate.

E. Adrenaline.

2. A man, 18 years old, was given an intramuscular injection of benzylpenicillin sodium salt for shoulder phlegmon. After that, he developed tachycardia, a threadlike pulse, blood pressure decreased to 80/60 mm RT. Art. What kind of pharmacological reaction has developed?

A. Potentiation.

B. Central action.

C. Reflex action.

D. * Anaphylactic shock.

E. Peripheral action.

3. In complex therapy for chronic insufficiency, the patient was prescribed analeptic, which also has a direct pacemaker and expectorant effect. Also, this drug can be used externally for rubbing with arthritis. Indicate this drug.

A. Bemegrid

B. Cordiamine

C. Etymizole

D. Caffeine

E. Camphor

4. The patient was admitted to the intensive care unit with cardiogenic shock. Choose a first aid drug:

A. Norepinephrine

B. Eufillin

C. Strofantin

D. Dobutamine

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.

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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

PRINCIPLES OF TREATMENT OF HYPERTENSIVE CRISES AND ACUTE HYPOTENSIVE CONDITIONS

Purpose of the topic.

Hypertension drug therapy is the most important area of activity of a practical doctor, which allows saving a patient's life in case of emergency conditions - hypertensive crisis, eclampsia, shock, collapse, impaired coronary and cerebral circulation, lead to effective secondary prevention of hypertension, symptomatic arterial hypertension, pregnant women and others.

Hypertensive crisis (HC) belongs to the category of life-threatening conditions and is caused by a sudden increase in systolic and diastolic blood pressure with subsequent dysfunctions of the autonomic nervous system, disorders of the cerebral, coronary and renal circulation. The severity and clinical picture of HA can be various, up to a coma with the development of acute respiratory and cardiovascular failure, requiring consistent IT in a specialized cardiology or resuscitation department.

Reasons for the development of HC. In 20-30% of cases, HC is observed in patients with arterial hypertension. At the same time, under certain conditions, hepatitis C can develop in individuals with symptomatic hypertension and somatically healthy people of young and middle age. Motivational characteristic of the topic.

Hypertensive crisis (HC) is a condition of increasing blood pressure, causing the appearance or significant deepening of clinical symptoms of damage to target organs.

Classification of hypertensive crises

Complicated hypertensive crisis implies the presence of acute damage to target organs (acute coronary syndrome, acute left ventricular failure, acute hypertensive encephalopathy, stroke, eclampsia, arterial bleeding, dissection of aortic aneurysm, head injury), requires urgent care (Hypertensike urgency) .

Uncomplicated hypertensive crisis - not associated with damage to target organs, emergency assistance (Hypertensike emergency) is required, does not require state nutrition.

The prevalence of hypertensive crises

Prevalence. Hypertensive crises develop in approximately 7% of patients with arterial hypertension. Hypertensive crises account for 20% of all reasons for calling an ambulance

History of the study of the problem of hypertensive crises

History of the problem. The first HA was described in 1903 by the Austrian physician J. Pahl, who believed that it was based on a sudden increase in blood pressure associated with spastic vasoconstriction. J. Pahl highlighted general and local vascular crises. The former, in his opinion, were accompanied by an increase in systemic blood pressure, the latter - only by a local disturbance of circulation in individual organs due to the spasm of the blood vessels supplying them (angina pectoris, intermittent claudication, migraine, Meniere's syndrome, Raynaud's syndrome, etc.).

Symptoms of a hypertensive crisis

According to the classification of A.L. Myasnikov, proposed in the 50's, there are two types of hypertensive crises

The crises of the first type develop suddenly, last from a few minutes to 2 to 3 hours, are accompanied from the very beginning by a sharp pulsating headache, a state of anxiety, agitation, increased irritability. Variations of vision are very characteristic - grid, fog before the eyes. The patient throws into a fever, he has hot flashes, sweating, cooling hands and feet, trembling hands and feet. Patients complain of stitching pains in the region of the heart, shortness of breath or a feeling of incomplete breathing, lack of air, rapid heartbeat, and a sinking heart. The skin is moist, covered with red spots.

For such HA, a predominant increase in systolic blood pressure (ADS), an increase in heart sounds during auscultation, the accent of the second tone on the aorta becomes especially loud. In addition, an increase in body temperature, slight hyperglycemia, and the appearance of a hemorrhagic rash are possible. According to the observations of A. L. Myasnikov, crises of the first type are more common in the initial stages of a hypertensive disease.

Crisis of the second type, according to A.L. Myasnikov, develop gradually, take a long time - from several hours to 4-5 days. Patients often experience cerebral symptoms - heaviness in the head, headache, lethargy, drowsiness, general stupor, ringing in the ears, dizziness, insomnia, nausea, and vomiting. Vision and hearing impair. Perhaps the appearance of focal neurological symptoms, anginal pain, suffocation, as well as shortness of breath and moist congestive wheezing in the lungs. For such hypertensive crises, a predominant increase in diastolic blood pressure (ADD) is typical. Heart rate (HR) is not changed or slowed down, the level of blood glucose usually also does not change. A.L. Myasnikov pointed out that a hypertensive crisis of the second type is more characteristic of stage III hypertension.

The pathophysiological basis for the classification of crises according to A.L. Myasnikov's differences in hemodynamics are crises: the first type is accompanied by an increase in cardiac output ("stroke volume hypertension"), the second type of crisis is accompanied by an increase in the total peripheral resistance of the vessels (OPSS, "peripheral resistance hypertension"). Hemodynamic differences, in turn, were associated with the action of specific mediators - adrenaline in crises of the first type, noradrenaline - in crises of the second type.

S.G. Moiseev proposed to distinguish between hypertensive crises in accordance with clinical manifestations. Cerebral and cardiac types were distinguished. The latter was divided into three options: asthmatic with the development of left ventricular failure and pulmonary edema, anginal (with angina pectoris and myocardial infarction (MI) and arrhythmic, accompanied by rhythm disturbance, for example, the development of atrial fibrillation (flutter).

A.P. Golikov (1976) belongs to a classification based on differences in the violation of central hemodynamics with the allocation of hyper-, hypo- and eukinetic variants of the course of

hypertensive crises

M.S. Kushakovsky distinguished three clinical forms of hypertensive crises - neuro-vegetative, water-salt (edematous) and encephalopathic. Thus, the basis for the separation of hypertensive crises by type were both clinical and hemodynamic characteristics.

The classification of hypertensive crises and the differential diagnostic technique proposed by J. Laragh (USA), 2001, are designed to determine the optimal regimen for the choice of drugs for the treatment of hypertensive crises depending on the pathogenesis.

According to this classification, crises are divided into renin-angiotensin- and tri-volume-dependent.

The key point for determining the type of hypertensive crisis is the determination of plasma renin activity index (ARP), which allows us to define the hypertensive crisis as sodium-volume-dependent at low ARP (<0.65 ng / ml / h) or as renin Dependent at high ARP (> 0.65 ng / ml / h).

Despite the intensive study of arterial hypertension (AH) and the presence of a number of national and international recommendations for its treatment, there are still no number of effective antihypertensive drugs for parenteral and oral use for practitioners of various specialties.

In international clinical practice, situations related to severe hypertension (blood pressure from 180/110 mm Hg and above) are divided into three groups:

1) emergency conditions (hypertensive emergencies);

2) emergency conditions (hypertensive urgencies);

3) stable, asymptomatic (low-symptom) uncontrolled severe hypertension.

Emergency and emergency conditions, as a rule, are the result of a hypertensive crisis.

Emergency conditions in most cases include:

• rapidly progressive or malignant hypertension;

• diseases of the central nervous system:

 hypertensive encephalopathy;

 hemorrhagic stroke;

 subarachnoid hemorrhage;

 atherothrombotic heart attack with very high hypertension;

• diseases of the cardiovascular system:

 acute aortic dissection;

 acute left ventricular failure;

 acute myocardial infarction or unstable angina;

• kidney disease:

 acute glomerulonephritis;

 renal crises in collagenoses;

 severe arterial hypertension after a kidney transplant;

• increase in the concentration of catecholamines:

 hypertensive crises with pheochromocytoma;

 hypertensive crises ("rebounding") after a sudden cessation of antihypertensive drugs;

 use of sympathomimetic drugs;

 the interaction of food or drugs with monoamine oxidase inhibitors;

 neurological disorders (autonomous dysfunction) with Guillain-Barre syndrome or after spinal cord injury;

• preeclampsia / eclampsia;

• surgical interventions:

 severe arterial hypertension in patients requiring urgent surgery;

 postoperative arterial hypertension;

 postoperative bleeding in the area of the vascular suture;

 condition after coronary artery bypass surgery;

• severe body burns;

• heavy nosebleeds.

A sudden, usually significant, increase in blood pressure (often systolic blood pressure (SBP) over 220-230 mm Hg and / or diastolic blood pressure (DBP) over 120-130 mm Hg) is accompanied by acute damage to the target organs: cardio -vascular system, brain, kidneys, eyes. This complicated hypertensive crisis is quite rare and requires a quick, but controlled decrease in blood pressure to a safe level (not necessarily to normal values), which is usually achieved by iv administration of drugs. Patients should be immediately hospitalized in specialized emergency departments with trained personnel and modern equipment for dosed iv administration of drugs and dynamic, including invasive, monitoring of hemodynamics and the condition of target organs. The primary goal of treating most of them is to reduce the average blood pressure (ADP) by no more than 25% over a period of several minutes to one or two hours, depending on the condition of the patient. Then you can continue to lower blood pressure to approximately 160/100 mm RT. Art. over the next two to six hours. An excessive drop in blood pressure should be avoided, as this can cause ischemia or even heart attack of the target organ.

The term "emergency state" (hypertensive urgency) is used for severe hypertension (according to some authors, it is not always a crisis course), which does not lead to rapid damage to target organs. If a hypertensive crisis is diagnosed in these patients, then it should be attributed to the “uncomplicated” form. From a practical point of view, this means that a decrease in blood pressure may not be as fast as in an emergency (hypertensive emergency), but for several hours or one to two days, and often using oral medication. Probably, sometimes, at a high risk of complications, treatment of emergency conditions should begin in the hospital (emergency room) and then continue on an outpatient basis

Shayne P.H. and Pitts S.R. It is proposed to include in the group of emergency conditions

patients with a significant increase in blood pressure (diastolic blood pressure (DBP) of more than 115-120 mm Hg) and a high risk of rapid progression of damage to target organs, but without the development of acute injuries. In their opinion, this group should primarily include patients who have a history of a target organ disease: coming cerebrovascular accident or stroke, acute coronary syndrome, coronary heart disease, congestive heart failure, impaired function kidney and others. These authors also refer to hypertensive urgency high blood pressure in pregnant women, not accompanied by preeclampsia. We think Shayne P.H. and Pitts S.R. quite specific and noteworthy in terms of its practical use.

Thus, the first two groups of conditions (hypertensive emergencies and hypertensive urgencies) require quick intervention, while in case of severe, but stable and low-symptom arterial hypertension, timely (according to some authors, within a week) scheduled examination and selection of effective antihypertensive therapy .

Hypertensive crisis, regarded as a condition characterized by a sudden, as a rule, significant increase in blood pressure, which is accompanied by damage to vital organs or presents a real threat of their defeat, is the main clinical situation requiring urgent antihypertensive therapy. Nevertheless, the need for emergency medical care in patients with arterial hypertension arises not only in its crisis course, and the level of blood pressure is not considered as the main criterion for the diagnosis of emergency and emergency conditions. The main reasons for the development of hypertensive crises are:

• sudden increase in blood pressure in patients with chronic arterial hypertension;

• sudden cancellation of some antihypertensive drugs;

• Renovascular arterial hypertension (atherosclerosis of the renal arteries, fibromuscular dyspla• parenchymal kidney disease (acute glomerulonephritis, collagenosis);

sia, etc.);

• pheochromocytoma, a renin-secreting tumor, primary hyperaldosteronism (rarely);

• use of tricyclic antidepressants (amitriptyline, clomipramine, imipramine, etc.), cocaine, amphetamines, sympathomimetics, cyclosporine, erythropoietins;

• the use of products containing tyramine during the use of MAO inhibitors; taking glucocorticoids, non-steroidal anti-inflammatory drugs;

• preeclampsia, eclampsia;

• traumatic brain injury, ischemic stroke, brain tumor.

Hypertensive crises are more often recorded in elderly patients. Complicated hypertensive crises develop in less than 1-2% of patients. In the United States, about 500 thousand such cases are registered annually. In most of them, the cause of hypertensive crises is the ineffective treatment of essential hypertension (hypertension). However, according to some reports, more than 20% of these patients have symptomatic (secondary) arterial hypertension. Among them, parenchymal kidney diseases predominate, renovascular hypertension (atherosclerosis of the renal arteries is more often (2/3 of all cases)) and pheochromocytoma, and primary aldosteronism (Conn syndrome) is rare. The cause of hypertensive crises may be the rapid discontinuation of antihypertensive drugs (especially b-blockers and central a-adrenergic agonists, such as clonidine), the use of certain drugs or drug use.

Complaints, anamnesis, physical examination, supported by a number of laboratory and

instrumental studies, determine the tactics of managing patients with acute hypertension syndrome (the need for hospitalization, the rate of decrease in blood pressure, the choice and method of administration of an antihypertensive drug, etc.). The key to their successful treatment is the differentiation between complicated and uncomplicated hypertensive crisis, finding out and, if possible, eliminating the causes of hypertensive crisis and / or determining an adequate treatment for the underlying disease that led to its development.

Physical examination should be aimed directly at finding signs of damage to target organs. Blood pressure should be measured on both hands (a significant difference in it can indicate, in particular, the dissection of the aortic aneurysm) lying and standing (if possible). Examination of the cardiovascular system focuses mainly on identifying symptoms of heart failure (shortness of breath, wheezing in the lungs, gallop rhythm, etc.). With a neurological examination, the presence of impaired consciousness, cerebral or focal symptoms is determined. Ophthalmoscopy can detect changes in the fundus (hemorrhage, exudate, swelling of the optic nerve nipple, etc.).

Registration of an ECG, a general blood test, a study of the concentration of creatinine, urea in the blood plasma and urinalysis are performed in all patients with hypertensive crisis. At the same time, chest x-ray, echocardiography, CT, MRI are performed according to indications. In most cases, these studies are conducted simultaneously with the start of antihypertensive treatment.

The main antihypertensive drugs used to treat hypertonic crises

A sufficiently large number of drugs (parenteral and oral) are used to treat hypertensive crises. The main requirements for them are: the rapid onset of action and the rapid manifestation of the maximum effect (preference is given to short-acting drugs), the possibility of titration of the dose over a wide range, low frequency of severe side effects. If the cause of the hypertensive crisis is unknown, then empirical therapy is carried out, and in some cases specific treatment is used (acute coronary syndrome, pheochromocytoma, eclampsia, etc.). In the absence of hypertensive agents for the treatment of hypertensive crises listed in the table. 1, iv forms of other drugs can be used: calcium antagonists (verapamil, diltiazem, etc.), b-blockers (for example, propranolol: intravenously 2.5-10 mg iv in 3-5 minutes; iv infusion 3 mg / h). At the same time, the appointment of diuretics in hypertensive crises should not be routine, but should be carried out only on special indications (for example, pulmonary edema).

Sodium nitroprusside, which is an active arterial and venous nitrovasodilator, remains one of the main drugs for the relief of complicated hypertensive crises. With intravenous infusion, it begins to act in a few seconds, and its effect disappears within three to five minutes after the drug is discontinued, which allows good control of the decrease in blood pressure and minimizes the risk of hypotension.

The use of nitroglycerin is preferable to sodium nitroprusside in patients with arterial hypertension and ischemic heart disease (unstable angina, coronary bypass surgery, myocardial infarction) due to the fact that it is known to have along with antihypertensive and pronounced antianginal (anti-ischemic) action. In patients with coronary heart disease, it is necessary to carefully monitor blood pressure, because a significant decrease in blood pressure can increase myocardial ischemia. With prolonged continuous infusion (more than 24-48 hours), nitroglycerin tolerance may develop.

Fenoldopam is a selective agonist of postsynaptic dopaminergic receptors, which, when used, does not impair renal perfusion, despite a decrease in systemic blood pressure. It can be used for most complicated hypertensive crises (the rival of sodium nitroprusside) and is an alternative to traditional antihypertensive drugs for the treatment of patients with renal failure.

The drugs, which, according to many cardiologists, are an alternative to sodium nitro-prusside in the treatment of complicated hypertensive crises (high efficiency and no danger of accumulation of toxic metabolites), include nicardipine (a calcium dihydropyridine antagonist), used in the form of iv infusions, and labetalol (a blocker of b-adrenergic and a-adrenergic receptors), administered as an IV bolus or IV drip.

The use of labetalol leads to a combined blockade of a- and b-adrenergic receptors, a decrease in total peripheral vascular resistance (OPSS), without negative effects on coronary, cerebral and renal blood flow. Therefore, it is effective and safe in many complicated hypertensive crises, including cases of exacerbation of coronary heart disease (unstable angina, myocardial infarction) and pathology of the central nervous system (hypertensive encephalopathy, acute disturbance of cerebral circulation, etc.).

Similar to the use of captopril sublingually, intravenous administration of enalaprilat has been successfully used for about 20 years to treat hypertensive crises. In a number of studies, it was noted that its effectiveness (the severity of lowering blood pressure) correlates with the concentration of angiotensin II and renin activity in blood plasma. Intravenous administration of enalaprilat does not give serious adverse reactions. However, its use, like other angiotensin-converting enzyme inhibitors, is contraindicated in pregnant women. It should not be used in the acute period of MI.

The pharmacological properties of esmolol make it an “ideal - adrenoblocker” for use in emergency situations, because it has a fast (within 60-120 seconds) and short (10-20 minutes) action. Esolol is recommended for lowering high blood pressure in patients with acute myocardial ischemia, stratified aortic aneurysm and arterial hypertension that occurred during surgery, during anesthesia withdrawal and in the postoperative period.

Oral antihypertensive drugs are often used to treat uncomplicated hypertensive crises.

Features of the treatment of certain types of emergency conditions in arterial hypertension (complicated hypertensive crises)

Myocardial ischemia or myocardial infarction

Since the goal of treating these patients is to stop or reduce myocardial ischemia, intravenous administration of nitroglycerin is preferred, which, along with a decrease in blood pressure (decrease in OPSS), causes dilation of large coronary arteries, reduces venous return to the heart (reduction of preload), and of course LV diastolic pressure. All this helps to improve myocardial perfusion. In patients with exacerbation of coronary heart disease and high arterial hypertension, in the absence of contraindications, the use of labetalol, b-blockers is possible esmolol, etc.), as well as non-dihydropyridine calcium antagonists (verapamil, diltiazem). Sodium nitroprusside or phenoldopam are recommended only for refractoriness to nitroglycerin, labetalol and b-blockers. It is inappropriate to use drugs that cause reflex tachycardia (diazoxide, hydra-lazine, dihydropyridine calcium antagonists), which can lead to the expansion of the area of myocardial ischemia.

Pulmonary edema

Reducing high blood pressure in patients with acute LV systolic dysfunction that caused pulmonary edema should be performed with vasodilators that reduce both pre- and afterload (sodium nitroprusside) in combination with loop diuretics. IV administration of nitroglycerin, enalaprilat (contraindicated in myocardial infarction) and phenoldopam may also be effective.

Drugs that increase myocardial function (diazoxide, hydralazine) or worsen its contractile function (labetalol, b-blockers, calcium antagonists) should not be used in acute systolic heart

failure.

Aortic dissection

This is the most dangerous acute aortic disease, which poses a significant threat to the patient's life. In the United States, about 2,000 aortic dissections are registered annually, with mortality rates of 3-4% of all cases of sudden death from cardiovascular disease. The most common risk factor for aortic dissection is arterial hypertension. Both the ascending and descending parts of the aorta can be affected.

Intravenous antihypertensive therapy should be started immediately in all patients with suspected aortic dissection (naturally, with the exception of patients with hypotension). At the same time, iv pain is stopped by the introduction of mor-fin. As a rule, it is recommended to lower blood pressure faster than with other complicated hypertensive crises. Decrease in GARDEN to 100-120 mm RT. Art. (or ADSr up to 60-75 mmHg) is achieved within a few minutes, provided that there are no symptoms of organ hypoperfusion. The goal of pharmacotherapy is to lower blood pressure, myocardial contractility (dp / dt), heart rate, and ultimately aortic wall tension. Therefore, the combination of a vasodilator (sodium nitroprusside) and a b-blocker (esmolol, pro-pranolol, metoprolol, etc.) is referred to standard treatment.

Instead of sodium nitroprusside, phenoldopam can be used. When there are contraindications for the use of b-blockers, it is advisable to administer iv verapamil or diltiazem, which reduce blood pressure and myocardial contractility. The intravenous administration of an a- and b-adrenergic receptor antagonist labetalol is an alternative to a combination of a vasodilator and a b-blocker. The use of a trimethafan ganglion blocker, which causes a decrease in both blood pressure and dp / dt, is also probably possible without b-blockers. At the same time, monotherapy with drugs that can increase tachycardia, cardiac output and aortic wall tension (hydralazine, diazoxide, dihydropyridine calcium antagonists) should not be carried out in these cases.

With dissection of the ascending aorta, emergency surgical treatment is indicated (aortic prosthetics and sometimes aortic valve prosthetics), and in patients with a lesion of the descending aorta, prolonged medical treatment is possible.

Hypertensive encephalopathy

Stability of cerebral blood flow is supported by the mechanism of autoregulation with changes in blood pressure in healthy individuals ranging from 60 to 120 mm Hg. Art., and in patients with chronic hypertension - from 110 to 160 mm RT. Art. If systemic blood pressure exceeds the upper limit of autoregulation, then a significant increase in cerebral blood flow and the development of cerebral edema, which is the main cause of hypertensive encephalopathy.

The main symptoms of hypertensive encephalopathy are headache, nausea, vomiting, blurred vision. There may be a violation of consciousness, convulsions, and in the absence of adequate treatment, the development of cerebral hemorrhage, coma, and death. During the examination, in addition, swelling of the nipple of the optic nerve is detected, which may or may not be combined with other manifestations of retinopathy. To confirm the diagnosis of hypertensive encephalopathy, the exclusion of a number of diseases that have similar symptoms (stroke, subarachnoid hemorrhage, brain tumor, etc.) is required. To this end, most patients are shown to conduct computed or magnetic resonance imaging.

With hypertensive encephalopathy, it is necessary to quickly (within about an hour) reduce blood pressure (average ADcp by 25% or DBP to 100-110 mm Hg) iv by administration of labetalol, sodium nitroprusside, nicardipine or fenoldopam.

The use of antihypertensive drugs that have a sedative effect (clonidine, methyldopa, reserpine)

is contraindicated. After lowering blood pressure, the symptoms of hypertensive encephalopathy disappear within a few hours.

Ischemic, hemorrhagic strokes and subarachnoid hemorrhage

Current recommendations suggest abstaining from antihypertensive therapy for at least 10 days after the development of ischemic stroke. The exception is patients in whom cerebrovascular accident is combined with acute heart failure, acute coronary syndrome, aortic dissection, or when their blood pressure exceeds 220/120 mm Hg. Art.

These recommendations are justified by the fact that in most people with ischemic stroke, high blood pressure, which is probably a protective reaction in these cases, decreases independently within a few days, and a decrease in blood pressure in the first hours and days of the disease can lead to a deterioration in blood flow in peri-infarction zone and expansion of the focus of brain damage.

If it is necessary to lower blood pressure (BPA not more than 25% for several hours), it is currently recommended to use labetalol first of all,

As with ischemic stroke, it is not recommended to lower blood pressure in patients with subarachnoid hemorrhage (SAH), with the exception of special cases when it is excessively elevated (more than 220/120 mm Hg). As a number of studies have shown, antihypertensive therapy does not improve the course of the disease: a decrease in blood pressure in SAH, reducing the risk of repeated hemorrhages, significantly increases the number of cases of cerebral infarction

If a decision is made on the need to control blood pressure in patients with subarachnoid hemorrhage, you need to remember about the possibility of increasing intracranial pressure when using sodium nitroprusside or nitroglycerin (although this is rare in the clinic), therefore, labetalol is preferred. It is advisable to prescribe nimodipine, which helps to reduce cases of cerebral spasm (which is characteristic of this disease) and therefore reduces the risk of cerebral ischemia.

Despite the fact that the optimal tactics of controlling hypertension in patients with hemorrhagic stroke is still not clear, most of them recommend a gradual and cautious decrease in blood pressure if it is more than 180/105 mm Hg. Art. The goal of treatment is to maintain a CAD between 140 and 160 mmHg. Art., carefully controlling the patient's condition in order to prevent the increase in neurological symptoms associated with a decrease in blood pressure and cerebral hypoperfusion.

With ischemic, hemorrhagic strokes and subarachnoid hemorrhage, as well as with hypertensive encephalopathy, the use of antihypertensive drugs that have a depressing effect on the central nervous system (clonidine, methyldopa, reserpine) is contraindicated.

Preeclampsia and Eclampsia

Pregnant women with preeclampsia and eclampsia need hospitalization and bed rest. With therapy-resistant preeclampsia or the development of eclampsia, immediate delivery is indicated. For a quick but controlled decrease in blood pressure in these clinical situations, safe and effective parenteral medications are recommended: hydralazine, labetalol, nicardipine. Despite the fact that hydralazine is traditionally widely used in the treatment of preeclampsia and eclampsia, some experts prefer labetalol and nicardipine due to fewer adverse reactions and high efficacy. Thus, a number of studies have shown that iv administration of labetalol at a dose of 1 mg / kg women with hypertension in the last trimester of pregnancy did not affect the utero-placental blood flow and fetal heart rate, despite a significant decrease in maternal blood

pressure and heart rate

At the same time, there is evidence that sodium nitroprusside may pose a certain risk to the fetus, so it should be a reserve drug and used during pregnancy only as a last resort. Trimethafan is not recommended for the treatment of preeclampsia and eclampsia - because of the increased risk development of meconium bowel obstruction - and diuretics, since pre-eclampsia almost always shows a decrease in uteroplacental blood flow. For the prevention of seizures, magnesium sulfate is used: 4-6 g IV for 15-20 minutes, then a continuous IV infusion at a speed of 1-2 g / h

Postoperative hypertension

Arterial hypertension quite often, in 25-75% of cases, develops after surgery. It increases the number of complications in the postoperative period (bleeding from the area of vascular sutures, myocardial ischemia, acute heart failure, etc.), and also has a negative effect on the prognosis. Severe postoperative hypertension is more often recorded in patients in whom blood pressure was poorly controlled before surgery. Obviously, many patients in the postoperative period cannot take a specific time of the drug orally, and therefore they need to use parenteral administration of antihypertensive drugs.

Before extracardiac surgery in patients with arterial hypertension, it is necessary to achieve a stable decrease in blood pressure. Most oral antihypertensive drugs can be prescribed on the morning of the day of surgery, with the exception of diuretics, because of the danger of hypovolemia. Drugs that cannot be discontinued (e.g., b-blockers) should be administered parenterally. In the days following surgery, antihypertensive therapy, selected before surgery, continues.

After coronary artery bypass grafting, blood pressure rises in more than 33% of cases. Arterial hypertension, in the pathogenesis of which the main role is denervation of the heart and immunosuppressive therapy, is a frequent companion of heart transplantation.

The main drugs for lowering blood pressure in patients undergoing cardiac surgery are sodium nitroprusside, nitroglycerin, labetalol, b-blockers and calcium antagonists. There is evidence of the effective use of phenoldopam for this purpose, including after the operation of coronary artery bypass grafting After heart surgery, it is not recommended to prescribe hydralazine and diazoxide, which, causing tachycardia, increase the load on the myocardium.

Hypertensive crises due to increased activity of the sympathetic nervous system

Pheochromocytoma in 85-90% of cases is a benign tumor of the adrenal medulla producing catecholamines. In approximately 70% of cases, arterial hypertension with pheochromocytoma is critical. Hypertensive crises are characterized by palpitations, headache, sweating, pallor of the skin, polyuria. Leukocytosis, eosinophilia, hyperglycemia are often determined in the blood.

To stop the hypertensive crisis with pheochromocytoma, 5-10 mg of phentolamine is administered iv (the use of b-blockers without a-adrenergic blockers is contraindicated). Sodium nitroprusside and labetalol may be reserve drugs. At the same time, according to some reports, the use of labetalol for this purpose is unreasonable due to insufficient effectiveness or even an increase in blood pressure.

The sudden cessation of certain antihypertensive drugs that affect the activity of the sympathetic nervous system (clonidine, b-blockers) can also cause a significant increase in blood pressure (“rebound” hypertension) and the appearance of several other symptoms, such as tachycardia, heart rhythm disturbances and etc. The treatment of rebound hypertension consists in the continuation of interrupted antihypertensive therapy after a rapid decrease in blood pressure with phentolamine, sodium nitroprusside or labetalol. It should be remembered that the use of b-

blockers in patients taking clonidine adversely affects the course of "rebound" hypertension.

Some other clinical situations lead to a significant increase in adrenergic activity and the appearance of severe hypertension.

1) the use of drugs with sympathomimetic activity (cocaine, amphetamines, phencyclidine, phenylpropanolamine, etc.);

2) the interaction of monoamine oxidase inhibitors with foods containing tyramine (we talked about them earlier);

3) Guillain-Barre syndrome (inflammatory disease of the nervous system);

4) spinal cord injury

In the treatment of these arterial hypertension (as in patients with pheochromocytoma), monotherapy with b-blockers should be avoided, because the inhibition of vasodilation associated with stimulation of b-adrenergic receptors leads to the elimination of the counterbalance of a-adrenergic vasoconstriction and a further increase in blood pressure. High blood pressure is reduced in / in the introduction of phentolamine, sodium nitroprusside, phenoldopam, labetalol. However, the data on the effectiveness of the latter in these patients are contradictory and require clarification

Renal failure

For antihypertensive therapy in patients with renal failure, drugs are used that do not adversely affect renal blood flow and glomerular filtration: calcium antagonists, phenoldopam, labetalol, sodium nitroprusside, a-adrenergic blockers. Diuretics (mainly loopback and often in fairly high doses) are used only in the presence of hypervolemia. Thiazide diuretics with glomerular filtration rate less than 30 ml / min are ineffective. Since b-blockers can reduce renal blood flow, their administration in renal failure should be avoided. Patients with this pathology, weighed down by hyperaemia, are contraindicated in potassium-sparing diuretics. A dose adjustment of antihypertensive drugs excreted by the kidneys is necessary.

A number of controlled clinical trials have shown that, compared with sodium nitro-prusside, phenoldopam infusion improves diuresis, natriuresis and clearance creatinine When sodium nitroprusside is administered to patients with renal insufficiency, the risk of intoxication with cyanide and thiocyanate increases (it is necessary to reduce the initial rate of drug administration and control their level in blood plasma). In connection with the foregoing, it is probably necessary to give preference to phenol-dopam rather than sodium nitroprusside, when emergency therapy of hypertension is necessary against the background of renal failure. Some patients may require emergency hemodialysis to control blood pressure. Bilateral nephrectomy followed by permanent hemodialysis or kidney transplantation is also used as a treatment for hypertensive pharmacotherapy with hypertension.

The main antihypertensive drugs used to treat hypertensive crises

Currently, there are a large number of parenteral and oral medications (Table 1, 2), which are used to stop hypertensive crises. The main requirements for them: the rapid onset of action and the rapid development of the maximum effect, the possibility of titration of the dose over a wide range, low frequency of severe side effects. If the cause of the hypertensive crisis is unknown, then empirical therapy is performed, but in some cases specific treatment is used (acute coronary syndrome, pheochromocytoma, eclampsia, etc.). In the absence of antihypertensive agents for the treatment of hypertensive crises listed in the table. 1, iv forms of other drugs can be used: calcium antagonists (verapamili etc.), b-blockers (for example, propranolol: iv 10–10 mg iv for

3-5 minutes; iv infusion 3 mg / h). At the same time, the appointment of diuretics for hypertensive crises should not be routine, but should only be carried out according to special indications (for example, pulmonary edema).

Sodium nitroprusside, which is an active arterial and venous nitrovasodilator, remains one of the main drugs for the relief of complicated hypertensive crises. With intravenous infusion, it begins to act in a few seconds, and its effect disappears within 3-5 minutes after the drug is discontinued, which allows good control of the decrease in blood pressure and minimizes the risk of hypotension.

The use of nitroglycerin is preferable to the use of sodium nitroprusside in patients with arterial hypertension and coronary heart disease (unstable angina, coronary artery bypass surgery, myocardial infarction) due to the fact that, along with antihypertensive, it is also known to have a pronounced anti-angiogenic (anti-ischemic) action. In patients with coronary artery disease, it is necessary to carefully monitor blood pressure, because a significant decrease in blood pressure can increase myocardial ischemia. With prolonged continuous infusion (more than 24–48 hours), nitroglycerin tolerance may develop.

Drugs that can be an alternative to sodium nitroprusside in the treatment of complicated hypertensive crises include the dihydropyridine calcium antagonist nicardipine, used as an intravenous infusion, and labalol (a blocker of b-adrenergic and a-adrenergic receptors), administered as in / in stream, and drip (table. 1).

The use of labetalol leads to a combined blockade of a- and b-adrenergic receptors, a decrease in total peripheral vascular resistance (OPSS) and does not adversely affect coronary, cerebral and renal blood flow. In this regard, it is effective and safe in complicated hypertensive crises, including in cases of exacerbation of coronary heart disease (unstable angina pectoris, myocardial infarction) and pathology of the central nervous system (hypertensive encephalopathy, acute cerebrovascular accident, etc.).

Similar to the use of captopril sublingually in / in the introduction of enalaprilat has been successfully used for about 20 years to treat hypertensive crises. In a number of studies, it was noted that its effectiveness (the severity of lowering blood pressure) correlates with the concentration of angiotensin II and renin activity in blood plasma. Intravenous administration of enalaprilat does not give serious adverse reactions. However, its use, as well as other angiotensin-converting enzyme inhibitors, is contraindicated in pregnant women. It should not be used in the acute period of MI.

The pharmacological properties of esmolol make it an ideal b-blocker for use in emergency situations, because it has a fast (within 60–120 seconds) and short (10–20 minutes) action. Esmolol is recommended to reduce high blood pressure in patients with acute myocardial ischemia, stratified aortic aneurysm and arterial hypertension that occurred during surgery, during anesthesia withdrawal and in the postoperative period

The drugs used in shock and collapse have a multifunctional purpose, since they affect the pathological mechanisms underlying the regulation of vascular tone, cardiac arrhythmias and conduction, acute and chronic heart failure, etc. Their use is of particular importance. in combination with other drugs leading to this pathology. The ability to navigate the world of drug action mechanisms, to use them scientifically to control the etiology and pathogenesis of diseases, to use drug therapy as a method for verifying the diagnosis - forms the clinical thinking of a future doctor.

This topic will allow students to effectively master the diverse pathology in all clinical departments, formulate a clinical worldview and use basic knowledge and skills in practical

activities.

Emergency treatment

In urgent conditions associated with the development of arterial hypotension against the background of severe hypovolemia, emergency replenishment of the circulating blood volume is necessary. In combination with heavy drinking, intravenous (iv) administration of sodium bicarbonate, sodium chloride / potassium chloride 400–1200 ml and / or sodium acetate / sodium chloride / potassium chloride 400–1200 ml can be used. In acute blood loss, iv administration of dextran 400–1200 ml is indicated once and / or an isotonic 0.9% sodium chloride solution 400–1200 ml. The reason for stopping rapid fluid infusion is an increase in systolic blood pressure to 100 mmHg. Art. and the absence of severe tachycardia (heart rate of not more than 100 beats / min).

With drug-induced arterial hypotension, the introduction of 1% phenylephrine (1.0 ml in 100 ml of physiological saline) or 5% intravenous glucose solution is recommended. In combination with phenylephrine or on its own, midodrine may be used.

In case of arterial hypotension of unclear origin, potentially life-threatening, administration of colloidal solutions of at least 400 ml iv can be used once in combination with iv dopamine in a dose of 2 to 15 μg / kg / min to increase blood pressure and / or norepinephrine in / c, starting at 10 mcg / min with a gradual increase in dose.

In emergency hypotensive conditions caused by adrenal insufficiency, substitution therapy with glucocorticoids - hydrocortisone at a dose of 100 mg iv is used, followed by a prolonged infusion of hydrocortisone.

Collapse is a form of acute vascular insufficiency, characterized by a sharp drop in vascular tone or a rapid decrease in the mass of circulating blood, which leads to a decrease in venous flow to the heart, a drop in arterial and venous pressure, hypoxia of the brain and inhibition of the vital functions of the body. Causes: acute infections (typhoid fever, typhus, meningoencephalitis, pneumonia, etc.), acute blood loss, diseases of the endocrine and nervous system (tumors, syringomyelia, etc.), exogenous intoxications (poisoning with carbon monoxide, organophosphorus compounds etc.), spinal and peridural anesthesia, orthostatic redistribution of blood (overdose of certain drugs - ganglion blockers, insulin, antihypertensive drugs, etc.), acute diseases of the abdominal organs (peritonitis, etc.). Collapse can be a complication of acute impairment of myocardial contractile function, combined by the concept of "low cardiac output syndrome", which occurs in the acute period of myocardial infarction, with pronounced tachycardia, with deep bradycardia, with impaired sinus node function, etc.

Shock is a combination of disturbances in cardiac activity, respiration, metabolism, and neuro-endocrine regulation in response to extreme irritation.

The most common form is traumatic shock (with multiple injuries and injuries to the head, chest, abdomen, pelvic bones and extremities, with thermal and chemical burns, electric shock). The victim in the beginning is in an excited state, cannot critically assess the severity of his condition, is anxious, seeks to flee somewhere. In the future, excitement is replaced by lethargy, depression, indifference to the environment. The patient is pale, blood pressure drops, pulse increases, breathing is superficial, skin is covered with clammy sweat. Shock can be a reaction to severe pain in diseases of internal organs, for example, with myocardial infarction (cardiogenic shock) or perforation of a stomach ulcer, bacterial shock occurs with sepsis, toxic shock with toxic substances. A special form is the emotional shock, which is possible with severe mental trauma associated, for example, with a fire, flood, train crash, sudden news of a great grief. Treatment of shock Treatment is directed to the underlying disease; if possible, eliminate the

factor that caused the shock. Treatment of shock should be adequate to the mechanism of its occurrence. In case of cardiogenic shock, along with anesthesia, 1-2 ml of norepinephrine are dripped intravenously, trying to maintain systolic blood pressure at a level of 80-100 mm Hg. st .; Corglycon is carefully administered (which should be used in lower doses under conditions of hypoxia, hypokalemia, acidosis), if necessary, antiarrhythmic treatment is carried out, glucagon is prescribed. To combat metabolic acidosis, 150-200 ml of 5% sodium bicarbonate solution is administered. With hypovolemia, whole blood, plasma, isotonic sodium chloride solution and other fluids are transfused (under the control of arterial and venous pressure). With anaphylactic shock, 1 ml of 0.1% adrenaline solution is administered intravenously, and then prednisone in a dose of up to 150 mg; artificial respiration and indirect heart massage may be necessary. If shock is associated with sepsis, perforation of internal organs, then the treatment of the underlying disease is of primary importance.

The purpose of the lesson.

1. To learn:

a. etiopathogenetic factors of hypertensive crises

b. pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of drugs used in factors of hypertensive crises:

a) beta-blockers:

- non-selective: propronalol / anaprilin /, nadolol / korgard /, oxprenolol, pindolol, etc .;

- cardioselective: atenolol, metoprolol, talinolol, acebutolol, etc.

at. pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of hypertensive drugs:

1. Adrenomimetics: epinephrine, ephedrine, norepinephrine, mesatone, dobutamine, mydodrine;

2. Dopaminomimetics - dopamine.

3. Glucocorticosteroids - hydrocortisone, prednisone.

4. Mineralocorticosteroids - DOXA.

5. Analeptics - caffeine, cordiamine, camphor, sulfocamphocaine.

6. Agents affecting the angiotensin system - angiotensinamide.

7. Adaptogens (preparations of Eleutherococcus, Ginseng, Leuzea, Rhodiola rosea, Za-Manichae, Echinacea, Aralia, Schisandra).

2. To know the main pathogenetic mechanisms that are the object of medication effects with:

a) hypotonic conditions listed in paragraph c.

- Calcium channel blockers. Mechanisms of antianginal action. Undesirable effects. Contraindications to the appointment.

- Beta-blockers. Comparative characteristics. Advantages and disadvantages.

3. Be able to:

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

b) prescribe combination therapy;

c) substantiate and provide urgent differentiated medical assistance with:

- shock, collapse;

- angina attack

- with myocardial infarction.

Control questions of the studied topic.

1. List the clinical and pharmacological principles of the selection and selection of drugs for hypotonic conditions and hypertensive crises.

3. What are the indications for the appointment of adrenaline, its undesirable effects?

4. What effect does mesatone have on blood pressure, heart function, peripheral circulation? The main indications for his appointment.

5. List the diseases contraindicated for the introduction of cordiamine, explain the mechanisms.

6. Explain the antianginal effect of nitroglycerin, approaches to the selection of a single dose and frequency of administration of the drug.

7. What are the undesirable effects of nitroglycerin and therapeutic measures when they occur.

Enumeration of practical work.

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 basic drug for the patient to be supervised and the rationale for the appointment of combination medication therapy.

4. To highlight the signs in a subjective and objective study of the patient, characterizing a violation of vascular tone, leading clinical syndromes - arterial hypotension, angina pectoris, 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, select drugs for the patient to be supervised.

7. Choose the optimal dosage regimen for the drug, taking into account the characteristics of 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 for: acute vascular failure, with hypertensive crises

Control of the intermediate level of knowledge.

The solution of situational problems.

1. A woman, 34 years old, with acute bronchopneumonia, after an intradermal test for penicillin, after 5 minutes, suddenly had a cough, shortness of breath, fear, anxiety, headache, dizziness, tinnitus, nausea, vomiting, and abdominal pain. Objectively: the general condition is serious. Consciousness is blurred. Foam, cramps, involuntary bowel movements and urination. The skin is pale with a cyanotic hue. Pulse 120 beats. in 1 min, rhythmic, small filling, filiform. AKD - 60/20 mm RT. Art. Heart sounds are deaf. In the lungs, hard vesicular breathing, scattered dry rales.

Formulate a diagnosis. Make an intensive care program, justify its purpose.

2. The patient has an attack of cardiac asthma AKD - 140/80 mm RT. The doctor gave the patient a tablet of nitroglycerin under the tongue, intravenously administered 4.0 ml of lasix, strophanthin - 0.05% - 0.5 ml per 10 ml of physiological solution of sodium chloride, and inhaled oxygen

Are the doctor's actions correct? Explain the pharmacodynamics of each drug in this situation.

3. Patient, 62 years old, was hospitalized with complaints of severe pain behind the chest, which lasts 1 hour and is not stopped by nitroglycerin. Suffering angina pectoris, before the attack stopped with nitrates. There are no concomitant diseases. Objectively: cyanosis of the lips. Heart sounds are deaf, rhythmic activity. ECG: acute phase of transmural infarction of the anterior wall of the left ventricle.

Your actions.

A man, 62 years old, was hospitalized in an intensive care unit with a prolonged attack of chest pain, which cannot be stopped with nitroglycerin. Objectively: HELL - 80/60 mm RT. Art., heart rate - 106 in 1 min, BH - 22 in 1 min. During auscultation, heart sounds are deaf, gallop rhythm. What explains the decrease in blood pressure?

TESTS

1. The patient has an uncomplicated hypertensive crisis. How long does blood pressure normalize?

A. 10 - 15 minutes.
B. * 1 - 3 hours.
C. 1 - 3 days.
D. 10 - 12 hours.
E. 5 - 60 minutes.

2. The patient was admitted to the therapeutic department with complicated hypertensive crisis (acute left ventricular failure). How fast should blood pressure normalize?

A. Within a week.
B. 1 - 3 hours.
S. * 5 - 60 minutes.

D 1 to 3 days.
E. 10 - 12 hours.

3. The patient was admitted to the department with a complicated hypertensive crisis (cardiac asthma). The drug of choice for urgent care is:
A. Clonidine sublingually.
B. Clonidine intravenously.
S. Anaprilin sublingually.
D. Adelfan orally.
E. * Furosemide intravenously

4 .. The patient has a diencephalic sympathoadrenal uncomplicated hypertensive crisis. The drug of choice for treatment is:
A. Furosemide intravenously.
B. * Diazepam intravenously.
S. Eufillin intravenously.
D. Nitroglycerin sublingual.
E. Verapamil intravenously.

5. A 53-year-old patient suffers from acute Q-infarction, which was complicated by cardiogenic shock (decreased cardiac output, low total peripheral vascular resistance). Specify the antihypertensive drug recommended by the patient:
A. Adrenaline.
B. Mesaton.
S. * Dobutamine.
D. Noradrenaline.
E. Ephedrine.

5. A 40-year-old patient with bacterial meningitis at the end of the first day of treatment experienced an infectious toxic shock. Specify a hypertensive drug in this case:
A. Noradrenaline.
B. Mesaton.
C. Dopamine.
D. * Prednisolone.
E. Ephedrine.

6. What hypertensive drug is used for fainting?
A. Adrenaline.
B. * Cordiamine.
C. Prednisolone.
D. Hydrocortisone.
E. Dobutamine.

7 .. What receptor stimulation causes an increase in systolic cardiac output?
A. * Beta-1-adrenergic receptors.
B. Beta-2-adrenergic receptors.
C. M-cholinergic receptors.
D. Alpha-1-adrenergic receptors.
E. Alpha-2-adrenergic receptors.

8. The introduction of which adrenomimetic increases blood glucose and is contraindicated in diabetes?
A. * Adrenaline hydrochloride.
B. Norepinephrine hydrotartrate.
S. Izadrin.
D. Mesaton.
E. Angiotensinamide.

9 .. The mechanism of the hypertensive effect of adrenaline hydrochloride is associated with:
A. Non-selective stimulation of M-cholinergic receptors.

B. Stimulation of the central nervous system.
C. Analeptic effect.
D. * Activation of alpha-1 and beta-1-adrenergic receptors.
E. An increase in circulating blood volume.

10. The patient, 44 years old, who suffers from hypertension, developed headache, "internal" trembling, palpitations, and fear. Objectively: pulse - 100 beats. in 1 min, blood pressure - 200/100 mm RT. Art., the left border of cardiac dullness is 1.5 cm shifted to the left of the left mid-clavicular line, heart sounds are sonic, vesicular breathing. On an ECG: sinus tachycardia, signs of left ventricular hypertrophy. Which drug is most appropriate to prescribe?
A. Reviewed.
B. Dibazole.
C. Reserpine.
D. Magnesium sulfate.
E. Furosemide.

11. A woman, 42 years old, complains of a severe headache of a pulsating nature in the frontoparietal region, a feeling of palpitations. He has hypertension for 3 years. A significant increase in blood pressure is noted 2-3 times a month lasting 3-8 hours. The attack ends with excessive urination. The left ventricle is enlarged, heart sounds are clean, pulse is 105 beats per 1 min, blood pressure is 225/115 mm Hg. Art. The shock and minute volume of the heart is increased. Total peripheral vascular resistance is moderately elevated. On an ECG: signs of left ventricular hypertrophy. In the fundus: a symptom of Salus-Hun. Which of the following drugs is most effective for stopping cerebral crisis?
A. Losartan.
B. Hypothiazide.
C. Captopril.
D. Atenolol.
E. Clonidine.

12. In a patient, 59 years old, who has been suffering from hypertension for 15 years, acute left ventricular failure developed against the background of a hypertensive crisis. What drug is most appropriate for this patient?
A. Anaprilin.
B. Nifedipine.
C. Sodium nitroprusside.
D. Veroshpiron.
E. Captopril.

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 HYPOLIPIDEMIC MEDICINES

Purpose of the topic.

Atherosclerosis is a common disease of the arteries of elastic and muscular-elastic types (large and medium caliber), characterized by infiltration of atherogenic lipoproteins into the vessel wall with subsequent development of connective tissue, atheromatous plaques, organ and general circulatory disorders, which is the main cause of many diseases of the cardiovascular system .

The transport of cholesterol in the body is carried out as a part of various fractions of lipoproteins, each of which has its own specific value for the clinical prediction of the risk of cardiovascular complications. These fractions are: low density lipoprotein cholesterol (LDL), very low density lipoprotein cholesterol (VLDL) and high density lipoprotein cholesterol (HDL). To predict the risk of complications of atherosclerosis, the level of blood triglycerides (TG) is also important.

The most important aspect of the comprehensive drug treatment of patients with atherosclerosis is the use of lipid-lowering drugs. They are prescribed in cases where a strictly adhered diet (with a restriction of saturated fats) and lifestyle correction (weight loss, smoking cessation, increased physical activity) do not lead to those target blood lipids that are desirable for 1.5-2 months for patients with cardiovascular disease. The use of drugs of this group for coronary heart disease leads to a decrease in total and coronary mortality, major coronary events, the need for invasive interventions on the heart, and strokes. It should be guided by the levels of low-density lipoprotein cholesterol (LDL cholesterol), total cholesterol (OXC) and high-density

cholesterol lipoprotein (HDL-C)

Motivational characteristic of the topic

It is imperative to realize that the time of doubt about the need for lipid-lowering therapy has passed. It is necessary to act in accordance with the appeal of the largest European cardiologists M. Oliver and Poole-Wilson: “Lower your patient’s cholesterol level now,” meaning that you need to lower LDL cholesterol. ”The main mechanisms that lead to an improvement in the course of IHD and other diseases under the influence of lipid-lowering therapy (with a decrease in the level of LDL cholesterol) are: "stabilization" of atherosclerotic plaque; improvement (restoration) of the functional state of the endothelium, which contributes to the expansion of the coronary arteries in connection with by increasing endothelial production of vasodilating substances; improving blood flow; normalizing platelet function - reducing their "thrombotic potential"; slowing the formation of foam cells; decreasing the inflammatory response - decreasing macrophage activity; increasing HDL and increasing lipid removal from atherosclerotic plaques. It is known that acute coronary insufficiency (myocardial infarction, unstable angina) is to some extent associated with the "instability" of atherosclerotic plaque - naru a decrease in its integrity, subsequent contact of the lipid contents with blood, hemorrhage in the plaque, thrombosis. Hypolipidemic therapy allows to stabilize the state of atherosclerotic plaque, to reduce the severity and progression of these changes. For this purpose, anti-atherogenic (hypotidemic) drugs are used - these are drugs that reduce the pathologically high blood level of atherogenic lipoproteins, and therefore total cholesterol, low and very low density lipoprotein cholesterol, triglycerides

Normal lipid profile

Level	indicator			
	Total cholesterol, mmol / l	LDL mmol / l	HDL mmol / l	TG mmol / l
Normal	5,2	3,4	0,9	2,3
borderline	5,2-6,2	34,-4,1	-	2,3-4,5
elevated	> 6,2	>4,1	-	>4,5

In addition to hyperlipidemia, “risk factors” are important in the prognosis of complications. People with at least one risk factor are more likely to develop atherosclerosis than people who do not. The presence of several risk factors further contribute to the development and progression of atherosclerosis.

Risk factors for the development of atherosclerosis.

1. Irreversible:

• age (in most patients, atherosclerosis appears at the age of 40-50 years and older);

• male sex (in men, atherosclerosis appears more often and 10 years earlier than in women);

• genetic predisposition to the development of atherosclerosis;

2. Reversible:

• smoking;

• arterial hypertension (blood pressure> 140/90 mmHg)

• obesity.

3. Potentially or partially reversible:

• hyperglycemia - hypercholesterolemia and / or hypertriglyceridemia;

• hyperglycemia and diabetes;

• low level of HDL (α-LP) in the blood (<0.9 mmol / l)

4. Other possible factors:

• low physical activity (lack of exercise);

• mental and emotional stress

There is evidence (Ornishetal, 1990) convincingly proving that "lifestyle modification", i.e. The combination of an almost completely vegetarian diet, intensive physical training and psychotherapy (relaxation) can cause a regression of stenosis of the coronary arteries. Superko and Krauss (1994) believe that a strict diet, physical training and their combination cause a more pronounced regression of coronary artery stenosis than prolonged use of lipid-lowering drugs. Currently, the literature discusses the role of viral and chlamydial infections in the occurrence of atherosclerosis.

An increase in plasma cholesterol and disorders in the system of lipoproteins transporting it (atherogenic dyslipoproteinemia) play a leading role in the manifestation and progression of atherosclerosis. The main lipids of human blood plasma are cholesterol esters, triglycerides and phospholipids. The causes of hyperlipidemia can be either primary (genetic) or secondary (endocrine pathology - diabetes mellitus, hypothyroidism, growth hormone deficiency; kidney pathology - chronic renal failure, nephrotic syndrome; cholelithiasis, liver pathology, alcoholism; medication - thiazides, β-blockers, glucocorticoids, estagens, vitamin A, diphenin).

In clinical practice, this classification of hyperlipidemia is most often used:

Type I is associated with a large number of chylomicrons, is rare (1% of cases). With this type of atherosclerosis does not happen, but there is a risk of developing severe destructive pancreatitis and pancreatic necrosis, because chylomicronemia increases the risk of thrombosis and embolism.

Clinical manifestations: weight gain, attacks of intestinal colic, enlarged liver and spleen, pacreatitis, xanthomatous skin rashes.

Type IIa - an increase in blood LDL, found in 10% of cases.

Type IIb - an increase in blood of LDL and VLDL, found in 40% of patients.

Clinical manifestations: Achilles tendon xanthomas and

tendons of the four-headed muscle of the thigh, lipoid arch on the cornea, xanthomatosis of the eyelids, skin of the elbows and knees, coronary heart disease, arterial hypertension, liver steatosis, xanthomatosis and atherosclerosis of lunate valves.

Type III - an increase in the blood of STDs, is very rare - less than 1%.

Clinical manifestations: palmar and plantar xanthomas, lipoid arc on the cornea, liver steatosis, weight gain, coronary heart disease, arterial hypertension, pancreatitis, severe peripheral vascular

atherosclerosis.

Type IV - an increase in blood VLDL, occurs in 45% of cases.

Clinical manifestations: enlarged liver and spleen, arterial hypertension, obesity (android type), liver steatosis.

Type V - an increase in blood VLDL and chylomicrons, occurs in 5% of cases, is practically not atherogenic.

Clinical manifestations: attacks of intestinal colic, enlarged liver and spleen, increased body weight, rarely - IHD.

It should be noted that the type of hyperlipidemia can change in response to diet, treatment, and changes in body weight. The fight against hyperlipidemia is currently considered to be a decisive factor in the successful prevention and treatment of atherosclerotic lesions of the vessels of the heart, brain, lower and upper extremities, as well as the aorta and other large and medium arteries.

HYPOLIPIDEMIC AGENTS:

• Statins: lovastatin (mevacor), simvastatin (zokor), rosuvastatin, pravastatin (lipostat), fluvastatin (leskol), cerivastatin (lipobay), atorvastatin (lipitor);

• Niacin: (vitamin PP, niacin, enduracin) and its derivatives (acipi-mox, albetam);

• Fibrates: clofibrate (miskleron, atromide), bezafibrate (bealip, beamidine), gemfibrozil (normolip, hempar, hevilon, hemopharm), fenofibrate (lipantil), ciprofibrate (lipanor);

• Sequestrants of bile acids: cholestyramine (questran), quantalan, cholestipol (cholestide), guaram;

• Cholesterol absorption blockers: Ezetimibe (Ezetrol). Combined: Vitorin (Simvastatin + Ezetemib).

• Antioxidants: probucol (lipomal);

• Drugs that increase HDL levels: essentialia, lipostabil.

• Polyunsaturated fatty acid preparations: ω-3 fatty acids (Omacor).

Hypolipidemic agents must be used for a long time, therefore, the effectiveness and safety of drugs is of great importance. Currently, of all hypolipidemic agents, statins are more likely to meet these requirements. They are the most active hypocholesterolemic drugs.

Statins

 Natural: Lovastatin (Mevacor), Pravastatin (Lipostat) Simvastatin (Zokor).

 Synthetic:

I generation: Fluvastatin (Leskol, Leskol forte).

II generation: Atorvastatin (Liprimar).

III generation: Rosuvastatin (Krestor), Pitavastatin (Nisvastatin).

 Combined drugs: Vitorin (Simvastatin + Ezetemib), Cadou (Atorvastatin + Amlodipine), Advicor (Lovastatin + Niacin).

Pharmacodynamics Statins are vital products of the fungal microorganism Aspergillus terreus or their synthetic analogues. They belong to a new class of antibiotics - monokalin. Their mechanism of action is associated with the blockade of the key enzyme for cholesterol synthesis - 3-hydroxy-3-methyl-glutaryl CoA reductase (HMT-CoA reductase). Statins, inhibiting the activity of the enzyme HMG-CoA reductase, reduce the formation of endogenous cholesterol.

As a result of lowering the cholesterol content in the liver, the activity of hepatocyte receptors, which capture low-density lipoproteins (LDL), increases, which leads to a significant decrease in the blood of LDL cholesterol and total cholesterol. Simultaneously, there is a moderate decrease in very low density lipoproteins (VLDL) and triglycerides (TG)

Under the influence of statins, the lipid profile of blood plasma changes as follows: the level of total cholesterol decreases (↓ cholera and ↓ TG). It should be noted that under the influence of statins, potentially toxic sterols (isopentiniline, squalene) do not occur in the body. In addition, HMG-CoA, after inhibition of HMG-CoA reductase, is easily metabolized back to acetyl-CoA, which is involved in many biochemical reactions of the body.

It should be noted that a decrease in total cholesterol by only 1% leads to a 2% reduction in the risk of developing vascular accidents (IHD, strokes). Another important effect of statins is also known - increasing the resistance of the endothelium to the effects of damaging factors, stabilizing atherosclerotic plaques, suppressing oxidative processes

Pharmacokinetics Statins are prescribed orally (before or after meals) in the evening, because maximum synthesis of cholesterol in the liver occurs at night. All drugs (especially fluvastatin) are well absorbed and actively (70%) are captured by the liver during the first passage. This is important because all statins (fluvastatin) are inactive - they are a prodrug, and in the liver they turn into active substances. Only 5% of the orally administered dose reaches the bloodstream in the form of an active form (where it is 95% bound to blood proteins), most of it remains in the liver, where it mainly has its effect. The maximum concentration of drugs in the blood occurs after about 1.5 hours. Hypocholesterolemic effect develops 3 days to 2 weeks after the start of treatment. The maximum therapeutic effect occurs mainly after 4 weeks. Statins are prescribed once a day (exception: fluvastatin - 2 times a day). Elimination is carried out mainly by the liver. With chronic renal failure, dose adjustment is not required.

Given the biological rhythms of cholesterol synthesis in the body (its synthesis is carried out mainly at night), it is recommended to take natural statins and synthetic preparations of the first generation once in the evening. For synthetic preparations of II-III generations, this recommendation is not mandatory

Statin treatment should be carried out continuously, because after a month the field of stopping the drug levels of blood lipids returns to the original. Typically, therapy with drugs of this group begins with small doses (for most drugs 5-10 mg / day) with a gradual increase to a dose that allows you to reach the target level of LDL. In the table. 3. The doses of statins needed to lower LDL cholesterol by 20-55% are shown. The value of the relative (in percentage) reduction of this level does not depend on the initial value of the indicator, but the dose of the drug depends.

It is necessary to increase the dose of any of the statins, observing the interval of 1 month, since during this time, as a rule, the greatest effect of the drug is achieved. The maximum doses of statins are prescribed for severe hyperlipoproteinemia, mainly with familial hypercholesterolemia.

The use of statins in primary and secondary prevention of coronary heart disease reduces cardiovascular mortality, significantly reduces overall mortality, the number of strokes of any

etiology, regardless of age, gender, previous medical history, or baseline cholesterol level.

Synthetic statins today provide the most powerful lipid-lowering effect and have a high safety profile, due to the peculiarities of their pharmacokinetics and pharmacodynamics (high selectivity for HMG-CoA reductase, long half-life, the presence of the “first pass” phenomenon). In addition, fluvastatin and rosuvastatin (as well as pravastatin) are metabolized in the liver mainly by the isoform of cytochrome P450 CYP2C9, which is associated with good drug tolerance and fewer drug interactions. For fluvastatin, a form with a slow release of the drug (Leskol forte) was created, which avoids a peak increase in the concentration of the active substance in the blood plasma.

Synthetic statins of I-II generations reduce LINI cholesterol by an average of 30-35%, while III-generation drugs (rosuvastatin and pitavastatin) are able to reduce this indicator to 50-65% of the initial level, which is comparable with the effect of extracorporeal procedures. The maximum effect is observed already on the 7-10th day. The level of triglycerides decreases by about 25-45%, and HDL increases by 5-10% (regardless of the drug and dose, with the exception of rosuvastatin). In addition, atorvastatin and rosuvastatin can cause regression of the phenomena of atherosclerosis, reducing the volume of atherosclerotic plaques

Statin treatment should be carried out continuously, because after a month the field of stopping the drug levels of blood lipids returns to the original. Typically, therapy with drugs of this group begins with small doses (for most drugs 5-10 mg / day) with a gradual increase to a dose that allows you to reach the target level of LDL. In the table. 3. The doses of statins needed to lower LDL cholesterol by 20-55% are shown. The value of the relative (in percentage) reduction of this level does not depend on the initial value of the indicator, but the dose of the drug depends.

It is necessary to increase the dose of any of the statins, observing the interval of 1 month, since during this time, as a rule, the greatest effect of the drug is achieved. The maximum doses of statins are prescribed for severe hyperlipoproteinemia, mainly with familial hypercholesterolemia.

The use of statins in primary and secondary prevention of coronary heart disease reduces cardiovascular mortality, significantly reduces overall mortality, the number of strokes of any etiology, regardless of age, gender, previous medical history, or baseline cholesterol level.

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In addition to the main hypolipidemic effect, statins have a number of additional (pleiotropic effects), due to which the morphological and functional state of the vascular wall in

patients with atherosclerosis improves. The existence of pleiotropic effects is explained not only by the blockade of HMT-CoA reductase, which reduces the formation of metabolic products of mevalonate (a family of isoprenoids), which are involved in the proliferation, differentiation, migration, apoptosis of cells, and the expression of endothelial NO synthetase. This allows statins to reduce the level of proinflammatory cytokines - tumor necrosis factor (TNF) a, interleukin-1 (IL-1), IL-6, prevent oxidative modification of lipoproteins, and increase the level of endogenous antioxidants.

There is evidence of anti-statin effects of angiotensin II. In addition, the level of fibrinogen, an inhibitor of plasminogen activator I, decreases, and blood viscosity decreases (partly due to a decrease in the cholesterol content in the phospholipids of platelet membranes).

Statins are able to inhibit platelet proliferation induced by platelet growth factor in response to endothelial damage by various agents. The ability to suppress the migration and proliferation of smooth muscle cells is most pronounced in simvastatin and fluvastatin, and least in pravastatin.

The favorable results of statin treatment can also be associated with stabilization of atherosclerotic plaques, a decrease in their size (only atorvastatin and rosuvastatin) and rupture, as well as elimination of endothelial dysfunction under the influence of drugs.

If the positive effects of statins, due to the actual hypocholesterolemic effect, develop relatively slowly (sometimes up to 3-5 years), then pleiotropic effects are realized quite quickly (from several days to several months).

A new direction was the creation of combination drugs. The use of two lipid-lowering agents in such formulations allows one to achieve a pronounced potentiating effect not only in terms of lowering total cholesterol or LDL (vitorin), but also significantly increasing the level of HDL (advi-core).

All statins are generally well tolerated.

Undesirable effects. Hepatotoxicity. Rhabdomyolysis (“melting” of muscles), myositis, muscle weakness (constant monitoring of CPK! Blood). Impotence. Dyspeptic syndrome. Thrombocytopenia, anemia. Skin rashes, photosensitivity. Side effects include an increase in transaminase activity. When taking statins, control of liver function tests and creatine phosphokinase activity is necessary. If the activity of creatine phosphokinase exceeds the norm by 2 times, then the drug should be discontinued.

Statins increase life expectancy by 0.2 years from each unexplored year.

A nicotinic acid. (Vitamin B3, Vitamin PP, Niacin, Enduracin)

Combined drugs:

• Corceptive (Nicotinic acid + Laropiprant).

• Advicor (Nicotinic acid + Lovastatin).

Nicotinic acid (niacin) is part of NAD and NADP, which are co-enzymes of several hundred dehydrogenases involved in tissue respiration and metabolic processes, inhibits cAMP (triglyceride lipase activator), inhibits lipolysis (due to blockade of tissue lipases) and mobilization of free fatty acids from which VLDL are synthesized. As a result, the formation of VLDL is reduced in the liver, from which dangerous atherogenic lipoproteins, LDL (↓ FFA, ↓ TG, ↓ LDL) are synthesized and the content of VLDL and TG cholesterol in the blood is reduced. Secondarily,

there is a decrease in the level of LDL cholesterol and total cholesterol. At the same time, the destruction of HDL is slowed down.

Pharmacodynamics The drug and, as a consequence, reduces the release of free fatty acids, reduces the formation of TG and their inclusion in VLDL.

When taking nicotinic acid (2-6 g / day), TG levels decrease by 35-50%, and the maximum effect is achieved after 4-7 days. At a dose of 4.5-6 g / day, it can cause a decrease in LDL cholesterol by 25%, but it takes 3-6 weeks to achieve the maximum effect. In combination with sequestrants of bile acids can reduce LDL by 40-60%. The level of HDL increases on average by 15-35%, however, at the initially normal rate, the increase can be large. The drug is prescribed during meals, starting with 100 mg 3 times a day, gradually increasing the dose to 3-4 g / day in 3 divided doses over the course of a month. Large doses of the drug in which it exhibits a lipid-lowering effect, and the unpleasant sensations associated with it (nausea, rash, harmless skin vasodilation, a feeling of heat at the time of starting or increasing the dose) cause many patients to refuse treatment. These symptoms can be reduced by prescribing 0.25-0.3 g of acetylsalicylic acid 30 minutes before taking nicotinic acid. In addition, the drug causes itching, decreased glucose tolerance, increased levels of uric acid, impaired liver function, exacerbation of peptic ulcer of the stomach and duodenum.

An attempt to reduce the side effects of nicotinic acid was the addition of laripiprant to it, which eliminates cutaneous vascular vasodilation and hot flashes. A fixed combination of a prolonged form of niacin and laropiprant is marketed under the trade name Koraptiv.

To a large extent, the disadvantages inherent in nicotinic acid are reduced in enduracin, which is nicotinic acid deposited on a wax matrix. This dosage form allows for a long time to maintain a sufficiently high concentration of the active substance in the blood, so the dose usually does not exceed 1.5 g / day. The drug is prescribed in the first week of 500 mg once a day; the second week - 500 mg 2 times a day and from the third week - 500 mg 3 times a day.

Compared with statins, nicotinic acid has a less pronounced effect on total cholesterol and cholesterol in LDL, but it more effectively reduces TG and increases cholesterol in HDL. Therefore, it is more effective for ↑ TG (IIc, III, IV types) and less effective for IIa.

Pharmacological effects.

- Regulates tissue respiration; synthesis of proteins, fats; glycogen rape;

- Provides the transition of the trans form of retinol to the cis form, which goes to the synthesis of rhodopsin;

- Increases the activity of the fibrinolytic system and reduces platelet aggregation (↓ formation of thromboxane A2);

- Reduces the synthesis of VLDL and ↑ the inclusion of cholesterol in HDL;

- Stimulates the formation of reticulocytes and normochromic red blood cells.

Pharmacokinetics Nicotinic acid and its amide (nicotinamide) are administered parenterally and per os. They are well absorbed in the lower part of the stomach and in the upper parts of the duodenum. Therefore, with inflammatory diseases of the absorption zone, the process of its transportation can be disrupted. Biotransformation is carried out in the liver with the formation of its metabolites. Elimination of nicotinic acid mainly with urine unchanged. It should be noted that nicotinic acid can be synthesized by the liver and red blood cells from tryptophan with the mandatory participation of vit. B2 and B6.

Undesirable effects. Many complications are the result of the release of histamine and activation of the kinin system: a drop in blood pressure, dizziness, reddening of the skin, urticaria, skin itching, increased secretion of gastric juice, severe burning during urination. At the same time, nicotinamide does not cause these effects. With prolonged use or an overdose of nicotinic acid, there may be: diarrhea, anorexia, vomiting, hyperglycemia, hyperuricemia, gastrointestinal mucosa ulceration, impaired liver function, atrial fibrillation.

Indications. Hypovitaminosis B3. Pellagra (dysfunction of the central nervous system, impaired motor function of the digestive tract - diarrhea or constipation, dry skin and mucous membranes - dermatitis, glossitis, stomatitis). Atherosclerosis. (prescribed in very large doses - 3-9 g / day, normal body need for vitamin 30 mg / day). Obliterating endarteritis, Raynaud's disease, migraine, spasms of the bile and urinary tract (nicotinamide is not prescribed). Thrombosis. Prevention of type 1 diabetes (use nicotinamide).

Anion-exchange resins or sequestrants of bile acids and agents that suppress intestinal cholesterol absorption:

I generation:

• Cholestyramine (Vazosan).

• Colestipol (Cholestipol).

• Hewar resin (Guarem).

II generation:

• Kolesevelam (Velhol).

• Colestimide (cholebin).

Sequestrants (sorbents) of bile acids are anion-exchange resins, insoluble in water and not absorbed in the intestine.

Pharmacodynamics These drugs are not absorbed from the digestive tract. They have the ability to bind bile acids in the intestinal lumen, which reduces the re-absorption of the latter and enhances their excretion from the body. To make up for the loss of bile acids in the liver, their synthesis from cholesterol is activated. The consequence of this is a compensatory increase in the activity of hepatocyte receptors that capture LDL, and a decrease in the level of cholesterol in the blood. At the same time, there is a slight increase in HDL cholesterol. The content of triglycerides either does not change, or slightly increases with subsequent normalization.

The lipid profile of plasma changes as follows: the level of total cholesterol decreases, a small decrease in TG. Most effective in type IIa hyperlipidemia. The decrease in total cholesterol for these drugs (with prolonged use) is on average 13%. The LDL content decreases by 12-19% at average therapeutic doses and can reach 25% at maximum doses after 1-2 weeks. However, high doses of drugs are poorly tolerated by patients. In combination with statins or nicotinic acid, LDL reduction can reach 40-60%. HDL levels increase by 3–8%.

Undesirable effects. Sequestrants of bile acids are not absorbed in the intestine, therefore, do not cause systemic side effects. Dyspeptic syndrome (constipation, stool formation, nausea, flatulence); steatorrhea, which disrupts the absorption of fat-soluble vitamins, especially vitamin K. Preparations of the second generation are characterized by slightly

higher efficiency and better tolerance. The tolerance of bile sequestrants can be improved by gradually increasing the dose of drugs. With prolonged regular intake, the effect of the drugs decreases.

Indications.

Indication for the appointment of anion-exchange resins is severe hypercholesterolemia, refractory to the recommended dietary measures. Large studies have shown that the prolonged use of these drugs as monotherapy, in combination with a diet or other lipid-lowering drugs slows the progression of atherosclerosis and significantly reduces mortality from coronary heart disease. These drugs have a peculiar taste, texture, so they are recommended to drink with juices, syrups, milk. Apply with primary hypercholesterolemia 2-3 r / day, the therapeutic effect occurs after about 1 month.

Fibrates 3 generations

The basis of their division into generations is based on pharmacokinetic features, efficacy and frequency of complications.

I generation: • Clofibrate (Miskleron).

II generation: • Gemfibrozil (Gavilon). • Bezafibrat (Bezamidin).

III generation: • Fenofibrate (Lipantil). • Tsiprofibrat (Lipanor).

Derivatives of fibroic acid include lipid-lowering drugs that lower the level of triglycerides in the blood mainly. The ancestor of this group is clofibrate (miskleron), subsequently displaced by other fibrates.

The mechanism of action of drugs in this group is associated with the activation of peroxisomal proliferator of activated nuclear receptors (PPAR), which play an important role in the metabolism of fatty acids, cholesterol esters, carbohydrate metabolism, regulation of the production of inflammatory factors, stimulation of lipoprotein lipase and many other important metabolic processes. Fibrates, activating PPARa receptors, mainly located in the liver and brown adipose tissue, increase the production of apoprotein apo-A-1 (the main HDL protein) and lipoprotein lipase that breaks down VLDL, which leads to a decrease in blood levels of VLDL and, accordingly, triglycerides. Additionally, PPARa receptors are likely to regulate the expression of genes that affect monocyte renewal, adhesion, and foam cell formation.

In addition, fibrates, like statins, block the activity of HMG-CoA reductase, reducing cholesterol synthesis and slightly lowering LDL cholesterol. However, this effect is much less pronounced than that of statins.

Drugs of this group are able to reduce the level of TG by 50% while simultaneously increasing HDL by an average of 15% (up to 18-20%). At the same time, the level of LDL does not change or even rises (especially against the background of severe triglycerinemia during treatment with clofibrate or gemfibrozil) or decreases (with therapy with fenofibrate, bezafibrat or ciprofibrate).

The main effect of fibrates is ↓ TG and VLDL plasma, as well as a decrease in the formation of LDL from them.

Pharmacokinetics Studied insufficiently. Fibrates are well absorbed from the intestines and appear in the blood in a deesterified form. Fibrates are a prodrug, turn into an active

substance in the intestines, liver, and kidneys. The maximum concentration in the blood, depending on the drug, occurs from 1.5 to 4 hours. All drugs are very well associated with albumin (more than 90%) and can displace other drugs from their connection. Biotransformation of fibrates occurs in the liver with the formation of glucuronic acid conjugates and is excreted mainly in the urine. Therefore, with chronic renal failure, they accumulate in the body. The drug of 1 and 2 generations is prescribed 3 times a day, and 3 generations - 2 times a day.

- Hepatotoxicity (↑ transaminases, alkaline phosphatase).

- Violation of the colloidal stability of bile (there is a danger of the formation of stones in the w / bladder).

- Myositis, myasthenia gravis, myopathy, rhabdomyolysis.

- Dyspeptic syndrome (belching, nausea. Vomiting, constipation, diarrhea, flatulence).

- Arrhythmias of the heart.

- Leukopenia, thrombocytopenia, anemia.

- Carcinogenesis !!! (rectal tumors)

- Rarely - alopecia, impotence, headache, dizziness, pancreatitis, rash, dermatitis. Impaired vision, laryngeal edema.

Indications.

Effective as an additional means of primary prevention of hyperlipidemia.

- Hyperlipidemia IV, V types; Type III in combination with obesity and type II diabetes.

- Reducing the risk of developing coronary heart disease in patients with type II hyperlipidemia (with ↓ HDL).

Cholesterol Absorption Blockers - Ezetimibe (Ezetrol). Combined: Vitorin (Simvastatin + Ezetemib).

Cholesterol absorption blockers, the main representative of which is ezetimibe, have become a new group of lipid-lowering drugs. After entering the small intestine, this drug is localized on the border of the border brush of villi and slows down the absorption of cholesterol (including cholesterol of vegetable fats), which leads to a decrease in its intake from the intestine into the liver and a compensatory increase in the activity of HMT-Co-A reductase, a decrease in the level of LDL cholesterol, triglycerides and increased plasma concentrations of HDL cholesterol. After 2 weeks of use, ezetimibe reduces cholesterol absorption in the intestine by 54% compared with placebo.

Preparations of this group can be used both as monotherapy, and in combination with statins or sequestrants of bile acids. The dose of the drug in this case is 10 mg once a day (not later than 2 hours before taking the sequestrant of bile acids, or not earlier than 4 hours after it). With simultaneous administration with statins, ezetimibe exhibits an addictive effect (at a dose of 10 mg / day in combination with any statin, it provides an additional decrease in LDL cholesterol by 17-22%). It is believed that in order to successfully reduce LDL cholesterol and from a safety point of view, it is more advisable to add ezetimibe to low and medium doses of statins than to use statins alone in unsafe high doses.

The combined preparation Vitorin (simvastatin + ezetimibe) was created, which can become one of the most effective means of combating atherosclerosis. However, a final judgment on its effectiveness and safety can be made after extensive clinical trials.

Cholesterol absorption blockers are usually well tolerated. Side effects include headache and dyspeptic disorders, when combined with statins, fatigue and myalgia may be added.

Antioxidants • Probucol (Fenbutol).

A certain role in the development of atherosclerosis is played by the free radical oxidation of lipids. The antioxidant effect of probucol protects lipoproteins from peroxidation, reduces their antigenicity and inhibits the formation of "foamy" cells in the intima of blood vessels. This action is very important because the formation of “foamy” cells proceeds with the formation of O2 free radicals. In addition, macrophages of atheromas are known to produce free radicals that destabilize atherosclerotic plaques. The drug has high lipophilicity, is included in LDL, modifies them, and thus increases the non-receptor transport of LDL into liver cells. Probucol increases the synthesis of a protein that transfers cholesterol esters from a cell. In the blood, the drug causes a decrease in LDL cholesterol, but at the same time reduces the level of HDL cholesterol. Probukol practically does not affect the level of TG.

Pharmacokinetics The drug is used orally during meals, 500 mg 2 times a day, preferably with products containing vegetable oil. It is poorly absorbed (approximately 20%) from the digestive tract. The maximum concentration in the blood occurs after a few hours. However, it should be emphasized that there is no correlation between the concentration of probucol and its anti-sclerotic effect. It penetrates very well into various tissues, where it accumulates and continues to be secreted into the blood after its cancellation for another 6 months. Bitransformation in the liver occurs slightly, excreted in the urine in an unchanged and altered form. Hypocholesterolemic effect is manifested no earlier than 2 months after the start of treatment.

Undesirable effects: Extension of the QT interval on the ECG (which creates the risk of severe ventricular arrhythmias). Myopathy. Hyperuricemia. Hyperglycemia. Thrombocytopenia. Dyspeptic syndrome - diarrhea, flatulence, nausea, abdominal pain.

Indications. It is used as an additional means of primary prevention of hyperlipidemia that occurred in patients with patients with a homozygous form of hereditary hyperlipidemia, when there are practically no LDL receptors. Currently, the use of this drug is limited due to low efficacy and serious side effects.

Preparations that increase the level of HDL, preparations of essential phospholipids: Lipostabil. Essential, Apolipoprotein A-1 Milano (ETS-216).

A promising direction of lipid-lowering therapy is the creation of drugs that can increase the level of HDL in the blood, since even a small increase in the concentration of this fraction of lipoproteins can reduce the risk of coronary heart disease. Statins, effectively lowering the level of LDL cholesterol, weakly affect the concentration of HDL, increasing it by only 5-10%. For fibrates and nicotinic acid derivatives, this indicator does not exceed 25%.

Lipostabil, as a representative of phospholipid preparations, consists of essential phospholipids, represented mainly by polyunsaturated phosphotidylcholine and polyunsaturated fatty acids (linoleic, linolenic, oleic, arachidonic). The possibility of using this group of drugs is based on their ability to solubilize excess cholesterol in biological membranes (1 phospholipid molecule dissolves up to 3 cholesterol molecules). The main acceptor of exogenously administered phospholipids is HDL, which is the main antiatherogenic fraction of LP in the body. According to the hypolipidemic effect, the drug is inferior to the main classes of lipid-lowering drugs.

Lipostabil is rarely prescribed, 2 capsules 3 times a day; course of treatment up to 6 months or more.

Pharmacodynamics The composition of the preparations includes phosphatidylcholine, which activates the enzyme lecithin-cholesterol-acetyltransferase (LHAT). This enzyme converts free cholesterol into cholesterol esters, which are not dangerous for the development of cholesterol. In addition, phosphatidylcholine is included in HDL, which helps to accelerate the transport of cholesterol from endothelial membranes and platelets, preventing the aggregation and adhesion of the latter.

These drugs do not lower LDL cholestenia and do not affect TG levels.

It should be noted that these drugs are complex in composition. In addition to phosphatidylcholine, they contain various water-soluble vitamins: nicotinic acid (and its amide), pyridoxine, cyanocobalamin, pantothenic acid, as well as adenosine-5-monophosphate.

Indications. Used in combination with other lipid-lowering drugs. They are used to improve peripheral blood circulation and liver function, especially in patients with diabetes.

Polyunsaturated fatty acid preparations: ω-3 fatty acids (Omacor).

Polyunsaturated fatty acids of the class (ω-3-PUFA) -eicosapentaenoic (EPA) and docosahexaenoic (DHA) are essential (essential) fatty acids that have an active effect on plasma lipids (lower VLDL), on hemostasis and blood pressure. The lipid-lowering effect is realized due to the delay in the ω-3-PUFA synthesis of triglycerides in the liver, since EPA and DHA inhibit the esterification of other fatty acids. They reduce the level of TG and contribute to a decrease in the amount of free fatty acids involved in their synthesis (due to an increase in the peroxisome of β-oxidation of fatty acids). As a result, the level of VLDL is reduced. In some patients with hypertriglyceridemia, LDL levels increase simultaneously. The HDL content increases inconsistently and very slightly (by the effect on this indicator, ω-3-PUFAs are significantly inferior to drugs of other classes). During treatment with the drug, the synthesis of thromboxane A2 decreases and the coagulation time slightly increases.

Prescribing ω-3-PUFA preparations (1 g / day) to patients with coronary heart disease can significantly reduce the combined indicator, including mortality from all causes, the development of myocardial infarction, as well as non-fatal angina attacks. When using ω-3-PUFA (Omacor) after an initial myocardial infarction, overall mortality is reduced by 20%, mortality from cardiovascular diseases by 30%, and the risk of sudden death by 45%.

The preparations of ω-3-PUFA are currently considered as adjuvant therapy for secondary prophylaxis after myocardial infarction, as well as for endogenous hypertriglyceridemia: type IV (monotherapy); lib / Ill types (in combination with statins). Doses of the drug in this case are 2 g / day with a possible increase to 4 g / day with insufficient effectiveness.

The purpose of the lesson:

1. To learn:

A. Pharmacodynamics, pharmacokinetics, pharmacotoxicodynamics of lipid-lowering drugs:

Classification:

• Statins: lovastatin (mevacor), simvastatin (zokor), rosuvastatin, pravastatin (lipostat), fluvastatin (leskol), cerivastatin (lipobay), atorvastatin (lipitor);

• Niacin: (vitamin PP, niacin, enduracin) and its derivatives (acipi-mox, albetam);

• Fibrates: clofibrate (miskleron, atromide), bezafibrate (bealip, beamidine), gemfibrozil (normolip, hempar, hevilon, hemopharm), fenofibrate (lipantil), ciprofibrate (lipanor);

• Sequestrants of bile acids: cholestyramine (questran), quantalan, cholestipol (cholestide), pectin;

• Cholesterol absorption blockers: Ezetimibe (Ezetrol). Combined: Vitorin (Simvastatin + Ezetemib).

• Antioxidants: probucol. Probucol (lipomal);

Drugs that increase HDL levels: essentialia, lipostabil.

• Polyunsaturated fatty acid preparations: ω-3 fatty acids (Omacor).

Characterization of drugs, mechanisms of action, undesirable effects. Indications and contraindications for use. Interchangeability and pharmacosafety.

The classification of anti-atherogenic (hypolipidemic) drugs adopted by the International Society for Atherosclerosis,

1 Anion-exchange resins or sequestrants of bile acids and agents that suppress intestinal cholesterol absorption.

2 Nicotinic acid (niacin) and its derivatives.

3 Probukol.

4 Fibrates or derivatives of fibric acid.

5 3-hydroxymethyl-glutaryl-coenzyme-A-reductase inhibitors

(GMK-CoA reductase), or vastatin (or statins).

Classification of lipid-lowering drugs, taking into account their main mechanism of action.

I Drugs that prevent the formation of atherogenic lipoproteins

• statins (vastatin),

• derivatives of fiber acid;

• a nicotinic acid,

• probucol,

• benzaflavin.

II Drugs that inhibit the absorption of cholesterol in the intestine.

• sequestrants of bile acids,

• r-sitosterol;

• guarem

III Physiological correctors of lipid metabolism containing essential phospholipids and unsaturated fatty acids that increase HDL

• essentials,

• lipostabil

2. To know the main pathogenetic mechanisms that are the object of the copper-stone effect in hyperlipidemia.

3. Be able to:

a) Choose a method of therapy depending on the level of serum triglycerides.

1. Normal triglycerides (<250 mg / dl, or <2.7 mmol / l). A rational diet and a healthy lifestyle are recommended.

2. The borderline level of triglycerides (250-500 mg / dl, or 2.7-5.7 mmol / l). Treatment begins with a diet. Drug treatment is indicated for coronary heart disease, the ineffectiveness of diet therapy, weighed down by coronary heart disease, heredity and the presence of other risk factors for coronary heart disease.

3. High triglycerides (> 500 mg / dl, or> 5.4 mol / l). Treatment begins with a diet. Due to the high risk of pancreatitis in those patients in whom the level of triglycerides on the background of the diet remains above 500 mg%, drug therapy is indicated.

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

c) prescribe combination therapy;

Assignment for self-testing of the initial level:

1. List the risk factors for developing atherosclerosis:

Irreversible:

• age (in most patients, atherosclerosis appears at the age of about 40-50 years and older);

• male sex (in men, atherosclerosis appears more often and earlier than in women);

• genetic predisposition

Reversible:

• smoking:

• arterial hypertension (blood pressure greater than 140/90 mm RT. Art.):

• obesity

Potentially or partially reversible:

• hyperlipidemia, hypercholesterolemia and / or hypertriglyceridemia.

• hyperglycemia and diabetes;

• low level of high density lipoproteins (a-LP) in the blood (less than 35 mg / dl or 0.9 mmol / l)

Other possible factors:

• low physical activity (lack of exercise);

• mental and emotional stress.

Indicate the normal limits of cholesterol and blood triglycerides in the human body.

Control questions of the studied topic.

1. What are the clinical and pharmacological criteria for choosing a lipid-lowering agent.
2. What principles are the basis for the classification of lipid-lowering drugs?
3. Sequestrants of bile acids, their mechanism of action and undesirable effects (cholestyramine, colestipol).
4. The principles of treatment of hyperlipidemia with niacin.
5. Probucol (fenbutol, lorelco) - mechanism of action and application.
6. Comparative characteristics of fibrates - Gemfibrozil (lopid, hevilon) Non-afibrate (bealip), fenofibrate (lipantil), Lipantchl 200M, clofibrate (miskleron), Tsiprofibrat.
1. 3-hydroxymethyl-glutaryl-coenzyme-A-reductase inhibitors (vastatin, statins) - simvastatin (zocor), rosuvastatin, pravastatin (lipostat), fluvastatin (leskol), cerivastatin (lipobay), atorvastatin (primitor) .
2. Comparative characteristics of the effectiveness of lipid-lowering drugs.

Enumeration of practical work.

Independent practical 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 on the selection and selection of lipid-lowering drugs for this patient.
4. To highlight the signs in a subjective and objective study of the patient, characterizing hyperlipidemia.
5. Determine the group of drugs needed by the patient.
6. Choose a specific drug, its dose and mode of administration.
7. Select clinical and instrumental criteria for assessing the effectiveness and safety of the applied drugs, carry out an assessment.
8. Substantiate the need for combination drug therapy and propose possible options for a safe combination of drugs.
9. Make a forecast of side effects of drugs prescribed to the patient, and outline a plan for identifying them at an early stage.
10. Justify the duration of the main and supporting therapy.

Control of the intermediate level of knowledge.

The solution of situational tasks:

1. A man, 72 years old, smokes 2 packs of cigarettes a day, is treated in the therapeutic department with a diagnosis of coronary heart disease, stable angina pectoris III FC, cardiosclerosis atherosclerotic and post-infarction (MI 2004). The level of total cholesterol (200-240 mg%, or 5.2-6.2 mmol / l). The tactics of prescribing hypolipidemic drugs, depending on the presence of IHD and its risk factors:
2. A patient, 40 years old, without bad habits has a high level of total cholesterol (> 240 mg%, or> 6.2 mmol / l). Tactics of clinical nutrition and drug hypolipidemic therapy.
3. The patient is 68 years old, against the background of the diet, the level of triglycerides (> 500 mg / dl, and> 5.4 mmol / l). Tactics of the appointment of hypolipidemic drugs.
4. A 73-year-old patient with a diagnosis of coronary artery disease has a borderline level of triglycerides (250-500 mg / dl, or 2.7-5.7 mmol / l), diet therapy is ineffective, heredity is burdened. Tactics of prescribing lipid-lowering drugs.

5. The patient has an increased number of chylomicrons, containing mainly triglycerides and transporting them from the intestine to the blood. Prescribe the most effective hypolipidemic drug.

6. It is known that lipoproteins of very low density (pre-r-LP, VLDL), which mainly contain triglycerides, to a lesser extent cholesterol, are the main transport form of endogenous triglycerides. Prescribe an adequate hypolipedimic drug in this type of impaired fat metabolism.

7. Prescribe a lipid lowering drug for low density lipoproteinemia (p-lipoproteins, LDL) of the main class of cholesterol-carrying lipoproteins; containing predominantly cholesterol, in a smaller amount - triglycerides synthesized in the liver, and also formed in blood plasma during the breakdown of VLDL;

8. Choose the optimal lipid-lowering medication of intermediate density lipoproteinemia (STD) - formed as an intermediate product on the conversion of VLDL to LDL, rich in cholesterol and triglycerides;

9. High density lipoproteins (HDL, a-LP) - are formed in the liver, in the small intestine, are rich in phospholipids, protein, play a major role in the removal of cholesterol from body tissues, ie have an anti-atherogenic effect - suggest a drug that increases their amount in Organism.

10. In the complex treatment of cerebrosclerosis, the doctor prescribed a drug that lowers cholesterol (an inhibitor of cholesterol synthesis). Name the drug and indicate the undesirable effects.

11. In a man L., 39 years old, an office worker, during prophylactic examination, an elevated level of serum total cholesterol was revealed. No complaints. Smokes for 15 years. Family history is not burdened. Objectively: increased power, emergency - 76 strokes per 1 minute, AKD - 160/100 mm RT. Art. The boundaries of the heart are not changed. Biochemical analysis of blood: total cholesterol - 6.6 mmol / l, LDL cholesterol - 4 mmol / l, HDL cholesterol - 0.8 mmol / l, triglycerides - 1.8 mmol / l. ECG: moderate diffuse changes in the myocardium.

What type of dyslipidemia is detected in the patient? Your recommendations for non-mediocentetic management of the patient. Justify the differentiated choice of hypocholesterolemic drugs, indicate their mechanism of action.

Patient E., 63 years old, has been observed for 12 years for hypertension. 6 years ago suffered a myocardial infarction. The maximum AKD figures are 180/115 mm Hg. Art. He regularly takes enap 10 mg / day. There are no complaints. Objectively: increased power, emergency - 74 strokes per 1 minute, AKD - 170/100 mm RT. Art. Borders of the heart - the left is displaced by 2.5 cm from the left midclavicular line, the emphasis is 2 tones above the aorta, there are no peripheral edema. ECG: in the III and aVF leads, the pathological Q wave, T wave is negative (compared to the ECG 1 year ago - without dynamics).

Biochemical blood test: glucose - 6.8 mmol / l, total cholesterol - 6.4 mmol / l, TG - 2.1 mmol / l, LDL cholesterol - 4.0 mmol / l, HDL cholesterol - 0.8 mmol / l Echocardiography: thickening of the interventricular septum and posterior wall of the left ventricle, PV - 54%, akinesia of the posterior-basal parts of the left ventricle.

Formulate a diagnosis. Justify the differentiated choice of drugs for this patient.

TESTS:

1. The patient, 38 years old, six months ago, during treatment in the clinic for peptic ulcer of the duodenum, an increase in cholesterol to 8.0 mmol / l was detected. 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

medication 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.
2. Does not affect lipid metabolism:
A. Mevacor
B. * Cozaar
S. Zokor
D. Leskol
E. Liprimar
3. Type IIB hypolipidemia is characterized by:
A. Elevated LDL
B. Moderate increase in cholesterol and triglycerides
C. Prevalence 40%
D. Elevated VLDL
E. * All of the above
4. For type I hypolipidemia, it is true:
A. Elevated Chylomicrons
B. Increased risk of thrombosis and embolism
C. Prevalence 1%
D. There is a risk of severe destructive pancreatitis and pancreatic necrosis
E. * All of the above
5. Type IIa hypolipidemia is characterized by:
A. Elevated LDL
B. Blood triglycerides are normal
C. Prevalence 10%
D. Moderate increase in cholesterol
E. * All of the above
6. Type III hypolipidemia is characterized by:
A. Elevated LDL
B. High triglycerides in blood
C. Prevalence of less than 1%
D. Clinical manifestations: palmar and plantar xanthomas, lipoid arc on the cornea, liver steatosis, weight gain, coronary heart disease, arterial hypertension, pancreatitis, severe peripheral vascular atherosclerosis
E. * All of the above
7. Type V lipolipidemia is characterized by:
A. Elevated LDL
B. Elevated Chylomicrons
C. Blood triglycerides elevated
D. Prevalence 5%
E. All of the above
8. Type IV hypolipidemia is characterized by:
A. Elevated LDL
B. Prevalence of 45%
C. Blood triglycerides elevated
D. Clinical manifestations: enlarged liver and spleen, arterial hypertension, obesity (android type), liver steatosis
E. * All of the above

9. According to the data of chronopharmacology, it is possible to increase the hypocholesterolemic effect of statins by prescribing them at the following time of day:
A. Night.
B. Dawn.
S. * Evening.
D. Morning.
E. Lunch.
10. A patient with signs of vascular atherosclerosis was prescribed one of the hypolipidemic drugs, which reduces cholesterol synthesis by blocking the enzyme 3-hydroxy-3-methylglutaryl-coa reductase. Specify this tool:
A. Nicotinic acid.
B. Cholestyramine.
C. Clofibrate.
D. Probucol.
E. * Lovastatin.
11. A man, 38 years old, is overweight. HELL - 130/90 mm RT. Art. There are no symptoms of coronary heart disease. In the blood: total cholesterol - 5.2 mmol / l, LDL cholesterol - 3.8 mmol / l, triglycerides - 1.7 mmol / l. What measures for the prevention of atherosclerosis should be carried out in this case?
A. Drugs that contain phospholipids.
B. Drugs that affect lipid synthesis in the body.
C. Drugs that affect liver cholesterol synthesis.
D. Drugs that affect intestinal cholesterol absorption.
E. A diet that lowers lipids in the body

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-ANGINAL AND ANTI-ISCHEMIC MEDICINES
CLINICAL-PHARMACEUTICAL PRINCIPLES OF THE CHOICE OF ANTICOAGULANTS, ANTI-AGGREGANTS, THROMBOLYTICS
PRINCIPLES OF TREATMENT OF UNSTABLE ANGINA, ACUTE MYOCARDIAL INFARCTION

Purpose of the topic.

Coronary heart disease is the main problem in the clinic of internal diseases; in WHO materials it is described as an epidemic of the twentieth century. The reason for this was the increasing incidence of coronary heart disease in people of different age groups, a high percentage of disability, as well as the fact that it is one of the leading causes of mortality.

Coronary heart disease is one of the main causes of death among the population of industrialized countries. It affects working men (to a greater extent than women) unexpectedly, in the midst of the most active activity. Those who do not die often become disabled.

For the first time, the criteria for angina pectoris were proposed by the English physician V. Heberden in 1772. Even 90 years ago, doctors rarely encountered this pathology and usually described it as casuistry. Only in 1910 V.P. Obraztsov and N.D. Strazhesko in Russia, and in 1911, Herrik in the United States of America gave a classic description of the clinical picture of myocardial infarction. Now myocardial infarction is known not only to doctors, but also to the general population. This is due to the fact that every year it occurs more often.

Coronary heart disease is one of the most common diseases. In Europe, 10% of the adult population and more than 20% of the elderly suffer from coronary heart disease, in Ukraine in 2010, 5.9 million patients with this disease were registered. IHD takes the first place among the causes of death of the population of European countries and makes up more than 21%. Mortality from coronary heart disease in Ukraine is 48.9% of total mortality.

Motivational characteristic of the topic.

Coronary artery disease (CHD; Latin morbus ischaemicus cordis from other Greek ἴσχω - “I restrain, restrain” and αἷμα - “blood”) is a pathological condition characterized by absolute or relative violation of the myocardial blood supply due to damage to the coronary arteries.

CHD is a myocardial damage caused by a disorder in coronary circulation, resulting from an imbalance between coronary blood flow and the metabolic needs of the heart muscle. IHD can occur acutely (in the form of myocardial infarction), as well as chronically (periodic attacks of

angina pectoris).
The variety of mechanisms that determine the nature and speed of the development and progression of coronary heart disease explains the existence of numerous variants of the clinical manifestations of this disease, the main ones being sudden cardiac death (SCD), angina pectoris, painless myocardial ischemia (BIM), myocardial infarction (MI) and post-infarction cardiosclerosis.
Unfortunately, there is still no generally accepted clinical classification of coronary heart disease. This is primarily due to rapidly changing ideas about the mechanisms of development of coronary insufficiency, the presence of a common morphological substrate of various forms of coronary heart disease and the possibility of a quick and often unpredictable transition of one clinical form of this disease to another, as well as the existence of the same patient immediately several forms of IHD (for example, post-infarction cardiosclerosis, angina pectoris and painless myocardial ischemia
IHD classification
1. Sudden cardiac death (primary cardiac arrest).
2. Angina pectoris.
   2.1. Stable angina pectoris (indicating the functional class from I to IV).
      2.1.1. FC I: seizures occur with high intensity loads;
      2.1.2. FC II: attacks occur when walking more than 500 m and climbing more than I floor;
      2.1.3. FC III: seizures occur when walking 100-500 m, climb to the 1st floor;
      2.1.4. FC IV: seizures occur when walking less than 100 m and at rest.
   2.2. Unstable angina pectoris:
      2.2.1. First-born angina pectoris (Air Force).
      2.2.2. Progressive angina pectoris (PS).
      2.2.3. Early post-infarction or postoperative angina pectoris.
   2.3. Spontaneous (vasospastic, variant, Prinzmetal) angina pectoris. **
3. Painless myocardial ischemia.
4. Microvascular angina pectoris (“Syndrome X”).
5. Myocardial infarction.
   5.1. Myocardial infarction with Q wave (large focal, transmural).
   5.2. Myocardial infarction without Q wave (small focal).
6. Postinfarction cardiosclerosis.
7. Heart failure (indicating the form and stage).
8. Violations of the heart rhythm and conduction (indicating the form).
Risk factors for coronary heart disease are circumstances whose presence predisposes to the development of coronary heart disease. These factors are largely similar to atherosclerosis risk factors, since coronary atherosclerosis is the main link in the pathogenesis of coronary heart disease.
Risk indicators can be classified as follows.
Biological determinants or factors:
 old age;
 male gender;
 genetic factors that contribute to dyslipidemia, hypertension, glucose tolerance, diabetes and obesity.
Anatomical, physiological and metabolic (biochemical) features:
 dyslipidemia;
 arterial hypertension;
 obesity and the nature of the distribution of fat in the body;
 diabetes.
Behavioral (behavioral) factors that can lead to an exacerbation of IHD:
 eating habits;
 obesity, as a factor in the development of coronary heart disease;

 smoking;
 insufficient motor activity, or physical activity exceeding the adaptive capacity of the body;
 alcohol consumption;
 behavior that contributes to coronary artery disease.

Pathogenesis

According to modern concepts, ischemic heart disease is a pathology based on myocardial damage, which is caused by coronary insufficiency (insufficient blood supply). The imbalance between the needs of the myocardium in blood supply and its real blood supply can be caused by a number of reasons:

Intravascular causes:

 Thrombosis and thromboembolism of coronary arteries;
 Atherosclerotic narrowing of the lumen of the coronary arteries;
 Spasm of coronary arteries.

Causes outside the vessel:

 Myocardial hypertrophy;
 tachycardia;
 Arterial hypertension.

IHD is a group concept that includes both acute and chronic chronically conditions (including those considered as independent nosological forms), which are based on ischemia and myocardial changes caused by it (sclerosis, dystrophy, necrosis), but only in in cases where ischemia is caused by narrowing of the lumen of the coronary arteries, which is associated with atherosclerosis, or the reason for the mismatch of coronary blood flow to the needs of the myocardium has not been established.

Clinical forms

To substantiate the diagnosis of coronary heart disease, it is necessary to establish its clinical form (according to the classification) according to criteria generally accepted for the diagnosis of this disease. In most cases, for the diagnosis, the recognition of myocardial infarction or angina pectoris, the most frequent and typical manifestations of coronary heart disease, is of key importance, other clinical forms of the disease are much less common, and their diagnosis is difficult.

Sudden coronary death

Primary cardiac arrest is suspected to be associated with electrical myocardial instability. It is referred to an independent form of coronary heart disease only if there are no grounds for making a diagnosis of another form of coronary heart disease or another disease. For example, death that occurred in the early phase of myocardial infarction does not belong to this category and is considered as death as a result of myocardial infarction. In the event that resuscitation measures were not carried out or did not give a result, primary cardiac arrest refers to sudden coronary death. The latter is defined as death that occurred in the presence of witnesses instantly or no later than 6 hours after the onset of a heart attack.

Angina pectoris

As a form of manifestation of coronary heart disease, angina pectoris combines angina pectoris, which is divided into:

 Emerging for the first time;
 Stable;
 Progressive;
 Spontaneous (the so-called "angina pectoris", one of the options is Prinzmetal angina).

Angina pectoris This form of the disease is characterized by transient bouts of chest pain, which are caused by physical or emotional stress, or other factors that cause an increase in the metabolic needs of the myocardium (tachycardia, increased blood pressure). In typical cases, chest pain (burning, discomfort) that appears during emotional or physical exertion radiates to the left arm and / or shoulder blade. Quite rarely, the localization and irradiation of pain are atypical. The duration of a tachycardia attack varies from 1 to 10 minutes, in rare cases up to 30

minutes. As a rule, the pain quickly stops after the load is stopped or within 2-4 minutes after sublingual (under the tongue) intake of nitroglycerin.
The diagnosis of “stable angina pectoris” is established with a steady-state manifestation of the disease in the form of a natural occurrence of bouts of pain (or preceding bouts of ECG changes) for a certain load for a period of at least 3 months.
The severity of stable exertional angina is characterized by a threshold level of physical exertion tolerated by the patient. The functional class of the severity of the disease is indicated without fail when formulating the diagnosis.
With progressive angina pectoris, a relatively rapid increase in the severity and speed of pain attacks is characteristic with a decrease in exercise tolerance. Attacks of pain occur at rest or at a lesser than earlier load, it is much more difficult to stop with nitroglycerin (often an increase in a single dose is required), and in some cases they stop only by the introduction of narcotic analgesics.
Spontaneous angina pectoris This form of CHD differs from angina pectoris by the absence of a visible relationship between the occurrence of pain attacks and factors that lead to an increase in the metabolic needs of the myocardium. The development of seizures can take place at rest, for no obvious reason, often during the night or early hours, in some cases have a pronounced cyclical nature. According to the localization, duration and irradiation, as well as the effectiveness of nitroglycerin, spontaneous angina attacks are slightly different from angina attacks.
Variant angina pectoris Under Prinzmetal angina denotes spontaneous angina pectoris, which is accompanied by transient ST segment elevations on the ECG.
Myocardial infarction
This diagnosis is established in the presence of clinical and / or laboratory (dynamics of enzyme activity) and electrocardiographic data that indicate the occurrence of a small or large focus of necrosis in the myocardium. In the event that a patient with a heart attack does not be hospitalized as quickly as possible in an ICU, there is the possibility of developing serious complications and a high probability of a fatal outcome.
Large focal myocardial infarction. Transmural myocardial infarction is justified by pathognomonic ECG changes or a specific increase in serum enzyme activity (lactate dehydrogenase, creatine phosphokinase, etc.) even with an atypical clinical picture. The above enzymes are enzymes of redox reactions and under normal conditions are observed only inside the cell. If cell destruction occurs (for example, with necrosis), enzymes are released and determined during laboratory studies. An increase in the concentration of these enzymes in the blood during myocardial infarction is called resorption-necrotic syndrome.
Small-focal myocardial infarction This diagnosis is made when developing changes in the ST segment or T wave in the presence of typical changes in enzyme activity, but without pathological changes in the QRS complex.
Postinfarction cardiosclerosis A reference to postinfarction cardiosclerosis as a complication of IHD is made to the diagnosis no earlier than two months after the onset of myocardial infarction. As an independent clinical form of coronary heart disease, post-infarction cardiosclerosis is established in the absence of angina pectoris and other forms of coronary heart disease, provided for by the classification, with the simultaneous presence of electrocardiographic and clinical signs of focal myocardial sclerosis (persistent conduction, rhythm disturbances, signs of cicatricial myocardial insufficiency, chronic heart failure detected on the ECG)) If during the long period of the patient’s examination there are no ECG signs of myocardial infarction, the diagnosis can be justified by the data available in the medical documentation that relate to the period of acute myocardial infarction. When making a diagnosis, the presence of internal myocardial ruptures, intracardiac thrombosis, chronic aneurysm of the heart, dysfunction of the papillary muscles of the heart is also indicated, and the nature of the heart rhythm and conduction disturbances is determined, the stage and form of heart failure are indicated.
Arrhythmic form Arrhythmia of the heart or signs of left ventricular heart failure (cardiac

asthma, dyspnea attacks, pulmonary edema) occur as equivalent to spontaneous angina pectoris or angina pectoris tension attacks. Diagnosis of these forms of the disease is difficult, the diagnosis is finally formed on the basis of the analysis of the set of ECG results in samples with a load, or with selective coronary angiography and monitor observation.

Diagnostics

Clinical symptoms

In coronary heart disease, the most common complaints are:

 Chest pain associated with physical exertion or stress;
 severe shortness of breath;
 Signs of heart failure (edema starting from the lower extremities, forced sitting position);
 Disruption of the heart;
 weakness;
 Sensation of heart rhythm disturbance.

Anamnesis

From the data of the anamnesis, the duration and nature of pain, arrhythmias or shortness of breath, their relationship with physical activity, the degree of physical exertion that the patient withstands without an attack, the effectiveness of various drugs during an attack (for example, the effectiveness of nitroglycerin) are essential. It is very important to find out the presence of risk factors.

Physical research

During this study, signs of heart failure (crepitus and moist rales in the lower lungs, hepatomegaly “cardiac” edema) can be detected. Objective symptoms characteristic of coronary heart disease that could be detected without instrumental or laboratory examination do not exist. Any suspected coronary artery disease requires an ECG.

Electrocardiography

ECG is an indirect method of research, which does not provide data on the number of dead myocardial cells, however, it allows you to evaluate some of its functions. In the diagnosis of most of the pathological conditions of the myocardium (hypertrophy, cardiomyopathy and some other diseases), electrocardiography performs an auxiliary function.

Some signs of acute myocardial infarction

A characteristic sign for transmural myocardial infarction is the presence of an abnormal Q wave in the ECG.

In lead I:

 The presence of a pathological Q wave (> 0.03c, the amplitude is more than a third of the amplitude of the R wave);
 The presence of a negative T wave.

In lead II there is a pathological Q wave (> 0.03c, the amplitude is more than a quarter of the amplitude of the R wave).

In lead III, there is a pathological Q wave (> 0.03c, the amplitude is more than half the amplitude of the R wave).

In leads V1, V2 and V.3 there is a QR wave or QS, and a T wave is negative.

In leads V4, V5 and V6 there is a pathological tooth Q (> 0.04s), and the tooth T is negative.

The T wave makes it possible to determine the stage of the process in dynamics. For example, in lead II:

It is sharply positive in the acute stage of a heart attack (“cat's back”, Pardi's curve);

Negative in the acute stage (usually with a lower amplitude);

It rises to the isoline at the stage of scarring and the subacute stage, but in most cases (if there is a large focal heart attack) it does not reach it).

A sign of a scar in the myocardial tissue is a mild negative T wave and a pathological Q wave.

The data obtained during the ECG are an objective instrumental criterion that allows to determine the presence of myocardial infarction, prescription and localization of damage.

Echocardiography

The essence of this method consists in irradiating tissues with ultrasonic pulses of a fixed frequency and the subsequent reception of the reflected signal. Based on the magnitude of the reflection, a density pattern of the tissues transmitted by the pulse is formed. Modern devices provide the output of graphical information in real time; in addition, it is possible to evaluate blood flow due to the Doppler effect.

With coronary heart disease, echocardiography makes it possible to assess the condition of the myocardium, as well as the safety and contractility of the valvular apparatus of the heart.

Laboratory indicators

Coronary heart disease is a combination of several diseases with various biochemical processes. The following changes may occur:

Characteristic changes in myocardial infarction. Increased concentration of specific proteins (such as troponin, creatine phosphosokinase, aminotransferase, myoglobin, lactate dihydrogenase). All proteins are contained exclusively within the cell. With the mass destruction of cells taking place as a result of necrosis, these proteins enter the bloodstream and are determined during laboratory studies.

Nonspecific reaction to myocardial damage. Neutrophilic leukocytosis (3-7 days) as an inflammatory process, manifested in response to necrotic changes, an increase in ESR (7-14 days) as a reflection of changes in the ratio of the amount between different fractions of proteins (also mainly occur for the development of inflammation) and an increase in the level of ALT AST - non-specific markers of cytolysis.

Characteristic changes in atherosclerosis. The concentration of triglycerides, high and low density lipoprotein cholesterol, total cholesterol, the concentration of apoliproteins A1 and B, as well as the atherogenic index

Functional Tests

As a rule, functional tests are different types of physical activity, which is accompanied by registration of parameters related to the work of the heart (usually an ECG). The purpose of such tests is to determine the pathology in the early stages of development, when at rest characteristic changes are not yet developing, and during exercise, the person experiences anxiety. Exercise tests are used to conduct a differential diagnosis and determine exercise tolerance.

This load can be given in different ways: Treadmill; Exercise bike; Step test; Climbing stairs; Walking to a certain distance.

Other instrumental diagnostic methods

Angiography and CT angiography of the coronary arteries are diagnostic methods in which a radiopaque substance is introduced into the vascular bed. Against this background, a series of CT scans or X-ray images is carried out, which allows you to contrast the myocardial vessels and, as a result, determine their patency, degree of occlusion and preservation of the lumen. This is usually used when deciding on the need and feasibility of surgical intervention. These studies are not completely safe, it is possible the development of allergic reactions and severe (up to anaphylaxis) complications.

Intraesophageal electrocardiography It is used as an additional method, which allows you to assess the absence or presence of additional foci of excitation that are not recorded in standard leads. The essence of the technique is the introduction of an active electrode into the esophagus cavity. The method makes it possible to evaluate in detail the electrical activity of the atrioventricular connection and the atria.

Holter monitoring It is a method of recording ECG during the day, used to detect cardiac abnormalities that occur periodically. It makes it possible to correlate the clinic with the received data.

ECG is recorded using a Holter monitor - a special portable device that the patient wears for a day on a belt or on a belt over his shoulder. During the study, the patient leads a normal lifestyle, noting in the diary the exact time and circumstances of the problems in the heart. At the end of monitoring, the data is transferred to a computer, where they are processed. Some monitors have the ability to directly print test data onto a cardiograph tape.

Treatment of angina pectoris involves the use of various groups of drugs that affect those or other links in the pathogenesis of coronary heart disease.
Classification of treatment for coronary heart disease
1. Antianginal drugs.
2. Antithrombotic agents.
3. Means that improve the metabolism of the heart muscle (trimetazidine, trimetazidine MV).
4. Hypolipidemic agents.
5. Inhibitors of angiotensin-converting enzyme (ACE inhibitor).
ANTANGINAL MEANS
Classification of antianginal drugs
I. Means that reduce myocardial oxygen demand:
• Nitrates.
• Sidnoniminy.
• β-blockers.
• Calcium channel blockers (phenylalkylamine derivatives, benzothiazepine).
• Selective If inhibitors.
II. Means that improve the delivery of oxygen to the myocardium:
• Calcium channel blockers (derivatives of dihydropyridine, benzothiazepine).
• Adenosine potentiators.
NITRATES
1. Nitroglycerin and its depot preparations: • Nitroglycerin. • Nitro Mac. • Trinitrolong. • Nit Ret. • Nitrong. • Sustak. • Nitroderm. • Sustonite.
2. Isosorbide dinitrate (Nitrosorbide, Iso-Mac).
3. Isosorbide mononitrate (Monizole, Mono-Mac).
In the vascular endothelium, a highly active vasodilator is formed - the endothelial relaxing factor (ERF).
The chemical structure of ERF is similar to nitric oxide (N0). It is believed that the endothelial dysfunction accompanying the pathology of the coronary and other vessels may be due to insufficient synthesis of ERF.
Nitrates in the process of metabolism release N0, which activates guanylate cyclase and increases the content of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells (Scheme 1).
Cyclic guanosine monophosphate promotes dephosphorylation of the myosin light chains, which leads to relaxation of smooth muscles and vasodilation.

Despite the fact that nitrates dilate the coronary vessels and redistribute blood flow in favor of the subendocardial layers of the myocardium, the main mechanism of their antianginal action is a decrease in heart function and, accordingly, oxygen demand of the myocardium by reducing pre- and afterload. In addition, the phenomena of endothelial dysfunction are reduced, platelet aggregation is inhibited.

At the same time, NO, the main effector substrate of nitrates, provides important physiological functions in the body, such as the regulation of vascular tone and anticoagulant properties of blood, the effect on leukocyte adhesion, proliferation of smooth muscle vascular elements, and apoptosis. There is experimental evidence for the antiatherosclerotic effect of NO. In the experiments, nitrates normalized endothelial function, reduced damage to vascular intima, and prevented LDL oxidation.

Indications for the appointment of nitroglycerin

• An attack of angina pectoris (sublingual).

• Unstable angina (sublingually, intravenously).

• An acute period of myocardial infarction (usually intravenously).

• Coronary artery spasm during coronary angiography (intravenously).

The effect of sublingual administration occurs in 1-3 minutes, lasts 20-30 minutes.

It should be borne in mind that the shelf life of the drug in its original packaging is 1 year, and after opening the convolute with proper storage about 1-2 months, after which the convolute should be replaced with a new one. Aerosol forms of nitroglycerin, in which the drug substance has no contact with air, are more convenient in this regard.

Criteria for the adequacy of the dose of nitroglycerin preparations for oral (sublingual) administration

• Lowering blood pressure (BP) by 10-15 mm RT.

• An increase in heart rate by 10-15 bpm.

• The increase in load time for paired bicycle ergometry is 2 minutes or more (one test before taking, one at the maximum effect of the drug).

To prevent angina attacks and prolong the antianginal effect of nitroglycerin, depot-nitroglycerin preparations were previously used: Sustak mite (2.6 mg), Sustak forte (6.4 mg), Nitrongmit (2.8 mg), Nitrong forte (6.5 mg) , Nitro-Macretard (2.5 mg, 5 mg), Nit-Ret (2.5 mg). The dose of depot-nitroglycerin preparations is set individually depending on the sensitivity of the patient to nitrates and the severity of the disease. A single dose is usually 1-2 tablets (2.6-6.4 mg), the maximum single dose is not more than 13 mg, the daily dose is 39 mg. Retard tablets are prescribed 2 times a day, the rest 4-6 times a day. It should be noted that the forms of preparations containing nitroglycerin up to 5 mg are almost completely destroyed in the liver, not reaching the systemic blood flow. Currently, depot preparations of nitroglycerin, due to their low effectiveness, can be recommended only to patients with a very high sensitivity to nitro drugs. Transdermal forms of nitroglycerin (skin patch, nitroglycerin ointment) are currently practically not used.

Isosorbide dinitrate Like nitroglycerin, isosorbide dinitrate has an antianginal effect due to “hemodynamic unloading” of the myocardium as a result of a preferential (40%) reduction in venous tone. With sublingual administration (after chewing a tablet), the effect develops in 3-5 minutes and lasts up to 60 minutes. When taken orally, the speed and duration of the drug are 20-30 minutes and 2-3 hours, respectively, so nitrosorbide can be used to treat coronary artery disease and to stop an attack of angina pectoris.

Prolonged forms of isosorbide dinitrate (Isomac retard) are prescribed 2-3 times a day. Isoket-retard and Cardiket-retard - drugs of a longer duration - can be prescribed 1-2 times a day.

Isosorbide mononitrate (Monomak, Olikard-retard) significantly differs from other nitrates in its pharmacokinetic parameters. Its bioavailability is 100%; in addition, the drug does not have a first-pass effect, and the half-life is 4-5 hours, which allows it to be prescribed 2 or 3 times a day, even ordinary, non-prolonged forms. The drug is used to treat coronary heart disease, starting with angina pectoris II functional class.

Side effects of nitrates

• Orthostatic hypotension, reflex tachycardia. It should be emphasized that the expansion of veins and arteries, leading to a decrease in blood pressure, underlies the therapeutic effect of

nitrates in coronary artery disease, but if the decrease in blood pressure exceeds the "therapeutic limits" by more than 10 mm RT. Art., a collaptoid reaction may occur.

• Headaches due to the expansion of cerebral vessels and increased intracranial pressure.

• Tolerance (addiction) to nitrates, developing with prolonged, regular, frequent use of drugs (especially in high doses) or non-compliance with the nitrate period.

Tolerance development mechanisms:

• Decrease in guanylate cyclase activity and cGMP level.

• Reducing the content of SH-groups, providing the conversion of nitrates to nitric oxide and nitrosothiols.

• Activation of the sympathoadrenal system (CAS) and the renin-angiotensin-aldosterone system.

• Increased production of hyperoxides.

• Decrease in biotransformation of nitrates.

Measures to prevent nitrate tolerance

• Increasing the dose of the drug. However, in most cases, this method gives a temporary effect, since addiction also develops to a larger dose.

• Intermittent nitrate administration. It is based on restoring the body's sensitivity to drugs during the "nitrate-free period", the duration of which should be at least 8-12 hours during the day. At this time, antianginal drugs of other groups can be used.

• The combination of nitrates with ACE inhibitors - captopril, perindopril, zofenopril - to restore the content of SH-groups in the endothelium and reduce the activity of RAAS

• The combination of nitrates with β-blockers, calcium channel blockers, or antioxidant vitamins.

For nitrates, the phenomenon of "recoil" is characteristic, when, with the sudden cessation of medication after prolonged therapy, a significant deterioration in the course of the disease is noted (angina attacks are more frequent, pain is aggravated). Prevention of the recoil phenomenon is carried out by a gradual decrease in the dose and frequency of taking the drugs.

Contraindications to the use of nitro drugs

• Blood pressure below 100/60 mm Hg. Art.

• Cardiogenic shock.

• Intracranial hemorrhage.

• Hypovolemia.

• Toxic pulmonary edema.

• Constrictive pericarditis.

• Hypersensitivity to nitro drugs.

The interaction of nitrates with other drugs. Of fundamental importance is the interaction of nitro

drugs with phosphodiesterase inhibitors, in particular with sildenafil (Viagra), since this combination creates a risk of potentially dangerous arterial hypotension. The use of sildenafil is possible only with at least a 24-hour break after taking nitrates, including NG. An increase in the hypotensive effect is observed with a combination of nitrates with barbiturates, opioid analgesics, tricyclic antidepressants, alcohol, as well as other drugs that lower blood pressure. The weakening effect of vasodilation is possible with the simultaneous use of nitrates with carbacholine, alpha-adrenergic agonists (norepinephrine, mesatone), histamine, angiotensin, corticosteroids, CNS stimulants, M-anticholinergics (atropine).

Sidnoniminy The only drug used in this group is molsidomine (Sidnofarm, Corvaton). The mechanism of its action at the cellular and systemic levels is close to that of nitrates, but unlike the latter, molsidomine increases the formation of cGMP without forming nitrosothiols. Therefore, tolerance practically does not develop towards it. The beginning of the action of molsidomine when taken orally is 20 minutes, lasting up to 6 hours. With sublingual administration, the effect occurs after 5 minutes and lasts 6-7 hours. Retard forms of the drug containing 8 mg of active substance are used more often. Such forms of molsidomine are conveniently used in the "nitrate-free period", since the drug does not give cross-resistance with nitrates. Side effects of molsidomine are similar to those of nitrates, but they are less pronounced and, in general, the drug is better tolerated.

Nicorandil is a new drug with a nitrate-like action that combines several mechanisms of action: the release of N0 and an additional vasodilating effect due to activation of potassium channels (in this case, hyperpolarization of the membranes of smooth muscle cells of blood vessels occurs, which leads to a decrease in the cytoplasmic concentration of calcium ions). The drug reduces the tone of arteries and veins, dilates the coronary vessels.

Classification of β-blockers and mixed blockers

1. β-blockers

1.1. Non-selective (β1, β2) without internal sympathomimetic activity

• Propranolol (Anaprilin).

• Timolol (Blockade).

• Nadolol (Korgard).

1.2. Non-selective (β1, β2) with internal sympathomimetic activity

• Pindolol (Wisken)

• Oxprenolol (Trazicor)

• Penbutolol (Betapressin)

• Bopindolol (Sandonorm)

1.3. Selective (β1) without internal sympathomimetic activity

• Talinolol (Cordan).

• Bisoprolol (Concor).

• Metoprolol tartrate (Egilok).

• Metoprolol succinate (Betalok ZOK).

• Atenolol (Tenormin).

• Betaxolol (Lokren).

• Esmolol (Breviblock).

1.4. Selective (β1) with internal sympathomimetic activity

• Acebutolol (Sectral).

1.5. Selective (β1) with vasodilating action

• Nebivolol (Nebilet).

• Busindolol.

• Celiprolol (Selectol).

2. Mixed adrenergic blockers (β, α1)

• Labetalol (Trandat

• Carvedilol (Dilatrend).

β-adrenergic blockers (BAB) is one of the main groups of drugs used to treat coronary artery disease. These are so far the only drugs that reduce the likelihood of sudden death in patients with coronary artery disease. In addition, they reduce mortality in the acute period of myocardial infarction and the frequency of recurrent myocardial infarction.

The main mechanism of action of BAB is reversible binding to β-adrenergic receptors and competitive blockade of adrenergic effects on various organs and tissues (Table 2.).

It is the blockade of sympathetic influences that underlies the main favorable effect of drugs of this group, namely, the ability to reduce mortality from cardiovascular causes.

The pharmacological classification of BAB is based on several specific characteristics, such as cardioselectivity - the ability of drugs in therapeutic doses to selectively block β1-adrenergic receptors of the heart. Cardioselective drugs give fewer side effects associated with blockade of β2-adrenergic receptors (bronchospasm, peripheral vascular spasm, increased contractile activity of the myometrium). Sometimes β1-adrenergic blockers are called “cardioselective”, but, unfortunately, cardioselectivity decreases or completely disappears with increasing doses, therefore the safety of these drugs, for example, in the treatment of patients with obstructive pulmonary diseases, is relative.

Some drugs have internal sympathomimetic activity (BCMA). They, screening β-adrenergic receptors from the action of catecholamines, at the same time maintain a certain level of activation of adenylate cyclase coupled to receptors. These drugs to a lesser extent reduce the strength and heart rate, rarely cause bronchospasm and spasm of peripheral vessels, practically do not affect carbohydrate metabolism and blood lipid levels

Of great clinical importance are the properties of β-blockers, such as lipo- and hydrophilicity. Based on this indicator, BAB are divided into three groups:

• lipophilic,

• hydrophilic;

• amphophilous (tab. 3.).

Lipophilic β-adrenergic blockers (betaxolol, metoprolol, propranolol, etc.) are quickly and fairly completely (up to 90%) absorbed in the gastrointestinal tract (GIT), metabolized in the liver (80-100%), penetrate well through the blood-brain barrier (BBB), which causes the development of central side effects. The dose of these drugs should be adjusted in patients with liver diseases, as well as with the simultaneous administration of drugs - microsomal oxidation inhibitors. The risk of cumulation of lipophilic β-blockers occurs with a decrease in blood flow through the liver (elderly patients, cirrhosis, venous congestion).

Hydrophilic β-blockers (atenolol, nadolol, etc.) are not completely (30-70%) and are unevenly absorbed in the digestive tract. Usually they are slightly metabolized in the liver and excreted by the kidneys either unchanged (40-70%), or in the form of metabolites. As a result, renal function should be taken into account when prescribing them, and in patients with low glomerular filtration (30-50 ml per minute), the dose of drugs must be reduced.

Hydrophilic β-adrenergic blockers penetrate the blood-brain barrier worse than lipophilic ones, so it is generally accepted that they are less likely to cause side effects from the central nervous system. Amphophilic β-blockers (acebutolol, celiprolol, bisoprolol), which dissolve both in lipids and in water, have two main ways of eliminating from the body - hepatic metabolism (40-60%) and renal excretion (unchanged).

Only lipophilic β-blockers (metoprolol, propranolol, timolol) and amphophilic bisoprolol have a cardioprotective effect, regardless of the presence or absence of selectivity. These drugs with prolonged use after myocardial infarction reduce mortality by 20-50%.

A special group is β-blockers with vasodilating properties. This property is implemented in various ways. So, for example, in celiprolol, vasodilation is achieved due to β2-adrenomimetic action and an additional direct vasodilating effect on vascular smooth muscle elements. In nebivolol, which is a racemate, the β-adrenergic blocking effect is realized due to the D-isomer (SRRR), and vasodilation, mediated by an increase in the ERF content in vascular endothelium, develops due to the antagonism of the G-isomer (RSSS) with N-monomethyl-G -arginine (Γ-NMMA), a competitive inhibitor of NO synthase.

The effect of non-selective β-adrenergic blockers on central hemodynamics is characterized by a decrease in cardiac output (both due to a decrease in heart rate and due to cardiac depression), a natural decrease in blood pressure .

Peripheral blood flow worsens due to the relative increase in peripheral vascular resistance (with prolonged use, the severity of this effect is less). The blood flow in striated muscles worsens, cerebral blood flow does not change, and the renal blood depends on the used β-blocker; during treatment with non-selective propranolol, it worsens, during treatment with selective atenolol, it increases, etc. Deterioration of bronchial obstruction under the influence of β-blockers can lead to severe respiratory distress in patients with obstructive pulmonary diseases.

The mechanism of antianginal action of β-adrenergic blockers is a blockade of β1-adrenergic receptors of the heart, leading to a decrease in the frequency and strength of heart contractions, and accordingly, the work of the heart and myocardial oxygen demand. In addition, BAB redistribute coronary blood flow in favor of ischemic subendocardial layers of the myocardium.

Indications for the use of β-blockers for coronary heart disease

1. Treatment of stable angina pectoris, starting from the II functional class.

2. Unstable angina pectoris.

3. Myocardial infarction (acute period).

4. Post-infarction period (1-3 years after myocardial infarction).

5. Ventricular arrhythmias in patients with coronary artery disease.

It is preferable to prescribe β-blockers to patients suffering from coronary artery disease with concomitant diseases: arterial hypertension, supraventricular tachycardia, ventricular extrasystoles. Considering that the stability of the antianginal effect of β-adrenergic blockers is determined not so much by the effect on β1-adrenergic receptors as by the uniformity of neurohumoral blockade, drugs with a long half-life are preferred to reliably suppress angina attacks.

Patients with coronary heart disease who have suffered myocardial infarction are more appropriate for the importance of lipophilic β-blockers, for which the possibility of reducing mortality in the long term after MI is proved - metoprolol, timolol, propranolol and mixed BAB carvedilol. At the same time, metoprolol and timolol are the drugs of choice in patients with unchanged ejection fraction of the left ventricle (LVEF), and carvedilol and metoprolol succinate in patients with decreased LVEF.

Therapy with β-blockers begins with minimal daily doses, followed by their increase after 4-5 days to the desired effect. The criterion of dose adequacy is considered to be a decrease in heart rate to 55-60 beats / min at rest. But when choosing doses of drugs with internal sympathomimetic activity, one should not be guided by the heart rate.

Side effects of β-blockers

1. Associated with the blockade of β1-adrenoreceptors of the heart (cardiac PE):

• bradycardia;

• atrioventricular block;

• decrease in heart rate - cardio depression;

• hypotension.

2. Associated with the blockade of β1-adrenergic receptors of smooth muscle (extracardiac):

• bronchospasm;

• spasm of peripheral vessels;

• increased contractile activity of the myometrium.

3. Others:

• β-blockers impair glucose tolerance by suppressing the mechanisms that counteract hypoglycemia in diabetes mellitus: in patients with type 1 diabetes, these drugs can cause hypoglycemia. In addition, they mask some symptoms of hypoglycemia (tremor, tachycardia), without affecting characteristic sweating.

• BAB have a pro-atherogenic effect, increasing the level of triglycerides, very low density lipoproteins and reducing the content of high density lipoproteins. These effects are most pronounced in the first 6 months of therapy (especially with the simultaneous administration of thiazide diuretics), and subsequently they are somewhat weakened.

• Perhaps the development of erectile dysfunction in men. Selective β1-blockers and β-blockers with BCMA cause these side effects to a lesser extent.

• Lipophilic β-blockers can cause PE from the central nervous system (weakness, apathy, drowsiness, nightmares, depression). BAB cause the phenomenon of "return", which can develop within 2-3 days (usually 3 months) of regular intake; it is associated with an increase in the sensitivity and density of β-adrenergic receptors (ir-regulation). Clinical manifestations of recoil syndrome include: the development of tachycardia or relapse of tachyarrhythmia, the appearance, increase or increase in angina pectoris, the development of myocardial infarction, heartbeat, trembling, anxiety. These symptoms occur on the 3-5th day after stopping the use of β-blockers and sometimes persist for a week or more (from 1 to 21 days). To prevent this complication, drugs should be discontinued within 2 weeks, gradually reducing the dose.

To a lesser extent, cardiac and extracardial side effects are caused by drugs with BCMA.

Calcium channel blockers

 Calcium channel blockers (CCBs) are drugs that block potential-dependent calcium channels of membranes and prevent calcium from entering the cell. Calcium channels are divided into 6 main types.

 The function of L-type calcium channels in the heart is the automatism of the cells of the sinus node, the conduction of an impulse through the atrioventricular node, the contraction of the muscle fibers of cardiomyocytes and smooth muscle cells of blood vessels. Selective L-type calcium channel blockers are verapamil, diltiazem, nifedipine, etc.

T T-type calcium channels are responsible for the automatism of the sinus node, the conduction of an impulse through the atrioventricular node, the contraction of smooth muscle cells, the regulation of protein synthesis and cell proliferation. Selective blockers are mibefradil, cinnarizine, flunarizin.

 Through the calcium channels of N-, P- Q-type, some neurotransmitters and hormones are released.

 R-type calcium channels are involved in the release of ERF.

A selective blocker is the drug isradipine. For the treatment of diseases of the cardiovascular system, mainly L-type calcium channel blockers are used.

The classification of calcium channel blockers is presented in table. 6.

Calcium channel blockers differ in tropic effects on myo-card and blood vessels.

Derivatives of phenylalkylamines act primarily on typical and atypical cardiomyocytes, derivatives of dihydropyridines on vessels. Derivatives of benzothiazepines have approximately the same effect on the smooth muscles of blood vessels and the heart. Diphenylpiperazines and nimodipine (dihydropyridine, group IIb) have a predominant effect on the cerebral vessels.

The mechanism of antianginal action of phenylalkylamines is associated with a decrease in calcium intake in typical cardiomyocytes, sinus node cells and the cardiac conduction system. Consequently, the strength and heart rate, heart function and myocardial oxygen demand are reduced. The antianginal effect of dihydropyridine derivatives is mainly due to a decrease in calcium intake in smooth muscle cells of both coronary and peripheral vessels, which leads to their expansion. The result of this is an improvement in coronary blood flow, a decrease in pre- and afterload.

The main components of the antianginal action of calcium channel blockers

• Direct reduction in myocardial oxygen consumption due to negative foreign and chronotropic effects.

• Indirect reduction in myocardial oxygen consumption due to reduced pre- and afterload.

• Improved oxygen delivery to the myocardium due to the expansion of coronary vessels.

• The presence of antiplatelet effect.

• Indirect anti-atherogenic effec

Note: * - only for relief of an attack of variant angina pectoris; ** - pharmacokinetics varies greatly depending on the manufacturer; prol. - prolonged forms.

Indications for use of calcium channel blockers

1. Stable angina pectoris, starting from the II functional class.

2. Variant angina (Prinzmetal).

Currently, short-acting nifedipine is not used for the systematic treatment of coronary heart disease and arterial hypertension, as long-term use of the drug increases the mortality of patients with these diseases. This restriction does not apply to retard forms of the drug.

II-III generation drugs have improved pharmacokinetic properties and cause fewer side effects

Side effects

• Most characteristic for phenylalkylamine derivatives:

- bradycardia;

- atrioventricular block;

- decrease in heart rate;

- hypotension.

• The most characteristic for derivatives of dihydropyridine:

- compensatory tachycardia;

- edema of cardiac origin;

- redness of the face;

- constipation.

Selective If Inhibitors

• Ivabradin (Coraxan).

In recent years, selective If- inhibitors (specific blockers of the incoming ionic current through mixed Na + / K + channels activated at the time of hyperpolarization) have been intensively studied. If current plays an important role in pacemaker activity, since it is responsible for the occurrence of a phase of spontaneous slow diastolic depolarization in the cells of the sinus node, and therefore determines the heart rate. As a result of blockade of If channels in the sinoatrial

node, due to a decrease in heart rate, the oxygen demand of the myocardium is reduced without a concomitant decrease in heart rate (dose-dependent effect).

One of the drugs - If-channel blockers - is Ivabradin (Korak-san), prescribed 5-10 mg 2 times a day. When applying the usual recommended dose (7.5 mg 2 times a day), a decrease in heart rate by about 10 beats per minute at rest and under load is noted. This reduces heart function and reduces myocardial oxygen consumption.

The drug is comparable in antianginal activity with atenolol, but unlike β-blockers, it does not cause bronchospasm, AV blockade and erectile dysfunction. Ivabradine is contraindicated in case of bradycardia (heart rate less than 50 beats / min), AV block II-III stage, sinus node weakness syndrome.

Side effects are mainly due to the effect of the drug on retinal h-channels related to f-channels, which is the reason for visual symptoms of varying severity in 10-15% of patients (photopsies, increased brightness in the visual field, blurred vision). These symptoms, as a rule, arise in the first 2 months of therapy, are mild, reversible and do not require special treatment.

Antiplatelet agents

1. Inhibitors of cyclooxygenase (COX):

• Acetylsalicylic acid (Aspirin).

2. Blockers of ADP (P2Y12) receptors (thienopyridines):

• Ticlopidine (Ticlide).

• Clopidogrel (Plaviks).

• Prasugrel.

3. Blockers of GP IIb / IIIa receptors

3.1. Monoclonal antibodies:

• Abciximab (Reo-Pro).

• Monafram (Framon).

3.2. Cyclic peptides:

• Eptifibatide (Integrilin).

3.3. Non-peptide blockers

• Tirofiban (Agrostat).

• Orbofiban.

• Xemilofiban.

• Lamifiban.

• Sibrafiban.

4. Phosphodiesterase (PDE) blockers and adenosine potentiators:

• Dipyridamole (Curantil)

One of the reasons for the development of coronary heart disease is a change in platelet function (TC), activation of the synthesis of thromboxane A2 and a decrease in the formation of prostacyclin. Cascade platelet activation is shown in Scheme 3. The general final mechanism for platelet activation is an increase in the expression of glycoprotein receptors (GP IIb / IIIa-R) on the surface of the platelet, which leads to the formation of platelet bonds, increased platelet aggregation and, as a consequence, the formation of a thrombus.

FL - phospholipase; TxA2 - thromboxane A2; 5-HT - serotonin; FAT - platelet activation factor; Tr - thrombin; R is the receptor; DAG - diacylglycerol; 3-PME - 3-phosphomonoesterase; KM - calmodulin; I3F - inositol triphosphate; AC - adenylate cyclase; PDE - phosphodiesterase; PK - protein kinase; KLMTS - kinase of light chains of myosin; GP IIb / IIIa-R - glycoprotein receptor; P2Y12-R is a purine receptor. Therefore, active, targeted and long-term antiplatelet therapy is a pathogenetically substantiated component of the treatment of patients with acute coronary syndrome.

General indications for the appointment of antiplatelet agents

• Stable angina II-IV functional class.

• Unstable angina pectoris and myocardial infarction.

• Primary and secondary prevention of cardiovascular events.

• Postinfarction cardiosclerosis.

• Prevention of thrombosis during intracoronary interventions.

Acetylsalicylic acid (ACSK) is a non-selective irreversible COX inhibitor, which leads to impaired synthesis of cyclic endoperoxides and their metabolites (thromboxane and simple cyclin). Thromboxane (Tx-A2), which is one of the most powerful aggregation factors, is synthesized mainly in platelets, whose lifespan is 7-10 days. With the introduction of ACSC, an irreversible blockade of COX occurs, resynthesis of which is impossible, since platelets are nuclear-free cells.

In the vascular endothelium under the influence of COX, predominant synthesis of prostacyclin (Pgl2), which is a functional antagonist of Tx-A2, occurs. ACSC blocks this process in endotheliocytes, but since they are nuclear cells, enzyme resynthesis quickly occurs in them and prostacyclin production is restored.

The antiplatelet effect when using ACSK is already achieved in small doses (30-325 mg / day) and lasts for several days.

With a stable course of IHD, ACSK is prescribed 75-125 mg orally 1 time per day, with exacerbation of the disease - 250-325 mg 1 time per day. In the same doses, the drug is prescribed for cardiac surgery. It should be borne in mind that in women, ACSK is less effective against primary and secondary prevention of myocardial infarction than in men.

The use of ACSC is limited to:

• peptic ulcer of the stomach and duodenum (due to a decrease in the production of cytoprotective prostaglandins in the gastrointestinal mucosa);

• bronchospastic conditions (due to the activation of the lipoxygenase pathway of arachidonic acid metabolism and a possible increase in the production of leukotrienes, including those that

are part of the slowly reactive substance of anaphylaxis - MRSA);

• increased bleeding;

• uncontrolled arterial hypertension (AH) or its crisis course (due to an increased risk of fatal hemorrhagic complications).

In addition, some caution should be observed when prescribing ACSK for the purpose of primary prevention of MI and ischemic stroke in patients older than 70 years of age, in whom, against the background of the drug, an increase in the number of cases of gastrointestinal bleeding and intracranial hemorrhage is noted.

ADF (P2Y12) receptor blockers

Thienopyridines (ticlopidine, clopidogrel, prasugrel) mainly inhibit ADP-induced platelet aggregation, reducing the number of functioning ADP (P2Y12) receptors and blocking the binding of ADP to them. As a result of this, calcium entry into platelets is limited and the expression of GP IIb / IIIa receptors is reduced.

The antiplatelet effect of ticlopidine is approximately equal to ACSK and develops on the 5th day, so the drug is not suitable for use in emergency situations. The maximum effect on ADP-stimulated platelet aggregation is observed on days 8-11 and persists for 10 days after discontinuation of the drug. Ticlopidine is prescribed at 500 mg / day in 1-2 doses, with good tolerance, the daily dose can be increased to 750 mg. It is the drug of choice for intolerance to ACSK. Side effects include leukemia and neutropenia, dyspeptic disorders, allergic reactions, and hepatotoxicity.

Clopidogrel, which is one of the metabolites of ticlopidine, when used at a dose of 75 mg / day, is significantly superior in activity and safety to ticlopidine and ACSK, but has a higher cost. It can be used in combination with ACSC in acute coronary syndrome, including myocardial infarction, and percutaneous interventions in the coronary arteries, when combination therapy with two antiplatelet agents is necessary. The dose of clopidogrel in this case is 75 mg / day (after a load of 300 mg / day), and the duration of combination therapy reaches 12 months. In addition, combination therapy can be indicated for a long time to patients at high risk and for ischemic stroke.

The new thienopyridine prasugrel, which at a loading dose of 60 mg (a maintenance dose of 10 mg) allows for faster and more pronounced inhibition of platelet aggregation compared with clopidogrel at a loading dose of 300 mg or higher - 600 mg (maintenance dose - 150 mg) . Prasugrel is more effective than clopidogrel in the prevention of ischemic events after percutaneous coronary intervention (decrease by 19% in cardiovascular death, non-fatal MI, non-fatal stroke; by 42% - risk of fatal MI, by 34% - risk of repeated emergency revascularization of the target artery , at 52% - the risk of stent thrombosis). However, compared with clopidogrel, prasugrel therapy is associated with an increased risk of major bleeding (32%) and life-threatening hemorrhages, including fatal ones (52%).

GP llb / llla receptor blockers - abciximab, monafram, eptifibatid, tirofi-ban

Selective GP IIb / IIIa receptor blockers, regardless of their nature, are able to completely block platelet aggregation induced by all known physiological inducers. In addition, they are able to inhibit the degranulation of TC and TC-dependent formation of thrombin. Drugs in this group are much more effective than all antiplatelet agents actually used.

Indications for use of GP IIb / IIIa receptor blockers

• Performing endovascular interventions.

• "Acute" period in patients with unstable angina and myocardial infarction without Q wave.

• As a means of secondary prevention for patients with a high risk of coronary and vascular events.

• In combination with thrombolytic and anticoagulant therapy in patients with transmural myocardial infarction in order to prevent retrombosis.

Side effects of this group of drugs include thrombocytopenia and bleeding.

Contraindications to the use of GP IIb / IIIa receptor blockers

• Internal bleeding, including recent (up to 6 weeks) or suspicion of it.

• Extensive surgery (up to 6 weeks).

• Severe injury (up to 6 weeks).

• Disorders of cerebral circulation (up to 2 years), residual effects after a violation of cerebral circulation, regardless of prescription.

• Severe hypertension.

• Malignant neoplasms.

PDE blockers and adenosine potentiators

Dipyridamole is a blocker of PDE and adenosine deaminase. Inhibition of PDE in platelets leads to the accumulation of cAMP and, through the activation of a number of intermediates, to a decrease in the concentration of Ca2 + in the cell. As a result, the Ca2 + -dependent platelet aggregation process decreases. In addition, the blockade of PDE in the vessels (including coronary vessels) leads to an increase in the level of cAMP, and, accordingly, their expansion.

