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Department of General and Clinical Pharmacology and Pharmacognosy

APPROVED

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TOPIC
"Clinical pharmacology of antihypertensive drugs"

Purpose:

To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of antihypertensive drugs:

- slow calcium channel blockers: dihydropyridine - nifedipine, amlodipine, isradipine, felodipine, lercanidipine;
- beta-blockers: - non-selective - nadolol, propranolol, timolol, pindolol; - beta-1-selective - bisoprolol, metoprolol, nebivolol, atenolol, betaxolol;
- alpha- and beta-blockers: carvedilol;
- ACE inhibitors: captopril, enalapril, perindopril, lisinopril, ramipril;
-angiotensin II receptor antagonists: losartan, telmisartan, irbesartan, valsartan, candesartan;
-diuretics: thiazide and thiazide-like (hydrochlorothiazide, indapamide);
-alpha-blockers: prazosin, doxazosin, tamsulosin.
-central adrenomimetics: clonidine, alpha-methyldopa.

Basic concepts (list of questions):

1. Primary arterial hypertension.
2. Secondary arterial hypertension.
3. Sympatho-adrenal system.
4. Renin-angiotensin-aldosterone system.
5. Antihypertensive drugs.
6. Hypotensive drugs.

Plan

1. Theoretical questions:

20-30% of the adult population and 50-65% of people over 65 years old suffer from arterial hypertension. In Ukraine, more than 10 million people suffer from hypertension. Of these, 57% are aware of their disease, 17% receive treatment, and only 8% suffer from hypertension and receive adequate pharmacotherapy.

Drug therapy of hypertension is the most important area of activity of a practicing physician, which allows saving the patient's life in emergency conditions - hypertensive crisis, eclampsia, shock, collapse, impaired coronary and cerebral circulation, to carry out effective secondary prevention of hypertension, symptomatic arterial hypertension, hypertension in pregnant women, etc.

The term "arterial hypertension" refers to the syndrome of increased blood pressure in "hypertensive disease" and "symptomatic arterial hypertension". The term "hypertensive disease" (HD) was proposed by G.F. Lang in 1948 and corresponds in other countries to the concept of "essential hypertension".

Under HD it is customary to understand a disease with a chronic course, the main manifestation of which is hypertension, not associated with the presence of pathological processes, in which the increase in blood pressure is due to known causes ("symptomatic arterial hypertension"). Due to the fact that HD is a heterogeneous disease with quite distinct clinical and pathogenetic variants and initial mechanisms of development, in the scientific literature instead of the term "hypertensive disease" the concept of "arterial hypertension" is often used. The reason for the prolonged and persistent increase in blood pressure above the upper limit of the range of normal fluctuations in 95% of patients aged 18 to 65 years usually remains not entirely clear. Such patients are considered to suffer from hypertension, i.e.

primary or essential hypertension. In essential hypertension, a prolonged and pathological increase in blood pressure is the primary link in the pathogenesis of the disease, its very essence, and is not a consequence of any other disease.

Secondary or symptomatic hypertension is a consequence of diseases and pathological conditions with a completely clear etiology and pathogenesis and is divided into the following main forms:

• Hemodynamic hypertension, i.e. caused by violations of hemodynamic conditions due to organic pathology of large vessels (mainly the aorta) or the heart. The causes of this type of hypertension can be: coarctation of the aorta; sclerosis of the walls of the aortic chamber, most often caused by atherosclerosis of the aorta; large arteriovenous fistulas; aortic valve insufficiency; severe bradycardia with complete atrioventricular block.

• Neurogenic hypertension: central nervous arterial hypertension (in encephalopathies as a result of craniocerebral injuries, encephalitis, in brain tumors); hypertension due to weakening of depressor reflexes from baroreceptors of reflexogenic zones of the aorta and carotid arteries (more often in their atherosclerosis); hypertension in diseases of the peripheral nervous system (poliomyelitis, poisoning with thallium salts).

• Endocrinopathic hypertension: in hormonally active tumors of the pituitary gland (Itsenko-Cushing's disease), adrenal glands (primary hyperaldosteronism, Itsenko-Cushing's syndrome, chromaffinomas, pheochromocytoma); in diffuse toxic goiter; during menopause.

• Nephrogenic or renal hypertension: with diffuse inflammation of the kidneys (nephritis, pyelonephritis), their compression (with paranephritis, tumors, injuries with hematoma formation, etc.), with urolithiasis; renovascular hypertension - with impaired arterial vascularization of the kidneys, for example, stenosis or dysplasia of the renal arteries.

• Drug-induced hypertension associated with the use of medications that increase blood pressure (ephedrine and other adrenomimetics) or affect its regulation systems (glucocorticoids and hormonal contraceptives).

Hypertensive disease is a disease whose main manifestations are caused by arterial hypertension, which is not symptomatic.

Classification of GH (WHO):

Stage 1 - there is an increase in blood pressure without changes in target organs.

Stage 2 - an increase in blood pressure is accompanied by initial changes in target organs without impairment of their functions (left ventricular hypertrophy, changes in the fundus, microproteinuria).

Stage 3 - increased blood pressure is accompanied by changes in target organs and impairment of their functions - brain (stroke), heart (infarction), kidneys (nephrosclerosis).

Arterial hypertension is a pathological condition of the adult body, caused by a prolonged increase in systolic blood pressure above the level of 140 mm Hg. and diastolic blood pressure above 90 mm Hg. If diastolic blood pressure is below 90 mm Hg. and systolic blood pressure above 140 mm Hg., then such arterial hypertension is defined as isolated systolic arterial hypertension.

Classification of blood pressure levels with the allocation of stages of hypertension

	SBP mm Hg.	DBP mm Hg.
Optimal blood pressure	Less than 120	Less than 80
Normal blood pressure	120-129	80-84
Normal high blood pressure	130-139	85-89
Grade I (mild)	140-159	90-99
Grade II (moderate)	160-179	100-109
Grade III (severe)	More than 180	More than 110

The main cause of hypertension: repeated, as a rule, prolonged psycho-emotional stress. The stress reaction has a pronounced negative emotional character. Risk factors for hypertension are divided into: those that are modifiable (controlled) and those that are not

modifiable (uncontrolled).

Uncontrollable risk factors include: heredity, gender, age, menopause in women, environmental factors.

Controlled risk factors include: smoking, alcohol consumption, stress, atherosclerosis, diabetes mellitus, excessive salt intake, physical inactivity, obesity.

The main goal of treating patients with hypertension is to minimize the risk of complications and death from them. To achieve this goal, it is necessary not only to reduce blood pressure to a normal level, but also to correct all controlled risk factors: smoking, hyperlipidemia, hyperglycemia, obesity, and treatment of concomitant diseases. The target blood pressure level in the treatment of hypertension is <140/90 mm Hg in all patients. With good tolerability of the prescribed therapy, it is useful to reduce blood pressure to lower values. When combined with hypertension with diabetes mellitus or kidney damage, a decrease in blood pressure <130/80 mm Hg is recommended. During antihypertensive therapy, it should be borne in mind that it is difficult to achieve a decrease in SBP <140 mm Hg in elderly patients. When achieving target blood pressure levels, it is necessary to take into account the lower limit of blood pressure reduction to 110 mm Hg - systolic blood pressure and 70 mm Hg - diastolic blood pressure.

Modern methods of treatment and prevention of hypertension

The criteria for the success of treatment of hypertension are the blood pressure level, which should be close to the age norm, be accompanied by satisfactory well-being, and the absence of treatment complications. It is necessary to avoid sharp drops in blood pressure, especially in patients with signs of atherosclerotic damage to the heart, brain, and kidneys. Normalization of blood pressure in these patients is sometimes accompanied by a deterioration in well-being. In such cases, it is advisable to maintain blood pressure at a slightly elevated level (diastolic up to 100 mm Hg). The approach to the treatment of hypertension - ordinary or malignant, and symptomatic secondary - does not differ fundamentally. The use of antihypertensive drugs should be based on the following basic principles:

1) treatment should be long-term, and in most cases - continuous. Changing drugs should be avoided, unless this is forced by ineffectiveness or poor tolerability of treatment;
2) the dose should be minimally effective and maximally safe;
3) the choice of drugs should correspond to the pathophysiological features of hypertension in a given patient. Inadequate treatment, especially long-term, is worse tolerated and more often leads to complications;
4) drug combinations should, as a rule, include drugs of multidirectional action, taking into account the pathophysiological features of hypertension in the patient and possible complications of drug treatment.

In the initial stages of the disease, non-drug treatment methods are widely used: rational psychotherapy, relaxation therapy, auto-training, physical exercises (while static loads and a large amount of physical work should be avoided). Patients with manifestations of emotional hyperreactivity are shown valerian, motherwort, corvalol or tranquilizers of the benzodiazepine group (elenium, seduxen, nosepam, phenazepam, etc.) in individually selected doses.

Drug therapy with antihypertensive agents includes 5 leading groups:

1. ACE INHIBITORS
2. ANTAGONISTS OF RECEPTORS SENSITIVE TO ANGIOTENSIN II
3. BETA-ADRENOBLOCKERS
4. CALCIUM CHANNEL BLOCKERS
5. DIURETICS

Mechanism of action and classification of ACE inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have been widely used in clinical practice for the treatment of hypertension since the 1970s and are generally recognized

standards. The widespread use of ACE inhibitors is due to the peculiarities of their action and the functions of the renin-angiotensin-aldosterone system (RAAS). Local angiotensin II plays a significant role in the development of structural changes in pathological processes such as myocardial hypertrophy and remodeling, ischemic heart disease, and atherosclerosis.

Acting by blocking 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 the activation of angiotensin II 1 receptors: they eliminate pathological vasoconstriction, inhibit cell growth and proliferation of myocardial and vascular smooth muscle cells, weaken sympathetic activation, reduce sodium and water retention. In addition, by affecting the pressor systems of blood pressure regulation, they also act on the depressor systems, increasing their activity by slowing the degradation of vasodepressor peptides - bradykinin and prostaglandin E2, which cause relaxation of vascular smooth muscle and promote the production of vasodilating prostanoids and the release of endothelial-relaxing factor.

Mechanisms of antihypertensive action of ACE inhibitors and A-II receptor antagonists

These pathophysiological mechanisms provide the main pharmacotherapeutic effects of ACE inhibitors: antihypertensive and organoprotective action, lack of significant effect on carbohydrate, lipid and purine metabolism, reduction of aldosterone production by the adrenal cortex, reduction of adrenaline and noradrenaline synthesis, inhibition of ACE activity, reduction of angiotensin II content and increase of bradykinin and prostaglandins in blood plasma. The initial effect of ACE inhibitors is due to their effect on the RAAS of the systemic circulation, which is manifested by inhibition of ACE activity, reduction of angiotensin II formation and leads to vasodilation, reduction of aldosterone synthesis, natriuresis and some increase in plasma potassium.

To date, 3 generations of ACE inhibitors have been introduced into clinical practice. Depending on the nature of the chemical group in the drug molecule, which is responsible for the interaction with the active center of ACE, there are:

-ACE inhibitors of the I generation, containing sulfhydryl groups: captopril, pivalopril, zofenopril;

-ACE inhibitors of the II generation, containing a carboxyl group: enalapril, lisinopril, cilazapril, ramipril, perindopril, benazepril, moexipril;

-ACE inhibitors of the III generation (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 active center of ACE. At the same time, the sulfhydryl group is associated with the development of some undesirable side effects of captopril, such as taste disturbance, rash. This same sulfhydryl group, due to easy oxidation, may be responsible for the shorter duration of action of the drug.

In order to improve absorption, most modern ACE inhibitors are produced in the form of prodrugs. ACE inhibitors in the form of prodrugs differ from non-esterified drugs in a somewhat more delayed onset of action and an increased duration of effect. All ACE inhibitors can be divided into active dosage forms and prodrugs.

The first class is lipophilic ACE inhibitors, which have pharmacological activity and are metabolized in the liver (captopril);

The second class is lipophilic prodrugs, which become active after metabolic transformation (hydrolysis) in the liver and other organs (enalapril, moexipril, trandolapril, fosinopril);

The third class - hydrophilic drugs that have pharmacological activity and are not metabolized in the body (excreted by the kidneys unchanged) - lisinopril.

According to the duration of the clinical effect, the following are distinguished:
-short-acting drugs that must 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);
-long-acting drugs that in most cases can be taken once a day (quinapril, lisinopril, perindopril, ramipril, spirapril, trandolapril, fosinopril).

Based on rational combinations of ACE inhibitors with diuretics, new drugs are being created, such as capozide (captopril 50 mg + hydrochlorothiazide 25 mg), enap HL (enalapril 20 mg + hydrochlorothiazide 25 mg). The combination of ACE inhibitors with potassium-sparing diuretics (amiloride, triamterene) is not justified due to the likelihood of developing hyperkalemia!

Long-term use of ACE inhibitors is most indicated in patients with GH with:
-initially reduced indicators of left ventricular myocardial contractile function (with/without clinical signs of CHF);
-left ventricular myocardial hypertrophy (myocardial mass index according to EchoCG data for men more than 134 g/m2, for women - 110 g/m2).

Organoprotective effects of ACE inhibitors:
-cardioprotective effect (regression of myocardial hypertrophy, prevention of heart remodeling processes, antiischemic effect, antiarrhythmic effect);
-vasoprotective effect (enhancement of endothelium-dependent vasodilation, inhibition of proliferation of arterial smooth muscle, cytoprotective effect);
-nephroprotective effect (increased natriuresis and decreased kaliuresis, decreased intraglomerular pressure, inhibition of proliferation and hypertrophy of mesangial cells, epithelial cells of renal tubules and fibroblasts);
-metabolic effects (improved glucose metabolism, increased sensitivity of peripheral tissues to insulin, antiatherogenic effects, anti-inflammatory effects).