Inhibition of adenosine deaminase by dipyridamole prevents the destruction of adenosine, which realizes its effects through adenosine receptors of the 1st or 2nd type. Activation of A1-adenosine receptors in the myocardium leads to a decrease in cAMP level (through inhibition of adenylate cyclase) and the development of a cardiodepressive effect with a decrease in oxygen demand of the myocardium. Activation of A2-adenosine receptors in the vascular muscle muscles helps increase adenylate cyclase activity, cAMP accumulation and vasodilation (including coronary vessels). Obviously, in addition, dipyridamole is able to enhance the synthesis of prostacyclin and ERF in the vascular endothelium. In addition, with prolonged use (at least 6 months), the drug is able to improve collateral circulation in the heart.

The average daily dose of dipyridamole is 75-600 mg (in 3-4 doses). The drug is significantly inferior to ACSK and thienopyridines in antiplatelet activity. Side effects include tachycardia (due to inhibition of PDE) and the phenomenon of "robbery" (redistribution of blood flow from the ischemic zone to the non-ischemic zone).

MEANS IMPROVING METABOLISM OF THE HEART MUSCLE

The main category of patients for whom metabolic drugs can be used as part of the treatment of coronary heart disease are patients with a resistant form of the disease when:

- the possibilities of basic therapy have been exhausted;

- myocardial revascularization is impossible (for various reasons);

- angina has a III-IV functional class;

- there is no way to apply any method of treatment of resistance.

It should be noted that metabolic therapy does not have a proven effect on the final hard points, but sometimes can give a certain clinical effect.

ANGIOTENSIN-CONVERSING ENZYME INHIBITORS

• Ramipril (Tritace).

• Perindopril (Prestarium).

Angiotensin-converting enzyme inhibitors are one of the promising classes of drugs to improve the prognosis of patients with coronary artery disease. Currently, ramipril and perindopril have been most studied according to this indication, having common properties that slightly distinguish them from other ACE inhibitors (pronounced affinity for the tissue component of the renin-angiotensin-aldosterone system (RAAS), long duration of action). The positive clinical effect of ACE inhibitors in coronary heart disease is based on the following mechanisms:

• Antianginal effect, mediated by the expansion of peripheral vessels (reduction of post- and preload), which is accompanied by a decrease in oxygen demand of the myocardium. In addition, there is a direct expansion of the coronary vessels and an improvement in coronary blood flow. This vasodilation is due to a decrease in the vasoconstrictor effect of angiotensin II and an increase in the synthesis of ERF in the vascular endothelium.

• Indirect profibrinolytic effect, developing due to blockade of the secretion of tissue plasminogen-1 activator inhibitor (ITAP-1).

• Anti-atherogenic effect due to normalization of endothelial function, anti-mitogenic, antioxidant and indirect profibrinolytic effects.

• A decrease in left ventricular hypertrophy, regardless of a decrease in blood pressure, associated with a decrease in the activity of RAAS and CAS.

The inclusion of ACE inhibitors in the treatment of coronary heart disease allows you to have a positive effect on the heart, blood vessels, kidneys, improving long-term outcomes (myocardial infarction, cardiovascular mortality).

The recommended dose of perindopril is 8 mg / day, ramipril - 10 mg / day. Apparently, the maximum effect of the use of ACE inhibitors in patients with coronary heart disease will be observed in people with medium and high risk, with uncontrolled risk factors (smoking, hypercholesterolemia) and other indications for taking ACE inhibitors (history of MI and / or left ventricular dysfunction, hypertension, diabetes). According to the recommendations of the American Heart Association, the appointment of these drugs is mandatory when combining coronary heart disease with diabetes and desirable for severe atherosclerotic lesions of the vessels of the lower extremities.

TREATMENT OF STABLE Angina

The treatment of angina pectoris has two main goals.

The first is to improve the prognosis and prevent the occurrence of myocardial infarction or sudden death, and, accordingly, increase life expectancy.

The second is to reduce the frequency and intensity of angina attacks to improve the quality of life.

Medicines that improve the prognosis in patients with angina pectoris are recommended for all patients with anginal attacks in the absence of contraindications. First of all, we are talking about antiplatelet agents (acetylsalicylic acid), β-blockers (as drugs of choice for patients with angina attacks or in the diagnosis of myocardial ischemia episodes using instrumental methods) and lipid-lowering drugs (in the presence of dyslipidemia), as well as ACE inhibitors. In relation to antianginal drugs in patients with stable angina pectoris, the following provisions are valid:

- antianginal drugs eliminate or reduce the symptoms of the disease;

- antianginal combination therapy is somewhat more effective than monotherapy;

- an increase in life expectancy when using antianginal drugs requires additional evidence;

- acute ischemic episodes prevent acetylsalicylic acid, β-blockers, statins, ACE inhibitors.

Treatment of patients with stable angina pectoris should be carried out taking into account its functional class (FC). This suggests that in patients with FC I, the relief of an angina attack during severe physical exertion. As a rule, nitroglycerin is prescribed sublingually (intermittent use). Further therapy consists of activities related to the normalization of work and rest, the elimination of psycho-emotional stress, risk factors. For the treatment of angina pectoris I FC, it is possible to prescribe antiplatelet agents and hypolipidemic agents (in the case of dyslipidemia).

In patients with FC II, antianginal drugs belonging to one of the following groups can be used: β-blockers, calcium channel blockers, nitrates, either as monotherapy or in combination. It is in this sequence that it is recommended to prescribe these classes of drugs for the treatment of stable angina pectoris, and also to use their various combinations. The drugs of choice in this case are β-adrenergic blockers, with inefficiency or pronounced side effects of which nitrates or BCC should be prescribed.

If concomitant diseases are arterial hypertension or tachyarrhythmias, it is advisable to prescribe β-blockers or phenylalkylamine BKK. In the presence of bronchial asthma, the drugs of choice are BCC or nitrates. If stable angina pectoris occurs against a background of heart failure, preference should be given to β-blockers or nitrates, and the appointment of phenylalkylamine BKK is not recommended. The presence of diabetes mellitus in patients with coronary heart disease makes an additional introduction to the treatment of ACE inhibitors necessary. In addition, patients with FC II are shown antiplatelet therapy and the appointment of lipid-lowering drugs (in the case of dyslipidemia).

If monotherapy is ineffective, then use combined antianginal therapy. Indications for its implementation are:

- inefficiency of monotherapy in patients with FC II;

- intolerance to standard doses of drugs;

- IHD with frequent cardiac arrhythmias (II-IV FC);

- IHD occurring with heart failure (IV FC) or other concomitant diseases;

- correction of adverse hemodynamic changes that occur during monotherapy.

The most commonly used combinations are:

1. β-blockers and nitrates. The combination of drugs of these groups gives a pronounced antianginal effect and has a positive effect on hemodynamic parameters. The combination is preferable in patients with cardiac arrhythmias and arterial hypertension. In addition, this combination can be used in patients with a combination of ischemic heart disease and heart failure.

2. Calcium channel blockers and nitrates. The results of the combined use of BCC and nitrates are contradictory. According to a number of researchers, when BCC is added to nitrates, a more pronounced antianginal effect can be obtained than with monotherapy. In addition, it was shown that the addition of nifedipine or verapamil to isosorbide dinitrate does not lead to an increase in the antianginal effect compared with monotherapy with these drugs. The additional purpose of CCB (phenylalkylamines and benzothiazepines) is certainly advisable for the prevention of nitrate resistance (in the nitrate-free period).

3. β-adrenergic blockers and BKK (derivatives of dihydropyridines) - the combination of drugs does not exceed the treatment of each of these drugs separately. Although the β-blocker in this combination is able to level the reflex tachycardia caused by dihydropyridine BCC. The combination of β-adrenergic blockers and BKK-derivatives of phenylalkylamines is practically not used due to the mutual potentiation of cardiodepressive action

In the treatment of patients with coronary artery disease, important tasks are solved within the framework of secondary prevention. These include: preventing premature death, inhibiting the progression and achieving partial regression of coronary artery atherosclerosis, preventing clinical complications and exacerbations of the disease, reducing the frequency and duration of hospitalizations, especially urgent ones. To do this, use antiplatelet agents, β-blockers, ACE inhibitors and statins.

Thus, we can draw the following conclusions:

• Treatment of stable angina pectoris II-III FC should be carried out with one or more antianginal drugs, which the patient should receive regularly.

• First-line drugs in the absence of contraindications are β-blockers.

• The intensity of drug therapy and the need to combine several antianginal drugs are largely determined by the severity of the manifestations of angina pectoris.

• In addition to antianginal drugs, the appointment of antiplatelet and hypolipidemic drugs is necessary, and in a significant part of patients - ACE inhibitors.

Treatment of variant angina

It has been established that the local spasm of the epicardial coronary artery, which causes transmural ischemia in the corresponding zone of myocardial blood supply, plays the leading role in the genesis of variant angina of Prinzmetal (BC). An increased sensitivity of this section of the coronary artery to vasospastic stimuli (ergonovin, acetylcholine, leukotrienes, serotonin, etc.) is noted. Variant angina can occur both against the background of stenotic atherosclerosis of the carotid arteries (often the spasm zone is in the area of the plaque), and in individuals with externally intact coronary arteries. The most effective means of stopping the attacks of variant angina are nitrates (sublingual tablets or spray), and their prolonged forms can be successfully used for the prevention of attacks. The central role in the treatment of VS is played by calcium channel blockers, which can prevent and resolve arterial spasm. Different points of application of the effect make a combination of BCC with nitrates advantageous - this is the basis for the treatment of BC. There is also evidence of the potential effectiveness of α-blockers (prazosin) in patients with AF.

In most patients, within 3-6 months, the symptoms of BC spontaneously regress, but relapses of the disease that are sensitive to previous treatment may occur.

TREATMENT OF ACUTE CORONARY SYNDROMES (UNSTABLE Angina pectoris AND THEM)

The main cause of ACS is rupture of an atherosclerotic plaque or endothelial erosion followed by coronary artery thrombosis and the occurrence of acute ischemia. As numerous studies have shown, the earlier the necessary treatment is started, the more hope there is for a favorable prognosis in a particular patient. At the stage of the initial examination, patients with suspected unstable angina or myocardial infarction are diagnosed with acute coronary syndrome. This means that treatment should be started until the final diagnosis is clarified, while patients should be treated as patients with myocardial infarction or unstable angina.

Acute myocardial ischemia may be a sign of developing MI, but it does not always mean necrosis of cardiomyocytes (unstable angina pectoris). When determining treatment tactics, it is important to differentiate ACS with persistent elevation of the ST segment on the ECG and ACS without persistent elevation of the ST segment).

Classification and outcomes of acute coronary syndromes

Patients with ACS with persistent ST elevation are patients with pain or discomfort in the chest and persistent elevation of the ST segment or the “new” (first-time or presumably first-time) complete blockade of the left bundle branch block on the ECG. Stable elevation of the ST segment implies the presence of acute complete occlusion of the coronary artery by a thrombus. The main objective of treatment in this situation is a quick and stable restoration of the lumen of the vessel - reperfusion of the ischemic myocardium. To do this, use both pharmacological methods - the introduction of thrombolytics, and surgical - percutaneous coronary intervention (ChKB).

Patients with ACS without persistent ST elevation are patients with pain or disk-fort in the chest and ECG changes, indicating acute myocardial ischemia, but without ST segment elevations. Persistent or transient ST depression, inversion, smoothness, or pseudo-normalization of the T wave may be noted in these patients, although in some patients the ECG may be normal upon admission. Thrombolytic agents are not used in the treatment of such patients. The main objectives of the treatment are to maintain coronary artery patency by limiting and preventing intracoronary thrombosis and distal thromboembolism, eliminating ischemia (conservatively or operatively).

The goal of the treatment of ACS is to eliminate ischemia and its complications, prevent the development of myocardial necrosis (or its further spread), and ultimately to improve the prognosis.

The main directions of their drug therapy, based on the common pathogenesis of ACS:

• lysis of a thrombus obstructing the coronary artery (for ACS with ST elevation);

• prevention of further thrombosis, microembolization and the creation of conditions for spontaneous lysis of a blood clot that does not block the lumen of the vessel;

• elimination of ischemia and prevention of its occurrence;

• anesthesia;

• prevention and treatment of complications (treatment of heart failure, shock, prevention and treatment of arrhythmias, etc.);

• start of secondary prevention activities.

The main groups of pharmacological agents used in the treatment of ACS:

• Antithrombotic agents (antiplatelet agents, anticoagulants, fibrinolytics).

• Anti-ischemic agents (nitrates, β-blockers, calcium channel blockers).

• Preparations of other groups (analgesics, ACE inhibitors, statins, etc.).

Antithrombotic agents

1. Antiplatelet agents (see above).

2. Anticoagulants:

2.1. Direct action.

2.1.1. Unfractionated heparin: • Heparin.

2.1.2. Low molecular weight heparins: • Dalteparin (Fragmin). • Nadropaprine (Fraxiparin) • Certoparin (Sandoparin). • Tinzaparin (Logiparin). • Enoxaparin (Clexane).

2.1.3. Heparinoids (parenteral Xa factor inhibitors): • Fondaparinux (Arikstra). • Idraparinux.

2.1.4. Oral Xa factor inhibitors: • Rivaroxaban (Xarelto). • Apixaban.

2.1.5. Hirudin and hirudinoids: • Hirudin (Lepirudin). • Bivalirudin (Angiomax, Angiox).

2.2. Indirect action.

2.2.1. Coumarin derivatives:

2.2.1.1. Monocoumarins. • Warfarin (Coumadin). • Fenprokumon (Marku-mar). • Acenocumarol (Sincumar).

2.2.1.2. Dicumarines. • Bishydroxycumarol (Dicumarin). • Ethyl biscum acetate (neodicumarin).

2.2.2. Indandion derivatives: • Phenindione (Phenylinum). • Difenadion (Dipaxinum).

2.2.3. Indirect fibrinolytics:

I generation:

• Urokinase (Urokidan).

• Streptokinase (Streptoliasis).

II generation:

• Acetylated plasminogen-streptokinase activator complex (Anistreplase, APSAK).

• Alteplase (Aktilize).

• Prourokinase (Purolyase).

III generation (mutant):

• Tenecteplase (Metalysis).

• Reteplase (Rapilizin).

The main points of application of funds that affect blood coagulation are presented in figure 5.

In patients with myocardial infarction without ST elevation, treatment begins with the administration of antiplatelet and anticoagulant drugs, while in patients with persistent elevation of the ST segment, therapy involves the use of fibrinolytics. In patients with myocardial infarction without ST elevation, the use of fibrinolytics is dangerous.

The principles of using antiplatelet agents in ACS:

 antiplatelet agents - an essential component of ACS therapy, they should be prescribed as soon as possible, while treatment begins with loading doses;

 acetylsalicylic acid is prescribed to all patients with ACS in the absence of contraindications; in case of intolerance to ACSK, the drug is replaced with clopidogrel;

 antiplatelet agents, as a rule, are combined with the introduction of heparin or its low molecular weight fractions;

 the activity of antiplatelet therapy is determined by the severity of ACS and prognosis of the patient, it is advisable to combine antiplatelet agents with different mechanisms of action before the planned ChKB and in patients with a high risk of an unfavorable prognosis.

Acetylsalicylic acid in the first dose of 250 mg is the means of choice among antiplatelet agents for ACS (it is advisable to chew a tablet with usual rather than enteric-soluble ACSK) and subsequently 75-160 mg once daily. It is necessary to take the drug indefinitely (for life). It is safer for patients in whom thrombolytic therapy is planned to limit the first dose of ACCC to 160 mg.

In case of intolerance to acetylsalicylic acid, antiplatelet agents from the thienopyridine group are prescribed (clopidogrel at a loading dose of 300 mg once with a subsequent transition to a dose of 75 mg / day; ticlopidine 250 mg 2 times a day with a loading dose of 500 mg). In recent years, the feasibility of combined administration to all patients with ACS (ACSK and clopidogrel) has been shown. Such therapy should be continued for at least 1 month, optimally up to 1 year.

Unfractionated heparin, low molecular weight heparins, fondaparimux or bivalirudin should be added to antiplatelet drugs (ACCC and / or thienopyridines).

Long-term use of drugs of this group in addition to ACSK is undesirable, as it is accompanied by an increase in mortality.

Principles for the appointment of direct anticoagulants in ACS

Direct-acting anticoagulants, primarily heparins - an indispensable element in the treatment of ACS, heparin therapy begins immediately upon admission.

 Unfractionated heparin in the treatment of coronary thrombosis is used intravenously to maintain a steady concentration in the blood.

 Instead of unfractionated heparin in ACS without ST elevation, low molecular weight heparins, fondaparinux or bivalirudin can be used.

 If heparins cause thrombocytopenia, hirudin or bivalirudin may be used as an anticoagulant.

 It is advisable to abolish heparins gradually to prevent possible reactive hypercoagulation.

 It is not recommended to change the anticoagulant during the treatment of ACS.

UFH is administered intravenously by a bolus of 60-70 PIECES / kg (but not more than 5000 PIECES) with the subsequent transition to constant intravenous infusion with an initial speed of 12-15 PIECES / kg per hour (but not more than 1000 PIECES / h). The duration of administration of UFH should be at least 48 hours, but not more than 7 days. It should be remembered that nitroglycerin reduces the anticoagulant activity of heparin.

Indirect anticoagulants in the treatment of acute myocardial infarction. Due to the slow onset of the effect in ACS, they are prescribed only for the prevention of thrombosis and embolism in special cases (concomitant atrial fibrillation, implanted artificial heart valves, signs of intracardiac thrombosis, deep vein thrombosis, history of thromboembolism) after stabilization of the patients' condition.

The mechanism of action of the drugs is associated with the blockade of the enzyme epoxy reductase in the liver, which leads to a decrease in the synthesis of II, VII, IX, and X coagulation factors, as a result of which the hydroxylation of γ-carboxyglutamic acid and, accordingly, the synthesis of vitamin K-dependent coagulation factors are disrupte

The rate of decrease in plasma levels of these factors is determined by their half-life, which is 80-120 hours for factor II, 4-6 hours for factor VII, 24 hours for factor IX, 48-72 hours for factor X. Thus Thus, clinically significant changes in blood coagulability after taking the first dose of an indirect anticoagulant are determined no earlier than after 8-12 hours, the maximum effect appears after 72-96 hours, and the duration of action of a single dose can be from 2 to 5 days.

The most widely used coumarin derivative is warfarin. The recommended doses of indirect anticoagulants and individual pharmacokinetic parameters are presented in table. 15.

Indirect anticoagulants can be used in combination with ACSK after several days of parenteral administration of direct anticoagulants in the early stages of the disease. When combining warfarin with ACSC, the dose of the latter should be 75 mg / day, while the dose of warfarin should be selected individually so that the MHO is 2. Moreover, it should be borne in mind that the combination of ACSC and warfarin doubles the risk of major bleeding , but more effective than acetylsalicylic acid alone, prevents major cardiovascular complications.

An important role in the treatment of indirect anticoagulants is played by the interaction of drugs of this group with other pharmacological agents, due to the peculiarities of their pharmacokinetics (high degree of binding to blood plasma proteins, competitive metabolism in the liver) and pharmacodynamics.

Drugs that enhance the effect of NAC

• Amiodarone.

• Ciprofloxacin.

• Co-trimoxazoles.

• Fluconazole.

• Cimetidine.

• Clofibrate.

• Erythromycin, azithromycin, roxithromycin, clarithromycin.

• Metronidazole.

Drugs that reduce the effect of NAC

• Barbiturates.

• Cholestyramine.

• Nafcillin.

• Carbamazepine.

• Griseofulvin.

• Rifampicin.

• Vitamin K.

Indirect anticoagulants are contraindicated in cases of bleeding, severe impaired liver and kidney function, uncontrolled arterial hypertension.

Thrombolytic therapy today is included in the list of standard therapeutic measures for patients with myocardial infarction with ST segment elevation. A persistent ST segment elevation implies the presence of acute complete occlusion of the coronary artery with a thrombus. According to generalized clinical trials, more than 100 000 patients have shown that effective thrombolytic therapy can reduce the risk of death by 10-50%.

Modern fibrinolytics can be divided into three main groups.

Preparations of the first generation, which approximately equally activate plasminogen associated with fibrin and circulating in the blood.

II generation drugs with relative specificity for fibrin-associated plasminogen. These drugs are considered more effective than streptokinase, but their common drawback is the need for a sufficiently long intravenous infusion.

3rd generation drugs (mutant fibrinolytics) have a higher fibrinolytic activity, due to their modification using genetic engineering methods. So, for example, tenecteplase, compared with alteplase, has a longer duration of action, 14 times higher specificity for fibrin and 70 times higher resistance to the tissue plasminogen activator inhibitor (ITAP-1). In addition, III generation fibrinolytics are much easier to use, since they can be administered by bolus.

Most controlled clinical trials show a linear relationship between the time from the start of treatment of MI and mortality. This explains the need for the earliest possible initiation of thrombolytic therapy. It is believed that thrombolysis during the first hour from the onset of symptoms of MI will not only help reduce mortality, but in 40% of patients it will interrupt the development of MI, and will also prevent the development of irreversible damage to the myocardium, its dysfunction and sudden death, more than half of which occur in the first hours of IM.

In the absence of contraindications, thrombolytic therapy should be started in the first hour from the onset of symptoms of MI ("golden hour"). However, even in patients for whom fibrinolytic (in particular, streptokinase) was injected late (12-24 hours after the onset of symptoms of MI), a decrease in mortality of 19% over 5 weeks of observation was also noted. The mechanisms for reducing mortality in “late” thrombolysis are unclear. It should be noted that intracoronary

administration of thrombolytics (in particular, drugs of I and II generations) in the acute period of MI is much more effective than its intravenous administration.

General principles of the use of thrombolytics in ACS

Thrombolytics should be used as soon as possible after the onset of the first symptoms of thrombosis. The best results of thrombolysis are observed within the first 1-4 hours from the onset of clinical symptoms, therefore, thrombolysis begins without waiting for the results of studies on markers of myocardial necrosis, especially since the result may be negative in the first hours. The time from the moment of patient admission to the start of thrombolytic administration should not exceed 30 minutes.

The decision to prescribe thrombolytics is made after a careful comparison of the possible benefits and risks of such treatment. With relative contraindications to thrombolysis, surgery is sometimes preferable if it is possible in a short time.

Thrombolytics are administered intravenously without mixing with other drugs. Due to the short half-life, a relatively long or repeated intravenous infusion of the drug is necessary to realize the effect. An exception is drugs with a longer half-life (anistreplase, reteplase, tenecteplase), which can be administered once a bolus, which is convenient at the prehospital stage.

Drug-induced fibrinolysis is accompanied by a reactive increase in blood thrombogenicity (mainly due to platelet activation), therefore, to prevent reocclusion in ACS (15-20% of patients), the simultaneous administration of antiplatelet agents (ACCC + clopidogrel) and antithrombins (heparin, NMG (enoxaparin) fondaparinux) for several days.

The positive effect of thrombolysis on the prognosis for ACS is significantly stronger in more severe patients, it increases in proportion to the risk of death.

In 10-40% of patients with arterial thrombosis, thrombolytics may be ineffective. Possible causes include: non-thrombotic artery occlusion (plaque hemorrhage, stratification, occlusion with a piece of tissue after ChKB, severe coronary spasm due to cocaine poisoning), poor access of thrombolytics (perfusion disorders due to cardiogenic shock or poor collateral blood flow), some features of thrombosis.

Constant monitoring of the patient is required for at least 3, and preferably 24 hours after the onset of thrombolysis to evaluate its effectiveness and timely recognition of complications.

The main complication of thrombolytic therapy is bleeding, including intracranial hemorrhage. Allergic reactions and rarely anaphylactic shock are also characteristic of streptokinase and anistreplase (APSAK).

Indications for thrombolysis (in the absence of contraindications):

• ACS with ST segment elevation during the first 12 hours from the onset of clinical symptoms, provided that the ST elevation is more than 1 mm in at least 2 adjacent chest leads or at least 2 limb leads;

• ACS during the first 12 hours from the onset of clinical symptoms with the occurrence of a “new” or presumably “new” complete blockade of the left bundle branch block.

Thrombolysis is also advisable if:

• posterior basal (true posterior) myocardial infarction during the first 12 hours from the onset of clinical symptoms (characterized by

• high R teeth in V1-2, ST segment depression in V1-3 and / or an isolated ST elevation in the posterior leads (V) and often high pointed teeth of TV V1-3); myocardial infarction with ST segment elevation (in the period of 12-24 hours after the onset of symptoms) with persisting symptoms of ischemia and ST elevation of more than 1 mm in at least two adjacent thoracic or at least two leads from the extremities. Despite the large number of fibrinolytics studied in angiographic and clinical studies, in practice preference is given to streptokinase, alteplase, as well as more convenient to use tenecteplase and reteplase.

Absolute contraindications to the use of fibrinolytics

• Previous intracranial hemorrhage of any nature.

• Known structural abnormalities of intracranial vessels.

• Known intracranial malignant tumor (primary or metastatic).

• Ischemic stroke within 3 months (excluding acute ischemic stroke up to 3 hours).

• Suspicion of aortic dissection.

• Active bleeding or hemorrhagic diathesis (except menstruation).

• Significant closed craniocerebral trauma or trauma to the face during the previous 3 months.

Complications of thrombolytic therapy are infrequent, but sometimes very dangerous. They can be associated either with the main mechanism of action (bleeding, hypotension, chills, reperfusion arrhythmias), or with specific properties and characteristics of the drug.

Some principles of the use of nitroglycerin and other nitrates in ACS

• It is advisable to prescribe nitrates to all patients with ACS with persistent ischemia, heart failure or hypertension in the absence of contraindications.

• The administration of nitrates should not prevent the use of drugs with proven efficacy in ACS (β-blockers, ACE inhibitors).

• In the treatment of ACS, various methods of nitrate administration are used; sublingual and inhalation are used at the prehospital and early hospital stages; intravenously - with persistent ischemia, left ventricular failure or uncontrolled hypertension; orally and transdermally - for the prevention of ischemia after relative stabilization of coronary blood flow.

• It is advisable to start the intravenous administration of nitrates in the near future after admission of a patient with ACS, the duration of continuous infusion is 24-48 hours, then the risk of tolerance increases significantly.

• Control of action during the intravenous administration of nitrates is carried out by the method of assessing hemodynamic effects: the degree of decrease in blood pressure and increase in heart rate

• To prevent the absorption of nitroglycerin on the walls of the infusion system, when it is administered intravenously, it is advisable to use only glass bottles and connecting tubes made of polyethylene or polypropylene (but not polyvinyl chloride or polyurethane). Otherwise, the loss of nitroglycerin must be compensated for by increasing the dose.

• Nitrates should be withdrawn gradually due to the risk of withdrawal syndrome; after the termination of intravenous administration, it is advisable to transfer the patient to oral forms of

nitrates, observing the dosage regimen necessary for the prevention of tolerance (nitrate interval 10-12 hours).

For intravenous administration, nitroglycerin is diluted in isotonic sodium chloride solution or in 5% glucose solution to a concentration of 100 μg / ml (20 ml of a 0.1% nitroglycerin solution per 200 ml of the total solution volume). The effective dose (5-200 micrograms per minute, usually 40-100 micrograms per minute) depends on the individual sensitivity of the patient. The initial rate of intravenous infusion is 10-20 micrograms per minute (2-4 drops per minute), if necessary, increase the dose by 10-20 micrograms per minute every 3-5 minutes until a clinical effect or side effects occur. A decrease in blood pressure by 10-20% of the initial level is considered an indicator of the hemodynamic effect of nitrates. Nitroglycerin is administered intravenously for 24 to 48 hours, and after 24 hours of continuous administration of nitroglycerin, an increase in the rate of infusion may be necessary due to the development of tolerance. After the end of intravenous administration, they switch to taking long-acting nitrates.

Especially shown is the intravenous administration of nitroglycerin in the complication of myocardial infarction with acute heart failure. The use of nitroglycerin reduces mortality from myocardial infarction by 35% in the first week and gives a good effect in the next few months.

Intravenous administration of isosorbide dinitrate is carried out according to the same indications and similar rules as nitroglycerin. The effective dose (33-200 mcg / min) depends on the individual sensitivity of the patient. The initial rate of intravenous infusion is 15-20 micrograms per minute (3-4 drops per minute), if necessary, increase the dose by 10-15 micrograms per minute (2-3 drops) every 5-15 minutes to a level of 200 micrograms per minute (40 drops in minutes). Effective dose criteria are the same as for nitroglycerin.

β-blockers

β-adrenergic blockers help reduce pain, limit the size of the focus of necrosis, reduce the risk of developing severe arrhythmias. Early treatment of BAB in patients with myocardial infarction reduces the overall mortality over 7 days by 14%, the frequency of reinfarction by 18%, and the frequency of cardiac arrest (ventricular fibrillation) by 15%. The greatest decrease in mortality is observed in the first 48 hours of the disease (an average of 25%), which indicates the importance of the appointment of β-blockers in the first day of heart attack. It was found that the restriction of the necrosis zone in myocardial infarction is achieved only by β-adrenergic blockers without BCMA, regardless of cardioselectivity, but there is no convincing evidence that a particular β-blocker is more effective than another.

Principles of the use of β-blockers in ACS - β-blockers should be prescribed as soon as possible to all patients with ACS in the absence of contraindications.

If there are contraindications to the use of β-blockers in the acute period of ACS, they can be prescribed later, with stabilization of the condition (compensation of heart failure, elimination of hypotension and bradycardia, effective pacemaking).

With relative contraindications to the use of β-blockers and a high risk of side effects, it is better to start treatment with small doses of short-acting cardioselective agents (metoprolol 12.5 mg orally or 2.5 mg intravenously; esmolol 25 μg / kg per min) rather than completely abandoning β-adrenergic blockers.

Intravenous administration of β-blockers followed by oral administration is advisable in patients with arterial hypertension or tachyarrhythmias, as well as in patients with ongoing ischemic pain and in high-risk individuals with ACS without ST segment elevation; for other patients, drugs are prescribed orally. The target dose of β-blockers should provide a reduction in heart rate at

rest to 50-60 beats / min, with intravenous administration, continuous monitoring of the ECG, frequent monitoring of blood pressure and auscultation of the lungs are necessary.

An important clinical criterion for the effectiveness of the treatment of BAB is a decrease in heart rate at rest to 55-60 beats / min. Achieving the indicated heart rate values is considered as the goal of therapy, since the risk of reinfarction and death increases in parallel with an increase in heart rate, and an adequate reduction in heart rate (regardless of thrombolytic therapy) improves the prognosis.

β-adrenergic blockers are not prescribed or their intravenous administration is stopped if the heart rate drops below 50 beats / min, the systolic pressure is below 100 mmHg. Art., PQ interval exceeds 0.22 s. The use of these drugs against the background of acute heart failure, bradycardia and atrioventricular block (without an implanted pacemaker), bronchospasm is undesirable.

Calcium channel blockers - Calcium channel blockers reduce the slow transmembrane influx of calcium into the cell from the extracellular space, which reduces contractility of the myocardium and vascular smooth muscle. Some BCCs also inhibit the automatism of the sinus node and slow down AV conduction. All drugs of this class cause the expansion of the coronary arteries. Thus, the anti-ischemic action of calcium channel blockers includes:

- improvement of coronary blood flow due to the elimination of coronary spasm (dynamic stenosis of the coronary arteries);

- reduction of myocardial oxygen demand by reducing postload (peripheral vasodilation) and inhibition of myocardial contractility, as well as by reducing heart rate (some representatives).

Despite the high clinical efficacy, calcium channel blockers have not yet proven their ability to positively influence the prognosis of ACS, and some of them (short-acting nifedipine) can worsen treatment outcomes. However, the accumulated data is too small for final conclusions about the place of this pharmacological class in the treatment of ACS, especially since the effectiveness of second-generation CCBs has not yet been studied.

Principles of use of calcium channel blockers in the treatment of ACS

Calcium channel blockers are not first-line anti-ischemic agents in the treatment of ACS due to the lack of a reliable effect on the prognosis. Their main purpose is to alleviate the symptoms.

Drugs that slow down the rhythm (verapamil or diltiazem) are prescribed for persistent ischemia or for heart rate control for atrial fibrillation-flutter, if BAB are ineffective or contraindicated (bronchial asthma, variant angina pectoris, vasospasm with cocaine intoxication).

Dihydropyridine calcium channel blockers are used only in combination with BAB, as a reserve in case of treatment failure; nifedipine in a short-acting dosage form for ACS is contraindicated due to sympathetic activation, tachycardia and possible hypotension.

Calcium channel blockers are contraindicated in patients with significant systolic dysfunction of the left ventricle, with chronic heart failure, with impaired AV conduct; their use is possible in individuals with mild systolic LV dysfunction in a hospital setting.

In the course of treatment with calcium channel phenylalkylamine blockers, a decrease in heart rate of less than 50-60 beats / min, pauses and hypotension (BP <90/60 mm Hg) should not be allowed. When prescribing dihydropyridine preparations, one should be wary of developing hypotension and reflex tachycardia.

Verapamil and diltiazem are contraindicated in cases of heart rate less than 50 beats / min, AD- less than 90/50 mmHg. Art., SA- and AV-blockade II-III Art. (without implanted pacemaker), WPW syndrome, digitalis, severe heart failure (Killip grade 2-4), bleeding, shock.

Analgesics

To stop the pain syndrome with myocardial infarction, opioid analgesics are used.

Morphine, which has a sufficient analgesic and sedative effect, slightly dilates the veins, reduces venous return to the heart, preload and, therefore, the need for myocardium in oxygen. However, morphine reduces A / D and, due to vagotonic action, causes bradycardia, atrioventricular block, especially in patients with inferior myocardial infarction. In addition, the drug inhibits the respiratory center, causes nausea, vomiting, constipation. But the beneficial effect - pain relief - prevails over these side effects. Morphine is administered intravenously in a dose of 2-4 mg (0.2-0.4 ml of a 1% solution) with severe pain. In the future, it is possible to re-introduce 2-4 mg of the drug until the pain is stopped or side effects appear. Complete pain relief when using the drug, as a rule, can be achieved in 15-30% of cases, incomplete - in 40-60%. In addition to morphine, other opioid analgesics (promedol, fentanyl, omnopon, pentazocine) can also be used.

When using morphine, hypotension may occur (can be eliminated in a horizontal position or with the introduction of a 0.9% NaCl solution), bradycardia (decreased by intravenous administration of 0.5-1.0 mg of atropine), nausea and vomiting (stopped by the intravenous use of 5-10 mg of metoclopramide) respiratory depression (relieved by intravenous administration of 0.1-0.2 mg naloxone).

Tramadol (tramal), which acts on opiate receptors (mu, delta and kappa), has greater safety and much lower narcogenic potential, compared with classical opioid analgesics. In myocardial infarction, the average doses of tramadol, giving sufficient pain relief in 58.8% of cases, are about 1.4 mg / kg.

In case of opioid analgesic inefficiency and in the absence of hypotension in the patient, neuroleptanalgesia (NLA) can be used: intravenous administration of 1-2 ml of a 0.005% solution of opioid analgesic fentanyl and 2-4 ml of a 0.25% solution of the antipsychotic droperidol.

Ataralgesia (AA) is the combined use of opioid analgesics and benzodiazepine tranquilizers (for example, 2 ml of a 0.005% solution of fentanyl and 2 ml of a 0.5% solution of diazepam (Sibazon, Seduxen, Relium)). At the same time, unlike NLA, ataralgesia is characterized by less respiratory and hemodynamic disturbances. Diazepam, which is part of AA, does not have a direct effect on the myocardium, but it is able to reduce OPSS for a short time, which leads to a certain decrease in blood pressure and cardiac output.

If the effect of opioid analgesics, NLA, or AA is insufficient, anesthesia should be performed using controlled anesthesia with nitrous oxide. The analgesic effect of nitrous oxide occurs at a concentration of 35-45 vol.%, And loss of consciousness is observed at a concentration of 60-80 vol.% (But not in all patients).

The purpose of the lesson.

1. To learn:

I. Etiopathogenetic factors of coronary heart disease.

II. pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of drugs used in coronary heart disease:

1. Antianginal drugs.

I. Means that reduce myocardial oxygen demand:

• Nitrates -

 Nitroglycerin and its depot preparations: (Nitroglycerin. Nitro-Mac Trinitrolong Nit-Ret Nitrong Sustak Nitroderm Sustonit).

 Isosorbide dinitrate (Nitrosorbide Iso-Mac).

 Isosorbide mononitrate (Monizole, Mono-Mac).

• Sidnoniminy. Molsidomin.

• β-blockers and mixed blockers.

1. β-blockers

 Non-selective (β1, β2) without internal sympathomimetic activity - Propranolol (Anaprilin), Timolol (Blockadren), Nadolol (Korgard).

 Non-selective (β1, β2) with internal sympathomimetic activity - Pindolol (Wisken) Oksprenolol (Trazikor) Penbutolol (Betapressin) Bopindolol (Sandonorm)

 Selective (β1) without internal sympathomimetic activity - Talalinol (Cordan) Bisoprolol (Concor) • Metoprolol tartrate (Egilok) • Metoprolol succinate (Betalok ZOK) • Atenolol (Tenormin) • Betaxolol (Lokren) • Esmolol (Bres) .

 Selective (β1) with internal sympathomimetic activity - Acebutolol (Sectral).

 Selective (β1) with vasodilating action - Nebivolol (No-ticket) Busindolol Celiprolol (Selectol).

2. Mixed adrenergic blockers (β, α1) - Labetalol (Trandate) Carvedilol (Di-Latrend).

• Slow calcium channel blockers.

 dihydropyridine - amlodipine (norvask), nifedipine, nifedi-pin retard - long-acting (adalat), isradipine (lomir), lacidipine (lacipil), nislodipine (siskor), felodipine, nitrendipine (bypass res);

 non-dihydropyridine - verapamil, diltiazem, mibefradil (position-cor);

• Selective If-Inhibitors - Ivabradine.

II. Means that improve the delivery of oxygen to the myocardium:

 Calcium channel blockers (dihydropyridine derivatives).

 Myotropic action - phosphodiesterase inhibitors (papaverine, no-spa, aminophylline, carbocromene / intencordin /); adenosine deaminase inhibitors (dipyridamole / curantyl /, etc.).

2. Antithrombotic agents (antiplatelet agents, anticoagulants, fibrinolytics).

 Antiaggregants.

1. Cyclooxygenase Inhibitors (COX) Acetylsalicylic acid (Aspirin).

2. Blockers of ADP (P2Y12) receptors (thienopyridines): Ticlopidine (Tic-lead) Clopidogrel (Plaviks) Prasugrel.

3. GP IIb / IIIa receptor blockers -

 Monoclonal antibodies: Abciximab (Reo-Pro) Monafram (Framon).

 Cyclic peptides: Eptifibatide (Integrilin).

 Non-peptide blockers - Tirofiban (Agrostat) Orbofiban Ksemi-lofiban Lamifiban Sibrafiban.

4. Phosphodiesterase (PDE) blockers and adenosine potentiators: Dipyridamole (Curantyl).

 Anticoagulants:

1. Direct action.

 Unfractionated heparin: Heparin.

 Low molecular weight heparins: Dalteparin (Fragmin) Nadropaprine (Fraxiparin) Certoparin (Sandoparin) Tinzaparin (Logiparin) Enoxaparin (Clexane).

 Heparinoids (parenteral Xa factor inhibitors): Fondapari-nuks (Arikstra) Idraparinux.

 Oral Xa factor inhibitors: Rivaroxaban (Xarelto) Apik Saban.

 Hirudin and hirudinoids: Hirudin (Lepirudin) Bivalirudin (Angio-max, Angioks).

2. Indirect action.

 Coumarin derivatives: Monocoumarins (Warfarin (Coumadin), Fen-procumon (Markumar), Acenokumarol (Sinkumar).

 Dicumarins: Bishydroxycumarol (Dicumarin), Ethylbiscum acetate (Neodicumarin).

 Indandion derivatives: Phenindione (Phenylinum), • Difenadion (Dipaksin).

 Fibrinolytics -

- direct (fibrinolysin),

- indirect.

 I generation: Urokinase (Urokidan), Streptokinase (Strepto-lyase).

 II generation: Acetylated plasminogen-streptokinase activator complex (Anistreplase, APSAK), Alteplase (Actilize), Prourokinase (Purorolase).

 III generation (mutant): Tenecteplase (Metalysis), Rete-plaza (Rapilizin).

3. Means that improve the metabolism of the heart muscle.

a) antihypoxants - trimetazidine / preductal /, mildronate, ATP-long, phosphaden, neoton, ascorbic acid, riboflavin, nicotinic acid, etc .;

b) antioxidants - tocopherol, dibunol, essentiale, etc .;

c) anabolic - steroid (retabolil, nerobol), non-steroid (r-boxin / inosine /, potassium orotate);

d) normalizing the exchange of electrolytes - panangin / aspark /.

4. Preparations of other groups (analgesics).

5. ACE inhibitors Ramipril (Tritace) Perindopril (Prestrium).

6. Hypolipidemic agents.

2. Know:

 The main pathogenetic mechanisms that are the object of drug exposure in coronary heart disease:

 Nitrate. Mechanisms of action. Pharmacodynamics, pharmacokinetics. Undesirable effects. Comparative characteristics of nitrates. Other nitrovasodilators.

 Features of application. Calcium channel blockers. Mechanisms of antianginal action. Undesirable effects. Contraindications to the appointment.

 Beta blockers. Comparative characteristics. Advantages and disadvantages.

 Means of myotropic action and agents that increase myocardial resistance to hypoxia. Undesirable effects. The concept of the "stealing" syndrome.

 Combined therapy of ischemic heart disease. The use of antiplatelet agents (acetylsalicylic acid, ticlopidine, dipyridamole). Prospects for the search for new highly effective antianginal agents.

 Principles of complex therapy of myocardial infarction:

 elimination of pain - narcotic analgesics;

 prevention and treatment of thrombosis - anticoagulants, fibrinolytics and antiplatelet agents;

 elimination of fear, emotional arousal - antipsychotics, tranquilizers;

 elimination of rhythm disturbances - antiarrhythmic;

 limitation of necrosis - nitrates;

 elimination of electrolyte balance and acid-base balance disturbances - sodium bicarbonate, panangin, etc .;

 fight against hypotension - adrenergic agonists, blood substitutes;

 prevention of vomiting - antipsychotics.

3. Be able to:

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

b) prescribe combination therapy;

c) justify and provide urgent differentiated medical and mental care with:

 angina attack

 with myocardial infarction.

Control questions of the studied topic.

3. List the clinical and pharmacological principles of drug selection and selection in coronary insufficiency.

4. What principles are the basis for the classification of antianginal drugs?

5. Explain the antianginal effect of nitroglycerin, approaches to the selection of a single dose and frequency of administration of the drug.

6. What are the undesirable effects of nitroglycerin and therapeutic measures when they occur.

7. Explain the antianginal effect of beta-blockers, approaches to the selection of a single dose and frequency of administration of the drug.

8. Explain the antianginal effect of slow calcium channel blockers, approaches to choosing a single dose and frequency of taking the drug.

9. Explain the antianginal effect of anticoagulants, approaches to choosing a single dose and frequency of taking the drug.

10. Explain the antianginal effect of antiplatelet agents, approaches to the selection of a single dose and frequency of administration of the drug.

Control of the intermediate level of knowledge.

The solution of situational problems.

1. In a man, 65 years old, suffering from coronary artery disease, stable angina pectoris III functional class, extrasystolic arrhythmia, CH I - there were strong, burning nature of the pain behind the sternum, suffocation, loss of consciousness. Objectively, the general condition is severe. The skin is pale, covered with copious cold sweat, pronounced acrocyanosis. Pulse -140 beats per 1 minute as atrial tachyarrhythmia, small AKD - 70/40 mm Hg. Art. Heart sounds are deaf. Anuria On the ECG - monophasic curve in leads III, AUR, \ / 4 - V 6

Formulate a diagnosis, emergency treatment program. Justify the choice of drugs

2. A man, 48 years old, is concerned about the compressive nature of the pain behind the sternum, arising when walking on flat terrain after 500 - 800 m, when climbing to the 2nd-3rd floor, after nervous stress. These attacks are noted within 3 months. I resorted to sublingual administration of nitroglycerin, but refused further use, as it caused a severe headache Objectively hypersthenic increased nutrition Pulse - 76 beats per 1 min, rhythmic, periodically extrasystoles - 2 - 4 per 1 min, AKD - 136/84 mmHg Art. Left ventricular hypertrophy. Weak accent II tone and systolic murmur over the aorta. On the ECG, signs of myocardial hypoxia in the anterior septum of the left ventricle. The doctor prescribed the following treatment of isodinite (20 mg) in 1 tablet. 3 times a day finoptin (80 mg), 1 tablet. 3 times a day and anaprilin (40 mg), 0.5 tab. 3 times a day

Formulate a diagnosis. Evaluate the correctness of the recommended treatment.

3. A patient, 62 years old, was hospitalized with complaints of severe pain behind the sternum, which lasts 1 hour and does not stop with nitroglycerin. It suffers from angina pectoris, before the attack stopped with nitrates. There are no concomitant diseases. Objectively: cyanosis of the lips. Heart sounds are deaf, rhythmic activity. ECG: acute phase of transmural infarction of the anterior wall of the left ventricle. Your actions.

4. A man, 62 years old, was hospitalized in an intensive care unit with a prolonged attack of chest pain that cannot be stopped with nitroglycerin. Objectively: HELL - 80/60 mm RT. Art., heart rate - 106 in 1 min, BH - 22 in 1 min. During auscultation, heart sounds are deaf, gallop rhythm. What explains the decrease in blood pressure?

5. A man, 60 years old, complains of angina attacks while walking, climbing to the second floor. For many years, ischemic heart disease. Objectively in the lungs vesicular respiration, BH - 18 per min. Heart sounds are muffled. Heart rate - coincides with the value of the pulse and is 90 in 1 min, blood pressure - 140/70 mm RT. Art., pastic shanks. ECG: left ventricular hypertrophy.

Formulate a diagnosis. Make a treatment plan.

6.A man, 52 years old, complains of angina attacks that occur when walking at a distance of 500 meters, interruptions in the work of the heart. Sick for about a year. Objectively: BH 16 in 1 min. The borders of the heart are shifted 1 cm to the left, the tones are muffled, heart rate is 84 in 1 min, single extrasystoles, pulse is 78 in min, blood pressure is 150/70 mm Hg. Art.
Formulate a diagnosis. Make a treatment plan. What drugs are indicated to improve long-term prognosis?
7. In a man, 47 years old, in the early morning there are attacks of angina pectoris. During Holter monitoring, an arched ST segment upward movement in the chest leads is recorded at this time, which persists for 15 minutes. Objectively: heart sounds are muffled, heart rate - 64 per minute, blood pressure - 140/80 mm RT. Art.
Formulate a diagnosis. What drug should be prescribed?
8. The patient, 48 years old, is concerned about the compressive pain in the region of the heart and behind the chest, which occurs when walking to a distance of 150-200 m and climbing to the 2nd floor and disappears at rest. Pulse and heart rate constantly 50-52 in 1 min, blood pressure - 120/70 mm RT. Art. On the ECG, the sinus rhythm is correct. On bicycle ergometry - ischemic changes on the ECG with a voltage power of 40 watts. What drug should be prescribed to the patient in the first place?
9. The patient, 62 years old, felt severe pain behind the sternum, shortness of breath. Objectively: the patient is pale, wet, acrocyanosis. BH - 28 in 1 min, orthopnea. HELL - 100/60 mm RT. Art. In the lungs, wet rales on both sides. On the ECG: heart rate - 240 rpm, tooth P is not determined, R-R are the same and make 0.25 s, QRS - 0.18 s, in leads V5 - V6 the arc-shaped depression of the ST segment is up to 3 mm.
Formulate a diagnosis. Suggest the most effective management tactics for this patient.
10. A patient, 50 years old, complains of intolerable pains behind the sternum, which appeared 5 minutes ago. The pain appears 1-2 times a month, more often between the 5th and 6th hours of the morning, lasts 15-20 minutes. Feels healthy throughout the day. Objectively: pulse - 78 beats per 1 min, blood pressure - 120/80 mm RT. Art. The boundaries of the heart are not changed. Rhythmic tones. On the ECG recorded at rest and after exercise, no changes were detected. At night, during the attack, a short-term increase in the S-T segment in leads I, aVL, V2-V6 was recorded.
Which drug should be prescribed

TESTS
1. A 57-year-old patient suffered a myocardial infarction. For the prevention of repeated coronary circulatory disorders, you will recommend:
A. Nitrong + panangin.
B. * Bisoprolol + aspecard.
C. Isoket + retabolil.
D. Anaprilin + verapamil.
E. Nifedipine + Nicospan.
2. Specify a drug that does not have selectivity for beta-adrenergic receptors:

A. Atenolol.
B. Metoprolol.
C. Bisoprolol.
D. Betaxolol.
E. * Propranolol.

3. For the treatment of Prinzmetal angina pectoris:
A. Beta-blockers.
B. Nitrates.
C. * Calcium channel blockers.
D. Antiplatelet agents.
E. Vitamins.

4. During treatment of stable angina pectoris with a combination of antianginal drugs, the patient complained of headache, tinnitus, dizziness. Which group of drugs can cause these side effects?
A. Calcium channel blockers.
B. Beta-blockers.
C. Anticoagulants.
D. * Nitrates.
E. Antiaggregants.

5. During physical exertion, the patient experienced contractive chest pain, accompanied by stiffness and a sense of fear. What can be recommended for stopping a sore throat?
A. Nifedipine.
B. * Nitroglycerin.
S. Anaprilin.
D. Verapamil.
E. Diltiazem.

6. Acetylsalicylic acid is used in coronary heart disease as an antiplatelet agent. Indicate the daily dose of the drug:
A. 500 mg.
B. 3000 mg.
S. * 100 mg.
D. 2000 mg.
E. 1000 mg.

7. What is the basis for the medical test with isadrine in the diagnosis of coronary heart disease:
A. * The occurrence of tachycardia.
B. Redistribution of coronary blood flow.
C. The occurrence of bradycardia.
D. Coronary spasm.
E. Reduced venous return of blood.

8. Indicate the route of administration of nitroglycerin for the relief of anginal attack:
A. Intramuscularly.
B. Subcutaneously.
C. Intravenously.
D. * Sublingual.
E. Rectally.

9. A 49-year-old patient with coronary heart disease and a duodenal ulcer needs a history of prescribing an antiplatelet agent. Which drug do you choose?
A. Aspirin cardio.
V. Curantil.
S. Aspecard.
D. * Plavix.
E. Warfarin.

10. A patient in the intensive care unit is given nitroglycerin intravenously as an antianginal therapy. What safety criterion for the use of the drug do you know?

A. * Decreased blood pressure.
B. Bradycardia.
C. Increased blood pressure.
D. Atrioventricular block.
E. Extrasystole.

11. After applying nitroglycerin to stop an attack of angina pectoris, the effect occurs through:

A. 45 minutes.
B. 15 minutes.
S. * 1 minute.
D. 30 minutes.
E. 60 minutes.

12. The mechanism of anti-aggregation action of aspirin is associated with:

A. Increased cyclooxygenase activity.
B. Inhibition of prostacyclin synthesis.
C. Normalization of adenosine synthesis.
D. Stimulating the synthesis of prostaglandin E.
E. * Inhibition of thromboxane A2 synthesis.

13. Chest pains disturb the patient when walking up to 200 m, climbing stairs to the 2nd floor. State of emergency and heart rate - 55-60 in 1 minute, blood pressure - 130/75 mm Hg. ECG - unchanged. What drug should treatment begin with?

A. Digoxin.
B. Propranolol.
S. * Diltiazem.
D. Riboxin.
E. Verapamil.

14. When a patient arrived in the cardiopulmonary resuscitation department with acute myocardial infarction, increasing shortness of breath, chest pain, dry cough, BH - 28-30 in 1 minute, heart rate - 125 in 1 minute, blood pressure - 90/70 mm Hg . Heart sounds are weakened, in the lower parts of the lungs are small bubbling rales. What drug should be used first?

A. Strofantin.
B. * Morphine.
S. Heparin.
D. Eufillin.
E. Digoxin.

15. A 52-year-old patient has acute transmural myocardial infarction. Which drug is the least indicated?

A. * Nifedipine.
V. Morphine.
S. Fentanyl.
D. Nitrosorbide.
E. Anaprilina.

16. A 62-year-old man suffers from coronary heart disease. Attacks of stenocardia occur when walking fast, climbing to the 2nd floor. Objectively: BH - 18 in 1 minute, PE - 94 in 1 minute, BP - 140/70 mm Hg, left ventricular hypertrophy. The most appropriate is the appointment:

A. Nitrosorbide.
B. * Metoprolol.
S. Nifedipine.
D. Cordarona.
E. Riboxin.

17. Given the leading mechanism of pathophysiological and pathological changes in acute myocardial infarction, make the choice of the most reasonable drug:

A. Nifedipine.
B. Nitrosorbide.
C. * Streptokinase.
D. Aspecard.
E. Verapamil.

18. An examination in the gastroenterological department of a 42-year-old patient revealed an increase in cholesterol, triglycerides, beta-lipoproteins. From the anamnesis it is known that his father died of coronary heart disease at the age of 51 years. What drug should be prescribed for the primary prevention of coronary heart disease?

A. Gemfibrozil.
B. Lipostabil.
C. Cholestyramine.
D. Nicotinic acid.
E. * Atorvastatin.

19. A 56-year-old patient suffers from coronary heart disease, stable angina pectoris voltage 2 f. within 1 year. Objectively: state of emergency - 100-110 in 1 minute, intense, arrhythmic, blood pressure - 170/100 mm Hg What drug is needed for long-term therapy?

A. Hypothiazide.
V. Kapoten.
S. Adelfan.
D. * Metoprolol.
E. Nitrosorbide.

20. If you are intolerant of nitrates for the relief of anginal attack, you can use:

A. Nifedipina.
B. * Molsidomina.
S. Analgin.
D. Verapamil.
E. Baralgina.

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.

13. 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
TRAINING AND RESEARCH WORK OF A STUDENT (UIRS): ANALYSIS OF PHARMACODYNAMICS OF MEDICINES.
CURATION OF PATIENTS. ANALYSIS OF PHARMACOTHERAPY, WORK WITH MEDICAL DOCUMENTATION.
CLINICAL AND PHARMACEUTICAL ANALYSIS

Relevance of the topic.

One of the most important tasks in practice is the reasonable appointment of an effective and safe treatment. It is important to choose the right drugs taking into account the individual characteristics of the patient, his condition and the nature of the course of the disease, to take into account the possibility of the interaction of some drugs with others, and to minimize side effects / reactions.

When studying this topic, students get the opportunity to creatively interpret the process of pharmacotherapy of various diseases and apply knowledge of the main indicators of the clinical and pharmacological characteristics of drugs for the implementation of a high-quality medical process.

Motivational characteristic of the topic.

Practical activity is composed of two interrelated sections: diagnosis and therapy, in particular pharmacotherapy. It is the correctly established diagnosis that is the quintessence of the idea of the painful process in a particular patient and makes it possible to formulate drug treatment. If the first part of the treatment work is completed by writing the rationale for the clinical

diagnosis, then the second part is the rationale for pharmacotherapy. The doctor does not set legal and moral responsibility for the results of the activity. Treating a patient is an art. Professional pharmacotherapy is always rational, it is adapted to a specific patient. In it, the criteria of sufficiency and protection of the patient from harmful consequences are thought out. It takes into account the features of the age periods, stages and physiological state of the female body, effects on the reproduction function, and others. A dangerous consequence of non-professional pharmacotherapy is polyprogrammy. When healing a patient with drugs, the doctor must take care of the "ecological purity" of his body at the moment and in the future. This practical lesson is called to help to solve a circle of these problems.

The purpose of the lesson:

1. To learn scientifically based approaches to the rational choice of drugs for a particular patient, methods of objective control of the effectiveness of their use.
2. Know:

a) methods of clinical, laboratory and instrumental examination, allowing to assess the patient's condition and its dynamics;

b) the principles of the choice of pharmacotherapy, control of its effectiveness and safety; unified algorithm.

3. Be able to:

a) identify the main symptoms of the disease and give them an assessment of the dynamics of treatment;

b) prescribe the necessary drugs, given their main pharmacodynamic effects, pharmacokinetics and side effects;

c) identify criteria for efficiency and safety;

d) prescribe and evaluate combination pharmacotherapy.

The task for self-checking the initial level.

1. Set out a unified algorithm for choosing pharmacotherapy, monitoring its effectiveness and safety.
2. Give an analysis of the main provisions of the pharmacodynamics of drugs:

- mechanism of action;
- pharmacological effects.

3. Describe the clinical relevance of the pharmacokinetics sections of drugs during pharmacotherapy.
4. Describe the pharmacodynamic, pharmacokinetic, pharmaceutical, physico-chemical effects of drugs.
5. Define the undesirable effects of drugs and indicate the methods of their prevention.
6. Describe methods for monitoring the effectiveness and safety of drugs.
7. Describe the main provisions of the pharmacogenetics of drugs.
8. Explain the importance of chronopharmacology for the implementation of effective and safe pharmacotherapy.
9. Define and state the negative effects of polyprograms.

Enumeration of practical work.

A. Homework.

1. To master the unified pharmacotherapy algorithm. To get acquainted with the basic principles of the choice of pharmacotherapy, control of its effectiveness and safety, given the following information about the patient:

a) age;

b) body weight;

c) clinical diagnosis (underlying disease, complications, concomitant diseases);

d) the limitation of the underlying disease;

e) the severity of the underlying disease;

f) previous pharmacotherapy of the underlying disease, its effectiveness;

g) the functional state of the gastrointestinal tract (GIT) and the main eliminating drugs of organs: kidneys, liver;
h) the presence of an allergic constitution and drug allergies.
2. Learn to prescribe pharmacotherapy, guided by the following plan:
a) get acquainted with the necessary information about the patient, listed in paragraph 1;
b) select drugs indicated for this disease (syndrome), taking into account:
- etiology and pathogenesis of the disease (syndrome);
- the mechanism of action of drugs.
c) narrow the circle of selected drugs by excluding:
- drugs contraindicated in connection with age-related immaturity or pathology of eliminating organs;
- drugs whose activity is insufficient taking into account the severity of the course of the disease;
- drugs that poorly penetrate the tissues of the affected organ;
- drugs to which allergic reactions have been noted in the past;
- drugs with high antigenicity (penicillins, protein preparations, etc.) - in the presence of allergic reactivity;
- highly toxic drugs;
- Drugs used in the treatment of this disease and proved to be ineffective (subject to an adequate regimen for their use).
d) finally select 1-2 drugs, based on their cost and degree of deficiency;
d) choose the route of administration of drugs, taking into account:
- the severity of the disease;
- localization of the lesion;
- the functional state of the digestive tract;
- age of the patient.
f) select the dose of the drug and the frequency of its use, taking into account:
- age of the patient;
- body weight of the patient;
- pharmacokinetic characteristics of the drug (clearance, half-elimination time);
- the severity of the disease;
- functions of eliminating organs.
g) plan the duration of the main and, if necessary, supportive treatment, taking into account:
- the nature of the disease;
- the severity of the disease;
- the potential hazard of the selected drug.
h) select criteria and terms for evaluating the effectiveness and safety of the therapy taking into account:
- therapeutic effects of drugs;
- the nature and severity of the disease;
- undesirable effects characteristic of the applied drug.
i) to solve the question of the necessity (appropriateness) of the appointment of additional drugs that enhance the therapeutic effect of drugs selected for the treatment of the underlying disease;
j) choose drugs for the treatment of concomitant diseases, taking into account:
- the degree of need for their use in the acute period of the disease;
- the consequences of their pharmacodynamic, pharmacokinetic and pharmaceutical interaction with drugs selected for the treatment of the underlying disease (syndrome).
B. Independent practical work in class.
1. Examine the supervised patient, diagnose the underlying and associated diseases.
2. Outline a treatment plan and prescribe pharmacotherapy.
3. To get acquainted with the data of the medical history and the list of medical appointments.
4. Compare the intended treatment plan with that in the list of medical appointments.
5. Carry out an expert assessment of the list of medical appointments.

6. To make the final choice of complex therapy for the patient.
7. Make a list of clinical and laboratory parameters, the dynamics of which is possible in the treatment process.
8. Make a list of possible side effects of each drug and their combinations.
9. To control the course of the disease and adverse reactions of the drug mono- and combination therapy according to the dynamics of clinical and laboratory parameters.
Control of the intermediate level of knowledge.
Perform the UIRS and fill out the protocol for studying the pharmacodynamics of drugs according to the attached scheme (reflecting the diagnostic and pharmacological criteria for choosing effective and safe drugs). Protection UIRS

TOPIC
CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF HEART GLYCOSIDES AND OTHER CARDIOTONICIANS WITH POSITIVE INOTROPIC EFFECT

Relevance of the topic.
A significant part of non-coronary and coronary diseases of the heart, multiple extracardiac pathology cause, to varying degrees, pronounced violations of the basic functions of the myocardium (automatism, excitability, conduction, contractility, tonicity). Clinically, this finds expression in the development of two syndromes: 1) heart failure (circulatory failure) - acute and chronic; 2) cardiac arrhythmias and conduction. The leading place in drug treatment is occupied by cardiac glycosides (CG) and drugs that normalize rhythm and conduction. A doctor of any clinical specialty should know and be able to use them well in urgent situations (acute heart failure: cardiac asthma, pulmonary edema) and with planned primary and preventive therapy. Despite a significant positive role, hypertension and LSDP cause serious complications (glycosid intoxication, collapse, etc.). Essential is their prevention, previously clinical recognition and treatment.
Motivational characteristic of the topic.
Medicines used to treat acute and chronic heart failure are an extensive group of drugs of different groups. Heart failure accompanies many acute and chronic heart diseases: coronary heart disease, myocarditis, valvular defects, myocardial dystrophy, etc. Today, the management of such patients has changed a lot. Cardiotonics of a non-glycosidic structure and new classes of cardiotropic drugs have appeared, but cardiac glycosides remain the main drugs for the treatment of this pathology.
Cardiac Glycosides
Cardiac glycosides - a group of herbal medicines that provide cardiotonic and antiarrhythmic effects in therapeutic doses
Cardiac glycosides are complex nitrogen-free compounds of plant nature that have a selective effect on the heart, which is realized mainly through a pronounced cardiotonic effect.
Preparations of this group have a certain advantage:
- they increase the efficiency of the myocardium, providing the most economical and, at the same time, effective activity of the heart.
As a result, the use of these agents for the treatment of patients with heart failure of various etiologies is justified.
Plants containing cardiac glycosides (about 400 in total) include, first of all, different types of digitalis. This plant got its name because of flowers that are similar to a thimble. There are a lot of digitalis containing heart glycosides, but the chemical structure of 13 cardiac glycosides from 37 digitalis species has been studied to date.

In medical practice, the most widely used preparations of cardiac glycosides obtained from the following plants of this genus:
- Digitalis purpurea (red), Digitalis purpurea.
Cardiac glycoside - digitoxin.
- Digitalis woolly, Digitalis lanata. Cardiac glycoside preparations - digoxin, celanide (isolanide, lantoside).
In addition, cardiac glycosides can be obtained from other plants:
- from the seeds of the African perennial creeper, Strophanthus gratus and Strophanthus Kombe) receive strophanthin (-G or -K, respectively);
- from the lily of the valley in May (Convallaria majalis), the preparation korglikon containing convallazide and convallatoxin is obtained;
- preparations of spring (Adonis vernalis) are obtained (adoniside, adonis grass), which include the sum of glycosides (cinarin, adoni-toxin, etc.)
The history of the discovery of cardiac glycosides is associated with the name of the English botanist, physiologist and practitioner Withering, who first described the use of digitalis for the treatment of patients with edema.
Botkin called digitalis grass "one of the most valuable medicines available to a doctor."
In 1865, E.P. Pelican first described the action of strophanthus on the heart. In 1983, N. A. Bubnov first drew the attention of doctors to spring adonis.
Currently, chemically pure, cardiac glycoside preparations isolated from plants are most often used.
All cardiac glycosides are chemically related to each other: these are complex organic compounds, the molecule of which consists of a non-sugar part (aglycon or genin) and sugars (glycon). The basis of aglycon is the steroid cyclopentaneperhydrophenanthrene structure, which is associated in most glycosides with an unsaturated lactone ring. Glycon (the sugar part of the molecule of cardiac glycosides) can be represented by different sugars: D-digitoxose, D-glucose, D-cymarose, L-rhamnose, etc. The number of sugars in the molecule varies from one to four.
The carrier of the characteristic cardiotonic action of cardiac glucosides is the steroid skeleton of aglycon (genin), and the lactone ring plays the role of a prosthetic group (non-protein part of complex protein molecules).
Although the sugar residue (glycon) does not have a specific cardiotonic effect, the solubility of cardiac glycosides, their permeability through the cell membrane, the affinity for plasma and tissue proteins, as well as the degree of activity and toxicity, depend on it. However, only a whole molecule of cardiac glycosides causes a clear cardiotropic effect.
Some cardiac glycosides may have the same aglycon, but residues of different sugars; others are the same sugar, but different aglycones; individual cardiac glycosides differ from others both in the sugar part and in the aglycon.
A similar structure (cyclopentaneperhydrophenanthrene) has some compounds that make up the poisons of toads, snakes (in Asian countries, the skins of these animals have long been used for medicinal purposes).
When choosing a cardiac glycoside for therapeutic use, not only its activity is important, but also the speed of the onset of the effect, as well as the duration of action, which, to a large extent, depends on the physico-chemical properties of the glycoside, as well as the methods of its administration.
According to their physicochemical properties, cardiac glycosides are divided into two groups: polar and nonpolar. Belonging to one or another group of cardiac glycosides is determined by the number of polar (ketone and alcohol) groups contained in the aglycon molecule.
1. Polar glycosides (strophanthin, korglikon, konvallatoksin) contain from four to five such groups.
2. Relatively polar (digoxin, celanide) - 2-3 groups.
3. Nonpolar (digitoxin) - not more than one group.

The more polar the molecule of cardiac glycosides, the greater its solubility in water, and the less its solubility in lipids. In other words, polar glycosides (hydrophilic), the main representatives of which are strophanthin and korglikon, are slightly soluble in lipids, and therefore poorly absorbed from the digestive tract. This determines the parenteral (intravenous) route of administration of polar glycosides.

Excretion of polar glycosides is performed by the kidneys (hydrophilic), in connection with which, in violation of the excretory function of the kidneys, their dose (to avoid cumulation) should be reduced.

Non-polar cardiac glycosides are readily soluble in lipids (lipophilins); they are well absorbed in the intestine, quickly bind to plasma proteins, mainly with albumin. The main representative of non-polar glycosides is digitoxin. The main amount of absorbed digitoxin enters the liver and is excreted in the bile, then absorbed again. Therefore, the half-life of non-polar glycosides (e.g., digitoxin) is on average 5 days, and the effect stops completely after 14-21 days. Nonpolar glycosides are given orally, and if it is not possible to administer per os (vomiting), they can be given rectally (suppositories).

Relatively polar cardiac glycosides (digoxin, isolanide) occupy an intermediate position. Therefore, these drugs can be administered both per os and intravenously, which is practiced

The mechanism of therapeutic action of cardiac glycosides (pharmaco-dynamics of cardiac glycosides)

Almost all cardiac glycosides have four main pharmacological effects:

I. Systolic action of cardiac glycosides.

The clinical and hemodynamic effect of cardiac glycosides is determined by their primary cardiotonic effect and lies in the fact that under the influence of cardiac glycosides, systole becomes stronger, more powerful, more energetic, and shorter. Cardiac glycosides, enhancing the contraction of a weakened heart, lead to an increase in stroke volume. At the same time, they do not increase myocardial oxygen consumption, do not deplete it, and even increase energy resources in it. Thus, cardiac glycosides increase the efficiency of the heart. This effect is called a positive inotropic effect (inos - fiber). The biochemical molecular mechanisms of action of cardiac glycosides are associated with their complex effect on the bioenergy of the myocardium (myocardiocyte). Cardiac glycosides are able to connect with special receptors both in the myocardium and in other tissues, in particular the brain. In the myocardium, such a receptor for cardiac glycosides is membrane sodium-potassium ATPase. By connecting to the receptor and inhibiting this enzyme, cardiac glycosides alter the conformation of the protein and phospholipid parts of both the outer membrane of cardiomyocytes and the sarcoplasmic reticulum membrane. This facilitates the flow of calcium ions from the extracellular medium and promotes the release of ionized calcium from intracellular deposition sites (sarcoplasmic reticulum, mitochondria). As a result, cardiac glycosides increase the concentration of biologically active calcium ions in the cytoplasm of myocardiocytes. Calcium ions eliminate the inhibitory effect of modulating proteins - tropomyosin and troponin, promote the interaction of actin and myosin, activate the myosin ATPase, which breaks down ATP. The energy needed to contract the myocardium is generated. In addition, in the mechanism of positive inotropic action of cardiac glycosides, it is likely that they increase the function of myocardial adrenergic structures. On the ECG, a positive inotropic effect is manifested by an increase in voltage, shortening of the QRS interval.

II. Diastolic effect of cardiac glycosides.

This effect is manifested by the fact that when cardiac glycosides are administered to patients with heart failure, a reduction in heart contractions is noted, that is, a negative chronotropic effect is recorded. The mechanism of the diastolic effect is multifaceted, but the main thing is that it is the result of a positive inotropic effect: under the influence of increased cardiac output, the baroreceptors of the aortic arch and carotid artery are more excited. Impulses from these receptors enter the center of the vagus nerve, the activity of which increases. As a result, the heart rate slows down.

Thus, when using therapeutic doses of cardiac glycosides, increased systematic contractions of the myocardium are replaced by sufficient periods of "rest" (diastole), which contribute to the restoration of energy in cardiomyocytes. Elongation of diastole creates favorable conditions for rest, blood supply, which is carried out only during the period of diastole, and nutrition of the myocardium, for a more complete restoration of its energy resources (ATP, creatine phosphate, glycogen). On the ECG, diastole lengthening will be manifested by an increase in the PP interval.

In general, the action of cardiac glycosides can be characterized by the phrase: diastole becomes longer.

The mechanism of diastolic action of cardiac glycosides is associated with the removal of calcium ions from the cytoplasm using the "calcium pump" (calcium-magnesium - ATPase) into the sarcoplasmic reticulum and the removal of sodium and calcium ions outside the cell via the exchange mechanism in its membrane.

III. Negative dromotropic effect.

The next effect of cardiac glycosides is associated with a direct inhibitory effect on the cardiac conduction system and a tonic effect on the vagus nerve.

As a result, conduction of excitation along the myocardial conduction system slows down. This is the so-called negative dromotropic effect (dromos - running).

Conductivity slows down throughout the entire conducting system, but it is most pronounced at the level of the AV node.

As a result of this effect, the refractory period of the AV node and the sinus node lengthens. In toxic doses, cardiac glycosides cause atrial - ventricular block. On the ECG, a slowdown in the excitation will be affected by a prolongation of the PR interval.

IV. Negative batmotropic effect.

In therapeutic doses, cardiac glycosides lower the excitability of pacemakers of the sinus node (negative batmotropic effect), which is mainly associated with the activity of the vagus nerve. Toxic doses of drugs of this group, on the contrary, increase myocardial excitability (positive batmotropic effect), which leads to the appearance of additional (heterotopic) foci of excitation in the myocardium and to extrasystole.

It should be remembered that under the action of cardiac glycosides, each calcium ion is exchanged for two sodium ions, the latter, due to the potassium-sodium pump, are exchanged for potassium ions. Cardiac glycosides increase the calcium content in the cytosol, but also lead to an increase in cytosolic sodium and to a decrease in potassium, which causes an electrically unstable state of myocardiocytes.

A healthy person under the influence of therapeutic doses of cardiac glycosides will not have the described changes (due to compensatory reactions). These effects are manifested only in conditions of cardiac decompensation, which can occur against the background of valvular defects, atherosclerotic lesions, intoxication, physical exertion, myocardial infarction, etc. In these conditions, cardiovascular insufficiency occurs. Under the influence of cardiac glycosides in these conditions, an increase in the force of contractions of the heart and its minute volume of blood improves hemodynamics throughout the body and eliminates the consequences of its disorders in patients with heart failure:

- first of all, venous congestion decreases, which contributes to the resorption of edema;
- impaired functions of internal organs (liver, gastrointestinal tract, kidneys, etc.) are restored;
- there is an increase in diuresis as a result of a decrease in reabsorption of sodium and potassium loss in urine;
- the volume of circulating blood decreases.

As a result, the working conditions of the heart are facilitated. Improving blood supply to the lungs increases gas exchange. Oxygen delivery to tissues is improved, tissue hypoxia and metabolic acidosis are eliminated. All this leads to the disappearance of the patient cyanosis, shortness of breath, to the normalization of blood pressure, sleep, processes of inhibition and excitation in the central nervous system.

Cardiac glycosides are cardiotonic agents. Their action must be distinguished from pacemakers (for example, adrenergic agonists), under the influence of which on the ECG amplification and increase in heart rate will be recorded. Against the background of cardiac glycosides, with an increase in heart contractions, a decrease in the latter is noted.

Pharmacokinetics of cardiac glycosides

The less polar the glycoside molecule, the better it dissolves in lipids and is absorbed from the digestive tract and vice versa. Therefore:

- strophanthin is practically not absorbed from the intestine;
- digoxin and celanide are absorbed by 30%;
- digitoxin - is absorbed 100%. Differences in the intensity of absorption of cardiac glycosides from the gastrointestinal tract determine the choice of the route of administration of these drugs into the body:
- polar cardiac glycosides are administered only parenterally;
- non-polar cardiac glycosides are prescribed by mouth;
- relatively polar - enteral and parenteral.

In plasma, drugs of this group can be bound to albumin or circulate in a free state. Polar glycosides are practically not bound to plasma proteins, while non-polar glycosides are almost entirely bound to them (digitoxin, for example, binds to proteins by 97%).

A bound glycoside fraction does not enter the tissue, but its value may be lower than usual with a decrease in the protein content in blood plasma (liver, kidney disease), in the presence of endogenous (free fatty acids) or exogenous (butadione, sulfonamides, etc.) in the blood .

Polar cardiac glycosides do not penetrate into the connective tissue, therefore, the concentration of strophanthin and digoxin in the blood is increased in obese people, as well as in older people (the maintenance dose should be much lower).

The free fraction of cardiac glycosides enters almost all tissues, but especially the myocardium, liver, kidneys, skeletal muscles, and the brain. Especially intensively accumulate drugs in the myocardium. The main focus of the action of cardiac glycosides is explained by the high sensitivity of the heart tissues to this group of drugs.

The cardiotropic effect occurs after the creation of the necessary concentrations of cardiac glycosides in the myocardium. The rate of development of the effect depends both on the ease of penetration of active substances through cell membranes, and on binding to blood plasma proteins. The effect of strophanthin develops 5-10 minutes after administration, digoxin - after 30-40 minutes (with intravenous administration). After oral administration, the effect of digoxin is observed after 1, 5 -2 hours, and di-histoxine - after 1-1.5 hours. The more and more strongly cardiac glycosides bind to proteins (digitoxin is especially strong, strophanthin and conval-lyatoxin are very easy), the longer their action lasts

The duration of the effect of drugs of this group is also determined by the speed of their elimination. Polar glycosides are excreted mainly by the kidneys unchanged, and non-polar ones undergo biotransformation in the liver.

During the day, not the entire dose of cardiac glycoside is eliminated from the body:

- strophanthin and konvallatoksina - 45-60%;
- digoxin and celanide - 30-33%;
- digitoxin (at the beginning of treatment) - 7-9%.

Most of the administered dose (different volume for different glycosides) remains in the body, which is the reason for their cumulation-accumulation in the body during repeated injections. Moreover, the longer cardiac glycosides act, the more significant is the cumulation (material cumulation, that is, the accumulation of cardiac glycoside itself in the body). The most pronounced cumulation was observed with the use of digitoxin, which is associated with slowly proceeding processes of inactivation and excretion of digitoxin from the body (half-life is 160 hours). Approximately 7/8 of the administered dose of strophanthin is excreted in the first 24 hours, therefore, with its use, cumulation is not pronounced.

Cardiac glycosides in the gastrointestinal tract are associated with absorbent, astringent, antacid agents. The maximum bioavailability is observed with reduced gastrointestinal motility, and with hyperacid conditions and swelling of the mucous membranes, a decrease in drug absorption occurs.

Indications for use:

1. As an ambulance in acute heart failure. To this end, it is best to prescribe intravenously rapidly acting glycosides (stro-phantin, korglikon, etc.)
2. In chronic heart failure. In this case, it is more expedient to prescribe long-acting glycosides (digitoxin, digoxin).
3. Cardiac glycosides are prescribed for certain types of atrial (supraventricular) rhythm disturbances (as a second choice for supraventricular tachycardia, ciliary and paroxysmal tachycardia, as well as for atrial flutter). In this case, the effect of cardiac glycosides on the conducting system is used, as a result, the speed of conducting the pulse through the AV node is reduced.
4. For prophylactic purposes, cardiac glycosides are used in the stage of compensation in patients with heart disease before the upcoming extensive surgery, before childbirth, etc.

PHARMACOLOGICAL CHARACTERISTICS OF HEART GLYCOSIDES

Each of the drugs of the group of cardiac glycosides has certain differences. This applies to activity, the rate of development of the effect, its duration, as well as the pharmacokinetics of the drug.

In medicine, drugs from different types of digitalis are used: digitalis purpurea (Digitalis purpurea), digitalis woolly (Digitalis lanata), digitalis rusty (Digitalis ferruginea).

DIGITOXIN (Digitoxinum; tablets of 0, 0001 and rectal suppositories of 0, 15 mg) is a glycoside obtained from various species of digitalis (D. purpurea, D. lanata). White crystalline powder, practically insoluble in water. When taken orally, it is absorbed almost completely. In the blood, the drug is 97% bound to plasma proteins. Unlike other cardiac glycosides, the connection with proteins in digitoxin is the strongest. In this regard, the drug does not begin to act immediately. After taking the digitoxin tablet, the cardiotropic effect begins to appear after two hours and reaches a maximum after 4-6-12 hours. In our country, digital-syn is available only in tablets and in suppositories; abroad, this drug also exists in the form of a solution for injection.

In the liver, digitoxin undergoes biotransformation. As a result, up to 24 different metabolites are formed, including 7 active ones. Eliminates the drug very slowly - about 8-10% during the day, therefore it has a huge ability to cumulate. This is due to the slow processes of inactivation and removal of the drug from the body (half-life is 160 hours). Therefore, the pronounced effect of the drug is observed within 1-3 days, and the duration of the therapeutic effect after cessation of the maintenance dose is 14-21 days. It is the slowest and longest acting cardiac glycoside.

Indications for use:

1. In chronic heart failure, especially with a tendency to tachycardia, but against the background of intravenous administration of strophanthin!
2. Digitoxin can be prescribed to prevent the development of heart failure in patients with compensated heart defects before the upcoming planned extensive surgery, childbirth.

When prescribing digitoxin, like all cardiac glycosides, one must remember the possibility of interaction of drugs of this group with other agents. At the same time, a number of agents (phenobarbital, antiepileptic drugs, butadion), being inducers of microsomal liver enzymes, can reduce the therapeutic effect of digitoxin. Rifampicin, isoniazid, ethambutol also act.

Quinidine, NSAIDs, sulfonamides, indirect anticoagulants (as a result of displacement of glycosides from the connection with plasma proteins) contribute to increasing the effectiveness of cardiac glycosides.

In practice, not only highly purified preparations of cardiac glycosides are used, but also galenic and neogalenic preparations (powders, infusions, tinctures, extracts) from plants containing glycosides. Thus, the use of powder from the leaves of digitalis purpurea or large-flowered.

When determining the activity of medicinal raw materials and many preparations of cardiac glycosides, biological standardization is used. Most often, the activity of cardiac glycosides is expressed in frog units of action (ICE) and feline units of action (CED). One ICE corresponds to the minimum dose of a standard preparation in which it causes cardiac arrest in most experimental frogs, cats, and pigeons. So, the crushed powder of the leaves of digitalis in activity corresponds to the following proportion: one gram of the powder of the leaves is 50-66 ICE or 10-13 CED. During storage, the activity of the leaves decreases. One gram of digitoxin is equal to about 5000 CED.

The main glycoside of woolly digitalis (D. lanata) is DIGOKSIN (Digoxinum; tab. 0, 25 mg, amp. 1 ml of 0, 025% solution, Gideon Richter, Hungary). By its effect on blood circulation, the drug is close to other cardiac glycosides, but it also has its own pharmacological features:

1. The drug is weaker than digitoxin binds to plasma proteins. Being a relatively polar cardiac glycoside, it is 10-30% (on average, 25%) associated with blood albumin;
2. When ingested, digoxin is absorbed in the intestines by 50-80%. This drug has a shorter latency than digitoxin. When taken orally, it is 1, 5-2 hours, with intravenous administration - 5-30 minutes. The maximum effect develops when taken orally after 6-8 hours, and when administered intravenously - after 1-5 hours. By the speed of the effect, especially with intravenous administration, the drug approaches strophanthin.
3. Compared with digitoxin, digoxin is more rapidly excreted from the body (elimination half-life is 34-46 hours) and has less ability to cumulate in the body. Complete elimination from the body is observed after 2-7 days.

Indications for use:

1. Chronic heart failure (pills).
2. Prevention of heart failure in patients with compensated heart defects during extensive surgical interventions, childbirth, etc. (in tablets).
3. Acute heart failure (the drug is administered intravenously).
4. Tachyarrhythmic form of atrial fibrillation, paroxysmal atrial fibrillation, paroxysmal supraventricular tachycardia (tablets).

In general, digoxin is a drug of medium speed and medium duration of action.

CELANID (synonym: isolanide) is a drug very similar to digoxin, also obtained from the leaves of digitalis woolly. Celanide is produced in tablets of 0, 00025 and ampoules of 1 ml of a 0.02% solution. The activity of one gram of the drug is 3200-3800 KED. There are no fundamental differences.

STROFANTIN (Strophanthinum; ampoules of 1 ml of 0, 025% solution) - polar cardiac glycoside obtained from seeds of tropical vines (Strophanthus gratus; Strophanthus Kombe).

Strofantin is practically not absorbed from the gastrointestinal tract (2-5%) and is prescribed only intravenously. The drug practically does not bind to proteins. The cardiotonic effect develops after 5-7-10 minutes and reaches a maximum after 30-90 minutes. The drug is excreted by the kidneys, the half-life is 21-22 hours, and complete elimination is noted after 1-3 days.

Strofantin is the fastest, but also the shortest-acting cardiac glycoside.

The severity of the systolic action of strophanthin is much more significant than its diastolic effect. The drug has relatively little effect on the heart rate and on the conductivity of the bundle of His. Almost does not cumulate.

Indications for use:

1. Acute heart failure, including with some forms of myocardial infarction;
2. Severe forms of chronic heart failure (II-III degree).

Strofantin is prescribed at 0, 5-1, 0 ml intravenously, very slowly (5-6 minutes) or drip, previously diluted in 10-20 ml of isotonic solution. With the rapid introduction of a high probability of shock. The drug is usually administered once a day.

From domestic raw materials, namely from the leaves of lily of the valley, the preparation KORGLIKON (Corglyconum; ampoules of 1 ml of 0.06% solution) containing the amount of glycosides is obtained.

Korglikon is very close to strophanthin, but inferior to the last speed of action. Inactivation of korglikon is somewhat slower, therefore, in comparison with strophanthin, it has a longer effect, as well as a more pronounced vagal effect. The drug is prescribed for:
- acute and chronic heart failure II and III degrees;
- with cardiac decompensation with a tachysystolic form of atrial fibrillation;
- for stopping attacks of paroxysmal tachycardia.

The above preparations of cardiac glycosides with parenteral use must be administered intravenously, as they have a sharp irritating effect. Accumulated glycoside solutions (strophanthin, korglikon, digoxin) should be diluted in an isotonic solution of sodium chloride or glucose, but only 5% (not 40%). The use of concentrated glucose solutions (20-40%) is not advisable, since they can partially inactivate glycosides even before administration to the patient. These concentrated solutions can have a damaging effect on the vascular endothelium, contribute to their thrombosis, increase the osmotic pressure of the plasma, and impede the flow of drugs into the tissues. Slow administration is mandatory as indicated in the recipe.

HORIZONTAN PREPARATIONS Spring adonis herb (Herba Adonis Vernalis) is a Montenegrin or Adonis spring. Active ingredients of adonis are glycosides, the main of which are CINARIN and ADONITOXIN.

By the nature of the action, adonis glycosides are close to digitalis glycosides, however, they are less active in systolic influence, have a less pronounced diastolic effect, less affect the vagus tone, are less resistant in the body, act briefly and do not cumulate. Well absorbed in the intestines. Campion preparations have one distinctive effect - they have a calming effect on the central nervous system.

Indications for use:

1. The mildest forms of chronic heart failure.
2. Emotional instability, cardioneurosis, vegetative dystonia, lung neurosis (as sedatives).

Preparations of adonis are usually available in the form of galenic and novogalenovye, are part of the mixture (for example, adoniside in the composition of ankylosing spondylitis).

PRINCIPLES OF APPOINTMENT OF HEART GLYCOSIDES

Cardiac glycosides cannot be prescribed spontaneously. This is a special section of the treatment of patients. Cumulation of the drug can lead to intoxication with cardiac glycosides. Thus, for the treatment of patients with chronic heart failure, cardiac glycosides are used in doses that ensure the creation of a stable therapeutic concentration of the drug in the blood.

Moreover, in the first phase of treatment ("saturating") in a particular patient, compensation of cardiac activity is achieved. For this, at the beginning of treatment, a dose is prescribed that allows to achieve the maximum therapeutic effect (saturation dose, loading dose or full dose of digitalization). Upon reaching the saturation dose, they proceed to the second phase of treatment (“supportive”), when cardiac glycoside preparations are prescribed in small doses sufficient to maintain the achieved compensation. For some patients, the maintenance phase can be very long, sometimes lifelong. In the first phase of treatment, the drug can be administered parenterally or orally, and in the second - orally. The saturation dose for digitoxin is 0, 8 - 1, 2 mg, that is, to achieve a saturation dose, it is necessary to prescribe from 8 to 12 tablets.

The maintenance dose compensates for the amount of the drug that is being eliminated. The maintenance dose is calculated according to certain formulas. For digitoxin, the maintenance dose is 0.05-0, 1 mg / day, that is, it is necessary to prescribe a whole tablet or half of it per day.

According to WHO, there are three main methods of digitalization (reaching a saturation dose):

1. Fast digitalization.

With this method, treatment is prescribed with a saturation dose, which is reached quickly, during the first 24-36 hours. This method is rarely used, only in a hospital, since there is a danger of an overdose of the drug. Fast digitalization is used in patients with severe acute cardiac insufficiency with great care, since they have a reduced tolerance to cardiac glycosides, so the drug is easy to overdose (strophanthin is prescribed in 1/4 of the ampoule volume every hour intravenously slowly).

2. Moderately fast digitalization. This method involves the use of medium doses with an effect in 2-5-7 days. The drug is prescribed fractionally, gradually selecting a dose. This method is used most often.
3. Slow digitalization.
With this method, treatment of the patient begins with small doses of cardiac glycosides, almost equal to the maintenance dose. This method can also be used on an outpatient basis.
Fast digitalization should be carried out in a hospital, controlling possible toxic effects, slow - with outpatient treatment.
The maintenance dose (PD) of drugs can be calculated by the formula:
PD = ND. % elimination.
It should be borne in mind that the excretion of digoxin is carried out mainly by the kidneys, therefore, in case of renal failure, the dose should be reduced by at least half. Since the excretion of digoxin is directly proportional to the level of glomerular filtration, and therefore to creatinine clearance (Clcr.), The maintenance dose (mg / day) can be calculated as follows:
PD = ND. (14 + Clcr. / 5)
Creatinine clearance can not always be quickly determined, therefore, the dose is usually calculated by the level of creatinine (K) in plasma (mg%):
for men, PD = ND. (11.6 + 20 / K),
for women, PD = ND. (12.6 + 16 / K).
There are various nomograms for calculating ND and PD depending on body weight, kidney function, the acceptable level of risk of adverse reactions.
Interaction of cardiac glycosides with other drugs.
The inotropic effect of cardiac glycosides is enhanced by adrenergic agonists (isoprenaline, norepinephrine, adrenaline), and the arrhythmogenic effect is eliminated by anti-arrhythmic drugs I (quinidine, procainamide) and II (lidocaine, phenytoin) groups.
Interaction with other drugs leads to a weakening of the main effect of cardiac glycosides or to an increase in their toxic effect:
 decrease in the absorption of cardiac glycosides is caused by antacids (increased motility of the gastrointestinal tract) and lipid-lowering drugs (cholera-styramin);
 increased absorption is observed under the action of anticholinergics that weaken intestinal motility (atropine);
 bradycardia increases while taking b-blockers, reserpine, quinidine, verapamil;
 atrial ventricular conduction slows to a greater extent under the action of b-blockers, quinidine and other antiarrhythmic drugs of group I;
 enhancement of arrhythmogenic properties is possible when interacting with diuretics, b-adrenergic agonists, reserpine, clonidine, calcium antagonists.

TOXIC ACTION OF HEART GLYCOSIDES

Cardiac glycosides are potentially some of the most toxic drugs. They have an exceptionally small therapeutic index - the toxic dose is 50-60% of the therapeutic. Every fourth patient taking cardiac glycoside preparations has symptoms of poisoning. The reasons for this may be:
1) low therapeutic index;
2) non-compliance with existing principles for the use of cardiac glycosides; 3) combination with other drugs:
- when cardiac glycosides are used in conjunction with diuretics, potassium loss occurs, which contributes to hypokalemia, which significantly reduces the excitability threshold of cardiomyocytes, and as a result there is a violation of the heart rhythm (extrasystole);
- the combined use of drugs of cardiac glycosides with glucocorticoids also leads to a loss of potassium with a corresponding violation of the rhythm of heart contractions;
4) severe damage to the liver and kidneys (places of biotransformation and excretion of glycosides);
5) individual high sensitivity of the patient to cardiac glycosides, especially with myocardial infarction.

The mechanism of development of intoxication with cardiac glycosides consists in the fact that toxic concentrations of cardiac glycosides, significantly reducing the activity of membrane ATPase, disrupt the function of the potassium-sodium pump. Inhibition of the enzyme leads to:
a) to a violation of the return of potassium ions to the cell, as well as to the accumulation of sodium ions in it, which contributes to an increase in the excitability of the cell and the development of arrhythmias;
b) to increase the input and disrupt the release of calcium ions, which is realized by hypo-diastole, leading to a decrease in cardiac output.
Symptoms of intoxication are divided into:
I. Cardiac intoxication symptoms:
1. Bradycardia.
2. Atrioventricular blockade (partial, full, transverse).
3. Extrasystole.
II. Extracardiac (extracardial) symptoms of intoxication:
1. From the digestive tract: decreased appetite, nausea, vomiting, abdominal pain. These are the earliest symptoms of intoxication from the gastrointestinal tract.
2. Neurological symptoms (it is associated with excessive bradycardia that occurs with an overdose of cardiac glycosides): adynamia, dizziness, weakness, headache, confusion, aphasia, impaired color sensation, hallucinations, "trembling of objects" when viewed, falling visual acuity.

HELP MEASURES FOR INTOXICATION WITH HEART GLYCOSIDES

1. Immediately discontinue cardiac glycoside preparations with the simultaneous administration of activated carbon, gastric lavage, and salt laxatives should also be prescribed.
2. Temporarily discontinue drug combinations. If the patient's condition is severe, use antiarrhythmic drugs. In a hospital, you can prescribe (4-5%) a solution of potassium chloride, intravenously, drip, under the supervision of an ECG.
3. Assign diphenin to the patient - a drug that stimulates microsomal liver enzymes and has a good antiarrhythmic effect. Currently, it is one of the best drugs for ventricular tachycardia due to digitalis intoxication. Lidocaine (xicain) is less effective for cardiac glycoside intoxication than diphenin. Sometimes, in order to combat intoxication with cardiac glycosides, beta-adrenoblockers (for example, anaprilin) are used. You can also prescribe unitiol, which is a donor of sulfhydryl groups, solutions of Trilon B, which binds ionized calcium, as well as specific antibodies to cardiac glycosides. The latter, in the form of commercial preparations (fragments of monoclonal antibodies to cardiac glycosides), are, in fact, antidotes.

PREVENTION OF INTOXICATION BY HEART GLYCOSIDES

1. Compliance with the principles of the appointment of cardiac glycosides and individualization of treatment of the patient.
2. A rational combination of cardiac glycosides with other drugs.
3. Constant ECG monitoring (lengthening of the PQ interval, the appearance of arrhythmias).
4. A diet rich in potassium (dried apricots, raisins, bananas, baked potatoes); the appointment of potassium preparations: PANANGIN (potassium asparaginate in combination with magnesium as paraginate),

CONTRAINDICATIONS FOR THE USE OF HEART GLYCOSIDES

There are absolute and relative contraindications to the use of cardiac glycosides. An absolute contraindication is intoxication with cardiac glycosides. Relative contraindications are:
1) extrasystole;
2) atrioventricular blockade;
3) hypokalemia;
4) ventricular paroxysmal tachycardia. Sometimes a positive inotropic effect can determine contraindications to the prescription of cardiac glycoside preparations - subaortic and isolated mitral stenosis with sinus rhythm.

NON-GLYCOSIDE (NESTEROID) NONADRENERGIC SYNTHETIC CARDIOTONICS

Due to the high toxicity of cardiac glycosides, a search was carried out for synthetic cardiotonic agents with a greater breadth of action, effectiveness in different types of heart failure, and the presence of other positive qualities. Thus, a number of drugs have been created that satisfy these conditions - AMRINON and MILRINON.
Mechanisms of action:
- inhibition of phosphodiesterase;
- an increase in the concentration of cAMP;
- activation of protein kinases;
- increased intake of calcium ions in the cell; - stimulation of muscle contraction.
The first synthetic cardiotonic drug of the non-steroidal structure AMRINON (Amrinone; amp. 20 ml of a solution containing 100 mg of active substance). The drug has a positive inotropic effect, a vasodilating effect, increases cardiac output, reduces pressure in the pulmonary artery system, and reduces peripheral vascular resistance. Indication for use:
- only for short-term therapy of acute congestive heart failure (in the intensive care unit under hemodynamic control).
Side effects: decreased blood pressure, tachycardia, supraventricular and ventricular arrhythmia, thrombocytopenia, impaired renal and hepatic function.
The drug MILRINON is similar in structure and action. It is more active than amrinone and, apparently, does not cause thrombocytopenia.
The purpose of the lesson:
I To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of drugs that affect the basic functions of the myocardium:
a) cardiac glycosides:
A) long-acting glycosides with pronounced cumulative properties - digitalis purpurea preparations (digitoxin, gitalen, cordigid);
B) glycosides of medium duration and medium cumulative effect - preparations of digitalis woolly (digoxin, celanide, lantoside), gori-spring (adoniside), oleander (neriolin);
C) glycosides characterized by quick and short action with insignificant cumulative properties - preparations of strophanthus (strophanthin), preparations of May lily of the valley (corglycon, tincture of lily of the valley), sea onion (co-relborin), etc.
Note: Glycosides of long and medium duration of action are conditionally called “digitalis group” (according to the classification of groups A and B); glycosides of the strophanthus, May lily of the valley, sea onions, etc. - by the "group of strophanthus" (according to classification group B).
Pharmacodynamics of cardiac glycosides. The mechanisms of cardiotonic action of cardiac glycosides. ECG changes.
therapeutic phase:
a) positive inotropic effect - shortening and strengthening of systole;
b) a positive tonotropic effect - an increase in myocardial tone;
c) negative chronotropic effect - a decrease in the frequency of heart contractions;
toxic phase:
d) negative dromotropic effect - a decrease in the conductivity of the myocardium;
e) positive batmotropic effect - increased excitability of the myocardium.
2. Hemodynamic changes under the influence of cardiac glycosides.
3. The most important concomitant effects of various cardiac glycosides (effect on the central nervous system, water-salt metabolism, etc.).
4. Pharmacokinetics of cardiac glycosides.
5. Comparative characteristics of various preparations of cardiac glycosides.
6. Indications and contraindications for the appointment of cardiac glycosides.
7. Principles of digitalization (phases of saturation and maintenance). Efficiency criteria.
8. Intoxication with cardiac glycosides. Treatment (potassium preparations, anti-arrhythmic, complex-forming and donors of sulfhydryl groups).

9. Non-glycosidic cardiotonics. Classification:
 phosphodiesterase inhibitors - amrinone, milrinone;
 sympathomimetic agents - dopamine, dobutamine, etc .;
 metabolic preparations - glucagon, riboxin, neoton, glutamic acid, etc .;
 different - sulmazole, springrinone, levosimendan.
10. Mechanisms of action. Indications and contraindications. Undesirable effects.
II. Know the main pathogenetic mechanisms that are the object of drug exposure in: acute (cardiac asthma, pulmonary edema) and chronic heart failure :.
III .. Be able to:
a) select and select for a specific patient the necessary drugs;
b) identify criteria for therapeutic efficacy and safety of the drugs used; acute (cardiac asthma, pulmonary edema) and chronic heart failure:
Control questions of the studied topic.
1. What are the indications and contraindications (absolute and relative) to the use of SG.
2. List the main groups of the most active and sufficiently studied SH. Give them a clinical and pharmacological characterization.
1. Give examples of classifications of SG and give them a clinical assessment.
2. Describe the cardiac effects of hypertension and give them a clinical assessment.
3. Non-cardinal effects of hypertension, their clinical significance
7. List the provisions that must be followed when choosing SG.
4. The concept and clinical significance of the therapeutic and toxic phases of the action of SG.
5. Dosing tactics of hypertension: principles of initial digitalization and maintenance therapy.
8. Clinical and electrocardiographic indicators of the therapeutic level of digitalization.
6. Symptoms and the mechanism of development of the toxic effect of SG. ECG changes in the toxic phase of action.
7. Features of the action of SG when combining them with anesthetic, antianginal, hypotensive, hypertensive, antiarrhythmic, diuretic, anticoagulants, anti-inflammatory drugs.
8. Treatment of SG intoxication (emergency assistance).
9. Urgent relief from cardiac asthma.
10. Urgent help with pulmonary edema.
Enumeration of practical work.
The solution of situational problems.
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 stand-up 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?
2. A patient, 65 years old, complains of shortness of breath at rest, an irregular heartbeat, swelling on the legs, an increase in the abdomen, heaviness in the right hypochondrium, daily diuresis - 0.6 l. In the anamnesis: suffered a large-focal myocardial infarction 5 years ago. Periodically, attacks of angina pectoris after a nervous load, ascent to the II floor. Shortness of breath and swelling on the legs for the past 2 years. I periodically took digoxin (1 t. 2 times a day, 5 days a week) "courses" for 2 months with a 1-month break (on the recommendation of the local therapist). The true deterioration occurred 3 weeks ago and is progressing. Objectively: general state of moderate severity, orthopnea. Lip cyanosis, acrocyanosis, neck vein swelling, pulse - 118 beats. at 1 min, arrhythmic as atrial fibrillation. Heart rate - 144 in 1 min. AKD - 120/90 mm RT. Art. Hypertrophy of both ventricles. Accent II tone over the pulmonary artery, systolic murmur over the aorta. BH - 26 in 1 min. Breathing is hard, in the lower lateral parts are small bubbling rales. The tongue is dry. The abdomen is round in shape, free fluid in the lateral

sections is determined. The liver protrudes 12 cm from under the edge of the costal arch along the right midclavicular line, dense, smooth, painful. Swelling of the legs, lumbosacral spine. ECG - atrial fibrillation, tachysystolic form (heart rate - 156 in 1 min), hypertrophy of both ventricles. Cicatricial changes in the myocardium in the posterolateral part of the left ventricle.
Formulate a clinical diagnosis. Justify the choice of SG, its dose, rate of saturation in the period of initial digitalization. Indicate the clinical and electrocardiographic criteria for the effectiveness of this stage of glycosidotherapy.
Justify the choice, dosage (daily, weekly) of SG in the period of maintenance therapy. What are the criteria for the prevention of SG intoxication, which the patient will use at the request of the doctor.
4. The doctor on call is called to the department of pregnancy pathology to the patient, 27 years old. Diagnosis: 35 weeks pregnancy. Rheumatism of the inactive phase, mitral stenosis. Complains of asthma attacks, cannot lie. In the lungs, harsh breathing, in the lower sections, moist, non-ringing rales. No swelling.
What is your diagnosis? Your urgent appointments?
5. The patient, 52 years old, developed an attack of cardiac asthma. When examining the pulse of 78 beats. in 1 min, rhythmic. AKD - 170/100 mm Hg. Art. Heart sounds are muffled. There is an increase in the liver, moderate swelling of the legs. The doctor prescribed intravenous administration of strophanthin.
Evaluate patient management tactics. Make a plan for the correction of patient treatment.
8. 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.

TESTS

1. Cardiac glycoside intoxications contribute to:
   A. Elderly
   B. Late stages of chronic heart failure
   C. Electropulse defibrillation
   D. Hypokalemia and hypomagnesemia
   E. * All of the above factors
2. Contraindication to the appointment of cardiac glycosides is:
   A. Progressive A-B block
   B. Wolf-Parkinson-White Syndrome
   C. Severe bradycardia
   D. Subaortic stenosis
   E. * All of the above factors
4. In acute heart failure for intravenous administration:
A. Strofantin, digitoxin.
B. Celanide, corglycon, adoniside.
C. * Strofantin, Korglikon.
D. Mesatone, digitoxin, strophanthin.
E. Fenoterol, strophanthin, korglikon.
5 .. The mechanism of cardiotonic action of cardiac glycosides is:
   A * Inhibition of Na +, K + - ATPase of myocardiocytes
   B. Suppression of prostaglandin synthesis
   C. Inhibition of the enzyme phospholipase A2
   D. Platelet Activation from Cell Membrane Phospholipids
   E. Accumulation of calcium ions in the cytoplasm of myocardiocytes, which in turn inhibits the excretion of sodium.
6. The main pharmacodynamic effects of cardiac glycosides are:

A. Negative inotropic, chronotropic and positive dromotropic and batmotropic effects
B. Positive batmotropic, inotropic, tonotropic, dromotropic and negative distinct chronotropic effects
C * Positive inotropic, negative dromotropic and chronotropic effects
D. Positive tonotropic, dromotropic, chronotropic effects
E. Negative batmotropic, inotropic, chronotropic and tonotropic effects

7. The choice of cardiac glycoside and the determination of the dosage regimen:
A. * It is carried out individually for each patient
B. It is carried out by the method of increasing doses
C. It is carried out on the basis of ECG indicators
D. Based on ECG and ultrasound
E. It is carried out on the basis of indicators of pulse and blood pressure.

8. Digitalis drugs intoxication develops in:
A. * 0-20% of patients
B. 1-5%
S. 50-60%
D. 70-90%
E. 100%

9. Indications for the appointment of cardiac glycosides are:
A. Ventricular paroxysmal tachycardia
B. Isolated mitral stenosis with sinus rhythm
C. Acute inflammatory and dystrophic changes in the myocardium
D. * Acute and chronic heart failure
E. Coronary heart disease

10. Choose a drug that has the most powerful cardiotonic effect:
A digoxin.
B. * Strofantin
C. Digitoxin
D. Amiodarone
E. Propranolol

11. Choose the correct statement:
A. * Highly polar glycosides are not absorbed in the digestive tract
B. Low-polar glycosides are poorly absorbed in the digestive tract, are not metabolized in liver
C. The choice of the rate of digitalization does not depend on their concentration in the blood
D. High glycoside efficacy observed in acute myocardial infarction
E. Due to the large number of side effects, digitoxin is used only parenteral

12. With concomitant chronic renal failure, the drug of choice is:
A. Korglikon
B. Digoxin
C * Digitoxin
D. Strophanthin
E. Eufillin

13. Among the pharmacological drugs that increase myocardial contractility, the leading place is taken by:
A. Bet1 adrenergic agonists
B. Non-glycoside inotropic drugs
C. * Cardiac glycosides
D. Beta-blockers

E. Nitrates
13. Choose the safest rate of saturation of hypertension for patients:
A. Fast and slow
B. * Medium and slow
C. Fast and medium
D. Fast
E. The rate of saturation is irrelevant
14. Choose the correct statement:
A. * The positive inotropic effect of SG is manifested by an increase in strength and speed myocardial contractions
B. The best effect of the use of hypertension manifests itself in patients with impaired ventricular conduction
C. SG is contraindicated in patients with atrial flutter and atrial fibrillation
D. Digitalization can only be done at a fast pace (during the day)
E. Slow saturation rate is necessary in patients with acute cardiac insufficiency
15. Cardiac glycosides according to the degree of cumulation can be arranged as follows - in decreasing order:
A. Korglikon, strophanthin, digoxin
B. Strofantin, digoxin, korglikon
C. Digoxin, strophanthin, korglikon
D. * Digitoxin, digoxin, strophanthin
E. Digoxin, digitoxin, strophanthin
16. The optimal indications for prescribing cardiac glycosides are as follows:
A. * Permanent tachysystolic form of atrial fibrillation
B. Severe CHF (III - IV functional class NYHA)
C. Emission fraction less than 25%;
D. Cardiothoracic index over 55%;
E. All of the above.
17. The action of cardiac glycosides is manifested:
A. Strengthening systolic contractions of the heart with diastole lengthening
B. Stimulation of the K + pump and the entry of Ca into the cell
C. Increased excitability of the conduction system of the heart
D. * All answers are correct
E. True a) and b)
18. Digoxin:
A. Reduces myocardial excitability
B. * Increases vagus tone
C. Reduces the refractory period of the conductive system
D. Toxicity is reduced by hypercalcemia
E. Metabolized in the heart muscle
19. Typical effects of cardiac glycosides on ECG include:
A. * Extension of the PR interval
B. Extension of QT interval
C. Depression ST
D. Tachycardia
E. Ventricular rhythm disturbances
20. Digoxin can cause the following ECG changes:
A Long QT Interval
B. Shortened RR Interval
C. * AB block of the first degree
D. Strong U waves

E. Effects proportional to treatment effectiveness

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 DIURETIC MEDICINES

Purposeof the topic.

Combined therapy of a number of diseases, syndromes requires the use of diuretic drugs (MLS). Diuretics are used for diseases in the genesis of which there are: hypervolemia, generalized and local edema, impaired renal excretory function, endo- and exogenous intoxications. Since almost all diuretics realize their effect due to the violation of certain mechanisms of salt and water reabsorption in the renal tubules, changes in the osmotic pressure of blood plasma and blood flow in the kidneys, their use is not completely safe for the patient's body and can cause significant disturbances in homeostasis and aggravate the defeat of the renal parenchyma. In this regard, a deep study of the clinical pharmacology of diuretics seems to be extremely important, which allows them to be used with the maximum therapeutic effect and minimal risk of side effects and complications.

Motivational characteristic of the topic.

Diuretics, or diuretics - a group of drugs that are used to regulate the volume or composition of body fluids. They increase the excretion of sodium and water, inhibiting the mechanism of active reabsorption in various sections of the renal tubules.

The object of their activity is edematous syndrome, which has a different pathogenetic structure. Based on the clinical picture, edema is formed when:

- hemodynamic myocardial insufficiency;
- cirrhosis of the liver (portal hypertension);
- glomerulonephritis;
- hemorrhagic nephritis;
- local disturbance of venous outflow;
- violation of the outflow of lymph;
- hormonal disorders (myxedema, hypersecretion of mineralocorticoid);
- allergic conditions, etc.

Diuretic drugs are effective for heart failure syndrome, arterial hypertension, acute and chronic renal failure, poisoning, cystic fibrosis, etc.

Diuretics change the excretion of not only sodium and water, but also potassium, calcium, magnesium, chlorine, phosphates and bicarbonates, which is manifested mainly by undesirable effects during prolonged therapy with these drugs. Diuretics differ in the mechanism and strength of action, the ability to change the acid-base state, in speed of onset and duration of action. They are one of the most commonly used drugs for the treatment of arterial hypertension, as they give an independent antihypertensive effect and enhance the effectiveness of almost all other antihypertensive drugs. The ability of diuretics to reduce pulmonary edema and venous congestion makes them indispensable in the treatment of both acute and chronic heart failure.

Physiological mechanisms of diuresis

Urine formation begins with the production of a protein-free ultrafiltrate of blood plasma. In 1 min, about 120-125 ml of liquid passes through the capillaries of the glomeruli. As a result, only 1 ml of urine is formed, since 99% of the entire filtered fluid is reabsorbed as it moves along the kidney tubules.

The rate of ultrafiltrate formation is determined by the ratio of hydrostatic and oncotic pressure on different sides of the capillary wall, the rate of plasma flow through the glomeruli, and the number of filtering capillaries. Ultrafiltrate in its composition differs from blood plasma in the absence of proteins and fats, i.e. substances whose molecular size is close to the size of the albumin molecules of blood plasma. Drugs bound to plasma proteins also do not pass through the capillary barrier.

In the renal tubules, there is a reverse absorption of water and electrolytes and the final urine is formed. Depending on the mechanisms of reabsorption of electrolytes and water, tubules can be

divided into 4 zones. The first zone, known as the proximal tubule, is highly permeable to water. Here, about 65% of all sodium filtered through the glomeruli is reabsorbed. Sodium and potassium are actively exchanged for oxygen. Accompanying anions for 2/3 consist of chlorides, the rest is bicarbonates. In the second zone (the ascending part of the nephron loop, or the Henle loop), 25% of the filtered sodium is reabsorbed. Ions of chlorine, sodium and potassium are reabsorbed here using active transport mechanisms. This part of the loop is impervious to water and the concentration of sodium and chlorine in the ultrafiltrate gradually decreases. The third zone, or the initial section of the distal convoluted tubules, like the previous one, is impervious to water, but actively passes sodium and chlorine ions, which further reduces the osmotic pressure of the ultrafiltrate. The volume of sodium reabsorption in this zone is about 5% of the total amount of filtered sodium. The fourth zone (the end of the distal tubules and the collecting duct system) is the site of final adjustment of the composition and volume of urine. Here is a further reabsorption of a certain amount of sodium in exchange for potassium and hydrogen. This process is controlled by aldosterone and the concentration of sodium in ultrafiltrate. Any diuretic that reduces sodium reabsorption proximal to the fourth zone will increase its concentration in this zone and stimulate the exchange of sodium to potassium, which leads to an increase in potassium loss in urine. Water reabsorption in this zone is controlled by antidiuretic hormone (ADH). The collecting ducts pass through the medulla of the kidney, the interstitial fluid of which contains a large amount of salts. In the presence of ADH, the collecting ducts become permeable to water, and it, in accordance with the osmotic pressure gradient, leaves the lumen of the ducts, where the salt concentration is lower than in the interstitial tissue of the medulla of the kidney. This process leads to the formation of concentrated urine.

Classification of diuretics

Diuretics are traditionally classified according to various characteristics: chemical characteristics, location, strength and mechanism of action.

Characterization of the main groups of diuretics

Group name	Key representatives	Main a place of action	Actio n power	Action	Chemical characterizati on
Loop diuretics	Furosemide, ethacrine acid, bumetanide, torasemide, peritanide	The ascending part of the nephron loop	Power ful	Inhibitors of sodium, potassium, chlorine transport	Sulfonamide derivatives excluding ethacrylic acid
Thiazide and the like	Hydrochlorothiazide, chlortalidone. clopamide, indapamide	Distal tubule	Mode rate	Sodium and chlorine transport inhibitors	Sulfonamide, thiazide and thiazide
Carbonic anhydrase inhibitors	Acetazolamide (Diacarb)	Proximal tubule	Weak	Carbonic anhydrase inhibitor	Sulfonamide derivative
Potassium-sparing diuretics	Triamteren amiloride	The end of the proximal tubule and collecting ducts	Weak	Kidney Epithelium Sodium Channel Blockers	Sulfanilamide compounds of various structures
Aldosterone receptor	Spironolactone, canrenone,	The final part is proxim. tubules	Weak	Aldosterone receptor blocker	Steroid compound

antagonists	Veroshpiron	and collecting tubes			
Osmotic diuretics	Mannitol, urea, concentrated glucose solutions, glycerin		Power full	Creates high osmotic pressure in the blood and urine	Hexatom alcohol

Loop (powerful) diuretics

Loop (powerful) diuretics - represented by a variety of chemical compounds. All of them, with the exception of ethacrylic acid, have a sulfonamide group in their structure. The drugs act in a thick segment of the ascending part of the nephron loop and have a powerful, but relatively short diuretic effect. Registered: furosemide, bumetanide, pyrethanide, torasemide and ethacrylic acid.

The mechanism of action, pharmacological effects and features of the headlights-macokinetics

Drugs in this group have the ability to block the active transport of sodium. The effect is realized through the inhibition of transport protein, which ensures the transfer of sodium, potassium and chlorine ions through the tubular epithelial cells.

Loop diuretics increase the excretion of not only sodium, but also potassium, chlorine, calcium and magnesium. Sulfanilamide drugs, with the exception of bumetanide and pyretanide, can block carbonic anhydrase and thereby increase the excretion of bicarbonates and phosphates. A single use of loop diuretics causes an increase in urinary acid excretion, and regular intake reduces its excretion. Drugs in this group can increase renal blood flow to varying degrees. Perhaps this effect is mediated by prostacyclin, the synthesis of which diuretics increase. Furosemide and other loop diuretics strongly stimulate the formation of renin, and when the volume of the circulating fluid decreases, they cause reflex activation of the sympathetic nervous system and stimulate the mechanisms of intrarenal baroreception. A compensatory increase in aldosterone synthesis limits further losses of electrolytes and water. An increase in prostacyclin synthesis leads to an expansion of the venous channel and a decrease in filling pressure in the left ventricle. This effect is especially pronounced in furosemide and manifests itself in pulmonary edema even before the diuretic action of drugs begins.

High doses of loop diuretics can block the transport of electrolytes in many tissues, but the electrolyte composition of the endolymph of the inner ear is of clinical importance, which is manifested in ototoxicity.

Loop diuretics are fully absorbed from the gastrointestinal tract. Due to the pronounced binding to plasma proteins, glomerular filtration of drugs is limited. However, due to the presence of an active transport mechanism, they are secreted in sufficient quantities in the proximal tubule and enter the place of their action unchanged.

Indications for use

Edema syndrome caused by sodium retention (chronic heart failure, chronic renal failure - chronic renal failure, nephrotic syndrome, edema and ascites with cirrhosis). The diuretic effect of drugs does not depend on shifts of the acid-base state. Drugs remain effective in conditions of renal failure, even with a decrease in glomerular filtration to 2 ml / min. With daily use, the diuretic effect of powerful diuretics is weakened, which is associated with compensatory activation of renin in response to a decrease in extracellular fluid volume. To preserve the diuretic effect of drugs, it is recommended to use in intermittent mode.

Pulmonary edema - The effect of powerful diuretics in pulmonary edema is due to the rapid expansion of the venous node and a decrease in the volume of intravascular fluid, which leads to a decrease in the filling pressure of the left ventricle and an increase in the efficiency of the heart.

Due to the pronounced but short action, powerful diuretics are not the drugs of choice for long-term treatment of hypertension. However, they can be prescribed for relief of hypertensive crisis or in patients with insufficient hypotensive effect of other diuretics.

Side effects

Most of the side effects of loop diuretics are associated with impaired electrolyte and water balance. Depletion of sodium in the body and a decrease in extracellular fluid volume may be accompanied by arterial hypotension, a decrease in glomerular filtration rate, vascular collapse, thromboembolic complications, and in patients with liver diseases, hepatic encephalopathy. Hypokalemia and hypomagnesemia can be complicated by the development of arrhythmias, especially in patients receiving cardiac glycosides. Hypocalcemia may develop, but it rarely causes seizures.

The rapid intravenous administration of powerful diuretics more often than taking them inside can lead to the development of various hearing impairments and even deafness, which in most cases, but not always, are reversible.

Loop diuretics can cause hyperuricemia and hyperglycemia, which rarely alone can stimulate the development of gout and diabetes.

Long-term use of loop diuretics causes an increase in low-density lipoproteins and triglycerides and a decrease in high-density lipoproteins.

Other side effects include skin rash, photosensitivity, paresthesias, thrombocytopenia, agranulocytosis, and gastrointestinal disturbances.

Interaction. Loop diuretics are able to enter into pharmacodynamic and pharmacokinetic interactions with many drugs.

They enhance the effect of anticoagulants, antihypertensive drugs, other diuretics and non-depolarizing muscle relaxants; increase the risk of side effects of aminoglycosides, cardiac glycosides, excreting potassium diuretics and glucocorticosteroids; increase the concentration of propranolol and lithium in blood plasma; reduce the effects of oral hypolipidemic agents.

The action of the most powerful diuretics can be reduced while using indomethacin and other non-steroidal anti-inflammatory drugs.

Thiazide and thiazide-like diuretics

This group of drugs includes sulfonamide derivatives of benzothiadiazine (hydrochlorothiazide, methiclothiazide) and nontiazide sulfonamides (chlortalidone, clopamide, indapamide). The main site of action of all these drugs is the initial section of the distal convoluted tubule. The proximal section is considered as an additional locus. All diuretics of this group have a moderate diuretic effect. A sufficient duration of the diuretic effect allows you to prescribe drugs 1 r / day.

Thiazide and thiazide-like diuretics can conditionally be divided into two generations. The first generation includes derivatives of benzothiadiazine (hydrochlorothiazide, bendroflumethiazide, polythiazide) and phthalimidine (chlortalidone), the second generation includes derivatives of chlorobenzamide (indapamide, xipamide) and quinazolinone (metolazone). The second generation of thiazide-like diuretics differs from the first generation in that they have a significant sodium and diuretic effect in renal failure.

The mechanism of action and pharmacological effects

Thiazide and thiazide-like diuretics inhibit the transport protein, which ensures the transfer of sodium and chlorine into the cells of the tubular epithelium, as a result of which the reabsorption of these ions in the distal tubules decreases. Some drugs of this group have a weak ability to suppress carbonic anhydrase in the proximal tubule and increase the secretion of bicarbonates and phosphates. An increase in the concentration of sodium in the collecting duct system stimulates its exchange for potassium, which leads to an increase in potassium losses. A single dose of drugs increases, and regular decreases the excretion of uric acid. Thiazide and thiazide-like diuretics cause weak magnesiumuria.

Diuretics of this group do not alter renal blood flow and only variably reduce glomerular filtration rate under certain conditions.

Unlike first-generation thiazide diuretics, indapamide increases the glomerular filtration rate and has an antihypertensive effect in patients with hypertension with both normal and impaired renal function.

The ability of diuretics to reduce vascular resistance and cause a hypotensive effect is associated with the main saluretic effect of these drugs. One of the possible mechanisms for reducing vascular resistance includes a decrease in the concentration of sodium in smooth muscle cells, which can indirectly lead to a decrease in the content of intracellular calcium. As a result, smooth muscle cells become more resistant to spasmodic stimuli. Effective antihypertensive therapy with diuretics is accompanied by a slight decrease in plasma volume and an increase in renin activity.

According to the main mechanism of action, indapamide is a peripheral vasodilator. The following mechanisms of its vasodilating action are supposed:

 blockade of calcium channels;

 stimulation of the synthesis of prostaglandin I and 2 (prostacyclin), prostaglandin E2, with vasodilating properties;

 potassium channel agonism.

When prescribed in high doses, indapamide is able to exert a diuretic effect.

Pharmacokinetics of drugs have high oral bioavailability. Due to sufficient lipophilicity and moderately pronounced binding with proteins, thiazide diuretics penetrate well into many organs and tissues. They are secreted in the proximal tubule using active transport mechanisms, a small part of them are filtered through the renal glomeruli. Hydrochlorothiazide and chlortalidone are slightly metabolized in the liver and are almost completely excreted by the kidneys unchanged. Indapamide undergoes almost complete metabolism in the liver and only a small part of the active drug is excreted by the kidneys.

Indications for use. As a diuretic for the treatment of edema in chronic heart failure, nephrotic syndrome, chronic renal failure, acute glomerulonephritis. The diuretic effect of drugs begins in about 1-2 hours, reaching a maximum effect in 3-6 hours. The duration of action of thiazide sulfonamides and clopamide is 6-15 hours, indapamide is about 24 hours, and chlortalidone is 24-72 hours. All drugs in this group, for with the exception of indapamide, they are ineffective at a glomerular filtration rate of less than 30-40 ml / min.

Thiazide diuretics are widely used for long-term treatment of hypertension. For this purpose, they are prescribed daily for a long time in small doses (not more than 25 mg / day of hydrochlorothiazide or chlortalidone), since it is shown that higher doses can increase the risk of sudden death.

The antihypertensive effect of drugs in most cases develops after 2-4 weeks of regular use. The antihypertensive effect of indapamide appears after several days of treatment and gradually increases, reaching a maximum after 12 weeks of regular use of the drug. The hypotensive effect of indapamide is more pronounced than that of other thiazide and thiazide-like diuretics. The severity of its antihypertensive effect depends on the severity of hypertension. In patients with mild to moderate hypertension, indapamide monotherapy provides a good antihypertensive effect in approximately 70% of patients. High efficacy of the drug is maintained during its prolonged use in more than 60% of patients. Indapamide evenly lowers blood pressure within 24 hours and effectively prevents the rise of blood pressure in the early morning hours. It has an antihypertensive effect in patients with both normal and impaired renal function. Along with the antihypertensive effect, indapamide causes the reverse development of left ventricular myocardial hypertrophy in patients with hypertension and has renoprotective properties. In patients with diabetic nephropathy, indapamide significantly reduces urinary albumin excretion.

Other applications Thiazide diuretics are sometimes used for hypercalciuria and osteoporosis to limit calcium loss. Thiazide diuretics are used to reduce polyuria in patients with diabetes mellitus, since with this pathology they increase the reabsorption of water in the proximal tubule and significantly reduce the total volume of urine formed. A new field of application of indapamide is secondary prophylaxis in patients after cerebrovascular accident.

Side effects

Electrolyte

Extracellular fluid depletion. Arterial hypotension. Hypokalemia. Hyponatremia. Hypochloremia. Metabolic alkalosis. Hypomagnesemia, hypercalcemia. Hyperuricemia Disorders of the central nervous system. Dizziness. Headache. Weakness. Paresthesia.
Gastrointestinal
Anorexia. Nausea. Vomiting, colic. Diarrhea. Constipation Cholecystitis. Pancreatitis
Sexual
Impotence. Decreased libido.
Hematologic (blood dysrasia)
Thrombocytopenia, agranulocytosis. Thrombocytopenic purpura.
Dermatological
Skin rash. Photosensitivity.
Other
Hyperglycemia. An increase in blood levels of total cholesterol. Increased triglycerides. Increased levels of low density lipoproteins.
Interactions. Thiazide and thiazide-like diuretics reduce the effect of anti-gout agents, sulfonylureas, insulin preparations. They can enhance the effects of anesthetics, diazoxide, cardiac glycosides, lithium preparations, and loop diuretics. Such drugs as NSAIDs and cholestyramine reduce the effectiveness of diuretic therapy, and amphotericin B and corticosteroids can enhance the hypokalemic effect of thiazide and thiazide-like diuretics.
Carbonic anhydrase inhibitors
Currently, drugs in this group have limited use as diuretic agents. One drug is used - acetazolamide, which is a sulfanilamide derivative. It has a weak diuretic effect, which is realized mainly at the level of the epithelium of the proximal tubule.
The mechanism of action, pharmacological effects and features of the headlights-macokinetics
Acetazolamide inhibits the membrane and cytoplasmic forms of the carbonic anhydrase enzyme, which catalyzes the formation of hydrogen ions in the cytoplasm of tubular epithelial cells. Hydrogen ions entering the lumen of the tubule are exchanged for sodium ions, which come from the lumen of the tubules into the epithelial cell. In the lumen of the tubule, carbonic anhydrase catalyzes the dissociation of bicarbonate into carbon dioxide and hydroxyl ion. As a result of inhibition of carbonic anhydrase, the reabsorption of sodium ions is reduced (due to a lack of hydrogen ions) and at the same time the excretion of bicarbonates increases (due to the blockade of their dissociation), accompanied by an increase in urine pH to 8 and the development of metabolic acidosis.
An additional site of action of acetazolamide is the collecting duct system, where the drug blocks carbonic anhydrase, which is involved in the secretion of titratable acids and ammonium, which also contributes to an increase in urine pH. A decrease in sodium reabsorption reduces the reabsorption of water, the reverse absorption of which in the proximal section is in accordance with the osmotic concentration gradient. An increase in the concentration of sodium, as well as chlorine ions in the ultrafiltrate entering the distal tubule, stimulates a compensatory increase in the reabsorption of electrolytes in these sections, so the total loss of sodium and chlorine is small. An increased concentration of sodium ions in the collecting tubes causes an increase in its volume by potassium ions, which again leads to significant losses of potassium in the urine. Acetazolamide increases the excretion of phosphates, but has little effect on the excretion of calcium and magnesium. The diuretic effect of carbonic anhydrase inhibitors is self-limiting: it decreases as metabolic acidosis in the extracellular fluid increases. This occurs after about 4 days of regular drug intake. When you stop taking acetazolamide, alkaline reserves are restored after 1-2 days. This feature of the action of carbonic anhydrase inhibitors necessitates intermittent treatment with these drugs.
Carbonic anhydrase inhibitors increase the resistance of afferent arterioles, decrease renal blood flow and glomerular filtration rate.
The enzyme carbonic anhydrase is also found in other tissues of the body, but the blockade of its action has clinical significance only (except for the kidneys) in the tissues of the eye and in the

central nervous system. Reducing the formation of bicarbonate leads to a decrease in fluid secretion in the anterior chamber of the eye and a decrease in intraocular pressure. The effectiveness of acetazolamide in epilepsy is partly due to the development of metabolic acidosis, and partly to a direct anticonvulsant effect.
Acetazolamide is almost completely absorbed from the digestive tract. In blood plasma, up to 95% of drugs bind to protein. Acetazolamide is not metabolized in the body and is completely excreted by the kidneys unchanged. Its T1 / 2 is 6-9 hours.
Indications for use - Open-angle glaucoma, secondary glaucoma and a preoperative decrease in intraocular pressure in acute form of angle-closure glaucoma. When taken orally, the effect of drugs begins in 1-1.5 hours, reaches its maximum in 2-4 hours and lasts for 6-12 hours. The rapid development of tolerance limits the use of acetazolamide as an anticonvulsant. Acetazolamide can be used to correct metabolic alkolosis caused by other diuretics.
Side effects - Most of the side effects of carbonic anhydrase inhibitors are caused by alkalization of urine and the development of metabolic acidosis. Among them: increased phenomena of encephalopathy in patients with cirrhosis of the liver (decreased excretion of ammonia), stone formation and development of renal colic due to precipitation of phosphates in alkaline urine, increased metabolic or respiratory acidosis in patients with hyperchloremic acidosis or severe respiratory failure. Drugs can cause hypokalemia and hyponatremia. Severe toxic reactions (suppression of bone marrow hematopoiesis, kidney damage) are rare. Perhaps the appearance of a skin rash as a reaction to the sulfanilamide structure of drugs. High doses of acetazolamide can cause paresthesia and drowsiness, due to inhibition of carbonic anhydrase in the central nervous system.
The main contraindications to the appointment are diseases and pathological conditions accompanied by acidosis (uremia, decompensated diabetes, severe respiratory failure).
Potassium-sparing diuretics
Triamteren, amiloride and spironolactone are traditionally combined into a group of potassium-sparing diuretics, since they are able to reduce the excretion of potassium by the kidneys. Another common characteristic for them is the ability to act in the final part of the distal tubules and the system of collecting ducts and cause a weak diuretic effect. All of them in their structure belong to different chemical compounds.
The mechanism of action and pharmacological effects
According to the mechanism of action, potassium-sparing diuretics can be divided into 2 subgroups: drugs that block the sodium channels of kidney epithelial cells, and aldosterone antagonists (blockers of aldosterone receptors).
Sodium channel blockers
Triamteren and amiloride block the sodium membrane channels of the epithelium lining the final part of the distal tubules and collecting ducts. They reduce the transmembrane potential, which is an important electromotive force in the transfer of potassium, hydrogen, calcium and magnesium ions through cell membranes into the lumen of the tubule. Thus, triamteren and amiloride increase the concentration of sodium in the lumen of the tubules and reduce potassium loss. However, the diuretic effect of drugs is rather weakly expressed, since the reabsorption capacity of collecting tubes is limited and amounts to approximately 2% of the total filtered volume of salts. Long-term use of drugs can lead to a decrease in urinary acid excretion.
Triamteren and amiloride do not have a clinically significant effect on renal hemodynamics.
Pharmacokinetic characteristics of drugs vary significantly. The absorption of triamteren is variable. It binds to plasma proteins by 56%, is metabolized relatively quickly by liver enzymes, forming the active metabolite 4-hydroxytriamterene sulfate, which is secreted into the lumen of the proximal renal tubule using the active transport mechanism. Both hepatic and renal failure reduce the clearance of triamteren or its active metabolite and may increase their toxicity.
Unlike triamteren, amiloride weakly binds to plasma proteins, is not metabolized in the body and is excreted unchanged in the proximal part of the renal tubules.

Indications for use. Due to the weak diuretic effect, triamteren and amiloride are practically not used as independent agents for the treatment of edematous syndrome and hypertension. The main purpose of their use is to enhance the diuretic action of other saluretics and to compensate for the hypokalemia that they cause.

Other applications Triamteren and amiloride give a good effect in pseudo-hyperaldosteronism (Liddle's syndrome), which is manifested by hypokalemic alkalosis and hypertension against a background of low levels of aldosterone in the blood.

Side effects, contraindications

The most dangerous side effect of sodium channel blockers is hyperkalemia, therefore drugs are contraindicated in the presence of this condition, as well as in situations of increased risk of its development (renal failure, taking other potassium-sparing drugs, in particular ACE inhibitors, or drugs containing potassium). In patients with cirrhosis of the liver, triamteren can increase the likelihood of developing a megaloblastic type of hematopoiesis, since it is a weak antagonist of folic acid. In rare cases, triamteren can reduce glucose tolerance, cause photosensitivity and urolithiasis (drugs are poorly soluble and may precipitate in the urine). The most common side effects of amiloride are nausea, vomiting, constipation, headache. Triamteren often causes nausea, vomiting, dizziness, spasms of the calf muscles. Both drugs in rare cases can cause blood dysrasia.

Aldosterone receptor antagonists

Spironolactone and its active metabolite canrenone belong to this group of drugs.

The mechanism of action and pharmacological effects. Both substances, having a steroid structure, compete with aldosterone to bind to aldosterone receptors, thus blocking the biological effects of the latter. The action of aldosterone itself develops in the cell nucleus and consists in regulating the synthesis of specific proteins. These proteins activate various parts of the mechanism of sodium transfer from the lumen of the tubules into the interstitial space, increasing the transmembrane potential, which, in turn, is an electromotive force for the transfer of potassium and hydrogen ions from cells into the tubule lumen.

Like sodium channel blockers, spironolactone increases the excretion of sodium and chlorine and reduces the excretion of potassium, hydrogen, calcium and magnesium. The severity of the clinical effect of spironolactone depends on the level of endogenous aldosterone. With a normal level of aldosterone in the blood, the drug is ineffective. The diuretic effect is manifested 3-5 days after the start of administration and persists for 2-3 days after the end of administration.

In addition to the renal tubules and adrenal glands, aldosterone receptors are found in the brain, heart, and artery wall. It is suggested that elevated plasma aldosterone concentrations are one of the causes of the development of diffuse interstitial myocardial fibrosis and its hypertrophy, as well as thickening of the middle lining of arteries and perivascular fibrosis in patients with chronic heart failure. Blockade of aldosterone receptors in the heart and coronary arteries can reduce the adverse effects of hyperaldosteronemia.

Spironolactone can inhibit the activity of aldosterone synthetase and thus reduce the synthesis of aldosterone. In addition, it inhibits the activity of 5α-reductase, resulting in a decrease in the formation of the α-isomer of aldosterone, which has a greater mineralocorticoid activity than its β-isomer. Spironolactone blocks not only aldosterone receptors, to which it exhibits a pronounced affinity, but also androgen receptors. The drug has a weak nonspecific effect and in some cases can be used to treat hirsutism caused by an excess of androgens.

Spironolactone does not have a clinically significant effect on renal hemodynamics. Spironolactone is slowly absorbed from the gastrointestinal tract and already at the first passage through the liver undergoes pronounced biotransformation. In this case, several metabolites are formed, two of which exhibit the same pharmacological activity as spironolactone. The relationship of spironolactones with plasma proteins exceeds 90%. The drug has a short half-life (1.6 hours), but the half-life of its active canrenone metabolite reaches 10-16 hours, which lengthens the biological effect of spironolactone.

Indications for use.

The place of spironolactone in the treatment of patients with mild to moderate degree of HF has not yet been determined, therefore, the use of the drug in such patients is not yet recommended.
As an independent diuretic, it can be useful in patients with clinically significant hyperuricemia, hypokalemia, and with a decrease in glucose tolerance. Spironolactone is especially indicated for the treatment of primary (adenoma or bilateral adrenal hyperplasia) and other forms of secondary hyperaldosteronism (cirrhosis, nephrotic syndrome).
Side effects. Like other potassium-sparing drugs, spironolactone can cause hyperkalemia. Therefore, it is contraindicated in patients with hyperkalemia and in patients with a high risk of its development (diseases or taking other drugs that can increase the level of potassium in plasma). Spironolactone can cause metabolic acidosis in patients with cirrhosis.
In addition, the development of nausea, vomiting, diarrhea, gastritis, peptic ulcer, dizziness, headache. In rare cases, drowsiness, ataxia, skin rash, and blood dysrasia may occur. With prolonged use, cases of gynecomastia, erectile dysfunction in men, menstrual irregularities and voices in women are described.
Spironolactone is contraindicated in conditions accompanied by hypercalcemia, hyponatremia, with acute renal failure, severe forms of chronic renal failure.
Interactions Spironolactone may increase the concentration of digoxin in blood plasma and increase the risk of its side effects, including arrhythmias. The combined use of drugs with ACE inhibitors, indomethacin and other potassium-sparing diuretics can lead to the development of hyperkalemia (especially against the background of renal failure). NSAIDs, reducing glomerular filtration and diuresis, weaken the diuretic effect of spironolactone.
The scope of the clinical use of diuretics in gastroenterological practice covers mainly patients with edematous ascites syndrome against the background of cirrhotic liver damage. Taking into account the complex pathogenesis of the development of edema in this disease, diuretics of various pharmacological groups are used in the treatment: aldosterone receptor antagonists (spironolactone), potassium-sparing, loopback, and thiazide diuretics. Features of the action of spironolactone make it possible to obtain a gradually developing and stable diuretic effect, which is the task of unloading therapy for cirrhosis.
An alternative to spironolactone may be the use of other potassium-sparing diuretics - triamteren, amiloride.
Osmotic diuretics
Mannitol, urea, concentrated glucose solutions, glycerin - osmotic diurietics
MANNITOL (MANNITOL; Mannitolum) - a six-atom alcohol, which is the most powerful of the existing osmotic diuretics. It is able to increase diuresis by 20% of all sodium filtered in glomeruli. Available in sealed 500 ml vials containing 30, 0 of the drug, as well as in ampoules of 200, 400, 500 ml of a 15% solution. It is displayed slowly. When administered intravenously, while in the blood, mannitol, like other diuretics of this group, sharply increases the osmotic pressure in the blood plasma, which leads to an influx of fluid from the tissues into the blood and an increase in bcc (“drying effect”). This leads to a decrease in the reabsorption of sodium and water in the distal part of the nephron, and also causes increased filtration in the glomeruli. In addition, mannitol is well filtered through the membrane of the glomeruli and creates a high osmotic pressure in the urine, and is not subjected to reabsorption in the tubules. Mannitol does not undergo biotransformation and is excreted unchanged, and therefore constantly attracts water and primarily removes it after itself. The use of osmotic diuretics is not accompanied by hypokalemia and a change in the acid-base state. By the ability to remove water from the body, mannitol is almost the most powerful drug.
Indications for use:
 Prevention of the development or elimination of cerebral edema (shock, brain tumor, abscess) is the most common indication.
 Mannitol is indicated as a means of dehydration therapy for pulmonary edema that occurs after the toxic effects of gasoline, turpentine, formalin; as well as with swelling of the larynx.

 When conducting forced diuresis, in particular when poisoning with drugs (barbiturates, salicylates, sulfonamides, PASK, boric acid), when transfusing incompatible blood.
 In an acute attack of glaucoma.
 To reduce damage to the tubules of the kidneys during a sharp drop in filtration (in patients with shocks, burns, sepsis, peritonitis, osteomyelitis, in whom the drug improves renal blood flow), in case of severe poisoning with hematological poisons (precipitation of proteins, hemoglobin, danger blockages of the renal tubules and the development of anuria).

Side effects: headache, nausea, vomiting, sometimes allergic reactions.

The purpose of the lesson.

1. To learn:

a) Pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of diuretic drugs (MLS):

b) Classification of MLS by chemical structure and mechanisms of action:

I. Disturbing sodium transport in the tubules:

1) Braking the transport of sodium from the lumen of the tubule into the cell (acting apically):

 aldosterone antagonists - spironolactone / veroshpiron /;

 sodium channel blockers - triamteren; amiloride;

2) Inhibiting the transport of sodium from the cell through the basement membrane:

 carbonic anhydrase inhibitors - diacarb, dorzolamide;

 loop *: derivatives of anthranilic acid - furosemide / lasix /; torasemide, dichlorophenoxyacetic acid derivatives - ethacrylic acid / uregite /;

 thiazide and thiazide-like sulfonamides - hydrochlorothiazide / dichlothiazide, hypothiazide /, cyclomethiazide / navidrex /, oxodoline / chlortalidone /, sulfamoylbenzoic acid derivatives - clopamide / brinaldix /, bufenox, indapamide;

II. Valid throughout the tubules:

 osmotic: mannitol / mannitol /, urea.

 acidifying - ammonium chloride.

III. Changing blood supply to the kidneys (xanthines) - theophylline, theobromine, aminophyllin.

IV. Plants with a diuretic effect - horsetail, adonis, bearberry leaf, birch buds, juniper berries, orthosiphon leaves, lingonberries, wild strawberries, cornflower flowers, special fees (kidney tea, nephrophyte), etc.

c) Classification by force:

1) Strong diuretics:

a) “loop” diuretics - furosemide, torasemide, ethacrylic acid, bufenox;

b) osmotic diuretics.

2) Medium-power diuretics (thiazide and thiazide-like) - dichlothiazide, cyclomethiazide, oxodoline, clopamide, indapamide.

3) Diuretics of weak action:

a) potassium-sparing - spironolactone, triamteren, amiloride;

b) carbonic anhydrase inhibitors - diacarb, dorzolamide;

c) various diuretic preparations - xanthine, herbal origin, etc.

4) Combined diuretics containing saluretic + potassium-sparing: mod-retic (hydrochlorothiazide + amiloride), triampur (hydrochlorothiazide + triamteren), furesis (furosemide + triamteren), etc.

Know:

A. Etiopathogenesis of edema.

B. The main pathogenetic mechanisms that are the subject of drug exposure for: cerebral edema, pulmonary edema, edema syndrome of various origins, arterial hypertension, intoxication with substances capable of renal excretion.

C. Points of application of the main groups of diuretics.

 Strong diuretics ("loop", osmotic). Mechanisms of action. Indications for use. Undesirable effects. The concept of forced diuresis.

 Diuretics of medium strength (thiazide and nontiazide). Mechanisms of action. Indications for use. Undesirable effects.
 Diuretics of weak potency (xanthine, potassium-sparing, carbonic anhydrase inhibitors). Mechanisms of action. Undesirable effects.
D. General principles for the appointment of diuretics and their combinations.
E. Medicinal plants with a diuretic effect.
Be able to:
a) select and select for a particular patient the necessary MLSs or their combination.
b) identify criteria for assessing the therapeutic efficacy and safety of used MLS
c) provide urgent medical care in case of: hypertensive crisis, cerebral edema, pulmonary edema, decompensation of chronic circulatory failure, renal failure, intoxication.
Control questions of the studied topic
1. List the clinical and pharmacological principles of the choice of MLS and the selection of their doses for general edema syndrome, cerebral edema, pulmonary edema, renal failure, systemic arteries. hypertension.
2. What diuretins should be preferred during detoxification therapy?
3. What drug should be used to relieve increased intracranial and intraocular pressure?
4. How is it advisable to combine MLS to obtain the maximum diuretic effect (forced diuresis)?
5. In which renal lesions, potassium-sparing MLS and potassium preparations should not be prescribed; Are these products compatible with each other?
6. What are the clinical and laboratory criteria for evaluating the effectiveness and safety of using MLS?
7. Explain the mechanism of formation of resistance to furosemide and justify its dosing regimen.
8. Describe the clinical signs of an overdose of saluretics and make a treatment plan for intoxication with these MLS.
The list of practical works
Control of the intermediate level of knowledge.
The solution of situational problems.
1. 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 diuretics is most appropriate to add to the treatment that is being done?
2. A 38-year-old patient was urgently taken to the ambulance hospital with poisoning by unknown poison. What activities are most appropriate to start intensive treatment with?
3. 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 RT. Art. In urine: protein - 9.2 g / l, microhematuria, cylindruria. In the blood, ESR, hypoalbuminemia, hypercholesterolemia are sharply increased.
Formulate a diagnosis. Make a combination therapy program. Give her a clinical and pharmacological rationale.
4. Patient N., 52 years old, developed edematous syndrome against the background of acute renal failure. Make a combination therapy program. Give her a clinical and pharmacological rationale.
5. A patient, 34 years old, was taken to an emergency hospital with a brain edema clinic, which developed as a result of a traumatic brain injury sustained in a road accident.
What drug is advisable to start treatment with. Justify the appointment of a diuretic drug.
7. Patient V., with a hypertensive crisis, was assisted in the form of parenteral administration of anaprilin 20 mg and furosemide 40 mg intravenously. After 20 minutes, blood pressure decreased.
Is the doctor’s tactics correct? Justify the appointment of a diuretic.

8. A patient with a diagnosis of Coronary heart disease, stable angina pectoris II f. C., chronic heart failure II B century, in complex therapy ethacrine acid was prescribed.

Assess the effectiveness of the prescribed drug and justify the feasibility of its appointment.

9. In the complex treatment of hypertension, the patient was prescribed a diuretic. After a few days, blood pressure decreased, weakness, nausea, diarrhea, hypokalemia, metabolic acidosis occurred. What drug could cause such complications? Further tactics of patient management.

10. The patient has acute cardiopulmonary failure, which is accompanied by pulmonary edema. What drug from the group of diuretics should be prescribed?

11. A patient with heart failure stage II regularly takes furosemide 40 mg on an empty stomach three times a week. He had acute bronchopneumonia, in connection with which the doctor prescribed combined pharmacotherapy. After 3 days, the patient began to lose hearing.

What drugs when interacting with furosemide cause deafness, for what reason?

12. A patient, 62 years old, has been suffering from hypertension for 10 years. 2 years ago, chronic obstructive bronchitis was diagnosed. Objectively: pulse - 64 beats per 1 min, blood pressure - 210/130 mm RT. Art., the left border of relative cardiac dullness is shifted to the left by 2.5 cm from the midclavicular line, I tone above the apex is weakened, the accent of II tone above the aorta. ECG: left ventricular hypertrophy. What drug is most appropriate in this case?

TESTS

1. In a patient with chronic heart failure with edematous syndrome in the blood revealed an increase in aldosterone. Which diuretic is most appropriate?

A. Triamteren
B. Hydrochlorothiazide
* C. Spironolactone
D. Diacarb
E. Furosemide

2. During the treatment of chronic edematous syndrome with furosemide, the patient experienced a violation of the cationic composition of blood plasma. What remedy should be used to correct it?

A. Calcium Chloride
B. Sodium Chloride
C. Lithium carbonate
D. Sodium bicarbonate
* E. Potassium chloride

3. A patient with hypertension in the complex therapy prescribed hydrochlorothiazide. What mechanism of action of the drug helps to lower blood pressure?

A. Increased angiotensin II formation
* B. Increased release of sodium and water ions
C. Blockade of calcium channels
D. Decreased release of sodium and water ions
E. Blockade of the enzyme carbonic anhydrase

4. To reduce swelling on the legs of a patient with chronic cardiovascular failure, the doctor prescribed a diuretic. After 5 days, the patient began to complain of general weakness, cramps in the calf muscles, extrasystoles appeared on the ECG. Which of the drugs could contribute to this?

A. Theophylline
B. Spironolactone
C. Triampur
* D. Ethacrylic acid
E. Triamteren

5. In the complex treatment of hypertension, the patient was prescribed a diuretic. After a few days, blood pressure decreased, there was weakness, nausea, diarrhea, hypokalemia, metabolic acidosis. What drug could cause such complications?

A. Spironolactone
* B. Furosemide
C. Allopurinol
D. Triamteren
E. Etaperazin

6. The patient has acute cardiopulmonary failure, which is accompanied by pulmonary edema. What drug from the group of diuretics should be prescribed?

A. Triamteren
B. Spironolactone
C. Dichlothiazide
* D. Furosemide
E. Diacarb

7. Patient K., 54 years old, was admitted to the ophthalmology department with a diagnosis of glaucoma. After an additional examination, the doctor prescribed 250 mg diacarb. 3-day courses with breaks. Specify the mechanism for reducing intraocular pressure under the influence of diacarb:

A. Decreased cerebrospinal fluid production
* B. Inhibition of the carbonic anhydrase of the ciliary body
C. Increased osmotic pressure of blood plasma
D. Blocking sodium reabsorption in the tubules of the nephron
E. Inhibition of adrenal gland synthesis

8. A diuretic that causes a strong and quick, but short-term (up to 1 hour) diuretic effect is:

*BUT. Torasemide
V. Mannit
C. Hydrochlorothiazide
D. Triamteren
E. Amiloride

10. The diuretic, which is the starting one in acute heart failure, is:

*BUT. Furosemide
B. Acetazolamide
S. Sorbitol
D. Mannitol
E. Spironolactone

11. In the case of acute fluid retention in the body during poisoning with NSAIDs, the drug of choice is:

A. Furosemide
B. Ethacrylic acid
S. Bumetanid
* D. Mannitol
E. Torasemide

12. Choose a diuretic other than potassium-sparing drugs:

A. Spironolactone
*AT. Oxodoline
S. Triampur
D. Amiloride
E. Triamteren

13. Select the pharmacological effect characteristic of triamteren and amiloride:

* A. Decreased urinary potassium excretion
B. Significant increase in urine output
C. Prevention of remodeling of the cardiovascular system
D. Decreased urinary calcium excretion
E. Increased glomerular filtration rate

14. Spironolactone is effective provided:

A. Concurrent administration of calcium

B. Concurrent administration of potassium preparations

*WITH. The presence of primary or secondary hyperaldosteronism

D. Sufficient fluid intake

E. Concurrent administration of other diuretics.

15. Patient S., 70 years old, was admitted to the therapeutic department with a diagnosis of liver cirrhosis. ascites. He suffers from rheumatoid arthritis, takes indomethacin for a long time, the intern doctor prescribed 40 mg furosemide inside. What complication can a patient develop with the combined use of indomethacin and furosemide?

*BUT. Hearing loss.

B. Significant increase in urine output

C. Decreased urine output

D. Decreased urinary calcium excretion

E. Decreased urinary potassium excretion

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 THE CHOICE OF ANTI-ARRHYTHMIC MEDICINES.
PRINCIPLES OF TREATMENT OF CARDIAC ASTHMA AND PULMONARY Edema
PRINCIPLES OF TREATMENT OF HEART RHYTHM DISORDERS

Purpose of the topic.

Arrhythmia of the heart (from other Greek. Ἀρρυθμία - "inconsistency, awkwardness") is a pathological condition in which violations of the frequency, rhythm and sequence of excitation and contraction of the heart occur. Arrhythmia - any heart rhythm that is different from the normal sinus rhythm (WHO, 1978). With this pathological condition, the normal contractile activity of the heart can be significantly impaired, which, in turn, can lead to a number of serious complications.

The term "arrhythmia" combines various in the mechanism, clinical manifestations and prognostic value of impaired formation and conduct of an electrical impulse.

Motivational characteristic of the topic.

Myocardium refers to actively excitable environments. It is capable of both generating and conducting electrical impulses. Originating in the sinoatrial node, the impulse along the atrial myocardium and atrial interstitial ducts (Bachmann, Wenckebach and Torel bundles) rushes to the atrioventricular node, where the conduction speed is the lowest in the conduction system of the heart. The result is a so-called atrioventricular delay. This contributes to the fact that the atria have time to contract before the ventricles. Then the impulse passes into the trunk of the bundle of His, then through the legs of the bundle of His and the conductive Purkinje fibers it enters the working myocardium of the ventricles, leading to their contraction. In some forms of congenital pathology, additional pathways of atrioventricular conduction are noted: Kent bundles with Wolf-Parkinson-White syndrome and James bundle with Clerk-Levy-Christesco syndrome. Kent bundles are usually located on the lateral sides of the fibrous rings and connect the atrial myocardium to the basal parts of the ventricular myocardium. The James bundle begins in the myocardium, most often, of the left atrium and, bending around the fibrous ring from the medial side, penetrates the interventricular septum, where it directly contacts the trunk of the bundle of His. The presence of these bundles in some cases can lead to paroxysms of tachycardia

The ability to generate impulses is normally present only in cells of the conduction system of the heart. Several phases of their action potentials are distinguished.

• Phase 0 - rapid depolarization. It is generated by the incoming calcium current in the sinoatrial and atrioventricular nodes and the incoming sodium current in the trunk and legs of the bundle of His, as well as conductive Purkinje fibers.

• Phase 1 - initial repolarization. It is generated by outgoing potassium tocom.

• Phase 2 - Plateau. It arises due to the incoming calcium current.

• Phase 3 - final repolarization. Like phase 1, it is generated by an outgoing potassium current.

• Phase 4 - slow diastolic depolarization. It arises due to the incoming calcium current in the nodes and the incoming sodium current in the remaining parts of the conduction system of the heart.
The action potential of the nodes is significantly different from the action potential of other areas of the heart. It practically lacks phase 1 and phase 2.
The action potential of the working ventricular myocardium is very similar to the action potential of the final Purkinje fiber. The main difference is phase 4. In Purkinje fibers, this is a slow diastolic depolarization, and in working cardiomyocytes, the resting potential.
The potential action of pathological pathways of atrioventricular conduction: Kent and James is very similar to that of the legs of the bundle of His and Purkinje fibers. These paths are also excited by the incoming sodium current.
The most common causes of heart rhythm and conduction disturbances:
1. Cardiac causes:
• IHD, including myocardial infarction and unstable angina
• Heart failure
• Cardiomyopathy
• Acquired heart defects
• Congenital heart defects
• Myocarditis
• Mitral valve prolapse
2. Medicinal effects:
• Cardiac glycosides
• Antiarrhythmic drugs (proarrhythmic effect)
• Diuretics
• Sympathomimetics
3. Electrolyte disturbances:
• Hypokalemia
• Hyperkalemia
• Hypomagnesemia
• Hypercalcemia and others
4. Toxic effects:
• smoking
• Narcotic substances (including alcohol)
• Thyrotoxicosis
5. Idiopathic arrhythmias
Arrhythmia classification
Depending on the impaired function of the heart, it is now customary to distinguish the following groups of arrhythmias:
1. Violations of automatism
1. Nomotopic (pacemaker - in the sinus node)
 sinus tachycardia (CT)
 sinus bradycardia (SB)
 sinus arrhythmia (SA)
 Sinus node weakness syndrome (SSSU)
 non-respiratory sinus arrhythmia
2. Heterotopic (pacemaker - outside the sinus node)
 lower atrial rhythm
 atrioventricular rhythm
 idioventricular rhythm

2. Disorders of excitability
1. Extrasystoles

1. By source: atrial, atrioventricular, ventricular
2. By the number of sources: monotopic, polytopic
3. By time of occurrence: early, interpolated, late
4. In frequency: single (up to 5 per minute), multiple (more than 5 per minute), paired, group
5. By ordering: disordered, allorrhythmias (bigeminia, trigeminia, quadrigeminia)
2. Paroxysmal tachycardia (atrial, AV, ventricular)
3. Conductivity disorders
1. Increased Conductivity (WPW Syndrome)
2. Reduction of conductivity (blockade: sinoauricular, intracardiac, AV, blockade of the bundle of His bundle)
4. Mixed (flutter / atrial fibrillation / ventricular)

TREATMENT OF ARRhythmias

Antiarrhythmic drugs - a group of drugs used for a variety of heart rhythm disorders, such as extrasystole, atrial fibrillation, paroxysmal tachycardia, ventricular fibrillation, etc.

Classification

By action localization

• Means that directly affect the myocardium
o Membrane stabilizing drugs
o Means that increase the duration of the action potential
o Calcium channel blockers (calcium ion antagonists)
o Potassium preparations
o Magnesium Sulfate
• Means that affect the innervation of the heart
o β-blockers
o β-adrenergic agonists
o Sympathomimetics (currently practically not used)
o M-anticholinergic
• Means that affect both the myocardium and the innervation of the heart
o Cardiac glycosides

For use in clinical practice

• Means used for tachyarrhythmias and extrasystoles
o I class. Membrane stabilizing drugs
o II class. β-blockers
o III Class. Means that increase the duration of the action potential
o IV Class. Calcium channel blockers (calcium ion antagonists)
o V Class. Other funds
 Potassium preparations
 Cardiac glycosides
 Adenosine
 Magnesium sulfate
• Means used for heart block.
o β-adrenergic agonists
o Sympathomimetics (currently practically not used)
o M-anticholinergic

Drugs used for tachyarrhythmias and extrasystoles

Comparative characteristics of drugs used for tachyarrhythmias and extrasystoles (according to Vogen-Williams)

Class	Name	Example	Mechanism of	Clinical application

			action	
Ia	Sodium channel blockers	Quinidine Novocainamide Disopyramids Aymaline	Moderate blockage of sodium channels	• • Ventricular arrhythmias • • Prevention of atrial fibrillation attacks caused by increased vagus nerve tone • • Novocainamide is used to prevent paroxysms of tachycardia in Wolf-Parkinson-White syndrome
Ib	Potassium channel activators	Lidocaine Diphenin Mexiletine	Activation of potassium channels. Slight blockade of sodium channels	• • Treatment and prevention of arrhythmias accompanying myocardial infarction. However, use is limited to the risk of ventricular asystole. • • Ventricular tachycardia • • Atrial fibrillation
Ic	Sodium channel blockers	Flecainide Propaphenone Etatsizin Etmosine (Moricizine)	Severe blockade of sodium channels	• Prevention of paroxysms of atrial fibrillation • • Treatment of paroxysms of arrhythmias in the presence of additional conduction bundles: Kent and James. • • Contraindications: post-infarction period.
II	β-blockers	Propranolol Timolol Oxprenolol Pindolol Alprenolol Metoprolol Talinolol Atenolol Betaxolol Bisoprolol Acebutolol Celiprolol Praktolol	Inhibition of the effect of the sympathetic nervous system on the myocardium Propranolol has a membrane stabilizing effect (class I)	• • Decreased mortality from myocardial infarction • • Prevention of relapse of tachyarrhythmias
III	Means that increase the duration of the action potential	Amiodarone Sotalol Ibutilide	Blockade of potassium channels Sotalol also has β-	• • Wolf-Parkinson-White Syndrome • • Sotalol: ventricular tachycardia, atrial fibrillation • • Ibululide: flutter and atrial

		Dofetilide Dronedaron E-4031	blocking activity	fibrillation
IV	Calcium channel blockers	Verapamil Diltiazem	Blockade of slow voltage-gated calcium channels	• • prevention of paroxysms of supraventricular paroxysmal tachycardia • • Reducing the frequency of ventricular contractions in atrial fibrillation due to difficulty in atrioventricular conduction
V	Other funds	Cardiac Glycosides Adenosine Magnesium sulfate Potassium preparations	Cardiac glycosides and adenosine cause inhibition of the atrioventricular node. Cardiac glycosides due to increased tone of the vagus nerve, adenosine due to binding to A1-adenosine receptors.	Cardiac glycosides and adenosine Used for supraventricular arrhythmias, especially atrial fibrillation and concomitant heart failure. Magnesium sulfate is used for paroxysmal ventricular tachycardia of the "pirouette" type (Torsade de Pointe)

Etiology and pathogenesis of arrhythmias. The main effects of antiarrhythmic drugs

Arrhythmias are functional and organic.

Functional arrhythmias can occur in healthy people with excessive physical exertion, psycho-emotional arousal, fever, etc. Adrenaline and norepinephrine released during these conditions increase the entry of sodium and calcium ions into the conducting cardiomyocytes. This leads to a decrease in the membrane potential of cells, an increase in their excitability, and the appearance of ectopic foci of automatism. Less commonly, the cause of functional arrhythmias is the so-called re-entry of excitation (English re-entry).

Pathophysiology of Arrhythmia Re-Entry Excitation in Purkinje Final Fiber

Arrhythmias associated with organic heart diseases (coronary heart disease, myocardial infarction, myocarditis, etc.) more often occur precisely by the mechanism of re-entry of excitation. Moreover, in one of the final fibers of Purkinje, an incomplete unidirectional block arises of conducting excitation to the myofibril of the working myocardium of the atria or ventricles. But in the same place the ability of antidromic conduction of the impulse is preserved. If the impulse goes in cycles one or two times, extrasystole occurs, if three or more - paroxysmal tachycardia. This is micro re-entry.

Pathophysiology of Arrhythmia Re-Entry Excitation in ERW Syndrome In Wolff-Parkinson-White and Clerk-Levy-Cristesco syndromes, when the nodular atrioventricular conduction is slowed down, the impulse reaches the ventricles faster along the pathological fast paths of the atrioventricular conduction: Kent and James, respectively. In Wolff-Parkinson-White syndrome, the impulse goes directly through the Kent's Beam to the ventricular myocardium, then retrogradely enters the Purkinje fibers, then into the His bundle and atrioventricular node. Then - into the myocardium of the atria and again through the Kent bundle - into the ventricles. In Clerk-

Levy-Cristesco syndrome, an electric stimulus along the fast James beam, bypassing the atrioventricular node, directly enters the trunk of the His bundle. And from there, it is antidromic into the atrioventricular node, the myocardium of the atria and again into the bundle of James and the ventricle. This is the so-called macro re-entry. Paroxysmal tachycardia, arising in a similar way, is called reciprocal. Antiarrhythmic drugs have various mechanisms of action. But in general, they all have:

• Negative batmotropic effect - a decrease in the excitability and auto-matism of the myocardium. It is positive, as it eliminates the ectopic foci of automatism

• Negative dromotropic effect - deceleration of conduction in different parts of the heart. On the one hand, it is positive, since in case of arrhythmias of the re-entry type it eliminates repeated antidromic excitation input. At the same time, in places of slow conduction, it can cause incomplete unidirectional block and re-entry arrhythmia. Danger with difficulty atrioventricular conduction.

• Negative chronotropic effect - slowing down the heart rate by reducing the excitability and automatism of the sinoatrial node or other pacemakers, as well as by the negative dromotropic effect on atrioventricular conduction in atrial fibrillation. Positive for tachycardia. Undesirable for eukardia and dangerous for bradycardia.

• Negative inotropic effect - a decrease in the strength of cardiac contractions. Inherent to calcium channel blocking preparations: groups Ia, III and IV, or indirectly decreasing the content of intracellular calcium (group II: β-blockers). It is always undesirable, as it reduces cardiac output.

Blockade of re-entry of excitation under the influence of drugs of class I

These drugs inhibit phase 0 (rapid depolarization) of the action potential in the cells of the working myocardium of the atria, ventricles, and also the ventricular part of the cardiac conduction system: the common trunk and legs of the bundle of His, conducting Purkinje fibers. The electrophysiological feature of these parts of the heart is that phase 0 of the action potential in them occurs due to the incoming current of sodium ions into the cardiomyocytes. Partial blockade of voltage-gated sodium channels leads to a slowdown of phase 0 of the action potential, which is accompanied by some slowdown of conductivity in these parts of the heart, and a slight blockage of potassium channels is accompanied by a slight increase in the effective refractory period. Due to this, Group Ia drugs translate an incomplete unidirectional block in the final Purkinje fiber to full bidirectional. The antidromic propagation of electrical impulses from the fiber of the working myocardium into the final Purkinje fiber is interrupted, which leads to blockade of the re-entry of excitation. Group Ia preparations have a weak effect on the sinoatrial node; its effect on the atrioventricular node is slightly more pronounced. This is due to the fact that phase 0 and phase 4 (slow diastolic depolarization) are provided in the sinoatrial node by an incoming calcium current through slow calcium channels. In the atrioventricular node, the incoming sodium current is also responsible for these phases, although its fraction is small. Nevertheless, preparations of group Ia somewhat impede atrioventricular conduction, mainly due to the blockage of sodium channels in the trunk and legs of the His bundle, as well as in Purkinje fibers. Sinoatrial node drugs of this class excite due to the M-anticholinergic action. This is least pronounced in novocainamide, enough - in quinidine, and very pronounced - in disopyramide. Since the point of application of sodium channel blockers is almost the entire working myocardium and the cardiac conduction system, except for nodes, they have found application in a variety of cardiac arrhythmias: ventricular arrhythmias, prevention and treatment of paroxysms of atrial fibrillation and paroxysmal tachycardia in Wolf-Parkinson-White syndrome. In the latter case, drugs of group Ia block the conductivity in the Kent beam and interrupt the re-entry of excitation. Sodium channel blockers are effective agents, however, the widespread use of these agents is limited by side effects, primarily arrhythmogenicity, which will be discussed below. In addition, for example,

procainamide can cause medicinal lupus erythematosus. In general, it can be said that group Ia drugs have moderate negative batmo-, dromo- and inotropic effects. And due to atropine-like action - a positive chronotropic effect.

The effect of group Ib drugs on the action potential of Purkinje fibers

Drugs in this group slightly block sodium channels and activate potassium. Phase 0 tilts somewhat, phase 3 (repolarization) is reduced. This leads to a shortening of the action potential and effective refractory period. However, the degree of shortening of repolarization is greater than the degree of decrease in refractoriness, i.e., a relative increase in the refractory period actually occurs. The blockade of voltage-gated sodium channels, as well as hyperpolarization associated with the activation of potassium channels, prolong the slow diastolic depolarization (except nodes), which leads to a weakening of ectopic automatism, that is, these drugs have a pronounced negative batmotropic effect on the working myocardium of the ventricles and atria, as well as on the conduction system of the heart below the atrioventricular node. Activators of potassium channels do not affect the nodes, therefore, do not cause bradycardia and do not slow down atrioventricular conduction. Lidocaine is used for ventricular arrhythmias associated with acute myocardial infarction. Nevertheless, lidocaine is contraindicated in case of complete atrioventricular block, since there is a risk of a decrease in the frequency of the ventricular pacemaker when it is used. Due to the short half-life, lidocaine is administered intravenously. Mexiletine is used for the same indications. However, in addition to intravenous administration, it can be used orally. It is contraindicated in atrioventricular blockade of the II — III degree. Biphenin, in addition to affecting the ion channels, affects the active transport of sodium and calcium ions through cell and subcellular membranes. Reduces the level of sodium in the cell, reduces its intake, stimulating Na + / K + -ATPase, facilitating the active transport of sodium from the cell. Activators of potassium channels have very weak foreign, chrono- and dromotropic effects. Due to the latter, they have significantly lower arrhythmogenicity compared to group Ia.

The effect of drugs of group Ic on the action potential of Purkinje fibers

Drugs in this group block voltage-gated sodium channels much more strongly than representatives of group Ia, which leads to a greater deceleration of phase 0 of the action potential. But, unlike Group Ia preparations, they practically do not affect potassium channels and the duration of the action potential. Phase 4 is also slowed down and the ectopic automatism of the working myocardium, His bundle and conductive Purkinje fibers is depressed. They are mainly used for ventricular arrhythmias. Among membrane-stabilizing drugs, group Ic has the greatest arrhythmogenicity.

The mechanism of arrhythmia by the mechanism of re-entry of excitation under the influence of antiarrhythmic drugs

There are areas in Purkinje fibers in a state of dystrophy in which an electrical impulse, albeit slowly, spreads to the myofibril of the working myocardium. Group I antiarrhythmic drugs block sodium channels and contribute to the occurrence of an incomplete unidirectional block in such areas and the occurrence of re-entry excitation arrhythmias. The more the drug has a blocking effect on sodium channels, the stronger its arrhythmogenic effect. That is why the preparations of group Ic have the greatest arrhythmogenicity, groups Ia - moderate, groups Ib - insignificant. The ability to provoke arrhythmias is the main limiting factor in the long-term use of group I drugs.

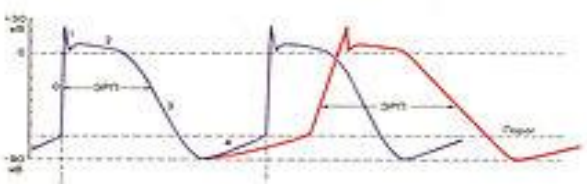
Comparative characteristics of drugs of group I

Comparative characteristics of group I drugs by the effect on the components of the action potential of cardiomyocytes

Group II β-blockers

These drugs block β1-adrenergic receptors found in all parts of the heart. Their blockade leads to a decrease in the activity of GTP-binding protein Gs. The breakdown of the Gs protein into subunits slows down. Deficiency of the α-subunit leads to a decrease in the activity of the adenylate cyclase enzyme and the conversion of ATP to cyclic AMP (cAMP). cAMP, as a secondary mediator, activates protein kinase A (cAMP-dependent A kinase). To activate this enzyme, two cAMP molecules are required that bind to each of the two regulatory subunits of this protein. As a result, regulatory units are disconnected from the catalytic subunits (and they are separated from each other). The activated catalytic subunits of A kinase phosphorylate various proteins, which are its substrates. In this case, the phosphate group is transferred from ATP to a specific amino acid residue (serine or threonine). In the myocardium, the activation of β1-adrenergic receptors increases the activity of sodium and calcium channels, exerting a positive chronotropic, batmotropic, dromotropic and intoroptic effect. β-blockers have a negative batmotropic effect: they reduce the automatism of the heart muscle, slowing down the slow diastolic depolarization, as well as a negative dromotropic effect: they complicate atrioventricular conduction. Despite the fact that β-blockers reduce myocardial contractility, their prolonged use reduces the total peripheral vascular resistance (OPSS), therefore, cardiac output does not decrease. β-blockers do not have an arrhythmogenic effect. Moreover, with their prolonged use, cardiovascular mortality is reduced, including by reducing the risk of fatal arrhythmias. See β-blockers for more details.

Group III. Means that increase the duration of the action potential



The mechanism of action of amiodarone. Thanks to the blockade of both potassium and sodium channels, the drug not only translates the unidirectional block into bidirectional, but also the delayed zone immediately into a complete bidirectional block

All drugs in this group block potassium channels. Due to this, the process of repolarization (phase 3) and the effective refractory period are increased. Amiodarone is one of the most popular and studied drugs in this group. In addition to inhibition of potassium channels, amiodarone blocks sodium and calcium channels. Amiodarone affects all departments of the working myocardium and the cardiac conduction system. It has negative batmo-, foreign-, chrono- and dromotropic effects. Due to a significant increase in ERP, amiodarone has a pronounced arrhythmic effect, which is also supported by the blockade of sodium channels. Unlike group I drugs, amiodarone has slight arrhythmogenicity. This is due to the fact that with a simultaneous blockage of sodium and potassium channels, a slowdown in conductivity and an increase in the EHP occur, which blocks the re-entry of the excitation and transfers the sections with delayed conduction into a complete bidirectional block. Amiodarone also uncompetitively blocks α-adrenergic receptors, lowering OPSS and lowering the load on the heart and β-adrenergic receptors, providing an additional antiarrhythmic effect like β-blockers. Due to the partial blockade of calcium channels, amiodarone inhibits the sinoatrial node, causing bradycardia and the atrioventricular node, inhibiting the conductivity in it. During myocardial infarction in ischemic areas, persistent depolarization of cardiomyocytes occurs. At the same time, the sodium channels are closed, since they "work" at a resting potential of minus 90 mV. If the resting potential in Purkinje fibers rises to minus 70 mV, slow calcium channels are activated. Their action potential becomes similar to nodal. Sodium channel blockers in this case

do not work. With arrhythmias associated with "slow pathological calcium potential" amiodarone and calcium channel blockers are effective. However, the use of amiodarone is limited to both multiple cardiac (decompensation of heart failure, atrioventricular block) and extracardiac side effects: impaired thyroid function (contains iodine), development of fibrosing alveolitis, deposition of the drug in the cornea, paresthesia, tremor, photosensitivity (blue skin color under the influence of sunlight).

Group IV Calcium channel blockers

The role of calcium ions in the body is diverse. They take part in exo- and endocrine secretion, platelet aggregation, and the reduction of smooth and striated muscles, including cardiac. In a normal conducting system of the heart, calcium takes part in the generation of the action potential of the nodes: sinoatrial and atrioventricular. It is responsible for the slow diastolic depolarization and the rapid depolarization phase. Heart rate and atrioventricular conduction rate depend on the degree of activity of calcium channels in the nodes. In the cell cytosol, the concentration of Ca +, like Na +, is low. Its main depot is the sarcoplasmic reticulum (SPR). When Ca + ions enter the cell, they, as already mentioned, cause depolarization of the cytoplasmic membrane (CPM) of cardiomyocytes. CPM invaginations come in contact with SPR furniture, causing its depolarization and release of Ca + ions into the cytosol. Calcium activates the actin-myosin complex, leading to a reduction in cardiomyocytes. With myocardial ischemia and a decrease in membrane potential in cardiomyocytes of the ventricles and Purkinje fibers less than 60 mV, a slow pathological calcium potential begins to be generated in them, accompanied by calcium-dependent ventricular arrhythmias:

Classification of calcium channel blockers

- **Phenylalkylamines: verapamil, gallopamil**
- **Benzothiazepines: Diltiazem**
- **Dihydropyridines: nifedipine, isradipine, amlodipine**
- **Diphenylpiperazines: cinnarizine, flunnarizine**

Calcium channel blockers (CCBs) used to treat arrhythmias affect the L-type of channels. It is present not only in the cells of the heart, but also in blood vessels. Therefore, almost all BKK to one degree or another reduce blood pressure.

In arrhythmias, representatives of only the first two groups are used: phenylalkylamines (verapamil, gallopamil) and benzothiazepines (diltiazem). BCC is used to treat supraventricular arrhythmias: sinus tachycardia (it has a negative chronotropic effect), supraventricular paroxysmal tachycardia, atrial fibrillation, etc. This group reduces the excitability of the nodes and the atrial ducts of rapid conduction, inhibiting phase 0 and phase 3. Atrioventricular node and batmotropic action. Increasing the ERP of the node, they partially block the conduction of impulses from the atria to the ventricles and transfer the tachysystolic form to the eusystolic. But calcium antagonists are contraindicated in Wolff-Parkinson-White and Clerk-Levy-Cristesco syndromes, since by slowing down nodular conduction, they can provoke the development of reciprocal paroxysmal tachycardia: the impulse reaches the atrioventricular node faster than the antidromic. BKK have a negative inotropic effect on the working myocardium, which is compensated by a decrease in OPSS, so cardiac output changes nominatively. In general, CCBs are well tolerated and have low arrhythmogenicity.

Group V. Other means

These are drugs that have a mechanism of action different from the drugs from groups I – IV, so some authors combine them in group V. This group is selective and includes substances that have a very diverse effect on the myocardium.

Potassium preparations

Potassium preparations have a mild antiarrhythmic effect. They are mainly used for arrhythmias caused by hypokalemia in various conditions (for example, with hyperaldosteronism), as well as with an overdose of cardiac glycosides. Potassium ions entering the blood via Na + / K + -

ATPase are actively transported and the cells, including cardiomyocytes. Since Na + / K + -ATPase is magnesium-dependent, oral potassium preparations are combined with magnesium (e.g. panangin and aspartame). Potassium preparations increase membrane potential and reduce myocardial excitability and automatism. Intravenously, K + and Mg2 + are often administered as part of the so-called polarizing mixtures (insulin + glucose + potassium + magnesium). Insulin promotes the transfer of glucose from plasma to the cell along with K + ions. The name of these mixtures was due to the restoration of the membrane potential, that is, an increase in the polarization of cardiomyocytes.

Adenosine

Adenosine is an endogenous antiarrhythmic. By acting on the adenosine receptor in A1, it inhibits adenylate cyclase and reduces the concentration of cyclic AMP, that is, it has the opposite effect of β-adrenergic agonists and methylxanthines. It opens potassium channels and causes hyperpolarization of cells, which leads to a decrease in their automatism and conductivity. However, a reduction in the effective refractory period can lead to increased excitability and arrhythmias. Adenosine is used mainly in supraventricular and nodular tachyarrhythmias, including re-entry arrhythmias. In some cases, atrial tachycardia can be stopped by adenosine. Due to the receptor-dependent activation of potassium channels, adenosine causes a shortening of the atrial myocardial refractory period. This is an undesirable effect, as it can cause atrial fibrillation, especially when given intravenously. In people with additional ducts, atrial fibrillation can lead to ventricular fibrillation. Fast heart rhythms localized in the atria or ventricles that do not affect the atrioventricular node usually do not stop after the administration of adenosine, however, due to a slowdown in atrioventricular conduction, it can cause a temporary decrease in the rate of response of the ventricles. With intravenous administration, adenosine causes a temporary complete atrioventricular block. When using adenosine as a means to stop arrhythmias, ventricular asystole within a few seconds is considered a normal effect. This effect can disorient the patient, who is conscious, and is associated with unpleasant sensations in the chest.

Magnesium sulfate

The mechanism of action of magnesium sulfate, presumably, is associated with the activation of the enzyme Na + / K + -ATPase and potassium channels. Magnesium sulfate is considered the drug of choice for the relief of an attack of a special ventricular tachycardia called “pirouette” (torsade de pointes). It is also called a spindle-shaped bidirectional ventricular tachycardia. It often occurs against the background of a prolonged QT interval. With this form, the QRS complexes are constantly changing in shape, direction, amplitude and duration: as if “dancing” around the contour. Elongation of the QT interval can be caused by electrolyte disturbances (primarily hypokalemia and hypomagnesemia), the use of class Ia and Ic antiarrhythmic drugs, as well as some drugs that prolong the QT interval: terfenadine, astemizole, phenothiazines, tricyclic antidepressants. Tachycardia pirouette can also occur when eating a liquid protein diet. Often, diseases such as stroke, bradyarrhythmias (especially AV blockade with 2: 1) can be complicated by spindle-shaped bidirectional ventricular tachycardia. Also, this tachycardia may be idiopathic.

Cardiac Glycosides

Cardiac glycosides, having a pronounced positive inotropic effect, enhance systolic ejection. As a result, cardiac baroreceptors (cardio-cardiac reflex), aortic arches and carotid glomerulus (baroreceptron depressor reflex) are activated. Along the afferent branches of the vagus nerve, impulses reach the nucleus of a single path (solitary tract, solitary bundle), exciting it. Further along the afferent fibers of the vagus nerve, the impulses rush to the posterior nucleus of the vagus nerve (nucleus dorsalis nervi vagi). As a result, efferent parasympathetic fibers of the vagus nerve innervate the heart. The consequence of this is a decrease in heart rate and difficulty atrioventricular conduction. The latter property is often used to treat heart failure complicated by atrial fibrillation: restoration of myocardial contractility is accompanied by normalization of heart rate. However, the pulse remains arrhythmic. Cardiac glycosides also eliminate tachycardia

by reducing pressure in the mouth of the vena cava, eliminating the Bainbridge reflex associated with activation of the sympathetic nervous system

Means used for heart block

Of the blockages, the most common are intraventricular. Blockade of one of the legs of the bundle of His does not require treatment. The blockade of two branches with a slowdown in atrio-vetericular conduction requires the installation of a pacemaker. In cases of intra-atrial conduction disturbances, treatment is also usually not usually required: since the impulse propagates into the nickname both through the three bundles and diffusely along the working myocardium of the atria, complete blockade is rare here. In clinical practice, the most dangerous violation of atrioventricular conduction. The atrioventricular junction is the bottleneck in the conductive system. With its lesions, it is possible to slow down atrioventricular conduction, as well as completely stop conducting with the development of complete transverse blockade of the heart. With the latter, the only treatment option is to install a pacemaker. In the case of incomplete blockade, the following agents may be prescribed as palliative therapy:

• β-adrenergic agonists (isadrine, orciprenaline)

• M-anticholinergics (atropine, scopolamine, platifillin)

• Sympathomimetics (ephedrine) due to lower efficacy and a large number of side effects (hypertensive crisis, insomnia, drug dependence) Currently not applicable

These funds, increasing the excitability of the conduction system of the heart, contribute to the acceleration of the impulse in it.

M-anticholinergics eliminate the effects of the vagus nerve, the tone of which increases significantly with lower myocardial infarction, as well as with operations on the organs of the gastrointestinal tract. Acetylcholine released from the efferent endings of the vagus nerve opens receptor-dependent potassium channels and causes hyperpolarization of the cells of the sinoatrial and atrioventricular nodes. The consequence of this are negative chrono-, batmo-, and dromotropic effects. Atropine and scopalamine eliminate these effects. Atropine has a small therapeutic breadth and in case of an overdose it can cause tachycardia, dry mucous membranes, urinary retention, especially in people with benign prostatic hyperplasia, as well as mental disorders. Side effects are significantly less pronounced in scopolamine and practically absent in platyphyllin.

β-adrenergic agonists have an effect completely opposite to M-anticholinergics. Interacting with β1-adrenergic receptors, they activate adenylate cyclase and increase the intracellular concentration of cAMP. This is accompanied by activation of the calcium channels of the node cells and is manifested by positive chrono-, dromo- and batmotropic effects. β-adrenergic agonists increase automatism and facilitate atrioventricular conduction. The most dangerous side effects are arrhythmias. Also β-adrenergic agonists increase the level of glucose and fat in the blood, cause tremor of skeletal muscles. In this regard, they can be used in a very limited period of time.

CLASS ANTIARRHYTHMIC MEDICINES (SODIUM CHANNEL BLOCKS)

The general properties of AAP class I are:

1) blockade of sodium channels;

2) a decrease in the rate of sodium current;

3) a decrease in the maximum depolarization rate;

4) an increase in the threshold of excitability;

5) a decrease in the rate of propagation of excitation in the myocardium

Quinidine

Quinidine has all the electrophysiological properties of AAA class IA.

Other pharmacological effects of quinidine:

1) blockade of α-adrenergic receptors;

2) blockade of cholinergic receptors;

3) negative inotropic effect.

Pharmacokinetics

The absorption of quinidine is 80-90%. The time of onset of the maximum concentration of the drug in plasma (Tmax) is reached within 3-4 hours. The therapeutic concentration in the blood is 3-6 μg / ml, toxic effects develop at concentrations above 8 μg / ml. Communication with blood plasma proteins - 70-90%, has a large volume of distribution. Permeability through the blood-brain (BBB) and placental barrier is low. The half-life (T1 / 2) of the drug is 5-8 hours. It is excreted by the kidneys, 10-50% unchanged.

Application

• Sinus rhythm restoration in patients with atrial fibrillation (recommendation level (SD) IIB / C).

• Maintaining sinus rhythm with recurrent atrial fibrillation in patients without organic heart disease.

• In patients with hypertension and coronary heart disease.

Quinidine is considered as a second-line drug used for the ineffectiveness of other, more active and safe drugs. To stop paroxysm of atrial fibrillation, a loading dose of 0.2-0.4 g is used, followed by 0.2 g every hour until a total dose of 1 g is reached. For long-term treatment, prolonged forms are used - 0.3-0.6 g after 8 -12 hours

Contraindications

1. Hypersensitivity.
2. AV block II-III degree.
3. Glycoside intoxication.
4. Disorders of intraventricular conduction.

Particular care should be taken when using quinidine in the following conditions:

- bronchial asthma;
- impaired liver or kidney function;
- hyperthyroidism;
- hypokalemia;
- myasthenia gravis;

psoriasis

- thrombocytopenia.

Undesirable effects of quinidine are recorded in 30-50% of patients and include:

ventricular tachyarrhythmias;

- systemic toxic effects:

gastrointestinal upset;

- symptoms of neurological disorders;
- hypersensitivity reactions in the form of hemolytic anemia and thrombocytopenia.

Relatively rare NLR is the development of lupus syndrome and hepatitis.

Security Control Methods

• Definition of blood pressure.
• ECG monitoring.
• Blood tests.
• Determination of liver and kidney function.
• Determination of serum concentration of K +.
• Determination of serum quinidine concentration.

Interactions

• Quinidine increases the effect of indirect anticoagulants, muscle relaxants, cardiac glycosides.

• The risk of arrhythmogenic effects of quinidine increases when used with tricyclic antidepressants, haloperidol and erythromycin.

• Antacids and antidiarrheal drugs slow the absorption and excretion of quinidine.

• Inhibitors of hepatic metabolism lengthen, and stimulants of hepatic metabolism shorten T1 / 2 of quinidine.

• Studies on the use of quinidine in pregnancy in humans have not been conducted.

• Quinine, which is close in structure, caused congenital malformations of the central nervous system and limbs, and had an ototoxic effect.
• Quinidine passes into breast milk, but no complications have been reported.
• Special studies on the use of quinidine in children have not been conducted, the use of prolonged forms is not recommended.
• No studies have been performed in elderly patients. Specific problems associated with the use of quinidine are not expected.
• Probable age-related changes in liver and kidney function may require a dose adjustment of quinidine.

Procainamide

Procainamide has the properties of AAA class IA. Other pharmacological effects of procainamide:
1) ganglion-blocking activity;
2) moderate blockade of cholinergic receptors;
3) moderate negative inotropic effect.

Pharmacokinetics

With intravenous administration, procainamide begins to act almost immediately. When taken orally, absorption is 70-90%. Communication with plasma proteins is low (10-20%). Penetrates through the BBB and the placental barrier. Tmax - 1-2 hours. Therapeutic concentration - 4-10 mg / l. T1 / 2 - 2.5-4.5 hours, with impaired renal function - 11-20 hours. Procainamide undergoes hepatic transformation with the formation of N-acetylprocainamide (up to 25%), an active metabolite with class III AAP properties. Procainamide is excreted by the kidneys (up to 50-60% unchanged).

Application

Existing recommendations support the use of procainamide only for the relief of paroxysmal arrhythmias. The use of procainamide (intravenously) is indicated for:
1) treatment of resistant to electropulse therapy of ventricular tachycardia or ventricular fibrillation (UR PV / S);
2) relief of stable ventricular tachycardia without significant hemodynamic disturbances (UR IIB / C);
3) treatment of continuously recurring ventricular tachycardia in combination with β-adrenergic blockers (UR I / C) in patients with acute coronary syndrome or myocardial infarction;
4) for relief of monomorphic stable or recurrent ventricular tachycardia (UR IIA / C);
5) highly effective (UR I / B) for stopping wide complex tachyarrhythmias of unknown origin [either ventricular tachycardia or supraventricular tachycardia with the participation of additional pathways (DPP)];
6) can be used to relieve paroxysms of atrial fibrillation (UR IIB / C).

Procainamide is administered intravenously at a rate of not more than 50 mg / min until the arrhythmia paroxysm is stopped or the total dose is reached
1000 mg

Contraindications

• Hypersensitivity.
• AV blockade degree).

Particular care must be taken when using procainamide in the following conditions:
- with blockade of the legs of the bundle of His;
- an overdose of cardiac glycosides;
- bronchial asthma;
- chronic heart failure;
- impaired liver or kidney function;
- a history of systemic lupus erythematosus;
- myasthenia gravis.

Adverse drug reactions

1. Ventricular arrhythmias (VA), ventricular fibrillation, or asystole with rapid intravenous administration or overdose.
2. Toxic effect on hematopoiesis (agranulocytosis, neutropenia, thrombocytopenia, aplastic anemia).
3. Hypotension (especially with rapid intravenous administration).
4. Allergic reactions.
5. Lupus-like syndrome.
6. Toxic effect on the central nervous system (confusion, hallucinations, depression).

Security Control Methods

• Monitoring of blood pressure and heart rate, including ECG analysis.
• Determination of serum concentrations of procainamide and N-acetylprocainamide.
• Determination of titers of antinuclear antibodies.
• General blood analysis.

The use of procainamide

• Increases the risk of developing arrhythmias in combination with other AARPs.
• Enhances the action of antihypertensives, antihistamines, anticholinergic and cytostatic agents, muscle relaxants.
• Reduces the activity of anti-asthenic agents. Procainamide crosses the placental barrier. Despite on the identification of procainamide and metabolites in the fetal blood serum, no adverse effects on the fetus and newborn were noted.

There is a potential risk of maternal hypotension and uteroplacental insufficiency.

In pediatric practice, no specific problems limiting the use of procainamide were found. To achieve a therapeutic effect, higher doses may be required than in adults.

In elderly patients, hypotension is more likely to develop. Probable age-related changes in kidney function may require the use of lower doses of procainamide.

Disopyramides

Disopyramide® has the electrophysiological properties of AAA class IA.

Other pharmacological effects of disopyramide□:

1. Blockade of cholinergic receptors.
2. Negative inotropic effect.

Pharmacokinetics

Absorption is fast and almost complete (95%). Protein binding is moderate (50%), depends on the concentration of the drug and can range from 35 to 95%. Penetration through the BBB and the placental barrier is low. Tmax - 0.5-3 hours. The therapeutic concentration in the blood serum is 2-4 μg / ml. Biotransformation in the liver, metabolites have antiarrhythmic and anticholinergic activity. T1 / 2 - 4-10 hours. Excretion mainly by the kidneys (about 50% unchanged and 30% - in the form of metabolites), with bile - about 15%.

Application

Existing recommendations support the use of disopyramide□ only for the treatment of recurrent focal atrial tachycardia and only in combination with drugs that slow down AV conduction (UR PA / B).

Disopyramide® is used in a loading dose of 300 mg, followed by 100-200 mg 4 times a day.

Contraindication to the use of disopyramide□: AV block II-III degree.

Caution must be observed under the following conditions:

1) with cardiomyopathy;
2) chronic heart failure;
3) diabetes;
4) angle-closure glaucoma;
5) impaired liver or kidney function;
6) hyperilia hypokalemia;
7) myasthenia gravis;
8) prostatic hypertrophy.

Adverse drug reactions
• Ventricular tachyarrhythmias.
• Anticholinergic effects: dry mouth, constipation, urinary retention, worsening of glaucoma.
• The development or progression of symptoms of heart failure.
• Hypotension.
• muscle weakness.
• Agranulocytosis.
• Exacerbation of glaucoma.
• Cholestasis.
• Hypoglycemia.
• Depression.
Security Control Methods
1. Control of blood pressure.
2. ECG monitoring (QRS broadening, Q-T lengthening).
3. Determination of liver and kidney functions, K + level, intraocular pressure.
Interactions
• With alcohol (the development of hypotension and hypoglycemia).
• With other AAPs (increased risk of developing arrhythmias), with β-adrenergic blockers (increased symptoms of heart failure).
• With anticoagulants (increased action).
• With oral antidiabetic agents and insulin, with inducers of liver enzymes (decreased concentration).
Disopyramide is found in the blood of the fetus, but without any clinical consequences. It passes into breast milk, but in fairly low concentrations. There were no specific problems associated with the use of disopyramide® in pediatrics.
In elderly patients, increased sensitivity to the anticholinergic effects of disopyramide® may occur. Age-related changes in kidney function may require dose adjustment of disopyramide®.
Lidocaine
Pharmacokinetics
Plasma protein binding varies from moderate to high (60-80%) and depends on the concentration of the drug. The therapeutic plasma concentration is 1.5-5 μg / ml. Penetrates through the BBB, the placental barrier and into breast milk. Lidocaine is mainly subjected to hepatic transformation (up to 90%), mainly with the participation of microsomal enzymes. T1 / 2 after a bolus injection - 1.5-2 hours, with prolonged infusion T1 / 2 increases to 3 hours. The half-life is also affected by the concentration of plasma proteins, especially acute phase proteins. Li-Docaine is excreted by the kidneys (up to 10% unchanged) and with bile. With CHF, cumulation of metabolites is possible.
Application
Existing recommendations support the use of lidocaine for stopping:
 ventricular arrhythmias - monomorphic and polymorphic, associated with acute myocardial infarction (AMI) or ACS (UR IIB / C);
 stable and recurrent monomorphic ventricular tachycardia and ventricular tachycardia of the pirouette type (level of recommendations IIB / C);
 wide complex tachycardia of unspecified origin (UR IIB / C).
Lidocaine is administered intravenously as a bolus of 1 mg / kg (50-120 mg) at a rate of 25-50 mg / min; if necessary, the dose is repeated after 5 minutes.
In diseases of the liver and heart failure, the dose is reduced by 30-40%.
Contraindication to the use of lidocaine: severe AV and intraventricular blockade.
With caution, lidocaine must be used in the following conditions:
1) in chronic heart failure;
2) impaired liver function;
3) impaired renal function;

4) hypovolemia or shock;
5) sinus bradycardia;
6) WPW syndrome;
7) hypersensitivity to lidocaine.
Adverse drug reactions
• Hypotension.
• Bradycardia.
• Risk of developing asystole.
• Respiratory arrest in case of overdose.
• Symptoms of neurotoxicity.
• Allergic reactions.
Security Control Methods
• Monitoring of blood pressure and ECG.
• Determination of serum concentration of K +.
• Determination of serum lidocaine concentration.
Interactions
• With β-blockers - the risk of developing bradycardia.
• When used with other AAPs - a negative effect on conductivity and contractility.
• When used together with barbiturates, the risk of respiratory arrest increases intravenously.
• Inducers of microsomal liver enzymes can reduce T1 / 2 of lidocaine.
Mexiletine
Pharmacokinetics
Mexiletin® is well absorbed from the upper gastrointestinal tract (up to 90%). Plasma protein binding is moderate (60-75%). Penetrates through the placental barrier and into breast milk. Biotransformation is predominantly in the liver (up to 85%) with the participation of the CYP1A2 enzyme system with the formation of inactive metabolites. The onset of action is after 0.5-2 hours, Ttah - 2-3 hours. The therapeutic concentration is 0.5-2.0 μg / kg. T1 / 2 - 10-12 hours, can increase up to 25 hours for diseases of the liver and kidneys, a decrease in minute blood volume. It is excreted with bile and kidneys (up to 10% unchanged).
Application
Existing recommendations support the use of mexiletine® for the treatment of ventricular tachycardia such as pirouette in patients with long QT syndrome (UR IIB / C).
Mexiletine dosing: oral loading dose of 400 mg with subsequent administration of 200 mg after 8 hours.
Mexiletine is contraindicated in high degree AV blockade and cardiogenic shock.
The use of mexiletine requires caution in the following conditions.
1. Chronic heart failure.
2. Violations of the liver.
3. Hypotension.
4. Sick sinus syndrome (SSS).
5. Epilepsy.
6. Hypersensitivity to mexiletine®.
Adverse drug reactions
• Pain in the chest.
• Shortness of breath.
• Leukopenia.
• Agranulocytosis.
• Thrombocytopenia.
• Cramps.
• Symptoms of neurotoxicity.
• Disorders from the gastrointestinal tract - taste disorders, nausea, constipation or diarrhea.
Security Control Methods

1. ECG monitoring.
2. Determination of the activity of liver enzymes.
3. Determination of the concentration of the drug in the blood.

Interactions

• Quinidine, β-blockers and amiodarone enhance the antiarrhythmic effect of mexiletine®.
• Inducers of hepatic metabolism can reduce the concentration of mexiletine® in the blood plasma.
• Gastrointestinal motility stimulants, narcotic analgesics, H2-histamine receptor blockers reduce the absorption of mexiletine®.
• Metoclopramide enhances the absorption of mexiletine®.
• Sodium bicarbonate and urine alkalizing diuretics reduce the excretion of mexiletine®.

Propaphenone

Propafenone has the electrophysiological effects of AAP IC class.

Other pharmacological effects:

1) moderate blockade of β-adrenergic receptors, as well as slow calcium channels;
2) negative inotropic effect.

Pharmacokinetics

Propafenone is rapidly and well absorbed in the digestive tract (up to 90%). The effect of the primary passage through the liver determines the systemic bioavailability of 5-50%. Eating and increasing the dose of the drug increase systemic bioavailability. Protein binding is very high (up to 97%). Permeability through the BBB and the placental barrier is low. Tmax = 1-3.5 hours. The concentration in the blood plasma is 500-1500 mcg / l. It is metabolized mainly in the liver.

Application

• Relief of hemodynamically stable focal atrial tachycardia (UR IIA / C).
• Prevention of recurrence of focal atrial tachycardia (SD IIA / C).
• Relief of hemodynamically unstable atrioventricular reciprocal tachycardia (HR IIA / C).
• Long-term treatment of atrioventricular reciprocal tachycardia (AVRT), resistant to β-blockers and verapamil, and when it is impossible to perform ablation (UR IIA / B).
• Treatment of AVRT in patients with DPP (UR IIA / C).
• Treatment of focal tachycardia of the AV compound (UR PA / C).

The use of propafenone is recommended for stopping paroxysm of atrial fibrillation up to 7 days old (UR I / A) and as the drug of choice for maintaining sinus rhythm in patients with “idiopathic” atrial fibrillation or in patients with hypertension without severe left ventricular hypertrophy.

For relief of arrhythmias, a loading dose of 600 mg orally or 1.5-3.0 mg / kg intravenously for 10-20 minutes.

With prolonged use, the starting dose of 150 mg after 8 hours (450 mg / day) with a gradual increase in dose to 300 mg after 8 hours (900 mg / day).

Contraindications

High degree AV block or “two-beam” intraventricular block in patients without ECS.

The use of propafenone requires caution:

1) with bronchial obstructive diseases;
2) sinus bradycardia and SSSU;
3) chronic heart failure;
4) impaired liver function;
5) hypoilia of hyperkalemia;
6) hypotension;
7) impaired renal function;
8) hypersensitivity to propafenone.

Adverse drug reactions

• Arrhythmogenic effects.
• Development of the AV blockade.

• Progression of heart failure.
• Hypotension.
• Agranulocytosis.
• Thrombocytopenia.
• The appearance of antinuclear antibodies.
• Symptoms of neurotoxicity (dizziness, ataxia).
• Allergic reactions.
• Arthralgia.
• Bronchospasm.

Interactions

• With digoxin - an increase in the concentration of digoxin in the blood plasma.
• With warfarin - increased plasma concentration of warfarin.
• With β-adrenergic blocking agents - increased antiarrhythmic effect, as well as increased concentrations of propranolol and metoprolol.

CLASS ANTIARRHYTHMIC MEDICINES

β-adrenergic blockers

Class II AAA (β-blockers) have the ability to block the effect of catecholamines on the rate of spontaneous diastolic depolarization of sinus node-driving cells, which leads to a reduction in heart rate. β-blockers slow down the momentum and increase the refractory period of the atrioventricular node. β-blockers inhibit pathological automatism and trace depolarization. The effectiveness of β-blockers in ventricular arrhythmias is due to their ability to eliminate and prevent ischemia - an essential factor in the induction of ventricular arrhythmias. β-Adrenergic blockers actively change the underlying pathological processes that underlie the structural and functional myocardial remodeling. Some β-blockers (carvedilol) have antioxidant properties. β-adrenoblockers block apoptosis of cardiomyocytes mediated by catecholamines. Thus, they are able to modify the processes that influence the formation of re-entry circles in the tissue of the ventricles, as well as block the mechanisms that can lead to their activation. Unlike AAP of other classes, β-blockers do not have an arrhythmogenic effect. β-blockers also have antianginal and antihypertensive activity. Efficiency and safety makes them the drugs of choice for various types of arrhythmias, both for supraventricular (CBA) and ventricular.

Application

1. Symptomatic sinus tachycardia against the background of psychoemotional stress, anxiety or panic attacks, as well as with thyroid toxicosis (UR I / C).
2. Paroxysmal sinoatrial reciprocal tachycardia (URI / C).
3. Focal atrial tachycardia (UR I-IIA / C).
4. Atrioventricular reciprocal tachycardia (UR IIA / C).
5. Reciprocal arrhythmia in patients with DPP (in the absence of abnormally fast paths) (HR IIA / C).
6. Focal tachycardia of the AV compound (UR PA / S).
7. Control of heart rate in patients with a constant form of atrial fibrillation (UR I / C).
8. Prophylactic use in the presence of ventricular extrasystole (PVC) and unstable ventricular tachycardia in patients with ACS or AMI (UR I / A).
9. Treatment of ventricular tachycardia not associated with ACS - recurrent monomorphic ventricular tachycardia (UR IIA / C), polymorphic ventricular tachycardia (UR I / B).
10. Ventricular tachycardia of the pirouette type (together with EX) (URI / B).
11. Continuously recurring ventricular tachycardia (UR IIB / C).
12. β-blockers (metoprolol, bisoprolol, carvedilol) are recommended for patients with myocardial infarction for primary prevention of SCD (UR I / A).
13. The use of β-blockers is also recommended for patients who have had myocardial infarction who have had episodes of ventricular fibrillation, persistent ventricular tachycardia with severe hemodynamic disturbances or episodes of persistent ventricular tachycardia without significant hemodynamic disturbances (PA / C).

14. Prevention of SCD in patients with DCMP, especially in the presence of risk factors - transferred ventricular fibrillation or an episode of persistent ventricular tachycardia (UR I / B).
15. In patients with Q-T congenital elongation syndrome for the prevention of ventricular arrhythmias as in the asymptomatic course of the disease (UR IIA / C).
16. In patients who have had an episode of pirouette type tachycardia (URI-IIA / C).
17. Primary (SD I / C) and secondary (SD IIA / C) prophylaxis.
18. In patients with catechol-dependent polymorphic ventricular tachycardia.
19. Treatment of ventricular arrhythmias in patients without organic myocardial damage (idiopathic left ventricular tachycardia or ventricular tachycardia from the outflow tract of the right ventricle) (UR IIA / C).

Contraindications

1. Syndrome weakness syndrome.

2. AV block II-III degree.

3. Bronchial asthma of severe course.

The use of β-blockers requires caution in:

- bronchial obstructive diseases;

- decompensation of heart failure;

- diabetes mellitus;

- peripheral arteriopathies.

Adverse drug reactions

• Bradyarrhythmias.

• Violations of AV conduction.

• Bronchospasm.

• Exacerbation of peripheral arteriopathies.

• Sexual dysfunction.

• Depression.

Interactions

With BMCC, amiodarone, digoxin - an increase in the risk of bradyarrhythmias and violations of AV conduction.

CLASS ANTIARRHYTHMIC MEDICINES

(POTASSIUM CHANNEL BLOCKERS)

The main electrophysiological property of class III AAPs is blockade of potassium channels and a slowdown in potassium current, which leads to an increase in PPD and ERP in the tissues of the atria and ventricles. Class III AAPs suppress automatism.

Amiodarone

Amiodarone has class III AAP effects. In addition, it slightly blocks sodium channels, slow calcium channels, and also exhibits moderately pronounced properties of the β- and α-adrenergic receptor blocker. Amiodarone affects the metabolism of thyroid hormones.

Pharmacokinetics

The absorption of amiodarone from the gastrointestinal tract is slow and variable (20-55%). Communication with proteins is high (up to 96%). Penetrates through the BBB and the placental barrier, is secreted with breast milk. Amiodarone is characterized by a large and variable volume of distribution as a result of intensive accumulation in adipose tissue and in organs with good blood supply. Pharmacokinetics of amiodarone require the use of high loading doses. The time to reach maximum plasma concentration is 3-7 hours. The onset of action ranges from 2-3 days to 2-3 months, even when using loading doses. The therapeutic concentration is 1-2.5 μg / ml. Amiodarone is metabolized in the liver, possibly by deiodination with the formation of an active metabolite - desethylamiodarone. The half-life of amiodarone is on average about 40 days. It is excreted mainly with bile (80-95%), less than 1% is removed by the kidneys.

Dosage

For hospitalized patients with oral saturation of 1.2-1.8 g / day to a total dose of 10 g and subsequent administration of a maintenance dose of 200-400 mg / day.

With combined saturation, the starting dose is 7-5 mg / kg intravenously for 30-60 minutes, then 1.2-1.8 g / day intravenously as a continuous infusion or by mouth until a dose of 10 g is reached and then a maintenance dose of 200- 400 mg / day.

For outpatients - 600-800 mg / day by mouth up to a total dose of 10 g and subsequent administration of a maintenance dose

200-400 mg / day.

Application

1. Treatment of patients with AVRT, especially in the presence of poorly tolerated paroxysms, accompanied by hemodynamic disturbances (UR IIA / C).

2. Treatment of supraventricular arrhythmias in patients with DPP - AVRT or atrial fibrillation (UR IIA / C).

3. Treatment of focal atrial tachycardia (UR IIA / C) and focal tachycardia of the AV compound (UR IIA / C).

4. The restoration of sinus rhythm with persistent atrial fibrillation (UR IIA / A).

5. Sinus rhythm maintenance in patients with heart failure, coronary heart disease or severe LVH, and in patients without organic heart damage with flecainide□, propafenone or sotalol ineffectiveness.

Emergency treatment of ventricular arrhythmias

1. In patients with ACS / AMI - ventricular tachycardia or ventricular fibrillation with cardioversion ineffectiveness (HR IIA / B).

2. Stable ventricular tachycardia without hemodynamic disturbances (UR I / B).

3. With ventricular arrhythmias not associated with ACS / AMI, ventricular tachycardia or ventricular fibrillation with cardioversion ineffectiveness (UR I / B).

4. Stable ventricular tachycardia with hemodynamic disturbances or resistant to other AAPs (UR IIA / C).

5. Recurrent monomorphic ventricular tachycardia (UR IIA / C).

6. Polymorphic ventricular tachycardia (in the absence of an elongated QT) (UR I / C).

7. Continuously recurring ventricular tachycardia (UR IIB / C).

Amiodarone is recommended for use:

- in patients after myocardial infarction, for the primary prevention of SCD (UR IIA / A);

- in patients with episodes of ventricular fibrillation or ventricular tachycardia (UR IIA / C);

- in case of relapse of ventricular tachycardia in the treatment of β-adrenergic blockers (UR IIA / B);

- in patients with dilated cardiomyopathy who have experienced episodes of ventricular tachycardia or ventricular fibrillation (UR IIB / B);

- in patients with hypertrophic cardiomyopathy for primary prevention (UR IIB / B);

- after a transferred episode of ventricular tachycardia or ventricular fibrillation when it is impossible to use an implantable cardioverter-defibrillator (UR IIA / C);

- in patients with arrhythmogenic dysplasia of the right ventricle after an episode of ventricular tachycardia or ventricular fibrillation when it is not possible to use an implantable cardioverter-defibrillator (HR IIA / C).

Amiodarone is contraindicated in II-III degree AV blockages, episodes of sinus bradycardia with the development of syncopal conditions, SSSU in the absence of EX.

The use of amiodarone requires caution in the following diseases / conditions:

1) in chronic heart failure;

2) impaired liver function;

3) hypokalemia;

4) hypersensitivity to amiodarone;

5) dysfunction of the thyroid gland;

6) a change in the morphology of the thyroid gland detected by ultrasound.

Adverse drug reactions

1. Symptomatic bradycardia.

2. Arrhythmogenic effect.

3. Symptoms of neurotoxicity.

4. Photosensitivity.

5. Fibrosis of the lungs.

6. Interstitial pneumonitis or alveolitis.

7. Disorders of the thyroid gland.

8. Keratopathy.

9. Allergic reactions.

10. Hepatitis.

Security Control Methods

1. Determination of ACT and ALT activity.

2. Chest x-ray.

3. Spirography.

4. Electrocardiography.

5. Ophthalmological examination.

6. Determination of the functional state of the thyroid gland.

7. Determination of the content of amiodarone in blood plasma.

Interactions

1. Other AAPs - the risk of developing ventricular arrhythmias.

2. Anticoagulants - inhibition of metabolism and increased effect of anticoagulants.

3. Digitalis preparations - increasing the concentration of digoxin, inhibition of the sinoarterial (CA) node and the AV node.

4. β-blockers - an increased risk of bradyarrhythmias and AV blockade.

5. Loop diuretics - the risk of arrhythmias associated with hypokalemia. Special studies on the use of amiodarone in children

not carried out. In them, the onset of amiodarone may be more rapid, and the duration of action may be shorter. It was noted that in children there is a more pronounced interaction of amiodarone with digitalis preparations.

In elderly patients, there may be a greater sensitivity to the effect of amiodarone on thyroid function, as well as an increase in the frequency of ataxia and other neurotoxic effects.

Sotalol

Sotalol has the electrophysiological effects of class III AAPs. This is a fairly active β-blocker with antianginal and hypotensive effects.

Pharmacokinetics

Sotalol is well absorbed from the digestive tract (up to 80%). It practically does not bind to plasma proteins. Permeability through the BBB and the placental barrier is low. It is metabolized in the liver. T1 / 2 - 7-18 hours, increases with chronic renal failure. It is excreted by the kidneys, up to 75% unchanged.

Application

Sotalol is used in a starting dose of 80 mg 2 times a day, the maximum daily dose is 320 mg per day (a further increase in the dose significantly increases the risk of pro-arrhythmias).

With intravenous administration, the total maximum dose of 1.5 mg / kg is recommended, slow administration (5-15 minutes), under the supervision of ECG and blood pressure.

It is applied for:

- relief of recurrent monomorphic ventricular tachycardia (UR IIA / C);

- treatment of recurrent ventricular tachycardia resistant to β-adrenoblockers in patients after myocardial infarction (UR IIA / C);

- treatment and prevention of persistent ventricular tachycardia in patients with arrhythmogenic dysplasia of the right ventricle when it is impossible to implant a cardioverter-defibrillator (UR IIA / C);

- primary prevention of BCC (UR IIB / C);

- relief of paroxysm of atrial fibrillation / flutter (AF) (UR IIA / C);

- treatment or prophylaxis of recurrent AFT (UR IIA / C);

- treatment of recurrent AVRT resistant to β-adrenergic blockers and BMCC (UR IIA / C);

- treatment or prevention of AVRT in patients with DPP (UR IIA / C);

- treatment of focal tachycardia of the AV compound (UR IIA / C);

- as a first-line drug for maintaining sinus rhythm in patients with atrial fibrillation, who do not have organic heart damage, with hypertension without severe LVH and patients with coronary artery disease.

Contraindications

1. AV blockade of the II-III degree.

2. SA-blockade and SSSU.

3. Arterial hypotension.

Due to the presence of non-selective β-blocking activity, contraindications and restrictions for β-blockers should be considered.

The use of sotalol requires caution in the following diseases or conditions:

1) in chronic heart failure;

2) renal failure;

3) hypokalemia;

4) hypersensitivity to sotalol;

5) depression.

Adverse drug reactions

1. Arrhythmogenic effect (ventricular tachycardia type pirouette).

2. Symptoms of neurotoxicity.

3. Side effects characteristic of β-blockers.

4. Thrombocytopenia.

5. Agranulocytosis.

6. Leukopenia.

7. Allergic reactions.

Security Control Methods

1. ECG monitoring.

2. Control of glucose concentration in patients with diabetes mellitus.

3. Evaluation of kidney function, especially in elderly patients.

Interactions

• Increased risk of arrhythmias when given together with class I AAA.

• With iodine-containing contrast agents - increased risk of anaphylactic reactions.

• With inhaled anesthetics - the risk of hypotension and cardiac depression.

• When combined with antihypertensive drugs - the risk of hypotension.

• With loop diuretics - increased risk of developing arrhythmias.

Ibutilide

Ibutilide® blocks outgoing potassium current and slow inward sodium current. Increases the PPD and ERP of cardiomyocytes of the atria, ventricles, AV node, His-Purkinje system, DTP. Ibutilide® suppresses automatism.

Pharmacokinetics

Ibutilide® is administered intravenously. Communication with proteins is low (about 40%). The drug is actively metabolized in the liver, about 80% is excreted by the kidneys in the form of metabolites, approximately 10% is unchanged. TU varies from 2 to 12 hours.

Application

Existing recommendations support the use of ibutilide® for copulating paroxysmal or persistent atrial fibrillation lasting up to 7 days (UR I / A) and more than 7 days (UR IIA / A).

Ibutilide® is administered intravenously at a dose of 1 mg for 10 minutes, if necessary, the dose is re-administered.

Contraindications

1. Hypersensitivity.

2. Pregnancy.

3. The period of lactation.

Caution should be used in the following diseases / conditions:

1) with sick sinus syndrome;

2) SA- and AV-blockades;

3) collapse;

4) hypokalemia;

5) chronic heart failure;

6) liver failure.

Adverse drug reactions

1. Polymorphic ventricular tachycardia or tachycardia type pirouette.

2. Bradyarrhythmias.

3. AV blockade.

4. Nausea.

5. Headache.

6. Renal failure.

Security Control Methods

• Monitoring ECG and blood pressure.

Interactions

• With other AAPs - increased risk of developing ventricular arrhythmias.

• With β-adrenergic blockers, BMKK - increased risk of bradycardia and AV block.

CLASS ANTIARRHYTHMIC MEDICINES (SLOW CALCIUM CHANNEL BLOCKS)

BMCC (verapamil and diltiazem) block slow calcium channels, which mainly determine the rate of depolarization - CA- and AV-nodes. BMKK suppress automatism, slow down and increase the refractoriness of CA- and AV-nodes. Slow calcium currents may be a necessary component in the development of trace depolarization. BMCC are able to suppress trace depolarization and can be effective in trigger arrhythmias. They also have anti-ischemic and antihypertensive properties.

Pharmacokinetics

Verapamil is well absorbed in the digestive tract (up to 90%). First-pass hepatic metabolism reduces bioavailability by 20-35%. Up to 90% of verapamil binds to plasma proteins. It is metabolized in the liver with the participation of the enzyme systems CYP3A4, CYP3A5 and CYP3A7, up to 11 metabolites are known, the most significant is norverapamil, which has moderate hypotensive activity. The half-life is 5-12 hours. It is excreted mainly by the kidneys (up to 70%). Diltiazem is well reabsorbed in the digestive tract (up to 90%), but the first-pass metabolism reduces its bioavailability to 40%. Up to 70-80% of the drug binds to plasma proteins. Diltiazem is metabolized in the liver with the participation of the cytochrome CYP3A4, CYP3A5

and CYP3A7 enzyme systems with the formation of deacetyldylthiazem, which has a much lower pharmacological activity than diltiazem. The elimination half-life is about 3.5 hours. It is excreted with bile (about 65%) and kidneys (about 35%).

Application

Existing recommendations support the use of BMCC for the treatment of the following arrhythmias:

- symptomatic sinus tachycardia (UR IIA / C);

- for stopping and preventive treatment of AVRT (UR IIA / C);

- for stopping (UR IIA / C) and preventive treatment (UR

I / C) FPT.

BMCC is recommended to be used to control heart rate in patients with a constant form of atrial fibrillation (UR I / A).

In addition, BMCC can be effective in the treatment of idiopathic (faith-sensitive) ventricular tachycardia (UR IIA / C).

For emergency control of heart rate or relief of supraventricular tachycardia, verapamil is administered intravenously 0.075-0.150 mg / kg for 2 minutes, diltiazem - 0.25 mg / kg for 2 minutes.

When taken orally, the dose of verapamil is 120-480 mg / day, diltiazem - 60-360 mg / day.

Contraindications

1. Hypersensitivity, hypotension.

2. SA or AV blockade.

3. Syndrome weakness syndrome.

4. Atrial fibrillation or atrial flutter in patients

with DPP.

5. CHF due to systolic dysfunction of the left ventricle.

With caution, BMCC should be used in the following diseases or conditions:

1) AV blockade of I degree;

2) bradycardia;

3) hepatic or renal failure;

4) the state of old age.

Adverse drug reactions

1. Bradycardia.

2. Hypotension.

3. Violations of AV conduction.

4. Symptoms of neurotoxicity.

5. Constipation.

6. Gingival hyperplasia.

7. Allergic reactions.

8. Pretibial edema.

Security Control Methods

• Monitoring of blood pressure and ECG.

• Determination of the activity of liver enzymes.

Interactions

• With β-blockers - potentiation of the development of bradycardia and conduction disorders.

• With AAA drugs of classes IA and III - the risk of a significant lengthening of QT.

• Digitalis preparations - violations of AV conduction.

• With inducers of hepatic metabolism - weakening the effects of BMCC due to a decrease in plasma concentration.

BMCC pass through the placenta, however, BMCC studies on fetal development have not been conducted. Hypotension caused in the mother by rapid intravenous administration of BMCC can cause fetal distress syndrome. BMKK pass into breast milk.

Special studies on the use of BMCC in pediatrics have not been conducted, specific pediatric problems that limit their use in children are not expected. There are reports of significant hemodynamic disturbances in newborns and infants with intravenous administration of verapamil.

In elderly patients, the half-life of BMCC may increase due to a decrease in renal clearance.

ANTIARRHYTHMIC MEDICINES NOT SUBJECT TO THE CLASSIFICATION

M-anticholinergics (atropine) - used to increase heart rate in brady-cardia.

Cardiac glycosides (digoxin) - used to control the frequency of ventricular contractions in atrial arrhythmias with a high frequency of atrial contractions due to the slowing of conduction in the atrioventricular node.

Electrolytes (solutions of potassium, magnesium, oral preparations of potassium and magnesium). Magnesium preparations are used to treat ventricular tachycardia of the pirouette type, which occurs according to the trigger mechanism. In addition, oral magnesium preparations can be successfully used for the symptomatic treatment of ventricular extrasystole in patients without organic heart disease.

Adenosine is mainly used to relieve paroxysmal supraventricular tachycardia.

Preparations that do not have direct electrophysiological properties

1. ACE inhibitors can reduce the risk of fatal ventricular arrhythmias and SCD in patients with

myocardial infarction and DCMP.

2. In patients after myocardial infarction, the use of blockers of aldosterone receptors, as well as statins, reduces the risk of fatal ventricular arrhythmias and SCD.

Apparently, drugs that do not have direct electrophysiological properties can affect myocardial remodeling. These drugs reduce the likelihood of substrate formation for re-entry arrhythmias or inhibit the activation of existing ones.

CLINICAL-PHARMACOLOGICAL APPROACHES TO THE SELECTION AND APPLICATION OF MEDICINES FOR HEART RHYTHM DISORDERS

Ventricular arrhythmias

The main types of ventricular arrhythmias:

1) ventricular extrasystole;

2) unstable ventricular tachycardia;

3) stable monomorphic or polymorphic ventricular tachycardia;

4) ventricular fibrillation.

Adequate treatment for ventricular arrhythmias

Adequate treatment is associated with the need to understand the mechanisms of development and etiology of arrhythmias, assess concomitant diseases (conditions) that can contribute to the development or provocation of arrhythmia, assess the risk due to arrhythmia, and information on the benefit / risk ratio of the planned antiarrhythmic intervention.

The main mechanism for the development of ventricular arrhythmias in patients with structural heart lesions is the re-entry and circulation of excitation. Circles of impulse circulation, as a rule, are formed in the border areas between normal and pathologically altered tissue in the myocardium of the ventricles. Trigger activity is considered as the main mechanism for the development of arrhythmias in patients without organic myocardial damage (elongated QT syndromes, catechol-dependent polymorphic ventricular tachycardia, idiopathic ventricular tachycardia from the outflow tract of the right ventricle). Pathological automatism may be responsible for the development of ventricular arrhythmias in acute myocardial ischemia, as well as, possibly, for idiopathic left ventricular tachycardia. ZhE and unstable ventricular tachycardia in patients without organic heart disease are not associated with an increased risk of SCD, therefore, in the absence of symptoms, treatment is not required. It is necessary only if there are severe symptoms that significantly reduce the quality of life.

The drugs of choice are β-blockers; if they are ineffective, amiodarone, sotalol or flecainide can be used.

The main goal of treating ventricular arrhythmias in patients with organic heart diseases, as well as with genetically determined electrical anomalies (prolonged QT syndrome), is to reduce the risk of SCD, mainly due to fatal ventricular tachycardia or ventricular fibrillation.

Primary prevention includes treatment methods aimed at preventing fatal arrhythmic episodes in patients without a history of ventricular arrhythmias or SCD, but with signs of high risk.

Secondary prophylaxis is used in patients who have experienced an episode of ventricular tachycardia or SCD.

Management of patients with ventricular arrhythmias includes the use of:

- antiarrhythmic drugs;

- implantable devices (defibrillators-cardioverters);

- various options for ablation;

- surgical interventions.

The basis of pharmacotherapy for ventricular arrhythmias is β-blockers. They effectively suppress ventricular arrhythmias and reduce the risk of SCD both in patients with organic heart lesions and in the absence of structural changes in the myocardium.

Data on the efficacy of amiodarone are controversial, although evidence of suppression of ventricular arrhythmias and decreased

lower risk of SCD in patients with myocardial infarction and DCMP. Long-term use of amiodarone may be limited by severe systemic toxicity.

Other AAPs have been found to be ineffective for preventing SCD and increasing survival. Currently available AAPs can be used in certain clinical situations, mainly for emergency treatment of ventricular arrhythmias, but should be used with caution due to the risk of developing proarrhythmia.

For the prevention of SCD in patients with organic heart damage, drugs that do not have antiarrhythmic activity are also effective. They are able to influence the processes that determine the development of the substrate for the development of ventricular arrhythmias: ischemia and pathological remodeling of the ventricular myocardium. So, the ability to reduce the risk of SCD has been proven for antiplatelet agents, statins, ACE inhibitors, aldosterone receptor blockers.

SUPRAVENTRICULAR ARRhythmias

The main types of supraventricular arrhythmias:
1) supraventricular extrasystole;
2) sinus reciprocal tachycardia;
3) atrial reciprocal tachycardia;
4) atrioventricular reciprocal tachycardia;
5) reciprocal tachycardia with the participation of additional pathways;
6) multifocal atrial tachycardia;
7) focal tachycardia of the atrioventricular junction.

Unlike ventricular arrhythmias, CBA in the vast majority of cases do not pose a threat to life. Their significance is determined by a fairly widespread prevalence, the presence of symptoms requiring emergency hospitalization, as well as a decrease in the quality of life as a result of limited physical activity or the development of symptoms of heart failure. The main mechanism for the development of reciprocal CBA is re-entry and excitation circulation. The most likely mechanism for the development of focal CBA is pathological automatism.

The main objective of treating CBA in most cases is to improve the quality of life of the patient.

Asymptomatic atrial extrasystole does not require treatment. It is necessary only in the presence of severe symptoms that significantly reduce the quality of life. In this case, β-adrenergic blocking agents or BMCC are the drugs of choice, if they are ineffective, amiodarone, sotalol or flecainide can be used. Treatment of CBA involves the relief of paroxysm and the use of prophylactic antiarrhythmic effects to prevent relapse.

The basis of the modern treatment of CBA are antiarrhythmic drugs of various classes (tab. 74-85) and various options for ablation. As a first-line drug, as a rule, drugs with low arrhythmogenic potential and low systemic toxicity - β-adrenergic blockers and BMCC are used.

Atrial fibrillation / atrial flutter

Atrial fibrillation or atrial flutter is a widespread arrhythmia. Atrial fibrillation is associated with an increased risk of cardiovascular complications, especially cerebral infarction. Perhaps the cardiovascular risk associated with atrial fibrillation is due to the severity of background (associated) diseases.

The main goals of treating atrial fibrillation are the prevention of systemic embolic complications, the prevention of hemodynamic disorders caused by an inappropriately high heart rate, and the control of symptoms.

Currently, there are two tactics for treating atrial fibrillation: restoring and maintaining sinus rhythm (rhythm control tactics) and maintaining atrial fibrillation with controlling the frequency of ventricular contractions (tactics of controlling heart rate). The results of the studies showed that the rhythm control tactics have no advantages over heart rate control tactics in terms of reducing the risk of cardiovascular complications and death. Moreover, for some groups, heart rate control tactics seem to be preferable.

For elderly patients with hypertension or cardiovascular disease, as an initial treatment, heart rate control tactics are more acceptable.

For younger patients, especially those with idiopathic atrial fibrillation, recovery tactics and maintaining sinus rhythm are preferred.

Recommendations for the pharmacological correction of atrial fibrillation (atrial fibrillation) are given in the tables

CLINICAL-PHARMACOLOGICAL APPROACHES TO THE SELECTION AND APPLICATION OF MEDICINES FOR PULMONARY Edema

CLINICAL RECOMMENDATIONS AND STANDARDS FOR MANAGEMENT OF PATIENTS

Pulmonary edema is the accumulation of fluid in the interstitial tissue and / or alveoli of the lungs as a result of transudation of plasma from the vessels of the pulmonary circulation.

Interstitial pulmonary edema - edema of the interstitial tissue of the lungs without the exit of transudate into the lumen of the alveoli. Clinically manifested by shortness of breath and cough without sputum. With the progression of the process, alveolar edema occurs.

Alveolar pulmonary edema is characterized by sweating of blood plasma into the lumen of the alveoli. Patients develop a cough with a separation of foamy sputum, suffocation, in the lungs, first, dry and then wet rales are heard.

Thus, interstitial and alveolar edema can be considered as two stages of the same process.

ETIOLOGY

• Cardiogenic pulmonary edema with low cardiac output

1. Myocardial infarction - a large area of damage, rupture of the walls of the heart, acute mitral regurgitation.
2. Decompensation of chronic heart failure - inadequate treatment, severe concomitant disease, severe anemia, arrhythmias.
3. Arrhythmias (supraventricular and ventricular tachycardia, bradycardia).
4. Obstruction in the path of blood flow - mitral or aortic stenosis, hypertrophic cardiomyopathy, tumors, blood clots.
5. Valvular insufficiency - mitral or aortic insufficiency.
6. Myocarditis.
7. Massive pulmonary embolism.
8. Pulmonary heart.
9. Hypertensive crisis.
10. Cardiac tamponade.
11. Heart injury.

• Cardiogenic pulmonary edema with high cardiac output

1. Anemia.
2. Thyrotoxicosis.

3. Acute glomerulonephritis with arterial hypertension.
4. Arteriovenous fistula.
3. Non-cardiogenic pulmonary edema. - Adult respiratory distress syndrome as a result of increased permeability of the alveolar membranes under the influence of toxins, as well as pneumonia, aspiration, pancreatitis.
CLINICAL PICTURE
1. Severe shortness of breath (dyspnea) and rapid breathing (tachypnea), participation in the act of breathing of the auxiliary muscles: inspiratory retraction of intercostal spaces and supraclavicular fossae.
2. Forced sitting position (orthopnea), anxiety, fear of death.
3. Cyanotic cold skin, profuse sweating.
Features of the clinical picture of interstitial pulmonary edema (cardiac asthma)
• Noisy wheezing, difficulty breathing (stridor).
• Auscultatory - against the background of weakened breathing, dry, sometimes sparse chalk-bubbling rales.
Features of the clinical picture of alveolar pulmonary edema
• Cough with foamy expectoration usually pink.
• In severe cases - aperiodic breathing of Chain-Stokes.
• Auscultation - wet, small-bubbling rales that initially occur in the lower parts of the lungs and gradually spread to the tops of the lungs.
Changes in the cardiovascular system
1. Tachycardia.
2. Alternating pulse (inconstancy of the amplitude of the pulse wave) in severe left ventricular failure.
3. Pain in the heart.
4. In the presence of heart defects - the presence of an appropriate clinical picture.
LABORATORY RESEARCH
• Hypoxemia (the degree changes against the background of oxygen therapy).
• Hypocapnia (concomitant lung diseases can complicate the interpretation).
• Respiratory alkalosis.
• Changes depending on the nature of the pathology that caused pulmonary edema (increased levels of MB-CPK, Troponins T and I with myocardial infarction, increased concentration of thyroid hormones with thyrotoxicosis, etc.).
INSTRUMENTAL RESEARCH
• ECG - signs of left ventricular hypertrophy are possible.
• Echocardiography is indicated for any pulmonary edema of unknown etiology. With echocardiography, zones of hypokinesia of the walls of the left ventricle are revealed.
• Introducing the Swan-Ganz catheter into the pulmonary artery to determine DZLA, which helps in the differential diagnosis between cardiogenic and non-cardiogenic pulmonary edema. DZLA <15 mm
Hg characteristic of adult respiratory distress syndrome, and DZLA> 25 mm Hg - for heart failure.
Chest x-ray
Cardiogenic pulmonary edema:
- expansion of the borders of the heart;
- redistribution of blood in the lungs;
- Curly lines (linear striation due to increased image of pulmonary interstitium) with interstitial pulmonary edema or multiple small foci with alveolar pulmonary edema;
- Often there is pleural effusion.
Non-cardiogenic pulmonary edema:
- the borders of the heart are not expanded;
- there is no redistribution of blood in the lungs;

- less pronounced effusion in the pleural cavity.
DIFFERENTIAL DIAGNOSTICS
1. Pneumonia.
2. Aspiration.
3. Bronchial asthma.
4. COPD.
5. TELA.
6. Hyperventilation syndrome.
TREATMENT
Emergency events
1. Giving the patient a sitting position with legs down (a decrease in venous return of blood to the heart, which reduces preload).
2. Adequate oxygenation using a mask with a supply of 100% oxygen at a rate of 6-8 l / min [better with antifoam agents - ethanol (ethanol□), polyoxymethylheptamethyltetrasiloxane (antifomsilan□)].
3. With the progression of pulmonary edema (determined by the coverage of all pulmonary fields with moist coarse wheezing), intubation and mechanical ventilation are performed under positive expiratory pressure to increase intralveolar pressure and reduce transudation.
4. The imposition of venous tourniquets (turnstiles) on the limbs to reduce venous return to the heart. As venous tourniquets, cuffs of the sphygmomanometer can be used, superimposed on three limbs, with the exception of the one where intravenous administration of drugs is carried out.
5. The cuff is inflated to values between the systolic and diastolic blood pressure, and the pressure in the cuff must be reduced every 10-20 minutes. Inflating the cuffs and reducing the pressure in them must be carried out sequentially on all three limbs.
Medical treatment

The purpose of the lesson.
1. To learn:
The concept of arrhythmias, types of arrhythmias
• A brief essay on electrophysiology of the heart
• Etiology and pathogenesis of arrhythmias.
1. Modern approaches to the pharmacotherapy of arrhythmias:
etiotropic: elimination of neurogenic and endocrine disorders (depressing central nervous system, antithyroid); myocardial inflammation (NSAIDs, glucocorticoids); acute or chronic oxygen starvation of the myocardium (angioprotectors, coronary expansion, etc.), normalizing electrolyte metabolism (potassium preparations), etc.
pathogenetic: elimination of disturbances in the exchange of electrolytes in the phases of the cardiac cycle and the concomitant changes in automatism and excitability (membrane-stabilizing, Ca2 + and K + channel blockers, potassium preparations); nervous regulation of cardiac activity (conduction) - with tachyarrhythmias (beta-blockers), bradyarrhythmias (M-cholinergic blockers, beta-adrenergic agonists).
2. Requirements for antiarrhythmic drugs.
3. Classification of antiarrhythmic drugs:
4 Means, used for tachyarrhythmias and extrasystoles
5 Tools for heart block
With tachyarrhythmias□:
Class I - sodium channel blockers (membrane stabilizing agents):
IA - extending the effective refractory period (ERP): quinidine, novokainamide, disopyramide, ethmosin, aymalin, and others;
IB - shortening ERP: lidocaine, mexiletine, tocainide, diphenin;
IC - having a different effect on the ERP: propafenone, etatsizin.

II class - beta-blockers:
non-selective: propronalol / anaprilin /, nadolol / korgard /, oxprenolol ** / trazikor /, pindolol□□ / viscene / etc .;
cardioselective: atenolol, metoprolol, talinolol, acebutolol **, etc.
Class III - potassium channel blockers (extending ERP): amiodarone, sota-lol, bretilium.
IV class - calcium channel blockers: cardiotropic - verapamil, gallopamil, diltiazem.
With bradyarrhythmias: M-anticholinergics (atropine, platifillin, etc.), beta-adrenergic agonists (isadrine, dobutamine, etc.), glucagon.
Pharmacology of antiarrhythmic drugs of different groups, mechanism of action, features of use. Comparative characteristics of drugs. Indications for use. Undesirable effects.
The clinical features of antiarrhythmic drugs depending on the type of cardiac arrhythmias.
Antiarrhythmic drugs based on medicinal plants (cardiac glycosides, alkaloids of rauwolfia, aconite, cinchona, hawthorn, etc.). Indications for use.
II. Know the main pathogenetic mechanisms that are the object of drug exposure in:
a) acute (cardiac asthma, pulmonary edema) and chronic heart failure:
b) cardiac arrhythmias and conduction
□ extrasystolic arrhythmias;
□ atrial fibrillation and flutter;
□ an attack of paroxysmal supraventricular tachycardia;
□ paroxysmal ventricular tachycardia;
□ atrioventricular blockade, an attack of Morgagni-Adams-Stokes.
III .. Be able to:
a) select and select for a specific patient the necessary drugs;
b) highlight the criteria for therapeutic efficacy and safety of the drugs used;
a) acute (cardiac asthma, pulmonary edema) and chronic heart failure:
b) cardiac arrhythmias and conduction
□ extrasystolic arrhythmias;
□ atrial fibrillation and flutter;
□ an attack of paroxysmal supraventricular tachycardia;
□ paroxysmal ventricular tachycardia;
□ atrioventricular blockade, attack of Morgagni-Adams-Stokes
Control questions of the studied topic.
1. Urgent relief from cardiac asthma.
2. Urgent help with pulmonary edema.
3. Clinical and pharmacological evaluation of drugs that normalize heart rhythm and conductivity: quinidine (quinidine durules); procainamide (procainamide); ethacisin, tyracine (bonnecor); lidocaine (trimecaine); verapamil (isoptin, finoptin); propranolol (anaprilin, obsidan); brasilia (ornid); amiodarone (cordarone); atropine; isoprenaline (isadrine, novodrin); orciprenaline (alupent); glucagon.
4. Relief of paroxysmal supraventricular tachycardia.
5. Justify the choice of LDLP for the relief of an atrial flutter.
6. Justify the choice of LSD to stop the paroxysm of atrial fibrillation.
Control of the intermediate level of knowledge.
The solution of situational problems.
1. A patient, 65 years old, complains of shortness of breath at rest, irregular heartbeat, swelling on the legs, an increase in the abdomen, heaviness in the right hypochondrium, daily diuresis - 0.6 l. In the anamnesis: suffered a large-focal myocardial infarction 5 years ago. Periodically, attacks of angina pectoris after a nervous load, ascent to the II floor. Shortness of breath and swelling on the legs for the past 2 years. I periodically took digoxin (1 t. 2 times a day, 5 days a week) "courses" for 2 months with a 1-month break (on the recommendation of the local therapist). The true deterioration occurred 3 weeks ago and is progressing. Objectively: general state of moderate severity, orthopnea. Lip cyanosis, acrocyanosis, neck vein swelling, pulse -

118 beats. at 1 min, arrhythmic as atrial fibrillation. Heart rate - 144 in 1 min. AP - 120/90 mm RT. Hypertrophy of both ventricles. Accent II tone over the pulmonary artery, systolic murmur over the aorta. BH - 26 in 1 min. Breathing is hard, in the lower lateral parts are small bubbling rales. The tongue is dry. The abdomen is round in shape, free fluid in the lateral sections is determined. The liver protrudes 12 cm from under the edge of the costal arch along the right midclavicular line, dense, smooth, painful. Swelling of the legs, lumbosacral spine. ECG - atrial fibrillation, tachysystolic form (heart rate - 156 in 1 min), hypertrophy of both ventricles. Cicatricial changes in the myocardium in the posterolateral part of the left ventricle.
Formulate a clinical diagnosis. Justify the choice of SG, its dose, rate of saturation in the period of initial digitalization. Indicate the clinical and electrocardiographic criteria for the effectiveness of this stage of glycosidotherapy.
Justify the choice, dosage (daily, weekly) of SG in the period of maintenance therapy. What are the criteria for the prevention of SG intoxication, which the patient will use at the request of the doctor.

A patient, 61 years old, complained of a random pulse with a frequency of 56-58 beats per 1 minute, shortness of breath with moderate physical exertion. These phenomena occurred 2 weeks ago, on the 15th day of taking the following drugs: Adelfan 1/2 table. and apressin 1 tab. (0.01 g) in 2300; isodinite - 10 mg 3 times a day. History: for 10 years, hypertension; bradycardia is inherent (heart rate 52-54 in 1 min), extrasystolic arrhythmia was recorded - for 8 years and blockade of the left bundle of the His branch, for the last 3 years - periodically sinoauricular block 2: 1.

The previous treatment of hypertension: Adelfan - 1 table. before bedtime; clonidine (0., 000075 g) - 1 tab. at the 3rd o'clock in the morning (the time of maximum daily activation of AKD). Objectively: the general condition is satisfactory. Arteries in the frontotemporal areas are convoluted, dilated, and densified. Pulse - 54 beats. at 1 min, arrhythmic as atrial fibrillation. Pulse deficiency - 0. AKD - in the morning and during the day 130/80 - 120/70 - 114/64 mm Hg. Art., at 3 a.m. - 130/70 mm Hg. Art. Left ventricular hypertrophy. Accent II tone over the aorta. Above the apex and aorta there is a rough systolic murmur. Vesicular respiration over the lungs. The liver protrudes 1 cm from under the edge of the costal meadow. No swelling. ECG - atrial fibrillation, bradycardial form (heart rate -56 beats per 1 min), left ventricular extrasystoles (4-5 in 1 min), blockade of the left bundle branch. Formulate a clinical diagnosis. Assess the correctness of therapy. Explain the mechanism of development of atrial fibrillation; could the therapy cause her? Justify the treatment of existing disorders.

5. The patient, 52 years old, developed an attack of cardiac asthma. When examining the pulse of 78 beats. in 1 min, rhythmic. AKD - 170/100 mm Hg. Art. Heart sounds are muffled. There is an increase in the liver, moderate swelling of the legs. The doctor prescribed intravenous administration of strophanthin.

Evaluate patient management tactics. Make a plan for the correction of patient treatment.

7. A patient with acute myocardial infarction complicated by an attack of paroxysmal tachycardia was delivered to the cardiology department. The attack was stopped by intravenous drip of lidocaine. After the attack: pulse - 80-88 beats. in 1 min, rhythmic, AKD - 100/70 mm Hg, heart sounds are deaf. In the lungs, a small amount of wet rales on both sides. A few hours after the cessation of lidocaine administration, the attack repeated, was stopped by novocainamide, but resumed.

Explain the reason for the failure of typical antiarrhythmic drugs. Correct the treatment. Make a list of drugs that can not be used in conjunction with strophanthin.

8. 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.

9. A man, 47 years old, complains of a periodic headache, palpitations and heart rhythm disturbance, Objectively: heart sounds are muffled, heart rate - 90 in 1 min, blood pressure - 170/100 mm RT. Art. On an ECG: left ventricular hypertrophy, ventricular extrasystoles with a frequency of 10-15 in 1 min. Diagnosed with hypertensive disease and coronary heart disease.

Formulate a clinical diagnosis. What drugs are appropriate for the treatment of this patient?

10. A patient, 70 years old, with coronary heart disease and post-infarction cardiosclerosis suddenly had a heart attack. Pulse - 140 per minute, weak. HELL - 100/60 mm Hg On the ECG, an extension of the QRS complex (0.13 s.) And negative T waves in classical leads. Reflex methods that were used to relieve heart attacks did not work.

Formulate a clinical diagnosis. What drugs are appropriate to use in this case? Give the clinical and pharmacological rationale for the prescribed drugs.

11. Due to prolonged pain of angina pectoris, the patient, 56 years old, was hospitalized in a hospital, where an ST segment elevation of 5 mm was detected with the formation of a QR wave in leads V1-V4. In the first day there was a state of clinical death, in the future - frequent episodes of extrasystole. What is the tactics for further outpatient treatment of this patient?

12. A man, 75 years old, with a diagnosis of coronary heart disease: atherosclerotic cardiosclerosis, atrial fibrillation, CH IIB stage and chronic pyelonephritis, assigned Digokin. In the first 6 days, the dose of digoxin was 0.25 mg twice a day, due to which shortness of breath, edema, cyanosis decreased. However, on the 7th day the patient developed nausea, bradycardia.

What is the cause of the complications? Tactics of treatment.

14. A patient, 45 years old, with small focal myocardial infarction complains of a sensation of interruptions in the region of the heart. On the ECG: absence of P waves, f waves in leads II, III, AVF, V1 V2, irregularity of the ventricular complexes, heart rate - 220 in 1 min, blood pressure - 100/70 mm RT. Art. To stop the attack, obzidan, verapamil, procainamide, cordarone, and hiluritmal were used, but without a positive effect for 2 days. Prescribe a treatment and justify it.

TESTS

1. Cardiac glycoside intoxications contribute to:

A. Elderly

B. Late stages of chronic heart failure

C. Electropulse defibrillation

D. Hypokalemia and hypomagnesemia

E. * All of the above factors

3. Select a drug for a patient with acute myocardial infarction with sinus bradycardia:

A ephedrine hydrochloride

B. Propranolol

C. Orciprenaline

D. Strophanthin

E. * Atropine sulfate

2. In acute heart failure for intravenous administration:

A. Strofantin, digitoxin.

B. Celanide, corglycon, adoniside.

C. * Strofantin, Korglikon.

D. Mesatone, digitoxin, strophanthin.

E. Fenoterol, strophanthin, korglikon.

3. The choice of cardiac glycoside and the determination of the dosage regimen:

A. * It is carried out individually for each patient

B. It is carried out by the method of increasing doses

C. It is carried out on the basis of ECG indicators

D. Based on ECG and ultrasound

E. It is carried out on the basis of indicators of pulse and blood pressure.

4. All class 1A drugs:

A. * Effective for restoring sinus rhythm with atrial fibrillation and flutter.

B. Used to treat sinus bradycardia

C. Indicated for severe heart failure

D. Cause atrioventricular blockade when administered intravenously

E. Contraindicated in ventricular extrasystole

5. Novocainamide can be administered intravenously in the absence of:

A. Ventricular fibrillation

B. Sustainable ventricular tachycardia

C. * Signs of circulatory failure

D. Arterial hypertension

E. Increases in blood creatinine

6. The most dangerous side effect of quinidine sulfate:

A. * Development of ventricular tachycardia of the pirouette type

B. Orthostatic arterial hypotension

C. Thrombocytopenia

D. QRS complex broadening by more than 40%

E. Jarisch-Herxheimer's Syndrome

7. Contraindications to the appointment of a disopyramide:

And hepatomegaly.

B. * Cardiogenic shock

C. Chronic pyelonephritis

D. History of thyroid disease

E. After electrical defibrillation

8. Which of the following is true?

A. * Giluritmal is effective for tachyarrhythmias with WPW syndrome

V. Aymalin is absorbed in the gastrointestinal tract by 95-97%

C. Lisinopril has a negative inotropic effect

D. Eufillin lowers myocardial oxygen demand

E. Nifedipine is contraindicated in bronchial asthma.

9. For the treatment of ventricular arrhythmias due to glycosid intoxication is effective

A. Clonidin

B. Orciprenaline

S. Verapamil

D. * Diphenin

E. Etatsizin

10. Choose the correct statement:

A. * Class I drugs have a pronounced antiarrhythmic effect

B. The most pronounced effect of class I drugs has on the conduct in the His-Purkinje system and in the myocardium of the ventricles

C. Etmozin is contraindicated in myocardial infarction with severe ventricular arrhythmia

D. Flecainide possesses simultaneously antiarrhythmic properties of classes I and III

E. All of the above is true.

11. Amiodarone:

A. * Inhibits the conversion of thyroxine to triiodothyronine

B. It is excreted mainly by the kidneys

C. Has a tachycardic effect

D. Virtually non-cumulative in the body

E. Safe for asthma

12. Treatment of the arrhythmogenic effect of antiarrhythmic drugs often includes:

A. Forced diuresis

B * Electropulse therapy, cardiac pacing

C. Plasmapheresis

D. Hemodialysis

C. Treatment with cardiac glycosides

13. Contraindications to the appointment of calcium channel blockers are:

A. * AB-conduction disorders and sinus node dysfunction

B. Arterial hypertension

C. Atrial flutter or flickering

D. Tachycardia

E. All of the above

14. The most commonly used antiarrhythmic drugs are:

A. Perlinganite

B. Digitoxin

S. Eufillin

D. * Strofantin and digoxin

E. Preductal

15. The combined use of beta-blockers with verapamil:

A. * Causes adverse effects

B. Increases cardiac contractility

C. Gives pronounced hypertensive effect

D. Significantly increases atrioventricular conduction

E. All of the above is true.

16. Antiarrhythmic drugs are not prescribed when there is:

A. Extrasystole with concomitant bradycardia

B. Sinus bradycardia with a heart rate of less than 40 per minute

C. Sinoauricular block and atrioventricular block 111 degrees

D. * Rare extrasystole without signs of organic damage to the heart

E. Arrhythmia caused by stimulation of the autonomic nerves

17. The elimination of the influence of the vagus nerve on sinus contractions and AV conduction is possible by:

A. * Appointments of M-cholinergic blockers

B. Use of adrenergic agonists

C. Electrical defibrillation

D. Long-term administration of organic nitrates

E. Direct heart massage

18. In a patient, 65 years old, with acute myocardial infarction on the 2nd day of illness, a complete atrioventricular block with heart rate 32 in 1 min developed. Which drug should be prescribed for emergency care?

A. Nifedipine.

B. Eufillin.

C. Atropine sulfate.

D. Platifillin hydrotartrate.

E. Myofedrine.

19. During treatment, the patient was prescribed strophanthin, the average rate of saturation, but the symptoms of digital intoxication developed: vomiting, extrasystole, visual impairment. What drug can lead to a worsening of the patient's condition, and as a result, it must be canceled?

A. Panangin.

B. Unitiol.

C. Calcium chloride.

D. Diphenin.

E. Surveyed.

20. A woman, 42 years old, called an ambulance doctor in connection with an acute attack of a heartbeat, which was accompanied by general weakness, fainting. Pulse - 200 beats per 1 min, rhythmic, blood pressure - 140/90 mm RT. Art .. The doctor suspected supraventricular tachycardia, which was confirmed by an ECG. Which of the following medications is the most effective in this situation?

A. Rhythmylene.

B. Novocainamide.

C. Awarded.

D. Cordaron.

E. Verapamil.

21. In a 72-year-old patient with acute myocardial infarction, an ECG monitor revealed paroxysmal ventricular tachycardia. At the same time, the patient developed a clinic of acute ventricular failure. HELL - 90/50 mm RT. Art. What is the most effective for the treatment of this patient?

A. Mexitil.

B. Novocainamide.

C. Cordaron.

D. Strophanthin.

E. Lidocaine.

22. In a patient, 54 years old, with a diagnosis of coronary heart disease, acute transmural antero-septal myocardial infarction, frequent ventricular extrasystoles appeared. Which of the following drugs should be administered to the patient?

A. Reviewed.

B. Digoxin.

C. Finoptin.

D. Lidocaine.

E. Strofantin.

23. The patient experienced a complex violation of the heart rhythm: atrial flutter, paroxysm of ventricular tachycardia. What is the universal antiarrhythmic drug that affects the indicated pathology.

A Verapamil.

B. Novocainamide.

C. Lidocaine.

D. Strophanthin.

E. Panangin.

24 A patient, 70 years old, with coronary heart disease and post-infarction cardiosclerosis suddenly had a heart attack. Pulse - 140 per minute, weak. HELL - 100/60 mm Hg On the ECG, an extension of the QRS complex (0.13 s.) And negative T waves in classical leads. Reflex methods that were used to relieve heart attacks did not work. What drug is appropriate to use in this case?

A. Verapamil.

B. Noradrenaline.

S. Strofantin.

D. Digoxin.

E. Lidocaine.

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 NON-STEROID ANTI-INFLAMMATORY MEDICINES (NSAIDs)

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF STEROID ANTI-INFLAMMATORY MEDICINES (GCS)

Purpose of the topic.

Anti-inflammatory (non-steroidal - NSAIDs and steroidal - GCS) drugs occupy one of the first places in the frequency of clinical use. This is due to their multifaceted pharmacodynamic effects.

NSAIDs are a group of drugs, many of which can be bought without a prescription. More than thirty million people worldwide take NSAIDs daily, with 40% of these patients over 60 years old. About 20% of inpatients receive NSAIDs, which have a polysyndromic effect.

In recent years, the arsenal of NSAIDs has replenished with a significant number of new drugs, and the search is conducted towards the creation of drugs that combine high efficiency with improved tolerance.

In the absence of the effect of the use of NSAIDs, there is a need for the use of glucocorticosteroids. The therapeutic potential of corticosteroids has led to their widespread use. Although the benefits of glucocorticosteroids can be substantial, there are numerous adverse effects, including serious metabolic disorders and suppression of the hypothalamic-pituitary-adrenal axis.

The topic under study allows students to effectively use the knowledge and skills acquired in various clinical departments, to shape clinical thinking and use them in practical activities. Students get the opportunity to master a diverse pathology, to form skills for managing pathological processes, to understand the body as a whole.

Motivational characteristic of the topic.

Knowledge of the main groups of anti-inflammatory drugs, the characteristics of pharmacodynamics, pharmacokinetics, the ability to rationally use them in a particular patient, correctly carry out combination therapy and prevent life-threatening complications determines the importance of this topic for a doctor of any clinical specialty. Students get the opportunity to master a diverse pathology, to form skills for managing pathological processes, and to understand how the mother-body is a whole.

NON-STEROID ANTI-INFLAMMATORY MEDICINES.

Nonsteroidal anti-inflammatory drugs (NSAIDs, NSAIDs, NSAIDs, NSAIDs, NSAIDs) - a group of drugs with analgesic, antipyretic and anti-inflammatory effects, reduce pain, fever and inflammation. The use of the term "non-steroidal" in the name emphasizes their difference from glucocorticoids, which have not only an anti-inflammatory effect, but also other, sometimes undesirable, properties of steroids.

NSAIDs are first-line drugs for the treatment of inflammatory diseases of the musculoskeletal system. These drugs are taken by every seventh patient suffering from rheumatic diseases, and every fifth with other pathological conditions associated with pain, inflammation and fever. However, despite the undoubted clinical effectiveness, anti-inflammatory drugs belong to the group of drugs, which are characterized by the so-called "pharmacological scissors", that is, in

addition to the therapeutic effect, they have serious side effects. Even short-term administration of these drugs in small doses in some cases can lead to the development of side effects, which occur in about 25% of cases, and in 5% of patients can pose a serious threat to life. Particularly high risk of side effects in the elderly, which make up more than 60% of NSAIDs consumers. It should also be noted that for many diseases there is a need for long-term use of NSAIDs. Therefore, each doctor faces the problem of a rational choice of the drug and an adequate treatment regimen taking into account the effectiveness and safety of the anti-inflammatory drug used.

Classification

NSAIDs are classified according to the severity of anti-inflammatory activity and chemical structure. The first group includes drugs with a pronounced anti-inflammatory effect. NSAIDs of the second group, which have a weak anti-inflammatory effect, are often indicated by the terms "non-narcotic analgesics" or "antipyretic analgesics."

From a practical point of view, it is important that drugs belonging to the same group and even close in chemical structure somewhat differ in both the strength of the effect and the frequency of development and the nature of undesirable reactions. So, among the NSAIDs of the first group, indomethacin and diclofenac have the most powerful anti-inflammatory activity, and ibuprofen is the least. Indomethacin, which is a derivative of indoleacetic acid, is more gastrotoxic than etodolac, also belonging to this chemical group. The clinical effectiveness of the drug may depend on the type and characteristics of the course of the disease in a particular patient, as well as on his individual reaction.

Classification of NSAIDs by activity and chemical structure

NSAIDs with pronounced anti-inflammatory activity	
Acids	
Salicylates	A) Acetylated: - Acetylsalicylic Acid (Ask) - (Aspirin); - Lysine monoacetylsalicylate (Aspizol, Laspal); B) Unacetylated: - Sodium salicylate; - Choline salicylate (sugar); - salicylamide; - Dolobid (Diflunizal); - disalcid;
Pyrazolidines	- Azapropazone (Reymox); - Clofeson; - Phenylbutazone (Butadion); - Oxyphenylbutazone.

Indole acetic acid derivatives	- Indomethacin (Metindol); - Sulindak (Clinoril); - Etodalac (Lodin);
Phenylacetic Acid Derivatives	- Diclofenac Sodium (Ortofen, Voltaren); - Diclofenac Potassium (Voltaren - Rapid); - Fentyazak (Donorest); - Lonazalak Calcium (Irriten).
Oksikama	Pyroxicam -Tenoxicam Lornoxicam -Meloxicam
Propionic Acid Derivatives	Ibuprofen (Brufen, Nurofen, Solpafleks); - Naproxen (Naprosin); - Naproxen Sodium Salt (Apranax); - Ketoprofen (Knavon, Profenid, Oruvel); - Flurbiprofen (Flugalin); - Phenoprofen (Phenopron); - Fenbufen (Lederlen); - Thiaprofenic Acid (Surgam).
Non Acid Derivatives	
Alkanones	-Nabumetone
Sulfonamide derivatives	Nimesulide - celecoxib Rofecoxib
NSAIDs with low anti-inflammatory activity	
Anthranilic Acid Derivatives	Mefenamic Acid (Pomstal); - Meclofenamic Acid (Meklomet); - Niflumic Acid (Donalgin, Nifluril); - Morniflumat (Nifluril); - etofenamat;

	- Tolfenamic Acid (Clotam).
Pyrazolones	Metamizole (Analgin); - Aminophenazone (Amidopyrine); - Propiphenazone.
Paraaminophenol derivatives	- Phenacetin; - Paracetamol.
Heteroaryl Acetic Acid Derivatives	Ketorolac; - Tolmetin (Tolectin)

Classification of NSAIDs (by duration)

1. Short action (T1 / 2 = 2-8 hours):

- ibuprofen; - ketoprofen;

- indomethacin; - phenoprofen;

- voltaren; - phenamates.

- tolmetin;

2. The average duration of action (T1 / 2 = 10-20 hours):

- naproxen;

- sulindak;

- diflunisal.

3. Long-term action (T1 / 2 = 24 or more hours):

- oksikama;

- phenylbutazone.

Classification of NSAIDs by selectivity for various forms of cyclooxygenase

Classification of NSAIDs by the effect on the processes of biosynthesis in cartilage.

I. Suppressing inflammation and neutral to arthrosis - Pyroxicam, diclofenac, sulindac, solpaflex;

II. Suppressing inflammation and enhancing arthrosis - Acetylsalicylic acid, indomethacin, phenoprofen, phenylbutazone;

III. Suppressing inflammation and contributing to the normalization of metabolic processes in the cartilage, Benoxaprofen, thiaprofenic acid (Surgam), paracetamol.

PHARMACODYNAMICS

Mechanism of action

Despite its widespread use, the mechanism of action of NSAIDs has long remained unexplored. It was believed that acetylsalicylic acid disrupts oxidative phosphorylation and inhibits the synthesis of a number of enzymes involved in protein biosynthesis. However, these effects were manifested in concentrations of the drug much higher than therapeutic and were not associated with its anti-inflammatory, analgesic and antipyretic effects. The most important NSAID mechanism is associated with inhibition of the synthesis of cyclooxygenase (COX) and lipoxygenase (LOG), the key enzymes of arachidonic acid metabolism. Arachidonic acid is part of membrane phospholipids and is released under the influence of the phospholipase A2 enzyme. COX and LOG catalyze the further conversion of arachidonic acid. The products of their metabolism include cyclic endoperoxides, prostaglandins (PG), thromboxane (TXA2), leukotrienes (RT) and other PGs produced by many cells and are among the most important paracrine and autocrine mediators.

GHGs have versatile biological activity:

a) are mediators of the inflammatory reaction: they cause local vasodilation, edema, exudation, leukocyte migration and other effects (mainly PG-E2 and PG-I2);

b) catalyze the release of other inflammatory mediators (histamine, serotonin, bradykinin, etc.). The pro-inflammatory effects of PG are potentiated by the action of free radicals formed during the enzymatic oxidation of arachidonic acid. Activation of free radical oxidation (CPO) promotes the release of lysosomal enzymes, which leads to further destruction of cell membranes, sensitize receptors to pain mediators (histamine, bradykinin) and mechanical effects, lowering the threshold of pain sensitivity;

c) increase the sensitivity of hypothalamic thermoregulation centers to the action of endogenous pyrogens (interleukin-1 and others), which are formed in the body under the influence of microbes, viruses, toxins (mainly PG-E2).

Thromboxane is a platelet aggregation factor that constricts blood vessels. Prostacyclin, formed from a damaged vascular wall, reduces platelet aggregation and adhesion, and dilates blood vessels.

The existence of two main isoforms of COX is known: COX-1 and COX-2.

COX-1 is a structural enzyme that is synthesized in most cells of a healthy body (excluding red blood cells) and catalyzes the formation of physiological PG, thromboxane and prostacyclin, which occupy an important place in the regulation of a number of physiological processes in the body, such as the protection of the gastrointestinal mucosa , ensuring renal blood flow, regulation of vascular tone, blood coagulation, bone metabolism, growth of nerve tissue, pregnancy, processes of regeneration and apoptosis.

COX-2 - is involved in the synthesis of prostaglandins with inflammation. Moreover, COX-2 is absent under normal conditions, but is formed under the influence of some tissue factors initiating the inflammatory reaction (cytokines and others). In this regard, it is assumed that the anti-inflammatory effect of NSAIDs is due to inhibition of COX-2, and their undesirable reactions are due to inhibition of COX-1 (gastrointestinal tract damage, impaired renal blood flow and platelet aggregation, etc.). The ratio of NSAID activity in terms of blocking COX-1 / COX-2 allows us to judge their potential toxicity. The smaller this value, the more selective the drug is in relation to COX-2 and, therefore, less toxic. For example, for meloxicam, it is 0.33, diclofenac - 2.2, tenoxicam - 15, piroxicam - 33, indomethacin - 107.

It is also assumed the existence of another isoform of COX - COX-3. The putative COX-3 is expressed in the brain, also affects GHG synthesis and plays a role in the development of pain and fever. However, unlike other isoforms, it does not affect the development of inflammation.

Various representatives of NSAIDs differ not only in the chemical structure and pharmacodynamics, but also in the degree of influence on various isoforms of COX. For example, acetylsalicylic acid, indomethacin, ibuprofen inhibit COX-1 to a greater extent than COX-2. The most widely used NSAID diclofenac equally inhibits both isoenzymes. Selective or selective COX-2 inhibitors include nimesulide, meloxicam, nabumeton. however, it should be borne in mind that with increasing doses, their selectivity is significantly weakened. Highly selective or specific COX-2 inhibitors are coxibs: celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricocosib, etc. The activity of COX-3 is inhibited by acetaminophen (paracetamol), which has a weak effect on COX-1 and COX-2.

Other mechanisms of action of NSAIDs

The anti-inflammatory effect can be associated with inhibition of lipid peroxidation, stabilization of lysosome membranes (both of these mechanisms prevent damage to cellular structures), a decrease in ATP formation (the energy supply of the inflammatory reaction is reduced), inhibition of neutrophil aggregation (the release of inflammatory mediators from them is disturbed), a decrease in the production of rheumatoid factor in patients with rheumatoid arthritis. To some extent, the analgesic effect is associated with impaired pain impulses in the spinal cord (metamizole).

Some NSAIDs relieve pain and inflammation of the articular cartilage, however, the metabolic processes inside the joint are grossly disrupted, and eventually the destruction of the articular cartilage occurs. Among these drugs, acetylsalicylic acid and, widely used in rheumatology, indomethacin should be put in the first place. These drugs, in terms of the effect on metabolic processes in the articular cartilage, should be used only to a limited extent.

The next group of drugs is drugs that are different from the metabolic processes in the cartilage itself, relieve pain and inflammation, but do not disturb the metabolism of the articular cartilage. These are drugs based on piroxicam, diclofenac, as well as sulindac and ibuprofen.

The third group of drugs that relieve pain and inflammation in varying degrees, but not only do not disturb the metabolism of articular cartilage, but also stimulate synthetic processes in articular cartilage. These are benoxaprofen, tiaprofenova acid and paracetamol.

The given example illustrates the complexity and inconsistency of the requirements for modern NSAIDs.

It should be noted that at present, COX-independent aspects of the mechanism of action of NSAIDs exist and are being widely studied, which will significantly expand the range of their application. So, there is evidence that a number of NSAIDs are able to some extent stimulate the proliferative response of T-lymphocytes and the synthesis of interleukin-2. The latter is associated with increased levels of intracellular calcium, inhibition of chemotaxis, increased aggregation of neutrophils, the formation of hypochlorous acid and oxygen superoxide radicals. The ability of salicylates to inhibit the activation of transcription factor in T-lymphocytes is known.

It is also believed that NSAIDs are able to change the physicochemical properties of cellular biomembranes. NSAIDs as anionic lipophilic molecules are able to penetrate the leukocyte bilayer and reduce the permeability of biomembranes by interrupting signal transmission at the

level of guanosine triphosphate binding protein, which prevents leukocyte cell activation under the influence of chemotactic stimuli in the early stages of inflammation.

There are results on the effect of NSAIDs on central pain mechanisms not associated with inhibition of COX. It is believed that the antinociceptive effect of NSAIDs is partially related to the release of endogenous opioid peptides.

The antiproliferative effect of NSAIDs can also be mediated by various mechanisms: both by enhancing the activity of natural killer cells with inhibition of GHG synthesis, and by COX-2 dependent regulation of cell apoptosis. It was established that the production of COX-2 precedes apoptosis of neuronal cells; therefore, selective COX-2 inhibitors have a certain neuroprotective activity. Their use will help to optimize the treatment of Alzheimer's disease, since one of the characteristic features of brain pathology in this disease is an inflammatory reaction characterized by activation of glial cells, an increase in the level of pro-inflammatory cytokines, and activation of complement . COX-2 metabolites also contribute to the growth of tumor cells, therefore, the ability to inhibit COX-2 will allow the use of NSAIDs in oncology in the treatment of a number of cancerous tumors.

Further study of the role of COX in the human body is very important for determining the mechanisms of pathogenesis and developing new approaches to the treatment of a number of diseases.

A key element in the mechanism of pharmacological effects of NSAIDs is inhibition of prostaglandin synthesis due to inhibition of the COX enzyme, the main enzyme of arachidonic acid metabolism.

Arachidonic acid, which is formed from membrane phospholipids under the influence of the phospholipase A2 enzyme, is, on the one hand, a source of inflammatory mediators (pro-inflammatory prostaglandins and leukotrienes), and, on the other hand, a number of biologically active substances involved in the physiological processes of the body are synthesized (prostacyclin, thromboxane A2, gastroprotective and vasodilating prostaglandins, etc.). Thus, arachidonic acid metabolism is carried out in two ways (see. Fig.):

• the cyclooxygenase pathway, as a result of which prostaglandins, including prostacyclin and thromboxane A2, are formed from arachidonic acid under the influence of cyclooxygenase;

• lipooxygenase pathway, as a result of which leukotrienes are formed from arachidonic acid under the influence of lipoxygenase.

Prostaglandins are the main mediators of inflammation. They cause the following biological effects:

• sensitize nociceptors to pain mediators (histamine, bradykinin) and lower the threshold of pain sensitivity;

• increase the sensitivity of the vascular wall to other inflammatory mediators (histamine, serotonin), causing local vasodilation (redness), increased vascular permeability (edema);

• increase the sensitivity of hypothalamic thermoregulation centers to the action of secondary pyrogens (IL-1, etc.), formed under the influence of microorganisms (bacteria, viruses, fungi, protozoa) and their toxins.

Thus, the generally accepted concept of the mechanism of the analgesic, antipyretic, and anti-inflammatory effects of NSAIDs is based on the inhibition of the synthesis of pro-inflammatory prostaglandins by inhibiting cyclooxygenase.

It was found that the three-dimensional structures of COX-1 and COX-2 are similar, but nevertheless there are “small” differences. Thus, COX-2 has “hydrophilic” and “hydrophobic” pockets (channels), in contrast to COX-1, in the structure of which there is only a "hydrophobic" pocket.

This fact made it possible to develop a number of drugs that selectively inhibit COX-2. The molecules of these drugs have such a structure that they bind to the “hydrophilic” pocket with their hydrophilic part and to the “hydrophobic” cyclooxygenase pocket. Thus, they can only bind to COX-2, which has both “hydrophilic” and “hydrophobic” pockets, while most other NSAIDs, interacting only with the “hydrophobic” pocket, bind like COX-2 and with COX-1.

It is known about the existence of other mechanisms of the anti-inflammatory action of NSAIDs:

• it was found that the anionic properties of NSAIDs allow them to penetrate the bilayer of phospholipid membranes of immunocompetent cells and directly affect the interaction of proteins, preventing cell activation in the early stages of inflammation;

• NSAIDs increase the level of intracellular calcium in T-lymphocytes, which helps to increase the proliferation and synthesis of IL-2;

• NSAIDs interrupt neutrophil activation at the G protein level. According to the anti-inflammatory activity, NSAIDs can be arranged in the following order: indo-metacin - flurbiprofen - diclofenac - piroxicam - ketoprofen - naproxen - phenylbutazone - ibuprofen - metamizole - acetylsalicylic acid.

NSAIDs have a greater analgesic than anti-inflammatory effect, which are neutral due to their chemical structure, accumulate less in inflammatory tissue, penetrate the BBB faster and suppress the central nervous system of COX, and also affect the thalamic centers of pain sensitivity. Noting the central analgesic effect of NSAIDs, one cannot exclude their peripheral action associated with the antiexudative effect, which reduces the accumulation of pain mediators and mechanical pressure on pain receptors in tissues.

The antiplatelet effect of NSAIDs is due to the blocking of the synthesis of thromboxan A2. So, acetylsalicylic acid irreversibly inhibits COX-1 in platelets. When taking a single dose of the drug, a clinically significant decrease in platelet aggregation in the patient is observed for 48 hours or more, which significantly exceeds the time of its removal from the body. The recovery of aggregation ability after irreversible inhibition of COX-1 by acetylsalicylic acid occurs, apparently, due to the appearance of new platelet populations in the bloodstream. However, most NSAIDs reversibly inhibit COX-1, and therefore, as their concentration in the blood decreases, restoration of the aggregation ability of platelets circulating in the vascular bed is observed.

REQUIREMENTS FOR MODERN NPS

 Anti-inflammatory effect

 The predominant inhibitory effect on COX-2

 analgesic effect

 Chondroprotective effect or lack of effect on articular cartilage metabolism; synovial fluid improvement

 Normalizing effect on the exchange of Ca2 + in bone tissue

 Myotropic antispasmodic action

 Immunomodulating properties

 Minimum side effects

 The ability to create dosage forms (mazi, candles, tablets, etc.) based on the substance that meet biopharmaceutical requirements.

A very important aspect of the use of NSAIDs is safety, characterized by the benefit / risk ratio. When taking NSAIDs, the spectrum of side effects can be quite wide.

The likelihood of developing unwanted effects determines the belonging of a drug (dose form) to a prescription or over-the-counter group.

It should be noted that the safety of the drug is significantly affected by the characteristics of the dosage form and the technology of production of the drug.

KEY EFFECTS

Anti-inflammatory effect. NSAIDs suppress mainly the exudation phase. The most powerful drugs - indomethacin, diclofenac, phenylbutazone - also act on the proliferation phase (decreasing collagen synthesis and the associated tissue sclerosis), but weaker than on the exudative phase. NSAIDs have almost no effect on the alteration phase. All NSAIDs are inferior to glucocorticoids in anti-inflammatory activity.

Analgesic effect. It manifests itself to a greater extent with pains of weak and medium intensity, which are localized in the muscles, joints, tendons, nerve trunks, as well as with headache or toothache. With severe visceral pain, most NSAIDs are less effective and inferior in strength to the analgesic effect of the drugs of the morphine group (narcotic analgesics). At the same time, a number of controlled studies showed a rather high analgesic activity of diclofenac, ketorolac, ketoprofen, metamizole for colic and postoperative pain. The effectiveness of NSAIDs in renal colic that occurs in patients with urolithiasis is largely associated with inhibition of the production of PG-E2 in the kidneys, a decrease in renal blood flow and urine formation. This leads to a decrease in pressure in the renal pelvis and ureter above the site of obstruction and provides a long-lasting analgesic effect. The advantage of NSAIDs over narcotic analgesics is that they do not inhibit the respiratory center, do not cause euphoria and drug dependence, and with colic, it also matters that they do not have an antispasmodic effect.

Antipyretic effect. NSAIDs are effective only for fever. They do not affect normal body temperature, which differs from "hypothermic" agents (chlorpromazine and others).

Anti-aggregation effect. As a result of inhibition of COX-1 in platelets, the synthesis of the endogenous thromboxane pro-aggregate is inhibited. The most powerful and long-lasting anti-aggregation activity is aspirin, which irreversibly inhibits the ability of a platelet to aggregate for its entire lifespan (7 days). The antiplatelet effect of other NSAIDs is weaker and is reversible. Selective COX-2 inhibitors do not affect platelet aggregation.

Immunosuppressive effect. It is expressed moderately, manifests itself with prolonged use and has a "secondary" nature: by reducing the permeability of capillaries, NSAIDs make it difficult for immunocompetent cells to contact the antigen and the antibody to contact with the substrate.

Desensitizing effect is associated with the following mechanisms:

• inhibition of prostaglandins in the focus of inflammation and leukocytes, which leads to a decrease in chemotaxis of monocytes;

• a decrease in the formation of hydroheptanotrienoic acid (reduces the chemotaxis of T-lymphocytes, eosinophils and polymorphonuclear leukocytes in the focus of inflammation);

• inhibition of blasttransformation (division) of lymphocytes due to blockade of prostaglandin formation.

The most pronounced desensitizing effect of indomethacin, mefenamic acid, diclofenac and acetylsalicylic acid.

PHARMACOKINETICS

All NSAIDs are well absorbed in the gastrointestinal tract. Almost completely bind to plasma albumin, displacing some other drugs, and bilirubin in newborns, which can lead to the development of bilirubin encephalopathy. The most dangerous in this regard are salicylates and phenylbutazone. Most NSAIDs penetrate well into the synovial fluid of the joints. NSAIDs are metabolized in the liver, excreted through the kidneys.

INDICATIONS FOR USE

1. Rheumatic diseases: rheumatism (rheumatic fever), rheumatoid arthritis, gouty and psoriatic arthritis, ankylosing spondylitis (ankylosing spondylitis), Reiter's syndrome.

It should be borne in mind that with rheumatoid arthritis, NSAIDs have only a symptomatic effect, without affecting the course of the disease. They are not able to suspend the progression of the process, cause remission and prevent the development of joint deformation. At the same time, the relief that NSAIDs bring to patients with rheumatoid arthritis is so significant that not one of them can do without these drugs. With large collagenoses (systemic lupus erythematosus, scleroderma and others) NSAIDs are often ineffective

2. Non-rheumatic diseases of the musculoskeletal system: osteoarthritis, myositis, tenosynovitis, trauma (household, sports). Often, in these conditions, the use of local dosage forms of NSAIDs (ointments, creams, gels) is effective.

3. Neurological diseases: neuralgia, sciatica, sciatica, lumbago.

4. Renal, hepatic colic.

5. Pain syndrome of various etiologies, including headache and toothache, postoperative pain.

6. Fever (usually at body temperature above 38.5 ° C).

7. Prevention of arterial thrombosis.

8. Dysmenorrhea. NSAIDs are used in primary dysmenorrhea to relieve pain associated with increased uterine tone due to overproduction of PG-F2a. In addition to the analgesic effect of NSAIDs, they reduce blood loss. Especially when using naproxen and its sodium salt, diclofenac, ibuprofen, ketoprofen. NSAIDs are prescribed at the first appearance of pain with a 3-day course or on the eve of menstruation. Adverse reactions, given short-term use, are rare.

CHARACTERISTICS OF SEPARATE MEDICINES

NSAIDs with pronounced anti-inflammatory activity

NSAIDs belonging to this group have a clinically significant anti-inflammatory effect, therefore, they are widely used, primarily as anti-inflammatory drugs, including for rheumatological diseases in adults and children. Many of the drugs are also used as analgesics and antipyretics.

ACETYL SALICYLIC ACID (Aspirin, Aspro, Colfarit)

Acetylsalicylic acid is the oldest NSAID. When conducting clinical trials, it usually serves as a standard, with the effectiveness and tolerability of which other NSAIDs are compared.

Aspirin is a trade name for acetylsalicylic acid, proposed by Bayer (Germany). Over time, it has become so identified with this drug that it is now used as a generic drug in most countries of the world.

The pharmacodynamics of aspirin depends on the daily dose: small doses - 30 mg-325 mg - cause inhibition of platelet aggregation; average doses - 1.5-2 g - have an analgesic and antipyretic effect; large doses - 4-6 g - have an anti-inflammatory effect.

At a dose of more than 4 g, aspirin enhances the excretion of uric acid (uricosuric effect), when administered in lower doses, its excretion is delayed.

Pharmacokinetics

It is well absorbed in the gastrointestinal tract. Aspirin absorption is enhanced by grinding the tablet and taking it with warm water, as well as using effervescent tablets that dissolve in water before use. The half-life of aspirin is only 15 minutes. Under the influence of esterases of the mucous membrane of the stomach, liver, and blood, salicylate is cleaved from aspirin, which has the main pharmacological activity. The maximum concentration of salicylate in the blood develops 2 hours after taking aspirin, its half-life is 4-6 hours. It is metabolized in the liver, excreted in the urine, moreover, with an increase in the pH of the urine (for example, in the case of the appointment of antacids), excretion is enhanced. When using large doses of aspirin, it is possible to saturate the metabolizing enzymes and increase the half-life of salicylate up to 15-30 hours.

Interactions

Glucocorticoids accelerate the metabolism and excretion of aspirin. The absorption of aspirin in the gastrointestinal tract is enhanced by caffeine and metoclopramide. Aspirin inhibits gastric alcohol dehydrogenase, which leads to an increase in the level of ethanol in the body, even with its moderate (0.15 g / kg) consumption.

Adverse reactions

Gastrotoxicity. Even when used in low doses - 75-300 mg / day (as an antiplatelet agent) - aspirin can cause damage to the gastric mucosa and lead to the development of erosion and / or ulcers, which are often complicated by bleeding. The risk of bleeding is dose-dependent: when prescribed at a dose of 75 mg / day, it is 40% lower than at a dose of 300 mg, and 30% lower than at a dose of 150 mg. Even slightly, but constantly bleeding erosion and ulcers can lead to systematic loss of blood with feces (2-5 ml / day) and the development of iron deficiency anemia.

Dosage forms with enteric-soluble coating are somewhat less gastrotoxic. In some patients taking aspirin, it is possible to develop adaptation to its gastrotoxic effect. It is based on a local increase in mitotic activity, a decrease in neutrophilic infiltration, and an improvement in blood flow.

Increased bleeding due to impaired platelet aggregation and inhibition of prothrombin synthesis in the liver (the latter with an aspirin dose of more than 5 g / day), therefore, the use of aspirin in combination with anticoagulants is dangerous.

Hypersensitivity reactions: skin rashes, bronchospasm. A special nosological form is distinguished - Fernan-Vidal syndrome ("aspirin triad"): a combination of nasal polyposis and / or sinuses, bronchial asthma and complete intolerance to aspirin. Therefore, aspirin and other NSAIDs are recommended with great caution in patients with asthma.

Reye's syndrome - develops when prescribing aspirin to children with viral infections (flu, chickenpox). It manifests itself as severe encephalopathy, cerebral edema and liver damage, which occurs without jaundice, but with high cholesterol and liver enzymes. It gives a very high mortality rate (up to 80%). Therefore, aspirin should not be used in acute respiratory viral infections in children of the first 12 years of life.

Overdose or poisoning in mild cases is manifested by symptoms of "salicilism": tinnitus (a sign of "saturation" with salicylate), stupidity, hearing loss, headache, visual impairment, sometimes nausea and vomiting. With severe intoxication, disorders develop on the part of the central nervous system and water-electrolyte metabolism. Shortness of breath (as a result of stimulation of the respiratory center), disturbances of the acid-base state (first respiratory alkalosis due to carbon dioxide loss, then metabolic acidosis due to inhibition of tissue metabolism), polyuria, hyperthermia, and dehydration are noted. Myocardial oxygen consumption increases, heart failure, pulmonary edema may develop. Children under 5 years of age are most sensitive to the toxic effect of salicylate, in which, like adults, it is manifested by severe violations of the acid-base state and neurological symptoms. The severity of intoxication depends on the dose of aspirin taken.

When taking 150-300 mg / kg, mild to moderate intoxication is noted, a dose of 300-500 mg / kg leads to severe poisoning, and a dose of more than 500 mg / kg is potentially lethal.

LYSINMONOACETHYL SALICYLATE (Aspizol, Laspal). Derivative of aspirin for parenteral administration. It surpasses it in speed and strength of the analgesic effect. Adverse reactions are the same as aspirin.

Indications. Relief of acute pain (rheumatic pain, sciatica, postoperative and post-traumatic pain, colic); In addition, it is used for hyperthermia, thrombophlebitis.

Dosage. Adults: single dose - 2 g, maximum - up to 10 g / day. Children: 20-50 mg / kg per day in 2-3 injections.

Release form: - 1 g vials (corresponding to 500 mg of aspirin) with a solvent (5 ml of water for injection).

DIFLUNISAL (Dolobid)

It belongs to the group of non-acetylated salicylates. It is not metabolized to salicylate and therefore does not cause salicylism. It has a powerful anti-inflammatory and, especially, analgesic effects, exhibits uricosuric effect. Unlike aspirin, diflunisal does not have an antipyretic effect, since it does not penetrate the central nervous system. It inhibits platelet aggregation only when maximum doses are prescribed (2 g / day), and this effect is reversible.

Pharmacokinetics

It is well absorbed in the gastrointestinal tract. The maximum concentration in the blood develops after 2-3 hours, but the analgesic effect is observed already in the 1st hour after

administration, especially in a loading dose (1000 mg). It has a longer half-life than aspirin, an elimination half-life of 8-12 hours.

Undesirable reactions. Similar to aspirin, however, gastrotoxicity is lower, and the development of Reye's syndrome is not described.

Indications. Rheumatoid arthritis, osteoarthritis, pain (including dysmenorrhea).

Dosage. Adults: with rheumatoid arthritis and osteoarthrosis, 0.5-1 g every 12 hours; for pain relief (including dysmenorrhea): 1st dose - 1 g, then 0.5 g every 8-12 hours. Children are not assigned.

Release form: - tablets on 500 mg.

Phenylbutazone (Butadion)

Surpasses aspirin in strength of anti-inflammatory effect. Enhances the excretion of uric acid from the body.

Pharmacokinetics

The maximum concentration in the blood develops 2 hours after ingestion and only 6-8 hours after administration intramuscularly (since the phenylbuton zone binds to tissues at the injection site). The half-life is about 70 hours. One of the metabolites of phenylbutazone - oxyphenbutazone - is released as a separate drug and is equal in value to phenylbutazone in all respects (including toxicity).

Interactions

Phenylbutazone is one of the most powerful “displacers” of other drugs due to plasma albumin, which leads to an increase in the concentration of the free (active) fraction of these drugs in the blood. In addition, it can inhibit the metabolism of certain drugs in the liver. Therefore, when combined with phenylbutazone, the action of indirect anti-coagulants, oral antidiabetic drugs, sulfonamides and other drugs is possible.

Deteriorating renal blood flow, phenylbutazone weakens the action of diuretics and antihypertensive drugs.

Adverse reactions

The widespread use of phenylbutazone is limited by its frequent and serious undesirable reactions, which occur in 45% of patients. The most dangerous depressant effect of the drug on the bone marrow, which results in hematotoxic reactions - aplastic anemia and agranulocytosis, often causing death. The risk of aplastic anemia is higher in women, in people older than 40 years, with prolonged use. However, with short-term use by young people, fatal aplastic anemia can develop. Leukopenia, thrombocytopenia, pancytopenia and hemolytic anemia are also noted.

In addition, there are adverse reactions from the gastrointestinal tract (erosive and ulcerative lesions, bleeding, diarrhea), fluid retention in the body with the appearance of edema, skin rashes, ulcerative stomatitis, increased salivary glands, disorders of the central nervous system (inhibited nostril, agitation, tremor), hematuria, proteinuria, liver damage.

Phenylbutazone has cardiotoxicity (in patients with heart failure, it may be exacerbated) and can cause acute pulmonary syndrome, manifested by shortness of breath and fever. A number of patients have hypersensitivity reactions in the form of bronchospasm, generalized lymphadenopathy, skin rashes, Lyell syndromes (toxic epidermal necrolysis, this is the most

severe variant of allergic bullous dermatitis) and Stevens-Johnson (refers to severe systemic allergic reactions of the delayed complex type (immune) and is a severe variant of the course of erythema multiforme, in which, along with skin lesions, mucosal lesions of at least two organs are noted). Phenylbutazone and especially its metabolite, oxyphenbutazone, can lead to exacerbation of porphyria.

Indications

Phenylbutazone should be used as a backup NSAID for the ineffectiveness of other drugs, a short course. The greatest effect is noted with ankylosing spondylitis, gout.

Warnings

Do not use phenylbutazone and its combined preparations (rheopyrite, pyrabutol) as analgesics or antipyretics in wide clinical practice.

Patients should be warned about the immediate termination of treatment and an urgent call to the doctor if the following symptoms appear:

 fever, chills, sore throat, stomatitis (symptoms of agranulocytosis);

 dyspepsia, epigastric pain, unusual bleeding and bruising, tarry stool (symptoms of anemia);

 skin rash, itching;

 a significant increase in body weight, swelling.

Dosage: adults: the initial dose is 450-600 mg / day in 3-4 doses. After the therapeutic effect is achieved, maintenance doses are used - 150-300 mg / day in 1-2 doses. In children under 14 years old is not applicable.

Method of release: - tablets of 150 mg; - ointment, 5%.

INDOMETACIN. (Indocide, Indobene, Metindol, Elmetacin). Indomethacin is one of the most powerful NSAIDs.

Pharmacokinetics

The maximum concentration in the blood develops 1-2 hours after ingestion of the usual and 2-4 hours after taking prolonged (“retard”) medication. Eating slows down absorption. With rectal administration, it is absorbed somewhat worse and the maximum concentration in the blood develops more slowly. The elimination half-life makes 4-5 hours.

Interactions. More than other NSAIDs, indomethacin worsens renal blood flow, therefore, it can significantly weaken the effect of diuretics and antihypertensive agents. The combination of indomethacin with a potassium-sparing diuretic triamteren is very dangerous, as it provokes the development of acute renal failure.

Adverse reactions

The main disadvantage of indomethacin is the frequent development of adverse reactions (in 35-50% of patients), and their frequency and severity depend on the daily dose. In 20% of cases, due to adverse reactions, the drug is canceled.

The most characteristic neurotoxic reactions are: headache (caused by cerebral edema), dizziness, stupor, inhibition of reflex activity; gastrotoxicity (higher than aspirin); nephrotoxicity

(should not be used for renal and heart failure); hypersensitivity reactions (cross-allergy with aspirin is possible).

Indications

Indomethacin is especially effective for ankylosing spondylitis and an acute attack of gout. It is widely used for rheumatoid arthritis and active rheumatism. In juvenile rheumatoid arthritis is a reserve drug. There is extensive experience with the use of indomethacin in osteoarthritis of the hip and knee joints. However, it has recently been shown that in patients with osteoarthritis it accelerates the destruction of articular cartilage. A special area of use of indomethacin is neonatology.

Dosage: adults: initial dose - 25 mg 3 times a day, maximum - 150 mg / day. The dose is increased gradually. Retard tablets and rectal suppositories are prescribed 1-2 times a day. Sometimes they are used only at night, and in the morning and afternoon, another NSAID is prescribed. Topically apply ointment.

Method of release: - enteric-coated tablets of 25 mg; - tablets "retard" 75 mg; - candles of 100 mg; - ointment, 5 and 10%.

SULINDAK (Clinoril)

Pharmacokinetics

It is a "prodrug" in the liver turns into an active metabolite. The maximum concentration of the active metabolite of sulindac in the blood is observed 3-4 hours after ingestion. The half-life of sulindac is 7-8 hours, and the active metabolite is 16-18 hours, which provides a lasting effect and the possibility of taking 1-2 times a day.

Adverse reactions

Unlike indomethacin, it is less gastro- and neurotoxic, has a much weaker effect on renal blood flow and glomerular filtration (since the active metabolite of sulindac does not interfere with the synthesis of PG in the kidneys), and almost does not interact with diuretics and antihypertensive drugs. It can cause crystalluria, therefore, should not be prescribed to patients with urolithiasis. Hepatotoxicity is higher than that of indomethacin.

Indications. It is used for rheumatic and non-rheumatic diseases.

Dosage. Adults: inside 400 mg / day in 1-2 doses. Children: 4.5-6 mg / kg / day in 2 divided doses.

Release form: - tablets on 200 mg.

DICLOFENAC-SODIUM (Voltaren, Diclobene, Diclonate P, Naklofen, Or-tofen). It is the most widely used NSAID in the world.

Pharmacokinetics

Diclofenac is well absorbed in the gastrointestinal tract. Bioavailability is 50-60%, which is due to the effect of the "first pass". The maximum concentration in the blood develops within 0.5-2 hours after ingestion and 10-30 minutes after administration intramuscularly. The elimination half-life is 1.5-2 hours.

Adverse reactions

Diclofenac is generally well tolerated. Undesirable reactions, as a rule, develop less frequently than when using many other NSAIDs. But with prolonged use, the drug can have a negative effect on the gastrointestinal tract and, especially, on the liver, therefore, clinical and laboratory monitoring is necessary.

Indications

Diclofenac combines high, at the level of indomethacin, anti-inflammatory activity with good tolerance with long-term use, it is widely used in rheumatology.

It has a strong and rapid analgesic effect. With severe pain (renal or hepatic colic, postoperative pain, pain during injury) is administered intramuscularly.

Dosage: Adults: 25-50 mg 2-3 times daily orally or rectally; tablets "retard" (100 mg) are prescribed 1-2 times a day. Intramuscularly, 75 mg 1-2 times a day, if the first dose is ineffective, the second can be administered after 30 minutes.

Children over 1.5 years of age: 2-4 mg / kg / day in 2 doses orally or rectally.

Method of release: - enteric-coated tablets of 25 mg; - tablets "retard" of 100 mg; - ampoules of 3 ml (25 mg / ml); - candles of 25 and 50 mg; - gel, 1%.

DICLOFENAC-POTASSIUM (Voltaren Rapid)

Compared with diclofenac sodium, it is absorbed more rapidly, and mainly in the stomach; has a faster analgesic effect - 20-30 minutes after ingestion

Indications. Same as diclofenac sodium. It is indicated for the rapid relief of pain.

Dosage Adults, by mouth 100-150 mg / day in 2–3 doses. With dysmenorrhea, the daily dose can be increased to 200 mg.

Release form: - tablets on 25 and 50 mg.