The complex of cardiac changes in GH, including hypertrophy of the left ventricular myocardium (LVMH) and changes in its structure and function, is called the "hypertensive heart". The formation of LVMH and cardiac remodeling in GH, in addition to hemodynamic factors, is also influenced by neurohumoral factors. In this case, the main role is assigned to the RAAS, the sympatho-adrenal system (SAS) 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, causes vasoconstriction of coronary arteries. Being initially compensatory, LVH during its progression carries a number of negative consequences, which is referred to as "overlap" of compensation. Among such consequences, the leading ones are recognized as disorders of diastolic and systolic functions, disorders of coronary blood circulation (acceleration of atherogenesis processes in large and medium-caliber coronary vessels, pathology of small coronary arteries, changes in coronary vasodilator reserve and autoregulation of coronary perfusion) and increased ventricular ectopic activity.

ACE inhibitors are original drugs that allow not only to interfere with the established balance of the pressor and depressor neurohumoral systems of the body, but also have the ability to influence the processes of left ventricular remodeling, causing regression of LVEF and preventing ischemic and reperfusion injury 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 the hypertrophied myocardium. A decrease in LVEF can be expected no earlier than after 4-6 months of continuous treatment.
Among the target organs in GC, the kidneys occupy a special place, since they play an important role in maintaining the activity of the RAAS, in the excretion of kallikrein with urine, in the synthesis of prostaglandins, in the regulation of water and electrolyte homeostasis by means of sodium-modulating hormones, in controlling the level of antidiuretic hormone.

The development of vascular changes in the kidneys, which are characteristic of GC, 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 nephropathies is the disruption of intrarenal hemodynamics with the development of intraglomerular hypertension and hyperfiltration, which lead to an increase in the permeability of the basement membranes of the glomerular capillaries and glomerulosclerosis.

Markers of renal involvement in the pathological process and indicators of intraglomerular hypertension are proteinuria, glomerular filtration rate (GFR), reabsorption, and the state of intraglomerular hemodynamics, which in the clinic is determined by the filtration fraction (the ratio of GFR to the value of renal plasma flow) or renal functional reserve - the increase in GFR after oral protein loading. With an increase in intraglomerular pressure, the filtration fraction increases, and the renal reserve is absent. ACE inhibitors are superior to other antihypertensive agents in terms of nephroprotective activity, which, at least partially, does not depend on their antihypertensive effect. By blocking the formation of angiotensin II, including in the tissues of the kidneys themselves, ACE inhibitors dilate the efferent arteriole of the glomeruli and thereby reduce intraglomerular hypertension. In addition, angiotensin II has a direct effect on the kidneys, accelerating the development of sclerosis by blocking the stimulation of mesangial cell growth, stimulating their production of collagen and epidermal growth factor of the renal tubules. In addition, ACE inhibitors have a pronounced antiproteinuric activity, independent of their antihypertensive effect.

Drug interactions of ACE inhibitors: ACE inhibitors have no pharmacokinetic interactions. All drug interactions with them are pharmacodynamic.

The combination of ACE inhibitors with diuretics, in particular with hypothiazide or furosemide, enhances the hypotensive effect, without significantly affecting the amount of diuresis or natriuresis. At the same time, the potassium-sparing property of ACE inhibitors eliminates potassium losses when taking saluretics. On the contrary, the combination of potassium-sparing diuretics with ACE inhibitors increases the risk of developing hyperkalemia. The simultaneous use of ACE inhibitors with other antihypertensive agents due to the additive effect allows to achieve a more pronounced hypotensive effect in hypertension refractory to monotherapy with ACE inhibitors. At the same time, increasing the hypotensive effect of ACE inhibitors in patients with CHF and normotonicity may be undesirable. Drug interactions with NSAIDs may lead to a weakening of the hypotensive effect of ACE inhibitors due to fluid retention and blocking the synthesis of prostaglandins in the vascular wall.

Intolerance to ACE inhibitors

When taking ACE inhibitors, specific (dry cough, first-dose hypotension, impaired renal function, hyperkalemia and angioedema) and non-specific (taste disturbance, leukopenia, skin rash and dyspepsia) side effects may be observed.

Dry cough is one of the most specific side effects of ACE inhibitors. The incidence varies from 0.2 to 33%. Cough can occur not only at the beginning of treatment, but also at a later stage. The mechanism of cough is associated with inhibition of bradykinin breakdown and accumulation of kinins, which, on the one hand, leads to larynx vasoedema, and on the other - to bronchoconstriction. Inhibition of bradykinin degradation causes an increase in prostaglandin synthesis, especially PGE2, which in turn can lead to stimulation of afferent C-fibers and the occurrence of a painful dry cough.

Arterial hypotension as an excessive manifestation of the main pharmacodynamic effect of ACE inhibitors usually develops after taking the first dose.

Renal dysfunction. During long-term therapy with ACE inhibitors, it is advisable to periodically monitor the level of creatinine and proteinuria.

Angioedema occurs much less frequently than dry cough - (0.1-0.5% of cases).

Contraindications to the appointment of ACE inhibitors:
-Increased individual sensitivity to the drug (intolerance)
-Pregnancy and lactation
-History of angioedema with any other ACE inhibitor
-Bilateral hemodynamically significant renal artery stenosis or stenosis of the renal artery to a solitary kidney
-Severe chronic renal failure (serum creatinine above 300 mmol/l) or severe hyperkalemia (above 5.5 mmol/l)
-HCM with obstruction of the left ventricular outflow tract, hemodynamically significant stenosis of the aortic or mitral valves, constrictive pericarditis
-Leukopenia (neutrophil count less than 1000 in 1 mm3), severe anemia (hemoglobin less than 70 g/l).

Angiotensin II receptor antagonists (ARBs)

The action of ARBs is based on inhibition of RAAS activity at the level of angiotensin II receptor subtype 1. Angiotensin II receptor antagonists neutralize the effects of angiotensin II on the cardiovascular system by selectively blocking AII receptors. The direct mechanism of antihypertensive action of ARBs is associated with the weakening of the effects of angiotensin II (and angiotensin III), which are mediated by AT1-angiotensin receptors. By blocking AT1 receptors, ARBs reduce vasoconstriction, reduce increased hydraulic pressure in the renal glomeruli, and also reduce the secretion of aldosterone, endothelin-1 and noradrenaline. With prolonged use, ARA II weaken the proliferative effects of angiotensin II on cardiomyocytes and smooth muscle cells of the vascular wall, as well as mesangial cells and fibroblasts.

ARA II are able to penetrate the blood-brain barrier and inhibit the activity of presynaptic AT1 receptors of sympathetic neurons, which regulate the release of noradrenaline. Therefore, central mechanisms of antihypertensive action of ARA II cannot be ruled out. The direct mechanism of antihypertensive action of AII receptor antagonists is associated with the blockade of AT1 receptors, and indirect mechanisms - with the 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 to these classes of drugs are 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 synthesis of adrenaline and noradrenaline.

Classification

According to the chemical structure, ARA II can be divided into three groups:
- biphenyl tetrazole derivatives: losartan, irbesartan, candesartan, tazosartan;
- non-biphenyl non-tetrazole compounds: eprosartan, telmisartan;
- non-heterocyclic compounds: valsartan.