PYROXYCAM (Velden, Pirokam, Erazon)

It has a strong anti-inflammatory effect, which develops slowly - within 1-2 weeks of constant use. The maximum effect is noted after 2-4 weeks. It has a quick and pronounced analgesic effect, especially with intramuscular administration.

Pharmacokinetics

It is well absorbed in the gastrointestinal tract. Food slows down the rate of absorption. The maximum concentration in the blood develops after 3-5 hours. It has a long half-life of 45-60 hours. An equilibrium concentration in the blood is created after 7-12 days, so the clinical effect develops slowly. More quickly, the equilibrium concentration is achieved when taking a dose of saturation.

Undesirable reactions. Piroxicam is one of the most gastro-toxic NSAIDs, especially with long-term administration at a dose of 30 mg per day or more. According to some reports, its gastrotoxicity is higher than that of indomethacin. Other adverse reactions are also possible: hematotoxicity (thrombocytopenia, aplastic anemia, decreased hemaglobin and hematocrit, not associated with gastrointestinal bleeding), nephrotoxicity, skin reactions (rash, photodermatitis).

Indications: it is used as an anti-inflammatory agent, including with juvenile rheumatoid arthritis, with gout. It can be used as an analgesic for postoperative and post-traumatic pain.

Dosage Adults: 20 mg / day in a single oral or rectal administration. For a quick effect in the first 2 days, a saturation dose of 40 mg / day is prescribed in one or several doses, and then reduced to 20 mg / day. In an acute attack of gout on the 1st day - 40 mg in one dose, in the next 4-6 days - 40 mg / day in one or more doses. Children: with a body weight of less than 15 kg - 5 mg / day, 16-25 kg - 10 mg / day, 26-45 kg - 15 mg / day, more than 45 kg - 20 mg / day.

Method of release: - tablets and capsules of 10 and 20 mg; - ampoules of 1 and 2 ml (20 mg / ml); - gel, 0.5%.

TENOXICAM (Tilkotil)

In activity and pharmacokinetic parameters, it is close to piroxicam. The maximum concentration in the blood develops after 1-2.6 hours when taken on an empty stomach and after 4-6 hours when taken after meals. The half-life is 60-75 hours. The full clinical effect develops after 2 weeks. Less gastrotoxic than piroxicam.

Dosage Adults: by mouth, rectally and intramuscularly - 20 mg / day in one dose (administration).

Method of release: - tablets of 20 mg; - capsules of 20 mg; - candles of 20 mg.

LORNOXICAM (Ksefokam)

NSAIDs from the oxycam group - chlortenoxicam. It is superior to other oxycams in its inhibition of COX, moreover, it blocks COX-1 and COX-2 to approximately the same degree, occupying an intermediate position in the classification of NSAIDs based on the principle of selectivity. It has a pronounced analgesic and anti-inflammatory effect.

The analgesic effect of lornoxicam consists of a violation of the generation of pain impulses and a weakening of the perception of pain (especially in chronic pain). With the on / in the introduction of the drug is able to increase the level of endogenous opioids, thereby activating the physiological antinociceptive system of the body.

Pharmacokinetics

It is well absorbed in the digestive tract, food slightly reduces bioavailability. Maximum plasma concentrations are observed after 1-2 hours. With the / m administration, the maximum plasma level is noted after 15 minutes. It penetrates well into the synovial fluid, where its concentration reaches 50% of the plasma, and lasts long in it (up to 10-12 hours). It is metabolized in the liver, excreted through the intestine (mainly) and the kidneys. The elimination half-life is 3-5 hours.

Adverse reactions

Lornoxicam is less gastrotoxic than oxycams of the "first generation" (pyroxicam, tenoxicam). This is partly due to the short half-life, which creates opportunities for the restoration of the protective level of GHGs in the gastrointestinal mucosa. In controlled studies, it was found that lornoxicam is superior in tolerance to indomethacin and practically does not concede diclofenac in effectiveness.

Indications

- Pain (acute and chronic pain, including cancer).

With the on / in the introduction of lornoxicam at a dose of 8 mg is not inferior to the severity of the analgesic effect of meperidine (close to domestic promedol). When taken orally in patients with postoperative pain, 8 mg of lornoxicam is approximately equivalent to 10 mg of ketorolac,

400 mg of ibuprofen and 650 mg of aspirin. In severe pain, lornoxicam can be used in combination with opioid analgesics, which reduces the dose of the latter.

- Rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, osteoarthritis).

Dosage Adults: for pain - inside - 8 mg x 2 times a day; it is possible to take a shock dose of 16 mg; in / m or in / in - 8-16 mg (1-2 doses with an interval of 8-12 hours); in rheumatology - inside 4-8 mg x 2 times a day.

Method of release: - tablets of 4 and 8 mg; - 8 mg vials (for the preparation of an injection solution).

MELOXICAM (Movalis)

He is a representative of a new generation of NSAIDs - selective COX-2 inhibitors. Due to this property, meloxicam selectively inhibits the formation of prostaglandins, which are involved in the formation of inflammation. At the same time, it inhibits COX-1 much weaker, therefore, it has less effect on the synthesis of prostaglandins that regulate renal blood flow, the production of protective mucus in the stomach, and platelet aggregation.

Controlled studies conducted in patients with rheumatoid arthritis showed that the strength of anti-inflammatory activity of meloxicam is not inferior to piroxicam, naproxen and diclofenac, but significantly less undesirable reactions from the gastrointestinal tract and kidneys.

Pharmacokinetics

Oral bioavailability is 89% and does not depend on food intake. The maximum concentration in the blood develops after 5-6 hours. Equilibrium concentration is created in 3-5 days. The half-life of 20 hours, which allows you to prescribe the drug 1 time per day.

Indications: Rheumatoid arthritis, osteoarthrosis.

Dosage Adults: inside and intramuscularly at 7.5-15 mg once a day.

Method of release: - tablets of 7.5 and 15 mg; - ampoules of 15 mg.

NABUMETON (Relafen)

Like meloxicam selectively inhibits COX-2. Quickly absorbed. Food speeds up absorption. An active metabolite is formed in the liver with a half-life of approximately equal to 24 hours.

Adverse reactions from the gastrointestinal tract are less common than with other NSAIDs.

Indications Rheumatoid arthritis, osteoarthrosis.

Dosage

Adults: 1000 mg once a day, in some cases 1500-2000 mg per day, in 1-2 doses, regardless of food intake. Children: doses not established.

Release form: - tablets on 500 and 750 mg.

IBUPROFEN (Brufen, Motrin)

The strength of the anti-inflammatory action is inferior to many other drugs of group I. However, when taking ibuprofen in daily doses of 1200 mg or higher, a satisfactory anti-inflammatory effect is achieved. Analgesic and antipyretic effects prevail over anti-inflammatory activity.

Pharmacokinetics

The maximum concentration in the blood develops 1-2 hours after ingestion. It is rapidly metabolized and excreted from the body. The elimination half-life of 1.8-2.5 hours, therefore, the analgesic and antipyretic effects are maintained up to 8 hours. The advantage of the drug is good tolerance, a rare development of adverse reactions. It is one of the least gastrotoxic among NSAIDs.

Indications. It is used more often as an analgesic, as well as in mild cases of rheumatoid arthritis, osteoarthritis.

Dosage

Adults: 400-600 mg 3-4 times a day, drugs "retard" - 600-1200 mg 2 times a day. Children: 20-40 mg / kg / day in 2-3 doses.

Ibuprofen is approved for over-the-counter use in children over 2 years of age with fever and pain syndrome of 7.5 mg / kg up to 4 times a day, with a maximum of 30 mg / kg / day.

Method of release: - tablets of 200, 400 and 600 mg; - tablets "retard" at 600, 800 and 1200 mg; - cream, 5%.

NAPROXEN (Naprosin)

One of the most commonly used NSAIDs. It is superior to ibuprofen in anti-inflammatory activity. The anti-inflammatory effect develops slowly, with a maximum after 2-4 weeks. It has a strong analgesic and antipyretic effect. The anti-aggregation effect is manifested only with the appointment of high doses of the drug. It does not have a uricosuric effect.

Pharmacokinetics

It is well absorbed by oral administration and rectal administration. The maximum concentration in the blood is observed 2-4 hours after ingestion. The elimination half-life makes about 15 hours that allows to appoint it 1-2 times a day.

Adverse reactions

Gastrotoxicity is less than that of indomethacin, aspirin and piroxicam. Nephrotoxicity is usually noted only in patients with renal pathology and heart failure. Allergic reactions are possible, cases of cross allergy with aspirin are described.

Indications

It is widely used for rheumatism, ankylosing spondylitis, rheumatoid arthritis in adults and children. In patients with osteoarthritis, it inhibits the activity of the proteoglycanase enzyme, preventing degenerative changes in the articular cartilage, which compares favorably with indomethacin. It is widely used as an analgesic, including for postoperative and postpartum pain, for gynecological procedures. High efficacy in dysmenorrhea, paraneoplastic fever was noted.

Dosage Adults: 500-1000 mg / day in 1-2 doses orally or rectally. The daily dose can be increased to 1500 mg for a limited period (up to 2 non-del). In acute pain syndrome (bursitis, tendovaginitis, dysmenorrhea), the 1st dose is 500 mg, then 250 mg every 6-8 hours. Children: 10-20 mg / kg / day in 2 divided doses. As an antipyretic - 15 mg / kg per dose.

Method of release: - tablets of 250 and 500 mg; - candles of 250 and 500 mg; - suspension containing 250 mg / 5 ml; - gel, 10%.

NAPROXEN-SODIUM (Olive, Apranax). Differs from naproxen in faster absorption in the gastrointestinal tract and increased bioavailability. The analgesic effect develops after 15 minutes, and the maximum concentration in the blood - after 1 hour. The half-life is 13 hours, which allows it to be used no more than 2 times a day.

Indications. First of all, it is used as a fast-acting analgesic for headache and toothache, postoperative pain, trauma, dysmenorrhea. For over-the-counter use, it is available under the name Olive. As anti-inflammatory activity is equal to naproxen, therefore, can be used in rheumatology.

Dosage - Adults: 220-550 mg 1-2 times a day. Children: 10-20 mg / kg / day in 2 divided doses.

Release form: - tablets on 220 mg (Olive), 275 and 550 mg (Apranax).

FLURBIPROFEN (Anseid, Flugalin, Froben)

In pharmacodynamics, it is close to naproxen. Adverse reactions, especially from the gastrointestinal tract, skin rashes, bronchospasm are noted more often than with naproxen. The maximum concentration in the blood develops 1.5 hours after ingestion. The elimination half-life varies in various patients from 3 to 9 hours.

Dosage Adults: 50-100 mg 3-4 times a day. Children: 4 mg / kg / day in 2-4 doses.

Method of release: - tablets of 50 and 100 mg; - candles of 100 mg.

KETOPROFEN (Ketonal, Knavon, Cannon, Profenid)

It has a pronounced anti-inflammatory and analgesic effect. Controlled clinical trials in patients with rheumatoid arthritis and osteoarthritis showed that it is not inferior in effectiveness to indomethacin, diclofenac and naproxen, superior to ibuprofen and piroxicam. At a dose of 50-100 mg, ketoprofen has a stronger analgesic effect than combinations of paracetamol / codeine and aspirin / codeine.

Pharmacokinetics

It is well absorbed in various routes of administration. The maximum concentration in the blood develops 1-2 hours after ingestion, 2.4-4 hours after rectal and 15-20 minutes after intramuscular injection. The elimination half-life makes 1,6-1,9 hours.

Adverse reactions

Basically, from the gastrointestinal tract in the form of dyspeptic and dyspeptic disorders. In rare cases, there are impaired renal and hepatic function, headache, tinnitus, visual disturbances. Allergic reactions are possible.

Indications

Rheumatoid arthritis, gouty arthritis, osteoarthritis, pain (dysmenorrhea, renal colic, postoperative and post-traumatic pain, pain in cancer). In acute closed soft tissue injury, ketoprofen can be used externally in the form of a gel. As controlled studies have shown, it is superior in effectiveness to similar dosage forms of diclofenac and piroxicam. For severe pain, ketoprofen can be used in combination with narcotic analgesics.

Dosage Adults: inside and rectally 100-300 mg / day in 2-3 doses, and taking tablets or capsules can be combined using candles, for example, 1 capsule (50 mg) in the morning and afternoon and 1 candle (100 mg) in the evening , intramuscularly - 100 mg 1-2 times a day; intravenous -

short-term infusion - 100-200 mg in 100 ml of physiological solution of sodium chloride for 0.5-1 hours every 8 hours; long-term infusion - 100-200 mg in 500 ml of physiological solution of sodium chloride (or glucose solution) for 8 hours at 8-hour intervals, with prolonged infusion, ketoprofen can be mixed with 10-20 ml of morphine, but can not be mixed with tramadol, since precipitates. Children: doses not established.

Method of release: - tablets of 50, 100 and 150 ("retard") mg; - 50 mg capsules; - candles of 100 mg; - ampoules of 2 ml (100 mg); - gel, 5%.

TIAPROPHENIC ACID (Surgam)

On anti-inflammatory activity is close to naproxen. It has a pronounced analgesic effect. Quickly absorbed by ingestion. The maximum concentration in the blood develops after 1 hour. The half-life of 3 hours. There is evidence of a positive effect of the drug on articular cartilage metabolism.

Undesirable reactions. It can cause irritation of the mucous membrane of the bladder up to the development of cystitis, which is manifested by hematuria and dysuric phenomena. Therefore, thiaprofenic acid should not be used in patients with diseases of the urinary tract and prostate gland (including a history of them).

Dosage Adults: 300 mg 2 times a day. In patients with renal, hepatic and heart failure - 200 mg 2 times a day. Children: doses not established.

Method of release: - tablets of 100 and 300 mg; - candles of 150 and 300 mg.

CELECOXIB (Celebrex)

The drug is from the group of non-acid derivatives (is a derivative of sulphonamide). Representative of a new generation of NSAIDs - selective COX-2 inhibitors. In this regard, it selectively violates the formation of prostaglandins, which are involved in the formation of the inflammatory reaction, and does not affect the production of prostaglandins that regulate renal blood flow and the integrity of the gastrointestinal mucosa. Does not interfere with the synthesis of thromboxane, therefore, does not affect platelet aggregation. It has a pronounced anti-inflammatory and analgesic effect.

Pharmacokinetics

It is well absorbed in the digestive tract, the peak concentration in the blood develops after 3 hours. Food, especially fatty, slows down the rate of absorption, but at the same time slightly increases its volume (by 10-20%). It is metabolized in the liver, excreted in the stool (mainly) and in the urine. T1 / 2 - 11 hours, may increase with moderate impairment of liver function.

Adverse reactions

Being a selective inhibitor of COX-2, celecoxib is much less likely than other NSAIDs to cause adverse reactions from the gastrointestinal tract. At the same time, the incidence of gastric and duodenal ulcers does not differ from placebo, and bleeding and perforation are not observed. Headache, dizziness, sleep disturbances, rash, and rhinitis may occur. Nephrotoxic reactions are not recorded.

Drug interactions

Fluconazole 2 times increases the concentration of celecoxib in blood plasma due to inhibition of its metabolism in the liver.

Celecoxib increases the concentration of lithium in plasma.

No interactions of celecoxib with diuretics, antihypertensive drugs, indirect anticoagulants, methotrexate have been established.

Indications Rheumatoid arthritis, osteoarthrosis.

Dosage Adults: inside - 100-200 mg / day in 1-2 doses. Doses for children under 18 have not been established. Method of release: capsules of 100 and 200 mg.

NSAIDs WITH WEAK ANTI-INFLAMMATORY ACTIVITY

Drugs in this group combine a pronounced analgesic and antipyretic effect with a weak anti-inflammatory effect. Therefore, they are not used as anti-inflammatory, they are used as analgesics and antipyretics.

MEPHENAMIC (MEPHENAMINE) ACID (PONSTEL)

The anti-inflammatory effect is significantly inferior to group I drugs. Used as an analgesic and antipyretic. The course of treatment should not exceed 1 week.

Pharmacokinetics

Slowly absorbed in the gastrointestinal tract, partially metabolized in the liver, elimination half-life - 4 hours.

Undesirable reactions. Often causes undesirable reactions (in 25% of patients), especially from the gastrointestinal tract. Diarrhea associated with inflammation of the large intestine is characteristic. It has hepatotoxic stoke, can cause hemolytic anemia, allergic reactions. The elderly may develop neoliguric renal failure, especially with dehydration.

Dosage. Adults: the first dose is 500 mg, then 250 mg 4 times a day. Children: over 14 years of age - a single dose of 6.5 mg / kg. In children under 14 years old is not applicable.

Method of release: - tablets of 500 mg; - syrup.

METAMIZOL SODIUM (Analgin, Baralgin M, Devalgin, Novalgin, Toralgin)

In some countries, Dipiron is used under the generic name. Despite the structural similarity with phenylbutazone, it has a significantly lower anti-inflammatory effect. This is due to the weak effect of metamizole on the synthesis of PG in the foci of inflammation. It has a pronounced analgesic effect, which is mainly due to central mechanisms, in particular, impaired pain impulses in the spinal cord. Unlike other NSAIDs, it has antispasmodic activity.

Pharmacokinetics

Quickly and almost completely absorbed. The maximum concentration in the blood develops after 1-2 hours. The elimination half-life is 2.5 hours.

Undesirable reactions. It is necessary to remember the danger of developing hematological complications inherent in all pyrazolones and pyrazolidines, and observe safety precautions.

Indications. It is used as an analgesic and antipyretic. To provide a quick effect, it is administered parenterally.

Dosage Adults: orally, 0.5-1 g 3-4 times a day, intramuscularly or intravenously, 2-5 ml of 50% solution 2-4 times a day.

Children: 5-10 mg / kg 3-4 times a day. With hyperthermia intravenously or intramuscularly in the form of a 50% solution: up to 1 year - 0.01 ml / kg, older than 1 year - 0.1 ml / year of life per administration.

Method of release: - tablets of 100 and 500 mg; - ampoules of 1 ml of 25% solution, 1 and 2 ml of 50% solution; - drops, syrup, candles.

PARACETAMOL (Kalpol, Lekadol, Mexalen, Panadol, Efferalgan)

Paracetamol (in some countries it has the generic name acetaminophen) is an active metabolite of phenacetin. Compared to phenacetin, it is less toxic.

More inhibits the synthesis of prostaglandins in the central nervous system than in peripheral tissues. Therefore, it has a predominantly "central" analgesic and antipyretic effect and has a very weak "peripheral" anti-inflammatory activity. The latter can occur only with a low content of peroxide compounds in tissues, for example, with osteoarthritis, with acute soft tissue injury, but not with rheumatic diseases.

Pharmacokinetics

Paracetamol is well absorbed when taken orally and rectally. The maximum concentration in the blood develops after 0.5-2 hours after administration. In vegetarians, the absorption of paracetamol in the gastrointestinal tract is significantly weakened. The drug is metabolized in the liver in 2 stages: first, intermediate hepatotoxic metabolites are formed under the action of the enzyme systems of cytochrome P-450, which are then cleaved with the participation of glutathione. Less than 5% of the administered paracetamol is excreted unchanged by the kidneys. The elimination half-life is 2-2.5 hours. The duration of action is 3-4 hours.

Adverse reactions

Recently, data have been obtained that with prolonged use of paracetamol more than 1 tablet per day (1000 or more tablets per life), the risk of developing severe analgesic nephropathy, leading to terminal renal failure, doubles. It is based on the nephrotoxic effect of paracetamol metabolites, especially paraaminophenol, which accumulates in the renal papillae, binds to SH groups, causing severe dysfunctions of the function and structure of cells, up to their death. At the same time, the systematic use of aspirin is not associated with a similar risk. Thus, paracetamol is more nephrotoxic than aspirin and should not be considered an “absolutely safe” drug.

You should also remember the hepatotoxicity of paracetamol when taken in very large (!) Doses. A simultaneous administration of it at a dose of more than 10 g in adults or more than 140 mg / kg in children leads to poisoning, accompanied by severe liver damage. The reason is the depletion of glutathione reserves and the accumulation of intermediate metabolic products of paracetamol with hepatotoxic effects. Symptoms of poisoning are divided into 4 stages.

Symptoms of paracetamol intoxication.

I The first 12-24 hours. Mild symptoms of gastrointestinal irritation. The patient does not feel sick.

II 2-3 days. Symptoms from the gastrointestinal tract, especially nausea and vomiting; increase in AST, ALT, bilirubin, prothrombin time.

III 3-5 days. Indomitable vomiting; high values of AST, ALT, bilirubin, pro-thrombin time; signs of liver failure.

IV. After 5 days, restoration of liver function or death from liver failure.

A similar picture can be observed when taking usual doses of the drug in the case of concomitant use of cytochrome P-450 enzyme inducers, as well as in alcoholics.

It must be borne in mind that forced diuresis in case of paracetamol poisoning is ineffective and even dangerous, peritoneal dialysis and hemodialysis are ineffective. In no case should antihistamines, glucocorticoids, phenobarbital and ethacrylic acid be used, which can have an inducing effect on the enzyme systems of cytochrome P-450 and enhance the formation of hepatotoxic metabolites.

Interactions. The absorption of paracetamol in the gastrointestinal tract is enhanced by metoclopramide and caffeine.

Inducers of hepatic enzymes (barbiturates, rifampicin, diphenin and others) accelerate the breakdown of paracetamol to hepatotoxic metabolites and increase the risk of liver damage.

Indications

Currently, paracetamol is considered as an effective analgesic and antipyretic for widespread use. It is primarily recommended if there are contraindications to aspirin and other NSAIDs: in patients with bronchial asthma, in patients with a history of ulcer, in children with viral infections. In terms of analgesic and antipyretic activity, paracetamol is close to aspirin. Warnings. Paracetamol should be used with caution in patients with impaired liver and kidney function, as well as in those who take drugs that affect liver function.

Dosage Adults: 500-1000 mg 4-6 times a day. Children: 10-15 mg / kg 4-6 times a day.

Method of release: - tablets of 200 and 500 mg; - syrup 120 mg / 5 ml and 200 mg / 5 ml; - candles at 125, 250, 500 and 1000 mg; - "effervescent" tablets of 330 and 500 mg. Soridone, solpadein, tomapirin, citramon P and others are part of the combined preparations.

KETOROLAK (Toradol, Ketrodol)

The main clinical value of the drug is its powerful analgesic effect, the degree of which it is superior to many other NSAIDs.

30 mg of ketorolac, administered intramuscularly, were found to be approximately equivalent to 12 mg of morphine. At the same time, adverse reactions characteristic of morphine and other narcotic analgesics (nausea, vomiting, respiratory depression, constipation, urinary retention) are noted much less frequently. The use of ketorolac does not lead to the development of drug dependence. Ketorolac also has antipyretic and anti-aggregation effects.

Pharmacokinetics

Almost completely and quickly absorbed in the gastrointestinal tract, oral bioavailability is 80-100%. The maximum concentration in the blood develops 35 minutes after ingestion and 50 minutes after administration intramuscularly. It is excreted by the kidneys. The half-life of 5-6 hours.

Undesirable reactions. The most commonly observed gastrotoxicity and increased bleeding due to anti-aggregation action.

Interaction. When combined with opioid analgesics, the analgesic effect is enhanced, which makes it possible to use them in lower doses. Intravenous or intraarticular administration of

ketorolac in combination with local anesthetics (lidocaine, bupivacaine) provides better pain relief than using only one of the drugs after arthroscopy and operations on the upper limbs.

Indications. It is used to relieve pain of various localization: renal colic, pain in injuries, in neurological diseases, in cancer patients (especially with bone metastases), in the postoperative and postpartum period.

There is evidence of the possibility of using ketorolac before surgery in combination with morphine or fentanyl. This allows you to reduce the dose of opioid analgesics by 25-50% in the first 1-2 days of the postoperative period, which is accompanied by a faster restoration of the gastrointestinal tract function, less nausea and vomiting, and reduces the length of hospital stay.

It is also used for pain relief in operative dentistry and during orthopedic medical procedures.

Warnings. Ketorolac should not be used before long-term operations with a high risk of bleeding, as well as for maintenance anesthesia during operations, to anesthetize labor, to relieve pain in myocardial infarction. The course of use of ketorolac should not exceed 7 days, and in people over 65 years of age, the drug should be prescribed with caution.

Dosage Adults: 10 mg orally every 4–6 hours; the highest daily dose is 40 mg; Duration of use no more than 7 days. Intramuscularly and intravenously - 10-30 mg; the highest daily dose is 90 mg; duration of use no more than 2 days. Children: 1st dose intravenously - 0.5-1 mg / kg, then 0.25-0.5 mg / kg every 6 hours. Method of release: - tablets of 10 mg; - ampoules of 1 ml.

COMBINED DRUGS

A number of combination preparations are produced, containing, in addition to NSAIDs, other drugs that, due to their specific properties, can enhance the analgesic effect of NSAIDs, increase their bioavailability and reduce the risk of adverse reactions.

Reopyrin

(Pirabutol). The composition includes aminophenazone (amidopyrine) and phenylbutazone (butadione). For many years it has been widely used as an analgesic. However, it does not have efficiency advantages over modern NSAIDs and significantly exceeds them in the severity of undesirable reactions. The risk of developing hematological complications is especially high, therefore it is necessary to observe all the above precautions and strive to use other analgesics. With intramuscular administration, phenylbutazone binds to tissues at the injection site and is poorly absorbed, which, firstly, delays the development of the effect and, secondly, causes frequent development of infiltrates, abscesses, and lesions of the sciatic nerve.

Dosage Adults: inside, 1-2 tablets 3-4 times a day, intramuscularly 2-3 ml 1-2 times a day. In children, not applicable.

Method of release: - tablets containing 125 mg of phenylbutazone and aminophenazone; - 5 ml ampoules containing 750 mg of phenylbutazone and aminophenazone.

BARALGIN

It is a combination of metamizole (analgin) with two antispasmodics, one of which - pitophenone - has a myotropic effect, and the other - fenpiverinium - an atropine-like effect. It is used to relieve pain caused by a spasm of smooth muscles (renal colic, hepatic colic and others). Like other drugs with atropine-like activity, it is contraindicated in glaucoma and prostate adenoma.

Dosage. Inside, 1-2 tablets 3-4 times a day, intramuscularly or intravenously 3-5 ml 2-3 times a day. Intravenously administered at a rate of 1-1.5 ml per minute.

Method of release: - tablets containing 500 mg of metamizole, 10 mg of pitofenon and 0.1 mg of fenpiverinium; - 5 ml ampoules containing 2.5 g of metamizole, 10 mg of pitophenone and 0.1 mg of fenpiverinium.

ARTROTEC

consists of diclofenac and misoprostol (a synthetic analogue of PG-E1), the inclusion of which aims to reduce the frequency and severity of adverse reactions characteristic of diclofenac, especially gastrotoxicity. Arthrotek is effective in case of rheumatoid arthritis and osteoarthritis diclofonac, and the development of erosion and stomach ulcers with its use is noted much less often.

Dosage. Adults: 1 tablet 2-3 times a day.

Release form: - tablets containing 50 mg of diclofenac and 200 mg of miso-prostol.

STEROID ANTI-INFLAMMATORY DRUGS (glucocorticosteroids).

Glucocorticosteroids are synthetic drugs (analogues of endogenous hormones produced by the adrenal cortex) that have anti-inflammatory, desensitizing, immunosuppressive, anti-shock and antitoxic effects.

This group includes drugs:

Alclomethasone (Afloderm). Betamethasone (Akriderm, Beloderm, Belosalik, Belogent, Diprosalik, Diprospan, Garazon, Nasobek, Triderm, Flucycort, Celeston, Celestoderm-B). Beclomethasone dipropionate (Aldecin, Bezlason Eco, Beclodget, Bekotid, Clenil, Rinoklenil). Budesonide (Benocort, Pulmicort, Symbicort Tour-buhaler, Tafen Nazal). Flumetazone (Lorinden S, Seretide). Hydrocortisone (Hydro-cortisone, Cortef, Laticort, Oxycort). Dexamethasone (Ambene, Dex-Gentamicin, Maxidex, Maxitrol, Polydex, Toradex). Methylprednisolone (Advantan, Meti-pred, Solu-Medrol). Mometasone furoate (Momat, Nazonex, Elokom). Prednisolone (Aurobin, Dermozolone). Triamcinolone acetonide (Kenalog, Polcortolone, Fluoro-court). Fluticasone Propionate (Flixonase, Flixotide). Flucortolone (Ultraproct).

Regulation of the allocation of glucocorticosteroids

The main endogenous GCS is cortisol, which is synthesized and secreted by the adrenal cortex in response to the stimulating effect of adrenocorticotropic hormone (ACTH). Normally, about 15-30 mg of cortisol is secreted daily. The release of the hormone occurs in pulses - 8-10 imp / day. The level of cortisol secretion does not remain constant during the day (the maximum concentration in the blood is reached by 7-8 a.m., the minimum - by midnight). Under stress (infection, surgery, hypoglycemia), the synthesis and secretion of GCS increases by about 10 times (up to 250 mg / day).

Regulation of the release of corticosteroids is controlled by the hypothalamic-pituitary mechanism. With a decrease in the concentration of free cortisol, the hypothalamus secrete corti-cotropin - a releasing factor that stimulates the release of adrenocorticotropic hormone (corticotropin) in the anterior pituitary gland. Adrenocorticotropic hormone (ACTH), in turn, causes the release of GCS from the adrenal cortex

MECHANISM OF ACTION OF Glucocorticosteroids

The action of glucocorticosteroid hormones on the cell is manifested by their effect on the genetic apparatus of the cell. The primary link in the action of glucocorticosteroids on the cell is their interaction with specific receptors of target organs.

GCS are lipid substances (cholesterol derivatives) and can dissolve in cell membranes. The penetration of the hormone into the cell is possible not only in a bound form (using a carrier protein), but also passively.

Steroid receptors are found in the cytoplasm of cells. However, their density in different cells is not the same: from 10 to 100 steroid-sensitive receptors, which, possibly, causes different tissue sensitivity to GCS. In addition, corticosteroids can have different tropics for GCR. Thus, endogenous glucocorticosteroid cortisol predominantly binds to SERS of the cytoplasmic membrane, while synthetic GCS - dexamethasone, to a greater extent, binds to cytosolic SERS. The number of glucocorticosteroid receptors (GCR) can vary significantly and change during GCS therapy.

The next step is to move the hormone receptor complex (GHC) into the cell nucleus. The penetration of GRK into the nucleus is possible after the restructuring of their structure (activation), which leads to the appearance of their ability to bind to the components of the nucleus.

Activated HFA binds to a specific DNA region in the nucleus. Complex GRK - DNA contributes to an increase in RNA synthesis. Recent studies have shown that the effect of glucocorticosteroid hormones on the biosynthesis of messenger RNA (mRNA) is the main step in the realization of the biological effects of GCS in the cells of target organs.

GCS can have both a specific stimulating effect and an inhibitory effect on the synthesis of various RNAs. Multidirectional effects can occur in the same organ and, possibly, the final response of the cell to the hormonal signal depends on their ratio. GCS also affect the activity of RNA polymerase. The possibility of interaction of steroids with non-histone chromatin proteins is described, which leads to a change in their structure. The anti-inflammatory effect of steroids is mediated through specific GKR, a change in the activity of GKH and the synthesis of RNA and proteins (nuclear pathway).

PHARMACODYNAMIC EFFECTS OF Glucocorticosteroids

1. The anti-inflammatory effect of GCS is manifested in the form of antiexudative and antiproliferative effects.

2. Immunosuppressive effect

3. Antiallergic effect

4. Effect on metabolic processes

The antiexudative effect of GCS is determined

 Membrane-stabilizing effect and, as a consequence of this, a decrease in the permeability of cell and subcellular membranes (mitochondria and lysosomes);

 Reduced permeability of the vascular wall, in particular, capillaries and vasoconstriction in the focus of inflammation. Vasoconstriction is a specific effect of corticosteroids on the vascular bed in the focus of inflammation. At the same time, their effect on other vessels can cause, on the contrary, vasodilation. The mechanism of this action of GCS is not fully understood, it is

associated with suppression of the release of lipid mediators and activators of the kinin system, a decrease in the activity of hyaluronidase;

 Suppression of the synthesis of some cytokines involved in inflammatory reactions, as well as the blockade of the synthesis of cytokine receptor proteins;

 Reducing the production of interleukins (IL): IL-1, IL-3, IL-4, IL-5, IL-b and IL-8, tumor necrosis factor - alpha (TNF - α), granulocyte macrophage-colony-stimulating factor (GM-CSF), by suppressing, transcribing or reducing the half-life of messenger RNA;

Inhibition of migration of mast cells and eosinophils into the focus of inflammation. Glucocorticosteroids are known to reduce eosinophils by suppressing the production of GM-CSF and IL-5;

 Suppression of mast cell degranulation and the release of biologically active amines (histamine, serotonin, kinins and prostaglandins) from mast cells;

 Reducing the intensity of energy production processes in the focus of inflammation;

 Inhibition of migration of neutrophils into the focus of inflammation, a violation of their functional activity (chemotactic and phagocytic). GCS cause peripheral leukocytosis both after a single appointment (for 4-6 hours), and with prolonged treatment (on the 14th day) with a subsequent decrease in the level of leukocytes;

 Inhibition of monocyte migration by slowing the release of mature monocytes from the bone marrow and reducing their functional activity.

Effects	The mechanisms underlying this effect
Antiexudative effect	o o stabilization of cell and subcellular membranes (mitochondria and lysosomes); o o a decrease in the permeability of the vascular wall, in particular, capillaries; o o reduction in the release of biologically active amines (histamine, serotonin, kinins and prostaglandins) from mast cells; o o inhibition of migration of neutrophils and macrophages into the focus of inflammation, a violation of their functional activity (chemotactic and phagocytic), peripheral leukocytosis; o o inducing the synthesis of lipomodulin, which blocks the phospholipase A of cell membranes, disrupts the release of phospholipid-bound arachidonic acid and the formation of pro-inflammatory prostaglandins, leukotrienes and thromboxane A2; o o suppression of the synthesis of certain pro-inflammatory cytokines and the blockade of the synthesis of cytokine receptor proteins in tissues. o o vasoconstriction at the site of inflammation; o o a decrease in the intensity of energy production processes in the focus of inflammation; o o suppression of migration of monocytes, slowing the release of mature monocytes from the bone marrow and reducing their functional activity; o o inhibition of the formation of leukotrienes (leukotriene B4 reduces leukocyte chemotaxis, and leukotrienes C4 and D4 (slow-reacting substance) reduce the contractility of smooth muscles, vascular permeability and mucus secretion in the airways);
Antiprolifer	o o violation of the differentiation of fibrocytes from fibroblasts; o o suppression of nucleic acid synthesis;

ative effect	o o decrease in the functional activity of fibrocytes

Currently, there is a hypothesis that in the mechanism of the anti-inflammatory action of GCS, their ability to induce the synthesis of some (lipomodulin) and inhibit the synthesis of other (collagen) proteins in cells is important. Most likely, the mediator of the anti-inflammatory effect of GCS is lipomodulin (macrocortin, lipocortin), the synthesis of which occurs under the influence of small concentrations of these hormones in various types of cells. Lipomodulin blocks phospholipase A2 of cell membranes and, thus, disrupts the release of phospholipid-bound arachidonic acid, which then turns into prostaglandins, leukotrienes and thromboxane. The latter are actively involved in the processes of inflammation. Inhibition of leukotriene B4 reduces leukocyte chemotaxis, and leukotrienes C4 and D4 (a slow-reacting substance) reduces the contractility of smooth muscles, vascular permeability and mucus secretion in the airways.

The decrease in the production of cytokines, in particular IL-1, due to GCS, also inhibits the activity of phospholipase A2 and, to a large extent, cyclooxygenase-2 (COX-2). Currently, nitrogen monoxide (NO) is also considered as a major initiator of the inflammatory reaction. Glucocorticosteroids reduce the production of nitric oxide by inhibiting the activity of the enzyme NO synthetase (NOS), as shown in the experiment on monocytes.

An increase in the expression of neutral endopeptidase is important in realizing the anti-inflammatory effect of glucocorticosteroids in neurogenic inflammation. Neutral endopeptidase plays a role in the breakdown of tachykinin, the latter being released from the sensitive nerve endings. Endopeptidases, as shown by studies, are also responsible for the degradation of bronchoconstrictor peptides, such as bradykinin, tachycinin and endothelin-1.

The antiproliferative effect of GCS is associated with:

o with their suppression of nucleic acid synthesis;

o violation of the differentiation of fibrocytes from fibroblasts;

o a decrease in their functional activity, which leads to inhibition of sclerosis processes in the focus of inflammation.

INFLUENCE OF GLUCOCORTICOSTEROIDS ON IMMUNE RESPONSE

The effect of glucocorticosteroids on the immune system is mediated by the presence of specific glucocorticoid receptors on lymphoid cells. Under the influence of steroids, the number of lymphocytes in the peripheral blood decreases. This is largely due to the redistribution of lymphocytes from the blood into the tissues, especially in the bone marrow and spleen. In this case, corticosteroids cause apoptosis of immature or activated T- and B-lymphocytes. There is a point of view that the immunosuppressive effect of glucocorticosteroids is realized by controlling the absolute number of lymphoid cells and their subpopulations.

An important role in immune responses belongs to cytokines. The key cytokine is IL-2, which takes part in the induction of immune responses that occur after the interaction of T cells with an antigen-presenting cell. GCS significantly reduce the production of IL-2, resulting in a decrease in IL-2-dependent phosphorylation of various proteins. This leads to suppression of T cell proliferation. In addition, glucocorticosteroids inhibit T-cell activation by inhibiting the production of IL-3, IL-4, IL-6 and other cytokines. Since glucocorticosteroids suppress cytokines secreted by other cells, there is a decrease in the function of T-helpers, T-suppressors, cytotoxic T-lymphocytes and, in general, immunological reactions. In this case, T-helpers are more sensitive to glucocorticosteroids than T-suppressors.

The inhibitory effect of corticosteroids in relation to b-cells is weakly expressed. Moderate and low doses of corticosteroids do not cause any significant changes in the level of immunoglobulins in the blood. A decrease in the content of immunoglobulins is achieved by prescribing high and very high doses of glucocorticosteroids (pulse therapy). Steroids inhibit the activity of the complement system and the formation of fixed immune complexes.

GCS have a pronounced effect on the activity of macrophages and monocytes. Given that monocytes and macrophages play a significant role in the development of the inflammatory process and the involvement of other types of cells in it, it is obvious that the effect of corticosteroids on their migration, secretion, and functional activity can be decisive in the inflammatory reaction itself.

Other effects of GCS are associated with inhibition of phagocytosis, release of pyrogenic substances, decreased bactericidal activity of cells, inhibition of secretion of collagenase, elastase and plasminogen activators, impaired release of macrophage factors causing mucus formation

IMMUNO DEPRESSIVE EFFECT OF GLUCOCORTICOSTEROIDS

The mechanisms underlying this effect

o a decrease in the number of lymphocytes in peripheral blood (lymphopenia) due to the transition of circulating lymphocytes (mainly T cells) to lymphoid tissue, possibly their accumulation in the bone marrow;

o increased apoptosis of immature or activated T and B lymphocytes;

o suppression of proliferation of T cells;

o decreased function of T-helpers, T-suppressors, cytotoxic T-lymphocytes;

o inhibition of the activity of the complement system;

o inhibition of the formation of fixed immune complexes;

o decrease in the level of immunoglobulins (high doses of glucocorticoids);

o inhibition of a delayed-type hypersensitivity reaction (type IV allergic reactions), in particular a tuberculin test;

o violation of cooperation between T - and B - lymphocytes;

o violation of the synthesis of immunoglobulins and antibodies, including autoantibodies;

o a decrease in the number of monocytes in the vascular bed.

In the immune inflammatory process, as well as in the development of a stress response, the hypothalamus – pituitary – adrenal cortex system plays a significant role. Many cytokines stimulate the functional system of the hypothalamus - pituitary gland - adrenal glands.

INFLUENCE OF Glucocorticosteroids on tissue metabolism

The effect of GCS on carbohydrate metabolism is to stimulate the processes of glyconeogenesis, i.e. synthesis of glycogen from products of protein and nitrogen metabolism. At the same time, the rate of glucose utilization by tissues is disrupted by reducing its penetration into the cell. As a result, transient hyperglycemia and glucosuria may be observed in a number of patients. Prolonged hyperglycemia leads to the depletion of the insular apparatus of the pancreas and the

development of "steroid" diabetes. The effect of corticosteroids on protein metabolism is manifested by increased protein breakdown in most organs and tissues, and especially in muscle tissue. The consequence of this is an increase in the content of free amino acids and nitrogen metabolism products in blood plasma. In the future, products of protein and nitrogen metabolism are used in the processes of glyconeogenesis.

The breakdown of muscle tissue proteins causes emaciation, muscle atrophy, muscle weakness, impaired growth of cartilage and bone tissue. Suppression of protein synthesis in the bone matrix of the vertebrae leads to a delay in the formation of the skeleton in children. Dystrophic processes occurring in other tissues are accompanied by the development of "steroid" ulcers, myocardial dystrophies, and skin atrophy (striae).

Strengthening the processes of protein catabolism is observed with the use of medium therapeutic doses of corticosteroids. The use of small doses of corticosteroids, in contrast, stimulates the synthesis of albumin in the liver from free amino acids in blood plasma. This is especially important in patients with impaired protein-synthetic liver function.

The effect of GCS on fat metabolism is manifested in the form of their lipolytic and, simultaneously, lipogenetic effects. The lipolytic effect is observed in the subcutaneous tissue of the arms and legs, the lipogenetic effect is manifested by the predominant deposition of fat in the anterior abdominal wall, interscapular region, on the face and neck. This process is most pronounced with prolonged use of GCS, leads to a change in the appearance of patients and is described in the literature as Ku-shingoid (moon-shaped face, pituitary-type obesity, impaired glucose tolerance, etc.). The action of GCS is manifested by an increase in the content of cholesterol and lipoproteins in the blood serum. GCS accelerate the process of converting carbohydrates into fats, which also contributes to the development of obesity.

The effect of GCS on water-mineral metabolism is associated on the one hand with the suppression of the secretion of antidiuretic hormone, which is accompanied by an increase in glomerular filtration rate, the release of sodium and water from the body. At the same time, in patients with severe heart failure, corticosteroids can stimulate the synthesis of aldosterone, which leads to a delay in sodium and fluid and an increase in edematous syndrome. The breakdown of protein in tissues is accompanied by an increase in potassium and calcium in blood plasma. Gradually developing hypokalisthia contributes to the strengthening of dystrophic processes in tissues and, first of all, in the heart muscle, which can be the cause of cardiac arrhythmias, cardialgia and lead to increased severity of heart failure. GCS inhibit the absorption of calcium in the intestine, increase its excretion in the urine. As a result, the yield of calcium from bone tissue is enhanced, which contributes to the formation of "steroid" osteoporosis. Hypercalciuria and, at the same time, an increase in the content of urea and uric acid in the urine leads to the development of uric acid diathesis and exacerbation of gout in a number of patients who take GCS for a long time. Calcium deficiency in bones can contribute to the occurrence of pathological bone fractures in children and the elderly.

The effect of GCS on the functions of other organs and systems that are not responsible for the formation of the main pharmacological response.

o The appointment of corticosteroids leads to an increase in the production of hydrochloric acid and pepsin in the stomach.

o The effect of corticosteroids on the endocrine organs is manifested in the inhibition of ACTH and gonadotropin secretion in the anterior pituitary gland, a decrease in the function of the sex glands with the development of secondary amenorrhea and infertility, and suppression of the secretion of thyroid hormones.

o GCS in the central nervous system can increase the excitability of the cortical structures of the brain and lower the seizure threshold. In some patients, they show a euphoric effect, and under certain conditions cause the development of depression.

o GCS have an effect on peripheral blood

Pharmacokinetics of glucocorticosteroids

When ingested, corticosteroids are absorbed mainly in the small intestine. Absorption occurs in the proximal (75%) and distal (25%) parts of the small intestine.

The adrenal cortex of a healthy adult under the influence of corticotropin produces daily 15-60 mg of cortisol and 1-4 mg of corticosterone. More than 95% of plasma cortisol forms complexes with plasma proteins, mainly with corticosteroid-binding alpha globulin (transcortin). The affinity of the hormone for transcortin is very high, however, the binding ability of transcortin is small and with an increase in the concentration of cortisol in the plasma over 20 μg / 100 ml is completely exhausted. In this case, drug transfer is carried out by plasma albumin (from 40 to 90% of corticosteroids in plasma are in a state associated with albumin). At the same time, only an unbound (free) GCS fraction is physiologically active, which exerts its pharmacological effect on target cells. Side effects in patients receiving corticosteroids are determined by the amount of free fraction of corticosteroids. However, there is no correlation between the half-life and the duration of the physiological action of a particular GCS drug.

GCS are classified into short, intermediate and long-acting drugs, depending on the duration of ACTH inhibition after a single dose. At the same time, the half-elimination period of GCS is much shorter: from 30 minutes for cortisone and 60 minutes for prednisone to 300 minutes for dexamethasone.

Interestingly, the maximum pharmacological activity of GCS falls on the period of time when their peak concentrations in the blood are already behind. Thus, according to pharmacokinetic studies, the peak concentration of prednisolone in plasma is reached after 1 - 3 hours, the half-life is 2 - 3.5 hours, and the maximum biological effect develops about 6 hours. This suggests that the effects of corticosteroids are more dependent on their induction of enzymatic activity within the cell than on direct action. The period of anti-inflammatory activity of GCS is approximately equal to the duration of their suppression of the hypothalamic-pituitary-adrenal axis - GGN (from 4 to 8 days).

Normally, the cortisol level begins to increase at 2 a.m. with a peak at 8 a.m. and returns to the basal level at 12 p.m. Symptoms of RA (stiffness, inflammatory activity) usually decrease a few hours after waking up at the peak of cortisol synthesis. Until recently, it was believed that taking GCS in the morning hours to a lesser extent depresses the synthesis of ACTH and cortisol than in the night and evening. Recently, evidence has appeared that a circadian increase in IL-6 level may also be associated with an increase in RA activity in the morning. Daily fluctuations of IL-6 are observed in normal patients with RA. Normally, the peak concentration of IL-6 occurs a little earlier than ACTH and cortisol between 1 - 4 hours in the morning. However, with RA, the peak of IL-6 is delayed and occurs between 2-7 hours of the morning and the concentration of IL-6 is significantly higher than normal. Therefore, the administration of GCS (5-7.5 mg) at night (approximately 2 a.m.) is more preferable from the point of view of suppressing the secretion of IL-6 and is associated with a significantly more pronounced decrease in the duration of morning stiffness, joint pain, Lansbury index, Richie index.

In untreated patients with an active form of RA, weakening of basal and corticotropin-stimulated synthesis of cortisol is also noted. Moreover, approximately 10% of patients with RA show signs

of adrenal insufficiency. Obviously, in these patients a higher efficiency of low doses of GCS can be expected than in patients without a defect of the GGN axis.

The different activity of corticosteroids is also determined by different degrees of binding to plasma proteins. So, most of the natural cortisol is in a bound state, while only 3% methylprednisolone and less than 0.1% dexamethasone binds to corticosteroid-binding globulin. Microsomal liver enzymes metabolize GCS to inactive compounds, which are then excreted by the kidneys. Metabolites are secreted with urine in the form of glucuronides, sulfates and unconjugated compounds. Conjugation reactions occur mainly in the liver and, to a lesser extent, in the kidneys. Metabolism in the liver increases with hyperthyroidism and is induced by phenobarbital and ephedrine.

Hypothyroidism, cirrhosis, concomitant treatment with erythromycin leads to a decrease in hepatic clearance of corticosteroids. In patients with hepatic cell failure and low serum albumin in plasma, the concentration of the free fraction of prednisolone increases, which contributes to a more rapid development of side effects. During pregnancy, on the contrary, the proportion of its free fraction decreases

CLASSIFICATION OF Glucocorticosteroids

Depending on the duration of ACTH suppression after a single dose of GCS, they are divided into: a) short-acting GCS - inhibit ACTH activity for up to 24-36 hours, b) GCS of average duration - up to 48 hours and c) long-acting GCS - over 48 hours.

I. NATURAL - Cortisol, Cortisone (Hydrocortisone), Cortisone acetate - inhibit ACTH activity for up to 24-36 hours.

II. SEMI-SYNTHETIC

1. Short-acting drugs - Prednisolone, Prednisone, Methylprednisolone (Urbazone, Metipred) - inhibit the activity of AGTG for up to 24-36 hours.

2. Medications of average duration of action - Triamcinolone (Polcortolone) - inhibits ACTH up to 48 hours.

3. Long-acting drugs - Betamethasone, dexamethasone - inhibit ACTH for more than 48 hours.

Glucocorticosteroid use

The classical sphere of therapeutic application of GCS is such general pathological processes as inflammation, allergies, sclerotherapy and degeneration of derivatives of connective tissue. GCS are used as anti-inflammatory, anti-allergic and immunosuppressive drugs, as well as replacement therapy for adrenal cortex insufficiency.

The following options for HA therapy are distinguished:

1. System:

o medium therapeutic doses

o alternative therapy

o pulse therapy

o "mini-pulse" therapy

o combined (primarily with cytotoxic drugs)

2. Local (intraarticular, inhalation, rectal administration, etc.);

3. Local (ointments, drops, aerosol).

Systemic therapy for corticosteroids is one of the most effective methods of treating a number of diseases. The use of steroids can significantly improve the prognosis and increase the life expectancy of patients.

In the treatment of corticosteroids, the following phases are conventionally distinguished:

o Induction: short-acting corticosteroids are used (prednisone or methylprednisolone) at a dose of approximately 1 mg / kg body weight per day with an 8-hour interval.

o Consolidation: involves switching to a single dose of the entire dose of GCS in the morning.

o Decrease: the rate of decrease in GCS is dose dependent. The transition to alternative therapy is possible.

o Supportive care: use of the lowest effective dose.

o Prevention of complications of corticosteroids therapy: begins with the induction phase.

When conducting systemic therapy for corticosteroids, it is necessary to take into account several general principles of pharmacotherapy, the observance of which allows to increase the effectiveness and safety of treatment, as well as reduce the frequency of undesirable side effects.

GC therapy should only be started if there are strict indications and as early as possible, without trying to apply the milder treatment methods first. In this case, hormone therapy should be used together with conventional therapy, and not be prescribed instead. Rational therapy involves the use of short-acting corticosteroids in the optimal dose and, if possible, for a period that is necessary to control the activity of the process. GCS should be prescribed only with medical supervision of their use with the aim of early detection of side effects and their correction. When prescribing hormone therapy, not only the doctor, but also the patient should be informed in detail about the possibilities and complications of this treatment method.

Пред Prednisolone is considered the standard among GCS and the effectiveness of other drugs of this group is evaluated in relation to it. The average therapeutic dose of corticosteroids based on prednisone is 0.5-1 mg per kg of body weight.

 When prescribing GCS, the principle of equivalent doses should be observed in order to obtain the same anti-inflammatory effect. Equivalent doses - prednisone - 5 mg: triamcinolone - 4 mg: methylprednisolone - 4 mg: dexamethasone - 0.5 mg: betamethasone - 0, 75 mg: hydrocortisone - 25 mg. In this case, the calculation always goes to prednisone. When transferring patients from parenteral administration of GCS to oral administration, it is necessary to reduce the daily dose by 5-6 times.

 In cases where long-term administration of GCS is expected, patients should be transferred as soon as possible to a single dose of the entire dose in the morning, and then to the alternating regimen of GCS therapy. At the beginning of treatment, the daily dose of the drug is usually divided into 3 doses (induction phase), then they switch to a single dose of the drug in the morning (consolidation phase).

 The choice of the initial dose of GCS, the determination of the duration of therapy and the rate of dose reduction should not be carried out empirically, but taking into account standardized clinical and laboratory indicators of the activity of the process and the nature of the disease. When prescribing corticosteroids therapy, attention should be paid to the following:

 the necessary daily dose should be selected individually, starting with the minimum average therapeutic doses, usually recommended for this disease;

 in case of chronically occurring diseases, corticosteroids should not be prescribed in large doses and for a long course, and when remission occurs, corticosteroids should be discontinued;

 in life-threatening conditions, large doses of GCS should be prescribed immediately.

 During hormone therapy in the peripheral blood, there is a decrease in the number of eosinophils, lymphocytes, erythrocytes, a decrease in hemoglobin levels while increasing the content of leukocytes due to neutrophils (up to 12000). Such a hemogram may be erroneously interpreted as a continuation of the exacerbation of the process. At the same time, these changes should be considered favorable and indicating a sufficient dosage of corticosteroids.

 The rate of dose reduction of corticosteroids. After the clinical effect is achieved, the dose of corticosteroids should be reduced to a maintenance dose. For this, the initial dose of corticosteroids is gradually reduced to the minimum level at which the obtained positive effect is preserved. If the daily dose of the course of treatment is in the range of 15-40 mg / day in terms of prednisone, then the cancellation should be 2.5-5 mg every 5-7 days until the physiological dose is reached.

With the appointment of GCS in doses of 40 mg or more, the dose reduction can pass faster (5 mg and even in some cases 10 mg per week) to a level of 40 mg, and then as mentioned above. In these cases, the rate of decrease in the dose of corticosteroids is determined by the duration of their use. The shorter the duration of the course of treatment, the more rapidly the cancellation of corticosteroids is possible. However, the lower the dose of GCS, the longer the periods between successive dose reductions should be. This tactic allows you to create conditions for restoring the functionality of the hypothalamic-pituitary-adrenal system already during drug withdrawal.

 In case of recurrence of the disease, hormone therapy is resumed. The dose of corticosteroids is increased to that at which the patient was observed stabilization of the process. In the future, cancellation should be carried out more carefully and gradually. Determination of the duration of therapy and the rate of dose reduction should not be carried out empirically, but taking into account standardized clinical and laboratory indicators of the activity of the process and the nature of the disease. There are several laboratory criteria for determining the effectiveness of corticosteroids therapy: stabilization of ESR over 7 days, a decrease in the level of C - reactive protein, fibrinogen, etc.

 Cancellation of glucocorticosteroids. Problems associated with the abolition of glucocorticosteroids occur after a long course of therapy. In this case, a sharper withdrawal of drugs threatens the development of two types of complications. Firstly, these are manifestations of adrenal insufficiency associated with suppression of the hypothalamic-pituitary-adrenal system. Secondly, this is a relapse of the inflammatory process that underlies the disease itself.

 Suppression of adrenal function depends on the dose of hormones taken and, to an even greater extent, on the duration of glucocorticoid therapy, as well as on the properties of the drug used and the underlying disease.

 A dose of prednisone in the range of 10-15 mg gives a complete substitution effect and is considered physiological. In this regard, the withdrawal of the drug to a physiological dose can be carried out quite quickly. A further reduction in the dose of GCS should take place at a much slower pace.

 During treatment, it must be remembered that inhibition of the hypothalamic-pituitary-adrenal axis persists in patients who received even small doses of GCS (more than 10 mg / day for three or more weeks) for a long time (up to 1 year) after cancellation the drug.

 Rapid drug withdrawal (within 1-2 days) is extremely rare only in case of acute steroid psychosis, or with generalization of herpes virus infection.

 In cases where it is not possible to completely avoid glucocorticosteroid therapy, patients should be transferred to maintenance doses of hormones that are individual for each patient and usually correspond to replacement doses at the rate of 5-15 mg of prednisolone per day. Reception of hormones should be carried out in the morning (from 6 to 9 in the morning), taking into account the natural biorhythm of their allocation.

 There is evidence of no significant inhibition of the hypothalamus-pituitary-adrenal axis, if the dose of prednisolone does not exceed 10 mg per day. During treatment with corticosteroids, the occurrence of adverse reactions is significantly more likely to occur in patients who received more than 10 mg of prednisolone per day. The risk of developing side effects is less with a decrease in the total dose of prednisone and taking the drug at a certain time. Moreover, treatment with low doses of corticosteroids can reduce the potential risk of osteoporosis due to inhibition of the synthesis of IL-6.

In order to reduce the dose of corticosteroids, it is recommended to combine them with NSAIDs, basic therapy. However, this increases the likelihood of developing ulcerative lesions of the gastrointestinal tract. To stimulate the production of own hormones, in some cases it is possible to prescribe ACTH (corticotropin) against the background of the gradual cancellation of GCS.

 When using corticosteroids as a replacement therapy for primary adrenal insufficiency (Addison's disease), both glucocorticosteroid and mineralocorticosteroid are indicated. As corticosteroids, cortisone acetate or hydrocortisone in combination with deoxycorticosterone acetate or flucrocortisone are recommended.

With secondary insufficiency of the adrenal cortex, due to the preserved basal secretion of aldosterone, in most cases it is possible to use one corticosteroids. With adrenogenital syndrome, patients should receive maintenance doses of GCS throughout their lives. Hormone-dependent patients with the development of severe intercurrent diseases or the need for surgical interventions must necessarily receive replacement therapy with corticosteroids at doses 5-10 mg higher than those that patients take constantly.

BASIC INDICATIONS FOR PURPOSE OF Glucocorticosteroids

1. Rheumatic diseases:

o rheumatism 2-3 tbsp. activity of the process in the presence of rheumatic heart disease, especially in combination with polyarthritis and polyserositis - medium therapeutic doses of corticosteroids;

o systemic lupus erythematosus in the period of exacerbation (pulse therapy), in chronic forms - medium therapeutic doses of corticosteroids or as maintenance therapy;

o systemic dermatomyositis during an exacerbation - pulse therapy of corticosteroids or as maintenance therapy;

o periarteritis nodosa during an exacerbation - pulse therapy of corticosteroids or as maintenance therapy;

o rheumatoid arthritis when combined with visceritis (febrile syndrome, carditis, nephritis, serositis); with rapidly progressive articular forms of rheumatoid arthritis and a high titer of rheumatoid factor - pulse therapy, then, often, maintenance therapy; the ineffectiveness of previous NSAID therapy and basic therapy - the average therapeutic dose of GCS, with monoarthritis - intra-articular administration of GCS;

o juvenile rheumatoid arthritis.

2. Systemic vasculitis - systemic therapy of corticosteroids.

3. Carditis (infectious-allergic myocarditis, Abramov-Fiedler myocarditis, subacute septic endocarditis - immunological phase) - systemic therapy of corticosteroids.

4. Diseases of the musculoskeletal system:

a. post-traumatic osteoarthritis - for short-term use in the acute period or for intra-articular administration of GCS;

b. ankylosing spondylitis (ankylosing spondylitis);

c. subacute gouty arthritis - for short-term use in the acute period or for intra-articular administration of GCS;

d. acute and subacute bursitis;

e. acute nonspecific tendosynovitis;

f. psoriatic arthritis.

5. Kidney disease (chronic nephritis with nephrotic syndrome - the most indicated is the appointment of corticosteroids in the membranous and membranous - proliferative variants; with lupus nephritis) - systemic therapy for corticosteroids.

6. Diseases of the gastrointestinal tract (ulcerative colitis, Crohn’s disease, SPRU) - systemic therapy of corticosteroids.

7. Liver diseases (autoimmune hepatitis) - systemic therapy of corticosteroids.

8. Diseases of the bronchopulmonary system (obstructive bronchitis, allergic bronchial asthma, sarcoidosis - systemic therapy and inhaled corticosteroids).

9. Hematologic diseases: acquired (autoimmune) hemolytic anemia, thrombocytopenic purpura - systemic therapy of corticosteroids.

10. Allergic conditions. Monitoring of allergic conditions with the ineffectiveness of conventional drugs: seasonal or chronic allergic rhinitis, nasal polyps, bronchial asthma (including asthma), contact dermatitis, atopic dermatitis (neurodermatitis), hypersensitivity to drugs and serum sickness (anaphylactic shock, Quincke's edema, syndrome Lyell, Stephen-Johnson, medicinal or food agranulocytoses, thrombocytopenia, giant brewery).

11. Eye diseases: severe acute and chronic allergic reactions and inflammatory processes in the eyes and adjacent structures, such as allergic conjunctivitis, keratitis, allergic marginal corneal ulcer, corneal herpes, iritis and iridocyclitis, chorioretinitis, anterior segment inflammation, diffuse posterior uveitis and choroiditis, retrobulbar neuritis, sympathetic ophthalmia.

12. Skin diseases: eczema (chronic dermatitis), in the treatment of keloids and localized hypertrophic infiltrating inflammations (introduction of corticosteroids into the lesion site),

lichen planus, psoriasis, annular granuloma, simple chronic lichen (neurodermatitis), discoid lupus erythematosus, diabetic lipoid necrobiosis , nasal alopecia, psoriasis, erythema nodosum and others are local therapy for corticosteroids.

13. Tumor diseases: palliative treatment of leukemia and lymphomas in adults, acute childhood leukemia.

14. Endocrine disorders: primary or secondary adrenocortical insufficiency, acute adrenal insufficiency, bilateral adrenectomy, congenital adrenal hyperplasia, acute thyroiditis and thyrotoxic crisis, hypercalcemia associated with cancer.

15. Shock conditions: hemodynamic, traumatic, endotoxic, cardiogenic (heart attack).

16. Cerebral edema (increased intracranial pressure) - GCS is necessary as an aid to reduce the intensity or prevent brain edema associated with surgical or other brain injury, strokes, primary or metastatic malignant brain tumors. The use of glucocorticosteroids should not be considered as a substitute for neurosurgical treatment.

17. Prevention of renal allograft rejection. The drug is used in combination with commonly used immunosuppressants.

Indications for use of intranasal glucocorticoids.

 Seasonal (intermittent) allergic rhinitis.

 Kuglogodichny (persistent) allergic rhinitis.

 Nasal polyposis.

 Non-allergic rhinitis with eosinophilia.

 Idiopathic (vasomotor) rhinitis.

Inhaled glucocorticosteroids are used to treat bronchial asthma, chronic obstructive pulmonary disease.

CONTRAINDICATIONS

Glucocorticosteroids are prescribed with caution in the following clinical situations:

 Itsenko-Cushing's disease.

 Diabetes mellitus.

 Peptic ulcer of the stomach or duodenum.

 Thromboembolism.

 Arterial hypertension.

 Severe renal failure.

 Mental illness with productive symptoms.

 Systemic mycoses.

 Herpetic infection.

 Tuberculosis (active form).

 Syphilis.

 Vaccination period.

 Purulent infections.

 Viral or fungal diseases of the eyes.

 Corneal diseases associated with defects in the epithelium.

 Glaucoma.

 Lactation.

Intranasal administration of glucocorticoids is contraindicated in the following cases:

• Hypersensitivity.

• Hemorrhagic diathesis.

• A history of repeated nosebleeds.

•Side effects

The term "pulse therapy" means the rapid (within 30-60 minutes) intravenous administration of large doses of HA (1000 mg in terms of methylprednisolone (MP)) once a day for 3 days.

When conducting pulse therapy, MP is most often used in the form of a solution of sodium hemisuccinate, less often dexamethasone. MP has the ability to be deposited to a greater extent in inflamed than in normal tissues, has minimal mineralocorticoid activity, which allows us to consider it as a means of choice when conducting pulse therapy. The level of MP in plasma after intravenous administration reaches a maximum within 1 hour and rapidly decreases over the next 6-7 hours. After 4 days, only trace amounts of active MP are found in the peripheral blood, but it actively accumulates in various tissues, especially in red blood cells , brain, some visceral organs. Pulse therapy is accompanied by adrenal suppression, but their function is restored within about 4 weeks.

Indications for pulse therapy:

• SLE (fever, arthritis, serositis, myositis, hematological disorders, central nervous system lesions), with lupus nephritis in combination with cytostatics (cyclophosphamide (CF)).

• Systemic vasculitis (with the exception of giant cell arteritis) in combination with cytostatics.

• Polymyositis / Dermatomyositis (in case of development of life-threatening complications).

• RA (rheumatoid vasculitis in combination with cytostatics).

The suggestion that the anti-inflammatory effect of HA lasts longer than undesirable metabolic effects has led to the emergence of alternative therapy for HA, a treatment method in which short-acting HA without pronounced mineralocorticoid activity are prescribed once every morning for 48 hours. effectiveness, but the severity of side effects is reduced. The positive properties of alternative therapy are manifested only with prolonged treatment of HA. It is not used for short-term administration of HA, as well as in the initial stage of treatment or during an

exacerbation of the disease. The alternating regimen does not in all cases prevent the development of Cushing's syndrome and suppression of the hypothalamic-pituitary-adrenal axis.

Indications for local therapy of HA:

o RA (in adults or juvenile).

o Microcrystalline arthropathies (gout and pseudogout).

o Arthritis in diffuse connective tissue diseases.

o Seronegative spondyloarthropathy.

o Osteoarthritis.

o Synovitis of the knee joint that occurs after arthroplasty of the hip joint from the opposite side.

o Other diseases associated with joint inflammation

o Periarthritis of the shoulder joint (adhesive capsulitis, frozen shoulder).

For intraarticular injections of HA, drugs of short and prolonged action are used.

The question of the need for repeated injections of HA should be decided individually. Unreasonable frequent administration can lead to GK-dependence, to the progression of secondary osteoarthrosis. If, after 1-2 injections, clinical improvement is absent or is expressed to a minimal extent, then further local HA therapy is inappropriate.

To increase the effectiveness of local therapy, rest the joints in which the HA was injected, for a period of at least 48-72 hours.

The purpose of the lesson:

1. To learn the pharmacokinetics, pharmacodynamics and pharmacotoxicodynamics of NSAIDs and GCS.

I. Classification of NSAIDs.

1 group.

NSAIDs with analgesic and mild anti-inflammatory effects.

1.1. Aniline derivatives: paracetamol (panadol, acetaminophen).

2 group.

NSAIDs with analgesic and moderate anti-inflammatory effects.

2.1. Derivatives of propionic acid: ibuprofen (brufen, brustan); naproxen (naprosin); ketoprofen (profenit, fastum, ketonal, etc.); clubiprofen (flugalin); oxaprozin (give pro).

2.2. Derivatives of fenamic acid: mefenamic (anthranilic) acid (pon-stan); meclofenamate.

2.3. Derivatives of thiaprofenic acid: thiaprofenic acid (Surgam 300).

3rd group.

NSAIDs with analgesic and pronounced anti-inflammatory effects.

3.1. Pyrazolone derivatives: phenylbutazone (butadione); analgin (baralgin, spasmalgon, etc.). Combined NSAIDs: pyrabutol (reopyrin) [butadione and amidopyrine]; perclusone (clofeson) [butadione and clofexamide].

3.2. Derivatives of salicylic acid: acetylsalicylic acid (aspirin, colpharitis), for intramuscular and intravenous administrations - acecelisine, aspizol; sodium salicylate; diflunisal (dolobid).

3.3. Acetic acid derivatives: diclofenac (voltaren, orthophene), sulindac, tolmitin, etodolac, nabumeton.

3.3.1. Derivatives of indole: indomethacin (methindole).

3.4. Derivatives of oxycams: piroxicam (erazon, pyrole); tenoxicam (tilkotil); meloxicam (movalis).

3.5. Derivatives of other chemical compounds: ketorolac (ketorol), nimesulide (mesulide), celebrex (celecoxib); amizone (carbamidopyridinium iodide).

II. Selective COX-2 inhibitors. Classification. Advantages and prospects of their use

III. Indications for use.

IV. Undesirable effects. Contraindications to the appointment. Acute and chronic salicylate poisoning. Treatment.

V. Combined drugs based on this group of drugs. arthrotek (diclofenac + misoprostol), ambene (phenylbutazone + dexamethasone), dolarene (diclofenac + paracetamol), baralgin or spazmagan (analgin + pitophenone (anticholinergic) + phenyverin (ganglioblocker), tempalgin (analgin + analgin + analgin + analgin + codeine + caffeine + phenobarbital), coldrex (paracetamol + phenylephrine + ascorbic acid + terpin hydrate + caffeine), solpadein (paracetamol + codeine + caffeine), sedalgin (ASA + paracetamol + phenobarbital + caffeine + codeine), citramone A + paracetam + caffeine), Alka-Seltzer (ASA + ascorb new acid) and others. The advantages and disadvantages.

VI. glucocorticosteroid preparations:

 short-acting: cortisone, hydrocortisone;

 medium duration of action: prednisone, methylprednisolone, flupred-nizolon,

 long-acting: triamcinolone (polcortalon, kenakort, kenalog); fluocortalon (ultralan); dexamethasone (dexon); betamethasone (celestone); parametasone (monocortin).

 inhaled HA: beclomethasone, budesonide, fluticasone, flunisolid.

 HA preparations for skin use:

one). highly active (betamethasone dipropionate, clobetasone propionate, halobeta-zola propionate);

2). HA of medium activity (triamcinolone acetonide, fluticasone propionate, desonide);

3) Weakly active (hydrocortisone, prednisone, flumethasone pivalate);

VII Know:

a) the main indications of pharmacotherapy of NSAIDs, HA and monitoring their effectiveness and safety;

b) the main pathogenetic mechanisms that are the object of drug exposure to HA;

c) the main types of hormone therapy (replacement, stimulating, inhibitory, pharmacodynamic);

d) the principles of hormone therapy for HA, the choice of a specific drug and its administration;

e) the pharmacodynamics of the main groups of HA and their synthetic analogues used for the purpose of anti-inflammatory, anti-allergic, immunosuppressive and anti-shock therapy;

f) the pharmacokinetics of HA and the state that changes the intake, distribution, metabolism and utilization of HA in the body;

g) unwanted effects of HA and methods for their correction;

h) the principles of combining HA with other drugs;

i) comparative characteristics of steroidal and non-steroidal anti-inflammatory drugs;

j) chronopharmacology of HA and their synthetic analogues;

k) the main pathogenetic mechanisms that are the object of drug exposure to NSAIDs: phases of inflammation, inflammatory mediators, macrophage monocyte systems, immune complexes and prostaglandin synthesis.

2. Be able to:

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

b) prescribe combination therapy;

c) substantiate and provide urgent differentiated drug assistance with:

 acute rheumatoid arthritis;

 acute attack of gout;

 lupus crisis.

 shock, collapse;

 bronchial obstruction syndrome;

 Quincke's edema;

 acute glomerulonephritis

Control questions of the studied topic.

1. Describe the classification of NSAIDs by chemical structure.

2. Describe the classification of modern NSAIDs taking into account the pharmacodynamic effect, its severity, chemical structure.

3. Explain the advantage of the second classification over the first.

4. List the pharmacodynamic effects of NSAIDs and explain their clinical significance.

5. State the process of formation and functional purpose of prostaglandins.

6. Describe the general mechanism for the development of pharmacodynamic effects of NSAIDs.

7. Define oxygen free radicals and state their clinical significance.

8. State the mechanism of anti-inflammatory action of NSAIDs.

9. What are the phases of inflammation and make a differentiated selection of NSAIDs for each of them.

10. Explain the mechanism of antipyretic action of NSAIDs.

11. Describe the mechanism of the analgesic effect of NSAIDs and compare it with the mechanism of action of narcotic analgesics.

12. Explain the mechanism of the irritating effect of NSAIDs on the mucous membranes of the stomach and intestines. Indicate drugs that prevent negative effects.

13. Indicate the mechanism of development of the bronchospastic effect of NSAIDs and ways to prevent it.

14. Explain the antiplatelet mechanism of NSAIDs and its clinical significance.

15. What features of pharmacokinetics combine naproxen and piroxicam?

16. What are the hallmarks of ibuprofen and mefenamic acid? Name the diseases where the use of these drugs is appropriate and explain why.

17. What mechanism of action is common and combines Movalis, Mesulide, Celebrex? At what concomitant pathology is their use preferred?

18. Position NSAIDs for anti-inflammatory effect.

19. Name the leading NSAIDs to stop the attack of gout and justify the choice of dose and route of administration.

20. Explain the principles of choosing NSAIDs for rheumatoid arthritis.

21. Describe the criteria for evaluating the effectiveness of NSAIDs in patients with rheumatoid arthritis.

22. List the methods and criteria for determining the safety of treatment of NSAIDs.

23. The modern classification of the Civil Code.

24. List the main types of hormone therapy for specific clinical examples.

25. The basic principles of hormonal anti-inflammatory therapy.

26. Explain the mechanisms of anti-inflammatory action of HA.

27. Explain the mechanisms of the influence of HA on the carbohydrate metabolism of the body and indicate what indications and contraindications may be in connection with this.

28. Specify the features of the effect of HA on lipid metabolism.

29. Give a clinical and pharmacological assessment of the state of protein metabolism against the background of course treatment of HC and the associated complications, indications and contraindications for their use.

30. Explain the mechanisms of violations of water-electrolyte metabolism arising from the use of HA and the associated complications, indications and contraindications for their use.

31. Indicate the general properties and individual differences of natural HA from their synthetic analogues in terms of the severity of the anti-inflammatory effect and the characteristics of metabolic disorders in the body.

32. Indicate the HA with the most pronounced antishock action, explain the mechanism of this action and antihypertensive conditions contraindicated for their use.

33. Explain the mechanism and preventive measures of the ulcerogenic action of HA.

34. Explain the mechanisms and measures for the prevention of hormone resistance, tolerance and "withdrawal syndrome."

35. Describe the tactics and dosage regimen of HA in conditions of asthmatic status. In what other conditions is the pulse therapy of HA indicated.

36. What are the advantages and disadvantages characteristic of inhaled glucocorticosteroids. What is the tactics of their use against the background of hormone-dependent bronchial asthma.

37. Define the concept of "rational hormone therapy" HA. What chrono-pharmacological features must be taken into account in the conditions of long-term administration of HA.

38. Formulate the significance of the leading pharmacokinetic characteristics in the rational choice of HA, tactics and dosage regimen, evaluation of efficacy and safety.

Control of the intermediate level of knowledge.

The solution of situational tasks:

1. The patient, 40 years old, is concerned about pains in the joints of the fingers, wrist, knee joints in the morning, at rest and during exertion, stiffness before lunch, fever. A small elastic nodule is defined below the right knee joint. Blood test: er. - 2.9 • 1012 / l; Hb - 97 g / l; l - 9.9 • 109 / l. Uric acid - 0.38 mmol / L; sialic acids - 0.26 units. The Waaler-Rose reaction - titer 1:64. On the roentgenogram of the brush - osteoporosis.

What is the tactics for treating a patient? What is the base drug? What effect do NSAIDs have on immunity?

2. The patient suffers from the articular form of rheumatoid arthritis for more than 1 year. Has a rapidly progressing course of the disease. Radiologically confirmed the presence of edge patterns. What basic drug treatment is most appropriate? What mechanisms underlie antiproliferative action of NSAIDs?

3. The patient has been suffering from rheumatoid arthritis for 27 years, edema of the elbow, wrist, knee, ankle joints, rheumatoid nodules in the region of the elbow joints are objectively observed for 7 months. In blood: ESR - 56 mm / h, CRP (+++). On radiographs of the joints - pronounced osteopo-roses.

Define a patient treatment plan. What drug should be used for basic therapy in this situation? What mechanism of action underlies the anti-inflammatory action of NSAIDs?

4. The patient takes prednisone in a dose of 2 tablets. in a day. Specify equivalent doses of triamcinolone. What other drugs can prednisone be replaced with?

5. Make a choice of HC for drugs with congestive circulatory failure: prednisone, dexamethasone, triamcinolone, prednisolone. Give the rationale for the choice.

6. The patient, 36 years old, diagnosed with rheumatism, active phase I degree, recurrent carditis, mitral heart disease with a predominance of insufficiency, circulatory failure IIB Art. Prescribed treatment: cardiac glycosides, diuretics, metabolic agents.

What anti-inflammatory drug is indicated for the patient? Justify the choice of drug.

7. The patient, 42 years old, turned to the clinic with complaints of low-intensity pain in the knee joints after work. Works as a loader. With an objective examination, there are no visible changes on the part of the joints; during movement, a rough crunch is determined. On radiographs - narrowing of the joint space, sharpening of the intercondylar elevations, along the edges of the tibial pineal gland - osteophytes. Diagnosed with deforming osteo-arthrosis of the knee joints.

Your patient treatment plan.

8. Select the medicine for the patient, 39 years old, with a diagnosis of ankylosing spondylitis, mixed course, activity II, FN II: voltaren, prednisone, indomethacin, acetylsalicylic acid.

9. A patient with pulmonary tuberculosis and concomitant bronchial asthma was prescribed treatment with rifampicin against the background of the long-used prednisolone. After 5 days of treatment, the patient experienced a sharp exacerbation of bronchial asthma, which could be duplicated only after 2 weeks with the use of large doses of HA drugs.

Explain the situation.

10. A patient, 39 years old, was admitted to the hospital with complaints of pain in the heart, shortness of breath during physical exertion, pain in the joints of the extremities, general weakness, sweating, and low-grade fever. She fell ill three weeks ago when she suffered a sore throat with high fever and joint pain, was treated at home with sulfadimezin in a dose of 0.5 g 4 times a day. The temperature returned to normal, went to work, and a few days later these complaints appeared and the patient was hospitalized. From the anamnesis it was possible to find out that the joints were swollen in childhood, because of which she lay at home for a long time (could not walk). With an objective study, the temperature is 38 ° C. The skin is wet. The joints are not apparently changed; wrist, elbow and shoulder pain on palpation. Pulse 80 beats. in 1 min, rhythmic, satisfactory filling, not tense. After 5 squats - 110 beats. in 1 min, after 3 min - 102 beats. in 1 min. Percussion - displacement of the left border of the heart by 1 cm to the outside of the mid-clavicular line. Heart sounds are muffled, I tone is significantly weakened, II tone accent above the pulmonary artery. Systolic murmur above the apex of the heart, conducted into the axillary region. Lungs and abdominal organs without pathology. Tonsils loose, with purulent plugs. Blood test: L - 4.9 109, hemoglobin - 7.4 mmol / L, ESR - 40 mm / h. Albumin - 50%, alpha globulins - 24%, gamma globulins - 17%, fibrinogen - 5.7 g / l. Antistreptolysin titer - 0-1: 1200; C - reactive protein - +++. When fluoroscopy: a heart of reduced tone, the left ventricle is enlarged, the contrasted esophagus is rejected along an arc of a large radius. On the ECG - a levogram, a deviation of the electrical axis of the heart to the left, signs of left ventricular hypertrophy, moderate muscle changes, PQ - 0.22 s.

Your diagnosis. Indicate the severity of the patient's condition. Choose drugs, determine the dose and method of administration, justify the need for combination therapy.

11. At the resort, before the beginning of balneotherapy (hydrogen sulfide baths), the doctor determined the patient's gout in remission. What drug should be prescribed to prevent exacerbation of the disease in the first days of treatment?

12. The patient has been suffering from rheumatoid arthritis for 27 years, edema of the elbow, wrist, knee, ankle joints, rheumatoid nodules in the region of the elbow joints are objectively observed for 7 months. In the blood: ESR - 56 mm / h, CRP (+++). On radiographs of the joints - pronounced osteoporosis.

Define a patient treatment plan. What drug should be used for basic therapy in this situation? What mechanism of action underlies the anti-inflammatory action of NSAIDs?

13. What are the pharmacodynamic effects of NSAIDs:

1) eliminate pain of any origin;

2) eliminate pain caused mainly by the inflammatory process;

3) have an anti-inflammatory effect;

4) have an antipyretic effect;

5) reduce the volume of pulmonary ventilation;

6) cause drug dependence.

14. Note the main indications for the use of NSAIDs:

1) headaches; 2) neuralgic pain; 3) pain with malignant tumors; 4) pain in skeletal muscle and joint pain in inflammatory diseases; 5) rheumatic pains; 6) pain syndrome with myocardial infarction.

15. What is the analgesic effect of NSAIDs associated with?

1) inhibition of the synthesis of prostaglandins and other mediators of pain in peripheral tissues and, therefore, a decrease in the sensitivity of nociceptors; 2) impaired conduction of impulses along nerve fibers; 3) the effect on the mental component of pain and its assessment.

16. Specify the mechanism of antipyretic action of NSAIDs:

1) reduction of heat transfer; 2) increase in heat transfer.

17. What properties does acetylsalicylic acid have?

1) analgesic effect; 2) anti-inflammatory effect; 3) antipyretic effect; 4) increased excretion of uric acid; 5) inhibition of urinary acid excretion; 6) antiaggregant action.

18. The main mechanism of action of NSAIDs is:

1) antihistamine; 2) antiserotonin; 3) antiprostoglandin; 4) antikinin.

TESTS

1. For headaches, the most effective combined NSAIDs, which include acetylsalicylic acid. What pharmacodynamic property of acetylsalicylic acid is taken into account?

A. Antipyretic.

B. Antiaggregant.

C. Anti-inflammatory.

D. Analgesic.

E. * All of the above.

2. Highly selective COX-2 inhibitors include :.

A. Acetylsalicylic acid.

B. * Celecoxib.

C. Ibuprofen.

D. Diclofenac Sodium.

E. Mefenamic acid.

3. At the resort, before the beginning of balneotherapy (hydrogen sulfide bath), the doctor determined the patient's gout in remission. What drug should be prescribed to prevent exacerbation of the disease in the first days of treatment?

A. Allopurinol.

B. * Butadion.

C. Suprastin.

D. Antoran.

E. Prednisolone.

4. The combined use of acetylsalicylic acid with warfarin can lead to gastrointestinal bleeding. What is the mechanism of interaction of NSAIDs with anticoagulants?

A. Displacement of anticoagulants from their association with proteins.

B. Decreased NSAID activity of prothrombin.

C. Inhibition of platelet aggregation.

D. Inhibition of liver oxidative enzymes by some NSAIDs.

E. * All of the above mechanisms.

5. The combined use of NSAIDs and sugar-lowering drugs leads to:

A. Increase blood sugar.

B. * Reduce blood sugar.

C. Reduce low density lipoproteins.

D. An increase in the number of low density lipoproteins.

E. Increased levels of high density lipoproteins.

6. What is the pathogenetic part of the inflammatory process that is affected by NSAIDs?

A. Decrease in capillary permeability.

B. Stabilization of lysosomes.

C. Inhibition of macroergic phosphate production.

D. Inhibition of the synthesis and secretion of inflammatory mediators.

E. * For all of the above.

7. The patient has trigeminal neuralgia. What drugs are most appropriate to prescribe?

A. * Movalis + finlepsin.

B. Analgin + diphenhydramine.

C. Butadione + diphenhydramine.

D. Baralgin.

E. Paracetamol + suprastin.

8. In the acute phase of rheumatism NSAIDs of choice:

A. Analgin.

B. Paracetamol.

C. Acetylsalicylic acid.

D. * Diclofenac Sodium.

E. Butadion.

9 What are the main differences between NSAIDs and glucocorticosteroids?

A. Combination of anti-inflammatory, analgesic and antipyretic effects.

B. Inhibitory effect on platelet aggregation.

C. Non-specificity of anti-inflammatory action.

D. Relatively good tolerance.

E. * All of the above.

10. Choose from the listed drugs NSAIDs with the most pronounced anti-inflammatory effect:

A. Paracetamol.

B. Analgin.

C. * Indomethacin.

D. Acetylsalicylic acid.

E. Piroxicam

11. Selective COX-2 inhibitor:

A. Paracetamol.

B. * Nimesulide.

C. Butadion.

D. Indomethacin.

E. Acetylsalicylic acid.

12. NSAIDs, for the prevention of heart attack and strokes.

A. Paracetamol.

B. Meloxicam.

C. Piroxicam.

D. Celecoxib.

E. * Acetylsalicylic acid.

13. NSAIDs, for topical use, with fibrinolytic, antiseptic effects and the ability to penetrate biological barriers.

A. Acetylsalicylic acid.

B. Indomethacin ointment.

C. Fastum gel.

D. * Dimexide.

E. Butadiene ointment.

14. A combined drug based on non-narcotic analgesics, which includes codeine.

A. Baralgin.

B. * Pentalgin.

C. Tempalgin.

D. Reopyrine.

E. Coldrex.

15. NSAIDs, with the most pronounced antiplatelet properties.

A. * Acetylsalicylic acid.

B. Paracetamol.

C. Piroxicam.

D. Meloxicam.

E. Celecoxib.

16. The patient, 32 years old, urgently admitted to the hospital with lupus crisis. Choose the most effective dose of prednisone.

A. 50-60 mg.

B. 10-20 mg.

C. * Pulse therapy 500-1000 mg.

D. 100-120 mg.

E. 5-10 mg.

17. With persistent moderate asthma, it is advisable to prescribe the course.

A. Inhalation beclomethasone 200-500 mcg per day.

B. * Inhalation beclomethasone 400-1000 mcg per day.

C. Inhalation beclomethasone 1000-2000 mcg per day.

D. Intravenous prednisone 60 mg per day.

E. Intravenous prednisone 120 mg per day.

18. A patient, 40 years old, was admitted to the admission department with a diagnosis of rheumatoid polyarthritis, Sh. activity, with impaired joint function Blood test - erythropenia, granulocytopenia. Which of the following drugs should be prescribed to the patient?

A. * Prednisolone.

B. Red blood cell mass.

C. Leukocyte mass.

D. Canned blood.

E. Leucogen.

19. A patient, 45 years old, a worker of a poultry farm, was diagnosed with exogenous allergic alveolitis. The drug of which group should be prescribed as a basic therapy?

A. Antibiotics.

B. Sulfanilamides.

C. Antidepressants

D. * Corticosteroids.

E. Antifungal drugs.

20. The patient developed a Quincke edema after a wasp sting. What drugs should I begin to provide first aid to the patient?

A. * C prednisoline, adrenaline.

B. With reopoliglyukina, hemodez.

C. With noradrenaline, mesatone.

D. With furosemide, hypothiazide.

E. With blood plasma.

6. Patient I., with a clinic of diffuse toxic goiter, is allergic to iodine and leukopenia from taking merkazolil. Which of the following medicines should be prescribed to the patient?

A. * Lithium carbonate with prednisone.

B. Prednisone with mercazolyl.

C. Prednisone with β-blockers.

D. Lithium carbonate.

E. Methyluracil.

22. A 40-year-old man has autoimmune hepatitis. During the examination, it was revealed in the blood: bilirubin - 42 μmol / l, AlAt - 23 μmol / (hour • l), AsAt - 1.8 μmol / (hour • l). Which of the following is most effective for the treatment of this patient?

A. * Glcocorticoids, cytostatics.

B. Antibacterial agents.

C. Hepatoprotectors.

D. Antiviral drugs.

E. Hemosorption, vitamin therapy.

23. The patient complains of facial swelling, hoarseness, pronounced shortness of breath, urticarial rashes throughout the body. An allergic history is burdened. An hour before the onset of the above symptoms, I ate a small amount of strawberries. What should be prescribed to the patient to prevent further deterioration?

A. * Prednisolone, diuretic.

B. Antihistamines, antibiotics.

C. Adrenergic agonists, β-blockers.

D. Sulfanilamides, dexamethasone.

E. Cholinolytics, cardiac glycosides.

24. A patient with croupous pneumonia was prescribed IM cephalexin. 2 g per day. 30 minutes after the administration of the antibiotic, a collaptoid state arose: blood pressure - 65/30 mm Hg, pulse 110 min, weak filling. Shortness of breath, sharp pain in the epigastric region. Palpation of the abdomen reveals symptoms of peritoneal irritation. What drugs do you prescribe first?

A. * Prednisolone, adrenaline.

B. Strofantin, adrenaline.

C. Analgin, dexamethasone.

D. Heparin, antibiotics.

E. Prednisolone, codeine.

25. The drug of choice for replacement therapy for Addison's disease is:

A. * Hydrocortisone at a physiological dose.

B. Dexamethasone.

C. Triamsinolone.

D. Polcartolone.

E. Beclamethasone.

26. Pick up a dose of prednisone to treat lymphocytic leukemia.

A. 20-30 mg.

B. 50-60 mg.

C. 10-20 mg.

D. 1 g / kg body weight.

E. * 2-3 g / kg body weight.

27. In case of adrenal hyperplasia, to suppress the activity of the hypothalamic-pituitary-adrenal system, the following are used:

A. Corticotropin.

B. * Prednisolone.

C. Prazosin.

D. Doxazosin.

E. Aldosterone.

28. The treatment regimen for lymphocytic leukemia.

A. * Prednisolone + cyclophosphamide + chlorobutin.

B. Prednisolone + quinidine + bleomycin.

C. Prednisolone + cytarabine + ampicillin.

D. Cytarabine + chlorobutin + chloramphenicol.

E. Prednisolone + cyclophosphamide + ampicillin.

29. A 48-year-old patient was taken to the admission department complaining of attacks of suffocation that were not stopped by iv administration of eufilin, cough with sputum that was difficult to separate. A history of asthma for 10 years. Ob-but: respiratory rate - 30 per min., Percussion - box sound, auscultation - breathing is not heard. Your patient treatment tactics.

A. * Glucocorticoids intravenously.

B. Mast cell stabilizers.

C. Methylxanthines.

D. Inhalation of glucocorticoids.

E. Inhalation of β2 antagonists.

30. An ambulance was called for the patient. Ob-but: consciousness is absent, “hepatic” odor from the mouth, skin and mucous membranes of jaundice with petechial rashes, breathing of the Kussmaul type, pulse 120 min, blood pressure 80/60 mm Hg The tongue is raspberry, the papillae are smoothed. The liver is 9 cm below the costal arch, the edge is sharp. The spleen is enlarged. What drug should be used for emergency treatment in the first place?

A. * Prednisolone.

B. Albumin.

C. Calcium gluconate.

D. Sirepar.

E. Atropine.

31. Indicate NSAIDs:

A. * analgin.

B. morphine

C. Promedol.

D. fentanyl.

E. pentazosine

32. What mechanisms underlie antiproliferative action of NSAIDs?

A. Membrane-stabilizing effect

B. * Impaired differentiation of fibroblasts and fibrocytes, decreased activity of fibrocytes in the focus of inflammation, decreased synthesis of nucleic acids

C. Enhanced Nucleic Acid and Killagen Synthesis

D. An increase in the content of biologically active amines in the focus of inflammation

E. Antihistamine effect

33. What effect do NSAIDs have on immunity?

A. Stimulate humoral immunity

B. Do not have a significant effect on immunity

C. Suppress cell immunity

D. Stimulate interferon synthesis

E. * Suppress humoral immunity

34. What other pharmacodynamic effect do NSAIDs have in addition to anti-inflammatory?

A. Normalize disturbances in water-mineral metabolism

B. Procoagulant action

C. * Analgesic effect

D. Immunostimulating effect

E. Normalize acid-base metabolism

35. In which of the NSAIDs does the analgesic effect prevail over the anti-inflammatory?

A. Ketoprofen

B. Acetylsalicylic acid

*WITH. Metamizole Sodium (Analgin)

D. Mefenamic acid

E. Flurbiprofen

36. How do indomethacin and phenylbutazone affect water-mineral metabolism?

A. Stimulate the excretion of sodium and fluid from the body by the kidneys

B. Delayed elimination of sodium and fluid from the body by the kidneys

C. Stimulate Aldosterone Production

D. Virtually no effect on the exchange of sodium and water

E. Cause hypocalcemia

37. For the treatment of newborns with open ductus arteriosus, the following are used:

A. Acetylsalicylic acid

B. Phenylbutazone

S. Diclofenac

D. Indomethacin

E. Nimesulide

38. The derivatives of alkanoic (propionic) acids that are superior to acetyl-salicylic acid in anti-inflammatory action include:

A. Diclofenac

B. Mefenamic acid

S. Naproxen

D. Indomethacin

E. Ketoprofen

39. A sufficiently pronounced, comparable to acetylsalicylic acid, anti-aggregation effect has:

A. Naproxen

V. Ibuprofen

C. Metamizole sodium

D. Phenylbutazone

E. Paracetamol

40. Prevention of the catabolic effect of glucocorticosteroids is carried out by one of the following drugs:

A. * Potassium orotate.

B. Famotidine.

C. Panangin.

D. Potassium chloride.

E. Hypothiazide.

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 FOR THE SELECTION OF BASIC ANTI-INFLAMMATORY MEDICINES

CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF CORRECTORS OF MERABROLISM OF CONNECTIVE TISSUE

AND CARTILAGE TISSUE

ADVERSE EFFECTS OF ANTI-INFLAMMATORY MEDICINES: THEIR PREVENTION AND TREATMENT

Purpose of the topic.

A distinctive feature of this group of drugs is that the effect from the beginning of their use arises only after 10-12 weeks, and to consolidate the effect obtained, a constant intake is needed for another 1.5-2 years, they are called anti-rheumatic drugs of slow action.

Slow-acting anti-rheumatic drugs are not able to suppress normal inflammation. These drugs inhibit inflammatory reactions in which delayed-type hypersensitivity is involved. They are used in the treatment of systemic (autoimmune, or autoallergic) diseases of the connective tissue.

In connective tissue diseases, connective tissue metabolism correctors are also used. Calcium and phosphorus play a crucial role in ensuring cellular functions, regulating homeostasis, and maintaining the structural basis of the body. Violations of the exchange of calcium and phosphorus leads to osteopathy in the form of osteoporosis, osteomalacia or fibrous osteitis.

Motivational characteristic of the topic.

To be able to choose a pharmacological agent for various systemic (autoimmune, or autoallergic) diseases of the connective tissue. To know the mechanisms of regulation of the metabolism of connective tissue, the forms of its violation. Know the basic principles of selection of connective tissue metabolism correctors.

BASIC, SLOW-ACTING, ANTI-INFLAMMATORY MEDICINES

The group of basic or “modifying" the disease includes drugs that are heterogeneous in chemical structure and mechanism of action, used for the long-term therapy of rheumatoid arthritis and other inflammatory diseases associated with damage to the connective tissue. Conventionally, they can be divided into two subgroups.

• Slow-acting drugs with non-specific immunomodulating effects:

- gold preparations (aurothioprol, myocrisin *, auranofin);

- D-pericillamines (penicillamine);

- quinoline derivatives (chloroquine, hydroxychloroquine).

• Immunotropic drugs, indirectly stopping inflammatory changes in connective tissue:

- immunosuppressants (cyclophosphamide, azathioprine, methotrexate, cyclosporin);

- sulfa drugs (sulfasalazine, mesalazine).

The general pharmacological effects that combine these drugs are as follows:

• the ability to inhibit the development of bone erosion and the destruction of cartilage joints in non-specific inflammatory reactions;

• the predominantly indirect effect of most drugs on the local inflammatory process, mediated through pathogenetic factors of the immune link of inflammation;

• slow onset of therapeutic effect with a latent period for many drugs for at least 10-12 weeks;

• preservation of signs of improvement (remission) for several months after cancellation.

The mechanism of action and the main pharmacodynamic effects

Gold preparations, reducing the phagocytic activity of monocytes, disrupt their capture of antigen and the release of IL-1 from them, which leads to inhibition of proliferation of T-lymphocytes, decreased activity of T-helper cells, suppression of the production of immunoglobulins by B-lymphocytes, including rheumatoid factor, and the formation of immune complexes.

D-penicillamine, forming a complex compound with copper ions, is able to suppress the activity of T-helpers, stimulate the production of immunoglobulins by B-lymphocytes, including rheumatoid factor, and reduce the formation of immune complexes. The drug affects the synthesis and composition of collagen, increasing the content in it of aldehyde groups that bind the C1 component of complement, prevents the involvement of the entire complement system in the pathological process; increases the content of the water-soluble fraction and inhibits the synthesis of fibrillar collagen rich in hydroxyproline and disulfide bonds.

The main mechanism of therapeutic action of quinoline derivatives is the immunosuppressive effect associated with impaired nucleic acid metabolism. This leads to cell death. They suggest that the drugs disrupt the process of macrophage cleavage and the presentation of autoantigens by CD + T-lymphocytes.

By inhibiting the release of IL-1 from monocytes, they limit the release of prostaglandins E2 and collagenase from synovial cells. A decrease in the release of lymphokines prevents the emergence of a clone of sensitized cells, activation of the complement system and T-killers. It is

believed that quinoline preparations stabilize cell and subcellular membranes, reduce the release of lysosomal enzymes, and therefore limit the focus of tissue damage. In therapeutic doses, they have a clinically significant anti-inflammatory, immunomodulatory, as well as antimicrobial, hypolipidemic and hypoglycemic effect.

Second group drugs (cyclophosphamide, azathioprine, and methotrexate) disrupt the synthesis of nucleic acids and protein in all tissues; their effect is noted in tissues with rapidly dividing cells (in the immune system, malignant tumors, blood-forming tissue, gastrointestinal mucosa, and gonads). They inhibit the deletion of T-lymphocytes, their conversion into helpers, suppressors and cytostatic cells. This leads to a decrease in the cooperation of T- and B-lymphocytes, inhibition of the formation of immunoglobulins, rheumatoid factor, cytotoxins and immune complexes. Cyclophosphamide and azathioprine more pronouncedly than methotrexate suppress blasttransformation of lymphocytes, antibody synthesis, inhibition of cutaneous hypersensitivity to the skin, and a decrease in the level of gamma and immunoglobulins. Small doses of methotrexate actively affect humoral immunity, a number of enzymes that play a role in the development of inflammation, inhibiting the release of IL-1 by mononuclear cells. It should be noted that the therapeutic effect of immunosuppressants in the doses used for rheumatoid arthritis and other immuno-inflammatory diseases does not correspond to the degree of immunosuppression. This probably depends on their inhibitory effect on the cellular phase of the local inflammatory process, and the anti-inflammatory effect itself is attributed to cyclophosphamide.

In contrast to cytostatics, the immunosuppressive effect of cyclosporine is associated with selective and reversible suppression of IL-2 production and T-cell growth factor. The drug inhibits the proliferation and differentiation of T-lymphocytes. The main target cells for cyclosporin are CD4 + T (helper lymphocytes). According to the effect on laboratory data, cyclosporin is comparable to other basic drugs and is especially effective in patients with skin anergy, low ratios of CD4, CD8 and T-lymphocytes in peripheral blood, with an increase in the level of NK cells (natural killers) and a decrease in the number of cells expressing IL -2 receptors.

Pharmacokinetics

Chrysanol (an oil suspension of gold salt, contains 33.6% of metallic gold) is used intramuscularly, the drug is absorbed from the muscles rather slowly. The maximum concentration in blood plasma is usually reached after 4 hours. After a single intramuscular injection of 50 mg (a water-soluble preparation containing 50% metallic gold), its level reaches a maximum (4.0-7.0 μg / ml) in a period of 15-30 minutes up to 2 hours. Gold preparations are excreted in urine (70%) and feces (30%). T1 / 2 in blood plasma is 2 days, and the half-life is 7 days. After a single injection, the level of gold in serum during the first 2 days decreases rapidly (up to 50%), remains at the same level for 7-10 days, and then decreases gradually. After repeated injections (once a week), the level of gold in blood plasma increases, reaching an equilibrium concentration of 2.5-3.0 μg / ml after 6-8 weeks, however, the relationship between the concentration of gold in plasma and its treatment and side no effects, and the toxic effect correlates with an increase in its free fraction. The bioavailability of the oral gold drug, auranofin (contains 25% metallic gold) is 25%. With his daily

admission (6 mg / day) equilibrium concentration is reached after 3 months. Of the dose taken, 95% is lost with feces and only 5% with urine. In plasma, gold salts are 90% bound to proteins, distributed unevenly in the body: they accumulate most actively in the kidneys, adrenal glands and the reticuloendothelial system. In patients with rheumatoid arthritis, the highest concentrations are found in the bone marrow (26%), liver (24%), skin (19%), bones (18%); in synovial fluid, its level is about 50% of the level in blood plasma. In joints, gold is

predominantly localized in the synovial membrane, and thanks to a special tropism for monocytes, it more actively accumulates in areas of inflammation. Crosses the placenta in a small amount.

Proteins contribute to its transformation into sulfide, which is poorly absorbed from the intestine, therefore, eating significantly reduces the bioavailability of D-penicillamine. The maximum concentration in blood plasma after a single dose is reached after 4 hours. In plasma, the drug is intensely bound to proteins, in the liver it turns into two inactive water-soluble metabolites excreted by the kidneys (sulfide-penicillamine and cysteine-penicillamine-disulfide). T1 / 2 in individuals with normally functioning kidneys is 2.1 hours, in patients with rheumatoid arthritis it increases by an average of 3.5 times.

Quinoline preparations are well absorbed from the digestive tract. The maximum concentration in the blood is reached on average after 2 hours. With an unchanged daily dose, their level in the blood gradually increases, the time to reach the equilibrium concentration in the blood plasma ranges from 7-10 days to 2-5 weeks. Chloroquine in plasma is 55% bound to albumin. Due to its association with nucleic acids, its concentration in tissues is much higher than in blood plasma. Its content in the liver, kidneys, lungs, leukocytes is 400-700 times, in brain tissue is 30 times higher than in blood plasma. Most of the drug is excreted in the urine unchanged, a smaller (approximately 1/3) is biotransformed in the liver. The half-life of chloroquine ranges from 3.5 to 12 days. With acidification of urine, the rate of excretion of chloroquine increases, with alkalization it decreases. After stopping the intake, chloroquine slowly disappears from the body, remaining in the places of deposition for 1-2 months, after prolonged use, its content in the urine is detected for several years. The drug easily penetrates the placenta, intensively accumulating in the pigment epithelium of the fetal retina, as well as binding to DNA, inhibits protein synthesis in the fetal tissues.

Cyclophosphamide is well absorbed from the gastrointestinal tract, its maximum concentration in the blood is reached after 1 h, the connection with the protein is minimal. In the absence of impaired liver and kidney function, up to 88% of the drug in the blood and liver is biotransformed into active metabolites, of which aldophosphamide is most active. It can accumulate in the kidneys, liver, spleen. Cyclophosphamide in unchanged form (20% of the administered dose) and in the form of active and inactive metabolites is excreted in the urine. T1 / 2 is 7 hours. In case of impaired renal function, all effects, including toxic ones, may increase.

Azathioprine is well absorbed from the digestive tract, turning in the body (in lymphoid tissue more actively than in others) into the active metabolite 6-mercaptopurine, T1 / 2 of which from the blood is 90 minutes. The rapid disappearance of azathioprine from blood plasma is due to its active capture by tissues and further biotransformation. T1 / 2 of azathioprine is 24 hours; it does not penetrate the BBB. It is excreted in the urine both unchanged and in the form of metabolites - S-methylated products and 6-thiourea acid, formed under the influence of xanthine oxidase and causing the development of hyperuricemia and hyperuricuria. The blockade of allopurinol xanthine oxidase slows down the conversion of 6-mercaptopurine, reducing the formation of uric acid and increasing the effectiveness and toxicity of the drug.

Methotrexate is absorbed from the gastrointestinal tract by 25-100% (on average 60-70%); with increasing doses, absorption does not change. Methotrexate is partially metabolized by intestinal flora, bioavailability varies widely (28-94%). The maximum concentration is reached after 2-4 hours. Eating increases the absorption time by more than 30 minutes, without affecting the level of absorption and bioavailability. Methotrexate binds to plasma proteins by 50-90%, practically does not penetrate the BBB, its biotransformation in the liver is 35% with oral administration and does not exceed 6% with intravenous administration. The drug is excreted by tubular filtration and tubular secretion, about 10% of the methotrexate received in the body is excreted

with bile. T1 / 2 is 2-6 hours, however, its polyglutamated metabolites are detected intracellularly for at least 7 days after a single dose, and 10% (with normal kidney function) is retained in the body, persisting mainly in the liver (several months) and kidneys (how many weeks).

In cyclosporine, due to the variability of absorption, bioavailability varies widely, amounting to 10-57%. The maximum concentration in the blood is reached after 2-4 hours. More than 90% of the drug is associated with blood proteins. It is unevenly distributed between individual cellular elements and plasma: in lymphocytes - 4-9%, in granulocytes - 5-12%, in red blood cells - 41-58% and in plasma - 33-47%. About 99% of cyclosporine is biotransformed in the liver. It is excreted in the form of metabolites, the main route of elimination is the gastrointestinal tract, with urine excreted no more than 6%, and unchanged - 0.1%. The half-life is 10-27 (on average 19) hours. The minimum concentration of cyclosporin in the blood at which the therapeutic effect is observed is 100 ng / l, the optimal is 200 ng / l, and the nephrotoxic concentration is 250 ng /

Gold treatment is called chryso, or aurootherapy. The first signs of improvement are sometimes observed after 3-4 months of continuous chrysotherapy.

Chrysanol is prescribed starting with one or more test injections in small doses (0.5-1.0 ml of 5% suspension) with an interval of 7 days and then switch to a weekly injection of 2 ml of 5% solution for 7-8 months. Evaluate the result of treatment most often after 6 months from the start of use.

Initial signs of improvement can appear after 6-7 weeks, and sometimes only after 3-4 months.

Upon reaching the effect and good tolerance, the intervals are further increased to 2 weeks, and after 3-4 months, while maintaining signs of remission, up to 3 weeks (maintenance therapy, carried out almost for life). When the first signs of exacerbation appear, it is necessary to return to more frequent injections of the drug. Myocrisine * is used similarly: trial dose - 20 mg, therapeutic - 50 mg. If there is no effect within 4 months, it is advisable to increase the dose to 100 mg; if there is no effect in the next few weeks, myocrisin * is canceled. 6 mg auranofin is equally used for a long time, divided into 2 doses. Some patients need a dose increase of up to 9 mg / day (with inefficiency for 4 months), others - only at a dose of 3 mg / day, side effects limit the dose. Complete anamnestic data on drug allergies, skin and kidney diseases, detailed blood count, biochemical profile and urinalysis. investigated before starting chrysotherapy, reduce the risk of side effects. In the future, every 1-3 weeks, it is necessary to re-perform clinical blood tests (with determination of the number of platelets) and general urinalysis. With proteinuria exceeding 0.1 g / l, gold preparations are temporarily canceled, although a higher level of proteinuria sometimes disappears without stopping therapy.

D-penicillamine for the treatment of rheumatoid arthritis is prescribed in an initial dose of 300 mg / day. If there is no effect for 16 weeks, the dose is increased monthly by 150 mg / day, reaching 450-600 mg / day. The drug is prescribed on an empty stomach 1 hour before or 2 hours after eating and no earlier than 1 hour after taking any other drugs. An intermittent regimen is possible (3 times a week), which allows to reduce the frequency of adverse reactions while maintaining clinical efficacy. Clinical and laboratory improvement occurs after 1.5-3 months, less often in the earlier stages of therapy, a distinct therapeutic effect is realized after 5-6 months, and radiological improvement - not earlier than after 2 years. If there is no effect within 4-5 months, the drug should be discontinued. Often during treatment, an exacerbation is observed, sometimes ending with spontaneous remission, and in other cases requiring an increase in dose or a transition to a double daily dose. When taking D-penicillamine, “secondary inefficiency” may develop: the clinical effect initially obtained is replaced by a persistent exacerbation of the rheumatoid process, despite ongoing therapy. In the process of treatment, in addition to careful

clinical observation, it is necessary to examine peripheral blood (including the number of platelets) every 2 weeks for the first 6 months, then once a month. Hepatic tests are performed once every 6 months.

The therapeutic effect of quinoline derivatives develops slowly: its first symptoms are observed no earlier than 6-8 weeks from the start of therapy (with rheumatism earlier, after 10-30 days, and with rheumatoid arthritis, subacute and chronic lupus erythematosus, only after 10- 12 weeks). The maximum effect sometimes develops only after 6-10 months of continuous therapy. The usual daily dose is 250 mg (4 mg / kg) of chloroquine and 400 mg (6.5 mg / kg) of hydroxychloroquine. With poor tolerance or when the effect is achieved, the dose is reduced by 2 times. Recommended low doses (not more than 300 mg of chloroquine and 500 mg of hydroxychloroquine), not inferior in effectiveness to the high ones, allow avoiding severe complications. In the process of treatment, it is necessary to re-examine the hemogram, before the start of treatment and then every 3 months ophthalmological monitoring should be carried out with the study of the fundus and visual fields, a thorough questioning of visual disorders.

Cyclophosphamide is prescribed orally after a meal, in a daily dose of 1-2 to 2.5-3 mg / kg in 2 divided doses, and large doses are administered intravenously in a bolus according to the intermittent schedule - 5000-1000 mg / m2. Sometimes they start treatment with a half dose. In both schemes, the level of leukocytes should not decrease less than 4000 per 1 mm2. At the beginning of treatment, a general blood test, determination of platelets and urinary sediment should be carried out every 7-14 days, and when the clinical effect and dose stabilization are achieved, every 2-3 months. Treatment with azathioprine begins with a trial daily dose of 25-50 mg during the first week, then increasing it by 0.5 mg / kg every 4-8 weeks, bringing it to the optimum - 1-3 mg / kg in 2-3 doses. The drug is prescribed orally after a meal. Its clinical effect develops no earlier than 5-12 months from the start of therapy. At the beginning of treatment, laboratory control (a clinical blood test with platelet counts) is performed every 2 weeks, and when the dose is stabilized, once every 6-8 weeks. Methotrexate can be used orally, intramuscularly and intravenously. As a basic remedy, most often the drug is used in a dose of 7.5 mg / week; when administered orally, this dose is divided into 3 doses after 12 hours (to improve tolerance). Its action develops very quickly, the initial effect appears after 4-8 weeks, and a maximum - by the 6th month. In the absence of a clinical effect, after 4-8 weeks with good tolerability of the drug, its dose is increased by 2.5 mg / week, but not more than 25 mg (prevention of toxic reactions and impaired absorption). In a maintenance dose of 1 / 3-1 / 2 of therapeutic methotrexate, you can prescribe with quinoline derivatives and indomethacin. Parenteral methotrexate is administered during the development of toxic reactions from the gastrointestinal tract or with inefficiency (insufficient dose or low absorption from the gastrointestinal tract). Solutions for parenteral administration are prepared immediately prior to administration. After the abolition of methotrexate, as a rule, an exacerbation develops between the 3rd and 4th week. In the course of treatment, the composition of peripheral blood is monitored every 3-4 weeks and liver tests every 6-8 weeks. The doses of cyclosporin used vary widely - from 1.5 to 7.5 mg / kg / day, however, exceeding the value of 5.0 mg / kg / day is impractical because, starting from the level of 5.5 mg / kg / day, the frequency of complications increases. Before starting treatment, a detailed clinical and laboratory examination is carried out (determination of the level of bilirubin and the activity of liver enzymes, the concentration of potassium, magnesium, uric acid in the blood serum, lipid profile, general urine analysis). During treatment, blood pressure and serum creatinine level are controlled: when it is increased by 30%, the dose per month is reduced by 0.5-1.0 mg / kg / day, while normalization of creatinine level, treatment is continued, and in its absence, it is stopped.

Side effects and contraindications

Basic drugs have many, including severe, side effects. When they are prescribed, it is necessary to compare the expected positive changes with possible undesirable reactions. The patient should be informed of the clinical symptoms that need attention and should be reported to the doctor.

Side effects and complications in the appointment of gold preparations are noted in 11-50% of patients.

The most common are skin itching, dermatitis, urticaria (sometimes in combination with stomatitis and conjunctivitis require cancellation in combination with the appointment of anti-histamine drugs). In severe dermatitis and fever, unitiol and glucocorticoids are added to the treatment.

Often observed proteinuria. With a loss of protein of more than 1 g / day, the drug is canceled due to the danger of developing nephrotic syndrome, hematuria, renal failure.

Hematological complications are relatively rare, but they require special alertness. Thrombocytopenia requires discontinuation of the drug, treatment with glucocorticoids, chelating compounds. Pancytopenia and aplastic anemia are possible; the latter can also lead to death (drug withdrawal is necessary).

Parenteral administration of myocrisin is complicated by the development of a nitritoid reaction (vasomotor reaction with a drop in blood pressure) - the patient is recommended to lie 0.5-1 hours after the injection.

Some side effects are rarely observed: enterocolitis with diarrhea, nausea, fever, vomiting, abdominal pain after discontinuation of the drug (in this case, glucocorticoids are prescribed), cholestatic jaundice, pancreatitis, polyneuropathy, encephalopathy, iritis (corneal ulcers), stomatitis, infiltra (infiltration) “Golden” lung). In such cases, discontinuation of the drug is sufficient to assist.

Possible perversions of taste, nausea, diarrhea, myalgia, megifonexia, eosinophilia, deposits of gold in the cornea and lens. These manifestations require the supervision of a physician.

Side effects when using D-penicillamine are noted in 20-25% of cases. Most often these are hematopoiesis disorders, the most severe of them are leukopenia (<3000 / mm2), thrombocytopenia (<100 000 / mm2), aplastic anemia (drug withdrawal is necessary). Perhaps the development of autoimmune syndromes: myasthenia gravis, pemphigus, a syndrome resembling systemic lupus erythematosus, Goodpasture syndrome, polymyositis, thyroiditis. After drug withdrawal, if necessary, glucocorticoids, immunosuppressants are prescribed.

Rare complications include fibrosing alveolitis, kidney damage with proteinuria of more than 2 g / day and nephrotic syndrome. These conditions require discontinuation of the drug.

It is necessary to pay attention to such complications as a decrease in taste sensitivity, dermatitis, stomatitis, nausea, loss of appetite. The frequency and severity of adverse reactions to D-penicillamine depend on both the drug itself and the underlying disease.

When prescribing quinoline drugs, side effects rarely develop and practically do not require cancellation of the latter.

The most common side effects are associated with a decrease in gastric secretion (nausea, loss of appetite, diarrhea, flatulence), with the development of dizziness, insomnia, headaches, vestibulopathy, hearing loss.

Very rarely, myopathy or cardiomyopathy develops (a decrease in T, ST on the electrocardiogram, impaired conduction and rhythm), toxic psychosis, convulsions. These side effects disappear after withdrawal and / or symptomatic therapy.

Rare complications include leukopenia, thrombocytopenia, hemolytic anemia and skin lesions in the form of urticaria, lichenoid and maculopapular rashes, and very rarely Lyell syndrome. Most often, this requires discontinuation of the drug.

The most dangerous complication is toxic retinopathy, which manifests itself as a narrowing of peripheral fields of vision, a central scotoma, and later - a deterioration in vision. Discontinuation of the drug, as a rule, leads to their regression.

Rare side effects include photosensitization, violation of pigmentation of the skin, hair, corneal infiltration. These manifestations are reversible and require observation.

Immunosuppressants have common side effects that are characteristic of any drug in this group, at the same time, each of them has its own characteristics.

The frequency of side effects of cyclophosphamide depends on the duration of use and the individual characteristics of the body. The most dangerous complication is hemorrhagic cystitis with an outcome in fibrosis, and sometimes - in bladder cancer. This complication is observed in 10% of cases. It requires discontinuation of the drug, even with symptoms of diarrhea. Alopecia, dystrophic changes in the hair and nails (reversible) are noted mainly with the use of cyclophosphamide.

For all drugs, it is possible to develop thrombocytopenia, leukopenia, pan-cytopenia, which, with the exception of azathioprine, develop slowly and regress after withdrawal.

There may be toxic complications in the form of interstitial pulmonary fibrosis with cyclophosphamide and methotrexate. The latter gives such a rare complication as cirrhosis. They are extremely rare for azathioprine, require withdrawal and symptomatic therapy.

The most common complications for this group are gastrointestinal disorders: nausea, vomiting, anorexia, diarrhea, and abdominal pain. They have a dose-dependent effect and are most often found with azathioprine. With it, hyperuricemia is also possible, requiring a dose adjustment and the appointment of allopurinol.

Methotrexate is better tolerated than other basic drugs, although the frequency of side effects reaches 50%. In addition to the above side effects, memory impairment, stomatitis, dermatitis, malaise, and fatigue are possible, which requires a dose adjustment or withdrawal.

Side effect. From the hemopoietic organs: leukopenia and thrombocytopenia, pancytopenia, anemia (including aplastic), neutropenia, agranulocytosis, eosinophilia, lymphadenopathy, lymphoproliferative diseases, hypogammaglobulinemia.

From the digestive system: anorexia, nausea, vomiting, stomatitis, gingivitis, pharyngitis, enteritis, erosive and ulcerative lesions and bleeding from the gastrointestinal tract (including melena, hematomesis), hepatotoxicity (acute hepatitis, fibrosis and cirrhosis of the liver, liver failure , hypoalbuminemia, increased activity of "liver" transaminases), pancreatitis.

From the nervous system: headache, drowsiness, dysarthria, aphasia, hemiparesis, paresis, convulsions; when used in high doses - transient violation of cognitive functions, emotional lability; unusual cranial sensitivity, encephalopathy (including leukoencephalopathy).

On the part of the skin: erythematous rash, itching of the skin, urticaria, photosensitivity, impaired skin pigmentation, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme (including Stevens-Johnson syndrome), toxic epidermal necrosis and ulceration skin, exfoliative dermatitis.

From the side of the organ of vision: conjunctivitis, visual impairment (including transient blindness).

From the respiratory system: rarely - pulmonary fibrosis, respiratory failure, alveolitis, interstitial pneumonitis (including fatal), COPD.

From the CCC: pericarditis, pericardial effusion, decreased blood pressure, thromboembolism (including arterial thrombosis, cerebral vascular thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, pulmonary embolism).

From the genitourinary system: severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria, impaired sperm and ovogenesis, transient oligospermia, decreased libido, impotence, dysmenorrhea, vaginal discharge, gynecomastia, infertility, miscarriage, fetal death .

From the musculoskeletal system: arthralgia, myalgia, osteopo-rose, osteonecrosis, fractures.

Infections: life-threatening opportunistic infections (including pneumocystis pneumonia), CMV (including CMV pneumonia), sepsis (including fatal), nocardiosis, histoplasmosis, cryptococcosis, infections caused by Herpes zoster and Herpes simplex (including disseminated).

Other: vasculitis, diabetes mellitus, lymphoma (including reversible), tumor lysis syndrome, soft tissue necrosis, anaphylactoid reactions, sudden death.

In the treatment of rheumatoid arthritis: more than 10% - increased activity of "liver" transaminases, nausea, vomiting; 3-10% - stomatitis, thrombocytopenia (less than 100 thousand / μl); 1-3% - skin rash, itching, dermatitis, diarrhea, alopecia, leukopenia (less than 3000 / μl), pancytopenia, dizziness, interstitial pneumonitis; others - decreased hematocrit, headache, infections (including upper respiratory tract), anorexia, arthralgia, chest pain, cough, dysuria, eye discomfort, nosebleeds, fever, excessive sweating, tinnitus, vaginal discharge.

In the treatment of psoriasis: alopecia, photosensitivity, burning sensation of the skin, rarely - painful erosive plaques on the skin.

In the treatment of juvenile rheumatoid arthritis: increased activity of “liver” transaminases (14%), gastrointestinal tract dysfunction (11%), incl. nausea, vomiting, diarrhea, stomatitis (2%), leukopenia (2%), headache (1.2%), alopecia (0.5%), dizziness (0.2%), skin rash (0.2%).

Overdose. Treatment: the introduction of a specific antidote - calcium folinate as soon as possible, preferably within the first hour, at a dose equal to or greater than the dose of methotrexate; subsequent doses are administered as needed, depending on the concentration of methotrexate in serum. To prevent precipitation of methotrexate and / or its metabolites in the renal tubules, the body is hydrated and alkalinized, which accelerates the excretion of methotrexate.

Interaction. It increases the anticoagulant activity of coumarin or indandion derivatives and / or increases the risk of bleeding by reducing the synthesis of a procoagulant factor in the liver and impaired platelet formation.

Increases the concentration of uric acid in the blood, therefore, in the treatment of patients with concomitant hyperuricemia and gout, a dose adjustment of anti-gout drugs (allopurinol,

colchicine, sulfinpyrazone) may be required; the use of uricosuric anti-gout drugs can increase the risk of nephropathy associated with increased formation of uric acid during treatment with methotrexate (it is preferable to use allopurinol).

The simultaneous administration of salicylates, phenylbutazone, phenytoin, sulfanilamides, sulfonylurea derivatives, aminobenzoic acid, pyrimethamine or trimethoprim, a number of antibiotics (penicillin, tetracycline, chloramphenicol), indirect anticoagulants and hypolipidemic dependence of L or decrease in tubular secretion, which in some cases can lead to the development of severe toxic effects, sometimes even fatal.

NSAIDs against the background of high doses of methotrexate increase the concentration and slow down the elimination of the latter, which can lead to death from severe hematological and gastrointestinal intoxication. It is recommended to stop taking phenylbutazone 7-12 days, piroxicam 10 days, diflunisal and indomethacin 24-48 hours, ketoprofen and NSAIDs with a short T1 / 2 12-24 hours before the methotrexate infusion in moderate and high doses and during at least 12 hours (depending on the concentration of methotrexate in the blood) after its completion. Caution should be exercised when combining NSAIDs with low doses of methotrexate (may decrease the excretion of methotrexate by the renal tubules).

Drugs that block tubular secretion (for example, probenecid) increase the toxicity of methotrexate by reducing its excretion by the kidneys.

Antibiotics that are poorly absorbed in the digestive tract (tetracyclines, chloramphenicol), reduce the absorption of methotrexate and disrupt its metabolism due to the suppression of normal intestinal microflora.

Retinoids, azathioprine, sulfasalazine, ethanol, and other hepatotoxic drugs increase the risk of hepatotoxicity.

Folate-containing drugs (including multivitamins) reduce the toxic effect of methotrexate on bone marrow.

L-asparaginase reduces the severity of the antitumor effect of methotrexate by inhibiting cell replication.

Anesthesia using dinitrogen oxide can lead to the development of unpredictable severe myelosuppression and stomatitis.

Acyclovir for parenteral administration with intrathecal administration of methotrexate increases the risk of developing neurological disorders.

The use of cytarabine 48 hours before or within 10 minutes after the initiation of methotrexate therapy may cause the development of a synergistic cytotoxic effect (it is recommended to adjust the dosage regimen based on the control of hematological parameters).

Hematotoxic drugs increase the risk of hematotoxicity of methotrexate.

Reduces clearance of theophylline.

Neomycin for oral administration may decrease the absorption of methotrexate for oral administration.

Several patients with psoriasis or mycosis fungoides treated with methotrexate in combination with PUVA therapy (methoxalen and UFO) had skin cancer.

Combination with radiation therapy may increase the risk of bone marrow depression.

Methotrexate can reduce the immune response to vaccination, so the interval between the introduction of live and inactivated viral vaccines varies from 3 to 12 months.

Cyclosporine in comparison with other immunosuppressants gives fewer immediate and long-term side effects. Possible development of arterial hypertension, transient azotemia with a dose-dependent effect; hypertrichosis, paresthesia, tremors, moderate hyperbilirubinemia and fermentemia. They most often appear at the beginning of treatment and disappear on their own; only with persistent complications is it necessary to cancel the drug.

> In general, the appearance of undesirable effects can significantly outstrip the slowly developing therapeutic effect of immunosuppressants. This should be considered when choosing a basic drug. Common complications for them are presented in table.

All drugs, except quinoline, are contraindicated in acute infectious diseases, and are not prescribed during pregnancy (except for sulfanilamide drugs). Gold preparations, D-penicillamine and cytostatics are contraindicated in various hematopoiesis; levamisole - with a medical history of agranulocytosis, and quinoline - with severe cytopenia, not associated with the underlying disease to be treated with these drugs. Diffuse lesions of the kidneys and CRF are a contraindication to the administration of gold, quinoline, D-penicillamine, methotrexate, cyclosporin; with chronic renal failure, the dose of cyclophosphamide is reduced. With lesions of the liver parenchyma, gold preparations, quinoline, cytostatics are not prescribed, cyclosporine is prescribed with caution. In addition, contraindications to the use of gold preparations are diabetes mellitus, decompensated heart defects, miliary tuberculosis, fibro-cavernous processes in the lungs, cachexia; relative contraindications - severe allergic reactions in the past (prescribe the drug with caution), rheumatoid factor seronegativity (in this case, it is almost always poorly tolerated). D-penicillamine is not prescribed for bronchial asthma; used with caution in case of penicillin intolerance, in the elderly and senile. Contraindications to the appointment of sulfa drugs are hypersensitivity not only to sulfa, but also to salicylates, and sulfa and quinoline are not prescribed for porphyria, glucose-6-phosphate dehydrogenase deficiency. Quinoline derivatives are contraindicated in severe heart muscle lesions, especially those associated with conduction disturbances, in diseases of the retina, psychosis. Cyclophosphamide is not prescribed for severe heart disease, in the terminal stages of the disease, with cachexia. A relative contraindication to the appointment of methotrexate are gastroduodenal ulcers. Cyclosporin is contraindicated in uncontrolled arterial hypertension, malignant neoplasms (with psoriasis it can be used for malignant skin diseases). A history of toxic-allergic reactions to any sulfonamides is a contraindication to the appointment of sulfasalazine.

Drug Selection

In terms of therapeutic efficacy, gold and immunosuppressive drugs occupy the first place, but the potential oncogenicity and cytotoxicity of the latter make them in some cases treat them as reserve agents; followed by sulfonamides and D-penicillamine, which is worse tolerated. Basic therapy is better tolerated by patients with rheumatoid factor seropositive rheumatoid factor arthritis.

The main indication for the appointment of gold salts is rapidly progressing rheumatoid arthritis with early development of bone erosion, the articular form of the disease with signs of active synovitis, as well as the articular-visceral form with rheumatoid nodules, Felty and Sjogren's syndromes. The effectiveness of gold salts is manifested by regression of synovitis and visceral manifestations, including rheumatoid nodules.

There is evidence of the effectiveness of gold salts in juvenile rheumatoid arthritis, psoriatic arthritis, some observations indicate effectiveness in the discoid form of lupus erythematosus (auranofin).

In patients who tolerate it well, the rate of improvement or remission reaches 70%.

D-penicillamine is mainly used for active rheumatoid arthritis, including in patients resistant to treatment with gold preparations; additional indications are the presence of a high titer of rheumatoid factor, rheumatoid nodules, Felty's syndrome, rheumatoid lung lesions. By the frequency of development of improvement, its severity and duration, especially remission, D-penicillamine is inferior to gold preparations. The drug is ineffective in 25-30% of patients, in particular, with the HLA-B27 haplotype. D-penicillamine is considered the main component in the complex therapy of systemic scleroderma, its effectiveness in the treatment of biliary cirrhosis, palindromic rheumatism and juvenile arthritis has been shown.

Indication for the appointment of quinoline drugs is the presence of a chronic immune immune process with a number of rheumatic diseases, especially during remission for the prevention of relapse. They are effective for discoid lupus erythematosus, eosinophilic fasciitis, juvenile dermatomyositis, palindromic rheumatism, and some forms of seronegative spondylarotropia. With rheumatoid arthritis as monotherapy, it is used for mild course, as well as during the period of achieved remission. Chino-lin preparations are successfully used in complex therapy with other basic drugs: cytotoxic drugs, gold preparations.

Immunosuppressants (cyclophosphamide, azathioprine, methotrexate) are indicated for severe and rapidly progressive forms of rheumatic diseases with high activity, as well as the insufficient effectiveness of previous steroid therapy: for rheumatoid arthritis, Felty and Still syndrome, systemic lesions of the connective tissue (systemic lupus erythematosus, dermatopolimiositis, systemic scleroderma, systemic vasculitis: Wegener's granulomatosis, periarteritis nodosa, Takayasu’s disease, Church-Stros syndrome, Harton’s disease, hemo ragicheskom vasculitis with renal disease, Behcet's disease, Goodpasture's syndrome).

Immunosuppressants have a steroid-preserving effect, which reduces the dose of glucocorticoids and the severity of their side effects.

There are some features in the appointment of drugs of this group: cyclophosphamide - the drug of choice for systemic vasculitis, rheumatoid vasculitis, lupus lesions of the central nervous system and kidneys; methotrexate - with rheumatoid arthritis, seronegative spondylitis, psoriatic arthropathy, ankylosing spondylitis; azathioprine is most effective for skin manifestations of systemic lupus erythematosus and lupus glomerulonephritis. A sequential administration of cytostatics is possible: cyclophosphamide with subsequent transfer to azathioprine with a decrease in the activity of the process and to achieve stabilization, as well as to reduce the severity of side effects from cyclophosphamide.

A specific immunosuppressor is cyclosporin A, which has a selective effect on T-helpers. The main indication for his appointment is psoriatic arthropathy. The use of the drug with systemic lupus erythematosus, dermatopolymiosis, rheumatoid arthritis is promising

Auronofin

Chemical name. (1 - thio - beta - D - glucopyrazinato) (triethylphosphine) gold 2, 3, 4, 6 - tetraacetate

Pharmachologic effect. The gold preparation for oral administration (contains 29% Au), has an anti-inflammatory effect. The mechanism of action is not fully understood: it is believed that the suppression of cellular immunity is due to the uptake of Au3 + by monocytes and polymorphic nuclear leukocytes, which leads to inhibition of phagocytosis and blockade of lysosomal enzymes. It reduces the activity of sulfhydryl systems and enzyme complexes of leukocytes and

lymphocytes, which leads to a decrease in the concentration of Ig and rheumatoid factor, inhibits the synthesis of collagen and Pg.

The therapeutic effect develops gradually and is observed after 3-4 months (sometimes 6 months) from the time of taking the drug.

Pharmacokinetics Absorption after oral administration - 25%. Communication with plasma proteins - 60%. Css is noted 3 months after the start of treatment, at a dose of 6 mg / day is 68 μg / ml.

It is rapidly metabolized in the liver (unchanged auranofin is practically not detected in the blood). T1 / 2 in the blood - 21-31 days, in the tissues - 42-128 days. It is excreted by the kidneys (60%) and with bile.

Indications. Rheumatoid arthritis (treatment and prevention in detecting early radiological changes in the joints), psoriatic arthritis, Felty's syndrome.

Contraindications Hypersensitivity, CHF, chronic renal failure, hepatitis (active phase), inhibition of bone marrow hematopoiesis, exfoliative dermatitis, enterocolitis, pregnancy, lactation, cachexia, urticaria, eczema, skin rash.

Dosage regimen. Inside: adults - 6 mg / day; children - 0.1 mg / kg / day in 2 doses.

If the reception is ineffective for 4 months and well tolerated, it is possible to increase the dose for adults to 9 mg / day in 3 divided doses, for children - up to 0.2 mg / kg / day. In case of treatment failure during the next 3 months, the drug is canceled.

Side effects. From the nervous system and sensory organs: lethargy, hallucinations, epileptic seizures, conjunctivitis.

From the respiratory system: pharyngitis, tracheitis, interstitial pneumonia, pneumofibrosis.

From the digestive system: gingivitis, glossitis, stomatitis, vomiting, diarrhea or constipation, gastralgia, gastritis, necrotic enteritis, ulcerative enterocolitis, colitis, gastrointestinal bleeding, cholestasis, cholelithiasis, hepatitis, liver failure.

From the genitourinary system: nephrotic syndrome with massive proteinuria, renal failure, vaginitis.

From the hematopoietic system: agranulocytosis, pancytopenia, anemia, leukopenia, thrombocytopenia.

Allergic reactions: skin rashes, itching of the skin, eosinophilia, dermatitis, hyperthermia.

Interaction. Incompatible with penicillins, levamisole, chloroquine; compatible with NSAIDs.

Side effects are enhanced by cytostatics, hepato- and nephrotoxic drugs, penicillamine.

Myelotoxic drugs enhance the hematotoxic effect of the drug.

Special instructions. Before and during therapy, it is necessary to control the picture of peripheral blood (Hb content, platelet count), kidney function (urea concentration, creatinine, urine protein content), liver function (activity of “liver” transaminases) during the first year of treatment - monthly, the second - every 2-3 months. With proteinuria more than 1 g / day, therapy should be discontinued.

Sulfasalazine, enteric-coated tablets.

The pharmacological group is an antimicrobial and anti-inflammatory intestinal agent.

Pharmachologic effect. An antimicrobial intestinal agent, sulfonamide, also has an anti-inflammatory effect. The possibility of using non-specific colitis in the treatment is associated with the ability of sulfasalazine to selectively accumulate in the connective tissue of the intestinal wall with the release of 5-aminosalicylic acid (5-ASA), which has anti-inflammatory activity, and sulfapyridine, which has an antimicrobial bacteriostatic effect, a competitive antagonist of PABA.

It acts against diplococci, streptococci, gonococci, intestinal coli.

Pharmacokinetics Absorption - 10%, is subjected to digestion by intestinal microflora with the formation of sulfapyridine - 60-80 and 25% 5-ASA. Communication with plasma proteins of sulfasalazine - 99%, sulfapyridine - 50%, 5-ASA - 43%.

Sulfapyridine is metabolized in the liver by hydroxylation to form inactive metabolites, 5-ASA by acetylation. T1 / 2 sulfasalazine - 5-10 hours, sulfapyridine - 6-14 hours, 5-ASA - 0.6-1.4 hours. It is excreted through the intestines - 5% sulfapyridine and 67% 5-ASA, kidneys - 75-91% of absorbed sulfasalazine (in within 3 days).

Indications. Nonspecific ulcerative colitis.

Contraindications Hypersensitivity, liver and / or renal failure, anemia, porphyria, congenital deficiency of glucose-6-phosphate dehydrogenase; lactation, children's age (up to 5 years).

Category of action on the fetus. B

Dosage Inside, 1 g 4-6 times a day, for 2-3 weeks, followed by a gradual decrease in dose by 0.5-1 g every 5-7 days; the course of treatment can last up to 4-6 months. Children 5-7 years old - 0.25-0.5 g 3-6 times a day, older than 7 years - 0.5 g 3-6 times a day.

Side effect. Headache, dizziness, dyspepsia: nausea, vomiting, diarrhea, abdominal pain, loss of appetite; an admixture of blood in feces, interstitial pneumonitis, drug-induced hepatitis, photosensitivity, staining of urine in orange-yellow color, agranulocytosis, leukopenia, thrombocytopenia, hemolytic anemia, allergic reactions: toxic epidermal necrolysis (Lyell's syndrome), malignant exudative erythema , anaphylactic shock.

Interaction. Enhances the effect of anticoagulants, antiepileptic and oral hypoglycemic drugs, as well as side effects of cytostatics, immunosuppressants, hepato- and nephrotoxic drugs.

Drugs that inhibit bone marrow hematopoiesis increase the risk of myelosuppression.

Chloroquine (Delagil), tablets. The pharmacological group is an antimalarial agent.

Pharmachologic effect. Antiprotozoal also has an immunosuppressive and anti-inflammatory effect. It causes the death of asexual erythrocyte forms of all types of plasmodia. It has a gametocidal effect, with the exception of Plasmodium falciparum (exhibits an anti-gametocidal effect). Due to inhibition of nucleic acid synthesis, it has a moderately pronounced immunosuppressive and non-specific anti-inflammatory effect.

Pharmacokinetics After oral administration, it is rapidly and almost completely absorbed from the digestive tract. Cmax is reached after 2-6 hours. 55% binds to plasma albumin.

It quickly spreads to the organs and tissues of the body (liver, kidneys, spleen, lungs). It easily penetrates the BBB and the placenta.

It is metabolized in a small amount (25%). It is excreted by the kidneys (70% - unchanged) slowly. T1 / 2 - 1-2 months.

With renal failure, it can accumulate. With an acidic reaction of urine, the elimination rate increases, with an alkaline reaction, it increases.

Indications. Malaria (prevention and treatment of all types), extraintestinal amoebiasis, amoebic liver abscess, SLE (chronic and subacute forms), rheumatoid arthritis, scleroderma, photodermatosis, late cutaneous porphyria.

Contraindications Hypersensitivity, liver and / or renal failure, inhibition of bone marrow hematopoiesis, severe rhythm disturbances, psoriatic arthritis, neutropenia, porphyrinuria, pregnancy.

Dosage Inside, for the prevention of malaria - 0.5 g in the first week 2 times, then 1 time always on the same day of the week. Treatment of malaria is carried out according to the following scheme: 1 day once 1 g, after 6-8 hours - 0.5 g, on days 2 and 3 of treatment - 0.75 g daily in 1 dose. If necessary - iv drip.

With amoebiasis, 0.5 g 3 times a day for 7 days, then 0.25 g 3 times a day for another 7 days, then 0.75 g 2 times a week for 2-6 months.

With rheumatoid arthritis - 0.25 g 2 times a day for 7 days, then - 0.25 g daily for 12 months.

With SLE - daily 0.25-0.5 g.

In photodermatosis, 0.25 g daily for 1 week, then 0.5-0.75 g weekly.

Side effect. From the digestive system: nausea, vomiting, gastralgia.

From the nervous system: dizziness, headache, sleep disturbances, psychoses, epileptic seizures.

From the CCC: myocardial damage with changes in the ECG, a decrease in blood pressure.

From the sensory organs: with prolonged use - clouding of the cornea, damage to the retina, impaired vision, ringing in the ears.

Allergic reactions: dermatitis, photosensitivity.

Other: myalgia, leukopenia, discoloration of the skin and hair.

UNWANTED NSAID REACTIONS

Gastrointestinal tract. Currently, it has been established that while taking NSAIDs, lesions of any gastrointestinal tract may develop - from the lower third of the esophagus (in the presence of gastroesophageal reflux) to the distal colon, enteropathy. But the lesions in the antrum of the stomach and onion of the duodenum are most often noted. When treating with drugs of this group, dyspeptic disorders are noted in 30–40% of patients, erosion and ulcers of the stomach and duodenal ulcer in 10–20%, and bleeding and perforation in 2–5%.

At present, a specific syndrome - NSAID gastropathy is isolated. Its appearance, on the one hand, is associated with a local damaging effect of drugs on the mucous membrane of the stomach and intestines, increased permeability of cell membranes, and decreased biosynthesis of gastric mucus. On the other hand, it is due to the inhibition of COX-1 and the suppression of the synthesis of physiological GHGs, as a result of which the synthesis of hydrochloric acid is not controlled, the production of bicarbonates decreases, and the blood circulation of the gastric mucosa is disturbed. Damage to the gastric mucosa proceeds in 3 stages:

1) inhibition of the synthesis of prostaglandins in the mucosa;

2) a decrease in prostaglandin-mediated production of protective mucus and bicarbonates;

3) the appearance of erosion and ulcers, which may be complicated by bleeding or perforation.

Damage is often localized in the stomach, mainly in the antrum or prepiloric department. Clinical symptoms of NSAID-gastroduodenopathy in almost 60% of patients, especially the elderly, are absent, therefore, the diagnosis in many cases is established with fibrogastroduodenoscopy. At the same time, in many patients presenting dyspeptic complaints, mucosal damage is not detected. The absence of clinical symptoms in NSAIDs-gastroduodenopathy is associated with the analgesic effect of the drugs. Therefore, patients, especially the elderly, who do not experience adverse effects of the gastrointestinal tract with long-term use of NSAIDs, are considered as a group at increased risk of developing serious complications of NSAID-gastroduodenopathy (bleeding, severe anemia) and require especially careful monitoring, including endoscopic study.

Risk factors for the development of NSAIDs for gastropathy are: age over 60, female gender, smoking, alcohol abuse, a history of gastrointestinal diseases, concomitant use of glucocorticoids, immunosuppressants, anticoagulants, prolonged therapy of NSAIDs, high doses or simultaneous administration of two or more drugs of this group.

Among all NSAIDs, acetylsalicylic acid, indomethacin, piroxicam, ketoprofen, etodolac have the most pronounced gastrotoxic effect. Patients with a history of gastrointestinal disease, the use of these drugs is strictly contraindicated.

In order to improve tolerance and minimize the ulcerogenic effects of NSAIDs, it is recommended to combine their administration with proton pump inhibitors, H2 histamine blockers or gastroprotectors; a change in the tactics of dosing NSAIDs (dose reduction), the use of enteric-soluble drug forms of drugs or prodrugs (for example, sulindac), as well as the transition to parenteral, rectal or local administration of NSAIDs. However, since NSAID gastropathy is not so much local as a systemic reaction, these approaches did not solve the problem. The use of selective NSAIDs that selectively block COX-2 and at therapeutic doses does not have a significant effect on COX-1 is recommended. Thus, the predominant COX-2 inhibitors meloxicam, etodolac, nabumeton and nimesulide have a favorable gastrotoxicity profile. At present, specific COX-2 inhibitors are widely used in clinical practice, for example, celecoxib, rofecoxib, which practically do not adversely affect the gastrointestinal tract.

The synthetic analogue PG-E2, a misopro-table, is highly effective, which can prevent the development of ulcers both in the stomach and in the duodenum. Combined drugs are produced, which include NSAIDs and misoprostol

Methods for improving the tolerance of NSAIDs.

I. Simultaneous administration of drugs that protect the mucous membrane of the gastrointestinal tract.

According to controlled clinical trials, the synthetic analogue PG-E2, misoprostol, is highly effective, which can prevent the development of ulcers both in the stomach and in the duodenum. Combined drugs are produced, which include NSAIDs and misoprostol (see below) .

The proton pump inhibitor omeprazole has about the same effectiveness as misoprostol, but is better tolerated and faster eliminates reflux, pain and digestive disorders.

H2 blockers can prevent the formation of duodenal ulcers, but, as a rule, are ineffective against stomach ulcers. However, there is evidence that high doses of famotidine (40 mg twice daily) reduce the incidence of both gastric and duodenal ulcers.

The cytoprotective drug Sucralfate does not reduce the risk of gastric ulcers; its effect on duodenal ulcers has not been fully determined.

II. A change in the tactics of using NSAIDs, which involves (a) a decrease in dose; (b) transition to parenteral, rectal or local administration; (c) administration of enteric-soluble dosage forms; (d) the use of prodrugs (e.g., sulindac). However, due to the fact that NSAID-gastroduodenopathy is not so much local as a systemic reaction, these approaches do not solve the problem.

III. The use of selective NSAIDs.

As noted above, there are two isoenzymes of cyclooxygenase, which are blocked by NSAIDs: COX-2, which is responsible for the production of prostaglandins in inflammation, and COX-1, which controls the production of prostaglandins, which maintain the integrity of the gastrointestinal mucosa, renal blood flow and function platelet count. Therefore, selective COX-2 inhibitors should cause fewer adverse reactions. The first such drugs are meloxicam and nabumeton. Controlled studies conducted in patients with rheumatoid arthritis and osteoarthrosis showed that they are better tolerated than diclofenac, piroxicam, ibuprofen and naproxen, not inferior to them in effectiveness.

The development of a stomach ulcer in a patient requires the abolition of NSAIDs and the use of antiulcer drugs. Continued use of NSAIDs, for example, with rheumatoid arthritis, is possible only against the background of concurrent administration of misoprostol and regular endoscopic monitoring..

Algorithm for the prevention and treatment of NSAIDs-gastroduodenopathy.

The kidneys.

Nephrotoxicity is the second most important group of adverse reactions of NSAIDs. Two main mechanisms of the negative effect of NSAIDs on the kidneys were identified.

I. By blocking the synthesis of PG-E2 and prostacyclin in the kidneys, NSAIDs cause vasoconstriction and impaired renal blood flow. This leads to the development of ischemic changes in the kidneys, a decrease in glomerular filtration and the volume of urine output. As a result, violations of water-electrolyte metabolism can occur: water retention, edema, hypernatremia, hyperkalemia, an increase in serum creatinine, an increase in blood pressure.

Indomethacin and phenylbutazone have the most pronounced effect on renal blood flow.

II. NSAIDs can have a direct effect on the kidney parenchyma, causing interstitial nephritis (the so-called "analgesic nephropathy"). The most dangerous in this regard is phenacetin. paracetamol. Serious kidney damage is possible, up to the development of severe renal failure. The development of acute renal failure using NSAIDs as a result of acute allergic interstitial nephritis is described.

Risk factors for nephrotoxicity are over 65 years of age, liver cirrhosis, previous renal pathology, decreased blood volume, gout, atherosclerosis, prolonged use of NSAIDs, concomitant use of diuretics, congestive heart failure, arterial hypertension.

The greatest nephrotoxicity among NSAIDs is paracetamol, indo-metacin, phenylbutazone, ibuprofen, phenoprofen, and piroxicam. These drugs are not recommended for patients with impaired renal function: chronic renal failure, nephrotic syndrome, etc. In these cases, the use of drugs with moderate nephrotoxicity, for example, sulindac, meloxicam, nimesulide, may be recommended.

Hepatotoxicity. Changes in the activity of transaminases and other enzymes may be noted. In severe cases - jaundice, hepatitis.

Risk factors for hepatotoxicity of NSAIDs include old age, impaired renal function, alcohol consumption, and other hepatotoxic drugs.

Hepatotoxic effect is most often observed with diclofenac, nimesulide, phenylbutazone, sulindac, paracetamol, indomethacin, which limits the use of these drugs in patients with a history of liver disease. For these patients, the use of coxib, meloxicam, and ketoprofen is rational.

Hematotoxicity: manifested by aplastic anemia, thrombocytopenia, agranulocytosis, methemoglobinemia (paracetamol). Paracetamol, indomethacin, acetylsalicylic acid, metamizole sodium, phenoprofen have the most pronounced inhibitory effect on the hematopoietic system.

Coagulopathies: manifested in the form of gastrointestinal bleeding (most NSAIDs inhibit platelet aggregation and have a moderate anticoagulant effect due to inhibition of prothrombin formation in the liver).

Allergic hypersensitivity reactions: rash, urticaria, erythema, Quincke's edema, anaphylactic shock, Lyell and Stevens-Johnson syndromes, allergic interstitial nephritis, which most often occur with the use of acetylsalicylic acid, indomethacin, phenylbutazone, clofeson. Patients with a clinical triad, including vasomotor rhinitis, nasal polyposis and bronchial asthma, are at high risk of developing hypersensitivity reactions to NSAIDs;

Bronchospasm: As a rule, it develops in patients with bronchial asthma and, more often, when taking aspirin - “aspirin” asthma (or Widal syndrome) develops most often when taking acetylsalicylic acid and its derivatives. The reasons for bronchospasm may be the predominant formation of leukotrienes and thromboxane A2 from arachidonic acid, as well as inhibition of the synthesis of PG-E2-endogenous bronchodilators, which is an endogenous bronchodilator.

Salicylates cause ototoxicity.

Prolongation of pregnancy and delay in childbirth. This effect is due to the fact that prostaglandins (PG-E2 and PG-F2a) stimulate the myometrium (mainly non-selective NSAIDs due to the effect on COX-1).

Teratogenicity, in particular, premature closure of the ductus arteriosus in the fetus. All NSAIDs are not recommended to be taken during pregnancy, indomethacin, salicylates, aminofenazone have the greatest teratogenic effects.

Retinopathies and keratopathies - as a result of deposition of indomethacin in the net chat and cornea.

Mutagenicity and carcinogenicity are possible. NSAIDs cross the placenta and can cause the development of congenital abnormalities in the fetus. If indicated, it is recommended to use derivatives of propionic (ibuprofen, flurbiprofen) or phenylacetic (diclofenac) acid, which have a short half-life and form inert metabolites.

The hypertensive effect of NSAIDs is due to several mechanisms: a decrease in sodium urease due to suppression of filtration and increased proximal tubular reabsorption of sodium ions; increased renal resistance due to inhibition of GHG synthesis, providing renal blood flow; increased release of norepinephrine from nerve endings; decreased glomerular filtration and renal blood flow, activation of the renin-angiotensin system, damage to the renal parenchyma ("analgesic nephropathy"); increased secretion of endothelin; mineralocorticoid activity of a number of NSAIDs (for example, phenylbutazone).

The development of cardiovascular diseases and disorders of hemostasis - care must be taken when prescribing specific COX-2 inhibitors (especially rofecoxib), since in recent years this group of NSAIDs has been shown to be capable of causing cardiovascular and cerebrovascular complications. This is due to inhibition of prostacyclin synthesis in the vascular endothelium. In this case, thromboxane production does not decrease, and an imbalance arises in the thromboxane-prostacyclin system (in favor of thromboxane). Adverse reactions caused by the use of COX-2 inhibitors include arterial hypertension, myocardial infarction, angina pectoris, cardiac arrhythmias, thromboembolic events, congestive heart failure, cerebrovascular bleeding, and others. It is considered advisable to abandon the use of specific COX-2 inhibitors in patients prone to thrombosis, who have a history of myocardial infarction, cerebrovascular accident.

Risk factors for the hypertensive effect of NSAIDs are old age, congestive heart failure, renovascular hypertension, and cirrhosis. Do not use piroxicam, phenylbutazone, indomethacin, rofecoxib in such patients; the use of ketoprofen, ibuprofen, meloxicam is recommended.

Neurological and mental -

indomethacin, phenylbutazone can cause headaches, dizziness, attention disorders, hand tremors, depression and even psychosis, so they are not recommended for people whose profession requires increased attention and quick reactions. With the use of ibuprofen, sulindac, especially in patients with lupus erythematosus, the development of aseptic meningitis is possible. It is noted that prolonged use of NSAIDs can lead to impaired memory.

CONTROL MEASURES FOR LONG USE

Gastrointestinal tract

Patients should be warned about the symptoms of damage to the gastrointestinal tract. Every 1-3 months, a fecal occult blood test should be performed. If possible, periodically conduct fibrogastroduodenoscopy.

Rectal suppositories with NSAIDs are advisable to use in patients undergoing surgery in the upper gastrointestinal tract, and in patients simultaneously receiving several drugs. They should not be used for inflammation of the rectum or anus and after recent anorectal bleeding.

Kidney

It is necessary to monitor the appearance of edema, measure blood pressure, especially in patients with hypertension. Once every 3 weeks, a clinical urine test is performed. Every 1-3 months, it is necessary to determine the level of serum creatinine and calculate its clearance.

Liver

With long-term administration of NSAIDs, it is necessary to timely identify clinical signs of liver damage. Every 1-3 months should monitor the function of the liver, determine the activity of transaminases.

Blood formation

Along with clinical observation, a clinical blood test should be performed once every 2-3 weeks. Particular control is needed when prescribing pyrazolone and pyrazolidine derivatives

RULES FOR PURPOSE AND DOSAGE

Individualization of drug selection

For each patient, the most effective drug with the best tolerance should be selected. Moreover, it can be any NSAID, but as an anti-inflammatory it is necessary to prescribe a drug from group I. The sensitivity of patients to NSAIDs even of one chemical group can vary widely, therefore, the inefficiency of one of the drugs does not yet indicate the inefficiency of the group as a whole.

When using NSAIDs in rheumatology, especially when replacing one drug with another, it must be borne in mind that the development of the anti-inflammatory effect lags behind the analgesic in time. The latter is noted in the first hours, while anti-inflammatory - after 10-14 days of regular intake, and with the appointment of naproxen or oxycams even later - at 2-4 weeks.

Dosage

Any drug new to this patient must be prescribed first in the lowest dose. With good tolerance, after 2-3 days the daily dose is increased. Therapeutic doses of NSAIDs are in a wide range, and in recent years there has been a tendency to increase single and daily doses of drugs that are characterized by the best tolerance (naproxen, ibu-profen), while maintaining restrictions on the maximum doses of aspirin, indomethacin, phenylbutazone, piroxicam. In some patients, the therapeutic effect is achieved only when using very high doses of NSAIDs.

Time of receipt

With prolonged course prescribing (for example, in rheumatology), NSAIDs are taken after meals. But to obtain a quick analgesic or antipyretic effect, it is preferable to prescribe them 30 minutes before or 2 hours after a meal with a 1/2 to 1 glass of water. After taking it for 15 minutes, it is advisable not to go to bed in order to prevent the development of esophagitis.

The time of taking NSAIDs can also be determined by the time of the maximum severity of the symptoms of the disease (pain, stiffness in the joints), that is, taking into account the chronopharmacology of the drugs. At the same time, you can depart from generally accepted schemes (2-3 times a day) and prescribe NSAIDs at any time of the day, which often allows you to achieve a greater therapeutic effect with a lower daily dose.

With severe morning stiffness, it is advisable to take the rapidly absorbed NSAIDs as early as possible (immediately after waking up) or prescribe long-acting drugs at night. Naproxen sodium, diclofenac potassium, water-soluble ("sparkling") aspirin, and ketoprofen have the highest absorption rate in the gastrointestinal tract and, therefore, the faster onset of the effect.

Monotherapy

The simultaneous use of two or more NSAIDs is not advisable for the following reasons:

- the effectiveness of such combinations is not objectively proven;

- in a number of such cases, a decrease in the concentration of drugs in the blood is noted (for example, aspirin reduces the concentration of indomethacin, diclofenac, ibuprofen, naproxen, piroxicam), which leads to a weakening of the effect;

- the risk of developing unwanted reactions increases. An exception is the possibility of using paracetamol in combination with any other NSAIDs to enhance the analgesic effect.

In some patients, two NSAIDs can be prescribed at different times of the day, for example, fast-absorbing in the morning and afternoon, and long-acting in the evening.

DRUG INTERACTIONS

Quite often, patients who receive NSAIDs are prescribed other medications. In this case, it is necessary to take into account the possibility of their interaction with each other. So, NSAIDs can enhance the effect of indirect anticoagulants and oral hypoglycemic agents. At the same time, they weaken the effect of antihypertensive drugs, increase the toxicity of antibiotic aminoglycosides, digoxin and some other drugs, which is of significant clinical importance and entails a number of practical recommendations (Table 5). If possible, the simultaneous administration of NSAIDs and diuretics should be avoided, in view of, on the one hand, the weakening of the diuretic effect and, on the other hand, the risk of developing renal failure. The most dangerous is the combination of indomethacin with triamteren.

Many drugs prescribed simultaneously with NSAIDs, in turn, can affect their pharmacokinetics and pharmacodynamics:

- aluminum-containing antacids (almagel, maalox and others) and cholestyramine weaken the absorption of NSAIDs in the gastrointestinal tract. Therefore, concomitant administration of such antacids may require an increase in the dose of NSAIDs, and intervals of at least 4 hours are necessary between doses of cholestyramine and NSAIDs;

- sodium bicarbonate enhances the absorption of NSAIDs in the gastrointestinal tract;

- the anti-inflammatory effect of NSAIDs is enhanced by glucocorticoids and “slow acting” (basic) anti-inflammatory drugs (gold preparations, aminoquinolines);

- the analgesic effect of NSAIDs is enhanced by narcotic analgesics and sedative drugs.

OVERCEPTURE USE OF NSAIDs

For over-the-counter use for many years, aspirin, paracetamol, metamizole, propiphenazone, and combinations thereof are widely used in world practice. In recent years, ibuprofen, n-proxene, naproxen sodium, and ketoprofen are approved for over-the-counter use.

Indications: to provide an analgesic and antipyretic effect for colds, headache and toothache, muscle and joint pain, back pain, dysmenorrhea.

It is necessary to warn patients that NSAIDs have only a symptomatic effect and have neither antibacterial nor antiviral activity. Therefore, while maintaining fever, pain, worsening general condition, they should consult a doctor.

The relative risk of complications from the gastrointestinal tract when using non-steroidal anti-inflammatory drugs

For an effective analgesic effect, NSAIDs should have high and stable bioavailability, rapid achievement of the maximum concentration in the blood, and a short and stable half-life.

Schematically, NSAIDs can be arranged as follows:

• in decreasing anti-inflammatory effect: indomethacin - diclofenac - pyroxicam - ketoprofen - ibuprofen - ketorolac - lornoxicam - acetylsalicylic acid;

• descending analgesic activity: lornoxicam - ketorolac - diclofenac - indomethacin - ibuprofen - acetylsalicylic acid - ketoprofen;

• by the risk of cumulation and undesirable drug interactions: pyroxy-cam - meloxicam - ketorolac - ibuprofen - diclofenac - lornoxicam.

The antipyretic effect of NSAIDs is well expressed in drugs with both high and low anti-inflammatory activity. Their choice depends on individual tolerance, possible interactions with the drugs used and the predicted adverse reactions.

Meanwhile, in children, as an antipyretic agent, paracetamol (acetaminophen *), not related to NSAIDs, is the drug of choice. Ibuprofen can be used as a second-line antipyretic for intolerance or inefficiency of paracetamol. Acetylsalicylic acid and metamizole should not be prescribed to children under 12 years of age because of the risk of Reye's syndrome and agranulocytosis, respectively.

In patients at high risk of bleeding or perforation due to ulcers induced by NSAIDs, consideration should be given to co-administration of NSAIDs and proton pump inhibitors or the synthetic analogue of prostaglandin misoprostal *. H2 histamine receptor antagonists have been shown to prevent only duodenal ulcers, and therefore are not recommended for prophylactic purposes. An alternative to this approach is the administration of selective inhibitors to such patients.

COX-2.

Evaluation of the effectiveness of non-steroidal anti-inflammatory drugs

The criteria for the effectiveness of NSAIDs are determined by the disease in which these drugs are used.

Monitoring the analgesic activity of NSAIDs. Despite the objectivity of its existence, pain is always subjective. Therefore, if the patient, presenting complaints about pain, makes no attempts (explicit or hidden) to get rid of it, it is worth doubting its presence. On the contrary, if the patient suffers from pain, he always demonstrates this either to others, or to himself, or seeks to see a doctor

There are several ways to assess the intensity of the pain syndrome and the effectiveness of the therapy.

The most common methods are using a visual analogue scale and a pain relief scale.

When using the visual-analogue scale, the patient notes the severity of pain on a 100-mm scale, where “0” is the absence of pain, “100” is the maximum pain. When monitoring acute pain, the level of pain is determined before administration of the drug and 20 minutes after administration. When monitoring chronic pain, the time interval for the study of pain intensity is set individually (in accordance with visits to the doctor, it is possible to keep a diary by the patient).

To assess the effectiveness of the anesthesia used, a pain relief scale is used. 20 minutes after administration of the drug, the patient is asked the question: "Have you decreased the intensity of pain after administration of the drug compared with pain before administration of the drug?" Possible answer options are rated in points: 0 - the pain has not decreased at all, 1 - has slightly

decreased, 2 - has decreased, 3 - has greatly decreased, 4 - has completely disappeared. It is also important to evaluate the time of onset of a distinct analgesic effect.

The duration of morning stiffness is determined in hours from the moment of awakening.

The articular index is the total severity of pain that occurs in response to pressure that is standard in strength on the joint under study in the joint space. Soreness in joints that are difficult to palpate is determined by the volume of active and passive movements (hip, spine) or compression (joints of the foot). Soreness is evaluated by a four-point system:

• 0 - no pain;

• 1 - the patient speaks of pain in the place of pressure;

• 2 - the patient speaks of pain and frowns;

• 3 - the patient tries to stop the effect on the joint. The articular score is determined by the number of joints in which

pain on palpation.

The functional index of LI is determined using a questionnaire, which consists of 17 questions explaining the possibility of

niya a number of elementary everyday activities involving various groups of joints.

Also, to evaluate the effectiveness of NSAIDs, the swelling index is used - the total numerical expression of the swelling, which is assessed visually by the following gradation:

• 0 - absent;

• 1 - doubtful or weakly expressed;

• 2 - explicit;

• 3 - strong.

Evaluation of the swelling is carried out for the elbow, wrist, metacarpophalangeal, proximal interphalangeal joints of the hands, knee and ankle joints. The circumference of the proximal interphalangeal joints is calculated in total for the left and right hands. The compression force of the brush is evaluated either using a special device, or by compressing the cuff of the tonometer, filled with air to a pressure of 50 mm Hg. The patient holds his hand in three squeezes. Take into account the average value. In case of damage to the joints of the legs, a test is used that assesses the travel time of a leg. A functional test that measures the range of motion in the joints is called Keitel's test.

CONTRAINDICATIONS

NSAIDs are contraindicated in case of erosive and ulcerative lesions of the gastrointestinal tract, especially in the acute stage, severe impaired liver and kidney function, cytopenia, individual intolerance, and pregnancy. If necessary, the safest (but not before childbirth!) Are small doses of aspirin.

Indomethacin and phenylbutazone should not be prescribed on an outpatient basis for persons whose occupations require increased attention.

WARNINGS

NSAIDs should be used with caution in patients with bronchial asthma, as well as in individuals who have previously identified adverse reactions when taking any other NSAIDs. For patients with hypertension or heart failure, those NSAIDs that have the least effect on renal blood flow should be chosen. In elderly people, it is necessary to strive for the appointment of minimum effective doses and short courses of NSAIDs.

INFLUENCE OF NPSA ON THE EFFECT OF OTHER DRUGS.

Pharmacokinetic interaction

Indirect anticoagulants + All NSAIDs, especially aspirin → Displacement due to plasma proteins, increased anticoagulant effect → Avoid NSAIDs, if possible, or carry out strict monitoring.

Oral hypoglycemic drugs (sulfonylurea derivatives) + Phenylbutazone, Oxyphenbutazone → Inhibition of liver metabolism, increased hypoglycemic effect. Avoid NSAIDs, if possible, or strictly monitor blood glucose.

Oral hypoglycemic drugs + All NSAIDs, especially aspirin → Displacement from communication by plasma proteins, increased hypoglycemic effect.

Digoxin + All NSAIDs → Inhibition of renal excretion of digoxin in case of impaired renal function (especially in young children and the elderly), increase its concentration in the blood, increase toxicity. With normal kidney function, interaction is less likely. Avoid NSAIDs, if possible, or strictly control creatinine clearance and blood digoxin concentration.

Antibiotics, aminoglycosides + All NSAIDs → Inhibition of renal excretion of aminoglycosides, increasing their concentration in the blood. Strict control of the concentration of aminoglycosides in the blood.

Methotrexate (high “non-rheumatological” doses) + All NSAIDs → Inhibition of renal excretion of methotrexate, increase in its concentration in blood and toxicity (interaction with a “rheumatological” dose of methotrexate is not observed) Concomitant use is contraindicated. It is acceptable to use NSAIDs during chemotherapy intervals.

Lithium preparations + All NSAIDs (to a lesser extent, aspirin, sulindac) → Inhibition of renal excretion of lithium, increase in its concentration in blood and toxicity Use aspirin or sulindac if NSAIDs are necessary. Strict control of lithium concentration in the blood.

Lithium preparations + Phenytoin, Phenylbutazone, Oxyphenbutazone → Inhibition of metabolism, increased blood concentration and toxicity. Avoid these NSAIDs, if possible, or strictly control the concentration of phenytoin in the blood.

Pharmacodynamic interaction

Antihypertensive drugs - Beta-blockers, Diuretics, ACE inhibitors + All NSAIDs - To the greatest extent - indomethacin, phenylbutazone. The smallest is sulindac → Weakening of the hypotensive effect due to inhibition of GHG synthesis in the kidneys (sodium and water retention) and blood vessels (vasoconstriction). Use sulindac and, if possible, avoid other NSAIDs for hypertension. Strict blood pressure control. Strengthening of antihypertensive therapy may be required.

Diuretics + All NSAIDs - To the greatest extent - indomethacin, phenylbutazone. In the smallest - sulindac → Weakening of the diuretic and natriuretic effects, worsening of condition with heart failure. Avoid NSAIDs (except sulindac) for heart failure, strictly monitor the patient's condition.

Indirect anticoagulants + All NSAIDs → Increased risk of gastrointestinal bleeding due to mucosal damage and inhibition of platelet aggregation.

High Risk Combinations!

Diuretics + All NSAIDs (to a lesser extent - sulindac) → An increased risk of developing renal failure - the combination is contraindicated.

Triamteren + Indomethacin → High risk of developing acute renal failure - the combination is contraindicated.

All potassium-sparing diuretics + All NSAIDs → High risk of developing hyperkalemia - avoid such combinations or strictly control the level of potassium in the plasma.

SYSTEMIC SIDE EFFECTS OF Glucocorticosteroids:

From the side of the central nervous system:

• Increased nervous irritability.

• Insomnia.

• Euphoria.

• Depression.

• Psychoses.

From the cardiovascular system:

• Myocardial dystrophy.

• Increased blood pressure.

• Deep vein thrombosis.

• Thromboembolism.

From the digestive system:

• Steroid ulcers of the stomach and intestines.

• Bleeding from the digestive tract.

• Pancreatitis.

• Fatty degeneration of the liver.

From the senses:

• Posterior subcapsular cataract.

• Glaucoma.

From the endocrine system:

• Inhibition of function and atrophy of the adrenal cortex.

• Diabetes.

• Obesity.

• Cushing's syndrome.

On the part of the skin:

• Thinning of the skin.

• Striae.

• Alopecia.

From the musculoskeletal system:

• Osteoporosis.

• Fractures and aseptic necrosis of bones.

• Growth retardation in children.

• Myopathy.

• Muscle hypotrophy.

From the reproductive system:

• Menstrual irregularities.

• Violations of sexual functions.

• Delayed sexual development.

• Hirsutism.

On the part of laboratory indicators:

• Hypokalemia.

• Hyperglycemia.

• Hyperlipidemia.

• Hypercholesterolemia.

• Neutrophilic leukocytosis.

Other:

• Retention of sodium and water.

• Edema.

• Exacerbations of chronic infectious and inflammatory processes.

LOCAL SIDE EFFECTS.

Inhaled glucocorticosteroids:

• Candidiasis of the oral cavity and pharynx.

• Dysphonia.

• Cough.

Intranasal glucocorticosteroids:

• Itching in the nose.

• Sneezing.

• Dryness and burning of the nasal mucosa and pharynx.

• Epistaxis.

• Perforation of the nasal septum.

Suppression of the hypothalamic-pituitary-adrenal axis (HPA)

HPA suppression is one of the more dangerous effects of steroids. The ability to respond to global physiological stress (for example, during surgery or trauma) can be weakened, putting the patient at risk of hypotension and hypoglycemia. Symptoms include behavioral disorders, nausea, postural hypotension, and hypoglycemia. The risk of occurrence depends on the dosage, duration and treatment regimen, although other factors are also possible. There are significant individual differences in the effects of steroid therapy. Some patients had HPA suppression with 15 milligrams of prednisone taken daily for several weeks, while others did not show any signs of HPA suppression despite using higher daily doses for longer periods. Thus, it is difficult to predict the risk of HPA suppression in a particular patient based solely on dosage and duration of therapy. Dose planning affects the degree of HPA suppression. Physiological doses of glucocorticosteroids (5-7.5 milligrams of prednisone) taken in the morning do not cause HPA suppression, but if the same dosages are given at night, normal daily secretion of cortisol is suppressed. Doses above the physiological level begin to exert an inhibitory effect after about a month. With therapy every other day (a two-day dose is taken at 8 a.m. every other day), there is no clinically significant suppression of HPA. Also, cyclic 5-day day therapy programs lasting from 2 to 4 weeks do not lead to suppression. However, a cycle of 2-week therapy and a 2-week discontinuation of therapy lead to suppression of HPA. A daily pharmacological dose of glucocorticosteroids taken in the morning produces less HPA suppression than the same dose divided and taken during the day.

HPA recovery can occur within 12 months. The hypothalamic-pituitary function returns first 2-5 months after discontinuation of therapy, and is manifested by the appearance in plasma of normal levels of adrenocorticotropic hormone (ACTH). Signs of adrenal recovery will begin to appear after 6–9 months, with normal levels of cortisol returning. The maximum adrenal response to ACTH cannot appear earlier than 9-12 months after discontinuation of therapy. There is no proven method to accelerate recovery of normal HPA function.

An increase in ACTH levels does not seem to accelerate adrenal recovery. It is very difficult to assess how long the clinically important absence of an adrenal response will last. Due to the significant individual characteristics of the patients, it was not possible to establish a reliable correspondence between the degree of HPA suppression and the concentration of cortisol in the blood. To address this uncertainty, HPA axis testing is becoming an important decision maker.

Of the various tests (insulin-induced hypoglycemia, etc.), the most widely used test is ACTH, so its results correlate well with cortisol levels measured during stress after surgery. The concentration of cortisol is determined, and then one ampoule (250 mug) of synthetic ACTH (cosintropin) is injected. Cortisol concentration is measured in blood samples taken after 30 and 60 minutes. Despite the fact that this test gives a certain percentage of false-positive results, many people think that it is much more convenient and safer compared to insulin-induced hypoglycemia - a test that is considered the `` gold standard " for the HPA test.

It is believed that a test using corticotropin-releasing hormone (CRH) combines the sensitivity of an insulin-induced hypoglycemia test with the convenience of an ACTH test. Although it is important to detect HPA suppression in time, this is not the only factor determining the ability of patients undergoing corticosteroid therapy to adequately respond to stress. Some patients have a hypotensive response despite the absence of HPA axis suppression, and patients with suppressed HPA may not have any clinical signs of adrenal insufficiency.

Precautionary measures

In patients with hypothyroidism, cirrhosis, hypoalbuminemia, as well as in elderly patients, the effect of glucocorticosteroids may be enhanced.

When prescribing glucocorticosteroids during pregnancy, the expected therapeutic effect for the mother and the risk of negative effects on the fetus should be taken into account, since the use of these drugs can lead to impaired fetal growth, some developmental defects (cleft palate), atrophy of the adrenal cortex of the fetus (in the third trimester) pregnancy).

In children and adults taking glucocorticosteroids, infectious diseases such as measles and chickenpox can be difficult.

Patients taking immunosuppressive doses of glucocorticosteroids are contraindicated in the administration of live vaccines.

Osteoporosis develops in 30-50% of patients who take systemic glucocorticosteroids for a long time (oral or injectable dosage forms). As a rule, the spine, pelvic bones, ribs, hands, feet are affected.

Steroid ulcers during treatment with glucocorticosteroids may be asymptomatic or asymptomatic, manifesting bleeding and perforation. Therefore, patients receiving oral glucocorticosteroids for a long time should undergo fibroesophagogastroduodenoscopy and occult blood feces periodically.

In various inflammatory or autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, and intestinal diseases), cases of steroid resistance may occur.

Interaction

With the simultaneous use of glucocorticosteroids with other drugs, the following effects may be noted:

• With antacids - reduced absorption of glucocorticosteroids.

• With barbiturates, hexamidine, diphenin, carbamazepine, diphenhydramine and rifampicin - accelerated biotransformation of glucocorticosteroids in the liver.

• With isoniazid and erythromycin - slowing down the biotransformation of glucocorticosteroids in the liver.

• With salicylates, butadione, barbiturates, digitoxin, penicillin and chloramphenicol - increased elimination of these drugs.

• With isoniazid - mental disorders.

• With reserpine, depressive states.

• With tricyclic antidepressants - increased intraocular pressure.

• With adrenomimetics - increased action of these drugs.

• With theophylline - the development of cardiotoxic effects and increased anti-inflammatory action of glucocorticosteroids.

• With diuretics, amphotericin, mineralocorticoids - increased risk of hypokalemia.

• With indirect anticoagulants, fibrinolytics, butadione, ibuprofen and ethacrylic acid - hemorrhagic complications.

• With indomethacin and salicylates - ulcerative lesions of the digestive tract.

• With paracetamol - increased toxicity of this drug.

• With azathioprine - an increased risk of myopathies, cataracts.

• With mercaptopurine, an increase in the concentration of uric acid in the blood is possible.

• With hingamine - it is possible to increase the undesirable effects of this drug (dermatitis, myopathy, clouding of the cornea).

• With methandrostenolone - increased therapeutic and undesirable effects of glucocorticosteroids.

• With androgens and iron preparations - increased erythropoiesis due to increased synthesis of erythropoietin.

• With sugar-lowering drugs - reducing the effectiveness of these drugs.

Long-acting inhaled glucocorticosteroids and β 2 -adrenomimetics have a complementary effect and synergism. Theophylline may enhance the anti-inflammatory activity of inhaled glucocorticosteroids.

Principles of therapy

When using glucocorticosteroids, it is necessary to obtain the maximum therapeutic benefit with a minimum of adverse effects. In most cases, steroids do not cure the disease; rather, they suppress or alter the inflammatory and immune response and reduce the symptoms of the disease. Therefore, the expected therapeutic benefits and potential risks need to be carefully weighed. The risk is negligible with a short course of therapy (7-14 days), even with the use of high doses, which can be very effective in some situations (for example, with acute asthma). Increased appetite and euphoria are the main side effects with short courses. There are no long-term consequences. The decision to start a longer course of steroid therapy requires taking into account the risks described above.

The choice of drug. Corticosteroids differ mainly in duration and degree of action. Fast acting agents are less likely to suppress the HPA axis, especially when a low-dose morning dose is used as part of a regimen every other day. Slow-acting agents are preferred for situations where large

doses should be used. Mineralocorticoid activity of the drug is desirable for adrenal insufficiency, but not for significant inflammatory processes or immunoreactivity. Regardless of the drug chosen, non-steroid therapy should be continued if this is primarily for replacement therapy for adrenal cortical insufficiency.

Theoretically, the use of ACTH would seem attractive because it would help to avoid HPA suppression, but ACTH also stimulates an undesirable mineralocorticoid and androgen response. In addition, it is not known which glucocorticoid response will be obtained from the administered dose. These inconveniences limit the use of ACTH.

Choice of scheme: daily or every other day

In the treatment of most diseases that require corticosteroid therapy (asthma, sarcoidosis and others), a scheme every other day is successfully applied, although often at the beginning of therapy should be daily. Important advantages of the regimen every other day are the prevention of significant suppression of the HPA axis and the minimization of the risk of Cushingoid without a significant loss of anti-inflammatory activity. The risk of most of the side effects described above is reduced or completely eliminated by applying the scheme every other day.

A day-by-day regimen alone cannot prevent HPA axis suppression if, for example, dexamethasone is used for therapy. In addition, the treatment regimen should be strictly observed. Failure to adhere to the schedule or dose variations of the first day does not prevent the suppression of HPA.

Daily corticosteroid therapy is used for exacerbations of the disease and for the treatment of certain diseases that can be affected only by the daily regimen (for example, temporal arteritis, pemphigus vulgaris). In the event that a daily regimen is unavoidable, HPA suppression can be minimized if the full daily dose is taken at a time in the morning, at the lowest possible dose. A single dose regimen is almost as effective as a single dose regimen. However, unlike the scheme every other day, the risk of developing Cushing's syndrome is greater.

Switching from daily to every other day

Most patients who have positive dynamics with daily therapy are candidates for switching to the regimen every other day (exceptions, see above). This allows you to switch to a less painful scheme without losing control of the disease. Unlike dosage reduction, the total dose taken does not change. The transition is performed by a gradual increase in the dose of the first day and a decrease in the dose on the second day, until a double dose is taken every other day, without additional drugs on an intermediate day. The rate of transition depends on the activity of the underlying disease, the duration of therapy, the degree of HPA suppression, and the clinical status of the patient. An approximate transition scheme consists in increasing the dose of the first day and decreasing the dose of the second day in increments of 10 milligrams of prednisone (or its equivalent) when the daily dosage was more than 40 milligrams, and in increments of 5 milligrams when the daily dosage was from 20 to 40 milligrams. At a dosage below 20 milligrams, the step should be 2.5 milligrams. The interval between the changes ranges from 1 day to several weeks and is determined empirically based on the clinical response of the patient. It is important to keep in mind that most patients taking corticosteroids daily for more than 2-4 weeks have HPA suppression.

Dosage reduction and discontinuation of therapy

Abrupt cessation of corticosteroid therapy lasting more than one month with a dosage of more than 20-30 milligrams of prednisone per day can lead to a sudden exacerbation of the underlying disease or lead to withdrawal syndrome. There are no proven ways to accelerate HPA recovery.

It is necessary to control the manifestations of the disease and reduce the dosage experimentally, observing a sudden exacerbation of the disease or signs of adrenal insufficiency (postural hypotension, weakness, and gastrointestinal distress).

An empirical approach to reducing dosage to physiological levels is to make changes in increments of 10 milligrams of prednisone or its equivalent every 1-3 weeks if the initial dosage is more than 40 milligrams per day. If the dosage was less than 40 milligrams, the step is 5 milligrams. Once the physiological dose of prednisone (5-7.5 mg) has been reached, the patient can be switched to 1 mg prednisone tablets or an equivalent dose of hydrocortisone, so that further dosage reductions can be made in smaller increments. Further weekly or two-week reductions can then be made in increments of 1 milligram.

During the dosage reduction process, some patients develop withdrawal symptoms characterized by depression, myalgia, arthralgia, anorexia, headaches, and nausea. Studies have failed to determine the relationship between these symptoms and levels of cortisol or 17-hydroxycorticosteroid. In most cases, complaints occurred when levels were normal. The HPA response was also normal in many of these patients. The mechanisms responsible for this syndrome are unknown, but they seem to be related to the rate at which dosage is reduced.

Steroid therapy-induced adrenal insufficiency identification

When waiting for stress (including during surgical interventions), it is important to know the state of the HPA axis and whether additional steroid therapy will be needed. As noted earlier, it is very difficult to predict the onset and duration of HPA suppression, which makes testing the HPA axis useful in deciding whether a patient will need additional steroid therapy. In this case, the cosintropin test (synthetic ACTH) is a convenient, safe and effective way to test the HPA axis. If the concentration of cortisol after 60 minutes is more than 18 mug / dL or there is an increase from the initial level of at least 10 mug / dL, then the adrenal response is sufficient so that the patient can withstand stress equivalent to general anesthesia. The test can be performed using 100 mug CRH intravenously. If the patient does not have an adequate adrenal response, additional corticosteroid therapy should be performed to overcome acute stress. Hydrocortisone is commonly used. Depending on the severity of the stress, 100-400 milligrams of hydrocortisone per day is used in several doses. The lower limit of the dose range (100 milligrams) corresponds to stress in case of a gastrointestinal upset, flu, or tooth extraction. In case of severe stress (trauma or surgery), the patient should be given 100 milligrams of hydrocortisone parenterally every 6-8 hours. A pre-prepared syringe containing 4 milligrams of dexamethasone should be used for parenteral use in emergency situations, if emergency medical care is not available, the patient is unconscious or cannot take steroids orally.

Patient education

Steroids should be used with caution in patients whose mental state or intelligence may be affected due to the risk of suppressing HPA. Patients taking the corticosteroid regimen every other day should receive instructions regarding the importance of adhering to the regimen and taking the drug before 8 a.m. to minimize the risk of HPA suppression. Patients should be informed about the need to increase the dosage if there is stress or illness during the entire course of corticosteroid therapy. Patients should understand the need to contact a doctor and increase the dosage of the drug if they are subjected to physical or psychological stress.

Many patients fear the termination of steroid therapy or refuse to reduce the dose of steroids due to fear of relapse of the underlying disease. A detailed review of the side effects of long-term therapy is necessary to explain the need for dosage reduction and the desirability of ultimately discontinuing corticosteroids. In cases where daily therapy with high dosages is required,

adverse mental effects (including with Cushing's syndrome) can be reduced by notifying the patient of the likelihood of their occurrence and their reversibility.

CORRECTORS OF BONE AND CARTILAGE TISSUE METABOLISM

General information

Metabolic bone diseases reduce the strength and weight of the skeleton, predispose to fractures. Bone growth, the content of mineral and osteoid (organic) components in them are regulated by thyroid and parathyroid hormones, glucocorticoids, sex hormones and vitamin D.

Osteoporosis (a progressive decrease in bone density) develops in women in the menopause, and is also observed in patients receiving corticosteroids or suffering from hypercorticism. For the prevention and treatment of osteoporosis, vitamin D, calcium, and calcitonin are used. Medicines containing fluorine are rarely prescribed for osteoporosis.

In the last decade, diphosphonic acid derivatives - bisphosphonates - have been used as "anti-osteoporotic" ones. These substances accumulate in bone tissue, inhibit the activity of osteoclasts, reduce bone pain, and repair foci of osteolysis. In postmenopausal women, a selective modulator of estrogen receptors raloxifene can be used.

New tools for the treatment and prevention of osteoporosis are: strontium ranelate and ossein-hydroxyapatite complex. All "anti-osteoporotic" drugs are effective only with prolonged use.

Hypoparathyroidism in most cases is a complication of surgical treatment. When it occurs, calcium and vitamin D preparations are prescribed. Dihydrotachysterol, alfacalcidol, calcitriol are also used.

Hypercalcemia is a consequence of hyperparathyroidism, the result of malignant neoplasms with osteolytic metastases in the bone tissue; occurs in blood diseases (myeloma, lymphogranulomatosis); develops with the use of medications (thiazide diuretics) or with prolonged immobilization. Calcitonin is used to treat hypercalcemia. Bisphosphonates are effective for hypercalcemia, which developed against the background of malignant neoplasms.

When cartilage tissue is damaged, chondroprotectors (e.g. glucosamine) are prescribed.

TYPES OF CORRECTORS OF METABOLISM OF BONE AND CARTILAGE TISSUE.

Calcium preparations.

Calcium Additive

Vitrum Calcium.

Ideos.

Calcemin.

Calcium Sandoz.

Calcium gluconate.

Calcium.

Necal D 3.

Osteokea.

Osteomag Vitrum.

Rennie

Vitamin D preparations

Ergocalciferol (Calciferol).

Colecalciferol (Wigantol).

Vitamin D 3 (Terpol).

Dihydrotachysterol (A.T. 10, Tachistin).

Alfacalcidol (Oxidevit, Etalfa).

Calcitriol (Osteotriol, Rockaltrol, Silkis).

Calcitonin (Alostin, Kalko, Miacalcic, Tonocalcin).

Derivatives of diphosphonic acid are bisphosphonates.

Alendronic Acid (Lindron, Ostalon, Ostealen,, Tevanate Fosamax).

Zolendronic acid (Zometa).

Ibandronic Acid (Bonviva, Bondronate).

Clodronic acid (Bonefos).

Pamidronic acid (Aredia, Pomegara).

Risedronic Acid (Actonel).

Tiludronic acid (Skelid).

Ethidronic acid (Xidiphon, Pleostat).

Selective estrogen receptor modulators.

Raloxifene (Evista).

Strontium ranelate (Bivalos).

Fluoride preparations.

Sodium fluoride (Corereron, Ossin).

Other drugs for the prevention and treatment of osteoporosis.

Ipriflavon (Osteokhin).

Ossein-hydroapatite complex (Osteogenon).

Means for correcting the metabolism of cartilage tissue (chondroprotectors).

Glucosamine (Aminoarthrin, Don).

Chondroitin sulfate (Mucosate, Structum).

Chondroitin Sulfate + Glucosamine Sulfate (Arthra Vitrum).

Chondroitin sulfate + Dimethyl sulfoxide (Chondroxide).

Rumalon.

Alflutol.

Analogs of parathyroid hormone.

Teriparatid (Forsteo).

The pathogenesis of osteoporosis.

Bone is one of the special forms of connective tissue consisting of a collagen matrix that is mineralized by inclusions of calcium phosphate crystals.

In the bone, the processes of resorption and the formation of new tissue occur (remodeling). Osteoblasts are responsible for bone formation, and osteoclasts are responsible for resorption. During the growth period of the body, the processes of bone formation prevail over the processes of resorption. In the age period of 30-50 years, the processes of bone formation and resorption are approximately the same intensity. After menopause in women and after 60 years in men, bone resorption begins to prevail over the processes of bone tissue formation.

A decrease in bone density occurs when osteoclasts create an oversized cavity, or when osteoblasts are not able to completely fill the cavity created by osteoclasts of normal sizes, or when a combination of these two factors occurs. In various types of osteoporosis, one of the above factors usually prevails.

So, with postmenopausal osteoporosis, the activity of osteoclasts increases, the activity of osteoblasts remains unchanged. With osteoporosis associated with aging, a decrease in the functional activity of osteoblasts is observed. With osteoporosis caused by prolonged use of glucocorticoids, the function of osteoblasts is inhibited.

The formation of bone tissue is influenced by calcitonin, insulin, sex hormones (androgens and estrogens), growth hormone, thyroid hormone, insulin and others. Osteoblast proliferation is enhanced by numerous growth factors, the most important of which are insulin-like growth factors I and II, as well as the transforming growth factor beta. The activity of osteoclasts is inhibited by the transforming growth factor beta, stimulated by the influence of interleukins 1 and 3, granulocyte-macrophage colony-stimulating factor produced by osteoblasts. Estrogens act directly on bone cells through specific estrogen receptors, inhibit the secretion of interleukin 1 and other cytokines produced by osteoblasts; estrogen deficiency leads to an increase in the level of factors contributing to the formation of osteoclasts and bone resorption.

Mechanism of action.

• Calcium preparations.

Calcium is a mineral element, the amount of which in the human body is almost 2% of the total body weight, significantly exceeding the content of all other minerals. With a person weighing 60-70 kg, the total amount of calcium in his body is 1.0-1.2 kg (about 20 g / kg). Moreover, 99% of the calcium is localized in the teeth and bones.

Approximately 1% of the calcium is in the blood or in the periosteal space (supra-bone). In blood, about 40% of calcium is present in a protein-bound state; 10% - in the form of salts

capable of diffusion (for example, in the form of calcium phosphate); 50% is an ionized form that determines the pharmacological effects of calcium.

One of the most important roles of calcium is to ensure the normal functioning and integrity of the bone skeleton and teeth.

In addition, calcium provides interaction and maintenance of cell membranes, transmission of nerve impulses, regulation of blood coagulation; contributes to the maintenance of a normal tone of skeletal and ocular musculature; participates in the regulation of heart rhythm, in immune processes, in the synthesis and work of enzymes.

The daily need for calcium is 15-20 mmol (400-600 mg). It increases in women during pregnancy (up to 30 mmol or up to 1200 mg) and lactation, and also increases in all people during the recovery period after illness, during stressful situations and when taking certain medications.

Calcium ingested is absorbed mainly in the duodenum (approximately 40%). The consumption of coffee, alcohol, salt, and sugar reduces absorption and enhances the excretion of calcium from the body.

Hormones regulate the amount of calcium in the extracellular fluid by changing the transport of calcium through the membrane that separates the extracellular fluid from the periosteal space. Parathyroid hormone and calcitriol have a stimulating effect on this transport.

It is important to remember that by the age of 40-50, bone destruction processes prevail over the processes of formation.

Bone loss begins early and is more common in women than in men. The result is osteoporosis and the associated risk of fractures of the radius, vertebrae, femoral neck and other bones. At the same time, a decrease in bone mass occurs for a long time without any external manifestations, that is, with osteoporosis, bone tissue is destroyed gradually, therefore, the diagnosis of osteoporosis is made, as a rule, after the occurrence of bone fractures.

Calcium-containing preparations have a positive effect on calcium-phosphorus metabolism, compensate for the deficiency of trace elements, calcium and vitamin D 3, help strengthen bones (reduce resorption and increase bone density), and prevent the occurrence of diseases of the musculoskeletal system.

Vitamin D preparations

Several fat-soluble compounds that are involved in the regulation of mineral metabolism are combined under the name Vitamin D: they enhance the absorption of calcium from the gastrointestinal tract, increase the reabsorption of calcium in the renal tubules, and decrease its excretion in the urine.

These compounds include ergocalciferol (vitamin D 2), which enters the body with food, and cholecalciferol (vitamin D 3), which is formed in the same under the influence of ultraviolet rays

Cholecalciferol and ergocalciferol have the same biological effectiveness, as in the body they turn into more active forms: al-facalcidiol and calcitriol. In addition, vitamin D is called its structural analogue dihydrotachysterol.

Vitamin D preparations are involved in the regulation of calcium and phosphorus metabolism. They enhance the absorption of calcium in the intestines and the reabsorption of phosphorus in the renal tubules, normalize the formation of the bone skeleton and teeth in children, and

contribute to maintaining the structure of bones. They increase the permeability of cell and mitochondrial membranes of the intestinal epithelium, facilitating the transmembrane transport of calcium ions, activate the secondary absorption of phosphates, increase the uptake of these ions by bone tissue, and enhance the process of ossification.

Calcitonin (Alostin, Kalko, Miacalcic, Tonocalcin).

Calcitonin is a hypocalcemic hormone. It is produced by parafollicular cells of the thyroid, thymus, and parathyroid glands of mammals, animals, and humans. By its chemical nature, calcitonin is a polypeptide consisting of 32 amino acid residues with a molecular weight of 3600-4000 daltons.

Currently, 8 types of calcitonin are known, of which salmon, pig and human calcitonin are of medical importance. Synthetic methods for producing calcitonin have been developed.

Calcitonin regulates calcium metabolism and bone metabolism, is an antagonist of parathyroid hormone.

The use of calcitonin in some forms of bone pathology is based mainly on its ability to interfere with the process of bone decalcification. Calcitonin reduces bone resorption due to primary suppression of osteoclast activity and a decrease in their number. These effects can be partially mediated by an increase in the concentration of cAMP in bone cells and a subsequent violation of the transport of calcium and / or phosphate through the plasma membranes of osteoclasts. Due to the suppression of osteolysis, calcitonin causes a decrease in increased serum calcium concentration (hypocalcemic effect).

In healthy adults with relatively low bone resorption, taking exogenous calcitonin leads to a slight decrease in serum calcium. In healthy children and in patients with generalized Paget's disease, bone resorption processes are faster, therefore, the hypocalcemic effect of calcitonin is more pronounced.

Calcitonin has a direct effect on the kidneys, enhances the excretion of calcium, phosphorus and sodium in the urine, inhibiting their reabsorption in the tubules. Short-term use of calcitonin leads to a decrease in gastric secretion and exocrine pancreatic function.

Calcitonin has an analgesic effect, especially for pain of bone origin (as a result of an effect on the central nervous system).

Derivatives of diphosphonic acid are bisphosphonates.

These drugs inhibit bone resorption, inhibit osteoclastic activity, regulate the calcium content in blood and bone tissue, and increase bone mass, especially in the spine.

The inhibitory effect on tumor osteolysis and on hypercalcemia of tumor origin is manifested in a decrease in conc serum calcium concentrations and decreased urinary calcium excretion.

• Selective modulators of estrogen receptors.

The selective estrogen receptor modulator raloxifene acts as an agonist on non-reproductive tissues; as an antagonist - on reproductive. It selectively affects estrogen-sensitive membranes, participates in the regulation of gene expression. Increases the concentration of globulins that bind sex hormones, thyroxine, corticosteroids. It normalizes bone resorption processes in the postmenopausal period, increases bone mass, and reduces calcium loss through the urinary system.

• Fluoride preparations.

Sodium fluoride induces osteogenesis by stimulating osteoblasts. In the process of mineralization, fluorine ions replace hydroxyl ions in apatite crystals with the formation of poorly soluble fluorapatite, which is more resistant to osteoclasts. Fluorinated bone absorption slows down. At the same time, the resorption of non-fluorinated bone tissue increases. In general, bone mass growth and bone compaction are observed.

• Other agents for the prevention and treatment of osteoporosis.

Ipriflavon is a synthetic derivative of natural flavonoids. It improves bone metabolism, reduces its resorption.

Ossein-hydroapatite complex - a regulator of calcium-phosphorus metabolism; used for systemic osteoporosis. This drug has a twofold effect on bone metabolism: a stimulating effect on osteoblasts and an inhibitory effect on osteoclasts. Calcium, which is part of the drug, is contained in the form of hydroxyapatite (in the ratio with phosphorus 2: 1), which contributes to a more complete absorption of calcium from the digestive tract; in addition, it inhibits the production of parathyroid hormone and prevents hormone-mediated resorption of bone tissue.

• Means for the correction of cartilage tissue metabolism (chondroprotectors).

Drugs in this group make up for endogenous glucosamine deficiency by correcting the metabolism of bone and cartilage; have chondroprotective, anti-inflammatory, analgesic, stimulating the regeneration of cartilage, anabolic, anti-catabolic effect.

Glucosamine is a natural component of articular cartilage that is physiologically present in the human body. It is an aminosaccharide with a low molecular weight.

Glucosamine blocks the mechanisms leading to degenerative changes in the joints and stops the progression of the disease.

It stimulates the synthesis of chondrocytes proteoglycans (glucosaminoglycans and hyaluronic acid) of synovial fluid; inhibits enzymes (collagenase, phospholipase A2), causing the destruction of cartilage; prevents the formation of superoxide radicals; inhibits the activity of lysosomal cartilage-destroying enzymes; prevents the damaging effects of corticosteroids on chondrocytes and impaired synthesis of glycosaminoglycans induced by NSAIDs.

Chondroitin sulfate is involved in the construction of the main substance of cartilage and bone tissue; improves phosphorus-calcium metabolism in cartilage, inhibits enzymes that disrupt the structure and function of articular cartilage, inhibits the degeneration of cartilage; stimulates the synthesis of glucosaminoglycans, normalizes the metabolism of hyaline tissue; promotes the regeneration of cartilage surfaces and articular bags.

Rumalon is a glycosaminoglycan-peptide complex; contains an ex tract from cartilage of young animals and bone marrow extract. It affects the metabolism in the cartilaginous hyaline tissue: it enhances the biosynthesis of sulfated mucopolysaccharides, stimulates the regeneration of articular cartilage and inhibits catabolytic processes in the cartilage tissue.

• Analogs of parathyroid hormone.

Teriparatide is an active fragment of endogenous human parathyroid hormone. The physiological effect of parathyroid hormone is to stimulate the formation of bone tissue through a direct effect on osteoblasts. The biological effect of parathyroid hormone is due to binding to specific receptors on the surface of the cells. Teriparatide acts on the same receptors and has the same effect on bone tissue and kidneys as parathyroid hormone. A single daily administration of teriparatide stimulates the formation of new bone tissue on the trabecular and cortical (periosteal

and / or endosteal) surfaces of the bones, with predominant stimulation of the activity of osteoblasts relative to the activity of osteoclasts.

• Pharmacokinetics.

o Calcium preparations.

Absorption of calcium in the digestive tract is about 40%. The parathyroid hormone and vitamin D increase, while fatty acids and oxalates reduce absorption.

o Vitamin D preparations

The onset of action of native preparations of vitamin D (ergocalciferol, kole-calciferol) after oral administration is 10-24 hours, and the maximum effect develops after 4 weeks; duration of action - more than 2 months. Di-hydrotachysterol, alfacalcidol, calcitriol have a faster effect and are less able to cause an overdose.

o Derivatives of diphosphonic acid - bisphosphonates.

The most active are zolendronic, risedronic and ibandronic acids. Alendronic and pamidronic acids are less active. The smallest activity is observed in clodronic and etidronic acids. Bisphosphonates are not metabolized in the body.

Fluoride preparations. Sodium fluoride when absorbed is well absorbed (93-97% fluoride ions), regardless of food intake. Cmax in plasma is reached after 4 hours. At any dose, 50% of the incoming fluoride accumulates in the tissues of the teeth and bones. It is excreted by the kidneys.

Other drugs for the prevention and treatment of osteoporosis.

About 95% of ipriflavone binds to plasma proteins. It is metabolized in the liver with the formation of active metabolites that do not cumulate. The elimination period is 9-10 hours.

Means for correcting the metabolism of cartilage tissue (chondroprotectors).

Pharmacokinetic properties of chondroprotectors.

Drug Absorption Bioavailability Cmax T1 / 2 Excretion

Glucosamine is rapidly and completely absorbed in the small intestine. - - T1 / 2 - 68 h. -

Chondroitin Sulfate After oral administration, it is rapidly absorbed from the gastrointestinal tract. 13% Cmax is reached after 3-4 hours. - It is excreted by the kidneys.

Analogs of parathyroid hormone.

2 hours after the administration of teriparatide, a short-term increase in the concentration of serum calcium is observed, which reaches its maximum value after 4-6 hours and returns to its original level within 16-24 hours.

Place in therapy.

o Calcium preparations.

Calcium preparations for oral administration are prescribed for the prevention of osteoporosis and for the treatment of hyperparathyroidism. Combined medicines containing, in addition to calcium salts, Vitamin D, are advantageous.

They can also be used to prevent pre- and postmenopausal demineralization of bones; be prescribed for conditions accompanied by an increased need for calcium (period of pregnancy and lactation, period of convalescence, period of intensive growth in children; with active sports, in old age for the prevention of osteoporosis).

o Vitamin D preparations

They are used to treat hyperparathyroidism, which in most cases is a complication of surgical treatment.

They are also prescribed for the prevention and treatment of rickets and hypovitaminosis D; with osteomalacia and osteoporosis (ergocalciferol, colecalciferol, alfacalcidol, calcitriol); with renal osteodystrophy (alfacalcidol, calcitriol).

o Derivatives of diphosphonic acid - bisphosphonates.

Indications for the use of these drugs are:

hypercalcemia in case of tumor diseases (alendronic acid, zolendroic acid, ibandronic acid, clodronic acid, pamidronic acid, etidronic acid);

 Paget's disease (alendronic acid, pamidronic acid, tiludronic acid);

 osteoporosis in postmenopausal women (alendronic acid, risedronic acid);

 osteoporosis in men and women with glucocorticosteroids ((alendronic acid, risedronic acid);

 confirmed bone metastases of solid tumors (zolendron acid, clodronic acid, pamidronic acid);

 prevention of the development of bone metastases of primary breast cancer (clodronic acid, pamidronic acid);

 hyperparathyroidism (ethidronic acid);

 nephrourolithiasis (tiludronic acid, ethidronic acid).

o Selective modulators of estrogen receptors.

They are used for osteoporosis in postmenopausal women and after hysterectomy (for prevention).

o Fluoride preparations.

Indication for use is primary osteoporosis (postmenopausal, pre-senile, senile, idiopathic). In addition, these drugs are prescribed for the prevention and treatment of steroid osteoporosis.

o Other agents for the prevention and treatment of osteoporosis.

They are used for the prevention and treatment of osteoporosis of various etiologies, including primary (premenopausal, menopausal, senile) and secondary, caused by rheumatoid arthritis, diseases of the liver and kidneys, hyperthyroidism, hyperparathyroidism, imperfect bone formation, as well as the use of corticosteroids, heparin, immobilization.

Ossein-hydroapatite complex can also be used to correct osteopenia and disturbances in the calcium-phosphorus balance (including during pregnancy and lactation); to accelerate healing of fractures.

o Means for the correction of cartilage tissue metabolism (chondroprotectors).

They are used for degenerative diseases of the joints and spine: primary arthrosis, intervertebral osteochondrosis, osteoarthritis, osteoporosis, periodontopathy, bone fractures (to accelerate the formation of bone marrow).

o Analogs of parathyroid hormone.

Teriparatide is used to treat osteoporosis in women in the postmenopausal period, as well as for the treatment of osteoporosis due to hypogonadism in men.

Contraindications

Corrections of bone and cartilage tissue metabolism are not prescribed for children, adolescents, as well as for women during pregnancy or lactation. Other contraindications for use depend on the individual characteristics of the drugs.

o Calcium preparations.

Contraindications for the appointment are: urolithiasis; hypercalcemia; hypercalciuria; hypersensitivity.

o Vitamin D preparations

Contraindications for the appointment are: hypersensitivity, hypercalcemia.

o Selective modulators of estrogen receptors.

Contraindications for use are: hypersensitivity, thromboembolism, pulmonary embolism and retinal vein thrombosis, deep vein thrombosis, liver failure, prolonged immobilization.

o Fluoride preparations.

Fluorine preparations are not used for hypersensitivity and severe impaired renal or hepatic function.

o Other agents for the prevention and treatment of osteoporosis.

Contraindications for the appointment are: hypersensitivity, hypercalcemia, exacerbation of peptic ulcer of the stomach and duodenum, inhibition of bone marrow hematopoiesis (erythro-, leukopenia, thrombocytopenia), liver and / or renal failure.

o Means for the correction of cartilage tissue metabolism (chondroprotectors).

These drugs are not used for phenylketonuria and hypersensitivity. Chondroitin sulfate is contraindicated in patients with a tendency to bleeding, thrombophlebitis.

o Analogs of parathyroid hormone.

Contraindications for the use of teriparatide are: hypersensitivity, previous hypercalcemia, severe chronic renal failure, metabolic bone disease, with the exception of primary osteoporosis (including hyperparathyroidism and Paget's disease); increased activity of alkaline phosphatase of unknown origin; previous radiation therapy of skeleton bones, a history of bone metastases or bone tumors.

C caution is prescribed for urolithiasis (in the acute stage or recently transferred); mild chronic renal failure; hypovitaminosis D, hypocalcemia (clinically significant); concomitant use of cardiac glycosides.

•Side effects.

o Calcium preparations.

Against the background of administration, epigastric pain, nausea, flatulence, constipation or diarrhea may appear

Exceeding the necessary doses of calcium can lead to hypercalcemia, which manifests itself as malaise, headache, anorexia, nausea, vomiting, muscle weakness, thirst, polyuria, lethargy.

In severe cases, the appearance of psychosis and the development of cardiac arrhythmia is possible.

Prolonged hypercalcemia can cause tissue damage, nephrolithiasis and calcification of the skin, blood vessels of the lungs; in children, hypercalcemia can contribute to stunted growth.

o Vitamin D preparations

Vitamin D preparations can accumulate in adipose tissue and are able to cumulate with the development of hypervitaminosis.

This condition is manifested by loss of appetite, nausea, headache, general weakness, irritability, sleep disturbances, fever, calcification of soft tissues, kidneys, blood vessels, lungs.

An overdose of drugs leads to hypercalcemia.

o Derivatives of diphosphonic acid - bisphosphonates.

Flu-like syndrome (fever, chills, myalgia, ossalgia); decreased renal excretion of calcium; decreased levels of calcium and phosphate in the blood. Rarely, allergic reactions (bronchospasm, angioedema), dyspepsia, impaired renal function, proteinuria.

o Selek(chondroprotectors).

Against the background of the use of chondroprotectors, the following can be observed: severity in the epigastric region, nausea, diarrhea; allergic reactions (itching, urticaria).

o Analogs of parathyroid hormone.

With the use of teriparatide in 10% of cases, pain in the limbs is noted.

In 1-10% of patients, anemia, hypercholesterolemia, depression, headache, dizziness, sciatica, palpitations, shortness of breath, dyspnea, nausea, vomiting, increased sweating, muscle cramps, general weakness, chest pain, asthenia are observed

In rare cases (0.1-1%), tachycardia, decreased blood pressure, emphysema, urinary incontinence, polyuria, painful urge to urinate, eri-theme and irritation at the injection site can be recorded.

The purpose of the lesson.

To be able to choose a pharmacological agent for various systemic (autoimmune, or autoallergic) diseases of the connective tissue. To know the mechanisms of regulation of the metabolism of connective tissue, the forms of its violation. Know the basic principles of selection of connective tissue metabolism correctors.

Test questions.

A. Slow-acting anti-rheumatic drugs.

1 Classification.

I subgroup (main drugs) with non-specific immunomodulatory effects,

 preparations of the 4-aminoquinoline series:

 chingamine (chlorochil, delagil),

 hydroxychloroquine (plaquenil)

 gold preparations (auronofin, krizanol, aurothioglucose, aurothiogomalate, etc.);

 penicillamine (cuprenyl),

II subgroup (reserve preparations) - immunotropic, indirectly stopping inflammatory changes in connective tissue,

 cytostatics (azathioprine - imuran, cyclophosphamide - cyclophosphamide - en-doxan, methotrexate - amethopterin),

 GKS,

 sulfanilamide preparations (sulfasalazine, mesalazine) and the like (diphenyl sulfane).

2. Pharmacokinetics, pharmacodynamics, indications for use, dosage regimen.

3. Undesirable effects of preparations of subgroup I and subgroup II, contraindications.

4. The principles and order of appointment of antirheumatic drugs of slow action.

5. Interaction of preparations of subgroup I and subgroup II.

6. Criteria for evaluating the effectiveness and safety of slow-acting antirheumatic drugs.

7. The choice of drugs for rheumatoid arthritis,

8. The choice of drugs for rheumatism,

9. The choice of drugs for SLE,

10. The choice of drugs for systemic scleroderma,

11. The choice of drugs for dermatomyositis,

12. The choice of drugs for nodular periarteritis,

13. The choice of drugs for ankylosing spondylitis,

14. Change in the pharmacokinetics of drugs of subgroup I and subgroup II in liver disease

B. Regulation of calcium-phosphorus metabolism.

1. The main regulators of mineral bone homeostasis.

• Parathyroid hormone and its biological role.

• Vitamin D - the interaction of vitamin D and parathyroid hormone (PTH).

2. Secondary hormonal regulators of bone mineral homeostasis. Their characteristic.

• Calcitonin - a biological role.

• Glucocorticoids and their importance in the regulation of mineral homeostasis.

• Estrogens, androgens - participation in mineral metabolism.

3. Non-hormonal substances affecting bone mineral tissue homeostasis.

• Bisphosphonates and their meaning.

• Thiazides. Fluorides. Their role in mineral metabolism.

4. Violations of the concentration of calcium and phosphorus in the blood.

 Hypercalcemia. Clinic. Treatment. Saluretics (furrosemide). Bisphosphonates (ethindronate, pamidronate, hydroxyethylidene diphosphonic acid). Calcitonin. Mitramycin. Phosphates Glucocorticoids. Characterization, application, undesirable effects.

 Hypocalcemia. Clinical manifestations. Treatment.

 Osteoporosis, causes and treatment. Calcium. Vitamin D. Estrogen Genes. Etidronate.

 Paget's disease, clinic and treatment. The combined use of calcium-tonin with bisphosphonates.

B. Principles for the treatment of osteoporosis and osteochondrosis.

1. Correction of intraarticular disorders.

 Normalization of biosynthetic processes in chondrocytes.

 Inhibition of catabolic processes in cartilage.

 Normalization of the secretion of synovial fluid.

 Protective action for cartilage damage.

 Inhibition of the inflammatory process.

2. Relief of pain.

3. Oppression of the inflammatory process.

4. Normalization of the tone of the periarticular muscles.

 Improving intraosseous and regional blood flow.

 Stimulation of metabolic processes in the body

G. Strategy for drug therapy of osteoarthritis.

1. Chondromodulating (chondroprotective and chondrostimulating) effects on articular cartilage - rumalon, arteporon, mucartrin, chondroitin sulfate, hyaluronic acid, alflutop, glucosamine. The physiological significance. Characteristic. Application.

2. NSAIDs. Derivatives of anthranilic acid (voltaren, orthophene, etc.), salicylic acid, pyrazolone (butadione, etc.), prpioionic acid (brufen, etc.). Characteristic. Application.

3. Corticosteroids. Hydrocortisone, cortisone, prednisone, triamsinolone, etc.

4. Osteotropic drugs. Osteokhin.

5. Stimulants of metabolic processes. Aloe extract, FIBS, vitreous. ATP.

6. Drugs that improve intraosseous and regional blood flow. Nicotinic acid, no-spa, etc. Characteristic. Application.

7. Drugs that inhibit the activity of lysosomal enzymes. Gordox, contracal, trisalol. Characteristic. Application.

8. Means of systemic enzyme therapy.

9. Drugs that exhibit a normalizing effect on muscle tone. Elenium, myolostane, etc.

10. Antioxidants, vitamins and minerals.

D. Uricosuric preparations. Classification. Mechanisms of action. Indications and contraindications for use.

1) Means that inhibit the synthesis of uric acid:

 inhibitory xanthine oxidase: allopurinol;

 with a different mechanism of action: benzbromarone (desuric).

2) Means that enhance the excretion of uric acid:

 reducing uric acid reabsorption in the renal tubules - benzobromarone, probenicide, sulfinpyrazone (anturan), ugly, cebuzon;

 drugs that shift the pH of the urine towards the alkaline reaction - uralit, soluran, magurlite, blemaren;

 combination preparations: allomaron (allopurinol + benzobromaron).

3) Means that enhance the excretion of nitrogenous toxins in urolithiasis - urolesan, phytolysin, cystenal.

4) Means used to stop acute attacks of gout (colchicine, indomethacin, ibuprofen, prednisone, etc.).

The list of practical works:

1. To study - pharmacokinetics, pharmacodynamics, indications, contraindications, adverse effects of slow-acting anti-inflammatory drugs.

2. The student must be able to:

a) select the necessary drug for a particular patient, select the dose, regimen and route of administration of the drug;

b) identify criteria for evaluating the therapeutic efficacy and safety of the drugs used;

c) provide differential medical assistance with:

 rheumatoid arthritis,

 rheumatism,

 SLE,

 systemic scleroderma,

 dermatomyositis,

 nodular periarteritis,

 ankylosing spondylitis,

 gout

 osteoarthrosis,

 spondylosis.

3. The student must know:

 What is the biological role of calcium and phosphorus.

 What are the mechanisms of regulation of calcium phosphate metabolism

 Basic principles for the treatment of osteoporosis and osteochondrosis.

 Classification, mechanism of action, and use of basic uricosuric drugs.

 Arthrosis: definition of a concept, clinical diagnostic criteria, directions of therapy.

 Gout: definition of the concept, clinical diagnostic criteria, directions of therapy.

 Rheumatism: definition of a concept, clinical diagnostic criteria, directions of therapy.

 Systemic lupus erythematosus: definition of the concept, clinical diagnostic criteria, directions of therapy.

 Rheumatoid arthritis: definition of a concept, clinical diagnostic criteria, directions of therapy.

Control questions of the studied topic.

 List the methods and criteria for determining the safety of NSAID treatment.

 List the main types of hormone therapy with specific clinical examples.

 Explain the mechanism and preventive measures of the ulcerogenic action of HA.

 Explain the mechanisms and measures for the prevention of hormone resistance, tolerance and “withdrawal syndrome”.

 Indicate the basic principles of combining HA with other drugs and the most dangerous combinations in terms of side effects.

 Describe the tactics and dosage regimen of HA in conditions of asthmatic status. In what other conditions is the pulse therapy of HA indicated.

 What are the advantages and disadvantages characteristic of inhaled glucocorticosteroids. What is the tactics of their use against the background of hormone-dependent bronchial asthma.

 Define the concept of “rational hormone therapy” HA. What chrono-pharmacological features must be taken into account in the conditions of long-term administration of HA.

 Formulate the significance of the leading pharmacokinetic characteristics in the rational choice of HA, the tactics and dosage regimen, and the assessment of efficacy and safety.

Control of the intermediate level of knowledge.

The solution of situational tasks:

1.. Patient I., 18 years old, suffering from systemic lupus erythematosus, with damage to the kidneys, myocardium, pleura, joints, was assigned a pathogenetic treatment. A month later, there were pains in the spine, burning, pain in the epigastrium after eating, blood pressure increased, and body weight increased. On examination: moon-shaped face, predominant deposition of fat in the upper half of the body, pasty lower limbs.

What drugs were prescribed to the patient? What kind of clinical syndrome are you thinking about? What are the methods of prevention and correction of the noted complications.

2. Patient G., 62 years old, has been suffering from systemic scleroderma for 5 years with a predominant lesion of the skin, joints, blood vessels, heart (sclerodermic karyosclerosis, CHF II FC). He constantly takes prednisone in a daily dose of 20 mg, nifedipine 40 mg per day, agapurin 0.3 g per day, ointment with nitroglycerin on the hands. Due to an infectious disease, the patient's temperature rose to 39.80 ° C. From the anamnesis it is known that the patient suffers from peptic ulcer of the duodenum.

Along with antimicrobial agents, recommend hypothermic drugs, write recipes. Choose a dose taking into account age and an accompanying pathology.

Patient P., 40 years old, suffering from rheumatism, III Art. activity, for which they were prescribed in the hospital: delagil 0.25 g at night, indomethacin at 0.025 g 4 times a day, bicillin-5 at 1500000 od / m 1 time per month. 2 weeks after the start of therapy, the patient developed pain in the epigastric region of moderate intensity.

Give an assessment of the situation. What is the tactics for further management of the patient (examination and treatment)?

8. Patient V., 66 years old, was admitted to the hospital with a diagnosis of rheumatoid arthritis, II tbsp. activity. An objective examination revealed: swelling and redness of the knee, ankle, wrist, elbow joints. The function of the joints is limited, with palpation pain is noted. The patient has arterial hypertension (blood pressure - 170/100 mm Hg). Regarding the main disease, he took non-steroidal anti-inflammatory drugs, which have recently become ineffective.

Give recommendations for further treatment of this patient. Select drugs, prescribe prescriptions, and select doses of drugs taking into account age and associated pathology.

9. A 54-year-old patient, for 5 years, has suffered from deforming osteoarthrosis of the lower extremities with severe synovitis. He has a history of drug allergies to butadion, heparin, methindole, penicillin, theophylline. In the hospital, the patient was prescribed reopyrin 5 ml IM once a day, hydrocortisone hemisuccinate 100 mg to the cavity of the knee joints, tavegil 0.001 g 2 times a day. After 3 days, the patient developed itchy erythematous rashes on the skin of the trunk.

What is the most likely cause of a worsening condition? Tactics of treatment.

10. A 35-year-old patient diagnosed with rheumatism of the II degree of activity permanently receives delagil 0.25 g per night, indomethacin 0.025 g 4 times a day, bicillin-5 1,500,000 units IM once every 4 weeks. In 2 weeks After the start of therapy, the patient developed periodic pain

in the epigastric region of moderate intensity. What additional research will you assign? Tactics of treatment.

11. The patient, 40 years old, is concerned about pains in the joints of the fingers, wrist, knee joints in the morning, at rest and during exertion, stiffness before lunch, fever. A small elastic nodule is defined below the right knee joint. Blood test: er. - 2.9 • 1012 / l; Hb - 97 g / l; l - 9.9 • 109 / l. Uric acid - 0.38 mmol / L; sialic acids - 0.26 units. The Waaler-Rose reaction - titer 1:64. On the roentgenogram of the brush - osteoporosis.

What is the tactics for treating a patient? What is the base drug? What effect do NSAIDs have on immunity?

12. The patient was additionally prescribed indomethacin 25 mg 3 times a day. After 2 days, the rash on the torso acquired a drainage character and spread to the limbs. A dermatologist called for consultation suspected allergic drug dermatitis. What are your recommendations?

a) change the route of administration of drugs (reopirin - inside, indomentacin - rectally);

b) cancel all drugs, prescribe ointment with diphenhydramine;

c) cancel reopirin, indomentacin, prescribe prednisolone at 20 mg / day. inside.

Q. Why did an allergic reaction occur after 3 days of treatment in a hospital?

a) due to the high sensitivity of the patient to drugs;

b) due to a cross allergic reaction;

c) due to the simultaneous administration of several drugs.

14. A 35-year-old patient diagnosed with rheumatism of the II degree of activity permanently receives delagil 0.25 g per night, indomethacin 0.025 g 4 times a day, bicillin 5 1,500,000 units IM once every 4 weeks. In 2 weeks After the start of therapy, the patient developed periodic pain in the epigastric region of moderate intensity.

A. What additional studies will you assign?

a) general analysis of urine;

b) a general blood test;

c) analysis of feces for occult blood;

g) x-ray examination of the chest;

e) X-ray examination of the stomach and duodenum;

e) esophagogastroduodenofibroscopy;

g) determination of the acidity of gastric juice;

h) ECG.

B. Is there a need for a change in antirheumatic therapy if, as a result of an additional examination, you do not find any additional deviations in the patient's condition? What changes might be needed?

a) changes in treatment are not necessary;

b) it is necessary to immediately cancel delagil;

c) indomethacin must be withdrawn immediately;

g) you should change the route of administration of indomethacin in oral to rectal;

d) it is necessary to cancel indomentacin and appoint voltaren / m;

e) an additional 15 mg / day prednisone should be prescribed;

g) it is necessary to carry out preventive antiulcer treatment;

h) the dose of indomethacin should be halved;

j) a short course in addition to prescribe antacids.

Q. Will anti-rheumatic therapy change if a stomach ulcer is detected? Indicate the correct answers from the previous question.

D. How is it necessary to continue taking indomethacin relative to food intake?

a) in 30 minutes before meals;

b) immediately before a meal;

c) during a meal;

d) immediately after a meal;

d) after 30 minutes after meal.

20. Fill the table:interactionNSAIDs

NSAIDs	**Another drugs**	**Effects**
Acetylsalicylic acid	Indirect anticoagulants Methotrexate Heparin Oral antidiabetic agents Glucocorticoids Vitamin C	
Phenylbutazone	Glucocorticoids Digoxin Insulin Barbiturates Penicillin Indirect anticoagulants	

NSAIDs	Another drugs	Effects
Indomethacin	Furosemide Glucocorticoids Propranolol Thiazide diuretics	

21. Adverse effects of NSAIDs

Drug	Hepatotoxicity	Nephrotoxicity	Blood effect	CNS effect	Skin manifestations	Idiosyncrasy
1.Diclofenac 2. Naproxen 3.Pyroxicam 4. Indomethacin 5. Salicylates 6.Phenylbutazone 7.Ketoprofen 8.Ibuprofen 9. Meloxicam 10 nimesulide						

22. What PV drugs cause osteoporosis: acetylsalicylic acid, butadion, prednisolone, ibuprofen, indomethacin.

23. A patient, 63 years old, with regard to bronchial asthma receives during the year maintenance therapy with prednisone in a dose of 2 tablets. per day. What complication do you expect from the use of HC GK?

24. A patient with pulmonary tuberculosis and concomitant bronchial asthma was prescribed treatment with rifampicin against the background of the long-used prednisolone. After 5 days of treatment, the patient experienced a sharp exacerbation of bronchial asthma, which was stopped only after 2 weeks with the use of large doses of HA HC.

Explain the situation.

25. What side effects from the central nervous system can develop as a result of prolonged therapy or the use of high doses of acetylsalicylic acid?

26. What side effects from hematopoiesis can develop with the use of indomethacin? How do indomethacin affect water-mineral metabolism?

27. Indicate the side effects of salicylates:

1) hearing impairment; 2) allergic reactions; leukopenia; 4) dyspeptic symptoms (nausea, vomiting); 5) ulceration of the gastrointestinal tract; 6) gastric bleeding; 7) swelling; 8) respiratory depression.

28. What are the side effects of pyrozalone derivatives:

1) hearing impairment; 2) allergic reactions; 3) leukopenia; 4) dyspeptic symptoms (nausea, vomiting); 5) gastric bleeding; 6) swelling; 7) respiratory depression.

TESTS

1. The combined use of acetylsalicylic acid with warfarin can lead to gastrointestinal bleeding. What is the mechanism of interaction of NSAIDs with anticoagulants?

A. Displacement of anticoagulants from their association with proteins.

B. Decreased NSAID activity of prothrombin.

C. Inhibition of platelet aggregation.

D. Inhibition of liver oxidative enzymes by some NSAIDs.

E. * All of the above mechanisms.

2. The combined use of NSAIDs and sugar-lowering drugs leads to:

A. Increase blood sugar.

B. * Reduce blood sugar.

C. Reduce low density lipoproteins.

D. An increase in the number of low density lipoproteins.

E. Increased levels of high density lipoproteins.

1. NSAIDs with the least pronounced ulcerogenic effect.

A. Paracetamol.

B. * Meloxicam.

C. Butadion.

D. Indomethacin.

E. Acetylsalicylic acid.

2. NSAIDs, contraindicated in leukopenia.

A. Piroxicam.

B. Miloxicam.

C. * Analgin.

D. Celecoxib.

E. Acetylsalicylic acid.

3. NSAIDs with nephro- and hepatotoxic effects.

A. * Paracetamol.

B. Piroxicam.

C. Meloxicam.

D. Celecoxib.

E. Acetylsalicylic acid.

4. NSAIDs, the undesirable effects of which include bronchospasm.

A. Paracetamol.

B. Piroxicam.

C. Meloxicam.

D. Celecoxib.

E. * Acetylsalicylic acid.

5. A 43-year-old patient with rheumatoid arthritis who has a history of gastric ulcer should be prescribed NSAIDs. Choose the most effective and safest drug.

A. Aspirin.

B. Mefenamic acid.

C. * Movalis.

D. Piroxicam.

E. Brufen.

10. Prevention of the catabolic effect of glucocorticosteroids is carried out by one of the following drugs:

A. * Potassium orotate.

B. Famotidine.

C. Panangin.

D. Potassium chloride.

E. Hypothiazide.

11. It is known that triamsinolone has less pronounced mineralocorticoid properties than prednisolone. What undesirable effects are more pronounced in triamsinolone than in other glucocorticoids?

A. Muscular atrophy.

B. Gastroduodenal ulcers.

C. Vasomotor syndrome

D. Sensation of a rush of blood to the head.

E. * All of the above effects.

12. With prolonged use of glucocorticoids for the prevention of necrosis of the femoral head, it is necessary to prescribe:

A. * Supplemental intake of calcium with food + vitamin D.

B. Potassium preparations.

C. Vitamin D.

D. Protein diet.

E. Salt-free diet.

13. When glucocorticoids are used for 30 days at a total dose of 1000 mg, peptic ulcers may appear in the patient. With an increased risk of ulceration, it is recommended for prophylactic purposes:

A. * H2 blockers - histamine receptors.

B. Potassium orotata.

C. Calcium preparations.

D. Carbohydrate-restricted diets.

E. Salt-free diet.

14. The frequency of undesirable effects when using glucocorticoids is:

A. 10%.

B. 20%.

C. 30%.

D. * 50%.

E. 90%.

15. Side effects on the central nervous system are more pronounced when prescribed:

*BUT. Indomethacin

V. Ibuprofen

S. Diclofenac

D. Piroxicam

E. Meloxicam

16. What side effects from the central nervous system can develop as a result of prolonged therapy or the use of high doses of acetylsalicylic acid?

A. General weakness

B. Increased irritability, sleep disturbance

C. Atrophy of the optic nerve

D. Vestibulocochlear disorders

* E. Memory impairment

17. What side effects from the gastrointestinal tract can develop as a result of long-term therapy or use in high doses of NSAIDs?

A. Dyskinesia of the stomach, 12 duodenum, gall bladder and biliary tract * B. Erosive gastroduodenitis, gastric and duodenal ulcers

C. Cholecystopancreatitis

D. Colitis, intestinal dysbiosis

E. Sphincteritis

18. What side effects from hematopoiesis can develop with the use of indomethacin?

A. Thrombocytopenia

B. Increased blood coagulation

*WITH. Leukopenia, agranulocytosis

D. Stimulation of platelet adhesion and aggregation

E. Anisocytosis, poikilocytosis

19. Nephrotoxicity is more pronounced when prescribed:

A. Naproxen

B. Piroxicam

S. ibuprofen

D. Acetylsalicylic acid

* E. Paracetamol

20. The main side effect of all NSAIDs is:

*BUT. Gastrotoxic

B. Hepatotoxic

C. Nephrotoxic

D. Cardiotoxic

E. Varicose veins

Recommended literature:
Basic:

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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.

13. 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 VITAMINS, DRUGS OF METABOLIC TYPE OF ACTION

Relevance of the topic.

The word "vitamin" entered our vocabulary only at the beginning of the 20th century.It is now known that vitamins take part in the basis of vital metabolic processes in the human body.

For the first time this idea was expressed, not yet knowing about the existence of vitamins, by the Russian doctor N.I. Lunin. In 1880, he discovered that for life support, food, in addition to proteins, fats, carbohydrates and minerals, should contain other components that are indispensable for nutrition, present in small quantities.

N.I. Lunin wrote:

"... if, as the aforementioned experiments teach, it is impossible to provide life with proteins, fats, sugar, salts and water, then it follows that milk contains, in addition to casein, fat, milk sugar and salts, other substances, indispensable for nutrition. It is of great interest to study these substances and to study their importance for nutrition. "

We can say that this is an assumption of N.I. Lunin gave an impetus to the study of a new problem.

In 1912, the term "vitamin" first appeared. It was introduced by the Polish scientist - biochemist Casimir Funk, who worked at the Listerovsky Institute in London. It was Funk who first isolated from rice bran a drug with healing properties that cured pigeons with neuritis (beriberi).

The presence of an amino group in this newly isolated preparation made it possible for Funk to call this entire class of nutrients the "amine of life." Although in the future it turned out that not all vitamins contain an amine group, this name remains.

Vitamins (lat. Vita - life + amines) are organic substances necessary for the life of the body.

Motivational characteristic of the topic.

Vitaminology (vitamin + Greek. Logos - teaching) - a section of biomedical sciences on the structure and mechanisms of action of irreplaceable nutrition factors, united by the general term "vitamins", methods of their use for preventive and therapeutic purposes. Vitaminology is closely associated with biochemistry, physiology, food hygiene and with various branches of clinical medicine, in which vitamin preparations are used as a means of preventing and treating diseases.

Vitamins - low molecular weight organic substances necessary to ensure biochemical and physiological processes in the body, they are components and catalysts of biochemical reactions. They participate in the processes of assimilation and dissimilation of substances, providing biochemical, physiological and morphological homeostasis of the body. Vitamins are part of enzymes in the form of coenzymes and have a diverse effect on biochemical processes by regulating the metabolism of proteins, fats, carbohydrates, and water-salt metabolism. The need for vitamins varies depending on age, work, climate, the nature of nutrition, etc. The harder the work and mental stress, the higher the need for vitamins. In children, the need is higher than in adults, a lack of vitamins often occurs with artificial feeding. Demand increases in polar and tropical climates, when working in hot shops, during pregnancy and lactation, etc. With a lack of vitamins, hypovitaminosis and vitamin deficiency occur. Long-term excessive use of vitamins is often accompanied by the development of hypervitaminosis, which are characterized by signs specific to each vitamin.

Causes of Hypovitaminosis

Depending on the reasons for the development of hypovitaminosis, exogenous, caused by external causes, and endogenous, caused by violations of internal factors of the body, are vitamin deficiency.

Causes of exogenous hypo- and vitamin deficiency

The causes of exogenous hypo- and vitamin deficiency may be a lack of vitamin intake:

• low content of vitamins in food;

• simultaneous unbalanced diet with a predominance of carbohydrates with a low content of animal proteins and fats, in the absence of fresh vegetables and fruits;

• destruction of vitamins in food due to long or improper storage;

• destruction of vitamins in food due to improper cooking;

• food perversions and religious prohibitions imposed on a number of products of some peoples.

Causes of endogenous hypo- and vitamin deficiency

The causes of endogenous hypo- and vitamin deficiency can be as follows:

• violation of the absorption of vitamins in the intestine in acute and chronic diseases of the gastrointestinal tract;

• helminthic infestations;

• violation of the digestibility of vitamins and their loss with urine and feces in acute and chronic diseases;

• prolonged use of laxatives by people prone to constipation;

• in the treatment of drugs that are antagonists of vitamins (streptomycin, chloramphenicol, sulfa drugs, etc.).

Vitamin preparations are medicines containing natural vitamins or their synthetic analogues or their isomers (vitamers).

Vitamin-like compounds are a group of conditionally irreplaceable nutrition factors resembling vitamins in physiological action, but with a deficiency of which vitamin deficiency is not observed. Medicines from such compounds are called vitamin-like drugs.

Coenzyme preparations are drugs that contain synthetic analogues of coenzymes and are used to correct various metabolic processes in the body. Coenzyme preparations are divided into 2 groups:

- vitamin origin
- non-vitamin origin

Anti-vitamins are derivatives of vitamins with substituted functional groups that have the opposite effect to the vitamin and partially or completely turn off vitamins from the body's metabolic reactions.

Classification of vitamin and coenzyme preparations:

1. Preparations of fat-soluble vitamins.

1) Vitamin A preparations (retinol):

- retinol acetate, palmitate; tigazone, roaccutane

2) Vitamin D preparations (calciferol):

- ergocalciferon, oxidvit, videohol, videin

3) Vitamin E (tocopherol) preparations:

- tocopherol acetate

4) Vitamin K preparations (caroquinones):

- Vitamin K1- Vikasol-Konahion

2. Preparations of water-soluble vitamins and their coenzymes

1) Vitamin B1 (thiamine) preparations:

- thiamine bromide (chloride)

Coenzyme preparation:

- cocarboxylase

Thiamine derivatives:

- phosphotiamine
- benfotiamine

2) Vitamin B2 (riboflavin) preparations:

- riboflavin

Coenzyme preparations:

- flavin mononucleotides - flavinate

3) Vitamin B3 preparations (pantothenic acid):

- calcium pantothenate

4) Vitamin B5 preparations (PP niacin):

- a nicotinic acid

Coenzyme preparations:

nicotinamide

5) Vitamin B6 (pyrodoxin) preparations:

- pyridoxine hydrochloride

Coenzyme preparations:

- pyridoxalphosphate

6) Vitamin B9 (Sun) preparations (folic acid):

- folic acid - calcium folinate

7) Vitamin B12 preparations (cyanocobalamin):

- cyancobalamin- oxycobalamin- cobamine

8) Vitamin C (ascorbic acid) preparations:

- vitamin C

3. Coenzyme preparations of non-nutritious origin

- carnitane chloride- lipoic acid- orotate K- ATP-Phosphaden

4. Multivitamin preparations

- undevit- dekamevit- gendevit- macrovit

5. Complex multivitamin preparations with macro- and microelements

- glutamevit-compliment-duovit-unicap T, M

Typical mechanisms of action of vitamin preparations:

1. Most vitamins are converted into coenzymes in the body and are part of enzymes. Thus, they are involved in carbohydrate, fat, protein and other types of metabolism. For example, vitamin B1 (thiamine) in the form of an active form is part of cocarboxinase. Cocarboxinase is a coenzyme: pyruvic acid and ketoglutaric acid dehydrogenases.

Due to this, thiamine preparations are involved in carbohydrate metabolism, in the formation of fatty acids, in the synthesis of a / choline nucleic acids; NAD, NADF.

2. Another typical mechanism of action of vitamin preparations is that vitamins can be donors or acceptors of various chemical groups and thus participate in biochemical reactions.

For example, ascorbic acid is a donor of hydrogen protons and is involved in redox processes in the body.

3. Some vitamins have a hormone-like effect. So the active form of vitamin D, together with the hormone of the parathyroid glands, regulates the exchange of Ca and R.

It is known that vitamins B12, BC, B6, A, E, K, B5 have a predominant effect on protein metabolism;

The predominant effect on carbohydrate - B1, B2, C, B5, A and lipoic acid;

The predominant effect on fatty tissue is B6, B12, PP, B5, choline, carnitine, and lipoic acid.

With insufficient intake of vitamins, the body first consumes reserves, and when they are depleted, subclinical and clinical signs of vitamin deficiency occur. The following stages of vitamin deficiency are distinguished:

• • subclinical - a decrease in the concentration in plasma and urine, tissues and cells, hypofunction of enzymes, functional defects manifested under stress;

• • clinical manifestations - symptoms of dysfunctions and damage to tissues and organs, an expanded clinical syndrome.

• Clinical signs of hypo- and vitamin deficiency, deficiency of various minerals are presented in table.

The following main types of vitamin therapy can be distinguished.

1. Preventive - the appointment of vitamin preparations, if there is a risk of hypovitaminosis. For example, in the winter-spring period. In these cases, the dose of the drug corresponds to the daily needs of the body. I prescribe drugs enterally.

2. Recently, adaptation vitamin therapy has begun to be allocated - this is the appointment of vitamin preparations to facilitate adaptation to adverse and difficult conditions. In such situations, the need for vitamins increases sharply, therefore, if they are supplied in usual amounts, hypovitosis can develop. In these cases, doses that are 2-3 times higher than the daily requirement are used.

3. Vitamin replacement therapy (etiotropic) - the appointment of vitamin preparations for the elimination and development of hypo- and vitamin deficiencies. Doses exceed daily requirement. The route of administration is enteral.

4. The next type of vitamin therapy is the use of vitamins to eliminate or reduce the negative effects of other drugs. For example, pyridoxine hydrochloride - eliminates the side neurotoxic effect of the drug phtivazide.

5. Non-specific (pharmacodynamic) is the use of vitamins in high doses in order to influence the metabolism and other processes of the patient's body. In this case, the vitamin preparation is not prescribed to supplement deficiency (such patients do not have it). Vitamin preparations are prescribed as medicines that have certain pharmacodynamics and vitamin therapy is in the nature of conventional pharmacotherapy.

Let us dwell on some types of vitamin therapy. Unfortunately, we have to admit that the problem of prevention and treatment of hypo- and even avitaminosis has again become relevant today.

Hypovitaminosis of recent years is characterized by 2 features:

1 all age groups are affected

2 hypovitaminoses persist in the summer-autumn period.

The main reason for hypovitaminosis in our country is known - this is a poor quality of nutrition and insufficient intake of fresh vegetables and fruits.

For the prevention and treatment of hypovitaminosis, the multivitamin preparations Undevit, Decamevit, Macrovit, etc. are used. For the prevention of vitamin zov, the dose is close to the daily requirement. Multivitamins are usually taken in the winter-spring time from 3-8 weeks to several months. With vitamin replacement therapy, the dose usually exceeds the daily requirement. The course depends on the disappearance of clinical signs; with the possibility of latent hypovitaminosis, the course is also from 1 to several months.

Adaptive vitamin therapy. There are many situations in which the need for vitamins, especially water-soluble, increases several times, this is primarily:

1.periods of adaptation to new or complicated living conditions

2. increased physical and mental stress.

Under such conditions, all enzyme systems begin to function with increased intensity. As a result, the utilization of vitamins increases and the need for them becomes higher than usual. Inadequate intake of vitamins leads to serious changes in metabolism. Persistent fatigue develops, immunity decreases, various pathological conditions appear. To prevent this from happening, the so-called vitamin therapy is carried out. In this case, doses that are 2-3 times higher than the daily requirement of a healthy person are applied. Therapy is carried out in courses from 3 to 8 weeks. But maybe longer. If necessary, courses are repeated after 3-5 months.

The need for vitamins increases during pregnancy (2 times). For pregnant women, a special special vitamin complex has been developed that contains vitamin D, folic acid, for example, “Gendevit”.

An increased need for vitamins is noted in old age. Vitamins in this case are used to stimulate the enzyme systems of an aging organism. Multivitamin preparations such as Undevit, Aerovit, and Decameviitis are also indicated.

Pharmacodynamic vitamin therapy is the use of vitamins as medicines for diseases that are not related to hypo- or avitaminosis. This is the first difference between pharmacodynamic vitamin therapy from substitution and adaptation. The second significant difference is in dosing. In case of replacement and adaptation therapy, the dose of vitamins as a whole corresponds to the daily requirement and exceeds it by no more than 2–3 times, i.e., it remains within the physiological norm of the intake of vitamins in the body. In order to get a certain pharmacological effect, vitamins are taken in doses, in tens, and sometimes hundreds of times higher than the daily norm. The pharmacodynamic properties of vitamins are manifested precisely with the appointment of high, non-physiological doses.

Finally, the third feature of pharmacological vitamin therapy is the appointment of one kind of vitamin that has the desired pharmacological effect.

1. Using the pharmacological properties of vitamin preparations, it is possible to influence both metabolic processes and executive systems and organs.

It was established that nicotinic acid has a vasodilating effect, in addition, at doses of 3 g or higher per day, it has a lipid-lowering effect (with a daily requirement of 15-20 mg).

Nicotinic acid preparations are used for hypertension, coronary heart disease, and peripheral circulation disorders. Abroad, nicotinic acid in large doses (3 g per day) is used to treat atherosclerosis.

Vitamins are essential for the body in relatively small quantities. In most cases, they are elements of food; they are not formed in the body or are synthesized in insufficient quantities (see table)

Vitamin A (Retinol)

One of the first vitamins identified. It was discovered in 1915 by McCollun (E.V. McCollum) and Davis (M. Davis), who established that the growth of experimental animals (rats) depends on a substance soluble in organic solvents.

Vitamin A (retinol) refers to fat-soluble vitamins, being a derivative of retinoic acid. It is found in animal products (butter, egg yolk, liver). Especially a lot of vitamin A is found in the liver of some fish (cod, sea bass, etc.) and marine animals (whale, walrus, seal).

In its pure form, vitamin A does not occur in plant foods. At the same time, many of them (apricots, almonds, carrots, spinach, avocados, eggplant, asparagus, beets, cherries, cabbage, lettuce, parsley, green onions, red peppers, black currants, gooseberries, peaches, figs, tangerines , mango, melon, etc.) contain carotene, which is provitamin A, from which vitamin A is formed in the body.

In addition, vitamin A is currently synthesized. Thus, in medical practice, preparations containing vitamin A are used, both of natural origin and synthetic: retinol acetate and retinol palmit.

Vitamin A is absorbed by the body upon parenteral administration (injection) and is absorbed in the intestine upon administration with animal products. With parenteral administration to humans, carotene does not turn into vitamin A, but is destroyed. The transition of carotene to vitamin A occurs in the intestine and depends on the intake of fat and protein with food and the presence of a sufficient amount of bile and active lipase. From the destruction of carotene in the intestine, natural antioxidants - vitamins E and C. protect

The richest sources of carotene are vegetables (mg /% wet weight):

• Red carrots - 6-25 mg /%,
• Pumpkin "Vitamin" - 17.6 mg /%,
• Head lettuce - 12.5 mg /%,
• Spinach (leaves) - 6-7 mg /%,
• Sorrel - up to 5 mg /%.

In the body, vitamin A plays a role associated with the processes of reproduction and growth, maintaining the immune status, the function of vision, and the differentiation of epithelial tissues.

The biological activity of vitamin A and its content in food products are expressed in retinol equivalents (micrograms or milligrams of retinol) or in international units (ME). 1 ME of vitamin A is equal to the activity of 0.3 μg of retinol.

The richest in vitamin A (found in 1 g):

• Cod liver oil (fish oil) - 350 ME,

• Liver of cattle - 500 ME,

• Pig liver - 200 ME.

Vitamin A deficiency (hypovitaminosis, vitamin deficiency)

It is more common in children in the developing countries of Asia, Africa and Latin America. Vitamin deficiency accompanies protein deficiency. With proper nutrition, large reserves of retinol are created in the body, which eliminate the phenomenon of vitamin A deficiency only after two to three years with its complete exclusion from the diet.

Clinical manifestations:

• ocular manifestations: impaired color sensation and visual impairment in the dark ("night blindness") due to changes in the retina and visual nerves; due to impaired development of the epithelium and the formation of a multilayered keratinizing epithelium in the cornea and conjunctiva, the corresponding areas become dry, whitish, opaque (xerophthalmia). In the future, if untreated, ulcers on the cornea and corneal necrosis may develop;

• skin changes: there is hyperkeratosis, atrophy of sweat and sebaceous glands. The skin becomes dry, flaky, often abscess lesions develop;

• changes in the mucous membrane: due to changes in the epithelium, a thickening of the oral mucosa appears, dryness appears due to a decrease in the secretion of the salivary glands;

• due to a decrease in the protective function of the bronchial epithelium, pathogenic microbes easily penetrate into the lungs, causing the development of pneumonia. If untreated in experimental animals, such pneumonia ends in death.

Hypervitaminosis A

In contrast to vitamin deficiency, increased intake of vitamin A (hypervitaminosis) can be observed. There are hypervitaminosis:

Acute - with a single meal of a large number of products containing vitamin A (liver of a polar bear, whale, walrus). It proceeds as an intoxication (acute poisoning). A few hours after eating this food appear:

•Strong headache,

•temperature rise,

•nausea, vomiting,

• redness of the skin of the face,

• dryness and itching of the skin,

• pain in joints and bones.

Chronic - develops, mainly in children, with prolonged ingestion of vitamin A in the maximum allowable daily doses. It appears:

•lack of appetite,

• increased excitability,

• limited mobility in the joints,

• liver enlargement,

• dryness, roughness and itching of the skin,

• minor painful seals in soft tissues,

• hair loss on the head,

• weight retention in children.

The blood contains high levels of retinol and cholesterol.

As a type of hypervitaminosis, carotinemia is released - an increased content of carotene in the blood. It is observed with large consumption of vegetables and fruits containing carotenoids (oranges, tangerines, carrots and juices from them). Unlike jaundice, carotinemia

results in yellowness of the skin and palmar surfaces of the hand, with sclera pallor, and with jaundice, yellowness of the sclera and skin, but pallor of the palmar surfaces of the hand.

The treatment of hypervitaminosis consists in the abolition of vitamin A preparations. The prognosis is usually favorable, although the phenomena disappear within a few months. With carotinemia, it is necessary to stop consuming vegetables and fruits.

Retinol (Vitamin A) is used in the treatment of:

• hypovitaminosis (vitamin deficiency) A,

• in the treatment of eye diseases (retinitis pigmentosa, xerophthalmia, hemerolopia, kerotomalacia, eczematous lesions of the eyelids),

• skin lesions and diseases (frostbite, burns, wounds, ichthyosis, follicular dyskeratosis, senile keratosis, some forms of eczema and other inflammatory and degenerative processes), in complex therapy during treatment:

• rickets,

• malnutrition,

• acute respiratory infections,

• chronic diseases of the bronchi and lungs,

• inflammatory and ulcerative lesions of the intestine,

• chronic gastritis,

• cirrhosis of the liver,

• to prevent the formation of urinary stones.

Despite the fact that vitamin A is essential for life, there are contraindications for prescribing additional doses for retinol treatment:

•cholelithiasis,

• chronic pancreatitis (exacerbation is possible),

• pregnancy (1 trimester),

• caution in case of kidney disease and decompensation of cardiac activity.

When treating with vitamin A, care must be taken so that hypervitaminosis does not develop.

Vitamin A preparations are prescribed orally, intramuscularly and topically (externally).

Forms of release of vitamin A:

Retinol Vitamin A (Syn: Avital, Akserol, Akseroftol, Alfalin, Alfasterol, Anavit, Afaksin, Viadenin, Vitaplex A, Vogan, Xeroftol, Primavit, etc.).

Retinol Acetate.

Retinol palmitate.

Retinol is part of a number of multivitamins, which will be discussed in the corresponding chapter.

Fish oil refined for internal use.

Obtained from the liver of cod fish. Transparent oily liquid from light yellow to yellow in color with a slight specific smell.

Externally, fish oil is used to moisten dressings and lubricate affected surfaces. Fish oil is part of the Livian aerosol used to treat burns.

Etretinate (Sin .: Tigazon, Tigason, Tigasan, Tegison).

A synthetic drug similar in structure to retinol.

It is used in the treatment of:

• psoriasis,

• ichthyosis,

• Darier's disease,

• discoid lupus erythematosus and some other skin diseases.

Contraindications:

•liver failure,

• renal failure,

• pregnancy and the childbearing period of women. Side effects:

• skin itch,
• dry mucous membranes of the oral cavity,
•hair loss,
• tissue calcification,
• high blood lipids and others.

Isotretinoin

(Sin: Accutane, Roaccutane). A synthetic drug similar in structure to retinol and etretinate.

It is used in the treatment of:
• seborrhea,
• severe forms of acne, not treatable by other means.

Irol

(Sin: Abarel, Aviderm, Aknavit, Ak-noten, Akretin, Dermirol, Retin A, Tretiy, Tretinoin, etc.).

It is applied topically in the form of a cream or lotion for acne. The drug is applied in a thin layer to the affected area of the skin 1-2 times a day. Protect the treated skin from sunlight.

Side effects:

- redness and irritation of the skin. Avoid contact with eyes and mucous membranes.

Carotene.

It is used as a nutritional supplement as a general strengthening and immuno-stimulating agent:
• for the prevention of colds,
• for cardiovascular diseases,
• for diseases of the gastrointestinal tract,
• with cataracts.

Available in tablets containing 5 mg of beta-carotene (dietary carotene).

Vetoron is a domestic drug developed on the basis of beta-carotene.

Carotolin,

Oil extract of rosehip pulp containing, in addition to carotenoids, tocopherol, unsaturated fatty acids and other substances.

Applied externally to treat:
• trophic ulcers,
• eczema
• atophic changes in the mucous membranes,
• some types of erythroderma (psoriatic, desquamative).

Carotinyl.

Beta-carotene solution in oil. Apply externally, applying a thin layer 2 times a day to the affected areas:
• with radiation lesions of the skin,
• sluggish wounds,
• for burns. Side effects:
•allergic reaction.

Dr. Pomier gives a complete list of foods that are a source of vitamin A. Here are some of them, dividing for convenience into two groups:

a) animal products (source of retinol - vitamin A): liver fat (cod, halibut, sturgeon, tuna), cow's heart, brains, raw and fresh milk, meat (lamb, beef), liver (animals and fish): fish (all without exception), pork fat, melted pork fat, cream, butter, cheese (all varieties), curd cheese, oysters, eggs,

b) vegetable products (the source of carotene is provitamin A): apricot, avocado, orange, peanuts, artichoke, eggplant, bananas, sweet potato, beans, rutabaga, cherries, peas, mushrooms, pears, melons, strawberries, cereals grains, figs, zucchini, cabbage (white, Brussels sprouts, cauliflower), potatoes, chestnuts, nettles, watercress, corn, lemon, onions, raspberries, mangoes,

tangerines, vegetable oil, olives, almonds, carrots, nuts (Greek and forest), pepper (Bulgarian and chilli), peaches, sunflower, lettuce (lettuce, lettuce), fresh la, celery, plums, currants, soybeans, asparagus, tomatoes, mulberries, pumpkin, fennel, beans, dates, chicory, blueberries, garlic, lentils, spinach, apples, barley.

Vitamin D (Calciferols)

This name unites groups of related chemical elements with anti-rachitic properties. These are two fat-soluble substances that are close in action and chemical structure: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol).

Vitamin D2 enters the human body in small quantities with food products, mainly of animal origin.

Vitamin D3 is formed in humans in the skin under the influence of sunlight.

In terms of biological activity, both of these vitamins practically do not differ and have the common name "Vitamin D".

For the first time, rickets as an independent disease was separated from other osteodystrophies and described in the 17th century by English doctors, although it was known from antiquity.

French doctors, including Bretono and Trousseau, discovered in the 18th century the antirachitic properties of cod liver. But this discovery was empirical in nature, with no scientific justification.

Only in 1919, the healing properties of ultraviolet rays were determined and the antirachitic role of sunlight was confirmed.

In its pure form, it was possible to isolate vitamin D and synthesize it only in 1931.

The main property of vitamin D is its control and participation in the metabolism of calcium in the body. It promotes the absorption of calcium from the digestive tract, promotes its accumulation in the bones, and prevents bone resorption. Vitamin D also regulates the phosphorus content in the body.

Currently, vitamin D is considered not only as a vitamin, but also as a hormone that regulates, together with the parathyroid hormone, the concentration of calcium ions in blood plasma.

When vitamin D is added to the diet of animals, its content in food products increases. So, milk and butter of cows treated with vitamin D are 2-10 times richer than ordinary vitamin D.

However, it should be said that with food a person receives an insufficient amount to provide the body with vitamin D, and in the absence of exposure to sunlight, the development of hypovitaminosis is possible.

A person's daily requirement for vitamin D is 400 ME. However, this is rather average statistical data, since the true need largely depends on the amount of vitamin D3 synthesized in human skin under the influence of sunlight. So in most cases, an adult is enough to provide the body with vitamin D3 synthesized in the skin. At the same time, the need for vitamin D is significantly increased in newborns (especially premature) babies, women during pregnancy and lactation, and residents of the Far North.

Rickets Vitamin D deficiency (hypo- and vitamin deficiency) of vitamin D is more common in children. Rickets is a disease of the first year of a child’s life, caused by a lack of vitamin D in the body, and characterized by a violation of phosphorus-calcium metabolism, a violation of bone formation and a disturbance in the functions of the nervous system and internal organs.

The cause of the disease is not only a deficiency in the intake of vitamin D into the body, but also a violation of the formation of its active forms in the body (insufficient ultraviolet rays in the winter, diseases of the liver, kidneys or gastrointestinal tract with malabsorption). Contributing factors in the development of hypo- or vitamin deficiency are: prematurity of the child (immaturity of the enzymatic systems), diseases accompanied by acidosis, lack of calcium and phosphorus salts in the body (nutritional factor).

In the manifestation of rickets, the following degrees are distinguished:

I-st degree (mild) - there are small changes in the muscular system, asthenic syndrome and developmental delay. With proper treatment, all symptoms disappear without residual effects.

II degree (moderate) - manifested by pronounced changes in the nervous, muscle (hypotrophy) and hematopoietic systems. In sick children, anemia, a slight increase in the liver and spleen, moderate impaired function of the internal organs are noted.

III degree (severe) - pronounced muscle hypotension of the lower extremities, progressive vagal deformity of the lower extremities (X-shaped legs), curvature and thickening of the tubular bones, rickety "beads" on the chest and "bracelets" on the hands, an increase in the frontal and parietal tubercles (the "Olympic" forehead), other disorders of the musculoskeletal system, disorders of the central nervous system, internal organs with the development of complications.

The course of each of the three degrees of rickets can be acute, acute, recurrent, divided into the initial period, the height of the peak and residual phenomena.

The initial period is often manifested at 2-3 months of a child's life in the form of anxiety and sweating, baldness of the neck, muscle dystrophy. Slight softening of the edges of the large fontanel is noted.

After 2-3 weeks, without timely treatment, the peak of the disease begins. The child is pale, appetite is reduced, hypotrophy appears. From the side of the nervous system, inhibition, decrease in reflexes, and bone changes (bones of the skull, chest, extremities) are hardly noticeable at the I degree, they are clearly manifested at the II degree and go into pronounced deformation at the III degree of rickets. Only by these signs can we judge the degree of rickets. During the height of the disease, disorders of the internal organs are noted in connection with deep metabolic disorders, trophic tissue and increased vascular conduction. These symptoms are most pronounced with rickets of the III degree: tachycardia, muffled heart sounds, decreased blood pressure, enlarged liver and spleen. Due to the weakening of the tone of the abdominal muscles, its volume increases ("frog-belly").

In the acute course, mainly in premature babies in the first months of life, rapid development of rickets symptoms is noted: severe anxiety, sweating, and at the height of the disease, muscle hypotension and bone softness are expressed.

The subacute course of the disease is more often manifested at 6–9 months in children with malnutrition. It is characterized by a slower development of the process.

A relapsing course is more prone to seasonal manifestations of rickets: improvement in summer and worsening in winter. Phenomena of late rickets develop in children over 4 years of age with malnutrition and prolonged diseases accompanied by acidosis. Often the phenomena of rickets (mainly of the first degree) are mistaken for vegetative dystonia, since bone changes occur later and rarely.

During treatment, it is necessary: normalization of the daily regimen, a balanced diet and a child's stay in the fresh air.

In addition to vitamin D, for patients with rickets, children receive massage, therapeutic gim-nastik and ultraviolet radiation.

During the treatment period, control is necessary to avoid the transition of hypovitosis to hypervitaminosis, which will be discussed later.

In adults, vitamin D deficiency is noted mainly among women in some countries where, due to religious traditions, they lead a reclusive lifestyle, avoiding exposure to the sun.

In addition, a deficiency of vitamin D can be of endogenous origin (impaired absorption of fat in diseases of the biliary tract).

In adults, hypovitaminosis D is manifested by lethargy, fatigue, osteoporosis, crumbling teeth, pain in the pelvic bones, duck gait, lameness, muscle pain, paresthesias.

Conduct complex treatment, prescribing vitamin D and ultraviolet irradiation, but also under control to avoid hypervitaminosis D.

Hypervitaminosis D can develop when prescribing large doses of vitamin D for the treatment and prevention of rickets in children with increased sensitivity to the drug, with increased ultraviolet radiation, eating foods rich in vitamin D. Contributing factors may include inefficient breastfeeding, endocrine disorders and impaired renal function.

More often, the causes of hypervitaminosis are the appointment of vitamin D drugs to themselves and their children in families where adults consider themselves too literate in this regard and do not consult with doctors.

The use of vitamin D in treatment

Vitamin D is used in the treatment of:

• rickets (prevention and treatment),

• disorders of the function of the parathyroid glands (tetany),

• osteomalacia,

• bone diseases caused by impaired metabolism of calcium and phosphorus in the body.

Contraindications for vitamin D

Contraindications for the appointment of vitamin D:

• hypercalcemia,

• active form of pulmonary tuberculosis,

• diseases of the gastrointestinal tract, peptic ulcer of the stomach and 12 duodenal ulcer,

• acute and chronic diseases of the liver and kidneys,

• organic damage to the heart.

Forms of release of vitamin D:

• Ergocalciferol (Vitamin D2) (Synonyms: Aldevit, Vigantol, Viosterol, Vitadol, Vitaplex D, Vitasterol, Decristol, Detamine, Dristol, Calciferol, Ostelin, Ultranol, Fordetol, etc.):

• Oksidevit (Synonyms: Calcidiol, Oxy-vitamin D3, Oxycholecalciferol):

• Videhol.

• Psorcutan.

Vitamin D is also a part of multivitamin complexes.

Vitamin E (tocopherols)

Under the general name Vitamin E, a group of tocol derivatives is integrated, which have vitamin E activity, as well as tocotrienols, which have less pronounced activity. Individual tocopherols differ only in their chemical structure. The most important of these biologically is tocopherol (alpha-tocopherol).

The role of vitamin E in the reproductive process was first revealed in 1920. In a white rat, usually very prolific, a cessation of reproduction was noted with a long milk diet (skim milk) with the development of vitamin E deficiency.

In 1922, Evans and Bishop found that with normal ovulation and conception, pregnant female rats died of the fetus with the exclusion of the fat-soluble food factor present in green leaves and germ of the grain from the diet. Avitaminosis E in male rats caused changes in the seed epithelium.

In 1936, the first preparations of vitamin E were obtained by extraction of grain sprouts from oil.

The synthesis of vitamin E was carried out in 1938 by Carrer.

Further research revealed that the role of vitamin E is not limited only to the control of reproductive function.

Vitamin E is a natural antioxidant (antioxidant). It plays an important role in the activity of the body: it participates in the biosynthesis of heme and proteins, cell proliferation, tissue respiration and other important processes of cell metabolism.

Tocopherols are widespread in nature. In the human body, they are present in all tissues, found mainly in the membranes of cells and subcellular organelles.

A person satisfies the daily need for tocopherols with food of plant and animal origin.

Vegetable oils, especially corn and cottonseed oils, as well as oil obtained from wheat germ are the richest in food products from food products. Most of the sunflower oil tocopherols

are accounted for by alpha-tocopherols (60-80%), and soybean and corn are accounted for by gamma-tocopherols (60 and 80%, respectively). Animal products are poor in tocopherols.

Physiological hypo- and vitamin deficiency E is observed quite rarely, since food products fully satisfy the human need for vitamin E.

Exogenous vitamin E deficiency can be detected with significant physical exertion (for example, in athletes).

Endogenous vitamin E deficiency in humans more often occurs when there is a violation of its digestibility in the body (for example, when there is a violation of the supply of bile to the duodenum, with an increased intake of unsaturated fatty acids with food), as mentioned above.

Vitamin E deficiency in newborns, mainly in non-term infants, can manifest as hemolytic anemia. Premature retinopathy may also occur, leading to blindness.

In adults, vitamin E deficiency is manifested by muscle weakness, muscle hypotension, and with the further development of insufficiency - muscle atrophy, the development of early forms of scleroderma. Women may have a tendency to repeat abortions.

Medical indications for vitamin E

The medical indications for vitamin E are:

• hypovitaminosis,
• high physical activity,
• menstrual irregularities,
• threatened abortion,
• menopausal autonomic disorders,
• violation of the function of the gonads in men,
• neurasthenia due to overwork,
• asthenic syndrome,
• amyotrophic lateral syndrome,
• primary muscular dystrophy,
• post-traumatic secondary myopathy,
• diseases of the ligamentous apparatus and muscles,
• degenerative and proliferative changes in the joints and ligaments of the spine and large joints,
• dermatomyositis,
• some dermatoses,
• psoriasis,
• during convalescence in diseases occurring with fever,
• in gerantology (advanced age),
• spasm of peripheral vessels,
• with epilepsy (to increase the effectiveness of anticonvulsants),
• in complex treatment for many diseases (as an antioxidant).

In pediatrics it is applied:

• with malnutrition,
• with scleroderma and other diseases.

Contraindications: hypersensitivity to the drug.

Side effects:

• allergic reactions,
• when taking large doses, diarrhea and pain in the epigastric region are possible.

Special instructions. Use with caution:

• with severe cardiosclerosis,
• with myocardial infarction,
• with an increased risk of thromboembolism.

Vitamin E release form:

For oral and intramuscular administration, Tocopherol acetate is produced (synonyms: Almevit, Biovit, Vitamin E acetate, Vitaplex E, Gonavil, Profecundin, Sant-e-gal, Tokofin,

Fertiligen, Fitoferol, Evion, Evitan, Evi-tol, Egevit , Esol and others). Available for oral administration and intramuscular injection.

All tocopherol preparations are stored in a well-packed container and protected from light, so that the sun does not destroy vitamin E.

Vitamin E is mainly used in complex treatment for various diseases.

Tocopherol acetate is a part of the combined (multivitamin) preparations: Aevit, Aekol, Aerovit, Gendevit, Undevit and others.

Vitamin K (Phylloquinones)

The biological role of vitamin K is due to the participation in blood coagulation processes. It is necessary for the synthesis in the liver of functionally active forms of prothrombin and other proteins involved in blood coagulation.

We can say that vitamin K is an antihemorrhagic vitamin, or coagulation.

Under the general name Vitamin K, a large group of substances that are close in their chemical composition and effect on the body (from vitamin K1 to K7) is combined.

Of this group, the two main forms of vitamin K present in nature are of greatest interest: vitamin K1 and vitamin K2.

Vitamin K1 (synonym: phylloquinone, phytomenadione) - a substance that is synthesized in plants and found in leaves. The richest in vitamin K1:

- alfalfa leaves,
- spinach leaves,
- cabbage (Brussels sprouts and cauliflower),
- nettle,
- needles,
- green tomatoes,
- dog-rose fruit.

Significantly less vitamin K1 is found in root crops and fruits.

Vitamin K2 (synonym: menachion-4, naphthoquinone) is a substance that is predominantly synthesized in the human body by microorganisms (saprophytic bacteria) in the small intestine, as well as by animal liver cells. Vitamin K can be found in all animal tissues. Of foods, the richest content of this vitamin in the liver of a pig (4-8 μg per 1 g of dry matter).

For the first time, it was suggested that there is a factor affecting blood coagulability in 1929. Danish biochemist Henrik Dam, independently of E. Doyzy, isolated a fat-soluble vitamin, which in 1935 was called Vitamin K. For this work he was awarded the Nobel Prize in 1943.

Medical Indications for Vitamin K

- bleeding and hemorrhagic diathesis associated with hypothrombinemia,
- obstructive jaundice,
- hepatitis, cirrhosis of the liver,
- prevention of bleeding in preparation for a planned surgical operation,
- postoperative period with the threat of bleeding,
- bleeding after wounds or surgical interventions,
- uterine juvenile and pro-menopausal bleeding,
- bleeding associated with a disease of the gastrointestinal tract (peptic ulcer, colitis, etc.),
- pulmonary bleeding with pulmonary tuberculosis,
- septic diseases accompanied by hemorrhagic phenomena,
- bleeding during radiation sickness,
- hemorrhages associated with an overdose of indirect anticoagulants and certain drugs (antibiotics, salicylates, sulfanilamides, tranquilizers, antituberculosis and antiepileptic drugs),
- prolonged diarrhea,
- intestinal atony,
- increased fragility of blood vessels,
- dysproteinemia,
- muscle weakness,

• hemorrhagic disease of the newborn,

• pregnant women during the last month of pregnancy to prevent bleeding in newborns.

It should be noted that the use of vitamin K for hemophilia and Verlhof disease is not effective.

Contraindications:

• hypersensitivity to the drug,

• increased blood coagulability,

• thrombosis, embolism.

Vitamin K release form:

a) Phytomenadion (Synonyms: Canavit, Kona-kion, Mefiton, Monodion, Phylo-quinone, Phimedion, Fitonadion, Evleven K, etc.).

For medical purposes, a synthetic preparation is obtained that is practically insoluble in water, slightly soluble in alcohol, easily soluble in vegetable oils. It decomposes in the light.

b) Vikasol (synonym: Menadione). A synthetic analogue of vitamin K, easily soluble in water, difficult - in alcohol.

Vitamin K is part of some multivitamins.

Vitamin B1 (Thiamine)

The water-soluble vitamin discovered by Casimir Funk in 1912 laid the foundation for an entire group called "vitamins." If at first vitamin B1 was considered as a vitamin of the “nervous system” that cures polyneuritis, then its biological role related to the participation of a number of important enzymes in the construction of co-enzymes was proved. These enzymes are involved in the regulation of the main stages of the metabolism of various nutrients and especially carbohydrates. Considering that carbohydrates make the main contribution to providing the human body with energy, thiamine is important for energy metabolism. Thiamine is also needed for the biosynthesis of the most important neurotransmitter, acetylcholine. By actively influencing various body functions, metabolism and neuro-reflex regulation, thiamine can cause a positive effect in various pathological processes and should be considered as a pharmacotherapeutic substance in the broad sense.

Thiamine is widespread in living nature: it is present in microorganisms, plants and in all tissues of the animal body. Yeast and wheat germ are especially rich in it. Thiamine is synthesized by many microorganisms and plants. In the human body and higher animals, it is not synthesized, and therefore must come from food.

The greatest amount of thiamine is found in the following products (mcg per 100 g of product):

Dry beer yeast - 5.0 mcg / 100 g,

• Peanuts - 0.84,

• Pea-0.72-0.81,

• Beans - 0.50-0.54,

• Walnuts - 0.48,

• Oatmeal - 0.44-0.50,

• Buckwheat - 0.42-0.53,

• Wallpaper wheat flour - 0.41,

• Pork - 0.40-0.60,

• Grain of wheat - 0.37-0.46,

• Rye flour - 0.17-0.42,

• Wheat flour (premium) - 0.17,

• Pasta - 0.17-0.25.

As can be seen from the above data, bread, bakery products, cereals (especially buckwheat, oat, wheat), legumes, lean pork are the richest in thiamine. Milk and dairy products, as well as most vegetables, are poor in thiamine.

Conventional heat treatment has little effect on the thiamine content in food, but heating in an alkaline environment causes a significant breakdown of the vitamin.

The daily need for thiamine is: 0.80 mg for newborns and children of the first year of life, for an adult, the need depends on the nature of the food and energy costs and is -1.5-2.4 mg.

Vitamin deficiency B1 (vitamin deficiency, hypovitaminosis B1)

Thiamine deficiency in the body leads to a violation of the oxidation of carbohydrates: the accumulation of unoxidized products in the blood and urine, inhibition of the synthesis of acetylcholine. These biochemical disturbances underlie a number of pathological symptoms of the nervous system (headache, irritability, memory impairment, peripheral polyneuritis, paresis, and in severe cases, paralysis), the cardiovascular system (tachycardia, pain in the heart, expansion of the borders of the heart, muffled heart tones, shortness of breath, swelling) and digestive organs (a sharp decrease in appetite, abdominal pain, nausea, decreased bowel tone, constipation), developing with thiamine deficiency. The severity of these symptoms depends on the degree of vitamin B1 deficiency.

More often, an endogenous (secondary) form of thiamine deficiency occurs in chronic alcoholism, neuritis, diseases of the gastrointestinal tract, thyrotoxicosis, diabetes mellitus, and various poisonings.

The exogenous (primary) form is called beriberi.

Take-berry (synonym: vitamin B1, alimentary polyneuritis) - develops due to insufficient intake of thiamine or a violation of its utilization in the body.

The mention of beriberi is found in the oldest medical treatise that has survived to this day - in the Chinese text of the second millennium BC. e.

The first detailed description belongs to the Dutch physician Eikman (S. Eihlman, 1897).

The main cause of the disease, which occurs mainly in the countries of South and East Asia, is the consumption of polished rice, poor not only with thiamine, but also with other B vitamins. Therefore, beriberi should be considered as a complex B-vitamin deficiency.

An unbalanced diet with a significant amount of carbohydrates, pregnancy and feeding, prolonged physical stress, as well as work at low or high ambient temperatures, at which the body's need for thiamine increases, contribute to the development of beriberi disease.

The clinical picture of vitamin B1 deficiency

The clinical picture is characterized by cardiovascular disorders, damage to the peripheral nervous system and edema.

During the disease, usually three forms are distinguished:

a) wet or acute form - signs of damage to the cardiovascular system prevail;

b) dry or atrophic form - a chronic disease characterized by a violation of the peripheral nervous system with damage to various muscle groups (often leads to paralysis and paresis of the lower extremities);

c) infant form - an acute illness in children of the first months of life whose mothers have had beriberi, as a result of which there is no vitamin B1 in breast milk.

The child develops anorexia, he refuses to take the chest, loses weight. Cooling of the extremities, difficulty in breathing, severe paroxysmal pains, causing the child to take a stationary position, hoarseness of voice and aphonia (the child cries soundlessly) are noted. Violations of the cardiovascular system join, but large edema is relatively rare. Within one to two days from the onset of the disease, the child becomes drowsy, alternating with a coma.

Treatment in the acute period is carried out in a hospital, but in most cases the prognosis is favorable.

Prevention: inclusion of thiamine-rich foods in the diet based on daily requirements. With a decrease in the content of thiamine in mother's milk (normally 0.1-0.2 mg per 1 liter), vitaminization of the mother with thiamine is necessary. Hypervitaminosis B1, food character not observed. With the introduction of large doses of thiamine, nausea may occur, less commonly, thiamine shock. But quite often individual intolerance is noted - an allergic reaction to thiamine preparations: skin itching, urticaria, Quincke's edema. Therefore, treatment with thiamine should be started with small doses.

Synthetic preparations of thiamine are used as therapeutic agents: thiamine bromide, thiamine chloride, phosphothiamine, bentothiamine and coenzyme form of vitamin B1 - cocarboxylase hydrochloride.

Medical indications for Vitamin B1:

• hypo- and vitamin deficiency B ,,
• neuritis,
• sciatica,
• neuralgia,
• peripheral paresis and paralysis,
• intestinal atony,
• myocardial dystrophy,
• malabsorption in the intestines,
• fasting,
• chronic alcoholism,
• severe impaired liver function,
• thyrotoxicosis,
• pregnancy. Side effects:
• sweating,
• tachycardia,
• allergic reactions (skin itching, urticaria). Anaphylactic shock is extremely rare.

Vitamin B1 Release Forms

1. Vitamin B1

(Synonyms: Anevril, Benerva, Berin, Betabion, Betamine, Betaneurin, Beta-Vitan, Betaxin, Betiamin, Bevital, Cristovibex, Oritsanin, Thiamin, Vitaplex B1, etc.).

2. Phosphothiamine.

Thiamine phosphorus ester, which does not differ in basic properties from other synthetic preparations of vitamin B ,.

3. Benfotiamine.

A synthetic compound similar in structure and action to thiamine and co-carboxylase.

4. Cocarboxylase.

It is a finished form formed from thiamine in the process of its transformation in the body. Indications for use:

• acidosis of diabetic origin,
• respiratory acidosis in chronic pulmonary heart syndrome,
• diabetic and hepatic coma,
•coronary heart disease,
• chronic circulatory failure,
• peripheral neuritis,
• chronic alcoholism,
• pathological conditions requiring improvement in carbohydrate metabolism.

Contraindications: hypersensitivity to the drug.

Vitamin B1 is part of many multivitamins.

Vitamin B2

(Riboflavin, Vitamin U, lactoflavin, ovoflavin, luminoflavin, urofla-vin, hepatoflavin)

A water-soluble vitamin was first isolated in crystalline form from whey of milk and egg protein in 1933 by Richard Kuhn and his associates, and their chemical structure was established by them. In 1935, riboflavin was synthesized in the laboratories of R. Kuhn and Carrera (R. Kaggeg).

The biological role of riboflavin is determined by the participation in the construction of flavin coenzymes, which are part of the catalytic centers of the most important redox enzymes. Thus, flavin enzymes occupy one of the central places in the processes of energy metabolism, participate in the synthesis of coenzyme forms of vitamin B6 and folacin (vitamin B9 or Sun). In

addition, riboflavin is part of visual purpura, which protects the retina from the harmful effects of ultraviolet rays.

In the human body, riboflavin is not synthesized, but only comes from food. The most rich in riboflavin are liver, kidney, heart, milk and dairy products, eggs and green vegetables.

In nature, riboflavin occurs in three forms: free riboflavin and its coenzymatic forms of FMN (flavin mononucleotide) and FAD (flavinadene indinucleotide).

Riboflavin, which comes with food, is absorbed in the small intestine, where it partially transforms into FMN and FAD, but the main formation of coenzyme forms of riboflavin occurs in the liver and kidneys. In the blood, riboflavin and its coenzyme forms are bound by proteins and transported to various organs.

The need for riboflavin increases in pregnant and lactating mothers, with various diseases and stressful conditions. The rate of consumption of ribo-flavin is established for different categories of the population, taking into account the age, gender, intensity and nature of labor.

Riboflavin is excreted through the kidneys, staining the urine in a light yellow color.

Vitamin deficiency B2

Hypo- and vitamin deficiency B2 develops quite rarely with a sharp decrease in the consumption of milk and dairy products - the most important sources of riboflavin, when its consumption is less than 0.25 mg per 1,000 kcal per day. Endogenous riboflavin deficiency occurs in diseases of the gastrointestinal tract, hepatitis, and skin diseases.

The earliest symptom of riboflavin deficiency is a mucosal lesion in the corners of the mouth with the formation of cracks, erosions and ulcers. Somewhat later, lesions of the mucous membrane of the lips with vertical cracks on their closure join in - chylosis. There is a change in tongue (glossitis), angular stomatitis, seborrheic peeling of the skin around the mouth, on the wings of the nose, ears, nasolabial folds and changes in the organ of vision.

Treatment for vitamin B2 deficiency

The treatment consists in the complete nutrition and prescription of vitamin B2 medications.

Hypervitaminosis B2 does not cause pronounced manifestations. But it must be noted that treatment with excessively high doses of riboflavin can lead to the creation of significant concentrations of riboflavin in the body. In this case, due to the poor solubility of riboflavin, blockage of the renal tubules is possible.

Medical indications for the use of riboflavin

Medical indications for the use of riboflavin, both independently and in combination therapy:

- hypo - and vitamin deficiency B2,
- conditions of increased body need for vitamin B2:
- heavy physical labor,
- prolonged neuropsychic stress,
- pregnancy
- lactation period,
- long-term use of antibiotics or sulfa drugs,
- general malnutrition,
- radiation sickness,
- conjunctivitis,
- iritis,
- keratitis,
- corneal ulcers,
- cataract
- long-term healing wounds and ulcers,
- asthenia,
- impaired bowel function,
- Botkin’s disease,

• porphyria,
• psoriasis,
• seborrhea,
• rosacea and youthful acne,
• streptoderma (angulitis, cheilitis),
• chronic liver disease,
• chronic diseases of the gastrointestinal tract.

Vitamin B2 Release Forms

1. Riboflavin (Vitamin B2)

(Synonyms: Betavit, Beflavin, Beflavit, Vitaplex B2, Vitaflavin, Lak-Tobene, Lactoflavin, Ovoflavin, Ribovin, Flavaxin, Flavitol and others).

Yellow-orange crystalline powder is slightly soluble in water and alcohol, unstable in the light.

2. Riboflavin - a mononucleotide

(Synonyms: Alloxazine mononucleotide, Kitoflav, Koflavinazi, Ribofla-vinfosfat, Ribofosfina, Flavin-mononucleotide, Flamotid and others).

Approaches in biological action to vitamins and enzymes. Being a product of riboflavin phospholation, riboflavin-mononuleotide is a ready-made form of coenzyme that is formed in the body from riboflavin.

It is used, like riboflavin, but mainly for eye and skin diseases.

3. Flavinate

(Synonyms: Adeflavin, Bioflavin, Flavinin, Flavitan and others).

Flavinate (FAD) is a coenzyme that is formed in the body from riboflavin. Obtained synthetically. Indications for therapeutic use are the same as for riboflavin.

Riboflavin is part of many multivitamin complexes.

Vitamin B3 (synonyms: vitamin PP, niacin, nicotinic acid)

Under the name Vitamin B3 is better known in foreign countries. In its main action: (antipellagric) is named after the first letters of "PP". Under the name vitamin PP is better known in Russia (see Vitamin PP).

Vitamin PP

(Syn .: Vitamin B3, niacin, nicotinic acid, nicotinamide)

Niacin is one of the main representatives of B vitamins, although it is better known in Russia under the name Vitamin PP. Its main biological role is associated with participation in redox reactions, ensuring normal growth, a beneficial effect on lipid metabolism and lowering blood cholesterol in patients with atherosclerosis.

Nicotinic acid was first synthesized by Huber (C. Huber) in 1867 by the oxidation of nicotine by chromic acid.

But only in 1937, nicotinic acid was identified with anti-pellagric factor vitamin PP (English pellagra preventing - preventing pellagra).

It is believed that the active principle is nicotinic acid and nicotinamide, which normalize the secretory and motor functions of the stomach, improve the secretion and composition of pancreatic juice, normalize liver function, its antitoxic functions, pigmentation, glycogen accumulation, etc.

Niacin is found in many foods. But the vitamin value of products depends not only on the amount of vitamin PP content, but also on the forms in which it is contained. So, in legumes it is in an easily digestible form, in cereals (rye, wheat) it contains an almost non-digestible form. A particularly nearly unapproachable form is found in corn, which poses a threat to the development of pellagra among residents of regions where corn is a staple food.

The need for vitamin PP increases with hard physical work, nervous strain, pregnancy.

In addition to the intake of vitamin PP with food, it has been proved that it can be synthesized in humans and animals from the amino acid tryptophan, but only with a high level of animal protein in the diet.

Niacin is one of the most persistent vitamins for cooking, storage, and preservation. It practically does not lose biological activity upon freezing and drying food products. With any food processing, the total loss of vitamin PP does not exceed 15-20%.

Thus, with the right diet with sufficient protein content, the human body's need for vitamin PP is fully satisfied.

Vitamin deficiency PP

Judging by the name of the vitamin, its vitamin deficiency is denoted by the term "pellagra."

Pellagra (Italian: pella agra - rough skin) is a disease that develops due to insufficient intake of food into the body or incomplete absorption of nicotinic acid in the body.

Before pellagra was observed mainly in areas with high consumption of corn.

Pellagra is found mainly in adults aged 20-50 years, the same - in school and youth, and very rarely - in early childhood.

In case of PP hypovitaminosis preceding vitamin deficiency, the following appear: rapid fatigue, the performance decreases in patients, lack of appetite, weight loss, dizziness, irritability, and depression are noted. In the future, in the absence of treatment, erosions and ulcers in the oral cavity, diarrhea (loose stools 3-5 times a day and more often) appear. The stool is liquid, watery, with putrid odor, but without impurities of blood and mucus.

Patients complain of a burning sensation in the oral cavity and severe salivation. Swelling of the lips, mainly the lower, cracks on the mucous membrane of the lips appears. The mucous membrane of the mouth is sharply hyperemic, ulcerations appear on the gums and under the tongue. The back of the tongue is covered with a touch of black-brown color, sometimes it is divided by cracks into fields. The edges and tip of the tongue are bright red. Gradually, redness passes over the entire language, it shines like varnished. Later, acute changes subside, the mucous membranes fade, and the papillae of the tongue atrophy.

In open areas of the skin, pellargic erythema appears, which is located symmetrically on the face, around the lips, on the nose, cheeks, neck and forehead, on the hands and feet, less often on the chest, forearms and legs. A few days later, pseudo-peeling occurs, followed by dark brown pigmentation or spots resembling vitiligo.

The most severe complication of pellagra is encephalopathy.

Treatment consists in a complete, animal-rich diet, the introduction of vitamin PP.

Medical Indications for Vitamin PP

For medical purposes, using also the vasodilating effect of nicotinic acid, vitamin PP is used both independently and in complex treatment for:

- hypo- and vitamin deficiencies,
- diseases of the gastrointestinal tract (gastritis with decreased secretory function),
- liver diseases (acute and chronic hepatitis, cirrhosis),
- spasms of the vessels of the limbs,
- spasms of cerebral vessels,
- neuritis of the facial nerve,
- atherosclerosis,
- long-term healing wounds and ulcers,
- infectious diseases.

Contraindications:

- peptic ulcer of the stomach and 12 humus colon in the acute stage,
- severe impaired liver function (large doses may have a hepatotoxic effect),
- gout and hyperuricemia,
- hypersensitivity to the drug.

Vitamin PP Release Form

1. Nicotinic acid. Vitamin PP (synonyms: Vitamin B2, Apellagrin, Vitaplex N, Induracin, Liplit, Niacin, Nikovit, Nicodan, Nicodon, Nikonacid, Nikotene, Pellagramin, Relonin, Peviton).

Nicotinic acid is a part of the complex preparations "Nikoverin", "Nikoshpan".

2. Enduracin.

Prolonged dosage form of nicotinic acid (US release).

Indications and contraindications for use are the same.

3. Nicotinamide (synonyms: Aminicotin, Benicot, Bepella, Niacinamide, Niacamide, Nicotol, Nicofort, Pelmin, etc.).

A synthetic drug in structure and action is close to nicotinic acid and is considered along with it as vitamin PP.

Indications for use and doses are basically the same as for nicotinic acid. Nicotinamide is not used as a vasodilator.

It is part of multivitamin complexes.

Vitamin B4 (synonym: Choline)

Metabolic disorders caused by a lack of choline allowed some researchers to consider choline as a vitamin of group B (vitamin B4) or a vitamin-like substance.

Choline is necessary for the synthesis of lecithins and sphingo-myelins, which are essential components of lipoproteins synthesized in the liver. Lipotropic substances normalize the metabolism of fats, facilitate their digestion, remove PI transfer from the liver to other parts of the body, prevent liver obesity, help prevent and prevent the development of atherosclerotic changes in blood vessels.

In the human body, choline is contained both in a free state and in the form of esters. Most of the free choline is found in bile - up to 550 mg per 100 ml. In the blood plasma of an adult, the concentration of free choline averages 0.44 mg per 100 ml.

The main part of choline enters the human body with food, but part of it is still synthesized in the body from ethanolamine and methionine.

The daily human need for choline is 0.5-4 g (depending on the methionine content in food).

In food products of plant and animal origin, choline is contained (in mg /%):

• egg yolk - 800-1700 mg /%,
• liver - 350-650 mg /%,
• wheat germ - 400 mg /%,
• kidneys - 300 mg /%,
• soy flour - 250-300 mg /%,
• peas - 260 mg /%,
• poultry meat - 299 mg /%, - fish - 85 mg /%,
• meat - 70-85 mg /%,
• cereals (oats, wheat, barley) -140 mg /%,
• rice -75-78 mg /%,
• corn - 70 mg /%,
• milk - 15 mg /%.

Vitamin deficiency B4

Chronic choline deficiency leads to anemia and hypoprotenemia.

In normal living conditions, there were practically no cases of either hypovitaminosis or B4 hypervitaminosis.

Medical Indications for Vitamin B4

Medical indications for vitamin B4:

• Botkin’s disease,
• chronic hepatitis,
• cirrhosis of the liver (mainly early stages),
• hypothyroidism,
• cystinuria,
• atherosclerosis,
• chronic alcoholism.

Vitamin B5 (pantothenic acid)

Pantothenic acid refers to water-soluble B vitamins and, like all vitamins, is involved in the metabolism of the body. The name comes from the Greek word pantothen, meaning everywhere.

In the human body, pantothenic acid is part of coenzyme A, which plays an important role in the processes of acetylation and oxidation. Vitamin B5 is involved in carbohydrate and fat metabolism, in the synthesis of acetyloline, is found in a significant amount in the adrenal cortex, stimulating the formation of corticosteroid hormones, has a pronounced effect on the formation and function of epithelial tissue, and has some anti-inflammatory activity.

Pantothenic acid not only enters the human body with food of plant and animal origin, but also is produced in significant quantities by Escherichia coli.

It should be borne in mind that in the process of heat treatment of products, the loss of vitamin B5 can reach 25-50%. So, when thawing meat, up to 30% of pantothenic acid is destroyed, and when cooking meat, it goes into the broth up to 50%.

The daily human need for pantothenic acid is 10-12 mg, but the amount of vitamin needed by the body increases to 20 mg per day during hard physical work, pregnancy and in lactating women.

Vitamin B5 is excreted from the body mainly through the kidneys with urine. The total daily amount of excretion of pantothenic acid with urine in the form of various forms of 5.5-6.2 mg.

Excretion in urine per day of less than 2 mg indicates insufficient supply of the body with vitamin B5.

Vitamin deficiency B5

In humans (due to the production of pantothenic acid in the intestines), vitamin deficiency is quite rare. In a number of animals in which vitamin B enters the body only with food, the manifestation of hypo- and vitamin deficiency B5 is easily caused in the experiment.

The development of vitamin deficiency is possible with impaired absorption or excretion of pantothenic acid, with prolonged intoxications, chronic diseases of the gastrointestinal tract, cardiovascular system and kidneys, with hormonal imbalance, prolonged chemo and antibiotic therapy, and diuretics.

The specific symptoms of B5 hypovitaminosis in humans are not adequately described. In addition to hair loss, a number of authors also note trophic damage to nails, trophic, long-time non-healing ulcers and wounds during vitamin B5 deficiency deficiency.

When diagnosing and assessing the degree of vitamin deficiency, the level of vitamin B5 excretion in daily urine is examined.

Medical indications for vitamin B5

Medical indications for vitamin B5:

For oral administration and topical application:

• various metabolic disorders,

• with neurological diseases (paresthesia, polyneuritis, neuralgia),

• circulatory failure (in combination with cardiac glycosides. Calcium pan-totenate improves the energy supply of myocardial contractile function and enhances the cardiotonic effect in the treatment of cardiac glycosides),

• chronic liver disease,

• chronic diseases of the pancreas,

• diseases of the gastrointestinal tract of non-infectious nature (gastritis, gastroduodenitis, etc.),

• for the treatment of alcoholism (withdrawal of withdrawal symptoms in complex treatment),

• allergic reactions (dermatitis, hay fever, etc.),

• to reduce the toxic effects of a number of drugs (anti-TB drugs, sulfonamides, antibiotics, arsenic drugs and others),

•bronchial asthma,

• toxicosis of pregnant women,
• bronchitis,
• inflammatory diseases of the oral cavity and nose,
• inflammatory diseases of the larynx,
• inflammatory diseases of the respiratory tract,
• after removal of the tonsils.

For parenteral (intramuscular or intravenous) administration:
• postoperative bowel obstruction,
• paralytic ileus,
• Pantothenic acid deficiency in case of low absorption syndrome.

For external use:
• long-term healing wounds and ulcers,
• burns,
• bedsores,
• diaper rash,
• abscesses,
• boils,
• dermatitis,
• eczema
• treatment and prevention of cracks and inflammation of the nipples of the mammary gland in nursing women,
• treatment of defects in the mucous membrane of the uterus.

Hypervitaminosis B5 practically does not occur. Its preparations are low toxic. But with prolonged use of large doses, dyspepsia (heartburn, nausea, vomiting) can occur, which quickly disappears when the drug is discontinued or the dose is reduced.

Contraindications:
• hypersensitivity to the drug,
• for parenteral administration:
• hemophilia,
• mechanical bowel obstruction.

Vitamin B5 Release Forms

1. Calcium pantothenate (Synonyms: Dexpanthenol, Calcipan, Kutivitol, Pankal, Pantavitol, Pantolin, etc.).

2. Panthenol (Synonyms: Bepanten, Bepantol, Pantevit, Panthenil, Pantonil and others).

It is a derivative of pantothenic acid. It is applied only externally.

Pantothenic acid (vitamin B5) is part of the combined multivitamin preparations.

***Vitamin B6 (Pyridoxine*)**

The water-soluble vitamin belonging to the B vitamins exists in nature in three forms (the so-called B6 vitamins):
• pyridoxol,
• pyridoxal,
• pyridoxaline.

All three forms of pyridoxine are equivalent in their biological effect and biological activity.

In the years 1938-1939. Richard Kuhn first isolated pyridoxine as a crystalline substance from yeast and established its structural formula.

The physiological meanings and biological role of pyridoxine are diverse. It is of paramount importance for maintaining the processes of growth, hematopoiesis, and normalizing the functioning of the central nervous system in humans and animals. Entering the body, pyridoxine is part of many enzymes that metabolize amino acids (tryptophan, methionine, cysteine, glutamic acid, etc.). He also participates in the process of fat metabolism, improves lipid metabolism in atherosclerosis.

Pyridoxine is ingested with animal and plant foods. All forms of pyridoxine are absorbed in the small intestine using a passive diffusion mechanism. Its absorption does not change with age, but worsens in alcoholics. Especially high in pyridoxine are yeast and liver.

Vitamin B6 content in foods

Vitamin B6 content in certain foods (in mg /%):

• dry brewer's yeast - 4.0 mg /%,
• liver - 0.7-0.9 mg /%,
• whole rice - 0.7 mg /%,
• millet - 0.52 mg /%,
• corn - 0.48 mg /%,
• flour of the 1st grade - 0.4 mg /%,
• fish-0.4 mg /%,
• meat - 0.37 mg /%,
• fruits (on average) - 0.05-0.2 mg /%,
• vegetables - 0.06-0.35 mg /%.