Losartan, valsartan and irbesartan are active dosage 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, ARA II also differ in the nature of binding to receptors. Thus, eprosartan and the active metabolite of tazosartan enoltazosartan are competitive antagonists of angiotensin II. On the contrary, valsartan, irbesartan, candesartan, telmisartan, and the active metabolite of losartan EXP-3174 act as non-competitive antagonists of angiotensin II. Eprosartan has an additional mechanism of vasodilating action, not characteristic of other antagonists of AII receptors - it blocks presynaptic AT1 receptors of the sympathetic nervous system. Due to this property, eprosartan inhibits the release of norepinephrine from the endings of sympathetic nerve fibers and thereby reduces stimulation of adrenoreceptors of

vascular smooth muscle.

ARA II have a number of important advantages over ACE inhibitors, which make their use promising in the treatment of patients with hypertension. First, AII receptor antagonists provide a more complete and more selective blockade of the RAAS than ACE inhibitors. Secondly, the action of AII receptor antagonists is more specific than that of ACE inhibitors. Unlike ACE inhibitors, they do not affect the activity of other neurohumoral systems, which are associated with such side effects characteristic of ACE inhibitors as dry cough and angioedema. The greater selectivity and specificity of RAAS blockade explain the better tolerability of ARA II compared to ACE inhibitors. The maximum antihypertensive effect of ARA II is achieved no earlier than 4-8 weeks after the start of therapy. Hypotension after taking the first dose is uncharacteristic for these drugs. Abrupt withdrawal of AT1-angiotensin receptor blockers is not accompanied by the development of rebound hypertension. With prolonged use, AII receptor antagonists cause the reverse development of left ventricular hypertrophy in patients with GC, increase renal plasma flow, without significantly affecting GFR. They reduce urinary albumin excretion in patients with GC with diabetic nephropathy. ARA II do not have an adverse effect on purine metabolism, glucose metabolism and blood lipid composition.

Side effects and contraindications to the appointment of AII receptor antagonists.

Drugs from this group have a good safety and tolerability profile. The most common side effects - weakness, dizziness, headache and dyspeptic phenomena (bitter taste in the mouth, nausea) - occur in 13 - 15% of patients. Dry cough with the use of AII receptor antagonists occurs in only 0.5 - 0.8% of cases. Contraindications to the appointment of AII receptor antagonists are individual hypersensitivity to the drugs, pregnancy and breastfeeding. They are not recommended for use in severe renal and hepatic insufficiency, as well as in obstruction of the biliary tract. In severe renal insufficiency, kidney function is maintained due to the activation of the renin-angiotensin system and in these conditions, inhibition of RAAS activity can cause further deterioration of kidney function.

Beta-blockers

Beta-blockers are a very homogeneous group of drugs in terms of their pharmacological effects, the only common property of which is competitive antagonism towards beta-adrenergic receptors. Along with the blockade of beta-1-adrenergic receptors, beta-adrenergic blockers can block beta-2-adrenergic receptors. In the first case, we are talking about non-selective beta-blockers, in the second - about beta-adrenoselective drugs. Beta-blockers also differ in the presence or absence of internal sympathomimetic activity (BSA), vasodilating action, lipophilicity. There is no generally accepted classification of β-blockers. Drugs used for long-term therapy of GC are conveniently divided into the following groups depending on the presence or absence of vasodilating properties and beta-adrenoselectivity:

1. Beta-blockers without vasodilating properties:
a) non-selective (propranolol, nadolol, oxprenolol, sotalol, timolol);
b) beta-1-adrenoselective (atenolol, betaxolol, bisoprolol, metoprolol).
2. Beta-blockers with vasodilating properties:
a) non-selective (bucindolol, labetolol, carvedilol);
b) beta-1-adrenoselective (nebivolol, celiprolol).

The vasodilating properties of beta-blockers can be due to the following mechanisms: - pronounced vasodilation of vascular beta-2-adrenoceptors (pindolol, celiprolol); - blockade of beta-1- and (or) beta-2-adrenoceptors (carvedilol, labetolol); - release of NO from endothelial cells, which has vasodilating properties (nebivolol).

Mechanisms of antihypertensive action of beta-blockers:
- reduction of cardiac output due to negative chrono- and inotropic effects;
- inhibition of renin secretion;

- restructuring of the baroreflex mechanism of the aortic arch and carotid sinus;
- reduction of the release of noradrenaline from the endings of postganglionic sympathetic nerve fibers as a result of blockade of presynaptic beta-2-adrenoceptors (non-selective beta-blockers);
-increased release of vasodilating substances (prostaglandins E2 and I2, nitric oxide, atrial natriuretic factor);
-decreased total peripheral vascular resistance (only beta-blockers with vasodilating properties);
-effect on the vasomotor centers of the medulla oblongata (lipophilic beta-blockers).

Based on solubility in fats and water, beta-blockers are divided into three groups:
1) lipophilic (betaxolol, metoprolol, propranolol, etc.);
2) hydrophilic (atenolol, nadolol, sotalol, etc.);
3) amphophilic (bisoprolol, nebivolol, acebutolol).

Differences in the physicochemical properties of beta-blockers not only determine the features of their pharmacokinetics, but also have important clinical significance. Apparently, it is lipophilic beta-blockers that have a cardioprotective effect, which was shown in two meta-analyses. For long-term therapy of GC, lipophilic beta-blockers without ICA (bisoprolol, betaxolol, metoprolol, nebivolol, timolol, etc.) should be used whenever possible, limiting the use of drugs with ICA and hydrophilic drugs.

In monotherapy, they allow to achieve adequate reduction of blood pressure in 50-70% of patients with mild and moderate forms of GC. The antihypertensive effect of beta-blockers is significantly enhanced when combined with thiazide diuretics, calcium antagonists of the dihydropyridine series (amlodipine, etc.). Of important clinical importance is the duration of antihypertensive action of beta-blockers used for long-term GC therapy. Sudden cessation of short-acting beta-blockers causes the development of withdrawal syndrome, which is manifested by both a sharp increase in blood pressure and the development of unstable angina and acute myocardial infarction. Sufficient antihypertensive effect when taken once a day is provided by atenolol, betaxolol, bisoprolol, nadolol, nebivolol, sotalol, as well as delayed forms of metoprolol and propranolol.

Along with antihypertensive efficacy, all beta-blockers also have antianginal effect. Therefore, they are especially indicated for the treatment of hypertension in patients with coronary artery disease, stable angina pectoris, after myocardial infarction.