Pyridoxine synthesis by intestinal microflora is also noted. But this synthesis can be disrupted with intestinal infection and other diseases of the gastrointestinal tract, with prolonged use of sulfonamide and anti-tuberculosis drugs, with the use of broad-spectrum antibiotics.

Pyridoxine is resistant to heat treatment, but is quite sensitive to the action of light. It must be remembered that in the process of cooking, the content of pyridoxine decreases by 20-35% in meat, while smoking and canning meat - by more than 50%. In the preparation of powdered or condensed milk, the loss of pyridoxine is 30%. If you keep milk in a glass dish in the light, then in two hours the content of pyridoxine in it will decrease by more than 50%.

The adult's need for pyridoxine is 0.7 mg per 1000 kcal per day.

The need for pyridoxine increases with the consumption of a significant amount of protein with food, during pregnancy and during the period of feeding the baby, when exposed to ionizing radiation, with the use of certain methods of drug therapy and with heart failure.

Vitamin deficiency B6

Hypovitaminoses associated with pyridoxine deficiency in foods are quite rare. But signs of hypovitaminosis can be noted in patients taking medications that are pyridoxine antagonists (anti-tuberculosis drugs, Dopa, etc.), drugs that inhibit the intestinal flora (antibiotics, sulfonamide drugs), in women, the use of contraceptives. Pyridoxine deficiency occurs in alcoholics, in patients with chronic diseases of the gastrointestinal tract, with a hereditary pathology of the functioning of pyridoxine-independent enzymes, in patients with atherosclerosis and chronic cardiovascular diseases.

Hypo- and vitamin deficiency B6 can occur in young children with growth retardation, increased excitability, hypochromic microcytic anemia, increased excitability, epileptiform convulsions. There is a disorder from the gastrointestinal tract, seborrheic dermatitis.

In adults, it manifests itself:

• disorders of the central nervous system (irritability, drowsiness, depression, polyneuritis),
• on the part of the skin and mucous membranes (seborrheic dermatitis, chylosis, angular stomatitis, glossitis, conjunctivitis),
•nausea, vomiting.

Hypervitaminosis B6 is not observed.

Medical indications for the use of pyridoxine

Medical indications for the use of pyridoxine both independently and in complex treatment:

• hypo - and vitamin deficiency B6,
• pregnancy toxicosis,
• anemia (especially with sideroblastic),
• leukopenia of various etiologies,

• atherosclerosis,
•diabetes,
• acute and chronic hepatitis,
• nervous diseases:
• parkinsonism,
• small chorea,
• Little's disease,
• sciatica,
• neuritis,
• neuralgia,
• Meniere's disease,
• sea and air sickness,
• depression of involutional age,
• seborrheic and non-seborrheic dermatitis,
• psoriasis,
• shingles,
• neurodermatitis,
• to reduce the toxic effects of a number of anti-TB drugs,
• exudative diathesis, etc.

Contraindications: individual intolerance to the drug.

Use with caution in patients with gastric ulcer and duodenal ulcer due to the possibility of increasing the acidity of gastric juice.

Vitamin B6 Release Forms

1. Pyridoxine (vitamin B6) (synonyms: Adermin, Beadox, Bedoxin, Benadon, Besatin, Betsilan, Geksavetalin, Geksavibeks, Geksavion, Pirivitol, etc.).

2. Pyridoxalphosphate (synonyms: Aderoxal, Aderomine, Codecarboxylase, Pyridoxalium, etc.).

A synthetic drug is a coenzyme form of vitamin B6 and has all the properties of pyridoxine. It has a faster therapeutic effect.

Pyridoxine is part of a number of complex multivitamin preparations.

Vitamin B8

(Myoinositol, Mesoinositis, Inositol, Vitamin U)

Vitamin-like substance myoinositis, an optically inactive isomer of inositol, has vitamin activity and belongs to the B vitamins.

Inositol was first isolated from muscles (the obsolete name is "muscle sahar"). A number of researchers transferred the term "vitamin B8", previously given to adenylic acid, to inositol.

In 1972, the International Union of Nutritionists (Nutrition Specialists) recognized the term "myoinositis."

At the same time, a number of domestic publications mainly use the term "inositol", sometimes with the addition of the synonym "vitamin B8".

It should be noted that Claude Binet in his book "Vitamins and Vitamin Therapy" considers vitamin B8 a synonym for vitamin H or biotype, and inositol - vitamin U.

In this section, vitamin B8 or inositol will be considered.

It is found in plants in the form of an ether of hexaphosphoric acid and its salts, and in animals and microorganisms in the form of inositol phospholipids.

Inositol and its compounds are involved in the metabolism of carbohydrates, in the metabolism of purines, in the biosynthesis of phospholipids, and affects cholesterol metabolism, helping to lower cholesterol in blood serum. It is present in all tissues of the human body and is distinguished by the ability to accumulate in some organs in a significant amount (mainly the brain).

Inositol enters the human body with food of animal and plant origin.

Vitamin B9

(synonyms: folic acid, folacin, vitamin Bc, vitamin M)

Along with the biologically active compound of folic acid, its derivatives, united by the common name "folacin", also belong to vitamins.

In domestic literature, the term "folic acid" is more common, less often - "vitamin B9". In foreign reference literature, along with folic acid, the term "vitamin Bs" is more common. The term "vitamin M" is considered obsolete and practically does not occur.

Folic acid is involved as a coenzyme in various enzymatic reactions, plays an important role in the metabolism of amino acids, in purine and pyrimidine metabolism, which determines the value of vitamin A for the normal growth process, development and proliferation of tissues, in particular during hematopoiesis and embryogenesis. Folic acid stimulates and regulates blood formation, ensures the normal formation of blood cells - red blood cells, platelets, helps to increase the number of white blood cells, and plays a role in preventing atherosclerosis.

Folic acid is widely distributed in nature and enters the human body with food products of animal and vegetable origin.

Folic acid in foods

Folic acid content in some products (mgk per 100 g of product):

• brewer's yeast - 1470 mcg,
• beef liver - 240 mcg,
• beans - 160 mcg,
• parsley - 117 mcg,
• spinach - 80 mcg,
• kidneys - 45 mcg,
• salad - 40 mcg,
• wheat - 37 mcg,
• rye - 35 mcg,
• bread - 18-32 mcg,
• cabbage - 10-31 mcg,
• corn - 24 mcg,
• green onions - 11 mcg,
• meat (beef) - 10 mcg,
• apricots - 8 mcg,
• potatoes - 9 mcg,
• eggs - 7.5 mcg,
• oranges - 5 mcg,
• onions - 5 mcg,
• milk - 4 mcg,
• grapes - 4 mcg,
• lemon - 3 mcg.

Folic acid and its coenzyme forms are rather unstable compounds and are easily destroyed by cooking. So, in vegetables during long cooking, the loss of folic acid reaches 80-95%. More resistant is the vitamin contained in meat products.

Typically, a balanced diet satisfies the daily requirement of the human body by about 60%. The missing amount of folic acid enters the body through the synthesis of the vitamin by intestinal microflora.

Folic Acid Vitamin Deficiency

Folic acid deficiency is considered the most common hypovitaminosis. It is more common in older people with low levels of affluence, in patients with alcoholism, in pregnant and lactating women, as well as in a number of diseases. Folic acid deficiency can be caused by malabsorption in chronic enterocolitis, after intestinal resection, with prolonged use of barbiturates, sulfonamide drugs.

With hypo- and vitamin deficiency B9, the blood-forming tissue and intestinal mucosa are primarily affected. Macrocytic hyperchromic anemia, leukopenia, thrombocytopenia

develops. Hypovitaminosis B9 causes the phenomena of stomatitis, gastritis, enteritis. During pregnancy, folic acid deficiency can be the cause of prematurity, impaired mental development of newborns.

Medical indications for folic acid use

Medical indications for the use of folic acid both independently and in complex treatment:

• hypo- and vitamin deficiency B9,

• prevention of folic acid deficiency, including during pregnancy and lactation.

As part of a comprehensive treatment:

• anemia and leukopenia caused by drugs,

• anemia caused by resection of the stomach or intestines,

• alimentary macrocytic anemia of the newborn,

• pernicious anemia,

•radiation sickness,

• spru,

• chronic gastroenteritis,

•pulmonary tuberculosis. Contraindications:

• hypersensitivity to the drug. Side effect:

• allergic reactions are possible,

• long-term use of folic acid (especially in high doses) is not recommended because of the risk of a decrease in vitamin B12 in the blood.

Folic acid

(Synonyms: Vitamin Bs, Millafol, Pteroylglutamic acid, Pyofolin, Folacid, Folacin, Folvit, Folean, Folcidin, Folicin, Cytofol, etc.).

Folic acid is part of multivitamin complexes.

Vitamin B10

(Para-aminobenzoic acid, n-aminobenzoic acid, vitamin H1)

Para-aminobenzoic acid (PABA) refers to vitamin-like substances, has the properties of B vitamins. It is a germ factor for a number of microorganisms, a metabolic precursor of folic acid. Para-aminobenzoic acid is not recognized by all researchers as vitamin min, and therefore it is quite rarely found under the name "Vitamin B10" or "Vitamin H1."

Para-aminobenzoic acid is poorly soluble in water, but soluble in alcohol and ether. It is a chemically resistant substance that does not collapse upon boiling in an acidic and alkaline environment.

PABA is widely distributed in nature and enters the human body with food, partially absorbed in the small intestine, and partially used by the microflora of the large intestine for the synthesis of folic acid. A significant amount of para-aminobenzoic acid is found in the liver, kidneys, mushrooms, rice cuts, etc.

Vitamin B12

(Cobalamin, cyanocobalamin)

Cyanocobalamin is a complex organic compound of cobalt with a cyan group and participates in the construction of a number of enzymatic systems, being a carrier of the methyl group. It has lipotropic properties, participates in the biosynthesis of nucleic acids, affects the metabolism, mainly proteins, and the blood formation process, activating the blood coagulation system.

In the human body, vitamin B] 2 is present in three coenzyme forms that have the ability to transform into each other:

• oxycobalamin,

• methylcobalamin,

• adenosylcobalamin.

Crystallized cyanocobalamin was first obtained in 1948.

Vitamin B12 is not formed by animal tissues. Its synthesis in nature is carried out by microorganisms, mainly bacteria, akinomycetes, blue-green algae. In humans and animals, it is synthesized by intestinal microflora, from where it enters the organs, accumulating mainly in the kidneys, liver, and intestinal wall. The amount of cyanocobolamin synthesized in the body does not fully ensure the vital activity of the human body. In addition, vitamin B] 2 enters the human body only with food of animal origin. People who eat only plant-based food without taking vitamin B12 as a medicine are at risk of developing vitamin B12 deficiency.

Vitamin B12 content in foods

Vitamin B12 content in some foods (mcg per 100 g of product):

• beef liver - 50-130 mcg,
• beef kidneys - 20-50 mcg,
• cod liver - 40 mcg,
• beef heart - 10 mcg,
• herring (fillet) - 13 mcg,
• cod - 10 mcg,
• flounder - 10 mcg,
• beef meat - 2-8 mcg,
• pork meat - 0.1-5 mcg,
• veal meat - 2 mcg,
• cheese - 1.4-3.6 mcg,
• egg (yolk) - 1.2 mcg,
• fat cottage cheese -1.0 mcg,
• cream 20% - 0.5 mcg,
• kefir - 0.4 mcg,
• sour cream 30% - 0.36 mcg,
• milk - 0.2-0.6 mcg.

Vitamin B12 is predominantly absorbed in the human ileum. To improve absorption, folic acid is co-administered.

Vitamin deficiency B12

The causes of nutritional deficiency of vitamin B12 can be eating disorders (for example, in vegetarians with a long absence of animal products in the diet). In addition to the exogenous cause, there may be an endogenous reason for the development of hypo- and vitamin deficiency: increased need for vitamin during pregnancy, chronic alcoholism, intestinal diseases, hereditary disease, which caused a violation of the synthesis of specific proteins involved in the transport of vitamin B12.

Manifestations of vitamin deficiency: fatigue, irritability, loss of appetite, glossitis, achilia, impaired intestinal motility. Patients have impaired hematopoiesis with the development of macrocytic hyperchromic anemia, damage to the nervous system, leading to paresthesias, and impaired digestion.

When revealing anemia in a patient, one should first of all think about vitamin B12 deficiency.

Medical indications for the use of cyanocobalaminde

Medical indications for the use of cyanocobalaminde as an independent drug, and in complex treatment:

• anemia of various etiologies,
•radiation sickness,
• dystrophy in newborns,
• after infection,
• spru,
• infectious hepatitis,
• chronic hepatitis and cirrhosis of the liver,
• polyneuritis,

• sciatica,
• trigeminal neuralgia,
• diabetic neuritis,
• migraine
• alcoholism (alcohol delirium),
• amyotrophic lateral sclerosis,
• cerebral palsy (cerebral palsy),
• Down's disease,
• encephalomyelitis,
•multiple sclerosis,
• skin diseases:
• psoriasis,
• photodermatoses,
• herptiform dermatitis,
• neurodermatitis. Contraindications:
• hypersensitivity to the drug,
• acute thromboembolic diseases. Side effects

With increased sensitivity, the following can be noted:
• allergic reactions in the form of urticaria,
• nervous agitation,
• pain in the heart,
• tachycardia.

Vitamin B12 release form

1. Cyanocobalamin. Vitamin B12 (synonyms: Actamine B12, Almeret, Anacobin, Antinem, Antipernicism, Arkavit B12, Bedimil, Bedodek, Bedoxil, Beru-Bigen, Biopar, Vibicon, Dankovit B12, Distivit, Dobetin, Dodecavit, Gepon, Gepagon Katavin, Kobavit, Cobastab, Cobion, Lentovit, Megalovel, Novivit, Per-napar, Redami, Reticulogen, Rubavit, Rubramin, Cycobemin, Cycoplex, Cytacon, Cytamen, Cytobex, Cytobionidr.).

2. Oxycobalamin.

It is a metabolite of cyanocobalamin. By pharmacological properties and action, it is close to vitamin B12, has the same indications for use.

3.Cobalamide (synonyms: Adenosylcobalamin, Coenzyme B12).

It is a coenzyme form of vitamin B12. Indications for use are the same as for cyanocobalamin.

Vitamin B12 is part of many multivitamin complexes.

Vitamin B13

(Syn .: orotic acid, uracil-6-carboxylic acid)

Orotic acid in animals and humans is a precursor of pyrimidine bases used for the synthesis of nucleotides and nucleic acids. Thus, it participates in protein metabolism, in methionine synthesis, folic acid metabolism, in pantothenic acid conversions.

Orotic acid is a growth factor in relation to some microorganisms. All this makes it possible for a number of researchers to attribute it to vitamin-like compounds (vitamin B13).

However, orotic acid is not a true vitamin, because It is synthesized in sufficient quantities in humans and animals.

Vitamin B13 is present in animal tissues, plants, and microorganisms. They are especially rich in yeast, liver and milk. It was from these sources that orotic acid was first isolated.

Given the sufficient amount of orotic acid produced in the human body, its daily need for food has not been established.

Also, cases of vitamin B13 deficiency or hypervitaminosis have not been described.

For medical purposes, potassium salt (potassium oratate) of orotic acid is used, where the main active principle is vitamin B13. The drug has an anabolic effect in violation of protein metabolism. Stimulates metabolic processes in the body.

Indications for the use of potassium orotate in complex treatment:

• diseases of the liver and biliary tract caused by intoxication (except for cirrhosis with acidosis),

• myocardial infarction,

• chronic heart failure,

• heart rhythm disturbances,

• alimentary-infectious malnutrition in children,

• dermatoses,

• progressive muscular dystrophy,

• with severe physical exertion (to improve anabolic processes).

Vitamin B15

(Pangamonic acid, calcium pangamate)

Pangamonic acid has vitamin-like properties. Its role as a vitamin has not been established: there is no evidence that a deficiency of pangamonic acid in the human body leads to metabolic disorders (an essential property of the vitamin).

The main biochemical and physiological functions of pangamonic acid are as follows: it serves as a source of free metal groups, participating in oxidative processes and stimulating their lipotropic effect in the liver, and has detoxifying properties.

Pangamonic acid is widely distributed in foods.

Vitamin B15 was first isolated from apricot kernel kernels, and then from rice sprouts, brewer's yeast, liver and blood. The largest amount of pangamic acid is found in the seeds of plants, sunflower, nuts, almonds, and in the liver.

The exact daily human need for pangamonic acid has not been established, but it is tentatively believed that for an adult it is 1-2 mg per day.

Medical Indications for Vitamin B15

In medical practice, the calcium salt of pangamonic acid is used - calcium pangamate (vitamin B15).

Vitamin B15 is used in complex therapy for:

• various forms of atherosclerosis:

• cerebral sclerosis,

• chronic coronary insufficiency,

• atherosclerosis of the vessels of the lower extremities I-II art.,

• emphysema,

• pneumosclerosis,

• chronic hepatitis,

• chronic alcohol intoxication,

• the initial stage of liver cirrhosis,

• intoxication with corticosteroids, sulfonamide drugs,

• pruritic dermatoses.

There are no contraindications for the use of calcium pangamate. However, it should be used with caution in individuals with significantly increased blood pressure.

Vitamin W

(Carnitine, beta - hydroxy - gamma - trimethylbutyric acid, vitamin B11, vitamin T, vitamin O)

Concerning carnitine in the literary sources, rather conflicting data. So, the most substantiated data in the domestic literature are that carnitine, as a low molecular weight, nitrogen-containing substance, has the properties of B vitamins and belongs to vitamin-like compounds.

At the same time, Claude Binet notes that a number of researchers consider carnitine to be vitamin B11, vitamin O, vitamin T, or even not separate by properties from vitamin B1.

In the human body, carnitine is not synthesized, and the need for it is ensured with proper nutrition.

The main sources of carnitine are yeast, animal products (liver, kidneys, heart, meat), dairy products.

Vitamin deficiency W is not described. Also, indications for the therapeutic use of carnitine have not been established.

Vitamin C

Vitamin C is an essential water soluble vitamin. Under natural conditions, it occurs in three forms:

•vitamin C,

• dehydroascorbic acid,

• Ascorbic.

Each of these forms has vitamin activity.

First allocated in 1923-1927. Zilva (S.S. Zilva) from lemon juice is a substance with a strong anti-scrub property. He established the basic properties of this substance.

In the years 1928-1933. Szent-Gyorgyi (A. Szent-Gyorgyi) isolated in crystalline form from the adrenal glands of the bull, and then from cabbage and paprika a substance, later called "ascorbic acid." This substance turned out to be identical with Zilva's anti-tiskorbut substance.

Ascorbic acid performs the following basic biochemical and physiological functions in the human body: it participates in many biochemical reactions that occur in the body, contributes to the normal process of tissue regeneration and healing, maintains resistance to various types of stress, and ensures the normalization of immunological and hematological status.

Ascorbic acid is synthesized by all plants and many animals. Man, along with monkeys, is an exception due to the lack of enzymes in the body that affect the synthesis of ascorbic acid. Vitamin C is not produced in the human body, but only comes with food. Ascorbic acid is contained mainly in plant products.

When cooking products, on average, up to 50% of ascorbic acid is lost. Even more is lost with prolonged standing ready meals.

A number of stabilizers found in egg protein, meat, liver, cereals, cottage cheese, starch, salt contribute to the preservation of ascorbic acid in cooking. The long-term preservation of ascorbic acid is facilitated by: pickling, freezing, dehydration, canning, boiling berries and fruits with sugar.

The amount of vitamin C needed by the body depends on many factors: pregnancy, physical and mental stress, climatic conditions, etc., in which the need for vitamin C increases significantly.

Vitamin deficiency C

The deficiency can be exogenous (due to a lack of ascorbic acid in food) and endogenous (due to impaired absorption and assimilation of vitamin C in the human body).

With insufficient vitamin intake, hypovitaminosis can develop over a long period of time, manifesting as general weakness, single skin hemorrhages, and disorders of the nervous system.

Vitamin C is called scurvy or mourn.

Scurvy.

Clinical manifestations depend on the degree and duration of vitamin deficiency. With the complete cessation of vitamin C intake, scurvy develops after about 4-12 weeks; with hypovitaminosis C, clinical manifestations are less pronounced and appear at a later date - after 4-6 months.

The first manifestations of scurvy are similar to the onset of hypovitaminosis and are manifested by general weakness, rapid fatigability, and the tendency of gums to traumatize with periodic bleeding. Children have a decrease in appetite, pallor, anxiety.

During scurvy, there are three degrees:

I-st degree: fatigue, especially during physical exertion, the appearance of pain in the muscles, pain in the muscles of the legs when walking. Objectively: swelling of the gums, pastiness and pallor of the face, small hemorrhages on the skin of the lower extremities and trunk; moderate anemia.

With the timely appointment of ascorbic acid, all phenomena pass quickly.

II degree: a sharp deterioration, disability (patients with difficulty serving themselves), noticeable weight loss, up to exhaustion; pronounced gin-givitis with gangrene of the gums, bleeding gums. Skin color darkens with areas of pigmentation. Extensive hemorrhages appear in the subcutaneous tissue, muscles, and joints. Macrohematuria is often found in urine. Anemia is detected in patients.

III degree: extremely serious condition of the patient requiring emergency medical care: exhaustion, gangrenous gingvitis, ulcerative skin lesions, massive hemorrhages in the skin, muscles, internal organs, in the cavity (pleura, pericardium), in the joints and under periosteum. Often there is macrohematuria (red urine), bleeding from the urinary tract is possible. Often infections join.

At any degree of scurvy, an increase in body temperature (up to 38 °), changes in the blood are noted.

In persons who have undergone scurvy of the II-III degree, often are formed in the process of recovery of contracture of the limbs, joint deformation with impaired limb function.

Treatment depends on the degree of the disease, but necessarily includes vitamin C.

Hypervitaminosis without the use of the vitamin C drug is practically not found. However, with prolonged use of large doses of ascorbic acid, it is possible to suppress the function of the insular apparatus of the pancreas, increase blood pressure and increase blood coagulation, associated with the stimulating effect of ascorbic acid on the formation of corticosteroid hormones by the adrenal glands.

At the same time, L. Polling is of the opinion that most colds can be prevented or weakened by a diet using ascorbic acid. He is convinced that in one to two decades, ascorbic acid can be used to eliminate colds in most parts of the world.

Medical indications of ascorbic acid

Medical indications of the use of ascorbic acid alone and in complex treatment:

• prevention and treatment of hypo- and vitamin deficiency,
• providing increased demand for vitamin C:
• during the growth period,
• during pregnancy and lactation,
• with severe physical exertion,
• in case of overwork,
• during recovery from a serious illness,
• in winter with an increased risk of developing infectious diseases,
• hemorrhagic diathesis,
• bleeding (nasal, pulmonary, uterine, etc.),
• overdose of anticoagulants,
• infectious diseases and intoxications,
• nephropathy of pregnant women,
• liver disease,
• Addison's disease,
• sluggishly healing wounds and bone fractures,
• dystrophy.

There is evidence of the use of vitamin C in complex treatment for atherosclerosis.

Vitamin F

The group under the general name "Vitamin F" conditionally combines polynene-saturated fatty acids (linoleic, oleic, arachidonic and others). These acids are synthesized only by plant organisms, but are indispensable for animals and humans. They are part of biologically active substances (colds).

The biological effect of prostaglandins is diverse. They act on the reproductive system and endocrine glands, regulate the activity of the kidneys, are mediators of recovery processes, have an effect on the tone of smooth muscles of organs, reduce the acidity of gastric juice.

Since polyunsaturated fatty acids are not synthesized in the human body, they must be contained in food. Their source is vegetable oils derived from peanuts, flax, rapeseed, soybeans, rosehips.

For medical purposes, linetol (a drug derived from linseed oil) was prescribed orally for the treatment of atherosclerosis. But it was discontinued due to low efficiency.

Currently, linetol is only part of the drugs used for external use in the treatment of:

• burns,

• trophic ulcers, bedsores,

• sluggishly healing and infected wounds.

Vitamin H (Biotin)

Biotin is of great importance for the processes of skin metabolism, it is necessary for processing in the intestine and assimilation of raw egg white by the body. With a deficiency or absence of biotin and with prolonged use in a large number of raw egg white, toxic effects are possible. It is assumed that biotin, being one of the strongest vitamins, catalysts, has a regulatory effect on the nervous system, is involved in fat metabolism.

Biotin is widely distributed in nature and is found both in plant and animal products.

In products of animal origin, biotin is associated with proteins, and plant-based - is contained in free form. Due to its high activity, the human need per day of biotin is 150-200 micrograms. However, biotin not only enters the human body with food. Most of the human need for biotin is provided by its synthesis by bacteria in the intestine.

Vitamin N

(Lipoic acid, thioctic acid)

This vitamin-like substance called lipoic acid is best known. However, C. Binet described it under the name "Vitamin N". Perhaps this is another name for lipoic acid, not common in domestic literature.

For the first time, lipoic acid was isolated in 1951 from a lipid extract of the liver of cattle by Reed and coworkers. It was subsequently obtained synthetically from adepinic acid.

In the body, lipoic acid is found in different organs, but mainly in the liver, kidneys, and heart.

Lipoic acid is involved in the regulation of lipid and carbohydrate metabolism, has a lipotropic effect, affects cholesterol metabolism, improves liver function, has a detoxifying effect in various intoxications, including poisoning with heavy metal salts.

The main source of lipoic acid for humans is food, mainly yeast, liver, kidneys, heart, beef, dairy products.

Medical indications for the use of lipoic acid

Medical indications for the use of lipoic acid:

• prevention of coronary atherosclerosis,

• liver disease:

• viral hepatitis (in the absence of intense or growing jaundice),

Vitamin P

(Bioflavonoids)

Vitamin P unites a group of biologically active substances that have the ability to normalize the permeability of capillaries to help reduce the permeability of the vascular wall, increasing its strength.

In addition to the widely known name "rutin", which is often associated with vitamin P, this group, which has the properties of vitamin P, includes about 150 bioflavonoids: hesperidin, coumarins (esculin), anthocyanins, catechins, and others.

The properties of bioflavonoids were first discovered in 1936 by St. György, who established these properties in a preparation isolated from red pepper and lemon juice. The substance had a strengthening effect on the strength of blood vessels (capillaries) and cured hemorrhagic diathesis in people who could not be treated with ascorbic acid.

This substance is called vitamin P (the first letter of the word permeabiliti - permeability).

The biological effects of vitamin P have much in common with vitamin C, which has given rise to some researchers giving vitamin P a second name - vitamin C2. These two vitamins (vitamins P and C) mutually enhance their physiological action in the human body.

Bioflavonoids are found only in plant products, with which they enter the human body.

Vitamin P Content in Foods

The vitamin P content in a number of plant products (vegetables, fruits, berries) 0.05-0.1 g (content in micrograms per 100 g of product):

- chokeberry - 4000 mg,
- cherry - 1300-2500 mg,
- black currant - 1000-1500 mg,
- wild rose (dry) - 680 mg,
- oranges - 500 mg,
- lemons - 500 mg,
- sweet red pepper - 500 mg, -
- sorrel - 500 mg,
- lingonberry - 320-600 mg,
- grapes (black) - 250-430 mg,
- cranberries - 240-330 mg,
- sweet cherry (darkly colored) - 225-900 mg,
- gooseberry - 225-550 mg,
- pomegranates - 200-700 mg,
- quince - 200-825 mg,
- strawberries - 180-210 mg,
- dill - 170 mg,
- parsley - 157 mg,
- plum - 110-300 mg,
- pear - 100-250 mg,
- peaches - 80-350 mg,
- carrots - 50-100 mg,
- potatoes - 15-35 mg,
- apples - 10-70 mg.

The estimated need for vitamin P per day is half the daily intake of vitamin C, i.e. 35-50 mg / day.

The insufficiency of vitamin P intake in the human body is often combined with the deficiency of vitamin C intake, since both of these vitamins have the same source of intake (fruits, berries, vegetables).

Bioflavonoids do not accumulate in animal tissues, but undergo oxidative degradation.

Vitamin deficiency P

It is usually combined with vitamin deficiency C and is characterized by pain in the muscles of the shoulders and legs, aggravated by walking, general weakness, lethargy, and rapid fatigue. More specific manifestations of vitamin P deficiency include small intradermal hemorrhages (petechiae) that occur spontaneously, especially in areas under pressure, and disappear after the appointment of bioflavonoids.

Bioflavonoid-based medications not only have specific effects on the capillaries, but also have a positive effect on the hematopoietic system, somewhat normalize blood pressure during hypertension, contribute to a decrease in the motor activity of the stomach, reduce spastic tension of the intestinal muscles, and have anti-inflammatory and anti-allergic effects.

Medical Indications for Vitamin P

Medical indications for the use of vitamin P, both independently and in complex treatment:

- hypo- and vitamin deficiency P,
- diseases accompanied by impaired vascular permeability,

• hemorrhagic diathesis,
• retinal hemorrhages,
• capillarotoxicosis,
•radiation sickness,
• septic endocarditis,
• rheumatism,
• glomerulonephritis,
•hypertonic disease,
• arachnoiditis,
• allergic diseases,
• measles
• scarlet fever,
• typhus,
• thrombopenic purpura,
• for the prevention of capillary damage associated with the use of anticoagulants, salicylates,
• in complex treatment for a vessel. complications caused by atherosclerosis:
• myocardial infarction,
•stroke,
• retinopathy,
• radiation therapy of malignant neoplasms.

Caution is required in patients with increased blood coagulation.

Vitamin P is usually given with ascorbic acid.

Vitamin P Release Form

1. Rutin (synonyms: Birutan, Idorutin, Melin, Mirticolorin, Neorutin, Oksiritin, Ruvit, Rutabion, Rutavit, Rutinon, Rutisan, Rutorbin, Rutetsin, Filomel in and others).

The drug is obtained from the green mass of buckwheat and buds of Japanese Sophora flowers, legume seeds. Rutin is part of a number of multivitamin complexes (Vitamin P min).

2. Quercetin (synonyms: Quercetol, Meletin, Soforetin, Flavin).

Indications for the appointment are the same.

Vitamin U

(S-methylmethionine, methylmegioninsulfonium, methyl methioninesulfonium chloride)

Vitamin U is a vitamin-like compound, since its necessity (indispensability) for the human body and animal has not been proven.

Methylmethionine sulfonium was first obtained in 1940 by synthesis from methionine.

The main biochemical and physiological actions of vitamin U is: in the body, it is actively involved in metabolism, as a source of free methyl groups it has a lipotropic effect.

In 1950-60. the antiulcer effect of vitamin U was discovered in the process of studying the antiulcer effect of cabbage juice. It turned out that the main factor in the therapeutic effect of cabbage juice in patients with gastric ulcer and duodenal ulcer is methylmethionine sulfonium chloride contained in this juice.

Vitamin U enters the human body only with plant foods.

In large quantities contains:

• asparagus - 100-260 mg per 100 g,
• white cabbage - 35-85 mg per 100 g.

Vitamin U is also found in parsley, turnips, peppers, carrots, tomatoes, onions.

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Medical indications for the use of vitamin P, both independently and in complex treatment:

• hypo- and vitamin deficiency P,
• diseases accompanied by impaired vascular permeability,
• hemorrhagic diathesis,

• retinal hemorrhages,
• capillarotoxicosis,
• radiation sickness,
• septic endocarditis,
• rheumatism,
• glomerulonephritis,
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• arachnoiditis,
• allergic diseases,
• measles
• scarlet fever,
• typhus,
• thrombopenic purpura,
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As a result of numerous clinical and experimental observations, it has been established that there are intervitamin interactions in the human body: in the process of exchange, the physiological effect of each vitamin is carried out in combination with the influence of others.

The boundaries of vitamins that make up multivitamins

Here are the boundaries of the vitamins that make up a multivitamin:

• Vitamin A from 1,000 to 100,000 ME
• Vitamin B1 from 0.1 to 100 mg,

• Vitamin B2 from 0.2 to 15 mg,
• Vitamin B5 from 0.075 to 25 mg,
• Vitamin B6 from 0.14 to 200 mg,
• Vitamin B from 0.008 to 2 mg,
• Vitamin B12 from 0.03 to 200 mcg,
• Vitamin C from 1 to 500 mg,
• Vitamin D from 50 to 100 ME,
• Vitamin E from 1 to 30 ME,
• Vitamin H from 1.3 to 200 mcg,
• Vitamin P from 20 to 50 mg,
• Vitamin PP from 0.1 to 100 mg.

Such a big difference in a single dose of vitamins is not accidental, since when compiling each drug, the interaction of vitamins, the effect necessary in each specific case, and possible side effects were taken into account.

Not only the beneficial effects of vitamins on the human body, but also the possible complications of their overdose have already been examined above. Therefore, when taking multivitamins, one must take into account not only the dose of vitamins that make up the drug, but also the amount of vitamins that make up plant and animal food. Like any medication, multivitamins should be taken only in cases where there are direct indications for this, and not just "to strengthen the body." For example:

ACTIVATORS AND CORRECTORS OF METABOLISM

The pharmacological properties and therapeutic efficacy of drugs in this group are determined mainly by the biological role of nucleotides, phosphates, amino acids and other substrates, activators, and regulators of metabolic reactions. Some of them have a pronounced antioxidant effect, others improve the metabolism and energy supply of tissues, restore trophism and stimulate regeneration processes, reduce hypoxia, activate metabolism in tissues

However, it should be noted that the effectiveness of such drugs in various diseases of the internal organs, and in particular IHD, has been demonstrated only in small studies. Therefore, their use is often referred to as therapeutic measures with unproven effectiveness. Metabolic preparations for systemic use can also include biogenic stimulants: ginseng, pantocrine, eleutherococcus rhizomes and roots, aloe tree leaves, humic sol *, royal jelly (apilak *), melatonin, etc.

Adenosine phosphate

Adenosine phosphate (AMP) - a component of the adenyl system; its biological role:

• activation under anaerobic conditions of a number of enzymes of the Krebs cycle, enhancement of ATP resynthesis with simultaneous inhibition of glycolysis;

• as a purine nucleotide promotes the synthesis of nucleic acids and, therefore, the synthesis of proteins;

• It is part of the most important respiratory coenzymes that transfer electrons and protons in the initial links of the tissue respiration chain (NAD, NADP and FAD);

• energy supply of synthesis processes - a precursor of macroergic compounds (the formation of ADP and ATP occurs during phosphorylation of AMP);

• participates in the regulation of carbohydrate metabolism.

It is able to penetrate into cells. Entering the body, adenosine phosphate (phospha-den *) cannot immediately be included in the macroergic pool - it is first metabolized to adenosine. The latter has biological activity - there is an expansion of arterial capillaries, which leads to the activation of metabolism due to an increase in oxygen flow, an increase in ATP synthesis. In addition, adenosine can be included in the synthesis of macroergs.

At the same time, with a sufficient amount of ATP in the cell, adenosine phosphate transitions not to adenosine, but to inosine monophosphate, metabolized differently. By the combination of properties, adenosine can be attributed to anabolic substances.

Indications for use. The drug is used to improve peripheral circulation, as well as to restore anabolic processes and microcirculation in acute and chronic myocardial diseases.

The method of administration and dose. Prescribe per os in tablets in a single dose of 25-50 mg, with a daily dose of up to 300 mg. The duration of the course is 15-30 days (if necessary, treatment is repeated with an interval of 5-7 days).

Inosine (riboxin) has antihypoxic, antiarrhythmic properties, has an anabolic effect. Being a precursor of ATP, the drug is directly involved in glucose metabolism and promotes the activation of metabolism during hypoxia, normalizes tissue respiration, energy balance, and stimulates nucleotide synthesis. increases the activity of a number of enzymes in the Krebs cycle. Inosine improves myocardial contractility and contributes to a more complete relaxation of the heart muscle in diastole due to the ability to bind calcium ions. The drug also activates the regeneration of tissues, especially the myocardium and the mucous membrane of the digestive canal. Riboxin is used in the complex treatment of coronary heart disease, cardiac arrhythmias, intoxication with cardiac glycosides, cardiomyopathies of various origins, myocarditis, which occur against the background of physical overwork.

The drug is prescribed orally and parenterally. Inside, tablets are taken before meals in a daily dose of 600-800 mg, with good tolerance, the dose gradually, over 2-3 days, initially increased to 1.2 g per day (2 tablets 3 times a day), then up to 2.4 g (4 tablets 3 times a day). The drug is also administered intravenously (40-60 drops in 1 min) or slowly in a stream, first 200 mg (10 ml of a 2% solution) once a day, then, with good tolerance, up to 400 mg (1-2 once a day). Inkjet administration is possible with cardiac arrhythmias in a single dose of 200-400 mg (10-20 ml of a 2% solution). With the intravenous drip of a 2% solution, the drug is diluted in a 5% glucose solution or in an isotonic sodium chloride solution.

Adenosine (adenocor) also has a positive effect on myocardial metabolism; but of greater importance is its ability to exert a negative chronotropic and dromotropic effect, and hence the antiarrhythmic effect. The drug slows down the conduction of impulses in the atrioventricular node and Purkinje fibers, blocks the calcium channels of the membrane and increases the permeability of the membranes of cardiomyocytes for potassium ions. It is prescribed for paroxysmal supraventricular tachycardia, Wolff-Parkinson-White syndrome, pharmacological load during radioisotope scanning of the myocardium.

Remained in demand are preparations containing potassium and magnesium. This is, first of all, aspartame (panangin), which is a potassium and magnesium aspartate and has antiarrhythmic and antihypoxic properties. Magnesium activates No. + / K + -ATPase, as a result of which the intracellular sodium level decreases, the potassium content increases, and ATP synthesis is stimulated. glycogen, proteins, acetylcholine. In addition, potassium and magnesium support the polarization of the cell membrane, therefore, the drug is used in conditions accompanied by hypoxia. Asparkam is included in the treatment regimen of angina pectoris, neurocirculatory dystopia, ventricular extrasystole, digitalis intoxication.

The drug is intended for enteral and parenteral use. Inside, they are prescribed tablets 3 times a day after meals, as well as intravenously and drip. When administered intravenously, the contents of 1-2 ampoules of 10 ml or 2-4 ampoules of 5 ml each are diluted in 50-200 ml of a 5% solution of glucose or sterile water for injection and injected at a rate of 25 drops per 1 minute 1-2 times per day. For intravenous injection, the contents of 1 ampoule of 10 ml or 2 ampoules of 5 ml are diluted in 20 ml of sterile water for injection or 5% glucose solution and administered at a rate of not more than 5 ml-min "1.

There are experimental data on the effectiveness of the rhythmocore preparation, which contains potassium and magnesium salts of glucuronic acid and, as a result, has a greater antiradical effect than Aspark.

Potassium bleach takes part in the regulation of myocardial excitability, conduction, automatism and contractility, increases the level of acetylcholine, reduces the cardiotoxic effect of cardiac glycosides, and has a moderate diuretic effect.

Potassium chloride is used for hypokalemia, including due to the use of saluretics or cardiac glycosides, indomitable vomiting. profuse diarrhea, myasthenia. Intravenous drip is administered at a rate of 20-30 drops in 1 min, diluting 50 ml of a 4% solution of the drug with water for injection up to 500 ml. Inside, prolonged-acting tablets are usually prescribed - potassium normin or caliposis prolongatum.

Other indications for use are potassium orotate, which refers to drugs that affect metabolic processes due to the content of orotic acid, which stimulates protein metabolism and to some extent normalizes lipid and carbohydrate. The drug is used in the complex treatment of patients with coronary heart disease, heart failure, with arrhythmias requiring stimulation of anabolic processes. Potassium orotate is prescribed orally for I hour before or 4 hours after eating 2-3 times a day before a daily dose of 0.5-1.5 g.

Magnesium sulfate is administered intravenously or intramuscularly to stop both hypertensive crisis and arrhythmias. Magnesium orotate (magnetum) has anabolic, antispasmodic, antiaggregant action. It is prescribed for the same indications as potassium orotate, as well as for conditions associated with magnesium deficiency.

Magnesium in combination with pyridoxine hydrochloride (Magne B6), in addition to cardio-protective, has a neuroprotective effect.

Cardonate is an effective form of amino acids and trace elements - L-carnitine, lysine, coenzyme vitamin B12 - cobamamide. coenzyme of vitamin B, - cocarboxylase, coenzyme of vitamins B6 - pyridoxal-5-phosphate. The drug stimulates all types of metabolism, normalizes the function of the cardiovascular system for angina pectoris, cardiac arrhythmias, and has a hypo-cholesterolemic effect.

Clinical trials of cardonate indicate that its inclusion in the treatment regimens of IHD, hypertension and arrhythmias increases the effectiveness of specific therapy and improves the general condition and adaptive capabilities of the body.

The preparations of metabolic, cardioprotective, antioxidant action also include cytochrome C, which is used in clinical treatment in the complex treatment of coronary heart disease and heart failure.

Trifosadenin

Trifosadenin (adenosine triphosphoric acid, ATP) is an adenosine triphosphate ester containing adenine, ribose, and three phosphoric acid residues. The path of incorporating exogenous ATP into the bioenergetic processes of the organism is complex and diverse. First, a large amount of the ATPase enzyme immediately metabolizes it. Secondly, in the course of further biotransformation, depending on the state of the enzyme systems of the body, metabolites of exogenously introduced ATP are turned on along either adenosine phosphate or inosine. The effect of administering a standard dose of trifosadenin (20 mg) is lower than that of nucleotides previously described. Since less active products are formed during its metabolism, ATP in large doses cannot be administered due to an increase in the number of adverse reactions. The most effective ATP, like other nucleotides, in combination with coenzymes and vitamin preparations.

Indications for use - ischemic heart disease, asthenic conditions, vegetative-vascular dystonia, i.e. then, when a moderate correction of microcirculation processes is necessary by changing capillary circulation, activating the synthesis of adenyl nucleotides in unchanged systems.

The method of administration and dose. The drug is administered intramuscularly at 1-2 ml / day of a 1% solution for 2-4 weeks.

Trimetazidine (preductal). Over the past 20 years, a new approach has been approved for the search for drugs with a metabolic type of action. Practical medicine included preparations of synthetic origin that have heterocyclic compounds in their structure that are most often found in body tissues. Currently, one of the most widely used metabolite drugs is trimetazidine (preductal, triductan), an imidazole derivative that has a cytoprotective effect on the myocardium and, according to the decision of the European Association of Cardiology, was recognized as one of the most effective. Cardioprotection with the introduction of trimetazidine is carried out due to

the intensification of myocardial energy supply, which is achieved by partially inhibiting the oxidation of fatty acids due to inhibition of the activity of 3-ketoacylcoenzyme A-thiolase and switching myocardial metabolism to glucose oxidation. This prevents the development of intracellular acidosis and calcium overload, ensures the maintenance of ATP production and the preservation of contractile function. The drug improves the functioning of the myocardium, restores the work of ion pumps. To some extent, membrane protection is due to an increase in phospholipids due to a change in the utilization of fatty acids, which ensures cell resistance to damage during ischemia-reperfusion.

Trimetazidine is able to restore systolic and diastolic myocardial function in patients with postinfarction ischemic syndrome. Improvement of diastolic function after treatment with this agent is caused by a decrease in the total number of ischemic segments, among which the segments with a hibernating myocardium most sensitive to metabolic therapy are of the greatest importance. In the absence of the possibility of performing surgical re-vascularization in patients with postinfarction ischemic syndrome and the presence of systolic or diastolic myocardial dysfunction, trimethazidine therapy is indicated along with drugs that affect hemodynamic parameters. Trimetazidine is prescribed for coronary heart disease (treatment and prevention of angina attacks) 20 mg 3 times a day with meals.

Recently, a new form of trimetazidine has been created - preductal MR tablets with modified release of the active substance (35 mg), which is used 2 times a day. At the same time, the concentration of the drug increases, the fluctuations in its level in the plasma of the CVI are reduced compared with the traditional triple dose of trimetazidine. In addition, this drug has a longer concentration plateau phase, i.e., its pharmacokinetic profile is able to optimize antianginal activity and cardioprotection.

When trimetazidine is included in the complex therapy of angina pectoris, its additive effect with the main antianginal drugs is established. So, it was found that the effect of the combined use of trimetazidine with propranolol and nifedipine is significantly higher in patients with stable angina and reduced sensitivity to these drugs.

As a result of three-month therapy with MR preductal in patients with stable angina pectoris, ^ insufficiently controlled therapy with hemodynamic drugs, the number of anginal attacks per week decreased by more than 3 times, the functional class of angina decreased in 38.6% of patients, the quality significantly improved life of patients. The addition of MR preductal to the therapy did not lead to a change in the dosages of p-blockers and calcium antagonists; the frequency of nitrate administration decreased by more than 3 times.

Mildronate The cytoprotective properties of mildronate are well expressed, although it cannot be considered a reference cytoprotector, since a significant place in its mechanism of action is occupied by a change in hemodynamic parameters. Under ischemic conditions, the oxygen supply to the cells is limited and insufficient for the oxidation of fatty acids. As a result of this, under-oxidized acylated forms of fatty acids (acylcarnitine and acylcoenzyme A) accumulate in mitochondria, which, on the one hand, block the transport of ATP into the cytosol, and, on the other hand, as detergents, destroy membranes. Therefore, by blocking the biosynthesis of the carnitine fatty acid transporter, Mildronate maintains a sufficient level of ATP, prevents the violation of the aerobic oxidation of glucose, and promotes biosynthesis; natural inhibitor of carnitine biosynthesis of y-butyrobetaine. The drug also activates the enzymes hexokinase and pyruvate dehydrogenase. normalizes the tone of the blood vessels, prevents the development of myocardial hypertrophy. Like trimetazi-din, mildronate has been successfully included in treatment regimens for angina pectoris and coronary heart disease, including emergency treatment. The drug is safe and has a very low toxicity.

Some studies have confirmed the high clinical efficacy of mildronate in cases of cerebrovascular accident, atherosclerosis of lower limb vessels, and a positive effect of the drug in the treatment of patients with chronic heart failure (CHF) was also recorded. The inclusion in the combination therapy of severe congestive CHF of mildronate at a dose of 1 g-day "1 oral for

30 days has a positive effect on the clinical and hemodynamic status of patients and does not cause side effects.

With heart failure, mildronate improves myocardial contractility, with coronary heart disease increases exercise tolerance, increases physical performance, weakens physical and mental stress. With stable angina, the drug is prescribed orally at 250 mg 3 times a day for 3-4 days, then 2 times a week for an average of 1-1.5 months. With unstable angina pectoris, myocardial infarction, intravenously injected 500-1000 mg once a day, then - as with stable angina pectoris. With cardialgia, Mildronate is prescribed orally at 250 mg 2 times a day.

Thiotriazolinum. From domestic cardioprotectors of synthetic origin, thiotriazoline, which has an antioxidant effect, is increasingly being introduced into clinical practice. membrane-stabilizing, anti-ischemic, immunomodulatory effect, improves the effectiveness of antianginal and anti-hypertensive drugs, is also a classic hepatoprotector. The results of the studies showed that the administration of a 2.5% solution of thiotriazoline 2 ml intramuscularly 2 times a day normalizes the processes of lipid peroxidation and increases the activity of the antioxidant system in patients with heart failure due to arterial hypertension, including symptomatic , against a background of chronic pyelonephritis.

Nucleoside preparations, such as inosine (riboxin) and adenosine (adenocor), are used in clinical practice.

Coenzyme Q10

Coenzyme Q10 (KoQ10), increasing the synthesis of ATP, stimulates the processes of cell respiration in cardiomyocytes. It has a clinically significant antioxidant protective effect. Protects the membrane of cardiomyocytes from peroxidation. Reduces the area of myocardial damage in conditions of ischemia and reperfusion. KoQ10 activates the Na + -K + -ATPase, which normalizes the process of membrane repolarization and, thus, prevents the lengthening of the Q-T interval.

The water-soluble form of ubiquinone has a higher bioavailability compared to fat-soluble.

The combination of coenzyme Q10 and vitamin E prevents the development of atherosclerosis by acting on low density lipoproteins. The drug stimulates metabolic processes, increases exercise tolerance.

Succinic acid

Succinic acid increases the activity of the antioxidant system of the cell due to the restoration of glutathione and the activity of vitamin E and CoQ10, antioxidant enzymes (glutathione peroxidase and catalase).

Drugs that do not significantly affect hemodynamic parameters, but are able to "switch" the cardiomyocyte metabolism under conditions of ischemia from FA oxidation to glucose oxidation, are called antianginal drugs with a metabolic mechanism of action, or myocardial cytoprotectors.

There is no generally accepted classification of drugs with metabolic mechanisms of action. This class of drugs is heterogeneous both in chemical structure and in mechanisms of action, pharmacokinetics and pharmacodynamics of individual drugs.

Preparations of various groups with antioxidant effect

Along with vitamins and minerals, antioxidant properties are possessed by drugs of various groups: carnitine, taurine, carnosine *, sibibinin (karsil *), essentiale *, allopurinol, dimephosphon *, dimercaprol (uni thiol *), cerebrolysin *, bioflavonoids , coenzyme Q

Carnitine normalizes fat metabolism, limits lipid oxidation, inhibits the formation of hydroperoxides of fatty acids, and this helps preserve the integrity of cell membranes.

Taurine - 2-aminoethylsulfonate acid (β-amino acid). The mechanism of action is associated with interference in the activity of a number of cations. The drug protects the lung tissue from damage by irritating substances.

Dimephosphon * increases the activity of the antioxidant system of the blood, increases the activity of the redox system of glutathione, preventing the oxidation of its thiol group.

Dimercaprol (unitiol *). The sulfhydryl groups in its composition divert various oxidizing radicals and thereby retain the activity of similar groups of various biologically active substances (for example, glutathione). Therefore, the drug is widely used as an antioxidant in obstetric-gynecological practice.

Cerebrolysin * reduces lactic acidosis in the brain, slows down the formation of highly reactive forms of oxygen free radicals and reduces the concentration of membrane lipid peroxidation products. The preparation has the properties of a stabilizer of cell membranes, promotes the maintenance of Ca2 + homeostasis and reduces the neurotoxic effect of high concentrations of excitatory amino acids (for example, glutamine).

The study of the pharmacology of drugs of metabolic type of action continues. Currently, it is obvious that most of these drugs can optimize the pharmacotherapy of various diseases, as well as be effectively used in the practice of training highly qualified athletes. It is metabolic pharmacotherapy that reveals the postulate "Primum pop poseg" (do no harm). Therefore, there is no doubt that drugs of the metabolic type of action will take their due place in sports medicine of the 21st century.

The purpose of the lesson. To master the general principles of substitution, adaptive and pharmacodynamic vitamin therapy. Know the pharmacokinetics and pharmacodynamics of vitamin preparations, enzymes, their inhibitors and other substances that affect metabolic processes, indications and contraindications. To be able to prescribe drugs of this group for various pathologies, including stomatological.

Control questions*:*

1. The role of vitamins in tissue metabolism.
2. Classification of VITAMIN PREPARATIONS: water and fat soluble.
3. Types of vitamin deficiency and their causes: a) hypovitaminosis (endogenous and exogenous); b) hypervitaminosis.
4. Types of vitamin therapy: a) substitution; b) adaptive; c) pharmacodynamic.
5. Features of treatment with vitamin preparations and coenzymes. The concept of preventive and therapeutic doses.

DRUGS OF WATER-SOLUBLE VITAMINS□.

1) Thiamine (Vitamin B1). Pharmacodynamics Importance for the functioning of nerve tissue. Effect on metabolism and myocardial metabolism. Kokar-boksilaza. Side effects. Application in medical practice.

2) Riboflavin (vitamin B2). Pharmacodynamics Indications and contraindications.

3) Nicotinic acid (vitamin PP, B3). Pharmacodynamics Undesirable effects. Indications and contraindications for use. Combined preparations based on nicotinic acid (nicoverin, nicospan, picamilon). Nicotinic acid derivatives synthesized at the Department of General and Clinical Pharmacology of the Omsk State Medical University (potassium and magnesium nicotinates, xanthinol nicotinate, lithonite).

4) Pyridoxine (vitamin B6). Hematopoietic, cardiotropic and hepatotropic effects. Indications and contraindications for the use of drugs.

5) Ascorbic acid (vitamin C). Biological role. Pharmacodynamics and pharmacokinetics. Indications and contraindications for use. Combined drugs based on ascorbic acid (Aspirin UPSA, Aspro S Forte, Coldrex).

6) Bioflavonoids (Vitamin P). Biological role. Indications for use of rutin, quercetin.

7) Pantothenic acid (vitamin B5). Biological role. Indications for the use of calcium pantothenate, panthenol.

8) Pangamic acid (vitamin B15). Biological role. Indications for use.

9) Vitamin U. Biological role. Indications for use.

10) Lipoic acid. Biological role. Indications for use.

DRUGS OF FAT-SOLUBLE VITAMINS□

1. Retinol (Vitamin A). Pharmacodynamics Hypo- and hypervitaminosis A. Use of retinol acetate, palmitate, vitadral, etc.

2. Calciferols (vitamins of group D). Pharmacodynamics Hypo-and hypervitaminosis D. The use of ergocalciferol, calciphediol, calcitriol, etc.

3. Tocopherols (vitamin E). Biological significance. The use of tocoferol acetate.

Indications for the use of vitamins

These vitamins can be used both independently in the form of injections (parenteral), for oral and external use, and in complex treatment. However, this does not exclude that with this disease other vitamins other than the indicated ones or multivitamin complexes can be used in complex treatment.

Abscess - Vitamin B5.

Acroparasthesia - Vitamin B5.

Alcoholism (chronic and for relief in the acute period) - vitamins: B1, B4, B5, B12, B15, Sun.

Allergy - Vitamins B5 and R.

Alimentary and infectious malnutrition in children - Vitamin B13.

Amyotrophic lateral sclerosis - vitamins E and B12.

Anemia - vitamins: B6, B12, B13, Sun, including:

• alimentary macrocytic - vitamin Bs,
• pregnant - B12,
• iron deficiency - B6, B12,
• macrocytic after resection of the stomach - vitamin B12,
• megaloblastic - vitamin B13, Sun,
• microcytic - vitamin B6.

Arachnoiditis - Vitamin R.

Arthritis - Vitamin C.

Arthrosis - Vitamin E.

Asthenia (asthenic syndrome) - vitamins B2 and E.

Atherosclerosis - vitamins: A, B4, B6, B8, B15, C, PP, N (lipoic acid).

Atherosclerosis of the vessels of the lower extremities - vitamin B15.

Atony of the intestine - vitamins B1 and K.

Atony of the intestine after surgery - vitamin B5.

Pregnancy - vitamins B1, B2, Sun, C, K (in the last month to prevent bleeding in newborns).

Blepharitis - Vitamin B2.

Addison's Disease - Vitamin C.

Botkin's disease - vitamins: B2, B4, B6, B12, N (lipoic acid).

Down Disease ~ Vitamin B12.

Little's disease is vitamin B6.

Meniere's disease - vitamins: B1, B6, PP.

Marine and airborne disease - Vitamin B6.

Bronchial asthma - vitamin B5.

Bronchitis - vitamins A and B5.

High neuropsychic load - vitamins B2 and C.

High physical activity - vitamins: B2, B13, C, E.

Sluggish and infected wounds and ulcers - vitamins: B2, A, C, F, P and PP.

Flaccid bone fractures - Vitamin C.

Gastritis anacid - vitamins C, PP.

Acute and chronic gastritis - vitamins: A, B6 and U.

Chronic gastroenerocolitis - vitamins: B1, B2, Sun.

Hemorrhages associated with an overdose of anticoagulants and taking drugs of other groups - vitamin K.

Hemorrhagic disease of the newborn - vitamin K.

Hemorrhagic diathesis - vitamins C, K, R.

Acute infectious hepatitis - see Botkin's disease.

Chronic hepatitis - vitamins: B1, B2, B4, B5, B6, B12, B13, B15, C, K, PP, N (lipoic acid).

Hypertension - Vitamin R.

Hypercholesterolemia - Vitamin PP.

Hypothyroidism - Vitamin B4.

Hypothrombium - Vitamin K.

Hypotrophy in children - vitamins A and E.

Glomerulonephritis - Vitamin R.

Starvation - Vitamin B1.

Depression of involutional age - vitamin B6.

Dermatitis - vitamins: B2, B6, B12, C, N, including:

• herpetiform - vitamins B12 and C,

• seborrheic - vitamins B2, B6 and N.

Dermatoses:

• allergic - vitamin PP,

• itchy - vitamins B15, Sun,

• the rest (including mycoses) - vitamins B12, B13, BC, E.

Dermatomyositis - Vitamin E.

Cerebral Palsy (Cerebral Palsy) - Vitamin B12.

Defects in the uterine mucosa - vitamin B5.

Diarrhea - Vitamin K.

Diproteinemia - Vitamin K.

Dystrophy - Vitamin C.

Dystrophy of newborns after infections - vitamin B12.

Muscular dystrophy posttraumatic - vitamin E.

Progressive muscular dystrophy - vitamin E, B6.

Progressive muscular dystrophy in children - vitamin B8.

Long-term use of antibiotics and sulfonamides - vitamin B2.

Diseases:

• inflammatory nasal cavities - vitamin B5,

• inflammatory oral cavity - vitamin B5,

• non-infectious gastrointestinal tract - vitamin B5,

• skin - vitamin B12,

• the skeletal system caused by a violation of the metabolism of calcium and phosphorus in the body - vitamin D,

• liver and biliary tract caused by intoxication - vitamin B13,

• ligamentous apparatus and muscles - vitamin E,

• accompanied by a violation of vascular permeability - vitamin R.

Stroke - Vitamin R.

Intoxication:

• alcohol - vitamin N (lipoic acid),

• vitamin D - vitamin E,

• corticosteroids - vitamin B15,

• arsenic, bismuth, mercury and other vitamins B1, C, D,

• when eating raw eggs - vitamin H,

• industrial poisons - vitamin E,

• anti-tuberculosis drugs (tuboside, phthivazide) - vitamins B5, B6,

• sleeping pills - vitamin N (lipoic acid),

• salts of heavy metals - vitamin N (lipoic acid),

• sulfonamides - vitamin B15.

Myocardial infarction - vitamins: B8, B13, R.

Infectious diseases and intoxications - vitamin C.
Irit - Vitamin B2.
Ichthyosis - Vitamin A.
Capillarotoxicosis - vitamins C and R.
Cataract - Vitamin B2.
Keratitis is a vitamin B2.
Keratoses - Vitamin A.
Climax - Vitamin E.
Colitis is Vitamin A.
Conjunctivitis - Vitamin B2.
Coronary insufficiency (chronic) - vitamin B15.
Korsakovsky syndrome - vitamin B1.
Measles - Vitamin R.
Retinal hemorrhage - Vitamin R.
Bleeding
• nasal - vitamins C and K,
• pulmonary (with pulmonary tuberculosis) - vitamins C and K,
• uterine (juvenile or premenopausal) - vitamins C and K,
• for diseases of the gastrointestinal tract
• vitamins C and K,
• postoperative or from wounds - vitamins C and K.
Bleeding and hemorrhagic diathesis associated with hypothrombia - vitamin K.
Lactation - Vitamins: B2, Sun, C.
Leukopenia - Vitamin B6.
Shingles - Vitamin B6.
Radiation sickness - vitamins: B2, B12, Sun, C, P, K (with bleeding).
Radiation Therapy - Vitamin R.
Lesser chorea - vitamin B6.
Alimentary melalgia - vitamin B5.
Migraine - Vitamin B12.
Myelosis (funicular) - vitamin B12.
Myocardial dystrophy - vitamin B1.
Myopathy (after a heart attack) - vitamin E.
Muscle weakness - Vitamin K.
Violations:
• intestinal absorption - vitamin B1,
• menstrual cycle - vitamin E,
• metabolic processes - vitamin B5,
• peripheral circulation - vitamin E,
• heart rate - vitamin B13,
• bowel function - vitamin B2,
• male gonadal function - vitamin E.
Neuralgia - vitamins: B1, B5, Wb.
Neurasthenia - Vitamin E.
Neuritis (vitamins B1, B6, B12, PP), including:
• facial nerve - vitamin PP,
• auditory nerve - vitamin PP,
• toxic - vitamin B1,
• trigeminal nerve - vitamin B12.
Heart Circulatory Failure - Vitamin B5.
Neurodermatitis - vitamins B6 and B12.
Bowel obstruction (paralytic) - Vitamin B5.

Bowel obstruction (surgery) - Vitamin B5.
Frostbite - Vitamin A.
Obstructive jaundice - vitamin K.
Burns - Vitamins A, B5 and F.
Diaper rash - vitamin B5.
Osteomalacia - Vitamin D.
Osteoporosis - Vitamin D.
Acute respiratory disease (ARI) - Vitamin A, B5, C.
Pancreatitis (chronic) - Vitamin B5.
Paresthesia - Vitamin B5.
Parkinsonism - Vitamin B6.
Pellagra - Vitamin PP.
An overdose of anticoagulants - vitamin C, K.
The recovery period after an infectious disease is vitamin E.
The recovery period after a serious illness is vitamin C.
The period of increased risk of colds is vitamin C.
Growth Period - Vitamin C.
Peripheral paresis and paralysis - vitamin B1.
Pneumonia - Vitamin A.
Pneumosclerosis - vitamins A and B15.
Increased fragility of blood vessels - vitamin E.
Old Age - Vitamin K.
Polyneuritis - vitamins B5 and B12.
Porphyria - Vitamin B2.
The postoperative threat of bleeding is vitamin K.
After removal of the tonsils - vitamin B5.
Renal stone disease - Vitamin A.
Progressive muscular dystrophy - vitamin B13.
Pressure ulcers - vitamins B5, and F.
Prevention of coronary atherosclerosis is vitamin N (lipoic acid).
Prevention of capillary damage associated with the use of anticoagulants and salicylates - vitamin R.
Prevention of bleeding in preparation for surgery - vitamin K.
Psoriasis - Vitamins B2 and E.
Radiculitis - vitamins: B1, B6, B12.
Multiple sclerosis - vitamin B12.
Parathyroid Disorder - Vitamin D.
Rickets - Vitamins A and D.
Rheumatism - Vitamin C and R.
Retinitis (pigmented) - Vitamin A.
Retinopathy - Vitamin R.
Diabetes mellitus - vitamins: B6, B8, B12, P, N (lipoic acid).
Septic conditions accompanied by hemorrhagic phenomena - vit. TO.
Heart failure (chronic) - vitamin B13.
Scarlet fever - vitamin R.
Scleroderma - Vitamin E.
Sclerosis of cerebral vessels - vitamin B15.
Peripheral Spasm - Vitamin E.
A cerebrovascular spasm is vitamin PP.
Spasm of the vessels of the lower extremities - vitamin PP.
Spru - vitamins: B2, B12, Sun.
Senile keratosis - vitamin A.

Angina pectoris - vitamins B13 and PP.
Streptoderma - vitamin B2.
Typhus - Vitamin R.
Thyrotoxicosis - Vitamin B1.
Toxicoderma - Vitamin C.
Pregnant toxicosis - vitamins: B5, Wb and C.
Nipple Cracks - Vitamins B2 and B5.
Thrombopenic Purpura - Vitamin R.
Thrombophlebitis, phlebitis - vitamin E.
Pulmonary Tuberculosis - Vitamin Bs.
Acne (pink and youthful) - vitamin B2.
The threat of abortion is vitamin E.
Reduction of toxic effects (anti-TB drugs, anti-biotics, sulfonamides, etc.) - vitamin B5.
Pharyngitis - Vitamin B5.
Phlebitis - see Thrombophlebitis.
Follicular Diskeratosis - Vitamin A.
Photodermatosis - Vitamin B2.
Furunculosis - Vitamin B5.
Zinga - Vitamin C.
Liver cirrhosis - vitamins: A, B1, B4, B8, B12, B15, C, K, N (lipoic acid), PP.
Cystinuria - Vitamin B4.
Schizophrenia - Vitamin PP.
Eczema - vitamins: A, B5, C.
Exudative diathesis - vitamin B6.
Emphysema - Vitamin B15.
Obliterating endarteritis - Vitamin E.
Septic Endocarditis - Vitamin R.
Chronic enterocolitis - vitamins: A, C, PP, U.
Encephalomyelitis - Vitamin B12.
Encephalopathy - Vitamin B1.
Epilepsy - Vitamins B and E.
Desquamative erythroderma - vitamin N.
Erythromelalgia - Vitamin B5.
Erosive and ulcerative lesions of the intestine - vitamin A.
Peptic ulcer of the stomach and duodenum 12 - vitamins: B1, B6, C, PP, U.
Corneal ulcers - vitamin B2.
Trophic ulcers - vitamins B2 and F.

4. Interaction of vitamin preparations with each other and with other medicinal products.

5. Multivitamin (neuroorubin, milgamma, neurovitan, etc.) and vitamin preparations in combination with trace elements (vitrum, aevit, undevit, unicap, oligo-vit, etc.). Indications and contraindications for use.

6. Medicinal plants containing vitamins (sea buckthorn, rose hips, lingonberries, currants, etc.).

7. The concept of anti-vitamins.

General characteristics of drugs. Indications and contraindications for use.

MISCELLANEOUS PREPARATIONS INFLUENCING SUBSTANCE PROCESSES: drugs that improve energy supply (oxygen, glucose, trimetazidine, ATP, riboxin, etc.), amino acid preparations (glutamic acid, calcium glutamate, methionine, cysteine, cerebrolysin, etc.); containing poison of bees, snakes, products of their vital activity (apilak, propolis, apisatron, viprosal, etc.); biogenic stimulants (carnitine, aloe extract, fibs, etc.); cytoprotectors and chondroprotectors (actovegin, solcoseryl, rumalon); antioxidants and antihypoxants (erisol, emoxy-pin, tocopherol, etc.) and others. General description. Indications for appointment.

The list of practical works:

1. To study - pharmacokinetics, pharmacodynamics, indications, contraindications for use, undesirable effects of the above drugs.

2. The student must be able to:

a) select the necessary drug for a particular patient, select the dose, regimen and route of administration of the drug;

b) identify criteria for evaluating the therapeutic efficacy and safety of the drugs used;

3. The student must know:

What is the biological role of vitamins.

What are the mechanisms of action

Basic principles of application.

classification,

Control of the intermediate level of knowledge.

The solution of situational tasks:

1. Patient T., 70 years old, underwent surgery for a large resection of the small intestine due to cancer. What type of anemia can develop in this case? What methods of prevention and treatment can you recommend?

2. Patient D., 43 years old, was admitted to the hospital with complaints of weakness, dizziness, shortness of breath with little physical exertion. Anemia was detected in the blood test (HB - 60 g / l, col. Pop. - 1.2). On examination of the tongue - glossitis. In the study of bone marrow punctate - megaloblastic type of hematopoiesis. What type of anemia can you think of? Suggest methods for further examination and pharmacotherapy of the patient.

TESTS

1. The patient who underwent a mastectomy in connection with breast cancer, was prescribed a course of radiation therapy. Which of the following vitamin preparations has a clear radioprotective effect, predetermined anti-oxidative activity?

A. Riboflavin

B. Ergocalciferol

C. * Tocopherol acetate

D. Cyanocobolamine

E. Follic acid

2. A woman of 25 years with a view to losing weight for 1.5 months was on a diet, which consisted of 2 cups of coffee without sugar, 3 crackers of white bread, 2 sausages or 2 eggs per day. Body weight decreased by 5 kg, severe headaches, persistent nosebleeds, bleeding gums, loosening of teeth, flaking of the skin and increased hair loss appeared. The purpose of which vitamin preparation is appropriate in this case?

A. Vikasola

B. Cyanocobalamin

C. Folic Acid

D. Retinol Acetate

E. Ascorbic acid

3. As a result of uncontrolled intake of a vitamin preparation, the child has anorexia, nausea, vomiting, diarrhea, hyperthermia, hemorrhages on the skin and mucous membranes, as well as the phenomena of meningism. What drug did the baby take?

A. Nicotinamide

B. Somatropin

C. * Retinol acetate

D. Routine

E. Tocopherol acetate

4. A woman turned to the pediatrician about the poor health of the child of 8 months: sweating, fontanel size increased, lagging in teething (only 2 teeth), anxiety. Which drug should be prescribed first?

A. Folic Acid
B. Thiamine
C. Cyanocobalamin
D. * Ergocalciferol
E. Calcium Pangamate

5 The patient has dementia, diarrhea, dermatitis. Diagnosed with pellagra. Do you use a vitamin preparation for treatment?
A. Tocopherol acetate
B. Thiamine bromide
C. * Nicotinic acid
D. Cocarboxylase
E. Riboflavin

6 A patient with symptoms of acute pancreatitis was admitted to the surgical department of the hospital: vomiting, diarrhea, severe operative pain in the abdomen, weakness, hypotension, and waterless body. What is a drug with antienzyme activity?
A. Adrenaline
B. Analgin
C. * Contrikal
D. Atropine sulfate
E. Sodium bicarbonate

7 The patient went to the doctor with a complaint of common caries. Should a vitamin action agent be added to complex therapy to strengthen tooth enamel?
A. * Ergocalciferol
B. Retinol Acetate
C. Tocopherol acetate
D. Vikasol
E. Thiamine bromide

8. A patient with chronic alcoholism has symptoms of polyneuritis and heart failure. Vitamin drug should be prescribed to the patient?
A. Phylloquinone
B. Ergocalciferol
C. Retinol
D. Routine
E. * Thiamine

9. A 39-year-old man has an increased risk of developing infectious processes, hyperkeratosis, impaired twilight vision. Vitamin drug should be prescribed?
A. Riboflavin.
B. Pyridoxine hydrochloride.
C. * Retinol acetate.
D. Ergocalciferol.
E. Tocopherol acetate.

10. The patient has a complex of symptoms: diarrhea, inflammation of the exposed surfaces of the skin and progressive dementia. The doctor associated the presence of this symptomatology with the lack of one of the vitamins in the food and prescribed its drug. What drug was prescribed by the doctor?
A. Pangamic acid
B. Folic Acid
C. Pantothenic acid
D. * Nicotinic acid
E. Cyanocobalamin

11. A patient with anemia is treated with iron preparations. How to increase the absorption of iron preparations?

A. Almagel

B. Trypsin

C. Festal

D. Gastrocepin

E. * Ascorbic acid

12. A patient with a skin disease has hyperkeratosis. Prescribe a vitamin remedy that stimulates epithelization and protects against excessive keratinization of the epithelium.

A. Vitamin C

B. Vitamin PP

C. Vitamin D

D. * Vitamin A

E. Ascorutin

13. The patient has a visual impairment - hemeralopia ("night blindness"). Vitamin preparation needs to be consumed by the patient in order to restore vision?

A. * Retinol acetate

B. Vikasol

C. Pyridoxine

D. Thiamine chloride

E. Tocopherol acetate

14. The patient was prescribed radiation therapy. Should a vitamin preparation with antioxidant properties be added to increase vascular resistance in this case?

A. * Pyridoxine

B. Thiamine chloride

S. Ascorutin

D. Cyanocobalamin

E. Folic Acid

15. In the complex treatment of periodontal disease prescribed a vitamin product with pronounced vasodilating properties. Identify this drug?

A. Retinol Acetate

B. Ascorbic acid

C. Thiamine chloride

D. Pyridoxine hydrochloride

E. * Nicotinic acid

16. Examination of a 3-year-old child revealed bone disorders, deformation of the spine and chest, and curvature of the lower extremities. Which drug is most effective in this situation?

A. Tocopherol

B. * Ergocalciferol

C. Thiamine bromide

D. Glucose

E. Adiurekrin

17. When rickets is shown:

1. Pyridoxine

2. Riboflavin

3. * Ergocalciferol

4. Vikasol

5. Lidase

18 A 39-year-old man has an increased risk of developing infectious processes, hyperkeratosis, impaired twilight vision. Vitamin preparation necessary to appoint?

A. Riboflavin.

B. Pyridoxine hydrochloride.

C. * Retinol acetate.
D. Ergocalciferol.
E. Tocopherol acetate.
19. With a salt-deficient form of dehydration:
A. Only salts are lost
B. Evenly lost water and salt
C. Water loss exceeds salt loss
D. * Loss of salts exceeds loss of water
E. Only water is lost
20. If dehydration is accompanied by decompensation of blood circulation:
A. Injection of a solution of strophanthin and cordiamine
B. Respiratory and vasomotor stimulants are used.
Centers
C. Treatment begins with intravenous administration of a 40% glucose solution
D Apply all of the above
E * Treatment begins with an infusion of drugs that replenish the volume of circulating blood
21. The most indicative method for monitoring efficacy and safety ... of infusion therapy in children is:
A. Liver size
B. * Central venous pressure
C. Lack of protrusion of the fontanel
D. Lack of periorbital edema
E. Osmotic pressure of urine
22. The main potassium preparation used to eliminate acute hypopotassemia ... is:
A. Asparkam
B Potassium orotat
C Panangin
D. Potassium Asparaginate
E. * Potassium Chloride

23. Insulin, magnesium and some other drugs:
A. Penetrate into the cell with hypoxia
B. * Facilitate the transport of potassium into the cell
C. Contraindicated in hypokalemia
D. Indicated for patients with AV block, with impaired renal excretory function
E. Irritating the gastrointestinal mucosa

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-ANEMIC MEDICINES

Relevance of the topic.

Anemia is a clinical - hematological syndrome, which is based on tissue hypoxia, which develops as a result of a decrease in the amount of hemoglobin in the blood. This may be a consequence of blood loss, impaired formation of red blood cells, their increased destruction, or a combination of these reasons. According to WHO, more than 800 million people worldwide suffer from this disease. Among patients, women predominate, the incidence of which is 2-8 times higher than in men. The prevalence of anemia among the population depends on the region, gender, age, environmental and climatic and geographic conditions. Iron deficiency anemia is most common, accounting for up to 90% in women and up to 80% in men. The prevalence of anemia among women aged 25-45 is 12%, and among teenage girls - 9%. The prevalence of anemia among women working in an industrial enterprise whose labor activity is not related to exposure to harmful hematotropic factors amounted to 5.9%, and among those who have contact with harmful hematotropic factors (organic solvents) - 36.4%; among medical students - in 13.7%; among pregnant women - 28.8%; among people over 60 years old - 20.2-

35.8%. The structure of anemia has features in each group. So, iron deficiency anemia among students (18-25 years old) was about 80%, in pregnant women - 35%, in women who have industrial contact with organic solvents - 37.4%, in the elderly - 10.2% . In persons of the older age group, in pregnant women and women who have contact with organic solvents, anemia of complex genesis predominant, requiring clarification in each case.

Motivational characteristic of the topic.

Anemia - (Greek. Αναιμία, anemia) - a group of clinical and hematological syndromes, the common point for which is a decrease in the concentration of hemoglobin in the blood, less often with a simultaneous decrease in the number of red blood cells (erythropenia). The term "anemia" without detail does not define a specific disease, that is, anemia should be considered one of the symptoms of various pathological conditions. It is necessary to distinguish between hydremia (pseudoanemia, for example, pregnant women) and anemia - with hydremia, the number of formed elements and hemoglobin remains the same, but the volume of the liquid part of the blood increases.

Anemia leads to a decrease in the respiratory function of the blood and the development of oxygen starvation of tissues, most often expressed by symptoms such as pallor of the skin, increased fatigue, weakness, headaches, dizziness, palpitations, shortness of breath, etc.

Anemia itself is not a disease, but is often included in the structure of a large number of independent diseases.

According to the mechanism of development of anemia are divided into three different groups

Anemia can occur as a result of blood loss due to bleeding or hemorrhage - posthemorrhagic anemia.

Anemia may be the result of an excess of the rate of destruction of red blood cells over their production - hemolytic anemia.

Anemia may be due to insufficient or impaired formation of red blood cells in the bone marrow - hypoplastic anemia.

Anemia is a decrease in the hemoglobin content per unit volume of blood (<100 g / l), more often with a simultaneous decrease in the number (<4.0 x 1012 / l) or the total volume of red blood cells. The incidence of anemia in 2001 was 157 per 100,000 population.

Classification criteria

Depending on the average erythrocyte volume, there are:

- microcytic [average erythrocyte volume (SEA) less than 80 fl (μm)];
- normocytic (SEA - 81-94 fl);
- macrocytic anemia (SEA> 95 fl).

According to the hemoglobin content in red blood cells, there are:

- hypochromic [average erythrocyte hemoglobin content (SGE) less than 27 pg];
- normochromic (SSGE - 27-33 pg);
- hyperchromic (SSGE - more than 33 pg) anemia.

Pathogenetic classification

1. Anemia due to blood loss.

• Acute posthemorrhagic anemia.

• Chronic posthemorrhagic anemia.

2. Anemia due to impaired hemoglobin synthesis and iron metabolism.

• Microcytic anemia:

- Iron-deficiency anemia;
- Anemia in violation of iron transport (atransferritinemia);
- anemia due to impaired iron utilization (sideroblastic anemia);
- Anemia due to impaired iron reuse (anemia in chronic diseases).

• Normochromic normocytic anemia:

- hyperproliferative anemia (with kidney diseases, hypothyroidism, protein deficiency);

- Anemia due to bone marrow failure (aplastic anemia, refractory anemia with myelodysplastic syndrome);

- metaplastic anemia (with hemoblastosis, metastases in the red bone marrow);

- dyserythropoietic anemia.

• Macrocytic anemia:

- deficiency of vitamin B12;

- folic acid deficiency;

- copper deficiency;

- deficiency of vitamin C.

3. Hemolytic anemia.

• Acquired:

- hemolytic anemia caused by immune disorders [isoimmune hemolytic anemia, autoimmune hemolytic anemia (with thermal or cold antibodies), paroxysmal nocturnal hemoglobinuria];

- hemolytic microangiopathic anemia;

- hemolytic anemia due to exposure to direct hemolysins [hemolytic poisons, bacterial toxins, parasites (malaria)].

• Inherited:

- hemolytic anemia associated with a violation of the membrane structure of erythrocytes (hereditary spherocytosis, hereditary elliptocytosis);

- hemolytic anemia associated with enzyme deficiency in erythrocytes (glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase);

- hemolytic anemia associated with impaired Hb synthesis (sickle cell anemia, thalassemia).

ICD-10 classification of anemia

• D50 - D53 Nutritional Anemia.

• D55 - D59 Hemolytic anemia.

• D60 - D64 Aplastic and other anemia.

When collecting anamnesis in patients with anemia, it is necessary to ask:

- about recent bleeding;

- recently appeared pallor;

- the severity of menstrual bleeding;

- following a diet and drinking alcohol;

- decrease in body weight (> 7 kg for 6 months);

- the presence of anemia in the family history;

- a history of gastrectomy (with suspected vitamin B12 deficiency) or intestinal resection;

- pathological symptoms of the upper gastrointestinal tract (dysphagia, heartburn, nausea, vomiting);

- pathological symptoms from the lower gastrointestinal tract (change in the usual functioning of the intestine, bleeding from the rectum, pain, decreasing during bowel movements).

When examining a patient, they look for:

- pallor of conjunctiva;

- pallor of the skin of the face;

- pallor of the skin of the palms;

- Signs of acute bleeding:

- + tachycardia in the supine position (heart rate> 100 per minute);

- + hypotension in the supine position (systolic blood pressure <95 mm Hg);

- an increase in heart rate> 30 per minute or severe dizziness upon transition from a lying position to a sitting or standing position;

- Signs of heart failure;

- jaundice (hemolytic or sideroblastic anemia can be assumed);

- signs of infection or spontaneous bruising (we can assume the lack of accuracy of bone marrow function);

- tumor formation in the abdominal cavity or rectum:

- + conduct a study of the rectum of the patient and a test for occult blood in feces.

Research to be done

• Counting blood cells and blood smear.

• Definition of a blood type and creation of a patient's own blood bank.

• Determination of urea concentration and electrolyte content.

• Functional liver function tests.

Determination of SEA and SGE can help identify potential causes of anemia.

The average volume of the red blood cell

SEA (MCV - mean corpuscular volume) - the average corpuscular volume - the average value of the volume of red blood cells, measured in femtoliters (fl) or cubic micrometers. In hematological analyzers, SEA is calculated by dividing the sum of cell volumes by the number of red blood cells, but this parameter can be calculated by the formula:

Ht (%) 10

RBC (1012 / L)

The values of the average volume of the red blood cell, characterizing the red blood cell:

- 80-100 fl - normocyte;

- <80 fl - microcyte;

-> 100 fl - macrocyte.

SEA cannot be reliably determined in the presence of a large number of abnormal red blood cells (for example, sickle cells) or a dimorphic population of red blood cells in the test blood

The average volume of the red blood cell is 80-97.6 microns.

The clinical significance of SEA is similar to the value of unidirectional changes in the color index and hemoglobin content in erythrocytes (SIT), since usually macrocytic anemia is simultaneously hyperchromic (or normohromic) and microcytic anemia is hypochromic. SEA is mainly used to characterize the type of anemia.

The average hemoglobin content in the red blood cell is 26-33.7 pg.

MCH does not have independent significance and always correlates with SEA, the color index and the average concentration of hemoglobin in the red blood cell (MCHC). Based on these indicators, normo-, hypo- and hyperchromic anemia are distinguished.

Decreased MSN (i.e., hypochromia) is characteristic of hypochromic and microcytic anemia, including iron deficiency, anemia in chronic diseases, thalassemia; with some hemoglobinopathies, lead poisoning, impaired synthesis of porphyrins.

An increase in MSN (ie, hyperchromia) is observed in megaloblastic, many chronic hemolytic anemia, hypoplastic anemia after acute hemorrhage, hypothyroidism, liver diseases, metastases of malignant neoplasms; when taking cytostatics, contraceptives, anticonvulsants.

Four main functions of iron

enzymes

• Electron transport (cytochromes, iron-seroproteins).

• Transport and deposition of oxygen (hemoglobin, myoglobin).

• Participation in the formation of active centers of redox enzymes (oxidase, hydroxylase, superoxide dismutase, etc.).

• Transport and deposition of iron (transferrin, hemosiderin, ferritin).

The level of iron in the blood determines the state of the body

Necessary research

• Microcytic anemia: - ± serum ferritin.

• Macrocytic anemia:

- folic acid in serum;

- Vitamin B12 (cobalamin) in the blood serum;

- ± methylmalonic acid in urine or blood serum (if vitamin B12 deficiency is suspected).

Follow up studies

• Iron-deficiency anemia:

- gastroscopy and colonoscopy.

Vitamin B12 deficiency

• + Antibodies to Castle factor.

• + Schilling test.

Iron-deficiency anemia

In 2/3 of cases, anemia occurs due to a disease of the upper gastrointestinal tract.

Common causes of iron deficiency anemia in the elderly:

- peptic ulcer or erosion;
- neoplasm in the rectum or colon;
- surgery on the stomach;
- the presence of a hernial foramen (> 10 cm);
- malignant disease of the upper gastrointestinal tract;
- angiodysplasia;
- varicose veins of the esophagus.

Vitamin B12 deficiency

Common causes:

- pernicious anemia;
- tropical spru;
- bowel resection;
- jejunum diverticulum;
- malabsorption of vitamin B12;
- vegetarianism.

Folic acid deficiency

Common causes:

- alcoholism;
- malnutrition.

Iron deficiency anemia

Clinical and hematological syndrome, characterized by a decrease in the number of red blood cells and hemoglobin in the blood, is called anemia. A wide variety of pathological processes can serve as the basis for the development of anemic conditions, in connection with which anemia should be considered as one of the symptoms of the underlying disease. The prevalence of anemia varies significantly from 0.7 to 6.9%. Anemia can be caused by one of three factors or their combination: blood loss, insufficient formation of red blood cells or their increased destruction (hemolysis).

Among various anemic conditions, iron deficiency anemia is the most common and makes up about 80% of all anemia.

According to the World Health Organization, every 3 women and every 6 men in the world (200 million people) suffer from iron deficiency anemia.

Iron exchange

Iron is an indispensable biometal that plays an important role in the functioning of cells in many body systems. The biological significance of iron is determined by its ability to be reversibly oxidized and reduced. This property ensures the participation of iron in the processes of tissue respiration. Iron makes up only 0.0065% of body weight. In a man’s body with a body weight of 70 kg, approximately 3.5 g (50 mg / kg body weight) of iron is contained. The iron content in the body of a woman with a body weight of 60 kg is approximately 2.1 g (35 mg / kg body weight). Iron compounds have a different structure, possess functional activity characteristic only of them, and play an important biological role. The most important iron-containing compounds include: hemoproteins, the structural component of which is heme (hemoglobin, myoglobin, cytochromes, catalase, peroxidase), enzymes of the non-heminous

group (succinate dehydrogenase, acetyl-CoA dehydrogenase, xanthine oxidase), ferritin, hemerin, transferrin, hemin. Iron is a part of complex compounds and distributed in the body as follows:

• gemzheleso - 70%;
• iron depot - 18% (intracellular accumulation in the form of ferritin and hemosiderin);
• functioning iron - 12% (myoglobin and iron-containing enzymes);
• transported iron - 0.1% (iron associated with transferrin).

There are two types of iron: heme and non-heme. Hemic iron is part of hemoglobin. It is found only in a small part of the diet (meat products), is well absorbed (20-30%), other components of the food practically do not affect its absorption. Non-heme iron is in free ionic form - ferrous (Fe II) or ferric iron (Fe III). Most of the edible iron is non-heme (found primarily in vegetables). The degree of its assimilation is lower than heme, and depends on a number of factors. Of the food products, only divalent non-heme iron is absorbed. In order to "convert" ferric iron to ferrous, a reducing agent is needed, the role of which in most cases is played by ascorbic acid (vitamin C). In the process of absorption in the cells of the intestinal mucosa, ferrous iron Fe2 + turns into oxide Fe3 + and binds to a special carrier protein - transferrin, which carries iron to hematopoietic tissues and places of iron deposition.

The accumulation of iron is carried out by proteins ferritin and hemosiderin. If necessary, iron can be actively released from ferritin and used for erythropoiesis. Hemosiderin is a higher iron ferritin derivative. From hemosiderin, iron is released slowly. The beginning (preferential) iron deficiency can be determined by the reduced concentration of ferritin even before the iron reserves are exhausted, while the normal concentration of iron and transferrin in the blood serum is still preserved.

Etiology and pathogenesis of iron deficiency anemia

The main etiopathogenetic factor in the development of IDA is iron deficiency. The most common causes of iron deficiency states are:

•-iron loss during chronic bleeding (the most common cause, reaching 80%):

- bleeding from the gastrointestinal tract: peptic ulcer, erosive gastritis, varicose veins of esophageal veins, diverticulum of the colon, invasion of hookworm, tumor, UC, hemorrhoids;
- long and heavy menstruation, endometriosis, fibromyoma;
- macro- and microhematuria: chronic glomerulo- and pyelonephritis, urolithiasis, polycystic kidney disease, tumors of the kidneys and bladder;

-nasal, pulmonary bleeding;
blood loss during hemodialysis;
uncontrolled donation;
• insufficient absorption of iron:
resection of the small intestine;
chronic enteritis;
malabsorption syndrome;
intestinal amyloidosis;
• increased need for iron:
intensive growth;
pregnancy;
lactation period;
playing sports;
• insufficient intake of iron with food:
newborns;
small children;
vegetarianism.

Recommended daily intake of iron with food: for men - 12 mg, for women - 15 mg (for pregnant women - 30 mg).

Pathogenetically, the development of an iron deficiency state can be conditionally divided into several stages:

1. preferential iron deficiency (lack of accumulation) - there is a decrease in the level of ferritin and a decrease in the content of iron in the bone marrow, increased absorption of iron;

2. latent iron deficiency (iron deficiency erythropoiesis) - additionally, serum iron decreases, the concentration of transferrin increases, and the content of sideroblasts in the bone marrow decreases;

3. marked iron deficiency = iron deficiency anemia - the concentration of hemoglobin, red blood cells and hematocrit is additionally reduced.

Diagnostics

The diagnosis of IDA is based on a characteristic clinical picture and a change in laboratory parameters.

Clinical picture

During the period of latent iron deficiency, many subjective complaints and clinical signs characteristic of iron deficiency anemia appear. Patients note general weakness, malaise, decreased performance. Already in this period, a perversion of taste, dryness and pinching of the tongue, impaired swallowing with a sensation of a foreign body in the throat, palpitations, shortness of breath can be observed.

An objective examination of patients reveals “small symptoms of iron deficiency”: atrophy of the papillae of the tongue, cheilitis, dry skin and hair, brittle nails, burning and itching of the vulva. All these signs of trophic disturbance in epithelial tissues are associated with tissue sideropenia and hypoxia.

Patients with iron deficiency anemia note general weakness, fatigue, difficulty concentrating, and sometimes drowsiness. Headache, dizziness appear. In severe anemia, fainting is possible. These complaints, as a rule, do not depend on the degree of hemoglobin reduction, but on the duration of the disease and the age of the patients.

Iron deficiency anemia is also characterized by changes in the skin, nails and hair. The skin is usually pale, sometimes with a slight greenish tint (chlorosis) and with an easily occurring blush of cheeks, it becomes dry, flabby, peeling, and cracks easily form. Hair loses its shine, turns gray, becomes thinner, easily breaks, thins and turns gray early. Nail changes are specific: they become thin, matte, flatten, easily exfoliate and break, and striation appears. With pronounced changes, the nails acquire a concave, spoon-shaped form (koilonychia). In patients with iron deficiency anemia, muscle weakness occurs, which is not observed with other types of anemia. It is attributed to the manifestations of tissue sideropenia. Atrophic changes occur in the mucous membranes of the digestive canal, respiratory organs, genitals. Damage to the mucous membrane of the digestive canal is a typical sign of iron deficiency conditions.

There is a decrease in appetite. There is a need for acidic, spicy, salty foods. In more severe cases, there is a perversion of smell, taste (pica chlorotica): eating chalk, lime, raw cereals, pohofagiya (attraction to the use of ice). Signs of tissue sideropenia quickly disappear after taking iron supplements.

Treatment

In all cases of iron deficiency anemia, it is necessary to establish the immediate cause of this condition and, if possible, eliminate it (most often eliminate the source of blood loss or treat the underlying disease complicated by sideropenia).

Treatment of iron deficiency anemia should be pathogenetically substantiated, comprehensive and aimed not only at eliminating anemia as a symptom, but also at eliminating iron deficiency and replenishing its reserves in the body (

Iron deficiency anemia treatment

Iron deficiency anemia - anemia caused by a deficiency of iron in the blood serum and bone marrow, which is accompanied by a violation of the formation of hemoglobin and red blood cells, the development of trophic disorders in organs and tissues.

The treatment program includes:

1. Elimination of etiological factors.
2. Therapeutic nutrition.
3. Treatment with iron preparations.
3.1. Elimination of iron deficiency and anemia.
3.2. Replenishment of iron stores (saturation therapy).
3.3. Anti-relapse therapy.
4. Prevention of iron deficiency anemia.
4.1. Primary.
4.2. Secondary.

1. Elimination of etiological factors

The successful elimination of iron deficiency and, therefore, the cure of gel-deficiency anemia is possible only after the elimination of the cause leading to a permanent iron deficiency.

The main causes of iron deficiency anemia are:

• diseases of the gastrointestinal tract, manifested by chronic blood loss (stomach and duodenal ulcer; cancer of the stomach and intestines; cancer of the esophagus; erosive esophagitis and gastritis; diaphragmatic hernia; diverticulosis and polyposis of the intestine; ulcerative colitis; Crohn's disease; abdominal a form of hemorrhagic vasculitis; hemorrhoids, a rectal fissure; angiomas and telangiectasias of the gastrointestinal tract);

• diseases of the gastrointestinal tract resulting in impaired absorption of iron (resection of a large part of the small intestine; chronic enteritis, intestinal amyloidosis and other diseases leading to the development of malabsorption syndrome; chronic pancreatitis with impaired exocrine pancreatic function);

• diseases of the liver and portal tract (Budd Chiari syndrome with bleeding from the dilated veins of the esophagus; cirrhosis and extrahepatic portal hypertension, complicated by bleeding from the veins of the esophagus, stomach, hemi-morroidal nodes);

• kidney diseases complicated by micro- and macrohematuria (IgA nephropathy or Bourget’s disease; alcoholic nephropathy; renal form of hemorrhagic vasculitis; hematuric variants of chronic nephritis and pyelonephritis; polyps and bladder cancer; hypernephroid cancer; urolithiasis; kidney tuberculosis);

• diseases of the cardiovascular system (hypertension with nosebleeds; exfoliating aortic aneurysm);

• respiratory diseases (pulmonary hemosiderosis, diseases of the lungs and bronchi that occur with bleeding - lung cancer, tuberculosis, bronchiectasis);

• diseases of the blood system (hemoblastosis and hypoplastic anemia complicated by bleeding; Markiathava-Mikeli disease with hemosiderinuria and hemoglobinuria);

• hemorrhagic diathesis (thrombocytopenia, hemophilia, Randu-Osler disease, coagulopathy, hemorrhagic phase of the BC syndrome, hemorrhagic vasculitis);

• hypothyroidism;

• diseases accompanied by intoxication (kidney diseases with chronic renal failure; liver diseases with chronic liver failure, etc.);

• menorrhagia and metrorrhagia with ovarian dysfunctions, fibromyomas, cancer of the body and cervix, endometriosis, childbirth, abortion, with heavy and lengthy menstruation;

• pregnancy and lactation;

• insufficient intake of iron with food;

• cancer of any localization;

• helminthic infestations;

• excessive donation.

Along with the above reasons, there are a number of diseases that cause anemia due to redistribution of iron. The leading pathogenetic mechanism of anemia in this case is the accumulation of iron in the depot in the form of ferritin and hemosiderin, as well as in the cells of the macrophage system and the foci of inflammation, which leads to its deficiency in erythroid cells of the bone marrow. The total amount of iron in the body is not reduced.

The main diseases leading to the development of iron deficiency anemia due to redistribution of iron:

1. acute infections (bacterial, viral, fungal);
2. sepsis;
3. tuberculosis of various localization;
4. sarcoidosis of various localization;
5. chronic osteomyelitis;
6. chronic mycoses;
7. chronic pyelonephritis and urinary tract infections;
8. acute pyelonephritis (apostematic nephritis, kidney carbuncle);
9. suppurative diseases of the bronchi, lungs, pleura (bronchiectasis, abscess, empyema of the pleura);
10. inflammatory diseases of the abdominal cavity (peritonitis, subdiaphragmatic abscess, hepatic abscess);
11. infectious endocarditis;
12. rheumatoid arthritis;
13. seronegative arthritis;
14. malignant tumors with or without metastases;

2. Therapeutic nutrition

With iron deficiency anemia, the patient is shown a diet rich in iron. The maximum amount of iron that can be absorbed from food in the gastrointestinal tract is 2 g per day. Bivalent iron, which is part of iron, is best absorbed. Meat iron is absorbed better, and liver iron is worse, since iron in the liver is contained mainly in the form of ferritin, hemosiderin, and also in the form of heme. In a small amount, iron is absorbed from eggs and fruits.

For normal hematopoiesis, it is necessary to get other microelements with food, except for the lesion.

Copper is a part of oxidative enzymes of cytochrome oxidase and diphenol oxidase, it stimulates hematopoiesis (hemoglobin synthesis, conversion of reticulocytes into red blood cells). The daily need of an adult in copper is about 2-3 mg. Copper-rich foods include cereals (wheat, rye, oats, barley), cereals (buckwheat, oat, pearl barley), legumes (peas, beans), mushrooms, strawberries, strawberries, cranberries, black currants, watermelon, horseradish , kidneys, liver, beef. Copper depletion of the body leads to anemia.

Manganese has a beneficial effect on erythropoiesis and the formation of hemoglobin, stimulates oxidative processes in the body. The daily requirement of the body in manganese is 5-7 mg.

Products of plant origin (from wheat, rye, oats, barley), cereals (oat, pearl barley, wheat, rice), legumes (beans, peas), parsley, sorrel, dill, beets, pumpkin, spinach, cranberries, mali are rich in manganese. on, blackcurrant.

Zinc stimulates the formation of hemoglobin and red blood cells. The daily human requirement for zinc is 10-15 mg. Zinc is rich in yeast, liver, kidneys, lungs, beef, Dutch cheese, legumes, cereal grains, mushrooms, chicken eggs, chicken meat.

Cobalt is part of cyanocobalamin (vitamin B12), potentiates the absorption of iron in the intestine and its use in the synthesis of hemoglobin and red blood cells. The daily human need for cobalt is 0.05-0.2 mg. Cobalt is rich in liver, kidneys, milk, fish, legumes, cereals and cereals, gooseberries, black currants, raspberries, parsley, beets, pears, cherries, peanuts, almonds, apricots.

It is advisable to take koumiss in a daily dose of 0.75-1 l, with good tolerance - up to 1.5 l. In the first two days, the patient is given no more than 100 ml of koumiss for each dose, from the 3rd day the patient takes 250 ml 3-4 times a day. It is better to take koumiss 1 hour before and 1 hour after breakfast, 2 hours before and 1 hour after lunch and dinner.

In the absence of contraindications (diabetes, obesity, allergies, diarrhea), the patient should be advised honey. In honey, there is up to 40% fructose, which helps to increase the

absorption of iron in the intestine. In addition, honey contains trace elements in the form most suitable for absorption. Varieties of dark honey are more preferable, since they contain iron 4 times, copper 2 times, manganese 14 times more than light varieties. The daily intake for honey is 100 g (in 3-4 doses). With a decreased secretory function of the stomach, honey is used immediately before meals, and with high acidity, it is consumed 1.5–2 hours before meals.

In case of iron deficiency anemia, phyto-collection can also be recommended, including nettle leaves, strings, strawberries, black currants. The dried leaves of these plants are mixed in equal parts. One tablespoon of the collection is poured with 1 glass of boiling water, insisted for 2 hours, filtered and taken before meals in a 1/3 cup 3 times a day daily for 6 weeks. At the same time, it is recommended to take a decoction or infusion of shi-chef fruits in 1 glass throughout the day. The infusion of shi¬povnik contains iron and Vitamin C.

3. Treatment with iron preparations

3.1. Iron deficiency

Without the use of iron preparations, it is impossible to eliminate anemia and iron deficiency. The intake of iron with food is able to make up for only its daily normal loss. The use of iron preparations is a pathogenetic method of treating reliably established iron deficiency anemia. Currently, preparations containing ferrous iron (Fe ++) are used, since it is much better absorbed in the intestine.

Iron preparations are usually used internally. To ensure an incremental increase in hemoglobin level, it is necessary to take such an amount of iron-containing preparations daily so that it corresponds to a daily dose of ferrous iron from 100 mg (minimum dose) to 300 mg (maximum before). The choice of the daily dose in the indicated doses is determined primarily by the individual tolerance of iron preparations and the severity of iron deficiency. Prescribing more than 300 mg of ferrous iron per day is useless, since the volume of its absorption does not increase.

Ferrous iron preparations are prescribed 1 hour before a meal or not earlier than 2 hours after a meal. For better absorption of iron, they simultaneously take ascorbic or succinic acid, absorption also increases in the presence of fructose.

Hemostimulin - 2-3 tablets are prescribed 3 times a day. The tablets are large, without a shell, taste unpleasant, many patients are poorly tolerated. Often there are dyspeptic disorders. Currently rarely used.

Feramide is a complex compound of iron chloride with nicotinamide. The disadvantage of the drug is a small dose of iron in a large tablet, so you have to take 3-4 tablets 3 per day. The composition of the drug does not include stimulators of iron absorption, and therefore it is necessary to take ascorbic acid at the same time.

Ferrocol - contains iron sulfate in combination with calcium fructose diphosphate, 1-2 tablets are prescribed 3 times a day after meals.

. Ferrocerone - sodium salt of ortho-carboxybenzoylferrocene, is easily absorbed by the mucous membrane of the gastrointestinal tract, 1-2 tablets are prescribed 3 times a day. The drug is usually well tolerated. In some cases, nausea is possible (usually in the first days of admission). When taking the drug, urine turns red due to its partial excretion with urine. When taking ferrocerone, ascorbic and hydrochloric acids cannot be taken; lemons and other acidic products (sour cabbage, etc.) must be excluded from the diet.

Conferon - produced in capsules, contains iron sulfate and sodium dioctyl sulfosuccinate, which is a surfactant that promotes absorption of iron by the intestinal mucosa. It is prescribed for 1-2 capsules 3 times a day. In the treatment with conferon, no additional intake of ascorbic acid is required.

Ferroplex - a complex of iron sulfate and ascorbic acid, is prescribed for 2-3 tablets 3 times a day. Tolerance to the drug is satisfactory. Its ascorbic acid promotes absorption of iron in the intestine.

Tardiferon is a long-acting iron sulfate preparation, the iron contained in it is slowly released in the small intestine, which contributes to its almost complete utilization. The drug is taken 1-2 tablets per day, tolerance is good.

Ferro-Gradumenpg - contains iron sulfate, enclosed in a special polymer sponge-like mass (degree), which provides a gradual release of iron within a few hours after ingestion. Thus, Ferro-Gradument is a long-acting drug. Only a small amount of iron dissolves in the stomach, the bulk of it is released in the intestine, so the drug does not have an irritating effect on the gastric mucosa. Ferro-Gradument is taken on an empty stomach (30 minutes before breakfast). The daily dose is 1-2 tablets.

Treatment with iron-containing drugs is carried out in the maximum tolerated dose until the hemoglobin content is completely normalized, which occurs after 6-8 weeks. Clinical signs of improvement appear much earlier (after 2-3 days) compared with the normalization of hemoglobin levels. This is due to the intake of iron in enzymes, a deficiency of which causes muscle weakness. The hemoglobin content begins to increase at the 2-3rd week from the start of treatment. Iron-containing drugs are usually taken orally and only in some cases, parenterally.

Indications for parenteral administration of iron preparations:

• pathology of the gastrointestinal tract, combined with malabsorption (enteritis, chronic pancreatitis with a lack of external receptor function and other diseases with malabsorption syndrome);

• extensive resection of the small intestine;

• gastrectomy;

• peptic ulcer of the stomach and 12 duodenal ulcer (when taking iron-containing drugs, nausea, vomiting, exacerbation of an ulcer are possible);

• intolerance to oral administration of iron preparations (nausea, vomiting, abdominal pain);

• the need to quickly saturate the body with iron in case of upcoming operations for uterine fibroids, hemorrhoids, etc.);

•nonspecific ulcerative colitis.

Parenteral iron preparations:

Ectofer - sorbitol-citrate iron, is produced in 2 ml ampoules, 100 mg in 1 ampoule, the drug is administered intramuscularly in 2 ml once a day.

Ferbitol is an aqueous solution of the iron-sorbitol complex; it is produced in 2 ml ampoules, 100 mg of iron is contained in 1 ampoule, 2 ml are administered intramuscularly once a day; the drug is close to ectofer.

Ferrum-Lek - contains tribasic iron in the form of a complex with maltose (produced in 2 ml ampoules for intramuscular injection; 1 ampoule contains 100 mg of iron) and as a complex with sucrose for intravenous administration (5 ml ampoules, 1 ampoule contains 100 mg of iron).

Ferrum-Lek is intramuscularly administered every other day; the maximum daily dose for adults is 4 ml (2 ampoules). 2.5 ml are administered intravenously on the 1st day, 5 ml on the 2nd day, 10 ml on the 3rd day, then 10 ml 2 times a week. Intravenously, the drug should be administered very slowly, the contents of the ampoule are diluted with 10 ml of isotonic sodium chloride solution.

The amount of parenteral iron preparation required for treatment is calculated using the following formula (Gailani, 1992):

Iron (mg) = (Hb normal - Hb patient) xmass (kg) x0.221 + 1000

To find out the required number of ampoules of the drug, the obtained value should be divided by 100 (the above parenteral forms contain 100 mg of iron in 1 ampoule). This amount is able to restore the level of red blood cells and hemoglobin in the blood and create a supply of iron in the body equal to 1000 mg.

Ferkoven - an iron preparation for intravenous administration, contains jelly for sugar, cobalt glkzhonat and a solution of carbohydrates. Contains 20 mg of iron and 0.09 mg of cobalt in 1 ml. Available in ampoules of 5 ml.

Ferkoven administered intravenously 1 time per day daily for 10-15 days: the first 2 injections of 2 ml, then 5 ml. The introduction of the drug is slow. Side effects are possible: hyperemia of the face, neck, a feeling of constriction in the chest, lower back pain. They are stopped by the introduction of subcutaneous analgin and atropine.

Intravenous administration of iron preparations may be complicated by phlebitis. Both with intramuscular and intravenous administration, anaphylactic reactions are occasionally possible, therefore it is necessary to first test with 0.5 ml of the drug and have adrenaline and prednisolone in ampoules ready for emergency care. Sometimes, on the 4-10th day of treatment, delayed reactions occur: arthralgia, myalgia, lymphadenopathy, splenic megalia.

In case of insufficient effectiveness of iron preparations (taken orally or parenterally), it is advisable to use antioxidants (vitamin E 1 capsule 2 times a day for a month) in complex therapy, which increase the effect of ferrotherapy. At a hemoglobin level of 40-50 g / l, a red blood cell transfusion is performed.

The causes of failures in the treatment with iron preparations are:

• incorrect diagnosis;

• inadequate doses of iron;

• ongoing loss of blood;

• intercurrent infections, malignant neoplasms.

The mechanism of action and the main pharmacodynamic effects of iron preparations

Iron (Fe) is a component necessary for the normal activity of various heminic and non-heminic substrates: hemoglobin, myoglobin, cytochromes, peroxidases and catalases. These enzyme systems are involved in the transport of oxygen, tissue respiration, and the removal of peroxides of free radical reactions. Adequate amounts of Fe are necessary for effective erythropoiesis (the formation of hemoglobin in erythroblasts). The transfer of Fe to ripened red blood cells occurs mainly when it is released from transferrin in the region of the receptor on the precursor membrane.

With the course use of Fe preparations, a gradual regression of clinical manifestations (weakness, increased fatigue, dizziness, tachycardia, soreness and dryness of the skin) and laboratory indicators of anemia occurs.

Pharmacokinetics of oral iron preparations

Absorption of iron in the digestive tract can occur in two ways:

• fast-saturating active ferritin transport ensures the intake of small amounts of edible, organic Fe (up to 3-4 mg / day) (absorption of Fe3 + occurs much worse than reduced Fe2 +) - physiological mechanism;

• passive transport - simple diffusion along the concentration gradient (observed when taking Fe in doses significantly exceeding its content in ordinary food).

The physiological absorption of Fe2 + occurs mainly in the duodenum and in the upper jejunum due to the ferritin mechanism. The apoferritin protein contained in the gastrointestinal mucosa binds part of the absorbable Fe2 +, forming the Fe2 + ferritin complex. After passing through the intestinal barrier, Fe2 + enters into the plasma bond with β1-globulin - transferrin. Fe2 + bound to transferrin enters various tissues, where it is released again. In tissue depots, Fe2 + is also in a bound state (in the form of ferritin or hemosiderin).

Passive absorption occurs throughout the intestine, but its intensity decreases towards the colon. Under the influence of hydrochloric acid, molecular Fe is ionized, which increases its absorption. However, this mechanism practically does not affect the absorption of drug Fe2 +. Absorption of Fe3 + is improved in the presence of substances possessing the properties of reducing agents (amino acids, peptides, fructose, ascorbic, succinic acid, etc.), which convert it to the divalent form.

Serine (α-amino acid) promotes more efficient absorption of iron and its entry into the systemic circulation.

The absorption of Fe2 + depends on the dose of the drug: as a single dose increases from 40 to 400 mg, its absorption decreases from 30-35% to 5-7%. Thus, at single doses of more than

130-150 mg and daily doses of more than 400-450 mg, there is no significant increase in the intake of Fe2 +. The maximum amount capable of being absorbed into the body per day is about 100 mg. The completeness of iron absorption also depends on the degree of its deficiency in the body: when the reserves in the body are close to normal, no more than 3-7% Fe2 + is absorbed. With latent iron deficiency without anemia, the value increases to 15-17%, and with anemia - up to 25-30%. In addition, a dose-dependent decrease in the absorption of the drug within 4-6 hours after taking the previous dose is noted. Absorption of iron preparations occurs better on an empty stomach.

Pharmacokinetics of parenteral iron preparations

Intravenous administration. A stable complex of FeOH3 with high molecular weight dextran is used. The bond of iron with dextran is very stable, therefore, almost no ionized iron enters the plasma and transferrin is practically not saturated.

Intramuscular injection A complex of FeOH3 with partially hydrolyzed low molecular weight dextran is used. After administration of the drug, its absorption from muscle tissue is slow, mainly by lymphatic drainage. So, with the introduction of FeOH3 dextran (CosmoFer *) for 72 hours, about 50% of the drug enters the body, up to 25% of it remains at the injection site for up to 3 weeks, and 5-10% - longer.

With the intramuscular administration of the Fe-sorbitol complex, about 85% of the drug is absorbed in the first 12 hours. The maximum concentration of Fe2 + (with almost complete saturation of transferrin) is determined after 2-8 hours, and after 12-24 hours its first portions are already found in red blood cells. Up to 30-40% of the drug is excreted in 24 hours with urine unchanged. Within 10 days, the drug is excreted completely.

After intramuscular administration of the iron-sorbitol complex (ferbi-tol *), up to 85% of the drug is absorbed in 12 hours, 20-30% is excreted by the kidneys unchanged. The drug is completely excreted in 20 days.

Intravenous administration. Fe3 + sugar is used (ferrum lek *, ferkoven *) - the body absorbs 90% of the injected substance, the rest is excreted from the body with urine.

After the use of parenteral preparations of iron, after 12-24 hours, its first portions are found in red blood cells. However, most of the iron for hemoglobin synthesis comes from the ferritin complex (Fe2 + apoferritin) of the EPR of the liver, spleen, and bone marrow, where it is deposited after absorption by macrophages from the bloodstream.

Indications for use and dosage regimen

Indications for use:

• iron deficiency anemia;

• latent iron deficiency without anemia from excessive Fe losses (blood loss, constant donation) or with increased

requirements in it (pregnancy, lactation, certain stages of treatment of B12-deficient anemia). Relative indications for parenteral use:

• anemia before surgery in the third trimester of pregnancy;

• pronounced true intolerance to oral preparations (severe forms of enteritis, ulcerative colitis, exacerbations of peptic ulcer disease);

• depletion of Fe in the body;

• malabsorption of oral drugs (prolonged, frequent diarrhea, malabsorption syndrome);

• severe, chronic, unremovable bleeding completely.

Calculation of the daily dose. The minimum daily dose of Fe should be such that the absorbed portion provides optimal daily average growth of hemoglobin.

Depending on the patient's body weight, gender, and constitution, it is usually necessary to administer a minimum of 20-30 mg Fe2 + per day (which can be achieved by oral administration of 100 mg Fe2 +). With good tolerance, the daily dose of the drug is gradually increased. Such tactics are favorable in patients with an erythropoiesis rate higher than average, for example, 3-3.5 g / l / day. Then, with good tolerance, it is necessary to introduce Fe2 + at a dose of 75-100 mg / day (i.e. 300-400 mg of the drug). If the body does not use all the absorbed

Fe2 + for erythropoiesis, then the remaining part is already deposited in the depot at the initial stages, which leads to an overall reduction in treatment time. It is pointless to increase the dose of Fe2 + above 300-400 mg / day, since this does not lead to a further increase in absorption. Consequently, the minimum effective daily dose of Fe2 + preparations for an adult is 100 mg (less often, 60-80 mg), and the maximum appropriate dose is up to 300-400 mg. In this, the choice of dose depends only on individual tolerance.

Dosage regimen and duration of treatment. Children under 6 years of age should preferably be given oral preparations in the form of syrup or drops.

• Oral drugs. The daily dose is divided into 3-4 parts so that the interval between doses is at least 4 hours, and with a single dose of 50 mg - at least 6-8 hours. With excellent tolerance to Fe, large daily doses are divided into 6-8 doses. Sometimes, more frequent doses of lower doses may improve tolerance to treatment. Fe preparations are consumed 1 hour before or 2 hours after a meal.

The total duration of treatment with oral drugs is at least 2-3 months, and often up to 4-6 months (it takes time to fill the depot). After reaching a hemoglobin concentration of 120 g / l, treatment is continued for at least another 1.5–2 months. After normalizing the concentration of hemoglobin, especially in people who are poorly tolerated, the dose can be reduced to the prophylactic level (30-60 mg / day). With continued loss of Fe (heavy periods), prophylactic administration can be continued for more than 6 months after the concentration of hemoglobin is normalized.

• Parenteral drugs. Before using them no later than 2-3 days later, it is necessary to cancel the intake of oral forms. The maximum amount of Fe2 + administered is not more than 100 mg / day, since large doses cause complete saturation of plasma transferrin, and excess Fe2 + can have a toxic effect. It is better (especially in patients with a history of allergic reactions) to gradually increase a single dose from 25 to 100 mg daily or with an interval of several days until the total estimated value is reached. For intravenous administration, it is strictly forbidden to use drugs administered intramuscularly. The solution is administered at a rate of not more than 20-50 mg / min (within 3-5 minutes, and preferably 8-10 minutes), injections are performed only in a hospital. The total dose of drugs for parenteral administration is calculated according to special nomograms and formulas that take into account the patient's body weight, the degree of Fe2 + deficiency (depending on the concentration of hemoglobin).

Side effects and contraindications

It is believed that, in terms of a unit mass of dissolved substance, all Fe2 + preparations have the same toxicity.

Preparations for oral administration. A drawback of rapidly absorbed preparations is the dissolution of a large number of Fe2 + ions in a short section of the gastrointestinal tract. Prolonged preparations (even with a large amount of Fe2 + in a daily dose) are distinguished by the best assimilation / side effects ratio. With an average daily dose of Fe2 + 180-200 mg, approximately 10% of patients experience side effects that lead to the rejection of further intake. The most common of them are redness of the skin, nausea, loss of appetite up to anorexia, constipation (binding by iron ions of hydrogen sulfide - a physiological stimulator of intestinal motility), less often diarrhea, pain in the epigastric region, intestinal colic, belching.

With an increase in the dose of Fe2 + to 300 mg / day, gastrointestinal tract disorders occur in 25% of cases; peptic ulcer, regional enteritis, and ulcerative colitis are possible. Good dose tolerance of 400 mg / day is noted in some cases, and for children, such an amount of Fe2 + administered can be fatal.

Tactics when side effects occur depends on their severity:

• lungs (nausea, slight discomfort, moderate intestinal dysfunction) - it is advisable to reduce the dose, take the drug during or immediately after eating, or replace it with another Fe salt, prolonged drug;

• moderate - possible transition to parenteral administration of drugs;

• severe (manifestations of resorptive action join) - further treatment is contraindicated.

Constipation, diarrhea, slight redness of the face, nausea, vomiting, dark urine (the formation of iron sulfide when taking large doses) require attention when they are prolonged or pronounced. Pain in the abdomen or chest and throat, especially when swallowing, the presence of fresh or digested blood in the stool can be associated with an ulcer or erosion of the mucous membrane. The earliest signs of Fe poisoning are diarrhea, nausea, stomach pain,

intestinal colic, repeated vomiting, sometimes with blood. When using drugs, staining of feces and, less often, urine in black is possible due to the formation of iron sulfide; false positive reaction to occult blood - test with guaiac tincture (the results of the benzidine test do not change); false positive orthotoluidine test; blackening of teeth (the formation of iron sulfide in the oral cavity, especially in people with caries). Long-term use of iron preparations, especially in large doses, affects the assimilation of phosphorus, which can cause severe in children

rickets; when using some prolonged preparations (ferro-degree *) porous plastic is found in the stool. The body cannot excrete excess iron for more than 6 months, therefore, in the absence of blood loss, prolonged intake of iron preparations can lead to the development of hemosiderosis.

Parenteral drugs When using them, general (resorptive) and local side effects are possible. The yield rate of ionized Fe depends on the strength of its bond with the carrier. It is less for sorbitol than for dextran, which determines a lower risk of using the latter when administered intravenously. At the same time, a stronger bond promotes Fe retention at the injection site, which is unsafe for intramuscular administration.

With intramuscular administration, local soreness, infiltrates are sometimes noted; Local inflammatory reactions with inguinal lymphadenopathy and pain in the lower abdomen are described. Perhaps brown staining of the skin at the injection site, lasting from several months to two years.

Side effects according to the severity of manifestations are divided into:

• lungs - moderate weakness, a feeling of a rush of blood to the face, slight dizziness, malaise, mild headache, moderate tachycardia;

• moderate - unpleasant sensations in the muscles, intense pain in the lower back, nausea, vomiting, diarrhea, severe weakness and headache, dizziness, chills, fever, lacrimation, sweating, urticaria, compressive chest pain;

• severe - shortness of breath, cough, constricting chest pain, severe tachycardia and sweating, anaphylactic shock, acute vascular insufficiency, cases of encephalopathy with convulsive syndrome are described.

By the frequency of detection, side effects are divided into:

• frequent (they are noted by more than 5% of patients) - a feeling of a rush of blood to the face, nausea, dizziness, slight headache, lethargy, weakness, a feeling of mild pressure behind the sternum, venous occlusion, local pain and in-filtrates;

• rare - other.

The risk of side effects is significantly higher with intravenous administration of the drug, especially by the method of "total" dose.

Side effects more often occur during the first injections, according to the time of occurrence, early (10-30 min after injection) and late (1-24 hours) are distinguished. Later there is a fever, rash, pain syndromes, arthralgia, generalized lim-phoadeno-

pathia, leukocytosis (up to the leukemoid reaction), hemolysis. The incidence of anaphylactic shock and fatal complications is -1 per 4 million injections. High concentrations of ionized Fe in the blood contribute to protein precipitation, a decrease in tone and an increase in the permeability of small vessels, and the destruction of red blood cells.

Isolation of the Fe-sorbitol complex with saliva can cause a metallic taste in the mouth or (up to 3%) loss of taste for 2-3 hours. Preparations can have a nephrotoxic effect. Leukocyturia, exacerbation of urinary infections are possible. Sometimes (more often in children), a decrease in immunity, an increase in the frequency of bacterial infections, hemolysis with paroxysmal hemoglobinuria is noted. After administration of large doses of FeOH3 dextran, false reactions to

serum bilirubin may occur. Since excess iron is not excreted from the body, the risk of developing hemosiderosis in violation of the dosing regimen is higher with the parenteral than with the oral route of administration. The early symptoms of an overdose are abdominal pain, diarrhea, vomiting (sometimes with blood), dizziness, weakness, then cyanosis, confusion, and symptoms of hyperventilation occur. Overdose treatment. With a slight overdose of iron preparations, it is necessary to immediately prescribe a diet enriched with dairy products; Useful raw chicken eggs.

Specific therapy for severe poisoning is carried out with deferoxamine (de-spheral *), the drug is prescribed orally and parenterally:

• in acute poisoning to bind iron ions not yet absorbed from the gastrointestinal tract - per os 5-10 g (dissolve the contents of 10-20 ampoules in water);

• to remove absorbed iron - intramuscularly 1-2 g every 3-12 hours;

• in case of shock - intravenously drip 1 g, symptomatic therapy is carried out.

Contraindications to the appointment of iron preparations:

• hypochromic anemia with normal or excessive Fe content in the body;

• violation of utilization of Fe already in the body at normal or elevated plasma concentration.

Parenteral use of iron is also contraindicated in severe coronary insufficiency, arterial hypertension, allergic diseases of the skin and lungs (and with a pronounced predisposition to them), acute glomerulonephritis, active pyelonephritis and hepatitis, severe violations of the liver and kidneys .

Comparison and selection of iron preparations for oral administration

• Monocomponent - contain one any Fe salt:

- polymaltose complex containing Fe3 + - FeOH3 (maltofer *);

- containing Fe2 + - gluconate (ferronal *), sulfate (hemofer prolangatum *, actiferrin *, tardiferon *, ferrogradumet *), fumarate (heferol *), chloride (hemofer *).

• Combined - the composition except for the iron salt includes:

- ascorbic acid (vitamin C transfers Fe3 + to the divalent state, which helps to improve absorption) - sorbifer durules *;

- folic acid - Maltofer Fall * [iron (III) hydroxide polymaltosate], Gino-Tardiferon * (iron sulfate), ferretab * (iron fumarate).

In childhood (especially younger than 6 years), it is preferable to use iron preparations in the form of syrup (actiferrin *), drops for oral administration (hemofer *), suspensions

Interaction

Pancreatic enzymes inhibit the absorption of Fe preparations for 1–2 hours. Within 3 hours, some antacids disrupt their absorption (Ca, Mg, Al ions, which are part of their composition, form poorly soluble complexes with iron). Colestyramine has a similar effect.

With the simultaneous intake of Fe and tetracyclines, poorly absorbed chelates are formed (at the same time, 200 mg of FeSO4 for 3 hours significantly reduce the absorption of therapeutic doses of tetracyclines). If necessary, a combination of tetracyclines with preparations containing iron ions, the latter should be taken only after the maximum concentration of the antibiotic in the blood plasma is reached. In a similar way, if necessary, simultaneous administration of iron and cipro-phloxacin, lomefloxacin and calcium-rich foods to the patient should be done. The degree of interaction is less when using Fe preparations with enteric coating.

On the other hand, ascorbic, succinic acid and their salts, lactose, fructose, dextrose (glucose *), sulfur-containing amino acids (cysteine, methionine), inosine while taking Fe2 + protect it from oxidation (conversion to Fe3 +) and increase absorption . The optimal dose of ascorbic acid, providing the greatest absorption, is 200 mg for every 30 mg of Fe2 +.

Chloramphenicol can slow down bone marrow response to iron ions. Ethanol, especially in high doses and with prolonged use, increases the absorption and liver accumulation of Fe. Iron preparations should not be washed down with tea (poorly absorbed compounds form with

tannin). Food reduces the absorption of Fe2 + by 30-80% (solid foods, bread, raw cereals, milk and dairy products, ice cream, eggs, vegetables have the greatest effect).

Evaluation of the effectiveness of treatment

The indicators of the effectiveness of treatment with iron preparations are shown in table

In the treatment of the first (manifest) stage of iron deficiency anemia, control over the number of red blood cells and reticulocytes, hemoglobin concentration, color index is carried out 1-2 times a week. The effect is considered good if the increase in hemoglobin is 1-2 (g / l) / day, and red blood cells - 0.04x1012 / day. Achieving a hemoglobin concentration of 115-120 g / l is a criterion for eliminating the first stage of the disease.

When treating the latent stage of iron deficiency anemia, the concentration of serum iron is additionally controlled (after a 5-7-day break in taking drugs). Normalization of the concentration of serum iron and the achievement of an individual norm of hemoglobin and red blood cells is the elimination of the latent phase.

More detailed studies are needed to identify the preferential phase of iron deficiency anemia, in particular, the test with deferoxamine, the radioimmune determination of ferritin, the determination of the degree of absorption of radioactive iron, etc.

3.2. Replenishment of iron stores (saturation therapy)

Iron reserves (iron depot) in the body are iron ferritin and hemosiderin of the liver and spleen. To replenish iron stores after reaching a normal level of hemoglobin, they are treated with iron-containing drugs for 3 months in a daily dose, which is 2-3 times less compared to the dose used at the stage of anemia relief.

3.3. Anti-relapse (supportive) therapy

With continued bleeding (for example, heavy menstruation), iron preparations are indicated in short courses of 7-10 days a month. With a relapse of anemia, a repeated course of treatment is indicated for 1-2 months.

Treatment of iron-saturated (siderohrestichny) anemia

Siderohrestichny (iron-saturated) anemia is a hypochromic anemia in which red blood cells contain little iron and hemoglobin not due to iron deficiency in the body, but because it is not used by the bone marrow to synthesize hemoglobin. At the heart of the development of siderochrestic anemia is a violation of heme synthesis. Many enzymes and coenzymes take part in heme synthesis. The most important role is played by the co-enzyme of vitamin Bb - pyridoxophosphate. Its deficiency causes the development of siderochrestic anemia, which is congenital (hereditary) and acquired.

There are two main forms of hereditary sidereal anemia: pyridoxin-dependent and pyridoxin-resistant. Their appearance is associated with the disruption of genes responsible for the synthesis of porphyrin metabolism enzymes. These genes are located in the X chromosome of the 23rd pair. Usually boys are ill, since girls have a second X chromosome that compensates for the defect.

In case of pyridoxine-dependent siderohrestical anemia, treatment with vitamin Bb and its coenzyme pyridoxalphosphate increases the content of hemoglobin, with pyridoxine-independent anemia there is no such effect, since there is a violation of other enzyme systems, and not pyridoxalphosphate.

In case of hereditary pyridoxine-dependent siderohrestical anemia, the administration of vitamin Bb is indicated intramuscularly in doses of 5-8 ml of a 6% solution per day. More effective is the treatment with pyridoxalphosphate (80-100 mg per day by mouth or 30-40 mg per day intramuscularly). It is advisable to combine vitamin C and pantothenic acid with vitamin Be or pyridoxalphosphate. In case of siderohrestical pyridoxin-resistant anemia, it is recommended to add anabolics or androgens to treatment with vitamin Bb or pyridoxalphosphate.

In order to remove excess iron, desferal is prescribed in a daily dose of 500-1000 mg for a month several times a year.

Acquired siderohrestical anemia is most often caused by lead intoxication, the use of certain medications (isoniazid, chloramphenicol), alcohol abuse and may also be a variant of myelodysplastic syndrome. Treatment consists of stopping myelotoxic drugs and alcohol, using complexones (EDTA) that bind lead and remove it from the body. For the treatment of myelodysplastic syndrome, see the corresponding section.

TREATMENT OF B12-DEFICIENCY AND FOLIEN-DEFICIENCY ANEMIA

B12-deficient and folic acid deficiency anemia is anemia caused by a deficiency of vitamin B12 or folic acid, which leads to impaired DNA synthesis, inefficient eritropesis (megaloblastic type of hematopoiesis).

Vitamin B12 has two coenzymes - methylcobalamin and dezoxyadenosylcobalamin.

Methylcobalamin deficiency causes the following changes:

• the conversion of folic acid into its active form, tetrahydrofolic acid, which is necessary for DNA synthesis, is impaired. With a deficiency of vitamin B12 and methylcobalamin, DNA synthesis is disrupted, including in blood cells, mainly in erythroblasts. As a result, erythroblasts increase, but do not mature to mature erythrocytes, retain nuclei, turn into megaloblasts, and become light;

• cell growth of leukocyte and platelet counts is disrupted;

• formation of an epithelium of the gastrointestinal tract is disturbed (atrophic changes).

Deficiency of deoxyadenosyl cobalamin causes a violation of the conversion of the fatty acid metabolism product - methyl malonic acid - to succinic acid. Methylmalonic acid is toxic to nerve cells, funicular myelosis develops (dystrophic processes in the posterolateral columns of the spinal cord).

Vitamin B12 enters the human body with meat, liver, milk, cheese, eggs. The vitamin B12 found in food binds to the gastromukoprotein produced by the parietal cells of the bottom of the stomach, forming a complex of vitamin B12 + gastromukoprotein. This complex enters the distal small intestine, where it interacts with specific receptors, after which vitamin Bi2 is absorbed and enters the bloodstream. 4-5 micrograms of vitamin B12 is absorbed per day, which makes up 80% of its total amount supplied with food. In the blood, vitamin B12 is connected to the transport protein transcobalamin, with the help of which it is delivered to tissues, bone marrow, and liver. Vitamin B12 is deposited primarily in the liver. When absorption of vitamin B12 in the intestine is stopped, its reserves in the liver last for 3-5 years.

Causes of Vitamin B12 Deficiency

1. Violation of the synthesis of gastromucoprotein:

• autoimmune reactions with the production of antibodies to parietal cells of the bottom of the stomach and to gastromucoprotein;

• atrophic gastritis of the bottom of the stomach;

• hereditary cessation of production of gastromucoprotein (the disease occurs among relatives of patients with identical twins);

• gastrectomy;

• stomach cancer;

• suppression of gastromucoprotein production under the influence of alcohol abuse.

2. Violation of the absorption of vitamin B12 in the small intestine:

• severe chronic enteritis, celiac disease, sprue, Crohn's disease, amyloi doses and other diseases of the small intestine, accompanied by severe mal absorption syndrome;

• resection of the small intestine;

• cancer of the small intestine;

• congenital lack of receptors for the vitamin-minB12 complex + gastromucoprotein in the small intestine (Immerslund disease).

3. Competitive capture of vitamin B12:

• invasion with a wide tape;

• pronounced intestinal dysbiosis.

4. Long-term use of a diet devoid of foods rich in vitamin N12 ·

5. Decreased production of transcobalamin-2 in the liver and a violation of the transport of vitamin B12 to the bone marrow (in rare cases with severe cirrhosis).

The source of folic acid is mainly fresh vegetables and fruits, in much smaller quantities - meat and dairy products. It is partially destroyed by culinary food processing.

Folic acid is absorbed in the ileum, its reserves are enough for 3-5 months, therefore, with a decrease in its consumption with food or a violation of its absorption, folic acid deficiency megaloblastic anemia quickly develops.

The main causes of folic acid deficiency:

• feeding newborns with goat milk;

• restriction of food intake containing folic acid;

• malabsorption in the small intestine (resection of the small intestine, Crohn's disease, severe enteritis and other diseases associated with malabsorption syndrome, alcohol abuse);

• taking certain drugs: folic acid antagonists (methotrexate, etc.); purine and pyrimidine analogs; anticonvulsants (diphenin);

• increased demand (chronic hemolysis of erythrocytes in thalassemia, sickle cell anemia; myeloproliferative syndromes; pregnancy, the neonatal period).

Treatment for B12-deficient anemia is carried out by intramuscular injection of vitamin B12 · There are two preparations of vitamin B12 - cyanocobalamin and oxicobalamin.

Cyanocobalamin is prescribed 400-500 μg intramuscularly 1 time per day (oxycobalamin 1 mg / day every other day). The duration of treatment is 4-6 weeks. On the 3-4th day from the start of treatment with vitamin B12, an increase in the content of reticulocytes in the blood begins.

After the course of treatment, a course of fixing therapy is prescribed: cyanocoba-lamin is administered 1 time per week for 2 months, and then constantly 2 times a month for 400-500 mcg. Oxycobalamin can be administered less often: for 3 months it is administered 1 time per week, and then constantly 500 mg per 1 time per month.

With funicular myelosis, large doses of vitamin B12 (1000 μg daily) are prescribed in combination with coenzyme vitamin B12 cobamamide (500 μg once daily intramuscularly), which is involved in the metabolism of fatty acids and improves the functional state of the spinal cord and nerve fibers. This vitamin B12 supplementation is administered before the disappearance of the myelosis clinic.

The criteria for effective treatment are:

• subjective improvement in the first days of treatment;

• reticulocytosis, the most pronounced (up to 20%) on the 5-7th day of treatment;

• an increase in hemoglobin and the number of red blood cells, starting from the 2nd week of treatment;

• normalization of red blood counts, leukocyte and platelet counts after 3-4 weeks of treatment.

Inefficiency of treatment indicates an incorrect diagnosis.

In symptomatic forms of B12-deficient anemia, treatment of the underlying disease has been indicated (surgical treatment of gastric cancer, deworming during invasion with a wide ribbon).

Folic acid preparations are prescribed only for patients with foliodeficit megaloblastic anemia.

Folic acid is prescribed orally in a daily dose of 5-15 mg. With B12 deficiency anemia, folic acid treatment is not indicated.

Clinical examination of patients In 12-deficiency anemia is carried out by a hematologist or local therapist. Patients are examined by a physician 4-5 times a year, and once a year they are visited by a neuropathologist, gynecologist (women), and ENT doctor. A general blood test is performed 4-5 times a year, the content of thrombocytes and reticulocytes in it is also determined 4-5 times a year, biochemical blood analysis and fibrogastroscopy are done 1 time per year.

Treatment of B12-deficient anemia is carried out for life, clinical observation should be carried out constantly. However, there is a point of view that after complete normalization of hematopoiesis, patients can be removed from the register.

TREATMENT OF HYPOPLASTIC (APLASTIC) ANEMIA

Hypoplastic (aplastic) anemia is a disease of the hematopoietic system, characterized by depression of hematopoiesis (contraction of three blood-producing sprouts in the bone marrow - red, myeloid, megakaryocytic), the development of pancytopenia and fatty degeneration of the bone marrow.

Etiological forms of hypoplastic (aplastic) anemia.

1. Idiopathic form (etiology of anemia is unknown).

2. The constitutional form (Fanconi anemia) is a disease inherited in an autosomal recessive manner, more often detected after 5 years of age.

3. Acquired hypoplastic (aplastic) anemia caused by physical and chemical agents (benzene, ionizing radiation, cytostatic agents, insectofungicides).

4. Acquired hypoplastic anemia, which develops through the idiosyncrasy mechanism after taking certain medications (chloramphenicol, butadiene, amidopyrine, gold preparations).

5. Acquired hypoplastic anemia caused by chronic active hepatitis.

6. Hypoplastic anemia during pregnancy (after delivery, it may disappear).

7. Hypoplastic anemia that develops with other diseases: miliary pulmonary tuberculosis, cytomegalovirus sepsis, goiter Hashimoto, thymoma.

Treatment program:

1. Treatment with glucocorticoids.
2. Treatment with anabolic drugs.
3. Treatment with androgens.
4. Treatment with cytostatics (immunosuppressants).
5. Splenectomy.
6. Treatment with antilymphocytic globulin.
7. Treatment with cyclosporine.
8. A bone marrow transplant.
9. Treatment with colony-stimulating factors.
10. Transfusion of red blood cells.
11. Desferalotherapy.
12. Transfusion of platelets.
13. Treatment with immunoglobulin.

1. Treatment with glucocorticoids

Glucocorticoid therapy is most effective if hypoplastic anemia is caused by autoimmune mechanisms, the appearance of antibodies against blood cells. However, glucocorticoids are also used for other variants of bone marrow depression due to the ability to stimulate erythrocyte, neutrophilic, and megakaryocytic hematopoietic cells. Glucocorticoids are also indicated for partial red cell anemia. The daily dose of prednisone is 1-2 mg / kg of patient weight per day, most often the dose varies between 60-80-120 mg per day. The duration of prednisone therapy depends on the effect in the first 2 weeks from the start of treatment. If there is an effect, then treatment with prednisolone is continued with the transition to a supported dose of 15-20 mg after a significant improvement in the hemogram. Treatment with prednisone can last from 4 weeks to 3-4 months. If there is no effect in the next 2 weeks of glucocorticoid treatment, they can be canceled due to the futility of their use in the future.

2. Treatment with anabolic drugs

Anabolic steroid drugs, on the one hand, neutralize the catabolic effects of glucocorticoids, and on the other, stimulate hematopoiesis.

Nerobol is prescribed at 20 mg / day or more effective Anapolon (oxyme-tolone) at 200 mg / day for 5-6 months. Anabolic treatment is also indicated after splenectomy.

3. Treatment with androgens

Androgens have an anabolic effect and stimulate erythropoiesis. An increase in hemoglobin level is observed in 50% of patients, neutrophilic white blood cells - in 30%, platelets - in 25% of patients. Daily doses of androgens are 1-2 mg / kg, sometimes 3-4 mg / kg. Testosterone propionate 5% solution is introduced, 1 ml 2 times a day, or prolonged-release drug

The effect of androgens occurs gradually, so the treatment is carried out for a long time for several months. With a decrease in dose or cancellation of anthrogens in some patients, exacerbation of the disease is possible.

Prolonged use of androgens can be complicated by cholestatic hepatitis. With an increase in the level of aminotransferases in the blood, the dose of androgens should be halved, with the development of persistent jaundice, androgens are canceled.

Treatment with androgens is performed for men. This therapy is not prescribed for women in connection with the development of severe virilization with prolonged use of large doses of androgens.

4. Treatment with cytostatics (immunosuppressants)

Immunosuppressive therapy is prescribed only in the absence of the effect of other methods of treatment in patients with an autoimmune form of hypoplastic anemia, including partial red cell aplasia. You can treat with azati-oprine (imuran) 0.05 g 2-3 times a day with a gradual dose reduction after receiving the effect. The duration of treatment can be 2-3 months.

However, it must be emphasized that treatment with immunosuppressants should only be carried out according to strict indications, since cytostatics themselves can cause a state of hematopoiesis depression.

6. Treatment with antilymphocytic globulin

Treatment with antilymphocytic globulin is recommended in the absence of the effect of splenectomy and other treatment methods. The drug inhibits the formation of antibodies against blood cells. 120-160 mg of antilymphocytic globulin is injected intravenously 1 time per day for 10-15 days. Immediately after the first injection of the drug, a decrease in the number of leukocytes with a tendency to normalize their content by the end of treatment is noted.

Similarly, hemoglobin and erythrocyte counts change. The number of neutrophils increases immediately after the first injection of the drug by almost 2 times. The number of lymphocytes and platelets decreases and remains low towards the end of treatment.

Treatment with anti-lymphocyte globulin can be complicated by the development of infectious and inflammatory processes, hemorrhagic syndrome (due to an increase in thrombocytopenia, coagulopathy), fever, skin itching, and urticaria rash. With the development of hemorrhagic syndrome, treatment with freshly frozen plasma, fibrinosis inhibitors, transfusion of platelet concentrate is indicated.

In the treatment of mild forms of aplastic anemia, small doses of antilymphocytic globulin (1-5 mg / kg / day) are highly effective, and treatment of severe forms of the disease should be carried out with large doses of the drug (above 10 mg / kg / day) against the background of adequate hemocomponent therapy. Immunosuppressive therapy with anti-lymphocyte globulin, moderate doses of glucocorticoid and androgen is the method of choice in patients with aplastic anemia who do not have an HLA-identical donor, and which therefore cannot be transplanted.

7. Treatment with cyclosporine

Cyclosporin A (sandimmune) - a drug that is a metabolite of the fungus Tolipocladium inflatum. It has an immunosuppressive effect, selectively inhibits the transcription of the interleukin-2 gene in T-lymphocytes, and inhibits the production of γ-interferon and tumor necrosis factor α. It is an effective treatment for aplastic anemia, hematologic remission is achieved in 40-50% of patients. It is applied orally in the form of an oil solution or in capsules at a dose of 4 mg / kg / day in 2 doses, it is advisable to carry out treatment under the control of the concentration of cyclosporin in the blood which should be maintained in the range of 150-300 ng / ml. In the absence of toxic effects, treatment can continue for several months. Side effects of the drug - nephrotoxicity, arterial hypertension, gum hyperplasia

9. Treatment with colony stimulating factors

Colony stimulating factors (CSF) or myeloid growth factors are glycoproteins that stimulate the proliferation and differentiation of various types of hematopoietic progenitor cells

Some CSFs are synthesized using the recombinant method and are used in the clinic.

Granulocytic CSF preparations filgrastim, lenograstim, nartograstim primarily stimulate the formation of neutrophils; granulocyte-macrophage CSF preparations, mgramramostim, sargramostim, leukomax stimulate the production of eosinophils, neutrophils, monocytes. The main indication for the use of CSF is neutropenia of various nature, including with aplastic anemia, which increases the risk of life-threatening infections.

CSF is used in addition to other methods of therapy; they are suggested to be combined with interleukins. Recombinant CSF preparations are used intravenously at a dose of 5 μg / kg / day for 14 days. In recommended doses, the drug is well tolerated. The main side effects are bone pain, skin rashes, myalgia, and fever.

• methylprednisolone - 1-4 days at a dose of 20 mg / kg / day orally; 5-8 days at a dose of 10 mg / kg / day orally; 9-10 days at a dose of 5 mg / kg / day three times a day for a short infusion; 12-15 days at a dose of 2.5 mg / kg / day as a short infusion; 16-19 days at a dose of 1 mg / kg / day as a short infusion.

11. Desferalotherapy

It has been established that with hypoplastic (aplastic) anemia there is a significant accumulation of iron in the cells of hematopoiesis, especially erythropoiesis. This is due to depression of hematopoiesis, a decrease in iron utilization, and insufficient formation of protoporphyrin IX. Excess iron can disrupt the function of hematopoietic cells until they die. In this regard, it is proposed to include in the complex therapy of hypoplastic (aplastic) anemia the preparation desferrioxan-lin (desferal), which selectively binds and removes ferric iron from human organs. The drug is rapidly excreted through the kidneys in the form of ferroxamine, giving the urine a reddish tint. Desferal is available in bottles of 500 mg of dry matter, which, before use, are diluted with 5 ml of distilled water and administered intramuscularly or intravenously 2 times a day for at least 2-3 weeks. After a break of 3-4 weeks, it is advisable to conduct another 2-4 such courses. The drug can be used without a break for 2-3 months. In 50% of patients after treatment with desferal, hematopoiesis indicators improve. A contraindication to the use of desfer-la is hemorrhagic syndrome.

13. Treatment with immunoglobulin

In recent years, for the treatment of hypoplastic anemia, intravenous administration of immunoglobulin at a dose of 400 mcg / kg body weight has been recommended for 5 consecutive days. The drug stimulates erythro- and thrombocytopoiesis.

Treatment of hemolytic anemia

Hemolytic anemia is a group of hereditary and acquired diseases characterized by increased intracellular or intravascular destruction of red blood cells.

Treatment of hereditary hemolytic anemia

The chapter outlines the treatment of the most common types of hereditary hemolytic anemia.

1. Treatment of microspherocytic hemolytic anemia

Microspherocytic hemolytic anemia (Minkowski-Schoffar disease) is a hereditary disease caused by a defect in the erythrocyte membrane proteins that take on a spherical shape and are subsequently destroyed by spleen macrophages.

The most effective treatment option is splenectomy, leading to clinical recovery.

2. Treatment of sickle cell anemia

Sickle cell anemia is a disease associated with a hereditary violation of hemoglobin synthesis (the appearance of hemoglobin S with reduced solubility - HbS), characterized by a sickle-shaped form of red blood cells and their autohemolysis.

The formation of sickle red blood cells increases blood viscosity and slows blood flow in the microvasculature, which contributes to hypoxia of organs and tissues. Sickle-shaped red

blood cells are subject to autohemolysis due to disruption of glycolysis processes in them, and a decrease in ATP. The sickle shape of red blood cells appears when Ras> 2 decreases to 60 mm Hg. Art. and below

3. Treatment of thalassemia

Thalassemia is a heterogeneous group of hemoglobinopathies with a hereditary violation of the synthesis of one of the globin chains.

In violation of the synthesis of the β-chain of globin, β-thalassemia develops; in violation of the synthesis of the α-chain - α-thalassemia. Also described are γ-, δ-, βδ-thalassemias with impaired synthesis of the corresponding globin chains. The most common is β-thalassemia.

3.1. Treatment of homozygous β-thalassemia

The main treatment method is to transfuse a patient with washed or thawed red blood cells from a child's age. Initially, a shock treatment course is used (8-10 transfusions in 2-3 weeks). Then transfusions are made less often, every 3-4 weeks ¬ based on the calculation of 20 ml / kg of body weight. The level of hemoglobin is maintained in the range of 90-100 g / l.

A complication of long-term transfusion therapy is hemosiderosis of the internal organs. In this regard, desferol is used to remove excess iron. It is prescribed for small children at a dose of 10 mg / kg body weight, for adults and adolescents - 500 mg / day. It is recommended to combine treatment with desferal with the ingestion of 200-500 mg of ascorbic acid, which enhances the action of desferal.

With a significant increase in the spleen, the development of leukopenia and thrombocytopenia, splenectomy is performed.

3.2. Treatment of heterozygous β-thalassemia

In most cases, patients feel satisfactory and do not need treatment. With a decrease in hemoglobin level due to infectious diseases, folic acid is used at 0.005 g 2 times a day, since the need for it increases with ineffective erythropoiesis due to thalassemia.

Iron preparations are contraindicated, since there is always some excess of it without a hemosiderosis clinic.

Treatment of acquired autoimmune hemolytic anemia

Autoimmune hemolytic anemia is anemia caused by the formation of antibodies to red blood cells' own antigens, which leads to their destruction.

1. Glucocorticoid therapy

Glucocorticoids inhibit the formation of antibodies to red blood cells and thereby reduce hemolysis.

In acute forms of autoimmune hemolytic anemia with incomplete heat agglutinins, prednisone is prescribed in a daily dose of 60-80 mg. The dose of prednisolone can be increased to 150 mg or more. The daily dose is divided into 3 doses in a ratio of 3: 2: 1. With a decrease in the manifestations of hemolytic crisis, the dose of prednisone gradually decreases (2.5-5 mg per day) to half the initial dose. Next, the dose of prednisolone is reduced by 2.5 mg every 4-5 days, then prescribed in even lower doses and at large intervals, after which it is canceled.

In chronic autoimmune hemolytic anemia with incomplete thermal agglutinins, prednisone is used in a daily dose of 20-40 mg, and as the patient's condition improves and anemia decreases, they switch to maintenance therapy (5-10 mg per day). Treatment with glucocorticoids is effective in patients, but recurrence often occurs.

With autoimmune hemolytic anemia with complete Cold agglutinins, the effectiveness of glucocorticoid therapy is lower than with a form with thermal antibodies, however, with a pronounced exacerbation of the disease and hemolytic crisis, significantly lower doses of prednisolone are required - about 25 mg / day.

2. Splenectomy

3. Treatment with cytostatics and immunoglobulin

Cytostatic therapy blocks the formation of antibodies to red blood cells and is prescribed in the absence of the effect of glucocorticoids and splenectomy. Azithioprine (imuran) is recommended in a daily dose of 100-150 mg; cyclophosphamide at a dose of 400 mg every other

day; vincristine 2 mg once a week; chlorbutin in a daily dose of 2.5-5 mg. Treatment is carried out until hemolysis is reduced, most often in combination with prednisone, then the patient is transferred to a maintenance dose, which is about 1/2 of the initial dose. The course of treatment can last up to 2-3 months.

It may be effective treatment with immunoglobulin G 0.5-1 g / kg / day intravenously for 5 days

4. Transfusion of red blood cells

6. Treatment of hemolytic uremic syndrome

Autoimmune hemolytic anemia can be complicated by severe kidney damage - hemolytic-uremic syndrome. Treatment of this syndrome includes the use of prednisone, freshly frozen plasma, plasmapheresis, hemodialysis, transfusion of washed red blood cells. The prognosis for the development of hemolytic uremic syndrome is unfavorable.

Treatment of paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (Markia-fava-Mikeli disease) is an acquired hemolytic anemia associated with a defect in the erythrocyte membrane, which increases their sensitivity to serum complement.

In paroxysmal nocturnal hemoglobinuria, there are two populations of erythrocytes: one is normal, the other is pathological, which appears as a result of somatic mutation and has defects in the erythrocyte membrane - a decrease in the content of acetylcholinesterase in it and an increase in hydrogen oxide. Red blood cells of a pathological clone are easily destroyed in the presence of complement.

During hemolysis, not all hemoglobin is bound by haptoglobin and excreted in the urine. Hemoglobinuria is observed mainly at night. This is due to the development of acidosis during sleep, as well as to an increase in the activity of properdine.

There is no pathogenetic treatment for paroxysmal nocturnal hemoglobinuria. The following treatment measures apply.

1. Red blood cell transfusion

2. Treatment with anabolic drugs

Anabolic steroid drugs have an anti-complementary action and can be effective in the treatment of paroxysmal nocturnal hemoglobinuria. Patients are prescribed nerobol (methandrostenolone) at 0.005 g 4 times a day for several months (at least 2-3) under the control of the functional capacity of the liver (development of cholestatic hepatitis is possible). After the cancellation of nerobol, hemolysis may increase.

Significantly less toxic than nerobol is the anabolic anapolone (ok-simetholone), which is prescribed at 150-200 mg per day. Long-acting anabolic steroids are less effective.

3. Antioxidant treatment

In the erythrocyte membrane with paroxysmal nocturnal hemoglobinuria, the formation of peroxides of unsaturated fatty acids is increased, which reduces the stability of the erythrocyte membrane. In this regard, it is recommended treatment with antioxidants that block lipid peroxidation and the formation of peroxides. The most active antioxidant drug is erevit (a vitamin E preparation). It is used intramuscularly at a dose of 3-4 ml per day (0.15-0.2 g of tocopherol acetate). You can use tocopherol acetate in capsules containing 0.2 ml of a 50% solution (100 mg of tocopherol), 2 capsules per day or in an injection of 30% solution of 1-2 ml intramuscularly 1 time per day.

Antioxidant treatment is carried out for 1-3 months.

4. Elimination of iron deficiency

In connection with the frequent and often constant hemoglobinuria, a significant loss of iron occurs. To eliminate iron deficiency, iron-containing drugs are used. However, iron preparations can enhance hemolysis in patients with paroxysmal nocturnal hemoglobinuria. Therefore, iron preparations are recommended for use with severe iron deficiency, in small doses and necessarily against the background of treatment with anabolic steroids and vitamin E. There

is an opinion that anabolics and vitamin E reduce the hemolysis that occurs under the influence of iron preparations.

5. Treatment of thrombosis

With Markiaphava-Mikeli disease, thrombosis may develop. To combat thrombosis, heparin is used, often in small doses (5000 units 2-3 times a day under the skin of the abdomen) for 2 weeks, followed by a gradual dose reduction. It is possible to use anticoagulants of indirect action.

Hemolytic crisis treatment

Hemolytic crisis is a syndrome characterized by a sharp exacerbation of clinical and laboratory signs of hemolysis of red blood cells.

Hemolytic crisis is an emergency. The following therapeutic measures are recommended.

1. Compensation of circulating blood volume

2. Neutralization of toxic products and stimulation of diuresis

3. Elimination of acidosis

4. Efferent (extracorporeal) therapy

In the absence of the effect of the above measures and an increase in acute renal failure, hemodialysis is performed (see the chapter "Treatment of acute renal failure"). In many patients, plasmapheresis sessions are effective.

5. Glucocorticoid therapy

Treatment with glucocorticoid drugs is carried out only in the case of a hemolytic crisis in patients with hemolytic anemia of the immune genesis, as well as with the development of shock and a sharp drop in blood pressure. Intravenous prednisone is prescribed at a dose of 1-1.5 mg / kg, it is possible to re-administer the same dose after 3-4 hours.

6. Relieving Anemia

With a decrease in hemoglobin to values of 40 g / l and below, it is necessary to transfuse individually selected washed red blood cells of 150-300 ml. When washing red blood cells, sensitizing factors (plasma proteins, white blood cells, platelets, antibodies to red blood cells) are removed. Defrosted red blood cells possessed under ultra-low temperature have the same properties.

In case of Markiafava-Mikeli's disease, it is possible to transfuse only an erythrocyte mass with a 7–9-day shelf life (during this time, perperdine is inactivated and the risk of hemolysis is reduced) or erythrocytes washed three times.

The purpose of the lesson.

To master the etiopathogenetic factors of anemia, to be able to determine the manifestations of these diseases, explain their causes and development mechanism, evaluate the outcome and determine the value of probable complications for the body.

Control questions.

1. Composition and physiology of blood: plasma, red blood cells, white blood cells and platelets.

2. Pharmacokinetic features of absorption, distribution and elimination of iron from the human body?

3. The total reserves of iron in the human body.

4. In which section of the digestive tract does iron absorption take place?

5. What chronic diseases lead to disruption of iron absorption in the human body?

6. The normal limits of the level of hemoglobin and red blood cells in human serum.

7. Under what pathology of the gastrointestinal tract is the development of hypochromic anemia possible?

8. Under what pathology of the gastrointestinal tract is the development of hyperchromic anemia possible?

9. Features of iron intake in pregnant women?

10. The system of regulation of the state of aggregation of blood - RASK.

11. Anemia - classification:

a) Anemia due to blood loss;

 acute posthemorrhagic anemia - etiology, pathogenesis, clinical presentation, pharmacotherapy;

b) Anemia due to a violation of erythropoiesis:

 iron deficiency anemia:

 with chronic blood loss;

 hypochromic macrocytic anemia;

 chlorosis;

 hypochromic anemia of pregnant women and children;

etiology, pathogenesis, clinical picture, pharmacotherapy;

 anemia in renal diseases - etiology, pathogenesis, clinical picture, pharmacotherapy;

 pernicious anemia (macrocytic, hyperchromic, megaloblastic, Addison-Birmer disease) etiology, pathogenesis, clinical picture, pharmacotherapy;

 folic acid deficiency anemia, etiology, pathogenesis, clinical presentation, pharmacotherapy;

c) hemolytic anemia:

 acquired hemolytic anemia: autoimmune hemolytic anemia, paroxysmal nocturnal hemoglobinuria - etiology, pathogenesis, clinical picture, pharmacotherapy;

 hereditary hemolytic anemia: macrospherical hemolytic anemia (Minkowski-Shoffan disease), enzymatic hemolytic anemia, sickle cell anemia, thalassemia, erythropoietic porphyria - etiology, pathogenesis, clinical picture, pharmacotherapy

12 .. Pharmacodynamics, pharmacokinetics, pharmacotoxicodynamics of substances that affect erythropoiesis:

13. The main pathogenetic mechanisms that are the object of drug exposure in anemia.

14. The basic principles of pharmacotherapy of bleeding.

15. Medicines affecting the blood system:

- affecting blood formation:

o erythropoiesis: stimulating and inhibitory;

o leukopoiesis: stimulating and inhibitory;

- affecting blood coagulation:

o antithrombotic: reducing coagulation (anticoagulants); increased fibrinolysis (fibrinolytic); antiplatelet agents;

o hemostatic: increasing coagulation (procoagulants); fibrinolysis inhibitors; thrombogenic;

- affecting the volume and composition of blood (blood and plasma substituting).

16. Classification of drugs INFLUENCING ERYTHROPOESIS:

1) Stimulants of erythropoiesis:

 with hypochromic (iron deficiency) anemia - IRON DRUGS:

a) for oral use:

 monocomponent: ferronal (iron gluconate), actiferrin, ferro-degree (iron sulfate), heferol (iron fumarate), hemofer (iron chloride), maltofer (iron hydroxide polymaltose complex), Feramide;

 combined: tardiferon, ferroplex (+ ascorbic acid), ferrocal (+ cerebrolecithin + calcium fructosodiphosphate), hemostimulin (+ copper), maltoferfol (+ folic acid), etc.

b) for parenteral use: ferbitol, zhektofer (iron-sorbitol complex), ferkoven, ferrum lek (iron sugar), coamide (+ cobalt)

 with hyperchromic (megaloblastic) anemia - cyanocobalamin, folic acid.

2) Drugs that inhibit erythropoiesis - sodium phosphate labeled with phosphorus 32.

17. Means used for hypochromic anemia. Pharmacokinetics, pharmaco-dynamics of iron preparations. Comparative characteristics. Indications for use. Dosage regimen. Undesirable effects. Poisoning with iron preparations and measures of relief (deferoxamine).

18. Pharmacological characteristics of drugs used to treat hyperchromic anemia. Pharmacokinetics, pharmacodynamics. Undesirable effects.

19. Erythropoietins (□, □, □). Biological role. The use of epoetin (epomax). Undesirable effects.

20. Phytotherapeutic agents and preparations of animal origin used for anemia.

Enumeration of practical work.

Homework.

1. To study the etiology and pathogenesis of anemia.

2. Know the classification and clinic of anemia.

2. To study the main directions of treatment of these diseases.

4. Be able to provide first aid to a patient with acute blood loss.

Control of the intermediate level of knowledge.

The solution of situational tasks:

1. A patient, 42 years old, weighing 67 kg, suffering from a severe form of iron-deficiency anemia, takes iron supplements.

After what time from the beginning of taking reticulocytosis appears in the blood, as a reaction of hematopoiesis to iron preparations?

2. A patient, 67 years old, weighing 86 years, with a diagnosis of hypochromic anemia, has been taking iron preparations for a long time. Against the background of treatment, she appeared constipated.

Explain the cause and mechanism of their occurrence.

3. The patient, 38 years old, weighing 65 kg, was admitted to the therapeutic department with a diagnosis of Addison-Birmer disease. A history of gastric ulcer. 2 years ago, a resection of the stomach was performed.

Explain the cause of the disease. Assign a treatment plan indicating the drugs and their route of administration.

4. The most common complication with intramuscular use of iron preparations is: Allergic reactions, infiltrates, hyperglycemia, brady cardia, tachycardia.

5. 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 milk products should be consumed with it. Explain why.

7. A woman, 26 years old, complains of general weakness, increased fragility of her legs, hair loss. Objectively: pulse - 94 beats per 1 min, blood pressure - 110/70 mm RT. Art. The skin is pale. Blood test: Hb - 90 g / l, er - 3.5 · 1012 / l, CP - 0.7, ESR - 20 mm / hour. The level of serum iron is 8.7 μmol / L.

What drugs should be prescribed to this patient? Explain the mechanism of their action.

9. A man, 45 years old, complains of general weakness, dizziness. Over the course of 15 years, 12 duodenal ulcer suffers. Objectively: temperature - 36.5 ° C, BH - 20 rpm, pulse - 96 rpm, BP - 115/70 mm Hg. The skin and mucous membranes are pale. In the blood of er. - 3.8 · 1012 / l, Hb - 90 g / l. Gregersen's reaction is slightly positive.

What is the tactic for treating anemic syndrome in this case?

10. Patient D., 43 years old, was admitted to the hospital with complaints of weakness, dizziness, shortness of breath with little physical exertion. Anemia was detected in the blood test (HB - 60 g / l, color col. - 1.2). On examination of the tongue - glossitis. In the study of bone marrow punctate - megaloblastic type of hematopoiesis. What type of anemia can you think of? Suggest methods for further examination and pharmacotherapy of the patient.

11. Patient T., 70 years old, underwent surgery for a large resection of the small intestine due to cancer. What type of anemia can develop in this case? What methods of prevention and treatment can you recommend?

12. Patient K., 54 years old, is examined by a gynecologist in connection with uterine bleeding. Development, what type of anemia can be in this case? Suggest preventative measures and principles of pharmacotherapy.

13. A patient with a disease of the hematopoietic system is prescribed a drug that contains iron (ferroplex). What is the indication for the appointment of this therapeutic agent:

14. A patient, 60 years old, who has been suffering from hemorrhoids for 10 years, developed chronic posthemorrhagic anemia.

Appointment, which drug is most appropriate in this case?

Patient V., 58 years old, complained of general weakness, rapid fatigability, periodically occurring dizziness, tinnitus, flickering of "flies" before the eyes, drowsiness during the day. She notes that lately she has a desire to eat chalk.

From the anamnesis

Over the past two years, the patient switched to vegetarian food.

Objectively: the skin and visible mucous membranes are pale, the nails are thinned. Peripheral lymph nodes are not enlarged. In the lungs, vesicular breathing, no wheezing. Heart sounds are muffled, rhythmic, systolic murmur at the apex. Heart rate of 80 per minute. HELL 130/75 mm RT. Art. The tongue is moist, covered with a white coating. The abdomen on palpation is soft, painless.

The patient was examined.

General blood analysis

Hemoglobin - 85 g / l, erythrocytes - 3.4x1012 / l, color indicator - 0.8, heme-tokrit - 27%, leukocytes - 5.7x109 / l, stab - 1, segmented - 72, lymphocytes - 19, monocytes - 8, platelets - 210x109 / l, anisochromia and poikilocytosis are noted.

SIT (average hemoglobin in the red blood cell) - 24.9 pg (normal 27-35 pg).

ICSU - 31.4% (norm 32-36%). SEA - 79.4 microns (norm 80-100 microns).

Blood chemistry

Iron in the blood serum is 10 μmol / l (normal 12-25 μmol / l).

The total iron binding capacity of serum is 95 μmol / L (normal 30-86 μmol / L).

The percentage of transferrin saturation with iron - 10.5% (normal

16-50%).

The ferritin content is 8 μg / L (normal 10-150 μg / L).

Fibrogastroduodenoscopy

Conclusion: superficial gastroduodenitis.

Colonoscopy Conclusion: no pathology was detected.

Consultation of an obstetrician-gynecologist. Conclusion: Menopause 5 years. Atrophic colpitis.

Based on the patient's complaints (general weakness, fatigue, periodically dizziness, tinnitus, flickering "flies" in front of the eyes, drowsiness during the day, desire to eat chalk) and laboratory examination data [in the general blood test, the hemoglobin content was reduced, red blood cells; the size of red blood cells is reduced, of various shapes, different in color intensity (signs of irritation of the red blood cell); a biochemical analysis of blood showed a decrease in the content of iron in blood serum, an increase in the total iron binding capacity of serum, a decrease in the percentage of transferrin saturation with iron and a decrease in serum ferritin]. The patient was diagnosed with moderate-grade iron deficiency anemia (of nutritional origin).

Prescribe a treatment.

TESTS

1. A woman, 26 years old, complains of general weakness, increased brittle nails, hair loss. Objectively: pulse - 94 beats per 1 min, blood pressure - 110/70 mm RT. Art. The skin is pale. Blood test: Hb - 90 g / l, er - 3.5 · 1012 / l, CP - 0.7, ESR - 20 mm / hour. The level of serum iron is 8.7 μmol / L. What purpose is appropriate for this patient?

A. Whole blood transfusion.

B. Parenteral iron preparations.

C. Transfusion of red blood cells.

D. * Iron preparations inside.

E. Vitamin B12 intramuscularly.

2. The child had subcutaneous hemorrhage. The appointment of a synthetic analogue of vitamin K (Vikasol) gave a positive effect. In the synthesis of which protein of the blood coagulation system does this drug take part in?

A. * Prothrombin.

B. Antihemophilic globulin.

C. Factor of Hageman.

D. Fibrinogen.

E. Collagen.

3. For a patient with myocardial infarction, a direct-acting anticoagulant was administered. What drug was administered to the patient?

A. Thrombin.

B. Neodicumarin.

C. Vikasol.

D. * Heparin.

E. Calcium gluconate.

4. A patient, 65 years old, who 9 years ago underwent subtotal resection of the stomach for peptic ulcer, was diagnosed with iron deficiency anemia: er. - 3.0 · 1012 / l, Hb - 58 g / l, CPU - 0.6. Which drug should be recommended in this case?

A. Askopher.

B. Tardiferon.

C. * Ferrum Lek.

D. Ferroplex.

E. Hemofer.

5. A patient, 60 years old, who for 10 years has been suffering from hemorrhoids, developed chronic posthemorrhagic anemia. What drug is most appropriate in this case?

A. * Ferroplex.

B. Vitamin B12

C. Tocopherol acetate.

D. Ferrum Lek.

E. Desferol.

7. A patient, 50 years old, complains of general weakness, dizziness, heaviness in the upper abdomen, paresthesia of the fingertips of the upper and lower extremities. Objectively: icteric skin, raspberry-colored tongue, smooth. Hepatomegaly. In the blood of Hb - 90 g / l, er. - 2.3 · 1012 / l; CPU - 1.2; macrocytosis; Jolly's corpuscles, rings of Cabot. What treatment method is most appropriate?

A. Reception of prednisolone.

B. Taking iron supplements.

C. Blood transfusion.

D. Reception of dysferol.

E. * Vitamin B12 intake.

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 35. CLINICAL-PHARMACEUTICAL APPROACHES TO THE SELECTION OF HEMOSTATICS

Purpose of the topic.

The process of hemostasis (hemostasis - stop bleeding. From the Greek. Haima - blood, stasis - stop) provides a thrombus-forming system (platelet aggregation, blood coagulation), which is functionally interconnected with the thrombolytic (fibrinolytic) system.

In the body, these two systems are in dynamic equilibrium, and one or the other prevails depending on specific conditions. So, if a vessel is damaged and bleeding occurs, the vessel is spasmodic, platelet aggregation and blood coagulation are activated, a blood clot forms and bleeding stops. However, in the norm, excessive thrombosis does not occur, since it is limited by the fibrinolysis process. Subsequently, the fibrinolytic system provides a gradual dissolution of the thrombus and restores the patency of the vessel. If the balance between the coagulation and anticoagulation systems is disturbed, either increased bleeding or widespread thrombosis can occur.

If the blood released from a blood vessel is left for a while, then it first turns from a liquid into a jelly, and then a more or less dense clot forms in the blood, which, contracting, squeezes out a liquid called blood serum. It is a plasma lacking fibrin. The described process is called blood coagulation (hemocoagulation). Its essence lies in the fact that fibrinogen protein dissolved in plasma under certain conditions goes into an insoluble state and precipitates in the form of long fibrin strands. In the cells of these threads, as in a grid, cells get stuck and the colloidal state of the blood as a whole changes. The significance of this process is that clotted blood does not flow from a wounded vessel, preventing the death of the body from blood loss.

Motivational characteristic of the topic.

The presence of a certain volume of blood in the vessels, its liquid state is a necessary condition for the existence of the body. These tasks are solved by the work of a coagulation and anticoagulation system. Imbalance between them is accompanied by severe consequences (loss of blood or intravascular thrombosis).

Hemostasis - blood stop. It occurs when the vessel wall is damaged.

Provided by:

1) narrowing of the vessel in case of damage.

2) platelet reaction - adhesion.

3) by the reaction of hemostasis factors contained in plasma, uniform elements and tissues. They form a blood coagulation system.

For a normal blood condition, three systems must work without interruption:

1. Coagulation.

2. Anticoagulant.

3. Fibrinolytic.

And these three systems are in a state of dynamic equilibrium. Violation of this balance can lead to both unstoppable bleeding and thrombophilia.

Thus, a hereditary or acquired deficiency of the components of the fibrinolytic system and primary anticoagulants can cause the development of thrombophilic conditions, which are characterized by a tendency to repeated thromboses. The most commonly acquired forms of thrombophilia are caused by:

 Firstly, increased consumption of anticoagulants or components of the fibrinolytic system, which is accompanied by massive intravascular coagulation;

 Secondly, by conducting intensive anticoagulant and fibrinolytic therapy, which accelerates the metabolism of the same anticoagulants or components of the fibrinolytic system. In this situation, in order to compensate for the lack of blood factors, intravenous administration of their concentrates or transfusion of freshly frozen plasma is performed.

A blood coagulation disorder, which is characterized by a tendency to frequently recurring vascular thrombosis and organ infarction, is also very often associated with a hereditary or symptomatic deficiency of antithrombin III, components of the fibrinolytic and kallikrein-kinin system, as well as factor XII deficiency and fibrinogen abnormalities.

The causes of thrombophilia include platelet hyperaggregation, as well as a lack of prostacyclin and other platelet aggregation blockers.

On the other hand, there is a certain condition in which, on the contrary, there is a decrease in blood coagulability. This condition is called hypocoagulation. Her appearance is associated:

• Lack of one or more coagulation factors.

• With the appearance in the bloodstream of antibodies to coagulation factors. The most frequent inhibition of factors V, VIII, IX, as well as von Willebrand factor.

• With the action of anticoagulant and thrombolytic drugs.

• With DIC (disseminated intravascular coagulation).

As for hereditary diseases in which there is a violation of blood coagulability, in most cases they are represented by hemophilia A and B, as well as von Willebrand disease. These diseases are characterized by bleeding that occurs even in childhood, and in men bleeding is

predominantly of the hematoma type, i.e. hemorrhages are observed in the joints and the entire musculoskeletal system is affected. A mixed type of bleeding - petechial spotted with rare hematomas occurs in both sexes, but already with von Willebrand disease.

Blood coagulation and anticoagulation systems

The ability of blood to coagulate with the formation of a clot in the lumen of blood vessels when they are damaged has been known since time immemorial. The creation of the first scientific theory of blood coagulation in 1872 belongs to Alexander Alexandrovich Schmidt, professor at Yurievsky (now Tartu) University. Initially, it boiled down to the following: blood coagulation is an enzymatic process; coagulation requires the presence of three substances - the fibrinogen, the fibrinoplastic substance, and thrombin. During the thrombin-catalyzed reaction, the first two substances, when combined, form fibrin. The circulating blood in the vessels does not coagulate due to the absence of thrombin in it.

As a result of further research by A.A. Schmidt and his school, as well as Morawitz, Gammarsten, Spiro, and others, it was found that the formation of fibrin occurs due to only one predecessor - fibrinogen. The proenzyme of thrombin is prothrombin, for the coagulation process, platelet thrombosis and calcium ions are necessary.

Thus, 20 years after the discovery of thrombin, the classical enzymatic theory of blood coagulation was formulated, which in the literature was called the Schmidt-Morawitz theory.

In a schematic form, the Schmidt-Morawitz theory can be represented as follows.

Prothrombin passes into the active enzyme thrombin under the influence of a thrombotic kinase contained in platelets and released from them upon destruction of blood platelets and calcium ions (1st phase). Then, under the influence of the formed thrombin, fibrinogen turns into fibrin (2nd phase). However, the Schmidt-Morawitz theory, which was comparatively simple in its essence, became unusually complicated in the future, overgrown with new information, “turning” blood coagulation into a complex enzymatic process, which is completely the matter of the future.

Plasma coagulation factors.

I. Fibrin and fibrinogen. Fibrin is the end product of the blood coagulation reaction. Coagulation of fibrinogen, which is its biological feature, occurs not only under the influence of a specific enzyme - thrombin, but can also be caused by the venoms of some snakes, papain, and other chemicals. The plasma contains 2-4 g / l. The place of formation is the reticuloendothelial system, liver, bone marrow.

II. Thrombin and prothrombin. Normally, only traces of thrombin are detected in the circulating blood. Its molecular weight is half the molecular weight of prothrombin and is equal to 30 thousand. Inactive thrombin precursor - prothrombin - is always present in the circulating blood. This is a glycoprotein, in the composition of which there are 18 amino acids. Some researchers believe that prothrombin is a complex compound of thrombin and heparin. 15-20 mg% prothrombin is contained in whole blood. This excess content is enough to convert all blood fibrinogen to fibrin.

The level of prothrombin in the blood is a relatively constant value. Of the moments causing fluctuations of this level, one should point out menstruation (increase), acidosis (reduce). The intake of 40% alcohol increases the content of prothrombin by 65-175% after 0.5-1 hours, which explains the tendency to thrombosis in people who regularly consume alcohol.

In the body, prothrombin is constantly used and simultaneously synthesized. An important role in its formation in the liver is played by antihemorrhagic vitamin K. It stimulates the activity of hepatic cells synthesizing prothrombin.

III. Thromboplastin. There is no active factor in the blood of this factor. It is formed during damage to blood cells and tissues and can be, respectively, blood, tissue, red blood cells, platelets. In its structure, it is a phospholipid, similar to phospholipids of cell membranes. According to the thromboplastic activity, the tissues of various organs are decreasing in the following order: lungs, muscles, heart, kidneys, spleen, brain, liver. Sources of thromboplastin

are also breast milk and amniotic fluid. Thromboplastin is involved as an essential component in the first phase of blood coagulation.

IV. Ionized calcium, Ca ++. The role of calcium in the process of blood coagulation was already known to Schmidt. It was then that he proposed sodium citrate as a blood preservative - a solution that bound Ca ++ ions in the blood and prevented its coagulation. Calcium is necessary not only for the conversion of pro-thrombin to thrombin, but for other intermediate stages of hemostasis, in all phases of coagulation. The content of calcium ions in the blood is 9-12 mg%.

V and VI. Proaccelerin and Acelerin (AS globulin). Formed in the liver. Participates in the first and second phases of coagulation, while the amount of pro-acelerin decreases, and the accelerin increases. Essentially V is a precursor of factor VI. It is activated by thrombin and Ca ++. It is an accelerator (accelerator) of many enzymatic coagulation reactions.

VII. Proconvertin and convertin. This factor is a protein in the beta globulin fraction of normal plasma or serum. Activates tissue prothrombinase. Vitamin K is necessary for the synthesis of proconvertin in the liver. The enzyme itself becomes active upon contact in damaged tissues.

Viii. Antihemophilic globulin A (AGG-A). Participates in the formation of blood prothrombinase. It is able to provide blood coagulation that did not have contact with tissues. The absence of this protein in the blood is the cause of the development of genetically determined hemophilia. Received now in dry form and is used in the clinic for its treatment.

IX. Antihemophilic globulin B (AGG-B, Christmas factor, plasma component of thromboplastin). It participates in the coagulation process as a catalyst, and is also part of the thromboplastic complex of blood. Promotes activation of the X factor.

X. Koller factor, Steward-Prouer factor. The biological role is reduced to participation in the processes of prothrombinase formation, since it is its main component. When coagulated, it is disposed of. It is named (like all other factors) by the names of patients in whom the form of hemophilia was first discovered, associated with the absence of this factor in their blood.

Xi. Rosenthal factor, a plasma thromboplastin precursor (PPT). Participates as an accelerator in the formation of active prothrombinase. Refers to beta blood globulins. It reacts in the first stages of phase 1. It is formed in the liver with the participation of vitamin K.

XII. Contact factor, Hageman factor. It plays the role of a trigger in blood coagulation. The contact of this globulin with a foreign surface (roughness of the vessel wall, damaged cells, etc.) leads to activation of the factor and initiates the entire chain of coagulation processes. The factor itself is adsorbed on the damaged surface and does not enter the bloodstream, thereby preventing the coagulation process from being generated. Influenced by adrEnaline (under stress) is partially able to activate directly in the bloodstream.

Xiii. Fibrin stabilizer Lucky-Lorand. Essential for the formation of completely insoluble fibrin. This is a transpeptidase that cross-links individual fibrin strands with peptide bonds, facilitating its polymerization. It is activated by thrombin and Ca ++. In addition to plasma, there are in uniform elements and tissues.

The 13 factors described are recognized as the main components necessary for the normal process of blood coagulation. The various forms of bleeding caused by their absence belong to different types of hemophilia.

Platelets. In healthy people, they have 200 - 400 · 109 in l., Life expectancy of 8 - 12 days. Formed from a stem cell. SK → KPM → TPGK → megaka-riocyte → platelet. Day more than night.

Properties:

1) They can form processes that attach to damaged walls of blood vessels, clogging the vessel.

2) Platelets contain 11 coagulation factors, indicated by Arabic numerals.

3) Participate in the restoration of vascular endothelium, delivering macromolecules to endothelial cells.

Platelet factors

• Platelet factor 1 is proaccelerin, or Ac globulin adsorbed on the surface of platelets. With platelets, about 5% of all blood pro-acelerin is associated.

• Factor 3 is one of the most important components of the blood coagulation system. Together with a number of plasma factors, it is necessary for the formation of thrombin from prothrombin.

• Factor 4 is an antiheparin factor that inhibits the antithromboplastin and antithrombin effects of heparin. In addition, factor 4 is actively involved in the platelet aggregation mechanism.

• Factor 8 (thrombostenin) is involved in the process of fibrin retraction, is very labile, and has ATPase activity. It is released during gluing and destruction of platelets as a result of changes in the physicochemical properties of surface membranes.

Red blood cells.

1) Contain almost all coagulation factors found in platelets

2) Fibrin filaments are attached to their surface during the formation of a fibrin thrombus.

White blood cells.

1) They contain substances that contribute to thrombosis, but they are few.

2) White blood cells activate the destruction of a blood clot - fibrinolysis.

3) Isolate heparin, which prevents blood coagulation

B. Cellular coagulation factors.

Along with plasma factors, the primary role in blood coagulation is played by cell released from blood cells. Most of them are found in platelets, but they are in other cells. It's just that during hemocoagulation, platelets are destroyed in a greater amount than, say, red blood cells or white blood cells, therefore platelet factors are of the greatest importance in coagulation. These include:

1ph. AS-platelet globulin. Like V-VI blood factors, performs the same functions, accelerating the formation of prothrombinase.

2f. Thrombin accelerator. Accelerates the action of thrombin.

3ph. Thromboplastic or phospholipid factor. It is in the granules in an inactive state, and can be used only after the destruction of platelets. It is activated by contact with blood, it is necessary for the formation of pro-thrombinase.

4f.Antigeparin factor. Binds heparin and delays its anticoagulating effect.

5ph. Platelet Fibrinogen It is necessary for the aggregation of blood plates, their viscous metamorphosis and the consolidation of platelet plugs. It is located both inside and outside the platelet. contributes to their bonding.

6ph. Retractozyme. Provides thrombus compaction. In its composition, several substances are determined, for example, thrombostenin + ATP + glucose.

7ph. Antifibinosilin. It inhibits fibrinolysis.

8ph. Serotonin. Vasoconstrictor. Exogenous factor, 90% is synthesized in the gastrointestinal mucosa, the remaining 10% - in platelets and central nervous system. It is secreted from the cells during their destruction, contributes to the spasm of small vessels, thereby contributing to the prevention of bleeding.

In other blood cells, these same factors are mainly found, but normally they do not play a noticeable role in hemocoagulation.

C. Tissue coagulation factors

Participate in all phases. These include active thromboplastic factors similar to III, VII, IX, XII, XIII plasma factors. In the tissues there are activators of V and VI factors. A lot of heparin, especially in the lungs, prostate gland, kidneys. There are antiheparin substances. With inflammatory and cancerous diseases, their activity increases. There are many activators (kinins) and fibrin-lysis inhibitors in the tissues. The substances contained in the vascular wall are especially important. All these compounds constantly come from the walls of blood vessels to the blood and regulate coagulation. The fabrics also provide for the removal of coagulation products from co-vessels.

The role of tissues in hemostasis (especially the walls of blood vessels).

1) Contains active thromboplastin, necessary in the formation of a thrombus.

2) Substances causing platelet adhesion and aggregation.

3) Contain substances that activate and inhibit the destruction of a blood clot and thrombus formation.

Types of hemostasis.

Vascular platelet coagulation

Vascular thrombocyte.

Role:

1) provides a stop of bleeding from the vessels of the microvasculature and in vessels with low blood pressure;

2) is a pre-phase of coagulation hemostasis.

Phase

The modern blood coagulation scheme includes 5 phases, successively replacing each other. These phases are as follows:

1. The formation of prothrombinase.
2. The formation of thrombin.
3. The formation of fibrin.
4. Polymerization of fibrin and organization of the clot.
5. Fibrinolysis.

The modern scheme of hemostasis.

The blood coagulation chain reaction begins from the moment the blood comes in contact with the rough surface of the wounded vessel or tissue. This causes the activation of plasma thromboplastic factors and then the phased formation of two prothrombinases distinctly different in their properties - blood and tissue neva occurs.

However, before the chain reaction of prothrombinase formation ends, processes associated with the participation of platelets (the so-called vascular-platelet hemostasis) occur at the site of damage to the vessel. Platelets, due to their ability to adhere, adhere to the damaged part of the vessel, adhere to each other, sticking together with platelet fibrinogen. All this leads to the formation of so-called lamellar thrombus ("Guyema platelet hemostatic nail"). Platelet adhesion occurs due to ADP released from the endothelium and red blood cells. This process is activated by wall collagen, serotonin, factor XIII and contact activation products. At first (within 1-2 minutes) the blood still passes through this loose plug, but then the so-called viscose rebirth of a blood clot, it condenses and bleeding stops. It is clear that such an end to events is possible only when small vessels are injured, where arterial pressure is not able to squeeze out this “nail”.

1 phase of coagulation. During the first phase of coagulation, the phase of prothrombinase formation, two processes are distinguished, which proceed at different speeds and have different meanings. This is the process of formation of blood prothrombinase, and the process of formation of tissue prothrombinase. The duration of phase 1 is 3-4 minutes. however, it takes only 3-6 seconds to form tissue prothrombinase. The amount of tissue prothrombinase formed is very small, it is not enough to convert prothrombin to thrombin, however tissue prothrombinase acts as an activator of a number of factors necessary for the rapid formation of blood prothrombinase. In particular, tissue prothrombinase leads to the formation of a small amount of thrombin, which translates into the active state V and VIII factors of the internal link of coagulation. The cascade of reactions ending in the formation of tissue prothrombinase (the external mechanism of hemocoagulation) is as follows:

1. Contact of destroyed tissues with blood and activation of factor III - thromboplastin.
2. . III factor translates VII into VIIa (proconvertin to convertin).
3. . Formed complex (Ca ++ + III + VIIIa)
4. . This complex activates a small amount of X factor - X goes into Xa.

5. . (Xa + III + Va + Ca) form a complex, which has all the properties of tissue prothrombinase. The presence of Va (VI) is due to the fact that there are always traces of thrombin in the blood, which activates the V factor.
6. The resulting small amount of tissue prothrombinase converts a small amount of prothrombin to thrombin.
7. . Thrombin activates a sufficient amount of V and VIII factors necessary for the formation of blood prothrombinase.
8. If this cascade is turned off (for example, if, with all precautions, using paraffinized needles, take blood from a vein, preventing its contact with tissues and a rough surface, and place it in a waxed tube), the blood coagulates very slowly, over a period of 20 -25 minutes and longer.
9. Well, normally, simultaneously with the process already described, another cascade of reactions associated with the action of plasma factors is triggered and ends with the formation of blood prothrombinase in an amount sufficient to transfer a large amount of prothrombin from thrombin. These reactions are as follows (internal mechanism of hemocoagulation):
10. Contact with a rough or foreign surface leads to activation of the XII factor: XII - XIIa. At the same time, hemostatic Guyem nail (vascular-platelet hemostasis) begins to form.
11. . The active XII factor turns XI into an active state and a new complex XIIa + Ca ++ + XIa + III is formed (f3)
12. . Under the influence of the indicated complex, the IX factor is activated and the complex IXa + Va + Ca ++ + III is formed (f3).
    . Under the influence of this complex, a significant amount of the X factor is activated, after which the last complex of factors is formed in large quantities: Xa + Va + Ca ++ + III (f3), which is called blood prothrombiase.
13. About 4-5 minutes are normally spent on the whole process, after which coagulation proceeds to the next phase.
14. Phase 2 coagulation - the phase of thrombin formation is that under the influence of the enzyme prothrombinase II, the factor (prothrombin) passes into the active state (IIa). This is a proteolytic process, the prothrombin molecule is split into two halves. The resulting thrombin goes to the implementation of the next phase, and is also used in the blood to activate an increasing amount of accelerin (V and VI factors). This is an example of a positive feedback system. The thrombin formation phase lasts several seconds.
15. The third phase of coagulation - the phase of fibrin formation - is also an enzymatic process, as a result of which a piece of several amino acids is split off from fibrinogen due to the action of the proteolytic enzyme thrombin, and the remainder is called the fibrin monomer, which differs sharply from fibrinogen in its properties. In particular, it is capable of polymerization. This compound is referred to as Im.

coagulation phase - fibrin polymerization and clot organization. It also has several stages. Initially, in a few seconds, under the influence of blood pH, temperature, and plasma ion composition, the formation of long strands of Is fibrin polymer Is occurs, which, however, is still not very stable, since it can dissolve in urea solutions. Therefore, at the next stage, under the action of the Laki-Laurand fibrin stabilizer (factor XIII), the fibrin is finally stabilized and converted into fibrin Ij. It falls out of solution in the form of long threads that form a network in the blood, in the cells of which cells get stuck. Blood from a liquid state passes into a jelly-like state (coagulates). The next stage of this phase is a long enough (several minutes) re-traction (densification) of the clot, which occurs due to the reduction of fibrin filaments under the influence of retractozyme (thrombostenin). As a result, the clot becomes dense, serum is squeezed out of it, and the clot itself turns into a dense cork that blocks the vessel - a blood clot.

5 coagulation phase - fibrinolysis. Although it is actually not associated with the formation of a thrombus, it is considered the last phase of hemocoagulation, since during this phase the thrombus is limited only to the zone where it is really needed. If the thrombus completely closed the lumen of the vessel, then during this phase this lumen is restored (the thrombus recanalizes). In practice, fibrinolysis always proceeds in parallel with the formation of fibrin, preventing the generalization of coagulation and limiting the process. The dissolution of fibrin is provided by the proteolytic enzyme plasmin (fibrinolysin), which is contained in the plasma in an inactive state in the form of plasminogen (profibrinolysin). The transition of plasminogen to an active state is carried out by a special activator, which in turn is formed from inactive precursors (proactivators) released from tissues, blood vessels, blood cells, especially platelets. Acid and alkaline blood phosphatases, trypsin of cells, tissue lysokinases, kinins, environmental reaction, and XII factor play a large role in the processes of transferring plasminogen proactivators and activators to an active state. Plasmin cleaves fibrin into individual polypeptides, which are then utilized by the body.

Normally, human blood begins to coagulate after 3-4 minutes after leakage from the body. After 5-6 minutes, it completely turns into a jelly-like clot. You will learn how to determine bleeding time, blood coagulation rate, and prothrombin time in practical exercises. All of them have important clinical significance.

Coagulation inhibitors (anticoagulants). The constancy of blood as a liquid medium under physiological conditions is supported by a combination of inhibitors or physiological anticoagulants that block or neutralize the effect of coagulants (coagulation factors). Anticoagulants are normal components of a functional hemocoagulation system.

Currently, it has been proven that there are a number of inhibitors with respect to each coagulation factor, and, however, heparin is the most studied and of practical importance. Heparin is a powerful brake on the conversion of prothrombin to thrombin. In addition, it affects the formation of thromboplastin and fibrin.

There is a lot of heparin in the liver, muscles and lungs, which explains the non-coagulation of blood in the small circle of bleeding and the associated risk of pulmonary bleeding. In addition to heparin, several more natural anticoagulants with antithrombin action were found, they are usually denoted by ordinal Roman numerals:

I. Fibrin (since it absorbs thrombin during coagulation).
II. Heparin.
III. Natural antithrombin (phospholipoproteins).
IV. Antiprothrombin (preventing the conversion of prothrombin to thrombin).

In addition to these physiological anticoagulants, many chemicals of various origins have anticoagulant activity - dicumarin, hirudin (from the saliva of leeches), etc. These drugs are used in the clinic for the treatment of thrombosis.

Prevents blood coagulation and fibrinolytic blood system. According to modern ideas, it consists of profibrinolysin (plasminogen), a proactivator and a system of plasma and tissue plasminogen activators. Under the influence of activators, plasminogen passes into plasmin, which dissolves a fibrin clot.

In vivo, the fibrinolytic activity of the blood is dependent on the plasminogen depot, the plasma activator, on the conditions providing the activation processes, and on the entry of these substances into the blood. The spontaneous activity of plasminogen in a healthy body is observed in a state of excitement, after an injection of adrenaline, during physical exertion and in conditions associated with shock. Among the artificial blockers of fibrinolytic blood activity, gamma aminocaproic acid (GABA) occupies a special place. Normally, the amount of plasmin inhibitors in the plasma is 10 times higher than the level of plasminogen reserves in the blood.

The state of hemocoagulation processes and the relative constancy or dynamic balance of coagulation and anticoagulation factors are associated with the functional state of the organs of the hemocoagulation system (bone marrow, liver, spleen, lungs, vascular wall). The activity of the latter, and therefore the state of the process of hemocoagulation, is regulated by neuro-

humoral mechanisms. There are special receptors in the blood vessels that perceive the concentration of thrombin and plasmin. These two substances and program the activities of these systems.

Regulation of hemocoagulation and antigoagulation processes.

Reflex influences. An important place among many stimuli falling on the body is painful irritation. Pain leads to a change in the activity of almost all organs and systems, including the coagulation system. Short-term or long-term pain irritation leads to an acceleration of blood coagulation, accompanied by thrombocytosis. Joining pain of fear leads to an even sharper acceleration of coagulation. Painful irritation caused to the anesthetized area of the skin does not accelerate coagulation. This effect is observed from the first birthday.

Of great importance is the duration of pain irritation. With short-term pain, the shifts are less pronounced and a return to normal occurs 2-3 times faster than with prolonged irritation. This gives reason to believe that in the first case only the reflex mechanism takes part, and with prolonged painful irritation, the humoral link is also activated, causing the duration of the oncoming changes. Most scientists believe that adrenaline is such a humoral link in pain irritation.

Significant acceleration of blood coagulation occurs reflexively when exposed to heat and cold. After the termination of thermal irritation, the recovery period to the initial level is 6-8 times shorter than after a cold one.

Blood coagulation is a component of the orientational response. A change in the external environment, the unexpected appearance of a new stimulus cause an orientational reaction and, at the same time, accelerate blood coagulation, which is a biologically appropriate protective reaction.

The effect of the autonomic nervous system. With irritation of the sympathetic nerves or after an injection of adrenaline, coagulation accelerates. Irritation of the para-sympathetic division of the NS leads to a slowdown in coagulation. It has been shown that the autonomic nervous system affects the biosynthesis of procoagulants and anti-coagulants in the liver. There is every reason to believe that the influence of the sympathetic-adrenal system extends mainly to coagulation factors, and the parasympathetic - mainly to factors that prevent blood coagulation. In the period of stopping bleeding, both sections of the ANS act synergistically. Their interaction is primarily aimed at stopping bleeding, which is vital. In the future, after a reliable stop of bleeding, the tone of parasympathetic NS increases, which leads to an increase in anticoagulant activity, which is so important for the prevention of intravascular thrombosis.

Endocrine system and coagulation. Endocrine glands are an important active link in the mechanism of regulation of blood coagulation. Under the influence of hormones, blood coagulation processes undergo a number of changes, and hemocoagulation either accelerates or slows down. If hormones are grouped by their effect on blood coagulation, ACTH, STH, adrenaline, cortisone, testosterone, progesterone, extracts of the posterior pituitary, pineal gland and goiter glands will be accelerating coagulation; thyroid-stimulating hormone, thyroxine and estrogen slow down coagulation.

In all adaptive reactions, in particular those proceeding with the mobilization of the body's defenses, in maintaining the relative constancy of the internal environment in general and the blood coagulation system, in particular, the pituitary-anrenal system is the most important link in the neurohumoral regulation mechanism.

There is a significant amount of evidence of the influence of the cerebral cortex on blood coagulation. So, blood coagulation changes with damage to the cerebral hemispheres, with shock, anesthesia, and an epileptic seizure. Of particular interest are changes in the rate of blood coagulation in hypnosis, when it is suggested to a person that he is wounded, and at this time, coagulability increases as if it was actually happening.

There is still no generally accepted scheme that fully reflects the complex, multi-stage process of blood coagulation. Without going into a series of insufficiently studied details, it can be represented as follows.

In case of vascular damage, a peculiar chain reaction occurs, the first link of which is the activation of Hageman factor (factor XII). This factor in contact with the damaged surface of the vessel or any wettable foreign surface turns into an active form. Activation of factor XII can also occur when interacting with chylomicrons, when an excess of adrenaline appears in the bloodstream, as well as under certain other conditions.

Active factor XII (factor XIIa) causes a series of sequential activation reactions in which other protein factors in blood plasma are involved (factors VIII, IX, X, etc.). In addition, factor XIIa promotes a change in the properties of the platelet membrane and the release of platelet factor 3.

It is believed that the tissue factor (factor III), which passes into the blood plasma after tissue damage, as well as, apparently, factor 3 of platelets, creates the prerequisites for the formation of a minimal (seed) amount of thrombin (from prothrombin). This minimum amount of thrombin is not enough for the rapid conversion of fibrinogen to fibrin and, therefore, for blood coagulation. At the same time, traces of the resulting thrombin catalyze the conversion of pro-accelerin and proconvertin to accelerin (factor Va) and, accordingly, to convertin (factor VIIa).

As a result of the complex interaction of these factors, as well as Ca2 + ions, the formation of active factor X (factor Xa) occurs. Then, under the influence of a complex of factors: Xa, Va, 3 and calcium ions (factor IV), the formation of thrombin from prothrombin occurs.

A number of researchers distinguish between the "internal" and "external" blood coagulation systems. Apparently, both systems are capable of independently converting prothrombin to thrombin independently of the other. The physiological significance of the participation of just both systems in the process of blood coagulation has not yet been fully determined. By an “external” system is meant the formation of an active tissue factor (factor III) and its participation together with a number of other factors in the processes of hemocoagulation. Further, under the influence of the thrombin enzyme, two peptides A and two peptides B are cleaved from fibrinogen (mol. M of peptide A –2000, and peptide B –2400). It was found that thrombin breaks the peptide bond arginine - lysine.

After cleavage of the peptides, called "fibrin peptides", fibrinogen is converted into a plasma-soluble fibrin monomer, which then quickly polymerizes into an insoluble fibrin polymer. The transformation of the fibrin monomer into a fibrin polymer proceeds with the participation of the fibrin-stabilizing factor - factor XIII in the presence of Ca2 + ions.

It is known that after the formation of fibrin filaments, their contraction occurs. Currently available data indicate that retraction of a blood clot is a process that requires ATP energy. Platelet factor (thrombostenin) is also required. The latter in its properties resembles muscle actomyosin and has ATPase activity. These are the main stages of blood coagulation.

Starting from the stage of formation of active factor X (factor Xa), the “internal” (a) and “external” (b) pathways of blood coagulation coincide (see diagram).

Blood coagulation system

Despite the presence of a very powerful coagulation system, blood is in a living organism in a liquid state. Numerous studies aimed at elucidating the causes and mechanisms of maintaining blood in a liquid state during its circulation in the bloodstream have made it possible to elucidate to a large extent the nature of the anticoagulant blood system. It turned out that in its formation, as well as in the formation of the blood coagulation system, a number of factors of blood plasma, platelets and tissues are involved. These include various anticoagulants - antithromboplastins, antithrombins, as well as the fibrinolytic blood system. It is believed that in the body there are specific inhibitors for each coagulation factor (antiacelerin, anticonvertin, etc.). A decrease in the activity of these inhibitors increases blood coagulability and promotes the formation of blood clots. An increase in the activity of inhibitors, on the contrary, complicates blood coagulation and may be accompanied by the development of hemorrhages. The combination of the phenomena of disseminated thrombosis and hemorrhage may be due to a violation of the regulatory relationship of the coagulation and anticoagulation systems.

The most rapidly acting components of the anticoagulation system are antithrombins. They belong to the so-called direct anticoagulants, since they are in active form, and not in the

form of predecessors. It is estimated that about six different antithrombin exist in the blood plasma. The most studied of them is heparin, which prevents the action of thrombin on fibrinogen and inhibits the conversion of prothrombin to thrombin. Heparin prevents blood coagulation both in vitro and in vivo. The effect of heparin in case of overdose can be eliminated by binding it with a number of substances - heparin antagonists. These primarily include protamine sulfate.

In blood vessels, there are chemoreceptors capable of responding to the appearance of active thrombin in the blood, associated with a neurohumoral mechanism that regulates the formation of anticoagulants. Thus, if thrombin appears in the circulating blood under conditions of normal neurohumoral control, then in this case it not only does not cause blood coagulation; but, on the contrary, reflexively stimulates the formation of anticoagulants and thereby turns off the coagulation mechanism.

Equally important is the use of so-called artificial anticoagulants. For example, given that vitamin K stimulates the synthesis of prothrombin, proaccelerin, proconvertin, and the Prauer-Stuart factor in the liver, anticoagulants such as antivitamins K are prescribed to reduce the activity of the blood coagulation system. These are primarily dicumarol, neodicumarol, marcumar, pelentan, syncumar, etc. Antivitamins K inhibit the synthesis of blood clotting factors listed above in liver cells. This method of exposure does not immediately produce an effect, but after several hours and even days.

Fibrinolysis

The body also has a powerful fibrinolytic system, which allows the dissolution (fibrinolysis) of already formed blood clots (blood clots). The mechanism of fibrinolysis can be represented in the form of a scheme.

A retracted clot of fibrin in humans and animals is exposed to a proteolytic enzyme of blood plasma, plasmin (fibrinolysin), which gradually dissolves to form a series of water-soluble hydrolysis products (peptides). Normally, plasmin is in the blood in the form of an inactive precursor, plasminogen (fibrinolysinogen, or profibrinolysin). The conversion of plasminogen to plasmin is accompanied by cleavage of 25% amino acid residues in the polypeptide chain. This reaction catalyzes by both blood activators and tissue activators. Tissue plasminogen activators are present in the largest number in the lungs, uterus, and prostate gland. Therefore, during operations on these organs due to the release of a significant amount of activator from the tissue into the bloodstream, acute fibrinolysis can occur.

The leading role in this process belongs to blood activators. However, the normal activity of blood plasminogen activators is extremely low, that is, they are mainly in the form of proactivators. A very rapid conversion of the blood proactivator to plasminogen activator occurs under the influence of tissue lysokinases, as well as streptokinase. Streptokinase is produced by hemolytic streptococcus and is absent in normal blood conditions. However, with streptococcal infection, the formation of streptokinase in large quantities is possible, which sometimes leads to increased fibrinolysis and the development of hemorrhagic diathesis.

It must also be borne in mind that, along with the human fibrinolytic system, there is also an antifibrinolytic system. It consists of various antikinases, antiplasmin and other anti-activators.

In practical medicine, for therapeutic purposes, enzyme preparations and their inhibitors are widely used in case of violation of the coagulation and anticoagulation systems of the blood. On the one hand, with thromboembolic disease, enzymes are used that promote either the lysis of the formed thrombus or a decrease in increased blood coagulation. On the other hand, in conditions accompanied by the development of fibrinolysis, enzyme inhibitors are used.

Recent studies suggest that the introduction of plasmin in combination with heparin (antithrombin) can be effective not only for pulmonary thrombosis, thrombophlebitis, but also for the treatment of myocardial infarction, if these drugs are administered in the first hours of the disease. As fibrinolytic drugs for myocardial infarction, plasminogen activators urokinase and streptokinase can also be used. It should be remembered that therapy with thrombolytic drugs is

associated with certain dangers and requires well-organized laboratory monitoring, because the proteolytic effect of plasmin is not strictly specific only for fibrin, the main component of a blood clot: administration of plasmin can cause unwanted cleavage of many important blood clotting agents substances, which in turn can lead to serious complications, in particular to the development of hemorrhagic diathesis.

Classification of drugs that affect blood coagulation.

I Substances that inhibit blood coagulation

1. Anticoagulants.

but). Anticoagulants of direct action.

Heparin, hirudin. sodium hydrocytrate.

b) Indirect anticoagulants.

Coumarin derivatives: neodicumarin, syncumar.

Indandion derivatives: fennlin.

2. Antiplatelet agents: acetylsalicylic acid, digpyridamole, pentoxifylline. ticlopidine.

3. Fibrinolytic agents

but). Direct-acting fibrinolytics: fibrinolysis.

b) Indirect fibrinolytics: streptokinase, streptodekase, uro kinase.

II Hemostatic agents.

1. Coagulants

but). Coagulants of direct action, thrombin, fibrinogen.

b) Indirect coagulants: preparations of vitamin K - phytomenenadnoy, Vikasol (see. Vitamins).

2. Stimulants of platelet aggregation (aggregates): calcium salts, adroxon.

3. Inhibitors of fibrinolysis.

but). Synthetic fibrinolysis inhibitors: aminocaproic acid, am-bin.

b) Inhibitors of fibrinolysis (proteolysis) of animal origin: pant-ripin, kontrikal, gordoks

4. Substances of plant origin.

STRUCTURE AND FUNCTIONS OF THE BLOOD AND ANTI-BLOOD BLOOD SYSTEMS

The blood coagulation system, platelets and the development of endogenous fibrinolysis are involved in the processes of thrombosis.

Blood coagulation factors (FGCs) are proteins involved in the implementation of a sequence of biochemical reactions leading to the formation of fibrin, which forms the basis of a blood clot. This process (coagulation cascade) is presented in a simplified form in Fig. Two key FGCs play a key role in it: activated FGC X (Ha) and activated FGC II (IIa), or thrombin. Thrombin is a multifunctional molecule that is involved in the conversion of fibrinogen to fibrin, controls the intensity of thrombosis by the feedback mechanism, affects the severity of fibrinolysis processes and causes platelet activation. Practically, it is important that the blood coagulation process is “avalanche-like” in nature. So, one FSA Xa molecule promotes the formation of several tens of thrombin molecules. Therefore, the neutralization of FGC at the earlier stages of the coagulation cascade can more effectively counteract the formation of fibrin.

In the body, there are opportunities to counteract the process of blood coagulation. Among them are the excretion of prostacyclin and nitric oxide by endothelial cells, the presence of antithrombin III, an inhibitor of the tissue factor pathway in the blood plasma, and the system of proteins C, S and thrombomodulin. The resulting fibrin can be destroyed by plasmin serine protease, a key enzyme of the endogenous system of fibrinolysis. Plasmin is formed from plasminogen circulating in the blood under the influence of plasminogen activators, which are secreted by endothelial cells. Inhibitors of plasminogen activator and a, 2-antiplasmin counteract these processes.

Activation, adhesion, and platelet aggregation begins with the interaction of a number of substances (aggregation inducers) with receptors on the cell surface. As a result, IIb / IIIa

glycoproteins interacting with fibrinogen, von Willebrand factor, and other adhesive adhesives become available on the outer side of the platelet membrane. molecules, which leads to the connection of platelets between themselves and the formation of stable aggregates.

In clinical practice, 4 groups of drugs are used that affect blood coagulation, platelet aggregation, or fibrinolysis.

1. Direct-acting anticoagulants: unfractionated heparin, low molecular weight heparin preparations (dalteparin sodium, calcium nadroparin, enoxaparin sodium), sodium fondaparinux and direct-acting thrombin inhibitors.

2. Anticoagulants of indirect action. Depending on the chemical structure, monocoumarin derivatives (warfarin, acenocoumarol), indanedione derivatives (phenindione) and dicumarin derivatives (ethyl biscum acetate) are isolated.

3. Antiplatelet agents: acetylsalicylic acid, thienopyridine derivatives (clopidogrel, ticlopidine), dipyridamole, platelet glycoprotein IIb / IIIa blockers (abciximab, tirofiban, eptifibatid).

4. Fibrinolytics. By the mechanism of action, an indirect plasminogen activator streptokinase, recombinant tissue (direct) plasminogen activator alteplase and its derivatives obtained by genetic engineering (tenecteplase), as well as a recombinant direct urokinase kinase type plasminogen activator (prourokinase) are isolated. Depending on the selectivity for fibrin, fibrinolytics are divided into non-fibrin-specific (streptokinase) and relatively fibrin-specific drugs (alteplase, tenecteplase, recombinant prourokinase).

Antithrombotic agents

1. Antiplatelet agents

I. Inhibition of thromboxane system activity

1. Decreased thromboxane synthesis

but. Cyclooxygenase inhibitors (acetylsalicylic acid)

b. Thromboxane synthetase inhibitors (dazoxyben)

2. Block. thromboxane receptors *

3. Substances of mixed action (ridogrel)

II. Increased activity of the prostacyclin system

/. Prostacyclin receptor stimulating agents (epopro-stenol)

III. Drugs that inhibit the binding of fibrinogen to thrombo-booster glycoprotein receptors (GP llb / IIIa)

A number of thromboxane receptor blockers were obtained, which are at the research stage (daltroban).

/. Glycoprotein receptor antagonists (abciximab, thyro-fiban)

2. Means blocking purine platelet receptors and preventing the stimulating effect of ADP on them (glycoprotein receptors are not activated at the same time) (ticlopidine, clopidogrel)

IV. Means of various types of action (dipyridamole, antoran).

2. Anticoagulants:

2.1. Direct action.

2.1.1. Unfractionated heparin: • Heparin.

2.1.2. Low molecular weight heparins: • Dalteparin (Frag-min). • Nadropaprine (Fraxiparin) • Certoparin (Sandoparin). • Tinzaparin (Logiparin). • Enoxaparin (Clexane).

2.1.3. Heparinoids (parenteral Xa factor inhibitors): • Fondaparinux (Arikstra). • Idraparinux.

2.1.4. Oral Xa factor inhibitors: • Rivaroxaban (Xarelto). • Apixaban.

2.1.5. Hirudin and hirudinoids: • Hirudin (Lepirudin). • Bivalirudin (Angiomax, Angiox).

2.2. Indirect action.

2.2.1. Coumarin derivatives:

2.2.1.1. Monocoumarins. • Warfarin (Coumadin). • Fenprokumon (Markumar). • Acenocumarol (Sincumar).

2.2.1.2. Dicumarines. • Bishydroxycumarol (Dikuma-rin). • Ethyl biscum acetate (neodicumarin).

2.2.2. Indandion derivatives: • Phenindione (Phenylinum). • Difenadion (Dipaxinum).

Fibrinolytics - fibrinolysin

Indirect fibrinolytics:

I generation:

• Urokinase (Urokidan).

• Streptokinase (Streptoliasis).

II generation:

• Acetylated plasminogen-streptokinase activator complex (Anistreplaza, APSAK).

• Alteplase (Aktilize).

• Prourokinase (Purolyase).

III generation (mutant):

• Tenecteplase (Metalysis).

• Reteplase (Rapilizin).

Mechanism of action and pharmacodynamics

Anticoagulants prevent thrombosis due to exposure to FSK in blood plasma, which ultimately leads to a decrease in the number of actively functioning thrombin molecules and suppression of fibrin formation.

1. Direct-acting anticoagulants. Direct-acting anticoagulants neutralize FSK in blood plasma. Currently, in practice, only drugs for parenteral administration are used (Table 1).

Unfractionated heparin is extracted from porcine intestinal mucosa. It is a mixture of sulfated polysaccharides (glycosaminoglycans) of different molecular weights (from 3,000 to 30,000 Daltons, an average of about 15,000 Daltons). About a third of the polysaccharides that make up non-fractionated heparin can bind to antithrombin III. As a result, the ability of antithrombin III to form a compound with a number of activated CSFs (IIa, Sha, Xa, XIa, and XIIa) is greatly increased. To inactivate FSK Xa, a sufficient connection with antithrombin of the III site of the heparin molecule containing a sequence of 5 monosaccharides (pentasaccharide) is sufficient. To inactivate thrombin, the formation of a bond of the heparin molecule with both antithrombin III and thrombin is required with the participation of at least 13 monosaccharides. Accordingly, molecules containing less than 18 monosaccharides are not able to catalyze the inactivation of thrombin. Almost all polysaccharides in unfractionated heparin contain at least 18 monosaccharides, and the ratio of activity against factor XA to activity against factor Pa in unfractionated heparin is 1: 1.

Unfractionated heparin also has a number of other effects:

• stimulates the release of tissue factor pathway inhibitor;

• inactivates the von Willebrand factor;

• inhibits the formation of osteoblasts and stimulates osteoclasts, which underlies the development of osteoporosis;

• binds to platelets and platelet factor 4, which underlies the development of immune thrombocytopenia;

• stimulates the release of lipoprotein lipase and may have a hypotriglyceridemic effect;

• may increase the permeability of the vascular wall.

Low molecular weight (fractionated) heparin preparations are obtained as a result of chemical or enzymatic depolymerization of unfractionated heparin (Table 2). Their molecular weight ranges from 1000 to 10,000 Daltons and averages 4,000-6,000 Daltons. According to the mechanism of action of the drug, low molecular weight heparin does not differ from unfractionated heparin, but to a greater extent affect FSK Xa than FSK IIa (thrombin). In addition, compared to unfractionated heparin, low molecular weight heparin preparations stimulate the release of the tissue factor pathway inhibitor to a greater extent, it better inactivates von Willebrand factor, binds less by platelets, platelet factor 4 and osteoblasts, and activates osteoclasts less. In addition to differences in the methods of preparation, low molecular weight

heparin preparations differ markedly in composition and biological activity. Therefore, they are considered as separate, non-interchangeable drugs.

Fondaparinux sodium is a synthetic sulfated pentasaccharide, an analogue of the site of the heparin molecule, with which it interacts with antithrombin III. As a result, FGC Xa is selectively removed from the blood coagulation cascade. Fondaparinux practically does not interact with platelets and platelet factor 4.

2. Anticoagulants of indirect action. Indirect anticoagulants inhibit enzymes that convert vitamin K to its epoxy form, which is necessary for the carboxylation of a number of FSK formed in the liver (prothrombin, VII, IX, and X). As a result, partially decarboxylated proteins with reduced coagulation activity are synthesized. At the same time, the synthesis of proteins C and S with anticoagulant properties is disrupted. Among the drugs that affect blood coagulation processes and are available in practice, these are the only drugs for oral administration. Therefore, indirect anticoagulants are called inhibitors of the synthesis of coagulation factors dependent on vitamin K, as well as anticoagulants for oral administration.

The speed of the onset of the effect depends not only on the influence of anticoagulants of indirect action, but also on the time the previously complete high-grade FSK is retained in the blood plasma (Table 3). T1 / 2 of FSK VII, IX and X is 6-24 hours, prothrombin 60-72 hours. The antithrombotic effect of drugs of this group is primarily associated with a decrease in the content of prothrombin in the blood. Given Ti / 2 of this FSK, the full effect of indirect anticoagulants is expected not earlier than 4 days after the start of dose selection. Ti / 2 protein C is about 8 hours. Therefore, a pronounced decrease in its content in the blood can occur before the manifestation of a sufficient antithrombotic effect of anticoagulants of indirect action. As a result, at the beginning of treatment, some patients may experience thrombotic complications.

3. Antiaggregants. Antiplatelet agents, due to various mechanisms, reduce the functional activity of platelets

Acetylsalicylic acid selectively and irreversibly acetylates the cyclooxygenase enzyme, which catalyzes the first step in the biosynthesis of prostanoids from arachidonic acid (Table 4). In low doses, the drug mainly affects the isoform of cyclooxygenase COX-1. As a result, the thromboxane A2, which has a pro-aggressive and vasoconstrictive effect, stops in the platelets circulating in blood, and the formation of prostacyclin, which inhibits platelet aggregation, and the secretion of acid in the stomach and has a vasodilating effect, decreases in the cells of the endothelium and gastric mucosa. The effect of low doses of acetylsalicylic acid on prostacyclin synthesis is not so pronounced and shorter because of the lower sensitivity to the action of the cyclooxygenase drug contained outside platelets, as well as the ability of cells with a nucleus to synthesize new enzyme molecules instead of those that have stopped their functional activity. In addition, prostacyclin can be formed by using the COX-2 cyclooxygenase isoform, which requires higher doses of the drug and shorter intervals between doses to inhibit it. The formation of thromboxane A2 ceases for the entire period of platelet life (7-10 days). Since about 10% of the platelet pool is updated daily, after 5-6 days after taking acetylsalicylic acid, approximately 50% of the platelets function normally. Usually this is enough to restore the full functioning of the platelet link of hemostasis. Experimental and clinical observations indicate that the effect of acetylsalicylic acid on COX-1 in platelets may have an inherent saturation effect that occurs when small doses are used.

Thienopyridine derivatives are prodrugs. Metabolites formed with the participation of enzymes of the cytochrome P450 family as they pass through the liver irreversibly modify 2PY12 receptors on the platelet membrane. As a result, the association of ADP with its receptor on the platelet membrane is blocked, which leads to inhibition of platelet aggregation.

Dipyridamole inhibits the phosphodiesterase enzyme in platelets, which leads to the accumulation of cAMP in platelets, which has an antiplatelet effect. In addition, it is able to block the capture of adenosine by red blood cells and endothelial cells, and also stimulate the synthesis of nitric oxide and prostacyclin in the endothelium of the vascular wall.

Platelet IIb / IIIa glycoprotein blockers act on the final stage of platelet aggregation, blocking the site of interaction of IIb / IIIa glycoproteins on the surface of platelets with fibrinogen, von Willebrand factor and other adhesive molecules. Only drugs for intravenous administration are used: the chimeric mouse and human antibody abciximab, which forms a non-specific and sufficiently stable compound with glycoprotein IIb / IIIa, as well as small molecules of tirofiban and eptifibatide, which selectively block glycoprotein IIb / IIIa by a competitive mechanism

4. Fibrinolytics. Fibrinolytics (plasminogen activators) convert the inactive plasminogen protein contained in the blood into the active plasmin enzyme, which causes fibrin lysis and destruction of a newly formed thrombus (thrombolysis) [table. 5]. Drugs in this group do not prevent further thrombosis, can increase the formation of thrombin and enhance platelet aggregation.

Streptokinase is an indirect plasminogen activator obtained from a culture of β-hemolytic streptococcus. Initially, the streptokinase molecule forms a compound with a plasminogen molecule, which acquires the ability to activate other plasminogen molecules, both associated with the thrombus and circulating in the blood. As a result, the levels of fibrinogen, plasminogen, FSK V, VIII decrease in blood plasma and hypocoagulation occurs, which persists for some time after the drug is discontinued. A few days after a single injection of streptokinase, antibodies may appear in the blood that can persist for many years.

Tissue plasminogen activator is a serine protease identical to the human plasminogen activator synthesized by vascular endothelium. Currently, a predominantly single-chain recombinant tissue plasminogen activator molecule (alteplase) is used. Alteplase has an increased affinity for fibrin. On its surface, it becomes much more active and selectively affects the plasminogen adjacent to fibrin, which turns it into plasmin. The systemic effect of this fibrinolytic is much less pronounced. In addition, compared with streptokinase, alteplase is able to destroy fibrin with more pronounced cross-linking, which is part of longer existing blood clots. The action of alteplase is prevented by plasminogen activator inhibitors. Unlike streptokinase, the drug is not immunogenic.

Tenecteplase is a derivative of alteplase created using genetic engineering by replacing amino acid residues in three parts of the original molecule. This led to an increase in fibrin specificity and the emergence of resistance to the influence of a type 1 plasminogen activator inhibitor.

Recombinant prourokinase is a modified molecule of native human prourokinase created using genetic engineering. Specifically interacts with fibrin-related plasminogen. In the thrombus area is not suppressed by inhibitors circulating in the blood plasma. Under the influence of plasmin, a single-chain molecule of prourokinase turns into a more active double-chain molecule of urokinase.

Pharmacokinetics

Unfractionated heparin. After intravenous bolus administration, the action begins immediately. When carrying out intravenous infusion of the drug without prior administration of a bolus, the effect appears later; time depends on the rate of infusion. With subcutaneous administration, unfractionated heparin begins to act in 20-60 minutes.

When administered intravenously, TS is dose-dependent and averages 60 minutes (30-150 minutes). With subcutaneous administration, bioavailability ranges from 10 to 40%. TS is dose-dependent and averages 90 minutes (60-120 minutes). When therapeutic doses are used, clearance of unfractionated is carried out by heparin mainly due to a rapidly saturating dose-dependent mechanism (connection with receptors of endothelial cells and macrophages followed by depolymerization). However, after intravenous administration of high doses, up to half of the drug is excreted unchanged by the kidneys. Accordingly, an increase in the intensity and duration of anticoagulation occurs disproportionately to increasing the dose. TS also depends on liver function and the presence of certain diseases (pulmonary embolism, infection). Due to the pronounced negative charge, unfractionated heparin binds non-specifically to blood plasma

proteins, endothelial cells and macrophages, which is the reason for the variable and unpredictable anticoagulant effect and cases of drug resistance. In addition, the antithrombotic activity of various lots of unfractionated heparin may be unstable. All this determines the need for individual selection of the dose of the drug, taking into account its effect on the blood coagulation process. To control the anticoagulant effect of unfractionated heparin, it is recommended in practice to use activated partial thromboplastin time (APTT), and when high doses of the drug are introduced during invasive manipulations in the lumen of blood vessels, operations with artificial blood circulation, hemodialysis, activated blood coagulation time. In some cases, it may be necessary to determine the activity against FSK Ha in the blood plasma.

Low molecular weight heparin preparations. After intravenous administration, the effect begins immediately, the maximum inhibition of FSK Xa and 11a in blood plasma is achieved in about 5 minutes. Depending on the dose and the drug, increased activity against FSK Ha may persist for 5-8 hours.

With subcutaneous administration, the bioavailability is more than 90%. Inhibition of FSK Xa is reached after a maximum of 3-4 hours and lasts 12-24 hours (depending on the dose and drug). Accordingly, when using low molecular weight heparin preparations to maintain a stable level of anticoagulation, there is no need to carry out continuous intravenous infusion, since the desired effect can be achieved with subcutaneous administration 1-2 times a day. Features of various drugs of low molecular weight heparin are given in table. 2.

Preparations of low molecular weight heparin to a much lesser extent than unfractionated heparin bind non-specifically to plasma proteins, endothelial cells and macrophages. Their clearance is carried out mainly by the kidneys and does not depend on the dose. Due to better bioavailability, longer T1 / 2 and dose-independent clearance, response to administration

drugs of low molecular weight heparin are more predictable than the introduction of unfractionated heparin. Therefore, it is believed that in most patients, the control of the anticoagulant effect of low molecular weight heparin drugs is not required. However, with renal failure, the elimination of drugs of this group decreases, and they can accumulate in blood plasma (especially pronounced changes occur at a glomerular filtration rate <30 ml / min). During pregnancy, the pharmacokinetics of low molecular weight heparins change due to changes in the volume of distribution and an increase in glomerular filtration. There is little data on the effect of drugs of this group with severe obesity (body weight> 150 kg, body mass index> 50 kg / m2). Accordingly, dose adjustment taking into account the achieved level of anti-FSK Ha activity in blood plasma may be required in case of severe renal failure (due to possible cumulation, repeated determinations are needed), during pregnancy (it is advised to evaluate every month) and severe obesity (it is recommended that at least one -fold). The control is carried out at the peak of the drug, approximately 4 hours after subcutaneous injection. The target values of activity against FSK Ha depend on the indications for which low molecular weight heparin is used, and the frequency of its administration.

Fondaparinux sodium. With subcutaneous administration, the bioavailability is 100%. After subcutaneous administration of 2.5 mg, the maximum stable concentration and activity against FSK Xa in blood plasma is reached after 2-3 hours. TS is 17-21 hours, the drug is excreted unchanged by the kidneys. Excretion of fondaparinux slows with creatinine clearance <80 ml / min; in patients with creatinine clearance <30 ml / min, its elimination lengthens especially strongly (about half). A similar pattern is observed in patients older than 75 years and with a body weight of less than 50 kg.

Indirect anticoagulants are rapidly and almost completely absorbed by ingestion and more than 90% bind to blood plasma proteins (mainly albumin). Drugs accumulate upon repeated use, are metabolized in the liver, inactive metabolites are excreted by the kidneys. Indirect anticoagulants noticeably differ in pharmacological properties

* May vary significantly in different patients and in the same patient; ** According to the effect on INR, it mainly reflects a decrease in the content of functioning FSK VII in the blood

(T1 / 2 for about 6 hours); *** According to the impact on INR; **** Time during which the INR returns to the values noted before treatment.

The individual response to indirect anticoagulants is not predictable. Their effect decreases with increased intake of vitamin K with food, drug interactions, genetic characteristics, a decrease in the catabolism of blood coagulation factors and vitamin K (hypothyroidism). The influence of drugs of this group is enhanced with insufficient intake of vitamin K from the diet (parenteral nutrition) or its reduced absorption in the intestine, drug interactions, genetic characteristics, impaired synthesis of FGC (liver disease), increased catabolism of FGC and vitamin K (fever, hyperthyroidism). Therefore, when using anticoagulants of indirect action, their effect must be controlled. For this purpose, the International Normalized Ratio (INR) is used, which is determined by the formula:

INR = (patient's PV / mean normal PV) MIC,

where: PV is the prothrombin time, MIC is the international thromboplastin sensitivity index, with which prothrombin time is determined.

Accordingly, for the calculation of INR, it is necessary to have thromboplastin with a known MIC (indicated by the manufacturer).

Warfarin provides the most stable anticoagulant effect and is the drug of choice. To a lesser extent, this applies to acenocoumarol. Phenindione is highly toxic, the anticoagulant effect of ethyl biscoucetitol is unstable, so these drugs should not be used if possible.

Acetylsalicylic acid is rapidly (in 5-16 minutes) and is completely absorbed from the stomach and upper intestines. Eating slows down absorption, but does not affect its severity. Absorption is accelerated with a smaller particle size of the drug.

The peak concentration in plasma occurs after 30-40 minutes. Most of the drug is absorbed in the small intestine and is rapidly hydrolyzed by esterases in the intestinal mucosa, blood plasma, red blood cells, and liver. However, since acetylation of the COX-1 cyclooxygenase isoform in platelets occurs when it passes through the portal section of the bloodstream, the antiplatelet effect of acetylsalicylic acid is little dependent on systemic bioavailability.

When using low doses of acetylsalicylic acid, the antiplatelet effect increases slowly, for the maximum effect, second doses of the drug are necessary. When taking sufficiently high doses (at least 150-160 mg), a pronounced effect is observed in the first 1-2 hours. The enteric coating delays the release of the active substance until the tablet enters the small intestine, where acetylsalicylic acid is hydrolyzed in an alkaline environment. As a result, absorption slows down, bioavailability decreases and the maximum concentration in the blood is reached after 3-4 hours.

Thienopyridine derivatives. After a meal, the bioavailability of ticlo-pidine increases by about 20%; when used after antacid, it decreases by 20%. The absorption of clopidogrel is not affected by ingestion of food and antacids. The need for preliminary metabolism of thienopyridine derivatives leads to a delay in the appearance of their antiplatelet effect. When using clopidogrel at a dose of 75 mg 1 time / day or ticlopidine at a dose of 250 mg 2 times / day, inhibition of ADP-induced platelet aggregation becomes noticeable on day 2. To achieve maximum effect in patients receiving clopidogrel, it takes from 3 to 7 days. When using ticlopidine, a clinically significant inhibition of aggregation is expected on the 4th day, the maximum - on the 8-11th day. The onset of action and the maximum effect of drugs can be accelerated using a loading (shock) dose. With prolonged use of thienopyridine derivatives, their clearance slows down. So, after applying ticlopidine at a dose of 250 mg 2 r / day, after 2-3 weeks, its T1 / 2 lengthens, and the blood content increases (cumulation occurs). After the cancellation of clopidogrel, platelet aggregation gradually normalizes within 7 days, after the cancellation of ticlopidine - 7-14 days.

Dipyridamole. After a meal, the bioavailability of dipyridamole is reduced. Absorption of the usual dosage forms of the drug may be unstable. Sustained release dosage forms and improved bioavailability exist. Dipyridamole is excreted mainly with bile after the formation of

conjugates with glucuronic acid in the liver and undergoes an enterohepatic circulation. The maximum concentration of the drug in the blood is noted after about 75 minutes.T1 / 2 is about 10 hours.

Platelet IIb / IIIa glycoprotein blockers. Approximately two-thirds of ab-cyclimab administered intravenously in the next few minutes binds to platelet IIb / IIIa glycoproteins. T1 / 2 is about 30 min. To maintain a constant concentration of the drug in the blood, intravenous infusion is necessary. After its completion, the concentration of abciximab decreases in the next 6 hours. Abciximab molecules in a bound state are able to switch to the platelet IIb / IIIa glycoproteins of new platelets entering the circulation. Therefore, the antithrombocyte activity of the drug remains for a long time - up to 70% platelet receptors remain inactive 12 hours after intravenous administration and a small amount of platelet-bound abciximab is detected for at least 15 days.

The antiplatelet effect of tirofiban and eptifibatide depends on the dose and, accordingly, their concentration in the blood plasma. It quickly disappears after cessation of intravenous infusion of drugs.

Fibrinolytics. The main properties of drugs of this group are presented in table. 13.5. T1 / 2 tenecteplase is noticeably larger than that of alteplase, which allows the drug to be administered by an intravenous bolus.

Indications and doses

Antithrombotic drugs are used to prevent and treat arterial and venous thrombosis and embolism.

1. Anticoagulants. Because of the rapid onset of the effect, parenteral administration of direct-acting anticoagulants is not an alternative if urgent antithrombotic action is required. The effect of anticoagulants for oral administration increases gradually, so they are not suitable for use in acute situations. However, there is no alternative to drugs of this group when long-term (long-term) use of anticoagulants is required. Direct-acting anticoagulants should be administered intravenously or subcutaneously into the anterior abdominal wall; intramuscular injections are unacceptable.

Unfractionated heparin. Indications. Early treatment of exacerbations of coronary heart disease; prevention and treatment of venous thrombosis and pulmonary artery thromboembolism; preparation for cardioversion or emergency cardioversion in patients with prolonged paroxysm of atrial fibrillation; valve prostheses of the heart; manipulations in the lumen of blood vessels (including percutaneous interventions); acute thrombotic occlusion of peripheral arteries; operations using cardiopulmonary bypass; hemodialysis; disseminated intravascular coagulation. It is also used to prevent thrombosis in the lumen of intravascular catheters.

Doses A sustained antithrombotic effect is maintained by continuous intravenous infusion or subcutaneous injection in doses sufficient to overcome low bioavailability. To quickly create the necessary concentration of the drug in the blood, an intravenous bolus is used. Taking into account body weight when choosing an initial dose can reduce the risk of an excessive level of anticoagulation at the beginning of treatment. The selection of therapeutic doses of unfractionated heparin is carried out individually; in this case, it is necessary to control the APTT, evaluating the degree of increase in the indicator relative to the normal (control) value for a particular laboratory. At the beginning of the administration of unfractionated heparin and after any change in its dose, APTT should be determined every 6 hours. Switching to more rare APTT determinations (1 time per day) is possible only when therapeutic values of the indicator are achieved in two consecutive analyzes.

With early treatment of venous thrombosis and pulmonary embolism, the size of an intravenous bolus should be 80 U / kg (alternatively 5000 U), the initial infusion rate should be 18 U / kg / h (minimum 1250 U / h); the target value of APTTV is 1.5-2.5 times higher than the control.

In acute coronary syndrome with ST segment elevations on the ECG in combination with fibrinolytic, unfractionated heparin is administered with a bolus of 60 PIECES / kg (not more than 4000 PIECES) and a continuous infusion of 12 PIECES / kg / h (not more than 1000 PIECES / h) is started, V subsequently, it is necessary to maintain the APTT 1.5–2 times higher than the control, determining it 3, 6, 12, and 24 hours after the start of administration of unfractionated heparin.

In acute coronary syndrome without ST segment elevations on the ECG, the bolus size is 60-80 PIECES / kg (maximum 5000 PIECES) at an initial intravenous infusion rate of 12-18 PIECES / kg / h (maximum 1250 PIECES / h). In the future, it is necessary to strive to increase the APTT 1.5-2.5 times higher than the control. Similar doses are suitable for the treatment of any acute arterial thrombosis.

To facilitate the selection of the dose of unfractionated heparin during intravenous infusion, protocols (nomograms) are used that regulate the nature of changes in the dose of the drug depending on the achieved values of APTT. One of the nomograms developed for the treatment of pulmonary embolism is given in table. 7.

In transdermal coronary interventions, large intravenous boluses of unfractionated heparin are administered (70-100 IU / kg in the absence of platelet IIb / IIIa glycoproten blockers and 50-70 IU / kg when they are administered). The control method is time-activated blood coagulation, which should be 250-350 s in the absence of platelet IIb / IIIa glycoproten blockers (250-300 s when using a HemoTec analyzer, 300-350 s when using a Hemochron analyzer) and 200-250 with their introduction. If the procedure is delayed, an additional bolus may be required.

In the first 24 hours, repeat every 6 hours. In the future, if APTT does not go beyond the therapeutic boundaries, you can go on to determine 1 time / day (every morning).

Subcutaneous administration of high doses of unfractionated heparin under the control of APTT is usually used instead of intravenous infusion of the drug in cases where it is necessary to maintain a therapeutic level of anticoagulation for a long time. The initial dose is 250 units / kg or 17500 units; to accelerate the effect, you can simultaneously enter the drug into a vein at a dose of 5000 units. In the future, unfractionated heparin is administered every 12 hours, the injection is selected in such a way that 6 hours after it the therapeutic values of APTT are preserved (1.5-2.5 times higher than the control). When this goal is achieved, APTT can be determined less frequently - from 2 times a week to 1 time in 2 weeks. Due to the peculiarities of the pharmacokinetics, it is very difficult to achieve a sufficient level of anticoagulation using subcutaneous injections of unfractionated heparin. Therefore, it is better to use indirect anticoagulants or a therapeutic dose of low molecular weight heparins.

Subcutaneous administration of low doses of unfractionated heparin (5000 units 3 times / day) is used to prevent venous thrombosis. APTT control is not required.

To prevent thrombosis in the lumen of catheters placed in the lumen of large vessels, they are periodically washed with small portions of a solution containing unfractionated heparin at a dose of 100 PIECES / ml, or a solution containing a preparation at a dose of 0.5-1 PIECES / ml is constantly administered. APTT control is not required.

Low molecular weight heparins. Indications. Can be used for the same indications as unfractionated heparin. Features of the use of each of these non-interchangeable drugs depend on their knowledge in a particular clinical situation and are described in the manufacturer's recommendations.

Doses Drugs are dosed in international units (IU) of activity against FSK Ha. The choice of treatment dose is based on the patient’s body weight.

With venous thrombosis and not massive pulmonary thromboembolism, the following are used:

• dalteparin at a dose of 200 IU / kg (maximum 18,000 IU) subcutaneously every 24 hours (with an increased risk of bleeding 100 IU / kg every 12 hours);

• nadroparin at a dose of 86 IU / kg subcutaneously every 12 hours or 171 IU / kg (maximum 17100 IU) every 24 hours;

• Enoxaparin at a dose of 150 IU / kg (1.5 mg / kg; maximum 180 mg) subcutaneously every 24 hours or 100 IU / kg (1 mg / kg) every 12 hours.

In acute coronary syndrome without ST segment elevations on the ECG, the following are used:

• dalteparin at a dose of 120 IU / kg (maximum 10,000 IU) subcutaneously every 12 hours;

• nadroparin, first intravenous bolus injection of 86 IU / kg, immediately thereafter subcutaneously 86 IU / kg every 12 hours;

• enoxaparin 100 IU / kg (1 mg / kg) subcutaneously every 12 hours (the first subcutaneous injection may be preceded by an intravenous bolus of 3000 IU [30 mg] of the drug).

If percutaneous coronary intervention is performed in the early stages of exacerbation of coronary heart disease amid continued subcutaneous administration of enoxaparin, it is undesirable to switch to unfractionated heparin during the procedure.

Moreover, if less than 8 hours have passed after the final administration of enoxaparin, the intervention can be performed without additional heparin, if 8-12 hours, immediately before the procedure, enoxaparin is administered intravenously at a dose of 0.3 mg / kg. There are no proven schemes for performing percutaneous coronary interventions with the use of dalteparin or nadroparin. In these cases, it is reasonable to start the procedure no earlier than 12 hours after subcutaneous injection of the drug, and during it to use unfractionated heparin.

For the prevention of venous thrombosis and pulmonary embolism in non-surgical patients, dalteparin 5000 IU or enoxaparin 4000 IU (40 mg) are administered subcutaneously every 24 hours.

Fondaparinux sodium. Indications. Currently, the drug is approved for use for the prevention of venous thrombosis and embolism in orthopedic surgery and after abdominal surgery. The results of large controlled studies indicate the possibility of its use in exacerbations of coronary heart disease, in the prevention of venous thrombosis in non-surgical patients, in the treatment of venous thrombosis and not massive pulmonary embolism.

Doses administered subcutaneously at a dose of 2.5 mg 1 time / day. In the treatment of venous thrombosis and non-massive pulmonary thromboembolism, higher doses are used.

Indirect anticoagulants. Indications. Long-term prophylaxis and treatment of venous thrombosis and pulmonary thromboembolism; prophylaxis of thromboembolism in atrial fibrillation in high-risk patients; heart valve prostheses; secondary prevention of exacerbations of coronary heart disease; thrombus in the cavity of the left ventricle after a recent myocardial infarction; prevention of thrombosis in antiphospholipid syndrome and other thrombophilic conditions.

Doses Drugs are taken orally. It is recommended to maintain the following INR values.

INR 2.5 (2-3): long-term prophylaxis and treatment of venous thrombosis and pulmonary thromboembolism, atrial fibrillation in patients with risk factors for thromboembolic complications, cardioversion with prolonged paroxysms of atrial fibrillation, rheumatic mitral heart disease in combination with arterial thromboembolism potentially embolized thrombus in the cavity of the left ventricle, some types of prosthetic heart valves, secondary prophylaxis of myocardial infarction (with the simultaneous use of acetylsalicylic acid), antifo spholipid syndrome without additional risk factors for thrombo-embolic complications.

INR 3 (2.5-3.5): the highest risk of thromboembolic complications (most mechanical mechanical heart valves, thromboembolism with adequate treatment with indirect anticoagulants, antiphospholipid syndrome with additional risk factors for thromboembolic complications), secondary prevention of heart attack myocardium (without the simultaneous use of acetylsalicylic acid). For patients with mechanical artificial mitral or aortic valve of the heart there is evidence of the feasibility of maintaining INR> 3.

It is recommended that the INR control during dose selection be carried out daily, starting with the 2nd or 3rd doses. When the therapeutic values of INR are achieved, the frequency of

determinations can be reduced to 2-3 times / week; with a persistent stable level of INR in 1-2 weeks - go to the definition of 1 time / month. A more frequent INR assessment is required for bleeding, liver disease, the emergence of intercurrent diseases, the beginning of the use of drugs that interact with indirect anticoagulants, major changes in the diet and the nature of alcohol consumption, and insufficient adherence to treatment. When the dose is changed by indirect anticoagulants, the INR determination cycle is repeated.

Dosage selection and correction schemes in various clinical situations have mainly been developed for warfarin. Its dose in the first two days is usually 5-10 mg, in the subsequent it is selected in accordance with the achieved INR. The initial dose of indirect anticoagulants should be lower in patients with initially increased INR, impaired liver function, chronic heart failure, who are on parenteral nutrition, have a small body weight. A similar approach is recommended in the elderly, with an increased risk of bleeding, as well as when using drugs that enhance the effect of indirect anticoagulants. To prevent thrombotic complications in patients with protein C deficiency or other thrombophilic conditions, it is recommended that therapeutic doses of heparin be administered at the beginning of the selection of a dose of indirect anticoagulants.

The use of a loading dose of 10 mg warfarin in the first two days compared with a dose of 5 mg allows you to quickly reach the therapeutic values of INR. Various protocols (nomograms) for the selection of a dose of warfarin are proposed

If a subtherapeutic level of INR is detected in patients who receive indirect anticoagulants for a long time, it is usually possible to limit themselves to an increase in the total dose per week by 10-20% and a more frequent determination of INR. Sometimes it is enough to take the drug at a higher dose on

Note. The dose of warfarin in the first two days of 10 mg.

Before major operations, indirect anticoagulants have to be canceled. Approaches to managing patients in this situation depend on the risk of thromboembolic complications with a decrease in the severity of anticoagulation and the likelihood of bleeding during the intervention When switching from the parenteral administration of anticoagulants to the administration of drugs inside, the selection of the doses of the latter begins simultaneously or almost simultaneously with the start of the administration of direct anticoagulants. Direct-acting anticoagulants are canceled when persistent therapeutic values of INR are achieved (with two consecutive determinations with an interval of at least one day), but not earlier than after 5 days.

Antiplatelet agents. There are noticeable differences in the indications for the use of individual drugs belonging to this group. Antiplatelet agents are used in doses whose efficacy has been proven in large controlled clinical trials. At present, it is not recommended in individual clinical practice to individually monitor the severity of the antiplatelet effect of drugs of this group and select drugs or their doses, focusing on the result of the assessment of platelet aggregation.

Acetylsalicylic acid. Indications. Primary and secondary prevention of thrombotic complications of atherosclerosis; exacerbation of coronary heart disease; acute ischemic stroke of vascular origin or transient cerebrovascular accident; percutaneous coronary interventions; coronary artery bypass grafting; prevention of thrombotic complications of atrial fibrillation in patients with a low risk of thromboembolic complications or with contraindications to indirect anticoagulants.

Doses The dose range of acetylsalicylic acid used to prevent and treat thrombotic complications is 75-325 mg 1 time / day. An increase in the dose of the drug does not lead to an increase in the effectiveness of treatment, but is accompanied by an increased risk of complications from the gastrointestinal tract. Therefore, it is recommended to prefer the minimum dose of acetylsalicylic acid, the benefit of which has been proven in this clinical condition.

For a quick onset of action in patients who have not regularly received acetylsalicylic acid in the last days, the first dose of 160-325 mg should be chewed and swallowed or taken dissolved in water. In this case, it is necessary to use a dosage form that is not coated with an

enteric-soluble membrane (if only dosage forms coated with an enteric-soluble membrane are available, the first tablet should be chewed). If you can not take acetyl-salicylic acid inside (vomiting, inability to swallow), it is permissible to enter intravenously or in suppositories. The minimum dose of acetylsalicylic acid with proven effectiveness in the first month of myocardial infarction or ischemic stroke is 160 mg 1 time / day. For long-term use, it is recommended to take no more than 100 mg of the drug per day; the minimum effective dose for secondary prophylaxis of ischemic stroke or transient cerebrovascular accident is 50 mg / day, in patients with clinical manifestations of atherosclerosis of a different location - 75 mg 1 time / day. With atrial fibrillation, the minimum recommended dose of acetylsalicylic acid is 80 mg 1 time / day. To reduce the adverse effects on the gastric mucosa, acetyl-salicylic acid should be taken simultaneously with food or washed down with a glass of water or milk.

Clopidogrel. Indications. As monotherapy: long-term prophylaxis of ischemic stroke, myocardial infarction and vascular death with obliterating atherosclerosis of the vessels of the lower extremities, after a recent myocardial infarction (from several days to 35 days) or ischemic stroke (from 1 week to 6 months) In combination with acetylsalicylic acid: exacerbations of coronary heart disease; stenting of the coronary arteries (long-term use).

Doses The drug can be taken regardless of the meal. For a quick onset of action in patients who have not previously received clopidogrel, the first loading (shock) dose of the drug for oral administration should be 300-600 mg. A loading dose of 300 mg is used in the medical treatment of exacerbations of coronary heart disease and coronary stenting in cases when the procedure will be performed at least 6 hours later (however, it is better to prescribe the drug a day before the invasive intervention). A loading dose of 600 mg is proposed to be used in cases where coronary stenting will be carried out after at least 2 hours. Subsequently, clopidogrel is taken orally at a dose of 75 mg 1 time / day.

Ticlopidine. Indications. As monotherapy: prophylaxis of vascular complications in obliterating diseases of the vessels of the lower extremities (intermittent claudication), after an ischemic stroke or transient disturbance of cerebral circulation, after an episode of unstable angina. In combination with acetylsalicylic acid: stenting of the coronary arteries (for a month).

Doses The drug is recommended to be taken with meals. For a quick onset of action in patients who have not previously received ticlopidine, the first loading (shock) dose of the drug for oral administration should be 500 mg. In the next drug is taken orally at 250 mg 2 times / day.

Dipyridamole. Indications. As monotherapy or in combination with acetylsalicylic acid: secondary prophylaxis of ischemic non-cardioembolic stroke or transient cerebrovascular accident (evidence of effectiveness obtained using a slow-release dosage form). In combination with anticoagulants of indirect action : prevention of thromboembolic complications with mechanical artificial heart valves and rheumatic mitral heart disease.

Doses It is taken orally before meals: a non-prolonged dosage form of 75-100 mg 3-4 times / day, prolonged - 200 mg 2 times / day.

Platelet IIb / IIIa glycoprotein blockers. Indications. In combination with acetylsalicylic acid, heparin and, possibly, clopidogrel: prevention of thrombotic complications during percutaneous interventions in the coronary arteries (abciximab, eptifibatid); early treatment of acute coronary syndrome without persistent elevations of the ST segment on the ECG (tirofiban, eptifibatid).

Doses Abciximab. Percutaneous interventions in the coronary arteries: 0.25 mg / kg bolus intravenously, followed by 10 mcg / min infusion. Start 10-60 minutes before the procedure, continue during and for the next 12 hours. Acute coronary syndrome without persistent ST segment elevations on the ECG: administration can be started within 24 hours before percutaneous intervention on the coronary arteries and continue 12 hours after him.

Tirofiban. Acute coronary syndrome without persistent elevations of the ST segment on the ECG: intravenously 0.4 μg / kg / min for 30 minutes, then 0.1 μg / kg / min for 48-96 hours

(after percutaneous intervention on the coronary arteries continue within 12-24 hours). In patients with creatinine clearance <30 ml / min, reduce the dose by half.

Eptifibatide. Percutaneous interventions in the coronary arteries: intravenous bolus 180 μg / kg, then infusion 2 μg / kg / min, after 10 minutes a second bolus 180 μg / kg. Start before the procedure, continue during it and for the next 18-24 hours. Acute coronary syndrome without persistent ST segment elevations on the ECG: intravenous bolus 180 mg / kg, then infusion 0.2 μg / kg / min for 72-96 hours (after percutaneous intervention on the coronary arteries continue for 18-24 hours).

3. Fibrinolytics. Indications. Acute myocardial infarction with persistent elevations of the ST segment on the ECG; massive pulmonary thromboembolism (streptokinase, alteplase); the first 3 hours of acute ischemic stroke in carefully selected patients (alteplase); acute thrombosis and embolism of peripheral arteries.

Doses Streptokinase. Acute myocardial infarction with ST segment elevations on the ECG: intravenous infusion of 1,500,000 IU for 30-60 minutes. Used in combination with acetylsalicylic acid. Concomitant use of heparin is optional. Massive pulmonary thromboembolism: intravenous infusion of 350,000-500,000 IU for 5-10 minutes, then 100,000 IU / h for 24-72 hours; intravenous infusion of 1,500,000 IU is possible for 2 hours. Concomitant administration of non-fractionated heparin is not recommended.

Alteplase. Acute myocardial infarction with ST segment elevations on the ECG: 15 mg by intravenous bolus, then infusion 0.75 mg / kg (maximum 50 mg) for 30 minutes, then infusion 0.5 mg / kg (maximum 35 mg) for 60 minutes . In patients with body weight <65 kg, the dose should not exceed 1.5 mg / kg. Used in combination with acetylsalicylic acid and unfractionated heparin. Massive thrombo-embolism of the pulmonary artery: intravenously 10 mg for 1-2 minutes, then infusion 90 mg for 2 hours. In patients with body weight <65 kg, the dose should not exceed 1.5 mg / kg. Concomitant administration of unfractionated heparin is optional. The first 3 hours of ischemic stroke: 0.9 mg / kg intravenously (maximum 90 mg), the first 10% bolus dose, the rest infusion over 60 minutes.

Tenecteplase. Acute myocardial infarction with ST segment elevations on the ECG: intravenously for 5-10 s 30 mg with body weight <60 kg, 35 mg

- with a body weight of 60- <70 kg, 40 mg - with a body weight of 70- <80 kg, 45 mg

- with a body weight of 80- <90 kg, 50 mg - with a body weight of 90 kg. Used in combination with acetylsalicylic acid and unfractionated heparin.

Prourokinase is recombinant. Acute myocardial infarction with ST segment elevations on the ECG: intravenously with a bolus of 2 million IU, then 4 million IU for 60 minutes. Used in combination with acetylsalicylic acid and unfractionated heparin.

ADVERSE EFFECTS AND CONTRAINDICATIONS

Heparin. Contraindications Allergy or hypersensitivity; hemorrhagic diathesis; blood platelet count less than 100,000 in mm3; a history of heparin-induced immune thrombocytopenia; acute ulcers of the stomach and intestines with the threat of bleeding; uncontrolled ongoing serious bleeding; recent intracranial bleeding; nonspecific ulcerative colitis; Crohn's disease; severe uncontrolled arterial hypertension; severe hepatic and / or renal failure; varicose veins of the esophagus; severe trauma or recent surgery in the eyes or nervous system; acute bacterial endocarditis.

Side effects. The main complication when using heparin is bleeding. For their timely detection, it is necessary to regularly monitor hemoglobin and hematocrit and actively look for signs of bleeding. For any significant deterioration in the condition of the patient receiving heparin, it is necessary to determine the content of hemoglobin, hematocrit and APTT (if therapeutic doses of unfractionated heparin are used). If there is a bleeding, in many cases it is enough to cancel the drug. The antidote of heparin is protamine sulfate, 1 mg of which completely neutralizes 100 IU of unfractionated heparin, but not more than 60% of the activity of low molecular weight heparins. When choosing a dose of protamine sulfate, the amount of the drug that continues to have an anticoagulant effect should be considered. To do this, you need to

know the dose of heparin administered, the method of its administration and the time after discontinuation of the drug. For example, to neutralize low molecular weight heparin, administered subcutaneously in the previous 8 hours, 1 mg of protamine sulfate is used for every 100 IU, and later, 0.5 mg per 100 IU. Due to the risk of severe side effects (bradycardia, arterial hypotension up to shock, anaphylactic reactions), protamine sulfate should be used only in cases where immediate cessation of heparin action is required, administered only intravenously slowly, after making sure that there is no hypovolemia, and have emergency supplies ready. Long-term maintenance of the effect with subcutaneous administration of heparin, which continues to come from the subcutaneous tissue, justifies infusion of the calculated dose of protamine sulfate for several hours or reuse of half the dose with continued bleeding.

A decrease in the number of platelets with the introduction of heparin occurs quite often, in most cases it does not require discontinuation of the drug and passes spontaneously. In rare cases, the occurrence of immune thrombocytopenia is possible. This extremely serious complication should be suspected with a significant decrease in platelet count (more than 50% of the original or below <100,000 in mm3), the occurrence of unexplained thrombosis and embolism, the appearance of skin necrosis at the injection site. The detection of antibodies to the complex of heparin and platelet factor 4 is characteristic. Upon first contact with heparin, this complication usually appears on the 4-14th day, however, in patients receiving the drug in the next few months, it can occur in the next few hours after start of drug administration. Therefore, at the beginning of treatment, a frequent determination of the number of platelets in the blood is necessary (at least every other day until the 14th day or earlier heparin withdrawal). If the patient received heparin in the previous 3.5 months, it is necessary to re-determine the platelet content in the blood within 24 hours after starting to use the drug. In addition, in the event of acute inflammatory, cardiovascular, neurological or other unusual symptoms within 30 minutes after administering a bolus of unfractionated heparin, it is necessary to urgently determine the platelet content in the blood and compare the result with the initial value. If immune thrombocytopenia is suspected, any use of heparin should be discontinued immediately. For treatment, direct-acting thrombin inhibitors (argatroban, lepirudin) are used, and after restoration of the normal platelet count, they switch to non-direct-acting anticoagulants.

Among other side effects: reactions at the injection site (tightening, irritation, pain, hematoma, rarely skin necrosis), osteoporosis (with prolonged use of high doses, more characteristic of unfractionated heparin), headache, chills, hyperthermia, nausea , vomiting, constipation, various manifestations of allergy. When using unfractionated heparin, cases of frequent or prolonged erections, peripheral neuropathy, and baldness have been described. In some patients, there is an increase in the level of aminotransferases in the blood, which is usually asymptomatic and does not require discontinuation of the drug (with continued treatment, the indicators can normalize). With spinal or epidural anesthesia, the risk of developing hematoma is increased.

With prolonged administration of heparin, there is a risk of hyperkalemia due to inhibition of aldosterone synthesis. Therefore, in patients with predisposing factors (diabetes mellitus, renal failure, acidosis, initially elevated potassium in the blood, taking angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, potassium-sparing diuretics), it is desirable to control the potassium content in the blood, especially when the duration of treatment exceeds 7 days.

24 hours before a major operation with a risk of massive blood loss, it is advisable to replace low molecular weight heparin with unfractionated.

Fondaparinux sodium. Contraindications Allergy or hypersensitivity; hemorrhagic diathesis; severe renal failure (creatinine clearance <30 ml / min); body weight <50 kg; active heavy bleeding; bacterial endocarditis.

Side effects. Bleeding hematomas, rash, or itching at the sites of subcutaneous injection; reversible asymptomatic increase in aminotransferases in the blood; thrombocytopenia. Other

side effects include headache, chills, hyperthermia, nausea, constipation, insomnia, and allergic reactions. With spinal or epidural anesthesia, the risk of developing a hematoma is increased.

Cautions. Impaired renal function (reevaluation is necessary so as not to miss the appearance of contraindications), old age, increased risk of bleeding, immune thrombocytopenia caused by heparin, a history of pregnancy, breastfeeding.

Indirect anticoagulants. Contraindications Allergy or hypersensitivity; hemorrhagic diathesis; pregnancy; active ulcers of the stomach and intestines; severe uncontrolled arterial hypertension; bacterial endocarditis; ongoing heavy bleeding; high risk of bleeding; thrombocytopenia; severe hepatic and / or renal failure; nonspecific ulcerative colitis; Crohn's disease; lack of laboratory control; alcoholism; social maladaptation.

Side effects. The main complication when using anticoagulants of indirect action is bleeding. Their risk increases with an increase in INR and becomes especially high with INR> 3. Predisposing factors also include age> 65 years, a history of stroke or bleeding, structural damage with an increased risk of bleeding (including a tumor), liver disease, renal failure, thrombocytopenia, diabetes mellitus, low adherence to treatment and poor control of treatment .

Other side effects include allergic reactions, rash, headache, asthenia, fever, baldness, anorexia, nausea, vomiting, diarrhea, taste disturbance, mouth ulcers, skin necrosis, jaundice, liver dysfunction, hepatitis, pancreatitis, and renal dysfunction. , paresthesia, osteoporosis, priapism, leukopenia, leukocytosis, leukemoid reactions, cholesterol microembolism.

Cautions. Take special care with diseases of the liver, kidneys, recent surgery, breastfeeding (do not use phenindione). Age is not a contraindication to the use of indirect anticoagulants, but elderly patients have an increased risk of bleeding (especially intracranial). Therefore, they need to control INR more often and strive to maintain minimally effective indicator values. It is important to regularly reevaluate the need for further use of indirect anticoagulants (risk to benefit ratio with continued treatment).

Acetylsalicylic acid. Contraindications Allergy or hypersensitivity to salicylates; hemorrhagic diathesis; erosive and ulcerative lesions of the gastrointestinal tract in the acute phase; ongoing heavy bleeding; severe liver failure.

Side effects. Any use of acetylsalicylic acid leads to an increase in the frequency of complications from the gastrointestinal tract (dyspepsia, nausea, less often ulceration, bleeding). The risk of gastrointestinal bleeding is doubled when using the drug at a dose of 75-100 mg / day and grows as it increases. Adverse effects on the gastric mucosa become less when using enteric-coated dosage forms, but their ability to cause serious gastrointestinal bleeding less often has not been proven. The use of anti-ulcer agents in all patients receiving acetylsalicylic acid is not recommended. After the healing of a stomach ulcer or duodenal ulcer that has occurred while taking acetylsalicylic acid and complicated bleeding, it is possible to resume taking low doses of the drug (<100 mg / day) in combination with lansoprazole at a dose of 30 mg 1 time / day or with esomeprazole in dose of 20 mg 2 times / day. In this case, a prerequisite is the initial absence or successful destruction of Helicobacter pylori. In general, severe gastrointestinal bleeding is rare (1-2 cases per 1000 treated patients per year).

Possible bleeding of a different location and allergic reactions. Sometimes bronchospasm, respiratory alkalosis occur, and liver function is impaired. Renal dysfunction is described mainly in elderly patients with hypoalbuminemia, in chronic renal failure, glomerulonephritis, glomerulosclerosis. However, it rarely occurs when doses of no higher than 325 mg / day are used and, as a rule, has no clinical significance. In children and adolescents under the age of 16 years, Reye syndrome is described.

Cautions. Bronchial asthma (in some patients, exacerbation is possible), uncontrolled arterial hypertension, pregnancy; avoid when breastfeeding, in children under 16 years of age (risk of Reye syndrome); combined use with other non-steroidal anti-inflammatory drugs and glucocorticoids is undesirable.

Thienopyridine derivatives. Contraindications Allergy or hypersensitivity; hemorrhagic diathesis; active bleeding, increased risk of bleeding (including hemorrhagic stroke and active

ulcerative lesions of the gastrointestinal tract); severe liver failure; neutropenia, thrombocytopenia; a history of thrombotic thrombocytopenic purpura; pregnancy (ticlopidine); breastfeeding (clopidogrel).

Side effects. Occur more often with the use of ticlopidine. In the first 3 months after the start of the use of ticlopidine, the development of neutropenia, thrombocytopenia, agranulocytosis and aplastic anemia is possible. When using clopidogrel, these complications are much less common. Drug withdrawal usually leads to normalization of indicators. A very rare but extremely serious complication is thrombotic thrombocytopenic purpura. This complication usually develops in the first 3 months after starting ticlopidine and in the first 2 weeks after starting clopidogrel (isolated cases have been described). It is characterized by thrombocytopenia, hemolytic anemia and an increased level of fragment cells in the peripheral blood. Clinically manifested by neurological symptoms (headache, impaired consciousness, paresis, aphasia) and the appearance of hemorrhagic diathesis (purpura, nose and gastrointestinal bleeding). Immediate withdrawal of thienopyridine derivatives is necessary; effective plasmapheresis. In order not to miss the occurrence of these complications, a detailed blood test should be performed every 2 weeks during the first 3 months of using ticlopidine. It is also reasonable to control the content of formed elements in the blood at the beginning of the use of clopidogrel. It is necessary to pay special attention to the appearance of fever, sore throat, sores in the mouth, purpura, bruising or bleeding.

Other side effects include allergic reactions, skin rashes and itching, abdominal pain, nausea, vomiting, diarrhea, cholestatic jaundice, and elevated liver enzymes. It is not excluded the formation of ulcers in the stomach and duodenum, aggravation of the course of peptic ulcer, hemorrhagic complications, headache, dizziness, paresthesia.

Cautions. Patients with an increased risk of bleeding, hepatic or renal failure, pregnancy; stop taking before planned surgery if the antiplatelet effect is undesirable (for 5-7 days when using clopidogrel, for 7-10 days for using ticlopidine).

Dipyridamole. Contraindications Allergy or hypersensitivity; hemorrhagic diathesis; exacerbation of coronary heart disease; common stenotic atherosclerosis of the coronary arteries; subaortic stenosis; decompensated heart failure; severe arterial hypotension; severe arterial hypertension; severe arrhythmia; increased risk of bleeding; chronic obstructive pulmonary disease; chronic renal or liver failure.

Side effects. Nausea; dizziness; headache; myalgia, arterial hypotension; flushed face; heartbeat. Symptoms of coronary heart disease, migraine, and thrombocytopenia are rarely aggravated.

Cautions. Aortic stenosis, chronic heart failure, arterial hypotension, myasthenia gravis, breast-feeding. Not recommended for children under 12 years.

Platelet IIb / IIIa glycoprotein blockers. Contraindications Allergy or hypersensitivity; hemorrhagic diathesis; bleeding in the previous month; major surgery or trauma before 6 weeks; cerebrovascular event in the previous 30 days (thyro-fiban, eptifibatid) or 2 years (abciximab); history of hemorrhagic stroke; the use of indirect anticoagulants with INR greater than 1.2; blood platelet count <100,000 in mm3; pathological processes in the cranial cavity (nodulation, arteriovenous malformation, aneurysm); severe uncontrolled arterial hypertension; severe renal failure (abciximab, eptifibatide); lactation.

Side effects. Most often, with the introduction of platelet IIb / IIIa glycoprotein blockers, bleeding occurs. Their risk can be reduced if you do not use excessive doses of heparin and perform invasive procedures quickly enough. During the introduction, it is necessary to control the level of hemoglobin, hematocrit, and also actively look for signs of bleeding. For urgent elimination of antiplatelet action, the abolition of tirofiban and eptifibatide is usually sufficient; when using abciximab, transfusion of fresh platelets may be required.

Thrombocytopenia may appear in the first hours after the introduction of drugs of this group and usually disappears after they are canceled. For the timely detection of this

complication, it is necessary to determine the content of platelets in the blood before treatment, after 2-6 and 12-24 hours, then daily.

Other side effects include arterial hypotension, nausea, vomiting, abdominal pain, headache, dizziness, back pain.

Cautions. Dysfunction of the liver and / or kidneys, increased risk of bleeding, anemia, puncture of blood vessels that cannot be pressed, in the previous 24 hours, pregnancy. Discontinuation of drugs should be necessary if thrombolytic therapy, intra-aortic balloon counterpulsation or surgery on the heart is necessary, if there is serious bleeding from blood vessels that cannot be pressed, as well as severe thrombocytopenia.

Fibrinolytics. Contraindications Allergy or hypersensitivity; hemorrhagic diathesis; ongoing or recent bleeding (except for menstruation); recent injury or surgery; suspected dissecting aortic aneurysm; history of hemorrhagic stroke; ischemic stroke in the next few months; acute ulcers of the gastrointestinal tract with the threat of bleeding; severe uncontrolled arterial hypertension (systolic blood pressure> 180 mmHg and / or diastolic blood pressure> 120 mmHg); active destructive pulmonary disease; severe liver disease; pregnancy. Streptokinase is not recommended to be reused if more than 5 days have passed after the first injection.

Side effects. The main complication with the introduction of fibrinolytics is bleeding. The frequency of intracranial bleeding is noticeably greater in old age, with increased systolic and / or diastolic blood pressure, in patients with low body weight, a history of stroke, in women, blacks, and also when using tissue plasminogen activator and its derivatives. For the modes of administration of fibrinolytics used to treat acute coronary syndrome without persistent ST segment elevations on the ECG, the risk of intracranial bleeding is the lowest when using streptokinase without heparin. Severe bleeding requires termination of fibrinolytic infusion; in some cases, the introduction of freshly frozen blood plasma, FSK and antifibrinolytic agents may be justified.

Allergic reactions are also possible (usually with the introduction of streptokinase), nausea, vomiting, back pain. In the treatment of acute myocardial infarction, reperfusion arrhythmias may occur. With the introduction of streptokinase, the occurrence of arterial hypotension is not excluded, which is associated with the formation of bradykinin. To eliminate it, it is usually enough to raise the patient's legs, reduce the infusion rate, or temporarily stop the administration of the drug. In some cases, intravenous administration may be required. fluid administration and / or infusion of pressor amines.

Cautions. The risk of bleeding increases with vascular puncture, non-compressive, invasive interventions, external compression of the chest during cardiopulmonary resuscitation, recent or ongoing use of anticoagulants.

DRUG INTERACTIONS

With the simultaneous use of several antithrombotic drugs, the frequency of hemorrhagic complications increases. However, this is not a reason to abandon their use in cases where the expected benefit significantly exceeds the risk.

Unfractionated heparin. The anticoagulant effect decreases with intravenous infusion of nitroglycerin (after stopping treatment with nitroglycerin, the dose of the drug should sometimes be reduced). The risk of hemorrhagic complications increases when combined with non-steroidal anti-inflammatory drugs. When combined with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, potassium-sparing diuretics, the risk of hyperkalemia increases.

Indirect anticoagulants. Due to various mechanisms, they interact with a large number of medicines and food products with a high content of vitamin K (Table 12).

Chronic and excessive alcohol consumption can both enhance and reduce the effect of indirect anticoagulants.

Acetylsalicylic acid. The weakening of the antiplatelet effect with the simultaneous use of ibuprofen or naproxen, an increase in ulcerogenic effects when combined with non-steroidal anti-inflammatory drugs, glucocorticoids and alcohol. Nonsteroidal anti-inflammatory drugs do not have sufficient antiplatelet effect, so when using them, you should not stop using low doses

of acetylsalicylic acid. Acetylsalicylic acid reduces the effect of spironolactone and uricosuric agents and helps to weaken some of the effects of ACE inhibitors.

Thienopyridine derivatives. With the simultaneous use of other drugs metabolized with the participation of cytochrome P450 isoenzymes 3A4 or 3A5, a decrease in the concentration of the active metabolite of clopidogrel in the blood plasma is possible. The absorption of ticlopidine decreases with the simultaneous use of antacids, its blood content increases with combination with cimetidine.

Dipyridamole. Enhances the action of vasodilators, antihypertensive drugs, antiarrhythmic drugs. Co-administration with antacids should be avoided. Derivatives of methylxanthine can weaken the vasodilator effect.

HEMOSTATIC PRODUCTS

Currently, it is customary to distinguish 3 types of hemorrhagic diathesis associated with damage to the vascular wall, the plasma component of hemostasis and platelets. It should be emphasized that such a separation is conditional, since the hemostasis system is a single whole and the interaction of its constituent parts can lead to the cessation of bleeding or hemorrhagic diathesis. It is necessary to distinguish between primary (mostly hereditary) and secondary (symptomatic) diathesis. Symptomatic diathesis is most often a manifestation of DIC. In the pathogenesis of coagulopathies (hemophilia, parahemophilia) lies a decrease in the content and activity of blood coagulation factors (factors VIII, IX, X, II, V, etc.). This ultimately leads to a disruption in the formation of fibrin and the consolidation of a platelet thrombus (phase 3 of hemostasis) and the occurrence of persistent bleeding (for example, with hemophilia).

There are diatheses associated with a decrease in the number of platelets (thrombocytopenic purpura) and a violation of their function (thrombocytopathy). It is known that a decrease in platelet count below 50,000-70,000 in 1 μl disrupts the formation of a primary platelet thrombus, limits the platelet endothelial reaction, and prevents the formation of thromboplastin due to an insufficient level of platelet factor 3 necessary for the activation of factors V, VIII and the formation of thromboplastin.

With hereditary thrombocytopathies (von Willebrand's disease, Glanzmann's thrombasthenia, Bernard-Soulier's thrombocytopathy, etc.) with unchanged platelet counts, their adhesion and aggregation process, the content of plate factors and their release from platelets are disrupted, which leads to a defect in the vascular thrombosis of the platelet vessels for shaped elements of blood.

Acquired thrombocytopathies are observed in various pathological conditions (nephritis, chronic renal failure; hepatitis and cirrhosis, collagenosis, etc.) and with the use of drugs with antiaggregatory activity (non-steroidal anti-inflammatory drugs, xanthine derivatives, etc.)

The vascular diathesis includes hemorrhagic vasculitis of Shenlein-Genoch, hereditary hemorrhagic telangiectasia of the Randu-Osler, giant angiomatosis of Kazabah-Merrit, mourning. The basis of bleeding in these diseases is a violation of the permeability of the vascular wall and / or multiple micro-thrombi with coagulopathy of consumption and hyperfibrinolysis (Shenlyayn-Genokh disease, Kazabakh-Merrit).

Most often, hemorrhagic diathesis is secondary and is a consequence of DIC and consumption coagulopathy. Disseminated intravascular coagulation is an intermediate in inflammatory, autoimmune, degenerative, neoplastic diseases; it plays an important role in the pathogenesis of cardiovascular diseases. The formation of common small microthrombi from shaped elements and fibrin leads not only to disrupt microcirculation, but also as a result to the consumption of coagulation factors and platelets. Consumption coagulopathy means a decrease in the concentration (amount) of hemostatic factors (procoagulants, fibrinolytic enzymes, anti-rhombin III, platelets and leukocytes) and depletion (distortion) of their function (consumption thrombocytopathy). Consumption coagulopathy can be latent and can only be detected by studying the activity and content of hemostatic factors (factors II, V, VII, VIII, XI, fibrinogen, antithrombin III, plasmin gene, platelets). A decrease in the activity and content of coagulating factors causes hemorrhage and bleeding. In DIC, hemorrhage can be a consequence of increased

activation of fibrinolysis, i.e. treat hyperfibrinolytic bleeding. Isolation of the phase of the DIC syndrome is extremely important, since at each stage, exposure to both antithrombotic and hemostatic agents is possible. A typical manifestation of bleeding in DIC is hemorrhagic vasculitis (thrombovasculitis of the small and medium arteries) of Shenlein-Genoch.

The cause of hemorrhagic syndrome determines the choice of a hemostatic drug.

Classification of hemostatic agents

There are several groups of hemostatic drugs: topical agents, replacement therapy, group K vitamins, heparin antidotes, fibrinolysis inhibitors, angioprotectors.

Local funds. They are a sponge or other porous material that is applied to a bleeding surface. The material can be impregnated with procoagulants (thrombin, fibrinogen, factor VIII, XIII, etc.) or with substances that activate local hemostasis (e-aminocaproic acid).

The drug contributes to the local formation of fibrin and mixed blood clots in arterioles, venules and capillaries. Used for superficial bleeding from the skin, nose, rectum, parenchymal bleeding and other organs.

Means of substitution therapy. With hereditary coagulopathies (hemophilia and parahemophilia), an acquired deficiency of plasma factors caused by a decrease in synthesis or loss (blood loss, cirrhosis, vitamin K hypo-vitaminosis, overdose of indirect anticoagulants, obstructive jaundice), drugs are often used for treatment and prevention, containing (or enriched) blood coagulation factors.

Hemopreparations containing factor VIII. Antihemophilic plasma is obtained by rapidly separating and freezing the plasma of a healthy person. 1 ml of antihemophilic plasma contains 0.2-1.6 PIECES of factor VIII; the plasma should be stored at -300 C, since at room temperature, factor VIII is rapidly inactivated. T1 / 2 of factor VIII in a sick person is about 6-8 hours, and after stopping the bleeding, it can extend up to 24 hours. In this regard, hemopreparations should be administered three times a day. The daily dose of antihemophilic plasma is 30-50 ml / kg for adults and children. Consideration should be given to the possibility of overloading with a volume of transfused fluid and provoking pulmonary edema.

Factor VIII cryoprecipitate is released from plasma by cryoprecipitation of proteins. It contains a sufficient amount of factor VIII, fibrinogen, factor XIII and a small amount of albumin and other proteins. Store at -200 C. Calculation of the dose of cryoprecipitate administered:

D = A (patient weight in kg) x B (predetermined factor VII level in%) / 1.3,

where D is the dose in units of activity.

Doses of cryoprecipitate, as well as antihemophilic plasma, depend on the purpose of the infusion and the severity of the bleeding. To stop a small bleeding, both drugs are administered at a dose of 15 ml / kg.sut, which causes an increase in the concentration of factor VIII in the blood to 15-20%. More severe external and internal bleeding requires an increase in the concentration of factor VIII by 30-40%, which requires the injection of hemopreparations at a dose of 20-30 U / kg / day or more.

There are hemopreparations with a high content of factor VIII.

Indications: prophylaxis and treatment of bleeding in patients with hemophilia, preoperative prophylaxis.

The PPSB complex contains factors whose synthesis depends on vitamin K: P - prothrombin (factor II), P - proconvertin (factor VII), S - Stuart factor (factor X), B - factor IX. Isolated from plasma by sorption on a gel followed by precipitation. 1 ml of PPSB contains 10-60 IU of factor IX. Introduce 30-50 ml / kg.sut in three doses, taking into account the half-cycle of the circulation of factors of the prothrombin complex. A single dose (in units) of the concentrate is calculated by the formula:

D = A (patient weight in kg.) X B (necessary increase in factor,%) / 1.2.

Indications: hemophilia B, an inhibitory form of hemophilia, hypovitaminosis K, bleeding with obstructive jaundice and cirrhosis, hemorrhagic disease of the newborn, an

overdose of coumarin. Concentrates of factors VIII, IX, X are also used to treat various coagulopathies.

Fibrinogen. It is a blood fraction containing, along with other proteins, human fibrinogen. Fibrinogen, when introduced into the bloodstream, turns into fibrin, which is an integral part of any blood clot, aggregates from platelets and red blood cells, the wall layer, which performs a barrier function in the bloodstream. True diseases that occur with hypofibrinogenemia, which could be the cause of hemorrhages, are few: hereditary a- and hypofibrinogenemia, hyper-fibrinolysis in the treatment of thrombolytic drugs, DIC with severe consumption coagulopathy, impaired synthesis of coagulation factors in liver cirrhosis, and gastric bleeding . However, it is assumed that infusion of fibrinogen in all cases of bleeding leads to the desired success.

T1 / 2 of fibrinogen is 3-5 days, however, it should be borne in mind that in diseases accompanied by DIC syndrome of acute and subacute course, T1 / 2 of fibrinogen can change dramatically (up to 1 day or less) due to the involvement of protein in the process intravascular microthrombosis.

Applied intravenously in average doses of 2-4 g.

Contraindications: tendency to thrombosis, microcirculatory disorders.

Vitamin K. In clinical practice, 2 methylnaphthoquinone derivatives from various raw materials with different activity are used: vitamin K1 (conacion) and K3 (Vikasol).

Pharmacodynamics Vitamin K belongs to the cofactors of the synthesis of the so-called K-dependent coagulation factors (factor II, V, VII, X, IX). With a deficiency of vitamin K or with the use of indirect anticoagulants (coumarins), which displace naphthoquinone from the sites of synthesis of coagulation factors, bleeding develops. Bleeding is mainly due to a violation of coagulation hemostasis. Only with a deep deficiency of vitamin K (or an overdose of coumarins) is hemostasis associated with thrombocytopathy due to a violation of the interaction of factor III and the prothrombin complex and damage to the vascular wall.

Vitamin K1 with subcutaneous, intramuscular and intravenous administration in a dose of 5-10 mg in 30-60 minutes increases the content of prothrombin complex factors and stops bleeding. The duration of action is 4-6 hours. The drug should be administered 3-4 times a day.

Vitamin K3 (Vikasol) is used orally at a dose of 0.15-0.3 g 3 times a day, as well as intravenously or intramuscularly 20-30 mg / day.

Indications: hemorrhagic diathesis due to vitamin K deficiency: obstructive jaundice, acute and chronic hepatitis, cirrhosis, overdose of indirect anticoagulants.

Contraindications: tendency to thrombosis.

Heparin antidotes. With bleeding, heparin antidotes (protamine sulfate, polybrene) that bind heparin (1 mg of protamine sulfate binds 80-100 units of heparin) have found limited use.

Used for hyperheparinemia caused by improper use of anticoagulants or after surgery with cardiopulmonary bypass, 50-100 mg intravenously slowly or intramuscularly. In newborns, doses are used taking into account the fact that 1 mg of the drug inactivates 100 PIECES of heparin.

Indications: hyperheparinemia, hyperheparinemia and similar hemorrhagic diathesis.

Contraindications: shock, adrenal insufficiency, thrombocytopenia.

Fibrinolysis Inhibitors These drugs include e-aminocaproic (eACA), para-aminobenzoic (PABA) and aminomethanocyclohexanoic (AMSNA) acid, as well as natural kinin system inhibitors and proteases - contracal (trasilol), gordox.

The pharmacodynamics of fibrinolysis inhibitors is the suppression of plasminogen, plasmin, activation of factor XII, the kinin system. Fibrinolysis inhibitors contribute to the stabilization of fibrin and its deposition in the vascular bed, indirectly induce aggregation and adhesion of platelets and red blood cells. Drugs are rapidly absorbed in the intestine and excreted by the kidneys, and when administered intravenously, they are also rapidly eliminated in the urine.

eAKK is administered orally every 4 hours at a dose of 2-3 g. The total daily dose of 10-15 g is also administered intravenously, 0.5-1 g in an isotonic solution every 4-6 hours. In newborns, the dose of eAKK is 0.05 g / kg per day intravenously drip 1 time per day.

Indications: bleeding from various organs and tissues due to hyperfibrinolysis, including in connection with DIC, with cirrhosis of the liver, peptic ulcer of the stomach and duodenum; uterine, pulmonary, renal bleeding; thrombocytopenia; hemophilia. They are also used for prophylactic purposes in hemophilia.

Contraindications and limitations: tendency to thrombosis and embolism, kidney disease with chronic renal failure, severe forms of coronary heart disease and ischemic brain disease, pregnancy.

PABA also refers to inhibitors of fibrinolysis, but a more powerful action. Indications and contraindications are the same as for ACC.

Apply 50-100 mg intravenously or in the same doses orally 2-3 times a day.

AMSNA is an even more powerful inhibitor of fibrinolysis. Apply the same as the previous drug.

Contrikal and trasilol (as fibrinolysis inhibitors) are used in newborns at a dose of 500 IU / kg per day intravenously once.

Drug selection

Hemophilia A. When stopping bleeding, in the pre- and surgical period use the introduction of antihemophilic plasma, cryoprecipitate, factor concentrate VIII. In children with hemophilia A, cryoprecipitate for the prevention of bleeding is used once every 2 weeks at the age of 1-3 years at a dose of 200 PIECES, from 4-6 years old - 400 PIECES, from 7-10 years - 600 PIECES intravenously.

The inhibitory form of hemophilia requires the introduction of large doses of a concentrate of factor VIII (500-1000 U / kg) or plasmapheresis with the replacement of fresh antihemophilic plasma. They also use “roundabout treatment” - an infusion of PPSB, as well as prednisolone or azathioprine. The latter can be used for rheumatoid syndrome.

Hemophilia B. Intravenous injection of dry or frozen plasma at a dose of 15-20 mg / kg 1 time per day is used, trying to increase the concentration of factor IX in the blood by 10-15%. T1 / 2 of factor IX is 30 hours. PPSB or factor IX concentrate are also used at a dose of 15 U / kg, including for the prevention of bleeding - once every 10-15 days. For hemophilia, for the prevention of hemorrhage from 1-5 years, 150 units are prescribed, from 6-10 years - 300 units of plasma containing factor IX every two weeks.

The combined use of eAKK, contraceptives and hemopreparations for all types of diathesis can lead to DIC or thromboembolism.

Von Willebrand disease. For the treatment and prevention of bleeding, the preparation and conduct of surgery for Vilebrand’s disease, fraction 0-I (blood plasma of hemophilia patients or healthy people devoid of factor VIII) is used, cryoprecipitate or fresh plasma.

Deficiency Factor VII. The stopping of bleeding is provided by increasing the concentration of factor VII in the patient's plasma to 15% and higher by jet injection of plasma at a dose of 15 ml / kg or PPSB in an adequate dose. T1 / 2 of factor VII - 3-6 hours, therefore, hemo drugs should be administered 3-4 times a day. The first plasma dose of 30 ml / kg, the subsequent 10 ml / kg 3-4 times a day.

PPSB is administered at a dose of 20-30 U / kg, and then at 15 U / kg every 12 hours. For prophylaxis, eACK, contraceptives that stimulate the synthesis of K-dependent coagulation factors, are used. Contraceptives are used to prevent and limit menstrual bleeding.

Factor X deficiency (Stuart-Prauer disease). Plasma transfusion is used 7-10 ml / kg 2 times a day, PPSB - 15-20 U / kg every 2-3 days, taking into account T1 / 2 factor X, equal to 37 hours.

Synthetic hormonal contraceptives (mestranol, etc.) are also used, 3-4 tablets in the first 2 days of the menstrual cycle and then 1 tablet per day.

Factor V deficiency. With large blood loss and in preparation for surgery, freshly frozen plasma is used, and in its absence, fresh donor blood is used in a volume of 40-50 ml / kg of weight every 12 hours, and then 15 ml / kg. At the same time, they strive to increase the level of factor V to 25-30%. Perhaps the introduction of cryoprecipitate and complex.

Deficiency Factor II. Use freshly frozen or regular plasma or PPSB concentrate in a dose of 20-40 U / kg once every 2-4 days to increase the concentration of factor II in the patient's blood plasma to 15-20%.

A - or hypofibrinogenemia. Bleeding from the mucous membrane and after tooth extraction is stopped by eACA at a dose of 0.2 g / kg by mouth or by irrigation with a 5% solution. For massive bleeding or in the pre- and postoperative period, 0.06 g / kg of fibrinogen is used per day (first dose) and then, after 2-3 days, fibrinogen is again infused in a maintenance dose of 0.03-0.04 g / kg of body weight. The frequency of administration is determined by T1 / 2 of fibrinogen, equal to 3-5 days.

Deficiency of factor XIII. It is well stored in dry plasma, which is administered 1 time in 4-5 days (T1 / 2 of factor XIII - 4 days) at a dose of 10-15 ml / kg. Cryoprecipitate and e-ACK are also used.

Vitamin K deficiency leads to impaired synthesis in the liver and a decrease in plasma concentration of K-dependent coagulation factors - VII, X, II and IX. There are forms associated with insufficient formation of vitamin K in the intestine (hemorrhagic disease of the newborn, enteropathy, dysbiosis), impaired absorption of vitamin K (jaundice), displacement of the vitamin by its antagonists (cumarina), and damage to the liver parenchyma.

Hemorrhagic disease of the newborn. It occurs in 0.5% of children. It should be emphasized that in healthy children, the concentration of K-dependent factors is reduced to 40-60% and even 20-26% of the level of adults, as well as a decrease in the aggregation ability of platelets and an increase in vascular permeability. In the pathogenesis of hemorrhage, they attach importance to a decrease in the synthetic function of the liver (depression of the synthesis of K-dependent factors), the mother's intake of anticoagulants, non-steroidal anti-inflammatory drugs, anticonvulsants (phenobarbital) in the last months, and the presence of hepato- and enteropathy in the mother, dysbiosis. In preterm and pregnant women with eclampsia and preeclampsia, the concentration and activity of not only K-dependent factors, but also factors I, VIII, XIII, are reduced. In children of the first days of life with bleeding, intramuscular administration of vitamin K at a dose of 2-5 mg / day (for premature infants) or vitamin K1 (conacion, mefigone), or 1% Vikasol solution (vitamin K3) at a dose of 0.3- is indicated 0.5 ml (for premature 0.2-0.3 ml). At a dose of Vikasol greater than 10 mg, hemolysis can be induced.

In children under 3 years of age with severe enteropathy and dysbiosis, hemorrhagic syndrome is sometimes observed. Vicasol, enzyme and bacterial preparations (lactobacterin, colibacterin) are mainly used and antibiotics are canceled.

Angioprotectors. This group includes drugs that affect the functional state of the vascular wall (permeability, vasoactivity, etc.): rutin, ascorbic acid, as well as etamsylate and dobesylate.

Ethamsylate (dicinone) is a synthetic non-hormonal drug that reduces the permeability of small vessels and capillaries. In the experiment, it sharply enhances the platelet-vascular reaction, does not affect the number of platelets, leukocytes and red blood cells, the activity of coagulation factors, fibrinolysis, and stops bleeding from small and tiny vessels (parenchymal bleeding).

The drug is indicated for gynecological operations, as it limits the volume of blood loss, in urological practice before and during prostatectomy, in dental surgery (tooth extraction, etc.), for the treatment and prevention of hemorrhage in the fundus. In addition, it helps to stop gastrointestinal, pulmonary hemorrhage, effective in case of an overdose of coumarin preparations.

For prophylaxis, 0.75-1.0 g is administered intravenously or intramuscularly 5-10 minutes before surgery, 0.75-1.0 g intravenously, intramuscularly or as an infusion 4-6 times a day is used for therapeutic purposes. Inside recommend 0.5 g 4-6 times a day.

Contraindications: tendency to thrombosis, acute hypotension.

Sodium dobesylate (Doxium) refers to angioprotectors. By the mechanism of action is close to dicinone. Used in ophthalmology as an effective tool for the treatment and prevention of diabetic retinopathy and the resulting hemorrhage into the fundus from microaneurysms of small vessels of the eyes. Apply for a long time for several months and years, 0.5 g 2 times a day.

Hemostatic characteristics

PROTAMINE SULFATE (Protamini sulfas)

Pharmachologic effect. The drug is an effective antidote ("antidote") of heparin in an equivalent dose: 1 mg of protamine sulfate neutralizes 1 mg of heparin. The action comes instantly. The effect lasts approximately 2 hours.

Indications for use. Protamine sulfate is used mainly if necessary to neutralize the effect of excess exogenous (added externally) heparin. Bleeding due to an overdose of heparin; before surgery in patients who take heparin for therapeutic purposes; after operations on the heart and blood vessels with extracorporeal circulation (using the "artificial heart" apparatus); hyperheparinemia (increased heparin in the blood).

Dosage and administration. A solution of protamine sulfate is injected intravenously, drip or drop, under the control of blood coagulability. Slowly injected slowly with a speed of 1 ml% solution for 2 minutes. The total dose is usually 5 ml of a 1% solution.

If necessary, the dose can be repeated at intervals of 15 minutes. The maximum dose should not exceed 150 mg in one hour. In case of spontaneous bleeding, a daily dose of 5-8 mg / kg of body weight is prescribed in 2 divided doses with an interval of 6 hours. Dissolve the calculated dose in 300-500 ml of isotonic sodium chloride solution and administer slowly or drip intravenously. The maximum course of treatment is 3 days.

Side effect. With the introduction of a solution of protamine sulfate, allergic reactions (such as urticaria) are possible.

Contraindications Pronounced hypotension, thrombocytopenia, insufficiency of the adrenal cortex. Rare cases of idiopathic or congenital hyper-heparinemia (high levels of reparin in the blood).

Release form. Ampoules of 5 ml of 1% solution in a package of 5 pieces.

Storage conditions. In a cool, dark place.

Fibrinolysis inhibitors

AMBEN (Ambenum)

Synonyms: Pamba, Gumbiks, Stippopur.

Pharmachologic effect. Antifibrinolytic (preventing the formation of a blood clot). By the structure and mechanism of action, it is close to the aminocaproic acid; inhibits fibrinolysis (dissolution of a blood clot) by competitively inhibiting a plasminogen-activating enzyme (a protein that takes part in the process of blood coagulation) and inhibiting the formation of plasmin (a protein that destroys blood clots). Compared to acid, aminocapron is more active.

Indications for use. It is used to stop bleeding during surgical interventions and various pathological conditions, accompanied by an increase in fibrinolytic activity (the ability to dissolve a blood clot) of blood and tissues, as well as hemorrhagic diathesis of thrombocytopenic origin (increased bleeding due to a decrease in the number of thrombocytes in the blood).

Dosage and administration. The drug is administered intravenously in jet doses of 50-100 mg (5-10 ml of a 1% solution). If necessary, re-administered at intervals of at least 4 hours. The introduction of ambene can be combined with the gluing of glucose solution, hydrolysates, anti-shock liquids.

In acute fibrinolysis (dissolution of a blood clot), fibrinogen, one of the coagulation factors, is additionally prescribed, controlling the fibrinolytic activity of the blood and the content of fibrinogen in it.

The maximum single dose of the drug is 100 mg (10 ml of a 1% solution). The total daily dose and duration of treatment depend on the course of the disease.

Side effect and contraindications. Same as for aminoka-pronic acid.

Release form. 1% solution in ampoules of 5 ml (50 mg).

Storage conditions. In the dark place.

HEMOSTATIC SPONGE WITH AMBEN (Spongia haemostatica cum Ambeno)

Pharmachologic effect. The sponge contains human blood donor plasma, amben and calcium chloride. It is a dry, porous, hygroscopic (moisture-absorbing) substance of white bloom with a yellowish tinge.

Indications for use. Apply topically to stop bleeding.

Dosage and administration. It is applied topically aseptically (sterile), they extract the necessary amount of the drug from ('/ 4 parts of the sponge to 4 or more sponges) and with it help plug (fill) the wound surface. To this end, the sponge is pressed to the surface with a gauze swab or flat surgical instrument for 3-5 minutes. If necessary, the entire wound surface is covered with a sponge or a sponge will be placed in a gauze swab, which is left in the wound cavity for a day.

Contraindications Bleeding from large vessels.

Release form. Dry porous substance (1 g) in 50 ml vials.

Storage conditions. In a dark place at a temperature of no higher than +25 ° C.,

APROTININ (Aprotinin)

Synonyms: Antagozan, Amprotibin, Gordoks, Kontrikal, Trasilol, Traskolan.

Pharmachologic effect. Multivalent inhibitor of proteinases (enzymes involved in the destruction of proteins). It also activates plasma proteinases (plasmin, kininogenase, trypsin, chymotrypsin), blood cells and tissues. Reduces the fibrinolytic activity of blood (the ability to dissolve a blood clot). It has a therapeutic effect in acute pancreatitis (inflammation of the pancreas), necrosis (tissue necrosis) of the pancreas.

Indications for use. Local gypsum fibrinolysis (local dissolution of a blood clot), for example, postoperative bleeding, hypermenorrhea (heavy menstruation). Generalized primary hyperfibrinolysis (systemic coagulation disorder) as a result of the massive influx of fibrinogen activators (one of the coagulation factors) into the bloodstream in the postoperative period, with carcinoma (malignant tumor) of the prostate, embolism with amniotic fluid (blockage of the vessels of the parturient woman with amniotic fluid) . Generalized secondary fibrinolysis (systemic coagulation disorder) in obstetrics. As an adjunctive therapy in the initial phase of coagulopathy development (blood coagulation disorders), after the use of heparin and the replacement of blood coagulation factors before the development of the effect. Massive bleeding during thrombolytic therapy (aimed at dissolving a blood clot).

Dosage and administration. Usually, the patient is first given an initial dose of 500,000 units, then every hour, 50,000 units. The patient should be in a supine position at the time of administration. In the following days, after improving the patient's condition and laboratory parameters, the daily dose is gradually reduced to 300,000-500,000 units.