Controlled studies have shown that bisoprolol, carvedilol and delayed form of metoprolol improve the long-term prognosis in patients with CHF. These beta-blockers, as well as nebivolol, which improves left ventricular contractility, can be recommended for the treatment of hypertension complicated by the development of overt or latent left ventricular dysfunction. With prolonged use, beta-blockers cause the reverse development of left ventricular hypertrophy in patients with GC. For long-term GC therapy, it is better to use beta-blockers that have beta-1-adrenoselectivity, lipophilic properties and long-term action (for example, bisoprolol, betaxolol, nebivolol or the retard form of metoprolol). According to modern recommendations, beta-blockers are the drugs of choice in patients with GC in combination with coronary artery disease, angina pectoris, who have suffered a myocardial infarction, with tachyarrhythmias, with hyperthyroidism, glaucoma, and migraine. Cardioselective beta-blockers (especially nebivolol, which has an inhibitory effect on the development of diabetic angiopathy by stimulating the synthesis of NO in the vascular endothelium and reducing the level of triglycerides in the blood) can be used in patients with diabetes mellitus; beta-blockers with vasodilating properties (carvedilol, nebivolol) - for CHF.

Side effects:
Negative inotropic and chronotropic effects (decreased myocardial contractile function and bradycardia).
Sick sinus syndrome.
Atrioventricular block.

Congestive heart failure.
Arterial hypotension (systolic blood pressure below 100 mm Hg).
Withdrawal syndrome (ricochet hypertension, exacerbation of coronary artery disease).
Increased hypertensive reaction to the abolition of clonidine and other central beta-2 adrenoceptor agonists, as well as in pheochromocytoma.
Peripheral vasospastic reactions (intermittent claudication, Raynaud's syndrome).
Bronchospasm (exacerbation of bronchial asthma or other obstructive pulmonary disease).
Development of hypoglycemia, especially in patients with labile diabetes mellitus, with simultaneous administration of a beta-blocker and insulin or oral hypoglycemic drugs.
Sexual dysfunction in men (frequency from 11 to 28% with long-term use of the non-selective beta-blocker propranolol, depending on the dose; less often with the use of beta-1-selective drugs in medium therapeutic doses).
Gastrointestinal disorders (most often constipation).
Depression, sleep disorders, agitation, aggressiveness, confusion.
Changes in the mucous membranes and skin (rash, urticaria, photophobia).

Combined treatment of hypertension

The purpose of treatment of patients with hypertension is to reduce blood pressure to optimal or normal values (<140/90 mm Hg). Lower target blood pressure values are established for young patients and patients with diabetes. Effective control of elevated blood pressure reduces cardiovascular morbidity and mortality in patients with hypertension. In practice, however, it is known that approximately half of patients with hypertension who receive drug treatment have inadequate blood pressure control. As a rule, 50-70% of patients require combined antihypertensive therapy to achieve target blood pressure values. The effectiveness of combined therapy is based on the effect on various pathogenetic mechanisms that complement each other. Combined therapy allows for effective blood pressure control against a background of good tolerability without increasing the dose of each drug. The combination of drugs with different mechanisms of action also allows to reduce changes in target organs, differently affecting the mechanisms of damage to the heart, blood vessels and kidneys.

Conducting combined therapy of AH allows:
- To influence different links of pathogenesis of AH with drugs from different groups;
- To reduce the doses of the drugs taken;
- To achieve adequate reduction of blood pressure with low doses of both drugs;
- To reduce the risk of side effects;
- To avoid the slippage effect;
- To mutually neutralize possible adverse effects of both drugs.

Requirements for the choice of drugs when conducting combined therapy of AH:
- Effect on different pressor mechanisms of increasing blood pressure;
- Synergism of action;
- Absence of strengthening of risk factors;
- Favorable effect on target organs;
- Possibility of combining different doses;
- Convenience of reception.

Rational combinations of antihypertensive drugs

Diuretics Beta-blockers, ACE inhibitors, AII receptor antagonists
Beta-blockers Calcium antagonists (dihydropyridine), alpha-blockers, diuretics
ACE inhibitors Diuretics, calcium antagonists, alpha-blockers
Calcium antagonists (dihydropyridine) Beta-blockers, ACE inhibitors
AII receptor antagonists Diuretics
Alpha-blockers Beta-blockers, ACE inhibitors
ACE inhibitors and diuretics

The combination of ACE inhibitors and diuretics is one of the most effective options for combined therapy of GH. The antihypertensive efficacy of such a combination reaches 80% and above and may increase against the background of a diet with salt restriction. The combination of a diuretic with an ACE inhibitor is more effective than the combination of the former with beta-blockers. ACE inhibitors eliminate the undesirable effects of diuretic therapy. Thus, hypokalemia, often observed during treatment with diuretics, is usually eliminated when they are co-administered with ACE inhibitors. The combination of ACE inhibitors with diuretics has an advantage in patients with GC in combination with chronic heart failure, with hypertrophy of the left ventricular myocardium, diabetic nephropathy, and in elderly patients.

Beta-blockers and diuretics

The antihypertensive efficacy of a combination of a beta-blocker and a diuretic according to clinical studies is about 75%. In addition, a decrease in morbidity and mortality has been noted in patients suffering from hypertension, and in particular, in elderly patients. The combination of β-blockers and diuretics has additional antihypertensive capabilities and may provide a cardioprotective effect. Beta-blockers neutralize the increase in plasma renin activity induced by diuretic administration. In turn, diuretics control the increase in sodium caused by beta-blockers. Despite these advantages, the use of a combination of beta-blockers and diuretics has a number of limitations associated with the ability of both classes of drugs to increase triglycerides, glucose and uric acid levels, as well as to cause sexual dysfunction. Metabolic side effects of therapy can be corrected by using reduced doses of each drug.

Beta-blockers and calcium antagonists

Beta-blockers are well combined with calcium antagonists of the dihydropyridine series, since the former reduce cardiovascular resistance and reduce cardiac output, and the latter are peripheral vasodilators and increase cardiac output. In addition, beta-blockers eliminate reflex tachycardia and activation of the sympathoadrenal system (SAS), which is caused by dihydropyridine derivatives. The antihypertensive effect when prescribing two drugs is mutually enhanced and well tolerated. This combination is effective and has advantages in patients with hypertension in combination with coronary artery disease, angina pectoris. The combination of beta-blockers and non-dihydropyridine calcium antagonists, such as verapamil and diltiazem, should be avoided, as they have a similar spectrum of side effects (bradycardia, slowing of atrioventricular conduction, especially in patients with coronary artery disease).

ACE inhibitors and calcium antagonists

ACE inhibitors and calcium antagonists lower blood pressure by peripheral vasodilation. The antihypertensive effect of calcium antagonists may be limited by their stimulating effect on the RAAS and SAS, which causes side effects such as edema and tachycardia, especially when using dihydropyridine calcium antagonists. The combined use of calcium antagonists with ACE inhibitors helps to reduce these effects. The decrease in angiotensin II levels during ACE inhibitor therapy enhances the antihypertensive effect of calcium antagonists, since the activity of the RAAS is inversely proportional to the degree of blood pressure reduction achieved with the calcium antagonist. With combined therapy of ACE inhibitors and non-dihydropyridine calcium antagonists, a combined renoprotective effect was noted due to a decrease in glomerular pressure and the degree of albumin excretion. Favorable effects in nephropathy in patients with diabetes were noted with the combination of ACE inhibitors with verapamil.

Clinical studies in recent years have shown that the appointment of fixed combinations of small doses of antihypertensive drugs belonging to different classes is more effective than the use of the same drugs in monotherapy.