With coagulopathies (impaired function of the blood coagulation system), combined with secondary hyperfibrinolysis (enhanced dissolution of blood clots), higher doses (1,000,000 units or more) are administered. With prolonged minor bleeding, the drug should be applied topically (1,000,000 units) using gauze soaked in 10 ml of aprotinin solution.

In the postoperative period and for prophylactic purposes, immediately before the operation, 200,000 units are administered intravenously, slowly. On the day of surgery, as well as on the first and second day after it, 100,000 units are administered every 6 hours intravenously, slowly; it is possible to use the drug in the form of a long drip infusion.

For children, the drug is prescribed according to the same schemes as for adults, but in lower doses, depending on the body weight of the child (the dose is calculated per kg of the child's body weight, based on the fact that the doses of the drug recommended by adults are set for body weight of 70 kg) .

Before starting the administration of aprotinin, if possible, a skin test should be performed to assess the individual tolerance of the drug. If side effects occur during the administration of aprotinin, it is necessary to immediately stop the administration of the drug. In

cases where for some reason it is impossible to carry out a continuous drip infusion, the drug can be administered subcutaneously every 2-3 hours.

Side effect. Allergic reactions.

Contraindications Disseminated intravasal coagulopathy (systemic intravascular coagulation disorder); hypersensitivity to the drug.

Release form. Raster for injection in ampoules of 10 ml (100 000 units) in a package of 25 pieces.

Storage conditions. List B. In a cool place.

INGITRIL (Ingitrilum)

A preparation obtained from the lungs of cattle.

Pharmachologic effect. Like pantripin, it inhibits the activity of proteolytic (enzymes (inhibits the activity of enzymes that promote protein breakdown), reduces the fibrinolytic activity of the blood (the ability to dissolve a blood clot).

The activity of the drug is determined by the decrease in trypsin activity and expressed in units; 1 g of the drug contains at least 550 units.

Indications for use. It is used to stop bleeding during surgical interventions and various pathological conditions, accompanied by an increase in the fibrinolytic activity of blood and tissues, as well as to prevent bleeding in patients operated on under extracorporeal circulation. Burn toxemia (the presence in the blood of toxins / substances /, formed as a result of absorption of decay products of burnt tissue, which can lead to poisoning or death of the body).

Dosage and administration. Apply intravenously (jet or drip).

In patients undergoing cardiopulmonary bypass surgery, Inhitril is prescribed for the prevention and treatment of fibrinolytic bleeding (bleeding due to bleeding disorders), as well as for the prevention and treatment of pancreatitis (inflammation of the pancreas), often complicating such operations. They begin with a slow jet injection of 100-200 IU of initrile (in 10-20 ml of isotonic sodium chloride solution), then 200 IU are administered intravenously dropwise during the first 3 days of the postoperative period '.

In case of gastrointestinal and other bleeding accompanied by fibrinolysis (dissolution of a blood clot), ingitrile is administered intravenously in a dose of up to 300 PIECES per day until the bleeding stops or the fibrinolytic activity normalizes.

In patients with Burn shock and acute burn toxemia, Inhitrile is administered for 5-7 days, 140-200 IU daily, drip intravenously at a rate of 40-60 drops per minute. It is allowed to dissolve the desired dose of ingitril in 200 ml of a 0.1% solution of novocaine.

Side effect. Allergic reactions in the form of urticaria, which can be easily stopped (removed) by antihistamines, can be observed during treatment with ingitril.

Contraindications The use of the drug is contraindicated in diseases accompanied by increased blood clotting, and in patients who have previously observed intolerance to ingitrile.

Release form. On 15 and 20 PIECES in bottles with a capacity of 5 ml, corked with rubber stoppers with metal caps.

Storage conditions. In a dry, sheltered from light place at a temperature of no higher than +20 ° C.

AMINOCAPRONIC ACID (Acldum aminocapronicum)

Synonyms: Epsilon aminocaproic acid, Acicapron, Afibrin, Amicar, Karpatsid, Karpamol, Epsamon, Epsicapron and others.

Pharmachologic effect. It has a specific hemostatic effect in case of bleeding associated with increased fibrinolysis (dissolution of a blood clot).

Indications for use. The need to stop bleeding during surgical interventions and various pathological conditions, accompanied by an increase in fibrinolytic activity (the ability to dissolve a blood clot) of blood and tissues (after operations on the lungs, prostate, pancreas and thyroid gland; premature detachment of a normally located placenta, disease liver, acute pancreatitis / inflammation of the pancreas / etc.).

Dosage and administration. Inside, at a rate of 0.1 g per 1 kg of patient's body weight after 4 hours, the daily dose is 10-15 g. In acute hypofibrinogenemia (low fibrinogen content in the blood / one of the coagulation factors /) is administered intravenously (drip) up to 100 ml of a 5% solution of the drug; if necessary, sewing is repeated at intervals of 4 hours.

Side effect. In some cases, dizziness, nausea, diarrhea, mild catarrh of the upper respiratory tract.

Contraindications Propensity to thrombosis (blood clot formation in the blood vessel) and embolism (blockage of a blood vessel), kidney disease with impaired function.

Release form. Powder; 5% solution of the drug in isotonic sodium chloride solution in 100 ml vials.

Storage conditions. Powder - in a cool dry place; 5% solution in bottles - at a temperature of 0 to + 20 ° C.

Thromboplastin activators

Ethamylate (Etamsylatiim)

Synonyms: Dicinon, Aglumin, Altodor, Cyclonamine, Dicinen, Ezelin, Impe-dil.

Pharmachologic effect. The drug increases the formation of large molecular weight mucopolysaccharides in the walls of capillaries (smallest vessels) and increases the stability of capillaries, normalizes their permeability during pathological processes, improves microcirculation (blood flow through the smallest co-vessels of the organ); also has a hemostatic (hemostatic) effect. The hemostatic effect is apparently associated with an activating effect on the formation of thromboplastin. The drug stimulates the formation of coagulation factor III, normalizes the adhesion (gluing speed) of platelets. The drug does not affect prothrombin time (an indicator of blood coagulation time), does not have hypercoagulation properties (does not cause increased blood coagulation) and does not contribute to the formation of blood clots (blood clots).

Indications for use. Ethamylate is used to prevent and stop capillary (from the smallest vessels) bleeding in diabetic angiopathies (vascular disease associated with an increase in blood sugar); surgical interventions in otorhinolaryngology (tonsillectomy / removal of the tonsils - tonsils /), microsurgical operations on the ear, etc.), ophthalmology (keratoplasty / surgical replacement of a part of the cornea /, cataract removal, anti-glaucomatous surgery and other thin surgical interventions), stomatology (removal of cysts, granulomas, extraction / extraction / of teeth, etc.), urology (after prostatectomy / removal of the prostate gland / etc.), in surgical and gynecological (especially during operations on severely vascularization n / abundant blood supply / tissue) practice, as well as in emergency cases with intestinal and pulmonary hemorrhages and hemorrhagic diathesis (increased bleeding).

Dosage and administration. Assign intravenously, intramuscularly, sub-conjunctivally (under the outer shell of the eye), retrobulbar (behind the eyeball) and inside.

The hemostatic effect of etamsylate develops after intravenous administration after 5-15 minutes, the maximum effect occurs after 1-2 hours, the effect lasts 4-6 hours or more. With intramuscular administration, the effect is somewhat slower. When administered, the maximum effect is observed after 3 hours.

For prophylactic purposes, the drug is administered intravenously or intramuscularly 1 hour before surgery at a dose of 2-4 ml (1-2 ampoules), which corresponds to 0.25-0.5 g of etamzi-lat, or 2-3 tablets are given orally (0 , 25 g) 3 hours before surgery. If necessary, inject 2-4 ml intravenously during surgery. If there is a danger of postoperative bleeding, prophylactically injected from 4 to 6 ml (2-4 ampoules) per day or give from 6 to 8 tablets per day (evenly during the day).

For therapeutic purposes (with bleeding), 2-4 ml are injected into a vein or intramuscularly immediately, and then every 2-6 hours - 2 ml or 2 tablets are given.

It can be injected into a vein, adding to the usual solutions for infusion. Ethamzilate should not be mixed in the same syringe with other drugs.

In the treatment of metro- and menorrhagia (dysfunctional uterine bleeding), etamsylate is prescribed 0.5 g orally or 0.25 g parenterally (bypassing the digestive tract) every 6 hours for 5-10 days, then - 0.25 g orally 4 times a day or 0.25 g parenterally 2 times a day during hemorrhage (bleeding) and the last two cycles.

In the treatment of hemorrhagic diathesis (increased bleeding) and diseases of the blood system, the drug is prescribed in courses of 1.5 g per day at regular intervals inward for 5-14 days. In severe cases, treatment begins with parenteral administration of 0.25-0.5 g 1-2 times a day for 3-8 days, and then prescribed by mouth.

In diabetic microangiopathies (lesions of small blood vessels), in particular with retinopathy with hemorrhages (damage to the retinal vessels of the eye, accompanied by a violation of their integrity), etamsylate is prescribed in courses of 2-3 months, giving 1-2 tablets 3 times per day or by intramuscular injection of 1 ampoule (2 ml) 2 times a day for 10-14 days.

Subconjunctival and retrobulbar injected 1 ml of solution.

Contraindications Ethamylate should not be used for hemorrhages (hemorrhages) caused by anticoagulants (agents that inhibit blood coagulation - see page 448). Caution is necessary in patients with thrombosis or embolism (blockage of a blood vessel) in the anamnesis (in the medical history).

Release form. 12.5% solution in ampoules of 2 ml (250 mg) in a package of 10 or 50 ampoules; tablets of 0.25 g in cans of light-protection glass of 50 or 100 pieces.

Storage conditions. List B. In the dark place.

Thrombogenic drugs

DECILATE (Decilatum)

Synonyms: Thrombovar, Obliterol, Sotradekol, Tergitol-4, Varikol, etc.

Pharmachologic effect. Decylate is a vein-sclerosing (causing a decrease in the lumen of the vein) drug with surface-active properties. When introduced into the veins, the decylate solution causes thrombosis (blood clot formation) with the subsequent organization of the thrombus and its fusion with the vessel wall.

Indications for use. They are used for conservative injection-sclerosing treatment of varicose veins (introducing drugs into the changed sections of the veins that cause the closure of their lumen) of the lower limbs. The drug is used in the treatment of patients with initial and uncomplicated forms of moderately severe varicose veins of the superficial veins, as well as in the disseminated type of varicose veins (an extensive type of varicose veins - changes in the veins, characterized by an uneven increase in their lumen with the formation of a protrusion of the wall due to dysfunction of their valve apparatus), when the surgical removal of all varicose veins (areas of altered veins) is practically impossible. In complex therapy, decylate is used in combination with surgical treatment, as well as in the postoperative period for sclerotherapy of “disconnected” varicose ducts of the saphenous veins (injections of drugs that cause closure of their lumen) into the altered sections of the veins.

Dosage and administration. Deilat treatment is carried out only with absolute confidence in the good patency of the deep and communicative (connecting large venous trunks with each other) veins of the lower extremities. Before conducting a course of venosclerosing therapy, it is necessary to make a trial introduction of decylate to identify possible individual intolerance. Before administering the drug, when the patient is in a standing position, one of the most distally located distal (further from the center) located varicose nodes (areas of altered veins characterized by an uneven increase in their lumen with the formation of a protrusion of the wall due to dysfunction of their valve apparatus) is selected, in which they are perpendicular to the skin surface a needle is inserted (without a syringe). As soon as blood begins to flow from the needle, the patient is laid on his back, and his leg is raised at an angle of 30-40 °. After the introduction of decylate, the injection site is pressed with a sterile gauze ball, and the needle is removed. The puncture site (puncture) is closed with a bandage, the leg remaining in the raised position is bandaged with an elastic bandage from the toes to the upper third of the thigh. To prevent a possible damaging effect of decylate on the endothelium (inner shell) of deep veins

with their subsequent thrombosis (blockage), patients should immediately walk for at least 2-3 hours immediately after injection of the drug.

If it is necessary to conduct a phased injection-sclerosing treatment, sclerosis of superficial veins begins from the lateral branches, and decylate is introduced last in the main venous trunk.

With moderate varicose veins and the presence of soft, easily collapsing nodes, a 1% solution of decylate is used, and in the presence of large nodes with thickened dense walls, a 3% solution of the drug. For one treatment session, the drug is administered in 2-6 points, 0.5-2 ml each.

In the presence of an extensive widespread varicose process, the injections of the decylate solution are repeated 2-10 times at intervals of 3-5 days. The maximum amount of the drug per treatment course is 6-30 ml of a% solution and 4-10 ml of a 3% solution.

Side effect. Decylate is well tolerated by patients, however, in some cases, the administration of the drug is accompanied by redness at the injection site, a burning sensation, soreness of sclerotic nodes (pathologically expanded, swollen sections of veins with low elasticity) and venous trunks. The indicated phenomena usually do not require special therapeutic measures and, as a rule, pass on their own within 3-4 days.

Due to the irritating effect of the solution, it is not allowed to enter the perivascular tissues (tissues surrounding the vessels).

Contraindications The main contraindication to venosclerosing therapy with decylate is obstruction of the deep veins of the lower leg and thigh. The drug is also contraindicated in concomitant acute thrombophlebitis (inflammation of the walls of the veins with their blockage), obliterating endarteritis (inflammation of the inner lining of the arteries of the extremities with a decrease in their lumen), phlebosclerosis (a disease of the veins, characterized by a decrease in their elasticity), general diseases, requiring bed rest, heart disease with decompensation (heart disease, characterized by a sharp decrease in its pumping function).

Release form. 1% and 3% solutions in 2 ml ampoules.

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

THROMBIN (Thrombinum)

Pharmachologic effect. Thrombin is a natural component of the blood coagulation system; it is formed in the body from prothrombin upon enzymatic activation of the latter by thromboplastin.

For use in medical practice, obtained from the blood plasma of donors.

Indications for use. A thrombin solution is used only locally to stop bleeding from small capillaries (the smallest vessels) and parenchymatous organs (internal organs / liver, kidney, etc. /) during cranial operations, operations on the liver, kidneys and other parenchymal organs; hemorrhages from the bone cavity, gums, etc., especially with Werlhof's disease (plural hemorrhages under the skin and / or mucous membranes due to a low platelet content in the blood), aplastic and hypoplastic anemia (a decrease in the level of red blood cells due to inhibition of the hematopoietic function of the bone marrow). When bleeding from large vessels, thrombin is not used.

Dosage and administration. Before use, observing the rules of asepticism (compliance with sterility), open the ampoule with thrombin and inject a sterile isotonic sodium chloride solution of room temperature into it with a sterile syringe. The amount of solution depends on the amount of thrombin contained in the ampoule and is indicated on the label. A solution of thrombin is impregnated with a sterile hemostatic sponge or a hemostatic collagen sponge or a sterile gauze swab, which is applied to a bleeding wound. A gauze swab is removed immediately after stopping the bleeding (if the wound is closed tightly) or during the next dressing (if the treatment is carried out in an open way).

Remove the swab from the wound carefully to avoid damage to the formed blood clots (blood clots). A hemostatic sponge soaked with thrombin can be left in the wound, as it subsequently resolves.

Contraindications Introduction to the vein and muscles is not allowed. Introducing into blood vessels can cause widespread thrombosis (the formation of blood vessel in a vessel) with a fatal outcome.

Release form. They are produced in glass vials or in ampoules with a capacity of 10 ml containing at least 125 activity units. The amount of the drug, activity is indicated on the vial or ampoule.

Storage conditions. In a dry place at a temperature of +2 to + 10 "C.

FIBRINOGEN (Fibrinogenum)

Pharmachologic effect. It is a natural component of blood. The transition of fibrinogen to fibrin, which occurs under the influence of thrombin, provides the final stage of the blood coagulation process - the formation of a clot. The fibrin gene used as a hemostatic (hemostatic) agent is obtained from the blood plasma of donors.

Indications for use. Fibrinogen is used for hypo- and afibrinogenemia (with a low content of fibrinogen in the blood and congenital absence of fibrinogen, accompanied by increased bleeding), bleeding in traumatological, surgical, oncological practice, massive bleeding in obstetric and gynecological practice (before. -cents, childbirth on the background of hypo- and afibrinogenemia, etc.) and other bleeding associated with a low content of fibrinogen in the blood.

For prophylactic purposes, fibrinogen is used in preparing patients with hypofibrinogenemia for surgery.

Dosage and administration. Fibrinogen solution is injected into a vein through a drip infusion system with a filter. The drug is dissolved ex tempore (before use) in water for injection, heated to a temperature of +25 to +35 ° C; the amount of water is indicated on the label (on the bottle). The solution should be used no later than 1 hour after its preparation. The dose of the drug depends on the indications and ranges from 0.8 to 8.0 g or more. Wed the dose usually stascha 2-4 g.

Contraindications Fibrinogen is contraindicated in pre-thrombotic conditions (conditions preceding clogging of a vessel with a blood clot), thrombosis (the formation of a blood clot in a vessel) of various etiologies (causes), increased blood coagulation, myocardial infarction.

Release form. In hermetically sealed glass bottles with a capacity of 250 or 500 ml, containing 1 g (1 + 0.2 g) or 2 g (1.9 + 0.1 g) of coagulated protein (fibrinogen), respectively. An infusion system with a filter is attached to the bottle. The drug should be dissolved within no more than 10 minutes in the amount of water indicated on the label heated to +25 or +35 ° C; the pH (indicator of the acid-base state) of the resulting solution is 6.5-7.4. The solution opalesces (scatters shine).

Storage conditions. At a temperature of +2 to +10 ° C in a dry, dark place. Storage of the drug at temperatures above +10 ° C causes denaturation (loss of specific activity) of fibrinogen.

SPONGE FIBRINIC ISOGENE (Spongia fibrinosa isogena)

Porous fibrin obtained from human blood plasma.

Pharmachologic effect. It has a hemostatic (hemostatic) effect, promotes tissue regeneration (restoration) and healing of wounds.

Indications for use. It is used topically for hemostasis (stopping bleeding) for injuries and surgical bleeding.

Dosage and administration. To stop bleeding, a sponge is placed on the wound surface until the bleeding stops completely. The sponge can be left in the wound, it gradually resolves.

Contraindications Contraindicated in purulent wound discharge, deep burns.

Release form. In glass bottles. Dry porous mass of white or cream color, size 2X2 * 1 or 6 ^ 2x1 cm.

Storage conditions. In a dry, dark place at a temperature of no higher than +25 ° C.

FIBRIC ISOGENE FILM (Membrana fibrinosa isogena)

Pharmachologic effect. Protein preparation from fibrinogen (one of the factors of blood coagulation) plasma of donated blood. Biologically active plastic material, which creates

favorable conditions for tissue regeneration (restoration) when applied to the wound surface and thereby contributes to the rapid healing of wounds, has an analgesic and hemostatic effect, protects the wound from mechanical damage and infection penetration.

Indications for use. In neurosurgical practice - to replace the defects of the dura mater. In the practice of general surgery, to prevent adhesions during various abdominal operations; for closing large scalp wounds (wounds with full or almost complete separation of an extensive flap of the skin) or skin defects resulting from traumatic injuries, burns, and also for the treatment of trophic ulcers (non-healing skin defects for a long time).

Dosage and administration. The film is applied to the wound, then the cellophane covering film is removed. When replacing the dura mater, the film is cut out according to the shape of the defect and laid with cellophane up directly onto the brain, then the cellophane is removed. For intestinal surgery, the film is placed in the form of a sleeve and fixed with a catgut.

Side effect. Not installed.

Contraindications It is not advisable to use with profuse purulent discharge from the wound, as well as with deep burns before separation of necrotic (dying) tissues.

Release form. It is produced by blood transfusion stations, delivered to medical institutions, 10-20 cm per pack.

Storage conditions. In the dark place at a temperature of no higher than +25 'C.

BLOOD DRUGS

Blood products are medical products derived from blood. Complex preparations, immunologically active (immunoglobulins) and hemostatic are isolated.

The complex effects include plasma and albumin solutions; they have simultaneously hemodynamic, anti-shock effect. The greatest effect is caused by freshly frozen plasma due to the almost complete preservation of its functions. Other types of plasma native (liquid), lyophilized (dry) significantly lose their healing properties in the manufacturing process, and their clinical use is less effective. Freshly frozen plasma is obtained by plasmapheresis (or centrifugation of whole blood with rapid subsequent freezing (in the first 12 hours from the time the blood was taken from the donor). It can be stored for up to 1 year at 125 and below. During this time, all blood coagulation factors are stored in it, anticoagulants, components of the fibrinolysis system. Immediately prior to transfusion, fresh-frozen thaw in water at t 35-37 (to accelerate thawing of the plasma, the plastic bag in which it is frozen can be kneaded in warm water by hand). plasma should be washed immediately after heating for the first hour in accordance with the attached instructions for use. Thawed fibrin may appear in thawed plasma, which does not prevent transfusion through standard plastic systems with filters. Significant turbidity, the presence of massive clots indicate about poor quality of plasma: in this case, it can not be transfused.

Repeated freezing and thawing of plasma is not allowed. Overfilled patients with freshly frozen plasma should be in the same group as the patient’s blood according to the AB0 system. In urgent cases, in the absence of a single-group plasma, transfusion of group A (II) plasma is allowed for patients with blood group 0 (I), plasma of group B (III) patients with blood group 0 (I) and plasma of group AB (IV) patients with any blood group ; a group compatibility test is not performed. Transfusions of freshly frozen plasma are indicated for thrombohemorrhagic syndrome, burn disease, purulent-septic processes, prolonged compression syndrome, as well as hemorrhagic diathesis due to a deficiency of plasma coagulation factors, including hemophilia A and B, massive blood loss (with blood loss of more than 25% of the volume, transfusion of freshly frozen plasma is combined with transfusion of red blood cells, better washed red blood cells) and others. Freshly frozen plasma is also used in patients with recurring thrombosis blood vessels, especially due to a deficiency of natural anticoagulants (antithrombin III, proteins C and S, etc.), against the background of heparin therapy and the use of fibrinolytic drugs (for example, streptokinase).

It is poured with rheologically active drugs (for example, rheopolyglucin) in case of lymphocytic disturbances. In hemophilia, transfusion of freshly frozen plasma is carried out in

the absence of concentrate VIII coagulation factor (cryoprecipitate) concentrate 300500 ml 34 times a day. In case of thrombohemorrhagic syndrome, the daily dose of freshly frozen plasma is 12 L or more; heparin is also administered dropwise in small doses (up to 20,000 units per day) and counter-cal in large quantities (up to 60,000 units per day).

Transfusion of freshly frozen plasma to several patients from one plastic bag or vial is prohibited; You can also not leave it for subsequent transfusions after depressurization of the plastic bag or bottle. Transfusion of freshly frozen plasma is contraindicated in patients who are sensitized to parenteral administration of the protein. To prevent pathological reactions, a biological test is performed, as with whole blood transfusion.

Albumin is released in the form of 5, 10 and 20% solution. Along with purified al-bumin, a protein preparation containing impurities of □- and нов-globulins is widely used. Thanks to the introduction of stabilizers, albumin solutions withstand pasteurization, which inactivates hepatitis viruses and HIV infection. Albumin has been shown for various types of shock, traumatic, surgical, burn, as well as for edema caused by violations of the protein composition of the blood, with violations of the synthesis of albumin in the liver and its large loss (for example, with cirrhosis, ascites, burns). Concentrated solutions of albumin are used in cases where it is necessary to limit the amount of fluid introduced into the body, for example, in case of traumatic brain injury, accompanied by cerebral edema, heart failure. Albumin (5% solution) should be used for blood loss, when it is necessary to normalize blood pressure. With massive bleeding, the administration of albumin should be combined with transfusions of red blood cells. Albumin in the form of a 10% solution is usually used in pediatric practice.

Plasma immunoglobulins secreted during blood fractionation constitute a group of immunological preparations that have specific activity against infectious diseases. In clinical practice, normal human immunoglobulin (gamma globulin) is most widely used. Specific immune preparations with targeted action against influenza, tick-borne encephalitis, tetanus, and others have a high therapeutic effect. Highly sensitive immunoglobulin is used in the treatment of idiopathic thrombocytopenic purpura. Immunoglobulin preparations are administered intramuscularly. Purified immunoglobulins suitable for intravenous administration are much more effective due to the fact that, once directly into the bloodstream, the protein is not cleaved by tissue proteases.

Hemostatic drugs include cryoprecipitate, prothrombin complex, fibrinogen. Cryoprecipitate contains in large quantities anti-hemophilic globulin (VIII coagulation factor) and von Willebrand factor, as well as fibrinogen, fibrin-stabilizing factor XIII and impurities of other proteins. The drugs are released in plastic bags or in bottles in frozen or dried form. They are used for hemophilia A, von Willebrand disease and some other types of bleeding.

For hemophilia B, hemorrhagic disease of newborns and an overdose of indirectly acting anticoagulants (pelentan, phenylin), use the prothrombin complex (PPSB, or CSF) complex II, VII, IX and X of blood coagulation factors; in its absence, freshly frozen plasma is administered intravenously.

Fibrinogen has limited use: it is indicated for bleeding caused by fibrinogen deficiency. In case of hypofibrinogenemia due to thrombohemorrhagic syndrome, its replacement, like other coagulation factors, should be carried out with freshly frozen plasma, since purified fibrinogen is not balanced with natural anticoagulants and may undergo coagulation in the bloodstream of the patient, which increases pulmonary and renal failure freshly frozen plasma contains enough fibrinogen to make up for its deficiency in the body.

In addition to intravenous drugs, there is a group of hemostatic agents that are applied topically to stop external bleeding that occurs during surgery. These include thrombin, fibrin film, hemostatic sponge, biological antiseptic swab, etc. The main active principle of these agents is thrombin, which causes the formation of a clot as a result of the conversion of fibrinogen K into fibrin, which thromboses the lumen of blood vessels at the site of bleeding. Especially effective is the use of drugs for hemostasis on the damaged surface of parenchymal organs.

Due to their mechanical properties, fibrin films and sponges are used not only to stop bleeding, but also as plastic material, for example, in the treatment of burn disease, trophic ulcers. In neurosurgical practice, fibrin films are successfully used to replace the deficiency of the dura mater. Isogenic films can be left during surgical intervention in the patient's body, which is impossible with the use of a heterogeneous preparation due to the threat of sensitization of the body by a foreign protein.

Hemostatic drugs

- Agemfil A (Lyophilisate for solution for injection)
- Agemfil B (Lyophilisate for solution for injection)
- Aimafiks (Lyophilisate for solution for infusion)
- Amben (Solution for intravenous administration)
- Amben (substance powder)
- Aminocaproic acid (solution for intravenous administration)
- Aminocaproic acid (Solution for infusion)
- Aminocaproic acid (substance-powder)
- Anti-hemophilic human factor-M (AHF-M) (Lyophilisate for solution for intravenous administration)
- Aprotex (Solution for infusion)
- Aerus (metered-dose aerosol for inhalation)
- Bebulin TIM 4 (Lyophilisate for solution for intravenous administration)
- Benefix (Lyophilisate for solution for injection)
- Vikasol (Solution for intramuscular administration)
- Vikasol (powder substance)
- Vikasol (oral tablets)
- Vilate (Lyophilisate for solution for infusion)
- Hemofil M (Lyophilisate for solution for injection)
- Gumbiks (Solution for injection)
- Gumbix (oral tablets)
- Dicinon (Solution for intravenous and intramuscular administration)
- Dicinon (oral tablets)
- Zhelplastan (Powder cutaneous)
- Immunate (Lyophilisate for solution for intravenous administration)
- Immunin (Lyophilisate for solution for intravenous administration)
- Ingitrile (Lyophilisate for solution for intravenous administration)
- Cogenate FS (Lyophilisate for solution for injection)
- LongEyt (Lyophilisate for solution for injection)
- Menadione sodium bisulfite (substance powder)
- Mononine (Lyophilisate for solution for infusion)
- NovoSeven (Lyophilisate for solution for intravenous administration)
- Octanine (Lyophilisate for solution for subcutaneous administration)
- Octanine F (Lyophilisate for solution for subcutaneous administration)
- Pamba (Solution for injection)
- Pamba (oral tablets)
- Prothromplex 600 (Lyophilisate for solution for infusion)
- Revoleid (oral tablets)
- Recombinant (Lyophilisate for solution for intravenous administration)
- Replenin-VF (Lyophilisate for solution for intravenous administration)
- Respicam (Solution for infusion)
- Refacto AF (Lyophilisate for solution for intravenous administration)
- Tranexam (Solution for intravenous administration)
- Tranexam (oral tablets)
- Transamcha (Solution for injection)

• Transamcha (oral tablets)
• Traskolan (Solution for infusion)
• Feiba (Lyophilisate for solution for infusion)
• Hemate P (Lyophilisate for solution for infusion)
• Exacil (Solution for injection)
• Exacil (oral solution)
• Exacil (oral tablets)
• Emoklot D.I. (Lyophilisate for solution for infusion)
• Ethamsylate (Solution for intravenous and intramuscular administration)
• Ethamsylate-Ferein (oral tablets)

The purpose of the lesson.

To learn:

A. Physiology of blood systems providing a normal liquid state of blood.

1. Coagulation.
2. Anticoagulant.
3. Fibrinolytic.

The hemostatic system includes three closely related processes:

1) cell primary hemostasis;
2) plasma (secondary) hemostasis;
3) fibrinolysis.

B. Classification of hemostatic drugs (procoagulants)

1. Direct coagulants:

a) hemostatic sponge, sponge and fibrin isogenic film, etc.
b) calcium salts (chloride, gluconate),

This group applies topically.

2. Indirect hemostatics affecting the various stages of hemostasis:

1) Heparin antagonists (protamine sulfate).
2) Serotonin adipate, as an activator of cell hemostasis
3) Activators of plasma hemostasis (vicasol, phytomenadion, etc.).
4) Inhibitors of fibrinolysis (aminocaproic acid, pamba, transamcha, kontrikal, gordoks, etc.).

B. Classification of antithrombotic agents

1. Antiplatelet agents

I. Inhibition of thromboxane system activity

1. Decreased thromboxane synthesis

but. Cyclooxygenase inhibitors (acetylsalicylic acid)
b. Thromboxane synthetase inhibitors (dazoxyben)

2. Block. thromboxane receptors *
3. Substances of mixed action (ridogrel)

II. Increased activity of the prostacyclin system

/. Prostacyclin receptor stimulating agents (epopro-stenol)

III. Drugs that inhibit the binding of fibrinogen to thrombo-booster glycoprotein receptors (GP llb / IIIa)

A number of thromboxane receptor blockers were obtained, which are at the research stage (daltroban).

/. Glycoprotein receptor antagonists (abciximab, thyro-fiban)

2. Means blocking purine platelet receptors and preventing the stimulating effect of ADP on them (glycoprotein receptors are not activated at the same time) (ticlopidine, clopidogrel)

IV. Means of various types of action (dipyridamole, antoran).

2. Anticoagulants:

2.1. Direct action.

2.1.1. Unfractionated heparin: • Heparin.

2.1.2. Low molecular weight heparins: • Dalteparin (Fragmin). • Nadropaprine (Fraxiparin) • Certoparin (Sandoparin). • Tinzaparin (Logiparin). • Enoxaparin (Clexane).

2.1.3. Heparinoids (parenteral Xa factor inhibitors): • Fondaparinux (Arikstra). • Idraparinux.

2.1.4. Oral Xa factor inhibitors: • Rivaroxaban (Xarelto). • Apixaban.

2.1.5. Hirudin and hirudinoids: • Hirudin (Lepirudin). • Bivalirudin (Angiomax, Angiox).

2.2. Indirect action.

2.2.1. Coumarin derivatives:

2.2.1.1. Monocoumarins. • Warfarin (Coumadin). • Fenprokumon (Mar-Kumar). • Acenocumarol (Sincumar).

2.2.1.2. Dicumarines. • Bishydroxycumarol (Dicumarin). • Ethyl biscum acetate (neodicumarin).

2.2.2. Indandion derivatives: • Phenindione (Phenylinum). • Difenadion (Dipaxinum).

3. Fibrinolytics

Direct action - fibrinolysin

Indirect fibrinolytics:

I generation:

• Urokinase (Urokidan).

• Streptokinase (Streptoliasis).

II generation:

• Acetylated plasminogen-streptokinase activator complex (Anistreplase, APSAK).

• Alteplase (Aktilize).

• Prourokinase (Purolyase).

III generation (mutant):

• Tenecteplase (Metalysis).

• Reteplase (Rapilizin).

Control questions.

1. Composition and physiology of blood: plasma, red blood cells, white blood cells and platelets.

2. Medicines affecting blood coagulation:

o antithrombotic: reducing coagulation (anticoagulants); increased fibrinolysis (fibrinolytic); antiplatelet agents;

o hemostatic: increasing coagulation (procoagulants); fibrinolysis inhibitors; thrombogenic;

- affecting the volume and composition of blood (blood and plasma substituting).

Enumeration of practical work.

Homework.

1. To study the etiology and pathogenesis of hemophilia, DIC

2. To study the main directions of treatment of these diseases.

4. Be able to provide first aid to a patient with acute blood loss.

Control of the intermediate level of knowledge.

The solution of situational tasks:

1. A boy, 12 years old, a year ago was operated on for a combined mitral heart disease: the mitral valve was prosthetized. In order to prevent thromboembolic complications, he constantly receives an indirect anticoagulant - syncumar. The prothrombin index is stably kept at the level of 50-55%. In connection with the activation of the rheumatic process, benzylpenicillin was administered intramuscularly at 1,000,000 units 8 times a day and sodium diclofenac was administered orally at 0.025 g three times a day. After 7 days, the baby developed a black tarry feces. The prothrombin index decreased to 12%.

Explain the cause and mechanism of the developed complication. Give suggestions for changing pharmacotherapy to correct a complication.

2. A patient, 19 years old, with acute right-sided lower lobar bronchopneumonia, after determining the sensitivity of microflora of sputum culture, kanamycin was administered intramuscularly at 20 mg / kg of weight 2 times a day. At the same time, in order to improve microcirculation in the focus of inflammation, the patient was administered 5000 units of heparin per day subcutaneously, under the control of blood coagulation time. Despite the ongoing therapy and the sensitivity of the flora to the antibiotic, the clinical picture did not improve within 4 days.

Explain the possible reason for the lack of effectiveness of pharmacotherapy. What are your recommendations for patient management?

3. A woman in labor for 21 years, gave birth to a full-term baby on time. From the anamnesis, it was revealed that the mother suffers from pulmonary tuberculosis, recently takes rifam-pitsin, isoniazid and PASK. A day after the birth, when examining the newborn, “bruises” were revealed on the trunk and upper limbs.

Explain the situation. Your further tactics.

4. At the patient of 15 years, after the transferred flu there appeared hemorrhagic rashes on the legs - symmetrical, some at the stage of remission with skin pigmentation.

Your preliminary diagnosis. Prescribe complex therapy.

5. A 54-year-old patient with diabetes for 5 years developed paresthesia in the feet, pain in the calf muscles. An objective examination: the pulse on the dorsal arteries of the feet is weakened.

What complication of diabetes have you encountered? Prescribe complex therapy.

6. The doctor on call is called to the patient with myocardial infarction on the 10th day of the illness. Complains of an intense increase in pain in the right lower limb.

Your guess about the cause of the pain. What objective symptoms to confirm your assumption? Justify the treatment of the patient.

7. A 37-year-old patient who had the flu developed attacks of severe shortness of breath with cyanosis, tachycardia, and decreased AKD. Clotted blood does not change shape when the tube is tilted. A clot formed quickly.

Your suspected diagnosis. What is the name of the condition characterized by these changes in blood? Provide a patient treatment plan.

8. A patient, 45 years old, has been suffering from hormone-dependent bronchial asthma for 8 years. Takes prednisone - daily - 2.5-5 mg. During the next outpatient treatment, he complains of nosebleeds that have occurred recently. Blood pressure is normal.

What hemostatic is necessary for the patient?

9. When a 61-year-old patient enters the cardiopulmonary resuscitation department with acute myocardial infarction, an increase in pain and a worsening of the clinic are observed. What drug is necessary to introduce the patient in the first place, in order to influence the processes of thrombosis?

10. The patient suffers from chronic viral hepatitis B. During the control examination revealed moderate anemia, there was a mention of the patient to change the color of the stool (to black) and also a single vomiting of “coffee grounds”. What hemostasis is necessary for the patient?

TESTS

1. A woman, 23 years old, complains of an increase in body temperature to 37.4 ° C, hemorrhagic rashes on the lower extremities, lower back pain, the appearance of red urine. Ill 3 days ago after hypothermia. Objectively: the skin is pale, a small hemorrhagic symmetrical rash is observed on the surface of the lower leg and thighs. Heart rate - 90 in 1 min. HELL - 115/90 mm RT. Art. Pasternatsky’s symptom is weakly positive on both sides. In the blood: l. - 9.6 · 109 / l, tr. - 115 · 109 / l, ESR - 31 mm / h. Urinalysis: protein 0.33 g / l, er. altered - 30-40 in the field of view, white blood cells - 5-8 in the field of view. Which of the following drugs is pathogenetically substantiated for treatment in this case?

A. Rutin.

B. Calcium gluconate.

C. Ascorbic acid.

D. Prednisone.

E. Vikasol.

2. A man, 48 years old, complains of severe baking pain behind the sternum, which gives to the left hand. The pain began 3 hours ago after psycho-emotional stress. Objectively: vesicular respiration is heard in the lungs, BH 18 per min. Heart sounds are muffled, heart rate corresponds to the value of the pulse and is 86 per minute, blood pressure - 130/80 mm RT. On the ECG: in the chest leads, the ST segment rises 3-4 mm above the contour, high T waves. Myocardial infarction is diagnosed. What is the most appropriate treatment tactic at the moment?

A. Anticoagulant therapy ..

B. Thrombolytic therapy.

C. Coronary artery bypass grafting.

D. Balloon angioplasty.

E. Antiplatelet therapy.

3. A patient, 45 years old, 3 months ago suffered a large-focal myocardial infarction; complains of periodic palpitations and shortness of breath with accelerated walking. Heart sounds are somewhat muffled. HELL - 170/90 mm RT. Art. Liver at the edge of the costal arch, no peripheral edema. On the ECG: heart rate - 94 per minute, cicatricial changes in the posterior wall of the left ventricle. There is no concomitant pathology. What combination of drugs can be prescribed for the most effective prevention of recurrent myocardial infarction?

A. Aspirin + Nitrong

B. Aspecard + Concor

S. Curantil + Corinfar

D. Theonicol + nitrosorbide

E. Tiklid + nitrong

4. A patient, 45 years old, 60 minutes after the onset of acute transmural anterior myocardial infarction, was taken to the intensive care and resuscitation unit. The condition of the patient is moderate, clear consciousness, pronounced cyanosis of the lips. Heart sounds are deaf, rhythmic. Pulse - 98 per minute. Breathing is normal, BH - 19 per min. The liver is not increased. No swelling. Which of the following is the most correct?

A. Heparin + aspirin intravenously.

B. Antiarrhythmic drugs + intravenous heparin.

C. Streptokinase.

D. Nitrates + heparin.

E. Glucose-potassium-insulin mixture.

5. A patient with myocardial infarction was given an intravenous anticoagulant every 6 hours. A few days later he had bleeding of the gums, nose, and red blood cells appeared in the urine. What drug was administered to the patient?

A. Thrombin

B. Neodicumarin

C. Vikasol

D. Heparin

E. Calcium gluconate

6. A woman during labor, complicated by premature detachment of the placenta, started massive uterine fibrinolytic bleeding. What drug should be prescribed to her?

A. Aminocaproic acid

B. Vikasol

C. Fibrinogen

D. Calcium chloride

E. Hemostatic Sponge

7. In a patient who takes neodicumarin in connection with thrombophlebitis, intestinal bleeding has opened. What drug should be prescribed?

A. Dichlothiazide

B. Protamine sulfate

C. Acetylsalicylic acid

D. Trental

E. Vikasol

8. In the postoperative period after heart bypass surgery, the patient was prescribed aspirin to improve the rheological properties of the blood. According to what scheme is it appropriate to prescribe aspirin for these purposes?

A. 0.5 g 2 times a week

B. 0.5 g 3 times a week

C. 1 g 3 times a day

D. 0.325 g once a day

E. 1 g 4 times a day

9. The doctor prescribed the patient the drug streptokinase, which has serious undesirable effects. What does not relate to the characteristic adverse effects of this drug?

A. Hematuria

B. Thrombosis

C. Nasal hemorrhages

D. Allergic reactions

E. Pyrogenic reactions

10. An agent that increases the formation of fibrin thrombi is:

A. Epsilon-aminocaproic acid

B. Contrical

C. Clopidrogel

D. Neodicumarin

E. Vikasol

11. Select the wrong one from the presented thrombin and fibrinogen clauses:

A. Thrombin and fibrinogen are obtained from donated blood

B. Thrombin is prescribed intravenously

C. Fibrinogen is prescribed topically and intravenously

D. Fibrinogen is used for premature placental abruption, DIC, stage II-III syndrome, after surgery on the prostate and lungs

E. Fibrinogen is used for hemophilia (form A)

12. To funds that inhibit the fibrinolysis system, do not include:

A. Epsilon-aminocaproic acid

B. Paraaminomethylbenzoic acid

S. Pantripin

D. Pentoxifylline

E. Contrical

13. The effects of epsilon-aminocaproic acid do not include:

A. Inhibition of plasminogen and plasmin

B. Inhibition of kinin formation

C. Inhibition of phospholipase A2

D. Inhibition of complement system

E. Hemostatic effect

14. Select the wrong one from the provisions on aspirin and ticlide:

A. These drugs are more effective in patients with venous and not with arterial thrombosis.

B. Tiklid in antiplatelet action surpasses aspirin

C. To obtain antiplatelet action, aspirin should be prescribed in small doses (50 - 100 mg / day)

D. Tiklid is not recommended to be combined with other antiplatelet agents and with anticoagulants

E. The mechanism of action of ticlide is fundamentally different from the mechanism of action of aspirin

15. If aspirin is contraindicated in patients with thrombosis of coronary vessels, brain vessels and lower extremities, then it can be replaced:

A. Paracetamol, ibuprofen, nimesulide

B. Clopidrogel, dipyridamole, pentoxifylline, ticlopidine

C. Etamsylate, hadroxone, calcium gluconate

D. Piracetam, aminalon, pyriditol

E. Depakine, carbamazepine, Lamictal.

16. Choose a drug that does not prevent the formation of fibrin clots:

A. Heparin

B. Fraxiparin

C. Sinkumar

D. Gordox

E. Warfarin

17. The patient was hospitalized with a diagnosis of renal stone disease, an attack of renal colic. Choose an ambulance in this case.

A. Furosemide

B. Analgin

C. Paracetamol

D. Promedol

E. Countrical

18. Patient 45 for rheumatoid arthritis was prescribed a medication. After 3 weeks, the condition improved, pain in the joints and swelling decreased, but there were pains in the epigastrium, black stools, swelling, blood pressure increased. What drug did the patient receive?

1. Analgin

2. Paracetamol

3. Baralgin

4. Aspirin

5. Buformin

19. The child had subcutaneous hemorrhages. The appointment of a synthetic analogue of vitamin K (Vikasol) gave a positive effect. In the synthesis of which protein of the blood coagulation system does this drug take part in?

A. Prothrombin.

B. Antihemophilic globulin.

C. Factor of Hageman.

D. Fibrinogen.

E. Collagen.

20. A patient with a myocardial infarction was given a direct-acting anticoagulant intravenously. What drug was administered to the patient?

A. Thrombin.

B. Neodicumarin.

C. Vikasol.

D. Heparin.

E. Calcium gluconate.

Recommended literature:
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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.

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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 THE BASIC GROUPS OF ANTIMOMROBIC DRUGS IN UROLOGY

Relevance of the topic.

Urinary tract infection (UTI) is an inflammatory process, mainly of bacterial origin, which can develop in various anatomical areas, starting from the perinephral fascia and ending with the external opening of the urethra.

UTI is one of the most common human bacterial infections. The prevalence of urinary infections (MI) is about 1,000 cases per 100,000 population per year. About 26–36 million cases of acute cystitis (OC) are recorded annually. It can be assumed that the true prevalence of the disease is much higher, since many patients do not go to the doctor and are treated themselves. Men are more likely to suffer from cystitis in old age, women in young. Only in the elderly and senile age (by 70–75 years) the incidence of men and women becomes approximately the same. Acute pyelonephritis (OP) is the most common kidney disease in all age groups. In general, women predominate among patients with OP. The frequency of occurrence of OP is much lower than that of OC, and according to calculated data it amounts to 0.9–1.3 million cases annually.

Motivational characteristic of the topic.

The problem of pyelonephritis is relevant and is in the center of attention of modern recommendations for antibiotic therapy of urological infections. Every year, around 150 million cases of urinary tract infections (UTIs) in men and women of all ages are recorded worldwide, with more than 100 thousand cases of UTIs (most of them pyelonephritis) requiring hospitalization, of which about 40% are catheters associated. Changes in the biological properties of pathogens of nosocomial infections under the influence of antibiotics leads to the development of resistant strains.

Currently, destructive forms of acute non-obstructive pyelonephritis, which in some cases end with nephrectomy, are more and more common. The incidence of ascending pyelonephritis among young women of working age is significantly higher in the presence of sexually transmitted infections (STIs).

In 2009, the Practical Recommendations of the European Association of Urology for the treatment of urinary tract infections were published. The recommendations are based on the principles of evidence-based medicine, which provides information on the classification, diagnosis, etiology, antibiotic therapy and prevention of complicated and uncomplicated MI of different localization. Also discussed are the tactics of treating MI in children, patients with renal failure, immunosuppression, a permanent urinary catheter, with urosepsis, the use of antibiotics for perioperative prophylaxis. However, when adapting these recommendations to practical use, it is necessary to take into account regional data on the etiology and resistance of the main pathogens that cause MI. Based on practical clinical findings, MI and male genital tract infections are classified according to the prevailing clinical symptoms.

CLASSIFICATION OF UTI (ACCORDING TO THE OPINION OF SPECIALISTS OF THE EUROPEAN ASSOCIATION OF UROLOGISTS, 2009)

By localization, UTIs are divided into lesions:

upper urinary tract

lower urinary tract

In the first case, the inflammatory process leads to pyelonephritis (acute and chronic), in the second - to acute cystitis and urethritis.

By the nature of the current, they distinguish:

uncomplicated UTI

complicated UTI

Uncomplicated infections include acute urethritis, cystitis, and acute pyelonephritis in non-pregnant women, without obstructive uropathies and neurological dysfunctions in the absence of functional or anatomical disorders of the genitourinary tract, intercurrent diseases. The complicated course of the inflammatory process in the urinary tract, in particular acute

pyelonephritis, occurs in patients with various obstructive uropathies, against the background of instrumental (invasive) methods of examination and treatment, in patients with serious concomitant diseases (diabetes mellitus, neutropenia). They can lead to the development of severe purulent-septic complications, up to bacteremia and sepsis.

At the place of infection, they share:

community-acquired

nosocomial

According to the patient's condition - the presence or absence of symptoms,

By the nature of the infection - recurrent, etc.

From a clinical point of view, it is important to differentiate uncomplicated and complicated MI, because they differ in the prognosis and tactics of antibiotic therapy. In uncomplicated infections, the clinical effect and eradication of the pathogen are achieved, as a rule, with short courses of antibacterial therapy. In addition, with uncomplicated infections, it is not necessary to routinely conduct microbiological diagnostics and laboratory monitoring of cure. Complicated MIs are associated with the presence of factors predisposing to their development, the long-term preservation of symptoms, the occurrence of complications and the unsuccessfulness of antibiotic therapy (Table 1).

To factors associated with complicated MI,

relate:

- male gender;
- elderly age;
- an infection that developed in a hospital;
- pregnancy;
- the presence of a urinary catheter;
- Recently undergone surgery on the organs of the genitourinary system;
- functional or anatomical disorders of the urinary tract;
- recent use of antibiotics;
- preservation of symptoms for more than 7 days;
- diabetes;
- immunosuppression.

t is also advisable to isolate asymptomatic bacteriuria, which is often detected in certain categories of patients (elderly, pregnant women, the presence of a constant urinary catheter, patients with diabetes mellitus), and requires a decision on the advisability of antibiotic therapy. Asymptomatic bacteriuria is rarely associated with adverse effects and non-prescription of antibiotics is not associated with an increased risk of developing infections in most patients.

The traditional quantitative criterion for the diagnosis of acute urinary tract infection of 105 colony forming units (CFU) of microorganisms in an average portion of urine has been revised in recent years

ETIOLOGY

The Enterobacteriaceae family is one of the most significant in the etiological structure of infectious diseases of various locations of the genitourinary tract, as well as nosocomial infection among opportunistic microorganisms.

In the overwhelming majority of cases, primary uncomplicated urinary tract infections (UTIs) are caused by Escherichia coli - according to various authors, from 80 to 90%, about 3-5% are coagulase-negative staphylococci (CNS), the remaining few percent are distributed among all other pathogens (Klebsiella, Protei, Serratia, etc.). More than 95% of BAT are caused by a single microorganism.

In recurrent and hospital infections, the distribution of pathogens is fundamentally different, due to the use of broad-spectrum antibacterial drugs and the introduction of a large arsenal of invasive diagnostic and therapeutic procedures.

In the etiological structure of recurrent and hospital MI, the percentage of gram-positive flora increased sharply: staphylococci (including MRSA up to 12%), enterococcus (up to 5%) occupies an important place with its extremely specific sensitivity spectrum that does not fall into almost any pattern empirical therapy.

ANTIBACTERIAL MEANS

The choice of antibacterial drugs for the treatment of MI in modern conditions is determined by the following factors: - local data on the sensitivity of the main pathogens;

- pharmacokinetic characteristics;

- localization of infection;

- safety and tolerability of drugs;

- proven in clinical trials the effectiveness of the antibiotic.

For the treatment of MI, beta-lactams, fluoroquinolones, nitrofuranes, phosphomycin trometamol, co-trimoxazole, aminoglycosides, glycopeptides are traditionally used.

Antimicrobial resistance is currently one of the main criteria for empirical choice of MI therapy. World studies in recent years have convincingly shown an increase in the number of resistant microorganisms that cause MI. This trend is noted both with complicated MI and with uncomplicated MI. In Russia, according to the UTIAP-3 multicenter study on UTI resistance to antimicrobials, in patients with outpatient BAT, E. coli has a high level of resistance to ampicillin (33.1%,) and co-trimoxazole (19.4%). Thus, at present, these drugs cannot be considered as first-line drugs for the treatment of BAT in adults. A relatively high level of resistance to non-fluorinated quinolones, 8.9%, was also revealed. Fluorinated quinolones, oral cephalosporins, nitrofurantoin, amoxicillin / clavulanate were highly active.

From the pharmacokinetic point of view, in MI, antibacterial drugs should be prescribed that, when taken 1-2 times a day, ensure high concentrations (above the minimum inhibitory concentration (MIC)) in both urine and the renal parenchyma (Table 3). Drugs that are rapidly excreted can have a lower therapeutic effect compared to those that are stored for a long time in high concentration in the urine. For example, the short half-life of most beta-lactams is one of the reasons for the low effectiveness in the treatment of short courses.

Acute uncomplicated cystitis in non-pregnant women

Cystitis is an infectious and inflammatory process of the bladder wall, localized mainly in the mucous membrane. Although acute cystitis is characterized by a favorable prognosis and a high level of spontaneous recovery, controlled studies have shown the advantage of antibiotics compared with placebo, both in clinical and bacteriological efficacy and the speed of termination of symptoms of the disease

Acute uncomplicated pyelonephritis in pregnant women

Pyelonephritis is a non-specific infectious and inflammatory process characterized by a simultaneous or sequential lesion of the pyelocaliceal system and renal parenchyma (mainly interstitial tissue).Recurrent infections

Recurrent urinary tract infection (RIMP) is defined as 2 or more episodes of acute infection within 6 months or 3 or more exacerbations during the year. It is now known that 25–40% of women experience a relapse of cystitis after the first episode.

With RIMP, various prophylactic methods have been proposed, including antibiotic coprophylaxis, emptying the bladder after intercourse. With regard to anti-biotic prophylaxis, at present, most experts believe that regular antibiotic therapy is necessary before bedtime or after sexual intercourse. The period of prophylactic use of antibiotics is from 6 to 12 months. The clinical effectiveness of the prophylactic use of antibiotics is shown in controlled studies for fluoroquinolones, nitrofurantoin, co-trimoxazole, cefalexin, cefaclor, trimethorime

Recently, it has become known that biofilms can be the cause of recurrent urinary infection. With the introduction of a confocal laser microscope in bacteriological practice in the 1990s, it became possible to study the ultrastructure of living biofilms. Biofilms are highly organized communities of bacteria united by complex intercellular bonds and protected by the matrix produced by them. Such communities are formed both on the surfaces of artificial materials of various origins (urethral catheters, drainages, stents, etc.), but the formation of communities within the urothelium cell — intracellular bacterial communities (VBS) is also possible.

Uropathogenic E. coli penetrate into the epithelial cells of the bladder wall and form a biofilm inside them. Growing bacteria colonies surrounded by a bio-film matrix form clusters in the bladder wall in the form of “cocoons” protruding into its lumen. From time to time, “cocoons” break and bacteria, falling into the urine, cause RIMP.

A distinctive feature of these microorganisms is their complete refractoriness to 3–10-day courses of antimicrobial therapy (limited penetration of antimicrobial substances into the biofilm, AB inactivation inside the matrix, microorganisms are in biofilms in different phases of development).

In postmenopausal women, antibiotics play a lesser role than in young women. They have a hormonal disorder with the development of hypoestrogenemia.

Hypoestrogenemia leads to atrophy of urothelium cells and a decrease in the production of muco-polysaccharide (protective) layer. The periurethral and intravaginal use of hormonal creams (or suppositories) containing estrogens at night every day for a week, then for a week every other day, followed by 2 times a week for several months (up to a year), significantly reduces the frequency of exacerbation of UTI and should be

recommended before the prophylactic use of AB drugs.

Asymptomatic Bacteriuria

By “asymptomatic bacteriuria” or asymptomatic urinary tract infection is meant the isolation of a certain amount of bacteria (105 CFU / ml) from a properly collected urine test obtained from people who do not have symptoms or signs of a urinary tract infection. Asymptomatic bacteriuria is a microbiological diagnosis, which is based on a study of urine collected with maximum sterility and delivered to the laboratory in the shortest possible time, which allows to limit bacterial growth to the greatest extent. Asymptomatic bacteriuria is often detected in certain categories of patients (elderly, pregnant women, the presence of a constant urinary catheter, patients with diabetes mellitus) and requires a decision on the advisability of antibiotic therapy. Further examination and antibiotic therapy for asymptomatic bacteriuria in the following patient categories is not recommended:

non-pregnant women before menopause;

- women with diabetes;

- elderly people living at home;

- elderly people in nursing homes;

- patients with spinal cord injuries;

- patients with a permanent urinary catheter.

Screening for bacteriuria and antibiotic therapy is recommended only in three situations:

- pregnant women;

- before transurethral resection of the prostate gland;

- before other traumatic urological interventions.

In the last two cases, antibiotics should be prescribed shortly before surgery - usually 1-3 days before. Perhaps the use of fluoroquinolones or nitrofurans.

In pregnant women, in case of asymptomatic bacteriuria, a 5–7-day course of therapy with one of the following antibacterial drugs is used: cefixime (400 mg / day), ceftibuten (400 mg / day), nitrofurantoin (400 mg / day), furazidine (300 mg / day), furamag (150 mg / day). A control bacteriological examination of urine should be carried out 1-4 weeks after treatment and again before childbirth.

COMPLICATED URINARY INFECTIONS

The main difference between complicated UTIs is the high recurrence rate and the difficulty of conducting effective antimicrobial therapy, which is due to:

- a wider spectrum of pathogens (the etiological role of E. coli decreases to 60–70%, while the proportion of Pseudomonas aeruginosa, Proteus, enterobacter, acinetobacter, Klebsiella, gram-positive cocci flora increases);

- a higher frequency of release of resistant forms of bacteria (polyresistant strains are often found);

- a high risk of complications.

Currently, patients with complicated MI are usually divided into two groups:

- patients whose risk factors for the development of complicated UTI can be eliminated during treatment (for example, removal of calculi, urethral catheter, etc.) initially, antibiotic therapy of an acute episode or exacerbation of complicated UTI is given to such patients, and then measures aimed at eliminating complicating factor (rapid restoration of urine passage, removal of catheters, kidney stones, etc.);

- patients in whom these factors cannot be completely eliminated (for example, neurogenic bladder, some abnormalities in the development of the kidneys, permanent catheter, calculus fragments). In such patients, the main goal of antibiotic therapy is to stop the clinical manifestations of UTI, to prevent the development of complications and damage to the renal parenchyma.

Complicated cystitis.

In case of complicated bladder infection, treatment with short courses, and even more with one dose of the drug, is contraindicated. Long courses of antimicrobial therapy are prescribed - from 7 to 14 days. Drugs of choice: oral fluoroquinolones (levofloxacin, norfloxacin, ofloxacin,

pefloxacin, ciprofloxacin), amoxicillin / clavulanate, nitrofurantoin, co-trimoxazole (in regions where the resistance level of E. coli is less than 10%).

Complicated pyelonephritis.

In the treatment of complicated pyelonephritis, the duration of therapy is at least 14 days. Drugs of choice: aminoglycosides (AH), fluoroquinolones, inhibitor-protected aminopenicillins, third-generation CS with anti-Pseudomonas activity, carbapenems + AH, with the release of Candida spp. - antifungal drugs (fluconazole, amphotericin B). Treatment begins with parenteral administration of antibiotics, then, 3-4 days after normalization of body temperature, they switch to oral administration of antibacterial drugs.

With apostematous pyelonephritis, kidney abscess, the choice of antimicrobial therapy depends on the location of the purulent focus). The duration of therapy is 4-6 weeks, determined by the clinical and laboratory picture.

PERIOPERATIVE ANTIBIOTIC PROPHYLAXIS

The main goal of antibiotic prophylaxis in urology is the prevention of infectious complications after diagnostic and therapeutic interventival

Classification of tubulointerstitial diseases (WHO, 1985)

1. Acute infectious tubulointerstitial nephritis - a classic acute bacterial pyelonephritis.

2. Acute interstitial nephritis in systemic infections.

3. Chronic interstitial pyelonephritis.

4. Specific infections.

For use in clinical practice, the classification of pyelonephritis proposed by N.A. remains relevant. Lopatkin in 1974, as it allows you to answer 2 main questions that determine the results of treatment and the outcome of the disease: primary or secondary pyelonephritis, as well as establish the stage of the disease (serous or purulent).

Pyelonephritis is a non-specific infectious inflammatory disease of the kidney, in which the renal pelvis, calyx and kidney parenchyma are involved in the process with a primary lesion of its interstitial tissue. In the final stage of the disease, the process spreads to the blood vessels and glomeruli. Pyelitis is currently considered not as an independent disease, but as one of the phases of the development of pyelonephritis, in which the pyelocaliceal system is affected. The pelvis, being part of the kidney, cannot be exposed to inflammation in isolation, which explains the conditionality of the allocation of this group of diseases. Numerous observations have shown that for every week of stay in the clinic, approximately 10% of patients acquire a hospital strain that is released into the external environment by patients who are long in the hospital. Urinary infections of the urinary tract (GIMVP) occupy the 1st place in the world (29–44%) among all types of hospital-acquired infections.

The predominant pathogens, especially in the first episode of the disease, are the Enterobacteriaceae family, mainly E. Coli (60–70%). A repeated episode of the disease reveals a wide range of microorganisms with a high prevalence of antibiotic-resistant strains (both community-acquired and nosocomial - P. aeruginosa, K. pneumoniae, Acinetobacter). The spectrum of GIMVP pathogens can vary in different medical institutions. In patients with urolithiasis (ICD), the main pathogens are urease-producing microorganisms (82%). The treatment failure rate is high with the impossibility of complete elimination of microorganisms

(ICD, recurring stone formation, the presence of catheters, stents, etc.). The change in the etiological structure of the causative agents of acute pyelonephritis is largely due to the widespread introduction into clinical practice of endoscopic diagnostic and treatment methods, ending with the provision of drainage in the organs of the urinary system, which become the input of the infection. According to our clinic, the incidence of STIs in patients with pyelonephritis is 83%, and in patients with recurrent cystitis - 72%. Based on the results of the experiment, we can talk about the undoubted role of STIs in the etiology of pyelonephritis. It was proved that infection of the upper urinary tract of animals with Ureaplasma urealiticum or Chlamydia trachomatis (when they are isolated) leads to the development of a primary chronic inflammatory process, and when combined with non-specific pathogens, to a more rapid and pronounced development of purulent inflammation in the kidney.

Predisposing factors for the occurrence of pyelonephritis are:

• the presence of a permanent catheter, stent (urethral, ureteric);

• periodic catheterization of the bladder;

• residual urine volume> 100 ml;

• obstructive uropathy of any etiology (including neurogenic urinary bladder), stones and tumors;

• vesicoureteral reflux and other functional disorders;

• reconstructive surgery on the urinary tract using a segment of the intestine or creating a conduit;

• chemical or radiation damage to the epithelium of the urinary tract;

• perioperative UTI;

• renal failure and kidney transplantation, diabetes mellitus and immunodeficiencies.

The leading symptoms of pyelonephritis are pain in the lumbar region, fever, chills, and urination disorders. A patient with acute pyelone frit should be hospitalized for urgent reasons. The diagnostic algorithm includes: general and biochemical blood analysis, urine analysis, urine culture on flora and sensitivity to antibiotics, complex ultrasound examination (ultrasound), survey and excretory urography, according to indications - blood culture for sterility, computed tomography with contrast. A urologist should be able to treat patients with acute pyelonephritis, who can fully provide the necessary assistance, including methods of urinary tract drainage and open surgery. In some cases, consultation of related specialists is required. Nephrologist consultation is necessary when acute purulent pyelonephritis develops acute renal failure (ARF), which is rare, or when a prolonged course of the chronic inflammatory process in the kidney leads to the development of chronic renal failure. If pyelone-frit occurs during pregnancy, then treatment is carried out together with gynecologists in order to monitor the course of pregnancy. I would also like to draw attention to the fact that treatment of asymptomatic bacteriuria is mandatory in pregnant women and in patients who are planning an invasive urological intervention (diagnostic or surgical).

The choice of treatment method depends on the stage and form of acute pyelonephritis, the presence and cause of the violation of urodynamics. Therapy of acute non-obstructive pyelone-frit requires an integrated approach and includes the following mandatory aspects: antibiotic therapy (empirical or etiotropic), maintenance of adequate drinking regimen, anti-inflammatory therapy, treatment of coagulation disorders, symptomatic therapy, prevention of relapses and exacerbations. The use of efferent methods of detoxification is indicated for patients with

complications of acute purulent pyelonephritis, such as sepsis, acute renal failure. The choice of method depends on the nature of the complication. At the beginning of treatment, antibiotic therapy is always empirical, it is necessary to choose the right antibiotic or rational combination of drugs, dose and route of administration. For adequate antibiotic therapy, it is important to choose a drug on the one hand acting on “problem” microorganisms, on the other hand, it accumulates in the kidneys in the required concentration. Therefore, the appointment of nitrofurantoin, non-fluorinated quinolones, tetracyclines and macrolides in acute pyelonephritis is erroneous, since they create low tissue and serum concentrations, and also, with the exception of nitrofurans, do not have activity against the main pathogens of pyelonephritis.

According to the recommendations of the European Association of Urology (EAU), empirical antibiotic therapy for complicated UTI includes:

1. Preparations recommended for “starting” therapy: fluoroquinolones (levo-phloxacin, pefloxacin, ciprofloxacin); protected aminopenicillins; cephalosporins II – IIIa generation; aminoglycosides.

2. 2nd-line drugs: severe infection, including the lack of effect: fluoroquinolones (if not used for starting therapy); generation III – IV cephalo-sporins (ceftazidime, cefepime); carbapenems; combination therapy: aminoglycosides + protected penicillins aminoglycosides + fluoroquinolones.

3. In the case of Candida: fluconazole, amphotericin B.

4. Antibiotics not recommended for empirical treatment of complicated UTI (due to high resistance): aminopenicillins (amoxicillin, ampicillin); co-trimoxazole (only in the case of known flora sensitivity); fosfomycin trometamol.

The most effective both from a clinical and from an economic point of view is "stepwise" antimicrobial therapy: parenteral administration of antibacterial drugs with the subsequent transfer of patients to the oral dosage method after normalizing clinical and laboratory parameters.

Patients at the stage of treating acute pyelonephritis and / or suffering from chronic inflammatory diseases of the urinary tract need antirecidative therapy. Numerous studies have proved that the drug of choice in this case is Kanefron® N., which has anti-inflammatory, antibacterial, diuretic and nephroprotective effects.

At the present stage of development of urology in the vast majority of cases, conservative therapy of acute non-obstructive pyelonephritis is indicated and possible. However, there are situations when emergency surgical intervention is required, the indication for which is acute purulent obstructive pyelone-frit in the presence of multiple carbuncles or abscesses.

I would like to pay special attention to medical tactics with a single carbuncle of the kidney. Conservative treatment is possible with a single kidney carbuncle in young patients in the absence of urinary tract obstruction, with apostematic pyelonephritis (at the very beginning of the disease), in the absence of diabetes mellitus and immunosuppressive state, in the presence of modern broad-spectrum anti-bacterial drugs, if possible daily perform ultrasound with dopplerography and determination of laboratory parameters.

Methods for the prevention of acute pyelonephritis are:

• treatment of urological diseases resulting or accompanied by a violation of urodynamics;

• rehabilitation of inflammatory foci (caries, inflammatory diseases of the pelvic organs, upper and lower respiratory tract, STI);

• treatment of asymptomatic bacteriuria of pregnant women;

• adequate treatment of recurrent lower urinary tract infections.

The purpose of the lesson.

To be able to choose a pharmacological agent for various diseases of the urinary system. Know the basic principles of the selection of antimicrobial drugs for diseases of the urinary system

Control questions.

A. Classification of urinary tract infections (UTIs):

upper urinary tract - pyelonephritis (acute and chronic)

lower urinary tract - acute cystitis, acute urethritis

By the nature of the current, they distinguish:

uncomplicated UTI

acute urethritis,

acute cystitis

acute pyelonephritis in non-pregnant women, without obstructive uropathies and neurological dysfunctions in the absence of functional or anatomical disorders of the genitourinary tract, intercurrent diseases.

complicated UTI

The complicated course of the inflammatory process in the urinary tract, in particular acute pyelonephritis, occurs in patients with various obstructive uropathies, against the background of instrumental (invasive) methods of examination and treatment, in patients with serious concomitant diseases (diabetes mellitus, neutropenia). They can lead to the development of severe purulent-septic complications, up to bacteremia and sepsis.

At the place of infection, they share:

community-acquired

nosocomial

According to the patient's condition - the presence or absence of symptoms,

By the nature of the infection - recurrent, etc.

B. Medicines for UTI.

1 Classification.

Inhibitor-resistant penicillins - Amoxicillin / clavulanate, Amoxicillin / sulbactam

Cephalosporins of the 3rd generation - Cefixim, Ceftibuten, Ceftriaxone, Cefotak-sim Carbapenems

Aminoglycosides - Gentamicin i / v or i / m, Netilmicin i / o or i / m (netromycin)

Non-fluorinated quinolones

PF - Norfloxacin Ciprofloxacin XR4 Levofloxacin Ciprofloxacin1 Lo-mefloxacin Ofloxacin Pefloxacin

Nitrofurantoin - Nitrofurantoin Furazidine Furamag

Fosfomycin -Fosfomycin trometamol

2. Pharmacokinetics, pharmacodynamics, indications for use, dosage regimen.

3. Undesirable effects of drugs, contraindications.

4. Principles and order of prescribing drugs.

5. The interaction of drugs.

6. Criteria for evaluating the effectiveness and safety of use.

7. The choice of drugs for rheumatoid cystitis,

9. The choice of drugs for pyelonephritis,

10. The choice of drugs for systemic urctritis,

B. Principles for the treatment of chronic pyelonifritis and acute. pyelonifrita

1. To study - pharmacokinetics, pharmacodynamics, indications, contraindications for use, undesirable effects of uroantiseptics.

2. The student must be able to:

a) select the necessary drug for a particular patient, select the dose, regimen and route of administration of the drug;

b) identify criteria for evaluating the therapeutic efficacy and safety of the drugs used;

c) provide differential medical assistance with:

acute pyelonephritis,

Chronic pyelonephritis

Ciste

Pielite

Urethritis,

3. The student must know:

Classification of uroantiseptics

What are the mechanisms of action of uroantiseptics

Undesirable effects of uroantiseptics

Control of the intermediate level of knowledge.

The

. Patient A., 17 years old, during a medical commission in the urine, the following changes were revealed: protein - 6.6 g / l, erythrocytes - 30 - 40 in the field of view. There are no complaints, no edema, no changes from the internal organs. In childhood, he often suffered from tonsillitis. With repeated urine tests, proteinuria and hematuria persist.

What disease is the clinical picture described above most likely to respond to? Your recommendations on the tactics of further examination and treatment of this patient? Prescribe prescriptions for your suggested medicines.

. Student V., 18 years old, considers himself healthy, undergoes a medical examination. At the age of 9 he suffered a sore throat, after which changes were found in urinalysis. After this, I was not examined. Urinalysis: relative density - 1,024; protein - 0.066 g / l; erythrocytes - 10 - 15 in the field of view; white blood cells - 4 - 6 in the field of view. Your preliminary diagnosis. What is the treatment tactic? Write out the recipes.

. Pregnant 28 years, gestational age 36 weeks. Complains of pain during urination, pain in the lumbar region, fever up to 380C. The above symptoms are observed within 2 weeks. An ultrasound examination revealed calculi in both kidneys. A history of pyelone frit, for which she had previously taken urosulfan. I went to the pharmacy to purchase this drug. What is the tactic of a pharmacist? Justify the answer. Write out the recipe.

. A 12-year-old patient has been given ceftriaxone for pyelonephritis. A history of allergic reaction to penicillins. Cephalosporins have not been accepted before. On the second day of treatment, an itchy erythematous rash appeared on the body. Parents went to the pharmacy for help. Your suggestions and recommendations about the possible cause of complications and further pharmacotherapy.

TESTS

1. Indicate data that are not used in the empirical choice of antibiotics:

A. Gram stained smear microscopy data

B. The clinical picture of the disease

C. Epidemic situation

D. * Microbial susceptibility to antibiotic

E.

2. The drug of choice for the treatment of candidiasis of MPS caused by Candida albicans is:

A. Clotrimazole

B. * Fluconazole

S. Levorin

D. Pimafucin

E. Amphotericin B

3. The drug of choice for the treatment of infections of MVP caused by Pseudomonas aeruginosa is:

A. Ampicillin

B. * Amikacin

C. Azithromycin

D. Amoxiclav

E. Cefuroxime

4. The drug of choice in the treatment of uncomplicated chronic pyelonephritis is:

A. * Amoxicillin

B. Benzylpenicillin or gentamicin

C. Ampicillin or tetracycline

D. Cefotaxime (claforan) or fosfomycin

E. Rifampicin or Aztreonam

5. The mechanism of action of fluoroquinolones:

A. Violate the synthesis of the microbial wall

B. Violate the function of the cytoplasmic membrane of microorganisms

C. Inhibit protein synthesis on the ribosomes of microorganisms

D. Form complexes with nucleic acids of microorganisms and thereby block these acids

E. * Inhibit DNA gyrase microorganisms

6. Name the fluoroquinolone with the highest activity against gonococci:

A. Ciprofloxacin

B. Levofloxacin

C. Ofloxacin

D. Norfloxacin

E. Pefloxacin

7. The patient, 22 years old, applied to the antenatal clinic with complaints of primary infertility. A history of chronic salpingoophoritis. During an in-depth analysis of a smear from the cervical canal, chlamydia was found in it. What drug should be chosen for etiological treatment?

A. Sulfadimethoxin.

B. Penicillin.

S. Nystatin.

D. * Sumamed.

E. Trichopol.

8. A 36-year-old woman was prescribed an 8-hydroxyquinoline derivative for the treatment of acute pyelonephritis, which is well absorbed in the intestines and excreted in a significant amount by the kidneys unchanged. Identify the drug.

A. Gentamicin sulfate.

B. Chlorchinaldol.

C. * Nitroxoline.

D. Furadonin.

E. Urosulfan.

9. The doctor prescribed metronidazole and warned the patient about abstinence from alcohol 24 hours before and 48 hours after a course of treatment with this drug. Explain what happens with the combined use of alcohol and metronidazole:

A. Decreased chemotherapy

B. Enhanced nephrotoxicity

C. Potentiation of alcohol

D. * Teturam-like action *

E. Enhanced myelotoxicity

10. For the treatment of exacerbation of chronic cystitis, the doctor prescribed a drug from the group of fluoroquinolones. What is the mechanism of antimicrobial action of fluoroquinolones?

A. Inhibition of peptidoglycan synthesis

B. * Inhibition of DNA gyrase *

C. Increasing the permeability of the bacterial wall

D. Inhibition of RNA polymerase

E. Antagonism with PABA

11. For a woman of 46 years old, for the treatment of acute cystitis, the doctor prescribed a combination drug from the group of sulfonamides with a high bactericidal effect. Name this drug.

A. Phthalazole

B. Sulfadimesin

C. * Co-trimoxazole

D. Salazopyridazine

E. Ethambutol

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 daily. 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

13. A 60-year-old patient with a cystostomy was hospitalized in the surgical department in connection with an infection caused by Pseudomonas aeruginosa, which is sensitive to the penicillin antibiotic. Indicate which of the listed penicillins has a pronounced activity against Psedomonas aeruginosa (Pseudomonas aeruginosa)?

A. Benzylpenicillin

B. Ampicillin

C. Phenoxymethylpenicillin

D. * Carbenicillin

E. Oxacillin

14. For a woman of 30 years who is 32 weeks pregnant, the doctor prescribed an antibiotic as part of a comprehensive cystia therapy. Indicate which of the following drugs can be recommended in this situation?

A. Ampicillin

B. Doxycycline

C. Chloramphenicol

D. Clarithromycin

E. Gentamicin

15. A 30-year-old patient with a diagnosis of acute osteomyelitis was prescribed an antibiotic that penetrates well into bone tissue. Within three weeks of using this tool, the patient's condition improved. What drug was used?

A. Polymyxin M

B. Bicillin-3

C. Benzylpenicillin

D. * Lincomycin

E. Ampicillin

16. A 40-year-old patient who suffers from chronic cystitis and has had hepatitis six months ago needs to undergo antibiotic therapy. Which of the following drugs can be prescribed to the patient?

A. Tetracycline

B. * Ampioks

C. Gentamicin

D. Metacycline

E. Doxycycline

17. A 56-year-old patient with acute cystitis showed penicillinazapro a producing staphylococcus strain. For treatment, a drug from the penicillin group was prescribed. Name this drug.

A. Benizlpenicillin sodium salt

B. * Oxacillin

C. Ampicillin

D. Ticarcillin

E. Meslocillin

18. The patient has a urinary tract infection. Which of these substances provides the highest concentrations of the active drug in active form in their lumen?

A. Erythromycin

B. Tetracycline

C. Chloramphenicol

D. Rifampicin

E. Amikacin

19. The patient read the instructions for the prescribed antibiotic, where in the section of undesirable effects noted the possibility of muscle relaxant, ototoxic, teratogenic, mutagenic effects. What drug was prescribed?

A. Chloramphenicol

B. Penicillin

C. * Streptomycin

D. Chloramphenicol

E. Dicloxacillin

20. The patient took an antibiotic for the treatment of chronic pyelonephritis. In patients receiving nausea, vomiting, stomatitis, dermatitis on the skin of the face and hands (photosensitivity), pain in the liver.

What drug did the patient take?

A. Ampicillin

B. * Tetracycline

C. Azithromycin

D. Polymyxin

E. Kanamycin

Recommended literature:

Basic:

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

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

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

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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.

4) 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 PREPARATIONS FOR TREATMENT OF URINARY STONE DISEASE

CLINICAL-PHARMACEUTICAL APPROACHES TO THE CHOICE OF PREPARATIONS FOR TREATMENT OF BENEFIT HYPERPLASIA OF THE PROSTATE GLAND

Relevance of the topic.

Urolithiasis (UL) is still one of the most common urological diseases. The incidence of ICD in the regions ranges from 25.5% to 41.5%, and patients with various forms of this pathology occupy 35-50% of the hospital bed capacity of urological hospitals. According to many authors, this disease as a manifestation of metabolic disorders will tend to increase due to the deterioration of the environmental situation.

Prostate adenoma, or rather benign prostatic hyperplasia (BPH), is the most common disease in middle-aged and elderly men. Studies conducted by domestic scientists indicate a gradual increase in the frequency of BPH with age - from 11.3% in the period 40-49 years to 81.4% - in 80 years. At autopsy, histological signs of BPH are detected in more than 40% of men aged 50 years and more than 90% of men older than 80 years. Most men over 50 have symptoms associated with BPH.

According to P. Sagnier et al., In France, 1.14 million men who turned to a urologist were found to have moderate or severe symptoms of impaired urination, characteristic of prostate adenoma. A survey of men from 40 to 79 years old, conducted in Scotland, revealed BPH in 14% in the fifth decade of life and in 43% in the seventh. An epidemiological examination of men aged 60 to 70 years, conducted in Copenhagen (Denmark), revealed in one third of them the urological symptoms typical of BPH.

Specific features of the development of BPH in the countries of the Far East, in particular in Japan, are that, unlike Europe and the countries of America, eastern men develop infravesical obstruction faster. An autopsy study reveals minor racial or geographical differences in BPH, while clinical findings have significant differences. When studying the spread of BPH depending on race, it was found that the probability of the need for surgical treatment for this disease is the same for representatives of the black and white race.

In general, in industrialized countries, the total number of patients with BPH is increasing, which is associated not only with early diagnosis of the disease, but also with an increase in life expectancy in civilized countries. This, of course, cannot but alarm, because the prostate gland, or, as it is figuratively called, the "second heart" of a man, plays a huge role not only in urination, but also in the sexual life of men.

Urolithiasis:

It occurs mainly between the ages of 20 and 50.

Stones are more often localized in the right kidney than in the left; 15-20% have bilateral stones. Mostly the stones are located in the pelvis, less often in the cups (or simultaneously in the calyx and the pelvis).

Stones filling the entire pyelocaliceal system, like a mold, are called coral-shaped.

The disease is endemic (related to a specific area).

calculi, or kidney stones, are formed by calcification or precipitation in the urine of crystals of calcium, uric acid, cystine, tripelfosphate or magnesium-ammonium-calcium-phosphate salts.

In 65-75% of cases, stones containing calcium are found (calcium salts of oxalic, phosphoric, less often carbonic acids). In 5-15% mixed stones are found containing phosphates of magnesium, ammonium and calcium (the so-called struvites). 5-15% of all stones are urate stones. In about 5% of cases, cystine, protein, and cholesterol stones are found.

Ethio-pathogenetic factors

Urolithiasis is a chronic disease characterized by metabolic disorders with the formation in the kidneys and urinary tract of stones that form from the components of urine.

Common factors contributing to stone formation

The appearance of each type of stone is associated with certain reasons, but there are general factors that contribute to stone formation:

Receiving a small amount of liquid and, accordingly, the allocation of a small amount of urine.

It is believed that precipitation of salts is possible either with an increase in their concentration in the urine, or with a decrease in their solubility:

a. due to their excessive secretion due to various metabolic disorders - for example, hyperparathyroidism and bone injury, lead to increased excretion of calcium and phosphate in the urine;

b. due to low urine output under conditions of urine reaction that impedes their dissolution, which can occur due to changes in urine pH and a decrease in the content of so-called protective colloids in the urine, which ensure the stability of oversaturated solutions. Urine is 2 substances (colloids and crystalloids) that hold each other and prevent salts from falling into the wasp dock.

Violation of urodynamics - abnormalities of the kidneys and urinary tract, hydronephrosis, pregnancy, etc. UL can be a professional disease for pilots (while overcoming the sound barrier of speed, the pilot’s body undergoes severe overloads, which sometimes causes hemorrhages in the kidneys; blood clots in the urinary tract serve as the nucleus for crystallization of urine salts and the formation of urinary stone). UL is caused by various foreign bodies in the urinary bladder, for example, threads (ligatures) after gynecological or urological operations.

Urinary tract infection. The products of the infectious and inflammatory process - bacteria, white blood cells and protein - form the organic core of the stone, which serves as a matrix for the deposition of salts.

 Alimentary factor. For example, drinking water oversaturated with calcareous salts; improper one-way power.

Theories of pathogenesis

UL can have many reasons, however, a final explanation of the occurrence of urinary stones in all details still can not be given. In principle, two categories of theoretical explanations for the formation of urinary stones can be distinguished:

• The first theory explains urolithiasis is explained solely by physicochemical processes such as hyperextension, oversaturation, and crystallization - i.e. processes that occur in the tubular lumens and do not affect the cells.

• The second theory - more fashionable and modern - is cellular. The defeat of cells precedes the formation of stones. Some studies support the concept of primary cell damage

Genetic nature of the UL

Some recent studies favor the concept of primary cell damage, including establishing the genetic nature of the UL.

Renal stone disease affects half of the families in which it is observed. This once again proves its genetic nature.

It has long been noticed that the UL is “linked” to the female X chromosome. Therefore, violations in this chromosome affect primarily in men who have only one such form of genetic material. Women have two of them, therefore, mutations in the gene quite often turn out to be “covered” by the normal gene in the second X chromosome. This explains the fact that kidney stone disease occurs in 12% of men and only 5% of women (although, of course, these data are very conditional, since it is unlikely that anyone managed to collect complete statistics).

It was proved that the gene of this disease is localized in the short arm of the X chromosome (mutations in this area lead to serious illness of people). What is this gene? This is a gene of a protein channel that "exchanges" chlorine ions for calcium ions. This is an amazing discovery, since until now it was believed that the same Dent disease is caused by a disorder of calcium, but by no means chlorine. Several types of chlorine channels are already known. The fifth type of chlorine channel (ChlK5) is specific for the kidneys, or rather, the epithelium of the renal glomeruli and tubules. Calcium, as is known, is freely filtered from the blood in the glomeruli of the nephron, but then 70-80% of it should be absorbed back into the tubules. A mutation in the chlorine channel gene disrupts normal ion exchange, with the result that excess calcium is deposited in the form of nephroliths.

The introduction of such cell-protecting drugs as calcium antagonists in the experiment allowed to reduce the formation of stones, despite the fact that there was no corresponding improvement in urine and blood serum.

Currently available research results do not yet allow us to draw final conclusions about whether cellular abnormalities precede the formation of stones or whether they occur a second time due to cell damage by stones.

Types of stones

Calcium Phosphate Stones

In appearance, such stones are white or light gray in color with a smooth or slightly rough surface, the texture is soft.

There are three forms of hypercalciuria:

Absorption. In turn, three reasons are possible:

due to hyperabsorption (overdose of vit.D or increased formation of its metabolites)

increased calcium excretion by the kidneys due to its intake in large doses - 800 mg / day

hypercalciuria with hyperparathyroidism

Renal - violation of tubular reabsorption of calcium.

Resorption - a consequence of primary or secondary hyperparathyroidism, also occurs in Peugeot, Cushing, Calera disease, sarcoidosis, trauma or paralysis, bone metastasis, renal tubular acidosis, vit.D. intoxication, in the postmenopausal period.

The reasons for hyperphosphaturia are:

• primary or secondary hyperparathyroidism

• phosphoric diabetes

• Fanconi syndrome

• Cushing's disease

• renal tubular acidosis

• Albright-Battler-Bloomberg, Boyd-Sterns syndromes.

Calcium Oxalate Stones

Oxalates are found in 2/3 of all stones, often in the form of calcium oxalate. Despite the fact that most kidney stones contain oxalates, hyperoxaluria with MKD is not so frequent. In appearance, such stones are dense black and gray with a spiky surface.

Hyperoxaluria is divided into primary and secondary

• Endogenous or primary hyperoxaluria can be caused by an enzyme deficiency or a deficiency of vitamin B6 (pyridoxine), which blocks the conversion of glyoxylate to glycine and thus increases the formation of oxalate.

• Secondary or exogenous hyperoxaluria is a consequence of increased absorption of oxalic acid in the intestine, which can occur for several reasons:

o significant consumption of products containing oxalic acid in large quantities.

o the use of high doses of vitamin C

o gastrointestinal diseases, accompanied by steatorrhea and insufficient absorption of fatty acids (Crohn's disease, UC, sprue, chronic pancreatitis, cirrhosis, diabetic enteropathy, condition after resection of the small intestine).

Urate stones

Their occurrence is associated with constantly concentrated and acidic urine (observed in many diseases of the gastrointestinal tract with diarrhea). In appearance, such stones are yellow-brick in color with a smooth surface, solid consistency.

Hyperuricuria is divided into primary and secondary

Possible causes of primary hyperuricuria may be enzymatic disorders.

Secondary hyperuricemia can cause:

increased exogenous intake of purines

alcohol load

leukemia

myeloproliferative diseases

diabetes

medicines (corticosteroids, estrogens, amino acid infusion)

Cystine stones

Cystinuria In appearance, such stones are yellowish-white in color, roundish, and solid.

Tripelphosphate stones

Or magnesium-ammonium-calcium-phosphate: urinary tract infection (chronic or recurrent) with urease-producing bacteria (urea-cleaving enzyme) - Proteus, Klebsiella, Pseudomonas, Providencia, Serratia, Enterobacter strains. Such stones are often accompanied by characteristic crystalluria - "grave-shaped" crystals.

Calcium-carbonate stones are white, smooth, soft.

Protein stones are white, soft.

Cholesterol stones are black, soft.

Clinic

The clinic may vary significantly. The pathognomonic sign of the disease is the discharge of the stone. A small stone gives a large clinic, because he is mobile.

1. Perhaps the hidden passage of "asymptomatic" stones of small sizes. However, more often asymptomatic stones are detected in the kidneys by chance during an X-ray examination for other conditions.

2. Hematuria usually accompanies the passage of a stone through the urinary tract and can be explicit or detectable by microscopic examination. May occur with pain or be painless. Hematuria is observed in 80-90% of cases, and 60% of patients may have pyuria.

3. Frequent urination and dysuria (typical when the stones are located in the intra-vesicular segment of the distal ureter) can be mistaken for symptoms of cystitis. Dysuria is also observed with the passage of clots. The lower the stone in the ureter, the more pronounced dysuria.

4. The leading symptom of nephrolithiasis is dull, aching, or acute pain. Abdominal pain, tenesmus and pain in the rectum are characteristic of the location of the stone in the renal pelvis and are often accompanied by nausea and vomiting.

5. Renal colic with pain in the side and irradiation into the inguinal ligament, urethra, labia, testicles or penis is typical of a stone located in the middle parts of the ureter.

6. Acute stone obstruction causes renal colic [and acute pyelonephritis?]. Subacute obstruction may be little - or asymptomatic.

7. Infection is a common complication of ICD and is usually accompanied by pain in the side or lower back, fever and chills, especially with obstruction of the urinary tract.

Diagnostics

1. Anamnesis. You need to learn about the use of drugs and vitamins (especially A, D and C) in the past or at the present time and the presence of ICD in other family members.

2. Objective examination. An acute attack of renal colic and pain in the abdomen, pelvic organs or lower back due to other reasons should be differentiated. At the time of renal colic, there may be symptoms of peritoneal irritation, in particular when the stone is located in the middle third of the ureter. Although the ureter is located retroperitoneally, nevertheless, it is adjacent to the posterior wall of the peritoneum, so any process in the ureter can simulate a disease of the abdominal organs.

3. Urine analysis is informative in all cases.

With a maximally acidic reaction, urine pH is less than 5.0, and with a maximally alkaline reaction, more than 7.5. An inadequate increase in urine pH is determined with renal tubular acidosis, which contributes to the formation of calcium phosphate stones.

Low urine volume with low urine pH is a risk factor for the formation of urate stones.

The type of crystals often corresponds to urine pH: uric acid and cystine crystals are detected in an acidic urine reaction, and calcium phosphate and tripelphosphate crystals (struvite) are detected in an alkaline reaction.

Bacteriuria may be a symptom of ICD, therefore urine culture should be performed.

At the time of renal colic, surgeons often focus on red blood cells in urine, believing that this symptom supposedly allows you to distinguish between renal colic and, for example, appendicitis. No hematuria, then we will do an appendectomy. Meanwhile, it should be remembered that at the time of the attack, urine is most often normal, because it enters the bladder from a healthy kidney. Speaking of hematuria as a symptom supposedly characteristic of renal colic, it must be remembered that if red blood cells in the urine appeared after colic was stopped, this indicates that the patient has an ICD. But if the hematuria arose at the very beginning of renal colic and then the attack intensified sharply, then this speaks in favor of the tumor.

4. Chemical analysis of urine and blood may be of some value in the study of metabolism in a patient with nephrolithiasis.

Blood test for electrolytes, creatinine, AMA, calcium, phosphate and lactic acid.

Analysis of daily urine: volume, pH (determined three times), levels of calcium phosphate, uric acid, oxalate, creatinine, sodium, potassium and cystine.

Biochemical analysis in the UL is an unreliable criterion, because it changes in other pathological conditions. For example, an increased content of uric acid indicates urate stones, but hyperuricemia can occur with liver failure, and with malignant neoplasms.

5. X-ray examination.

• A panoramic radiograph of the abdominal cavity reveals radiopositive shadows that are suspicious of calculus. However, not every shadow in the projection of the urinary system can be considered a calculus. Only a coral-like stone, repeating the shape of the pyelocaliceal system, is not in doubt. Phlebolitis, petrified lymph nodes of the mesentery of the intestine, fecal stones in the appendix, etc. can be mistaken for ureteral stones. If the shadow moves away from the shadow of the ureter by 0.5 cm - this is not a stone. A panoramic x-ray is also informative for determining the composition of the stones - with the exception of urate stones, the rest (containing calcium) are usually visible in the panoramic picture (the stone is not visible if it is located against the background of the pelvic bones). Calcium stones are intensely contrasting; cystine, tripelphosphate (caused by infection) and mixed calcium-calcium stones are moderately contrasted. An X-ray of the abdominal cavity also helps determine the localization and size of the stones (only the core can be contrasting, and the rest, consisting of, for example, urates, will be X-ray non-contrast), and serial images indicate the activity of the disease with an increase in the size of the stones and their numbers.

• Intravenous urography is extremely important and necessary for evaluating X-ray negative stones (urate) and obstruction of the urinary tract.

6. In some cases, ultrasound and CT may be informative (stones of any chemical composition are determined). Echolocation clearly detects stones with a diameter of at least 1.5 mm. The reliability of ultrasound averages 90%.

7. Diagnosis of renal colic is particularly promoted by endoscopic methods, in particular chromocystoscopy. Intravenous solution of indigo carmine is introduced, cystoscopy is performed, and dye from the ureters is observed. The method produces conflicting results in only 2-3% of cases. For example, a patient has a doubling of the ureter and the stone is located in one of the doubled ureters. In this case, there will be no delay in the release of

indigo carmine. the second half of the doubled urine is passable. Or with appendicitis, when the appendix is located retrocecally or retroperitoneally, the inflammatory infiltrate spreads to the ureters and then dye will not be released during chromocystocopy.

Cystocopy is indicated for the detection and extraction of stones from the bladder and removal of stones from the ureters located near the ureter-cystic anastomosis.

8. If, during pain (renal colic), a catheter is inserted into the renal pelvis, then urine will flow out under it under pressure. This indicates an increase in intrapulmonary pressure and confirms the diagnosis of renal colic. If, after the introduction of the catheter, the urine flows dropwise and the pain does not stop, then the pressure in the pelvis is normal and the pains in the lower back and abdomen are caused by some other reasons not related to the kidneys.

Differential diagnosis:

• hematuric nephritis (Ig A - nephropathy, with systemic diseases)

• kidney tuberculosis

• kidney cancer

• With UL, hematuria is observed after an attack of pain, while with a tumor of the kidney, it precedes a pain attack.

Treatment

The treatment of UL in the last 15 years has received new development due to the use of extracorporeal lithotripsy, as well as new types of endoscopy. Today, more than 80-90% of stones can be removed using non-invasive (extracorporeal lithotripsy) or minimally invasive (endoscopy) methods. Surgical as well as conservative methods of treatment are almost forgotten and occupy no more than 10-20%. However, the accumulating experience in the application of these methods of treatment reveals the boundaries of their application. It turned out that they are not completely free from unwanted side effects, for example, extracorporeal lithotripsy with the help of shock waves can cause impaired renal function. Therefore, studies of the pathogenetic factors of stone removal, as well as measures to prevent relapse (metaphylaxis) again cause lively interest. (4th European Symposium on Urinary Stones. Tübingen, April 1-3, 1993)

A paraffin-containing belt "Fizomed" is proposed. The belt is made of 8 cm cotton fabric, in the pockets of which are inserted the inserts of paraffin-containing material processed using special technology, as a result of which the stones are affected [nosodes or what ?!]

General principles of treatment

• Hydration.

• Diuretics.

• The expulsion of small stones and sand.

• Shift of urine pH.

• Impact on metabolic disorders.

1. Hydration

It is carried out in accordance with the established metabolic disorder. Conservative treatment is aimed at eliminating conditions conducive to stone formation, preventing relapse of nephrolithiasis and its complications, suppression of small stones, litholysis of stones (urate, possibly oxalate).

• The general principle of treatment is to reduce the concentration of dissolved substances by increasing the volume of urine - under all circumstances, the excretion of urine should be at least 2 l / day.

Liquid intake time is very important, as it is necessary to break the normal cycle of urine concentration (maximum during sleep). It is recommended to drink 1 glass of liquid every hour during wakefulness and 1-2 glasses before bedtime, in order to achieve nocturia; an additional intake of 1 cup of liquid after nightly urination and in the morning immediately after sleep is desirable. Hydration with urate lithiasis is especially effective.

It is best to drink water. Acidifying fluids, as well as those containing carbohydrates, can increase calcium excretion. Potassium fluids are useful in the simultaneous treatment with diuretics.

2. Pathogenetic therapy

Calcium Phosphate Stones

• In primary hyperparathyroidism, urgent parathyroidectomy is indicated.

• Distal tubular acidosis requires an independent evaluation.

• For idiopathic hypercalciuria, diuretics (thiazides or amiloride) or neutral potassium phosphate are prescribed. Hypothiazide in a daily dose of 50-100 mg in two doses reduces calcium excretion and prevents the formation of stones. Orophosphates (inorganic salts of phosphorus), which also reduce calcium excretion, are slightly weaker. The recommended dose is 750-2000 mg of elemental phosphorus. Allopurinol (200-300 mg / day) is also effective, which not only reduces hyperuricosuria, but also prevents the formation of calcium stones.

• Particular attention to the exclusion of dairy products that alkalize urine should be given with calcium-phosphorus stones (phosphaturia). Such a diet is especially effective for idiopathic hypercalciuria. Limit vegetables and fruits (alkalization of urine), recommend meat, fish, flour products, vegetable oils.

Calcium Oxalate Stones

Treatment consists in limiting food intake with a high content of ok-lettuce, the exclusion of large doses (more than 500 mg / day) of ascorbic acid, and the use of hypocalciuric diuretics (thiazides or amyloride) or neutral potassium phosphate inside. Oral administration of potassium citrate may be useful to increase urinary excretion of citrate, the main chelator of ionized calcium in urine and an inhibitor of the growth of calcium oxalate crystals.

Pyridoxine is recommended (especially with primary hyperoxaluria) 200 mg 2-3 times a day, ortho-phosphates, magnesium preparations, citrate preparations (see below).

Exclude foods containing a large number of vitamins. C - pepper, figs, wild rose, blackcurrant, sorrel, tea, green salad, rhubarb, spinach, beans. Limit the use of beans, potatoes, tomatoes, cheese, cottage cheese, eggs, strong meat broths.

Urate stones

Conservative therapy is most effective for urate nephrolithiasis. The main areas of therapy are hydration, alkalization of urine, decreased intake of purines, the appointment of allopurinol.

Allopurinol (milurite) - has a specific ability to inhibit the enzyme involved in the conversion of hypoxanthine to xanthine, and xanthine to uric acid. When you stop taking uricemia and uricosuria, they return to the initial level on the 3-4th day, so treatment should be long, omissions in taking the drug for more than 2-3 days are undesirable. They are used for the treatment and prevention of diseases accompanied by hyperuricemia: gout, ICD with the formation of urates, with enhanced decay of nucleoproteins and increased uric acid in the blood (hemoblastoses,

radiation and cytotoxic therapy, psoriasis), massive corticosteroid therapy. The minimum dose is 0.1 g / day, the maximum is 0.8 g / day.

Etamide - inhibits the reabsorption of uric acid in the renal tubules, promotes its excretion in the urine and a decrease in blood levels. Used for chronic gout, polyarthritis with impaired purine metabolism, ICD with the formation of urate. Assign 0.7 g (2 tablets of 0.35 g) 4 times a day for 10-12 days. After a 5-7 day break, a second course of 7 days is carried out.

Tsinghofen (atofan) - promotes the transition of uric acid from tissues to the blood and enhances its excretion by the kidneys, has an analgesic effect (effective for acute attacks of gout?). Apply with gout. Due to side effects (jaundice, liver atrophy, gastritis, cystitis), they are rarely used at present. Contraindicated in bronchial asthma, gastric ulcer, senna fever. In order to avoid complications, the drug is given in cycles of 5 days with weekly breaks.

Alkalize urine best with citrate preparations. These are medications for dissolving urate stones, they are buffer systems, the action of which is determined by their buffer capacity. The main active ingredients are citric acid and potassium and sodium citrates. The drugs have a similar composition and with proper therapy, the effect can be obtained using any of them. Magurlite, which contains components that contribute to the prevention of the formation of oxalates, has some advantage. The dose of the drug is regulated by the patients themselves according to the determination of urine pH immediately before taking the drug (it averages 5-7 g / day). To dissolve the stones, urine pH is maintained in the range of 6.2-6.6. Large alkalization of urine is fraught with the loss of phosphates and carbonates, the deposition of which on the stone makes it difficult to dissolve.

It is recommended that citrate preparations be taken 3 times a day before meals, and it is most advisable to take it 2-3 hours before the most acidic urine pH occurs during the day (before treatment, the patient independently draws a graph of the urine pH fluctuations for 7-10 days using the litmus test) pieces of paper at every urination in normal living conditions, including eating habits).

Contraindications: infected urine, circulatory failure (due to the high content of sodium and potassium in the preparation).

The composition of the drugs.

• Solimok: citric acid 14.5 g - potassium citrate 46.3 g - sodium citrate 39 g

• Uralit-U: 14.5 - 46.3 - 39

• Blemaren: 39.9 - 27.85 - potassium bicarbonate 32.25 g

• Soluran: 33.7 - calcium bicarbonate 35.6 g - sodium citrate 30.6 g

• Magurlite: 13.5 - potassium citrate 39.7 - sodium citrate 36.16 g - magnesium citrate 9 g - pyridoxine hydrochloride 0.4 g

It is necessary to use sodium bicarbonate orally to maintain an alkaline urine reaction (pH above 7.0) and to limit the intake of purines with food or the use of allopurinol (in some patients), which reduces hyperuricosuria, 200-300 mg per day.

The diet excludes meat broths, fried meat and fatty meat (pork, goose, duck), offal (liver, kidneys, brains, tongue), cocoa and chocolate, limit meat and alcohol. They include products that alkalinize urine to prevent the precipitation of crystals — cucumbers, beets, carrots, potatoes, cherries, grapes, currants, apples, and melons.

Cystine stones

To maintain urine pH greater than 7.5, sodium bicarbonate is prescribed, and to maintain an alkaline reaction at night, acetazolamide is prescribed before bedtime. urine output should be maintained at a level exceeding 4 l / day. patients not observing the regimen, and patients with severe or refractory nephrolithiasis, are shown oral administration of D-penicillamine.

Penicillamine (cuprenyl) has a high complexing activity against metal ions. It binds mainly ions of copper, mercury, lead, iron, calcium. The resulting complexes are removed by the kidneys. Therefore, penicillamine is used for poisoning with these metals, with Konovalov-Wilson's disease. Sometimes with nephrolithiasis (to accelerate the excretion of calcium), hemoside-rose. This is one of the "basic" treatments for rheumatoid arthritis. When taking blood, temperature control is necessary. Contraindicated in case of hypersensitivity to penicillin.

Or intrarenal dissolution of stones by irrigation of acetylcysteine or alkali.

Tripelphosphate stones

Treatment is aimed at combating bacteriuria, which determines the need for antibiotics. With mixed stones, conservative treatment is usually not very effective. Surgical treatment has been indicated (especially for coral stones), for the prevention of relapse, first of all, the fight against infection, heavy drinking and acidification of urine are also recommended.

3. Extracorporeal shock wave lithotripsy

It is carried out using electrically induced shock waves generated in a water bath and focused on the stone, which leads to its dissolution in situ. There are some limitations in using this method for very large coral stones, as percutaneous extraction may be required to increase non-invasive access during lithotripsy.

The results of the largest study of the results of extracorporeal lithotripsy with a shock wave are summed up. In 1000 patients with kidney and ureter stones, this method was applied in Canada. After 3 months, 801 patients underwent repeated studies. No stones were found at all in 52%, the rest (674) had kidney stones. The localization and focusing of the stone was determined using a biplanar fluoroscope, with which then the destruction of the stones was checked. The average duration of treatment was 64 minutes. Extremely important for the effective application of this method of treatment were the size, position, structure and number of stones:

• stones 10 mm or less in size were destroyed in 59% of patients, 11-20 mm - in 51%, large - in 33%

• stones located in the pelvic region and in the region of the lower renal calyces were better broken up than stones in the region of the upper and middle renal calyces

The most important danger is damage to tissues (kidney, peritoneum) with a fuzzy tip. Naturally, the patient cannot lie still, receiving 2-3 thousand strokes, and hold his breath in one position all the time, so the focus of the wave is shifted and the concentration of the shock falls not on the stone, but on the surrounding tissues.

By the way, with cholelithiasis, shock-wave lithotripsy is gradually abandoned, replacing it with endoscopic cholecystectomy. Perhaps this path will go with the ICD.

4. Surgical treatment

Pyelolithotomy or nephrolithotomy is rarely required, but is indicated if:

• stones causing obstruction, or in the presence of stricture, cicatricial changes in the ureter below the location of the stone;

• infections,

localized proximal to the stone;

• or if the roentgenogram shows that the size of the stone is too large, so that it could pass on its own (more than 1 cm in diameter);

• coral stones should be removed if there is a risk of impaired renal function.

Surgical treatment should be aimed not only at removing the calculus, but also at restoring normal outflow of urine, which sometimes requires plastic and reconstructive surgery.

After surgical treatment, stone recurrence occurs in 30%.

5. Activation of urodynamics

For this, drug treatment is used, which is aimed at the expulsion of small stones of the pelvis or ureter and involves the activation of urodynamics of the upper urinary tract.

It is indicated for calculi that can independently migrate, mainly when they do not interfere with the outflow of urine and did not cause hydronephrotic transformation or were not complicated by an attack of acute pyelonephritis. For this purpose, preparations of the terpenes group are prescribed (cystenal, olimetin, enatine, artemizole, aviation-san, cyston), which have an antispasmodic, bacteriological and sedative property, moderate diuretic effect and contribute to loosening of urinary calculi.

Extract madder dye (in the table. 0.25 g) for 2-3 tablets 3-4 p. per day (has a diuretic and antispasmodic effect, promotes loosening of urinary calculi containing calcium and magnesium phosphates). Marena stains urine in reddish color, with sharp staining in brown-red color - reduce the dose or temporarily stop taking the drug. The course is 20-30 days (if necessary, repeat after 4-6 weeks).

Cystenal is a complex preparation containing tincture of madder root, magnesium salicylate, essential oils, ethyl alcohol, olive oil. It has a spasmodic and mild diuretic effect, relaxes the muscles of the ureters and facilitates the passage of small calculi. Assign inside 4-5 capel on sugar 3 r. per day for 1 \ 2 - 1 hour before meals. With an attack of colic - once 20 drops. Contraindications: glomerulonephritis, ICD with impaired renal function, gastric ulcer.

Olimetin is a complex preparation containing essential oils. It is used for treatment (2 capsules 3-5 times a day) and prevention of ICD and cholelithiasis (1 capsule per day for a long time). The composition and mechanism of action of olimetin is similar to foreign drugs - Enatin, Rovatin, Rovakhol. Contraindications: glomerulonephritis, gastric ulcer, hepatitis.

Avisan is a herbal preparation, has a selective antispasmodic effect on the smooth muscles of the ureters, it is proposed as an antispasmodic for renal colic and ureteral spasms, and for cystitis it reduces dysuric phenomena. Apply inside 1-2 tablets 3-4 times a day after meals. The course of treatment is 1-3 weeks.

Pinabin is a solution of essential oils obtained from pine or spruce needles. It has an antispasmodic effect on the muscles of the urinary tract, has a certain bacteriostatic effect in relation to grams of positive bacteria. With renal colic and ICD, 5 drops 3 times a day on sugar 15-20 'before meals. The course of treatment is 4-5 weeks.

Urolesan is a herbal preparation. They are used for cholelithiasis and ICD, calculous pyelonephritis and cholecystitis, biliary dyskinesia (it has spasmodic action, promotes the passage of stones, reduces inflammation in the urinary tract, strengthens bile formation and biliary excretion. Inside, 8-10 drops 3 times in the day before meals.Course from 5 days to 1 month.With the number of drops of 20 drops at a reception.

Phytolysin is a vegetable paste. It has a diuretic, anti-inflammatory, antispasmodic effect, loosens stones and removes them with urine. Loosening of stones occurs slowly. Take 1 teaspoon in a half-can of sweetened water 3 times a day after meals.

The grass of the mountaineer bird (knotweed) contributes to the passage of calculi in the ICD, has a moderate anti-inflammatory effect. Inside, in the form of infusion, 2 tablespoons 3 times a day before meals.

SMT therapy in combination with water load (with stones of the ureter). Effectively administer iv 5 ml of baralgin with 20 mg of lasix against the background of a water load.

For the passage of small stones from the ureter prof. I. Derevyanko recommends drinking 1 liter of water in 30 minutes, injecting an antispasmodic and walking actively.

Folk recipe: No. 1. Take 1 kg of carrots + 1 kg of raisins, pour 5 cups of water and soak for 2 hours on a tile without opening the lid, until 0.5 l of water remains. Strain. Squeeze the lemon. Drink an hour before meals. No. 2. Take a glass of cucumber juice + juice of one lemon.

6. Sanatorium treatment

SCR is advisable 1.5-2 months after the stone leaves or promptly removes it with satisfactory renal function and with undisturbed passage of urine, as well as with small sizes of calculus - up to 6 mm.

• Spontaneous passage of stones from the ureter up to 4 mm in size is observed in 80-90% of patients, 4-6 mm in size in 50-60% of patients, more than 6 mm in size in 8-17% of patients. This is due to the size of the ureter, which is 4-7 mm in diameter, but can be stretched to 6-8 mm. If the calculus has dimensions more than 6 mm in diameter, it is not recommended to refer the patient to sanatorium-resort treatment.

Patients with coral stones require special attention. After sanatorium treatment in such patients, an increase in coral stone and a deterioration in the functional state of the kidneys are often observed, despite a decrease in the degree of inflammatory process in the urinary system. Patients with coral stones can be sent to a spa treatment only after surgery.

• Uric acid diathesis - alkaline mineral waters (Essentuki No. 4 and No. 17, Slavyanovskaya, Smirnovskaya, Borzhom).

• Oxaluria - slightly saline water (Essentuki No. 20, naphthus, sair-me).

• Phosphaturia - mineral water that promotes the oxidation of urine (dolomite narzan, naphtha, arzni).

7. Other

The ancients believed that some hard stones found in nature formed in the kidneys. And they called these stones jade (from the Greek "nephros" - kidney). There is a legend that according to the principle of similarity –anology with nephritis, it is good to treat people with kidney stones.

Prognosis and complications

Subject to the timely removal of stones and the systematic subsequent treatment of pyelonephritis to prevent recurrent stone formation, it is beneficial and pleasant. The most serious prognosis is for coral or multiple stones complicated by chronic renal failure.

Complications:

• acute and chronic pyelonephritis

• hydronephrosis

• ARF (with ureteral occlusion)

• CRF, due to the terminal stage of XP. pyelonephritis.

Medications used for urolithiasis

Pharmacotherapy of urolithiasis directly depends on the chemical composition of renal calculi.

1. Drugs that inhibit the synthesis of uric acid: allopurinol.

2. Drugs that alkalize urine and prevent the loss of urate stones (urates): blemarin, uralitis U.

3. Drugs that prevent the formation of urinary calculi, which contribute to the dissolution of urinary stones in the kidneys and facilitate their excretion in the urine: blemarin, Uralit U, madder extract, cyston, cystenal, phytolysin, Urofit and Urosan and others.

4. Drugs that contribute to the improvement of urodynamics and the elimination of calculi due to the diuretic and antispasmodic effect:

• kanefron N, urolesan, cystenal, phytolysin, phytolysin plus, ciston, herbal teas, urochol

• α1-blockers,

• doxazosin, tamsulosin, terazosin.

5. Antimicrobial agents: uroseptics, Kanefron N.

6. Phytotherapeutic agents: with antimicrobial and / or anti-inflammatory effect: nephrol, bearberry leaves, lingonberries, oregano, half-fallen (Erva woolly), with diuretic effect - kidney tea, urochol, birch buds and others.

7. Anticholinergic drugs:

• non-selective: atropine sulfate;

• selective: fenpiverinium, butylscopolamine;

8. Myotropic antispasmodics: drotaverine.

Benign prostatic hyperplasia (enlargement) (BPH)

Benign prostatic hyperplasia (BPH) is a medical condition associated with aging.

It does not pose a direct threat to the patient's life in the early stages of the disease, but clinical symptoms from the lower urinary tract (LUTS) reduce the quality of life of patients.

Etiology and pathogenesis of BPH

Back in 1940 Huggins C. and Stevens R.A. revealed a relationship between the volume of the prostate gland and hormonal status. Numerous studies have established that the prostate gland is a hormone-dependent organ under the control of the hypothalamic-pituitary-gonadal system, and its growth, development and function directly depend on the level of plasma testosterone (T). Androgen deficiency is clearly manifested in the morphological and functional state of target organs, and especially the pancreas. The occurrence of pancreatic hyperplasia is a consequence of complex hormonal-enzymatic processes.

The causes of urinary dysfunction in BPH are infravesical obstruction (IVO) and impaired detrusor function. IVO is based on an enlarged prostate with a gradual narrowing of the lumen of the urethra (mechanical component) and a spasm of smooth muscle fibers of the prostate, neck of the urinary bladder and posterior urethra (dynamic component) 1.

BPH is the most common disease of the genitourinary system in older men. The first clinical symptoms appear already in the age of 40-50 years. BPH is detected in 50% of men aged 50 years, in 80-90% - over the age of 80 years.

The clinical picture of BPH

The clinical picture is dominated by symptoms associated with obstruction of the urinary tract and irritation of the bladder receptors. Bladder and urethra dysfunction are the main factors in the BPH clinic. Despite the complex genesis of symptoms of BPH, they can be divided into 2 groups:

obstructive - a sluggish stream of urine, difficulty urinating, the need to strain the anterior abdominal wall when urinating, an increase in urination time, intermittent urination, dropping urine, incomplete emptying of the bladder, paradoxical ischuria.

Irritative - frequent urination in small portions, imperative urge to urinate, inability to retain urine when an urge occurs, nocturia. BPH diagnosis

The accuracy and timeliness of the diagnosis of BPH provides higher treatment outcomes and determines the choice of treatment options. Classical methodological recommendations were developed back in 2001 by the European Association of Urology and contain test sets, divided into mandatory, recommended and optional (Table 1).

It is recommended that you use the International Prostate Symptom Score (I-PSS) 2 to evaluate the symptoms of BPH. This system contains 8 questions, seven of which describe symptoms and one that describes quality of life. The maximum symptom score is 35. Symptoms are evaluated by the total score as weak (score 0-7), moderate (8-19) or severe (20-35). The quality of life indicator is evaluated on a 6-point scale. Finger rectal examination is a must. The functional state of the kidney is evaluated by plasma creatinine.

To assess the condition of the upper urinary tract, it is necessary and sufficient to conduct an ultrasound scan. A preferred method for determining prostate volume is transrectal ultrasound. The recommended test method is to measure the residual volume of urine (OM) after urination.

Another name for this disease is prostate adenoma.

At the age of 50 years, about 25% of men have manifestations of BPH, and at the age of 65 years - already 50%. When examining the tissue of the prostate gland, BPH occurs as early

as the age of 40. The frequency of its detection in 40 years is 10%, in 60 years - 50%, in 80 years - 90%.

Actually, this condition of the prostate is characteristic of adulthood. Moreover, if benign prostatic hyperplasia (BPH) does not cause a narrowing of the urethra and does not interfere with the outflow of urine from the bladder, then it does not require treatment. In this case, only dynamic monitoring is necessary (finger examination, ultrasound, laboratory tests). BPH becomes a medical problem when there are symptoms of impaired urine outflow from the bladder - symptoms of the lower urinary tract (LUTS). A mild degree of LUTS requires medical treatment, with a significant narrowing of the urethra by the growing prostate gland and severe LUTS, surgical correction is required.

Since the exact root cause of BPH is unknown today, there are various theories of this process. The most widely accepted theories today are the following theories:

Dihydrotestosterone theory

Dihydrotestosterone is considered as a key hormone for the development of BPH. As far back as the middle of the last century, it was found that in men with genetically deficient enzyme 5 alpha reductase deficiency, the prostate gland is practically not developed, although the level of testosterone is normal (the level of dihydrotestosterone was sharply reduced).

Theory of androgen / estrogen imbalance

It is known that with age, the level of testosterone in men decreases (starting from 35-40 years). At the same time, the level of estrogens (female sex hormones) does not undergo a special change. The ratio of androgens / estrogens changes in the direction of the relative predominance of estrogens. Studies have shown that estrogens are necessary for prostate growth and the development of BPH along with androgens. Especially pronounced is the effect of estrogen on stromal tissue. Thus, a relative excess of estrogen can lead to excessive growth of stromal tissue in the gland. There is evidence of an increase in the level of receptors for androgens and an imbalance in the proliferation and death of cells in the prostate under the influence of estrogens.

Theory of stromal-epithelial interactions

The normal functioning and interaction between cells in the prostate is maintained by a large number of biologically active substances - peptides that regulate cell growth and reproduction through inhibitory and stimulating effects (growth factors). The synthesis of these factors occurs mainly in the stroma, and they affect both stromal cells and the epithelium. There is a fairly large number of these substances, in the growth of the prostate the greatest importance are:

stimulating factors:

• epidermal growth factor,

• transforming growth factor alpha and

• the main fibroblast growth factor,

• insulin-like growth factors,

• keratinocyte growth factor,

• transforming growth factor beta.

The interaction of these factors in the prostate is a very complex and incompletely studied process. An imbalance of growth factors with a predominance of stimulating prostate growth leads to the development of BPH.

Theory of Apoptosis

Apoptosis is the process of programmed cell death (the term is taken from the Greek language and literally means "falling leaves from a tree"). A cell, having passed its life cycle, should die out and a new cell should take its place. When the balance of factors affecting cell proliferation and cell death is disturbed, apoptosis can be disturbed - its activity may decrease. Thus, new cells do not replace "old" cells, but "join" them. Thus, the total number of cells increases. One of the factors influencing the increase in the activity of cell proliferation is an excess of estrogen. Thus, a number of researchers consider BPH to be a disease associated not with excessive cell proliferation, but with insufficient cell death.

Stem cell theory.

This theory is based on enhancing stem cell multiplication under the influence of imbalance in stimulating and inhibiting factors of gland growth. In this case, BPH is considered as a disease of excessive cell reproduction.

The predominant site for the onset of hyperplasia is the transition zone and the periurethral region of the prostate gland. It is here that small nodules are formed that can be found in men as young as 40 years old, large nodes usually form after 70 years.

With the development of nodes within the transition zone, the so-called lateral (lateral) lobes are formed; with localization of the process, mainly in the periurethral region, an average lobe develops.

The direction of growth of the nodes also depends on the state of the prostate itself: in the presence of glue-sclerosing of its tissue, calcifications, high density of the capsule, expansive growth in the lateral directions can be difficult, then growth towards the urethra occurs with the rapid development of symptoms. It should be remembered that there is no direct correlation between the size of the prostate and the presence and severity of symptoms. The appearance of symptoms depends, in particular, on the nature of the growth of a hundred nodes of hyperplasia, on the degree and time of onset of impaired detrusor function.

A large mass of the prostate causes mechanical compression of the outlet of the bladder — a static or mechanical component of the obstruction.

The muscle tissue of the neck of the bladder, urethra, sphincter, prostate provides the development of a dynamic component of obstruction, which is the result of increased activity of the sympathetic nervous system. Due to sympathetic activity, the tone of the above structures of the lower urinary tract increases.

In addition to these two mechanisms for the development of the disease - static and dynamic obstruction - there is another link. It is associated with a violation of the function of the urinary

bladder that occurs against the background of narrowing. As a result of the narrowing (static and dynamic) at the level of the outlet of the bladder, its detrusor muscle experiences stress during the discharge of urine necessary to overcome obstruction. This leads to a condition called detrusor instability (hyperactivity) and manifests itself as symptoms of bladder irritation. Then there is a depletion of blood flow in the muscle of the bladder, ischemia (oxygen deficiency) develops, which leads to dystrophy, and in severe cases, atrophy of muscle fibers and the loss of muscle contractile function.

It is generally accepted to divide the symptoms of BPH into two groups: symptoms of irritation (irritative, filling) and symptoms of obstruction (emptying):

Symptoms of irritation:

• frequent daily urination of pollakiuria

• nocturia (nocturnal urination)

• urgent (imperative) urination

• imperative urinary incontinence

Symptoms of obstruction:

• difficulty in starting urination

• the need for pronounced tension of the anterior abdominal wall to begin urination

• weak urine stream

• intermittent urine flow

• dripping at the end of urination

• feeling of incomplete emptying of the bladder

Symptoms of irritation and obstruction can be caused not only by BPH, but also by many other diseases, some of which are given below:

Symptoms of obstruction:

• urethral stricture

• sclerosis of the bladder neck

• prostate sclerosis

• decreased contractility of the detrusor (primary or secondary)

• prostate cancer

Symptoms of irritation:

• urinary tract infection

• prostatitis

• overactive bladder

• bladder cancer

• foreign body of the bladder

All methods of treating BPH can be divided into 3 groups:

1. Pharmacotherapy.

2. Non-surgical treatment methods.

3. Surgical treatment methods.

Pharmacotherapy of BPH.

Pharmacotherapy of BPH is aimed at strengthening the muscles of the bladder and relieving edema and inflammatory reactions from the prostate gland that occur during its growth. All this allows to achieve a significant improvement in the quality of urination, which means to achieve an improvement in the quality of life. It should be emphasized that currently there are no drugs that would cause a complete regression of BPH !!!

Currently, there are 3 main groups of drugs used to treat BPH:

• 5 alpha reductase inhibitors

• Alpha blockers

• Herbal preparations (herbal remedies)

In the recent past, a large role in the treatment of BPH was given to herbal preparations, however, in recent years, the treatment of BPH has undergone serious changes. A large number of international studies were published at the annual meeting of the American Urological Association in 2005, which indicated the ineffectiveness of herbal therapy.

The basis of conservative therapy today are alpha-blockers (doxazosin, terazosin, alfuzosin, tamsulosin) and 5-alpha reductase inhibitors (finasteride, episteride, tourosteride, dutosteride).

Alpha-adrenergic blockers, acting on the alpha-adrenergic receptors of the lower urinary tract, lead to relaxation of smooth muscle cells in the neck of the bladder, stroma, capsule of the prostate and prostatic urethra, helping to reduce irritation symptoms to a certain extent obstructive symptoms. It was also found that bladder dysfunction in BPH is largely associated with the development of detrusor hypoxia (oxygen starvation). Alpha-blockers cause an improvement in metabolic processes in the detrusor due to the expansion of the cystic arteries.

The most studied drug of the group of 5-alpha reductase inhibitors is finasteride. By blocking the conversion of testosterone to dihydrotestosterone, drugs of this group cause relative androgen deficiency in the prostate gland, leading to a decrease in its volume and thereby affecting the passive mechanism of impaired urine outflow. It is important to note that the drugs of this group do not bind to androgen receptors and do not give side effects characteristic of hormonal drugs. They are effective in patients with residual urine of not more than 100 ml and a maximum urination rate of at least 5 ml / sec. While problems associated with taking finasteride remain unresolved, such as decreased sexual function (decreased libido, decreased erection, decreased ejaculate volume). A decrease in PSA levels can make it difficult to diagnose prostate cancer on time.

Recent studies have shown the high efficiency of the combined use of alpha-blockers (doxazosin, terazosin, alfuzosin, tamsulosin) and 5-alpha reductase inhibitors (finasteride: proscar, penester, fi-nast or dutasteride: avodart). The combined treatment regimen for benign prostatic hyperplasia leads to a clinically significant improvement in the quality of life of

patients, urination parameters, and reduces the volume of residual urine. Combination therapy can be recommended as the main treatment regimen for patients at risk of progression of benign prostatic hyperplasia.

Non-surgical treatments.

Non-surgical methods include treatment methods when the local gland is affected locally by some physical factor that partially causes its death, wrinkling and, as a result, a significant reduction in size, which leads to the removal of obstructions to free urination.

Such treatment methods include:

• cryotherapy of BPH (freezing)

• thermotherapy of BPH (warming up)

• ethanol ablation of BPH (introduction of alcohol into the prostate gland)

destination. Performing procedures without taking into account the specifics of the method leads to severe complications.

Intermediate methods include the introduction of a special spiral into the urethra. This spiral is installed in the narrowed section of the urethra, where it passes through the thickness of the prostate gland. The spiral extends the prostate gland, providing a free flow of urine.

Surgical treatments.

Despite the powerful development of pharmacotherapy, BPH surgery is still relevant, and this relevance will continue for a long time to come.

Given the rapid development of methods of conservative therapy, currently, general indications for surgical treatment of BPH have narrowed:

1. uroflowmetric indicator of volumetric rate of urination (Qmax.) Less than 8ml / s.

2. the total score of the international scale for assessing the quality of urination (I-PSS) from 25 to 35 and low quality of life (QL).

3. acute urinary retention, the inability to catheterize the bladder, the presence of residual urine (more than 100 ml).

4. repeated hematuria (the presence of blood in the urine) associated with the disease.

5. renal failure.

6. bladder stones.

7. recurrent urinary tract infection due to residual urine.

8. diverticulum of the bladder.

9. inefficiency of conservative therapy.

In the future, the following data obtained as a result of the examination are guided by the following data to select a surgical treatment method:

• the size of the prostate gland.

• condition of the upper urinary tract.

• the presence of concomitant diseases.

• anthropometric characteristics (body type, patient weight).

Surgical treatment is divided into open and transurethral (endoscopic).

With the development of modern progressive technologies, the creation of unique tools that allow the surgeon to significantly simplify their work and reduce the amount of "operating trauma", speed up recovery, and thus improve treatment outcomes, minimally invasive methods of treatment are becoming more common. However, there is a certain contingent of patients who are shown open surgical treatment (the volume of the prostate gland is more than 80 cm3, the presence of bladder stones, crushing or removal of which is impossible endoscopically, inflammatory diseases of the urethra, etc.).

The "gold" standard for the treatment of BPH (prostate adenomas) is considered to be transurethral resection of the prostate (TUR). The essence of the operation is to remove the proliferation of adenomatous tissue of the prostate gland through the urethra. Open surgical interventions are used less and less every year. Transurethral resection is performed with a prostate volume of up to 60 cm3. Transurethral resection revolutionized the surgical management of BPH. Low injuries, low percentage of complications, high efficiency made TUR the method of choice for the treatment of this disease. In connection with the advent of TUR, the contingent of people visiting an urologist has changed dramatically. Even 10 years ago, more than 20% of all urological patients were elderly men with a suprapubic tube from the bladder to divert urine. Due to the presence of concomitant pathology, these people could not perform an open operation, and they were forced to live with a suprapubic catheter for the rest of their lives. Currently, the percentage of such people is minimal. TUR allows you to help almost everyone in need. And if a man came to TUR with a suprapubic catheter, then after the operation the tube is removed and the patient urinates on his own.

Transurethral incision or dissection of the neck of the bladder without removing tissues of the enlarged prostate gland. It is used in patients with a large number of severe concomitant diseases. All operations are performed through the urethra without performing an incision on the skin.

Among the most common complications of surgical treatment are:

• TUR-syndrome (absorption of injected fluid through venous vessels during surgery) - occurs, approximately in 2% of cases.

• bleeding from the operation area, both during and in the postoperative period. Occurs in 2-5% of cases.

• irritative symptoms (the appearance of rapid, painful urination, imperative urination) occurs in 70% of patients who have undergone open surgery, and 71% of patients after TUR are idle.

• urinary incontinence - occurs in 1.8% of patients undergoing incision, 2.2% after TUR of the prostate, up to 10% after open interventions.

• sclerosis (narrowing) of the neck of the bladder, stricture of the urethra (narrowing of the lumen of the urethra) - occurs in 2.6% of cases after open surgery, in 3.8% after TUR, in 1.7% after incision of the prostate gland.

• sexual dysfunction - retrograde ejaculation (lack of natural ejaculation due to reverse sperm injection into the bladder) occurs in 80% after open surgery, in 65-70% after TUR of the prostate

and in 40% after incision of the prostate gland. According to recent data, erectile dysfunction after TUR of the prostate gland was observed only in 6.5% of cases.

Open methods of surgical treatment of benign prostatic hyperplasia.

Among the open surgical methods of treatment, the following are distinguished:

1. Transvesical

2. One-piece

3. Crotch

4. Ishiorectal

5. Transrectal

6. Suprapubic peritoneal.

Of the above approaches, ischiorectal, transrectal and transperitoneal and perineal accesses have retained academic interest and are practically not used.

Transbubble and post-cilia methods remain relevant at present and are the most radical methods of treating this disease, since it is their use that can successfully relieve patients from BPH.

Transvesical adenomectomy

The development of this operation is associated with the names E. Fuller (1895), P.J. Freyer (1901), S.P. Fedorova (1908). The operation consists in opening the front wall of the bladder through suprapubic access and further digitally husking the prostate adenoma, providing one way or another method of hemostasis and drainage of the bladder by installing an urethral catheter and / or cystostomy. The postoperative period before removal of drains takes an average of 10 days. Advantages: the ability to perform with any type of growth and size of BPH. Indications for this type of surgical treatment are:

• The volume of the prostate gland is more than 70 cm3.

• The presence of a pronounced average proportion.

• Retratrigonal growth of the prostate gland (under the area of the urinary bubble triangle with compression of the intramural parts of the ureters).

• Complications of the disease (bladder stones, intramural ureteral stone, detrusor hypotension, large bladder diverticulum)

• Various concomitant diseases of the musculoskeletal system that do not allow the use of other methods of treatment (coxarthrosis, deformation of the pelvic bones, etc.).

• The desire of the patient.

Cylindrical Adenomectomy

The behind-the-cylinder (extra-bubble) adenomectomy was developed thanks to the work of Van Stockum (1909), A.T. Lida (1923). The principal difference, which was the lateral access to the anterior surface of the prostate gland, the dissection of its capsule and the husking of adenomatous nodes, without opening the anterior wall of the bladder. In the postoperative period, the drainage of the bladder is carried out through the urethral catheter.

Advantages: no need to open the bladder and shorten the postoperative period to 7-8 days.

Indications for surgery are:

1. A large volume of the prostate gland

2. The lack of an average share

3. The absence of complications of BPH (stones of the bladder, stone of the ural ureter, hypotension detrusor, large diverticulum of the bladder).

4. Lack of deformation of the bones of the pelvis.

5. Various concomitant diseases of the musculoskeletal system, which do not allow the use of transurethral resection of the prostate gland (coxarthrosis, arthrosis of the knee joints, etc.).

6. The desire of the patient.

In conclusion, I would like to note that transurethral resection of the prostate gland takes a leading place in the surgical treatment of benign prostatic hyperplasia and is the optimal method for surgical correction of urination disorders in elderly men, however, open surgery still remains relevant. Thorough preoperative preparation, an experienced surgeon performing the operation, and proper postoperative management guarantee a favorable treatment of the disease.

Drugs for BPH

The goal of treatment is to improve the quality of life of the patient, the prevention of complications and is determined by the severity of symptoms of BPH, concomitant diseases. Currently, the following types of therapy are distinguished: dynamic observation (controlled expectation), drug therapy (5-alpha reductase inhibitors, alpha-adrenergic blocking agents, plant extracts), surgical methods (transvesical prostatectomy, peritoneal prostatectomy, perineal prostatectomy, ischiorectomy) and endoscopic, minimally invasive, treatment methods.

Dynamic follow-up is recommended by the American Urological Association (AUA) and the 5th International Agreement on BPH (ICBPH) for patients with mild symptoms and in the absence of any complications.

Drug therapy should be prescribed to patients with BPH:

• with initial manifestations of urination disorders without involvement of the upper urinary tract and complications;

• patients with relative and absolute contraindications to surgical treatment;

• patients who refuse surgical treatment or postpone it for various reasons.

Briefly, indications and contraindications for drug therapy of BPH can be formulated as follows

• Indications for conservative treatment of BPH:

o The total IPSS score is greater than 8 and less than 19.

o QOL (indicator characterizing the quality of life) at least 3 points.

o Maximum urine flow rate (Qmax) not more than 15 and not less than 5 ml / sec.

o A single urination volume of at least 100 ml.

o The volume of residual urine is not more than 150 ml.

o The presence of contraindications for surgical treatment in connection with concomitant diseases.

o Social reasons, in particular, the patient's categorical rejection of the invasive treatment method.

• Contraindications to conservative therapy of BPH:

o Suspicion of a malignant process in the prostate gland.

o Inflammatory diseases of the lower urinary tract in the acute stage.

o Neurogenic disorders of urination.

o Cicatricial process in the pelvis, which is the result of surgical interventions on the prostate gland.

o Bladder stones.

o Significant size of the "middle lobe", which is a "valve" in the neck of the bladder.

o Frequently recurring attacks of macrohematuria and severe renal and hepatic insufficiency.

Phytotherapy.

The treatment of BPH with phytotherapeutic agents has become quite popular in recent years, although the mechanism of action is not completely known and there are no high-quality, long-term placebo-controlled studies confirming their effectiveness. Depending on the country of residence of the patients, certain plant extracts may be used.

5-alpha reductase inhibitors.

Finasteride was the first 5-alpha reductase inhibitor to be used to treat BPH in order to reduce the size of the enlarged prostate gland and, accordingly, reduce infravesical obstruction. The mechanism of action of 5-alpha-reductase inhibitors is due to inhibition of the conversion of testosterone into its active form - dihydrotestosterone, which is responsible for the growth of the prostate gland. Large-scale clinical studies have demonstrated that the use of finasteride can reduce prostate volume by 20-30%, improve the assessment of symptoms of MSPS by 15% and cause an increase in urine flow rate 4-6. The effectiveness of finasteride is limited to use in patients with large (over 40 cubic cm) 7 sizes of the prostate gland. The effectiveness of finasteride therapy can only be evaluated after 6 months of continuous treatment8. Side effects are associated with impaired sexual function: a decrease in sexual desire, the development of impotence, impaired ejaculation are observed, respectively, in 5-10%, 9-16% and 2-8% of cases. It should also be remembered that the use of finasteride can reduce the level of prostate-specific antigen (PSA) in serum by about 50% 9-10.

Alpha blockers.

Over the past 10 years, the use of these drugs has increased significantly. Since the publication of M. Caine, A. Pfau (1976), materials on the effectiveness of alpha-blockers in the treatment of BPH have been studied in the world more than 20 different drugs. Alpha-adrenergic blockers cause a rapid onset of therapeutic action. In terms of eliminating symptoms, they are more effective than finasteride, and their therapeutic effect does not depend on the size of the prostate gland12,13,14. In addition, alpha adrenoreceptor antagonists do not have an effect on PSA15 levels. The mechanism of action of alpha-adrenergic blockers is due to blockade of alpha-1-adrenoreceptors of the prostate gland, bladder and prostatic urethra, with a subsequent decrease in intraurethral resistance and the dynamic component of IVO. Numerous international multicenter studies have shown that alfuzosin (including the new prolonged form of XL),

terazosin, doxazosin (including the new gastrointestinal form) and tamsulosin (0.4 mg) have approximately the same efficacy when given in adequate therapeutic doses . The total score on the Prostatic Symptom Scale (IPSS) improves by 30-45%, and the maximum urination rate is 25-30% relative to the baseline.

Given the high efficiency and the rapid onset of the clinical effect, many experts consider alpha-1-adrenergic blockers as a means of first-line mediation-stone therapy. Currently, alpha-1-adrenergic blockers are used to quickly eliminate the disturbing symptoms of the disease, prevention and relief of acute urinary retention (OZM), while the selective alpha-1A / D-adrenergic blocker - tamsulosin is preferred because of the practical lack of side effects, no effect on blood pressure. The therapeutic effect of tamsulosin therapy is noted after the first administration of the drug17. However, there is no need to titrate an effective dose18, which gives a high degree of compliance in treatment.

The purpose of the lesson.

To be able to choose a pharmacological agent for ICD. To know the basic principles of the selection of antimicrobial drugs for ICD and renal colic.

Control questions.

A. Etiology, pathogenesis, complications of the ICD, renal colic, benign prostatic hyperplasia.

1.Kinds of stones

a) Calcium phosphate stones

There are three forms of hypercalciuria:

Absorption. In turn, three reasons are possible:

due to hyperabsorption (overdose of vit.D or increased formation of its metabolites)

increased calcium excretion by the kidneys due to its intake in large doses - 800 mg / day

hypercalciuria with hyperparathyroidism

Renal - violation of tubular reabsorption of calcium.

Resorption - a consequence of primary or secondary hyperparathyroidism, also occurs in Peugeot, Cushing, Calera disease, sarcoidosis, trauma or paralysis, bone metastasis, renal tubular acidosis, vit.D. intoxication, in the postmenopausal period.

Causes of hyperphosphaturia:

• primary or secondary hyperparathyroidism
• phosphoric diabetes
• Fanconi syndrome
• Cushing's disease
• renal tubular acidosis
• Albright-Battler-Bloomberg, Boyd-Sterns syndromes.

b) Calcium oxalate stones

Hyperoxaluria is divided into primary and secondary

• Endogenous or primary hyperoxaluria can be caused by an enzyme deficiency or a deficiency of vitamin B6 (pyridoxine), which blocks the conversion of glyoxylate to glycine and thus increases the formation of oxalate.

• Secondary or exogenous hyperoxaluria is a consequence of increased absorption of oxalic acid in the intestine, which can occur for several reasons:

significant consumption of products containing oxalic acid in large quantities.

the use of high doses of vitamin C

gastrointestinal diseases, accompanied by steatorrhea and insufficient absorption of fatty acids (Crohn’s disease, UC, sprue, chronic pancreatitis, cirrhosis, diabetic enteropathy, condition after resection of the small intestine).

c) Urate stones

Their occurrence is associated with constantly concentrated and acidic urine (observed in many diseases of the gastrointestinal tract with diarrhea). In appearance, such stones are yellow-brick in color with a smooth surface, solid consistency.

Hyperuricuria is divided into primary and secondary

Possible causes of primary hyperuricuria may be enzymatic disorders.

Secondary hyperuricemia can cause:

increased exogenous intake of purines

alcohol load

leukemia

myeloproliferative diseases

diabetes

medicines (corticosteroids, estrogens, amino acid infusion)

d) Cystine stones

Cystinuria In appearance, such stones are yellowish-white in color, roundish, and solid.

e) Tripelphosphate stones

Or magnesium-ammonium-calcium-phosphate: urinary tract infection (chronic or recurrent) with urease-producing bacteria (urea-cleaving enzyme) - Proteus, Klebsiella, Pseudomonas, Providencia, Serratia, Enterobacter strains. Such stones are often accompanied by characteristic crystalluria - "grave-shaped" crystals.

e) Calcium-carbonate stones of white color, smooth, soft.

g) Protein stones of white color, soft.

h) Cholesterol stones are black, soft.

B. Medicines for UL and BPH.

1. Drugs that inhibit the synthesis of uric acid: allopurinol.

2. Drugs that alkalize urine and prevent the loss of urate stones (urates): blemarin, uralitis U.

3. Drugs that prevent the formation of urinary calculi, which contribute to the dissolution of urinary stones in the kidneys and facilitate their excretion in the urine: blemarin, uralit U, madder extract, cystone, cystenal, phytolysin, Urofit and Urosan and others.

4. Drugs that contribute to the improvement of urodynamics and the discharge of nodules due to the diuretic and antispasmodic effect:

• kanefron N, urolesan, cystenal, phytolysin, phytolysin plus, cystone, herbal teas, urochol

• α1-blockers, doxazosin, tamsulosin, terazosin.

5. Antimicrobial agents: uroseptics, Kanefron N.

6. Phytotherapeutic agents: with antimicrobial and / or anti-inflammatory effect: nephrol, bearberry leaves, lingonberries, oregano, half-fallen (Erva woolly), with diuretic effect - kidney tea, urochol, birch buds and others.

7. Anticholinergic drugs:

• non-selective: atropine sulfate;

• selective: fenpiverinium, butylscopolamine;

8. Myotropic antispasmodics

For the treatment of BPH, 3 main groups of drugs are used:

• 5 alpha reductase inhibitors

• Alpha blockers

• Herbal preparations (herbal remedies)

2. Pharmacokinetics, pharmacodynamics, indications for use, dosage regimen.

3. Undesirable effects of drugs, contraindications.

4. Principles and order of prescribing drugs.

5. The interaction of drugs.

6. Criteria for evaluating the effectiveness and safety of use.

7. The choice of drugs for renal colic,

9. The choice of drugs for IBD BPH,

B. Principles of treatment for ICD and renal colic

1. To study - pharmacokinetics, pharmacodynamics, indications, contraindications for use, undesirable effects of uroantiseptics and alpha adrenoblockers.

2. The student must be able to:

a) select the necessary drug for a particular patient, select the dose, regimen and route of administration of the drug;

b) identify criteria for evaluating the therapeutic efficacy and safety of the drugs used;

c) provide differential medical assistance with:UL,Renal colic, BPH

3. The student must know:

Classification of uroantiseptics, alpha-blockers

What are the mechanisms of action of uroantiseptics

Undesirable effects of uroantiseptics

Control of the intermediate level of knowledge.

The solution of situational tasks:

1. Patient M., was admitted to the emergency hospital with sharp pains in the lumbar region, tenesmus and pain in the rectum, which are accompanied by nausea and vomiting, dysuric phenomena.

Set a diagnosis. Give first aid.

2. The patient found blood in the urine, after severe acute pain in the lumbar region, accompanied by nausea. In the analysis of urine: hematuria pyuria. A history of UL.

Set a diagnosis. What additional examination methods are needed. First aid

3. The patient has frequent urination and dysuria (characteristic when the stones are located in the intravesical segment of the distal part of the ureter).

What disease can you suspect in a patient

4. The patient has renal colic with pain in the side and irradiation into the inguinal ligament, urethra, testicles or penis located in the middle parts of the ureter.

Give first aid.

6. Patient V., 48 years old, considers himself healthy, undergoes a medical examination. Urinalysis: a large amount of urate was detected. In the history of a gift. Your preliminary diagnosis. What is the treatment tactic? Write out the recipes.

7. Pregnant 28 years, gestational age 36 weeks. Complains of pain during urination, pain in the lumbar region, fever up to 380C. The above symptoms are observed within 2 weeks. An ultrasound examination revealed calculi in both kidneys. A history of pyelone frit, for which she had previously taken urosulfan. I went to the pharmacy to purchase this drug. What is the tactic of a pharmacist? Justify the answer. Write out the recipe.

TESTS

1. A man, 62 years old, has been treated by a local therapist for an ICD for a year. The doctor decided to prescribe him a drug that inhibits the synthesis of uric acid. Which of the following drugs was prescribed to the patient?

A. Magurlite.

B. Etamide.

C. Phenylbutazone.

D. * Allopurinol.

E. Antoran.

2. The patient, 35 years old, woke up at night from a sudden, sharp pain in the lumbar region, radiating to the groin. The pain is accompanied by nausea and repeated vomiting. Symptoms Pasternatsky positive. Which of the following is most effective for relieving an attack?

A. Anestezin.

B. Morphine.

C. * Atropine.

D. Metoclopramide.

E. Papaverine.

3. A woman, 41 years old, has been ill with UL for 8 years. Concerned by the almost constant aching pain or a feeling of heaviness in the lower back, dysuric phenomena. What drugs are most appropriate?

A. * Myotropic antispasmodics.

B. Peripheral M-anticholinergic drugs.

S. Choleretikov.

D. Non-narcotic analgesics.

E. Cholecystokinetics.

4. A woman, 30 years old, who suffers from chronic pyelonephritis for a long time, complains of general weakness, drowsiness, and a decrease in urine output to 100 ml per day. HELL - 200/100 mm RT. Art. In the analyzes: creatinine - 0.62 mmol / L, hypoproteinemia, albumin - 32 g / L, potassium - 6.8 mmol / L, normochromic anemia, increased ESR. What is the first in the treatment of the patient?

A. * Hemodialysis.

B. Antibacterial therapy.

C. Vitamin therapy.

D. Antispasmodics.

E. Blood transfusion.

5. When choosing a dose of doxazazine for BPH, the doctor takes into account the age of the patient. So, for patients over 60 years of age, the dose of the drug:

A. Do not reduce

B. * Reduce by 30-50%

C. Reduce by 60-70%

D. Divided into a more frequent number of receptions

E. Reduce the frequency of receptions.

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,

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/