The use of fixed combinations of drugs has been used in clinical practice for quite a long time. Such drugs as Adelfan, Adelfan Ezidrex, Brinaldix, Trirezid have been quite

popular for a long time. Today, they have been replaced by new drugs containing two active ingredients, created on the basis of modern recommendations on the rational combination of antihypertensive drugs of different classes. Fixed dosage forms, such as Logimax, Capozid, Co-Renitec, Equator, etc., are becoming increasingly widespread, displacing the "old" Brynnerdine, Adelphan, and Trirezid from clinical practice. Fixed dosage forms are advisable to use in those patients in whom blood pressure correction is possible with a single dose of drugs. Thus, modern views on the pathogenesis of GC, on the one hand, and the need to achieve a target blood pressure level for a real reduction in cardiovascular risk, on the other, explain the trend towards combined GC therapy that has been noticeable in recent years, especially with the use of fixed dosage forms, which allow increasing the effectiveness of treatment, reducing the risk of adverse events, and optimizing pharmacotherapy of AH patients.

2. Questions for self-control (list of questions):

1. List the pathogenetic mechanisms of arterial hypertension, which is the object of the influence of antihypertensive drugs.
2. List the main groups of antihypertensive drugs.
3. Explain the mechanisms of antihypertensive effects of the main groups of drugs, based on their pharmacodynamics.
4. Formulate the significance of the leading pharmacokinetic characteristics (T1/2el, plasma protein binding, Vd) in the individual selection of antihypertensive drugs.
5. Highlight the clinical and laboratory-functional criteria for therapeutic efficacy and safety of antihypertensive drugs.
6. Give a clinical and pharmacological characteristic of drugs that are widely used in disorders of vascular tone: amlodipine (norvasc), nifedipine, verapamil, diltiazem, bisoprolol (concor), metoprolol (betalok), carvedilol, captopril (capoten), enalapril (enap), perindopril (prestarium), lisinopril (dapril), ramipril, losartan (cozaar), valsartan (diovan), telmisartan (micardis), candesartan, alpha-methyldopa, clonidine (clophenin), including combined drugs - Enap N, Liprazid, Co-Diroton, Equator.
7. What principles are the basis for the classification of antihypertensive drugs?
8. List the drugs and the main mechanisms that cause vasodilation.
9. What hemodynamic changes occur in the body against the background of the action of slow calcium channel blockers? Indications and contraindications to their use.
10. Explain the mechanism of hypotensive action of drugs that affect the humoral links of blood pressure regulation. Formulate indications and contraindications for their appointment.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write prescriptions for the main antihypertensive drugs (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for appointment. Indicate and explain possible effective and undesirable drug combinations.
B. Independent practical work in class.
1. Curation of a thematic patient in the ward.
2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and the list of medical prescriptions.
3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.
4. To identify signs during subjective and objective examination of the patient that characterize vascular tone disorders, leading clinical syndromes - arterial hypertension, to write a clinical diagnosis of the disease.

5. To determine the group of drugs needed by the patient; based on theoretical data on pharmacodynamics and own observations, to select drugs for the patient.
6. To choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.
7. To identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.
8. To justify the need for combined drug therapy and to suggest possible options for a safe combination of drugs.
9. To make a forecast of side effects of drugs prescribed to the patient and to outline a plan for their detection at early stages.
10. To justify the duration of basic and maintenance therapy.

B. Solution of situational tasks.

1. A man, 60 years old, complains of headaches, dizziness, noise in the head, lack of night sleep, nausea in the morning, impaired vision, pain in the heart area of a stenocarditic nature after 50-100 m of walking, when climbing to the 2nd floor, shortness of breath during physical exertion, interruptions in heart activity. In the anamnesis - hypertension for 30 years. Maximum ACT - 200/140 mm Hg, working - 160/120 mm Hg. Five years ago he suffered a myocardial infarction, two years - acute cerebral circulation in the basin of the right middle cerebral artery. Objectively: general condition of moderate severity. Cyanosis of the lips. Left-sided pyramidal insufficiency. Pulse 84 beats per minute, arrhythmic in the type of extrasystolic arrhythmia (6-10 per minute), firm. ACT - 84/136 mm Hg. Hypertrophy of the left ventricle. Accentuation of the II tone and systolic murmur over the aorta. Vesicular breathing over the lungs, marginal crepitation. The abdomen is soft, painless. The liver protrudes 2 cm from under the edge of the costal arch along the right midclavicular line. There is no edema. Formulate a diagnosis. Select drugs. Make a program of combined therapy. Give it a clinical and pharmacological justification.
2. A 44-year-old patient suffering from hypertension developed a headache, "internal" tremor, palpitations, and a feeling of fear. Objectively: pulse - 100 beats. in 1 min, blood pressure - 200/100 mm Hg, the left border of cardiac dullness is shifted 1.5 cm to the left of the left midclavicular line, heart sounds are sonorous, breathing is vesicular. On ECG: sinus tachycardia, signs of left ventricular hypertrophy. Formulate a diagnosis. Make a program of combined therapy. Give her a clinical and pharmacological justification.
3. A woman, 42 years old, complains of a severe pulsating headache in the fronto-parietal region, a feeling of palpitations. She has been suffering from hypertension for 3 years. She notes a significant increase in blood pressure 2-3 times a month lasting 3-8 hours. The attack ends with profuse urination. The left ventricle is enlarged, heart sounds are clear, pulse - 105 beats per minute, blood pressure - 225/115 mm Hg. Stroke volume and cardiac output are increased. Total peripheral vascular resistance is moderately increased. On ECG: signs of left ventricular hypertrophy. On the fundus: Salus-Gun symptom. Formulate a diagnosis. Make a program of combined therapy. Give it a clinical and pharmacological justification.
4. A 62-year-old patient has been suffering from hypertension for 10 years. 2 years ago, chronic obstructive bronchitis was diagnosed. Objectively: pulse - 64 beats per minute, blood pressure - 210/130 mm Hg, the left border of relative cardiac dullness is shifted to the left by 2.5 cm from the midclavicular line, the I tone above the apex is weakened, the accent of the II tone above the aorta. On ECG: left ventricular hypertrophy. Formulate a diagnosis. Indicate the drugs necessary for the treatment of this patient, justify their choice taking into account the concomitant pathology.
5. A 52-year-old patient suffers from stage II hypertension. He smokes. He is not regularly treated. Objectively: blood pressure - 175/105 mm Hg, heart rate - 92 beats per minute, scattered dry rales in the lungs against the background of weakened vesicular breathing. The liver protrudes 2 cm from the edge of the costal arch, edema in the ankle joints. Formulate the

main and concomitant diagnosis. Make a program of combined therapy taking into account the concomitant disease. Give it a clinical and pharmacological justification.

Test tasks for self-control:

1. A 60-year-old man complains of difficulty urinating. A history of hypertension. Examination showed: A/D 160/100. The prostate is slightly enlarged. Which of the following drugs should be prescribed to the patient?
A. Doxazosin
B. Labetolol
C. Phentolamine
D. Propranolol
E. Isoproterenol

2. A 55-year-old patient has hypertension with an elevated blood renin level. Which antihypertensive drug should be preferred in the treatment of the patient?
A. Magnesium sulfate.
B. Clophene.
C. Enalapril.
D. Papaverine hydrochloride.
E. Prazosin.

3. The doctor prescribed losartan to a patient with hypertension. What pharmacological property of this drug provides a therapeutic effect?
A. β-adrenoceptor blockade.
B. α-adrenoceptor blockade.
C. Angiotensin receptor blockade.
D. Angiotensin-converting enzyme blockade.
E. Antagonism with calcium ions.

4. A patient with hypertension takes enalapril. What is the mechanism of action of this antihypertensive agent?
A. Blockade of angiotensin-converting enzyme.
B. Antagonism with angiotensin receptors.
C. Blockade of phosphodiesterase.
D. Blockade of cyclooxygenase.
E. Blockade of calcium channels.

5. A patient with arterial hypertension was prescribed one of the antihypertensive agents. A/T normalized, but the patient began to suffer from a constant dry cough. Which of the listed drugs has such a side effect?
A. Nifedipine.
B. Anaprilin.
C. Clophenin.
D. Reserpine.
E. Enalapril.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical Pharmacology of Hypertensive Drugs"

Purpose:

To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of hypertensive drugs:

- Adrenomimetics - epinephrine (adrenaline), ephedrine, norepinephrine (noradrenaline), phenylephrine (mezaton), midodrine;
- Dopamine mimetics - dopamine, dobutamine;
- Glucocorticosteroids - hydrocortisone, prednisolone, triamcinolone, dexamethasone;
- Mineralocorticoids - fludrocortisone acetate;
- Analeptics - caffeine, cordiamine, camphor, sulfocamphocaine;
- Agents that affect the angiotensin system - angiotensinamide;
- Adaptogens - preparations of Eleutherococcus, ginseng, Rhodiola, Echinacea, Schisandra.

Basic concepts (list of questions):

1. Primary arterial hypotension.
2. Secondary arterial hypotension.
3. Sympatho-adrenal system.
4. Renin-angiotensin-aldosterone system.
5. Antihypotensive drugs.
6. Hypertensive drugs.

Plan

1. Theoretical questions:

Arterial hypotension is one of the most significant risk factors for cardiovascular complications. In connection with convincing evidence of a close relationship between AH and mortality, obtained in population studies, the revision of normal blood pressure values has been ongoing for many years. Modern classifications and standards define as “optimal” systolic blood pressure below 120 mm Hg, and diastolic blood pressure below 80 mm Hg. But to what level is “the lower, the better”? There is abundant evidence of a bimodal relationship between blood pressure and mortality in the population, since excessive reduction in blood pressure - arterial hypotension - is also associated with an increased risk of cardiovascular complications.

Hypotension criteria: arterial hypotension is diagnosed with blood pressure below 100/60 mm Hg in men and 95/65 mm Hg in women. Blood pressure below 100/60 mm Hg in people aged 25 years or younger and below 105/65 mm Hg in people over 30 years. Arterial hypotension should be diagnosed both with a simultaneous decrease in systolic and diastolic blood pressure, and with a decrease in one of these indicators.

Causes of hypotensive states

There are physiological hypotension (a variant of the norm, which is characteristic of trained athletes, people who are in high mountains and in hot climates) and pathological hypotension (including neurocirculatory, primary or essential hypotension, the persistent or chronic form of which is called hypotonic disease, as well as idiopathic orthostatic hypotension and symptomatic forms of the disease).

A decrease in blood pressure in hypotension, as a rule, is due to a mismatch between the ratio between peripheral vascular resistance and cardiac output. Decrease in peripheral vascular resistance with dilation of resistive vessels, capacitive vessels, decrease in cardiac output, violation of regulatory vegetative 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 excessive decrease in blood pressure and orthostatic hypotension can occur when using centrally acting antihypertensives, tricyclic antidepressants, alpha- and beta-blockers, peripheral vasodilators, diuretics, neuroleptics, anesthetics and drugs of other groups), medical manipulations, anesthesia;

- endocrine pathology (adrenal insufficiency, hypothyroidism, diabetes mellitus - autonomous diabetic neuropathy, etc.);

- neurological pathology (spinal tuberculosis, syringomyelia, brain tumors, consequences of craniocerebral trauma, etc.);

- hypovolemia (due to dehydration during diarrhea, violation of the drinking regimen; with blood loss, redistribution of blood within the body, etc.);

- infections, intoxication (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 in a timely manner at the syndromic level. Arterial hypotension is relatively rarely persistent, more often the decrease in blood pressure and the associated symptoms are temporary (the most severe attacks of hypotension are usually accompanied by fainting).

Orthostatic hypotension is the most common form of arterial hypotension. Several criteria for orthostatic hypotension are distinguished:

- any decrease in blood pressure that occurs in a patient when moving from a horizontal to a vertical position and causing the appearance of symptoms, presumably indicates a decrease in cerebral blood supply;

- a decrease in systolic blood pressure by 20 mm Hg and/or diastolic blood pressure by 10 mm Hg, regardless of the appearance of clinical symptoms.

- The most significant risk factors for orthostatic hypotension include: advanced age, diabetes mellitus, arterial hypertension, widespread atherosclerosis. Symptoms are diverse - from asymptomatic forms to the appearance of weakness, dizziness, instability, visual disturbances, palpitations, tremor, fainting in orthostasis.

Postprandial hypotension - hypotension associated with eating is diagnosed if within 2 hours after the start of eating systolic blood pressure decreases by 20 mm Hg. or more, or if as a result of eating it is below 90 mm Hg. and was initially above 100 mm Hg. (in this case, clinical symptoms may be absent), or, finally, if the decrease in systolic blood pressure associated with eating does not exceed 20 mm Hg. (or its level remains above 90 mm Hg), but is accompanied by the appearance of malaise. The most significant risk factors for this hypotension also include advanced age, diabetes mellitus, systolic arterial hypertension, organic diseases of the nervous system (stroke, Parkinsonism, Alzheimer's disease, etc.). Postprandial decrease in blood pressure, sometimes even significantly pronounced, may not be accompanied by clinical symptoms, while moderate hypotension can lead to the development of weakness, nausea, angina pectoris, dizziness.

Hypotensive conditions associated with physical exertion are divided into those that develop at the height of physical exertion and after their completion. The first require the exclusion of organic pathology of the heart (primarily coronary insufficiency and arrhythmias) as the cause of hypotension, the second, usually associated with insufficiency of autonomic regulation of blood circulation and interpreted as "vasovagal".

Hypotensive states during psychoemotional stress are also associated with defects in autonomic regulation of blood circulation, as well as neurogenic fainting, caused by the reflex influence of the autonomic nervous system on the regulation of vascular tone (its weakening and the development of hypotension) and/or heart rate (its slowing down and the development

of bradycardia). Primary arterial hypotension, or hypotonic disease - these terms are usually used in chronic essential hypotension. They mean a decrease in blood pressure of unclear etiology inherent to a given individual, in which clinical symptoms are determined that limit daily activity and worsen the patient's quality of life. Among these symptoms are dizziness, headaches, weakness, increased fatigue, decreased performance, irritability, often occurring immediately after sleep. Blood pressure in patients with hypotension can fluctuate significantly, and significant increases can be observed against the background of reduced indicators.

Classification of hypertensive drugs

- Adrenomimetics - epinephrine (adrenaline), ephedrine, norepinephrine (noradrenaline), phenylephrine (mezaton), midodrine;
- Dopamine mimetics - dopamine, dobutamine;
- Glucocorticosteroids - hydrocortisone, prednisolone, triamcinolone, dexamethasone;
- Mineralocorticoids - fludrocortisone acetate;
- Analeptics - caffeine, cordiamine, camphor, sulfocamphocaine;
- Agents that affect the angiotensin system - angiotensinamide;
- Adaptogens - preparations of eleutherococcus, ginseng, rhodiola, echinacea, schisandra.

Treatment of hypotensive conditions

For targeted treatment of patients with hypotension, it is important to establish the main diagnosis. In general, treatment tactics in people prone to hypotensive states are as follows:

• Cautious use of drugs that can cause orthostatic disorders, especially in elderly and senile patients (diuretics, vasodilators). The selection of antihypertensive drugs in them should be carried out taking into account the reactions of blood pressure in orthostasis, the features of the blood pressure profile determined during daily monitoring. In patients with transient hypotensive states, preference should be given to drugs of short or medium duration of action.

• Elimination of factors and triggers of hypotensive states (avoid sudden standing and prolonged standing, as well as prolonged stay in a horizontal position during the day, stay in stuffy rooms, at high ambient temperature, avoid hyperventilation, overexertion, etc.). After breakfast, patients with postprandial hypertension are recommended a short rest for 15-30 minutes in a lying or semi-recumbent position.

• Treatment of the underlying disease in primary and secondary autonomic insufficiency, hypovolemia.

• Increased salt and fluid intake (up to 2-2.5 liters of fluid, 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.

• Food intake should be small portions (preferably 4-5 meals). Refusal of hot food and restriction of the amount of carbohydrates in the diet significantly reduce the risk of postprandial hypotension and the likelihood of its occurrence. Overeating should be avoided, alcohol should be excluded.

Additionally, the following can be used:

• sleep with the head of the bed raised (by 20-30 cm or up to 15 °);
• abdominal bandages, compression hosiery;
• portable seats if necessary for a long stay in orthostasis;
• special exercises with crossing legs, activation of calf, gluteal muscles;
• special "maneuveres" - exercises for the arms (tension of the arms in the shoulder girdle), legs and abdominal press;
• physical training (both dynamic loads and tilt training - special training of orthostatic stability), regularity of physical training is the main factor in improving endurance and tolerability of orthostasis.

In case of ineffectiveness of non-drug methods of correction of hypotensive states,

pharmacotherapy can be used.

Midodrine - an adrenomimetic that causes arterial and venous vasoconstriction with increased peripheral vascular resistance and redistribution of blood volume, recommended for all types of hypotension as monotherapy or in combination with fludrocortisone. Midodrine was used in an individual dosage depending on the severity of clinical manifestations - usually 2.5 mg (1 tablet or 7 drops) 2-3 times a day. The dose can be increased at intervals of 1 week up to 30 mg/day. Midodrine can worsen the patient's existing arterial hypertension (determined in a horizontal position), so 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 are equivalent to 2.5 mg) 10-15 minutes before meals provides a preprandial pressor effect, reducing the degree of postprandial decrease in blood pressure. Fludrocortisone acetate is a mineralocorticoid, for many years used to treat all types of hypotension in a dose of 0.1-0.2 mg/day. Its main therapeutic effect is sodium and fluid retention by reducing aldosterone secretion. Potential complications of long-term therapy - hypokalemia, hypomagnesemia, progression of heart failure, arterial hypertension.

Emergency therapy

In emergency conditions associated with the development of arterial hypotension against the background of severe hypovolemia, urgent replenishment of the circulating blood volume is necessary. In combination with abundant drinking, a single intravenous injection 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, a single intravenous injection of dextran 400-1200 ml and/or isotonic 0.9% sodium chloride solution 400-1200 ml is indicated. The reason for stopping rapid fluid infusion is an increase in systolic blood pressure to 100 mm Hg and the absence of pronounced tachycardia (heart rate not more than 100 beats/min).

In case of drug-induced hypotension, it is recommended to administer 1% phenylephrine (1.0 ml in 100 ml of saline) or 5% glucose solution intravenously. Midodrine can be used in combination with phenylephrine or alone.

In case of arterial hypotension of unclear genesis, which is potentially life-threatening, the administration of colloidal solutions of at least 400 ml intravenously can be used once in combination with dopamine intravenously at a dose of 2 to 15 mcg/kg/min until blood pressure increases and/or norepinephrine intravenously, starting with 10 mcg/min with a gradual increase in dose.

2. Questions for self-control (list of questions):

1. Etiology, pathogenesis, classification of arterial hypotension.
2. List the pathogenetic mechanisms of arterial hypotension, which is the object of influence of hypertensive drugs.
3. List the main groups of hypertensive drugs.
4. Explain the mechanisms of hypertensive effects of the main groups of drugs, based on their pharmacodynamics.
5. Formulate the significance of the leading pharmacokinetic characteristics (T1/2el, plasma protein binding, Vd) in the individual selection of hypertensive drugs.
6. Highlight the clinical and laboratory-functional criteria of therapeutic efficacy and safety of hypertensive drugs.
7. What principles are the basis for the classification of hypertensive drugs?
8. Name and explain the mechanisms of hemodynamic changes in the body after the administration of adrenomimetics, analeptics, adaptogens and other hypertensive drugs.
9. What are the undesirable effects inherent in hypertensive drugs?

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write prescriptions for the main hypertensive drugs (tablets and/or ampoules), indicate possible use, the spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol for independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize vascular tone disorders, leading clinical syndromes - arterial hypotension, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, select the drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the characteristics of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Justify the need for combined drug therapy and suggest 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 their detection at early stages.

10. Justify the duration of basic and supportive therapy.

B. Solution of situational tasks.

1. A 56-year-old patient is hospitalized for hypertension. He took medications: capoten 25 mg three times a day, adverzuten - 1 mg 3 times a day. 30 minutes after taking the drugs, the patient fell and lost consciousness for a few seconds. Objectively: the skin is pale, moist. Pulse - 100 in 1 min, rhythmic. Blood pressure 60/20 mm Hg. What complication did the patient have? Indicate the drugs necessary for the treatment of this pathological process.

2. A 34-year-old woman with acute bronchopneumonia, after an intradermal test for penicillin, after 5 minutes, suddenly developed cough, shortness of breath, fear, anxiety, headache, dizziness, tinnitus, nausea, vomiting, abdominal pain. Objectively: the general condition is severe. Consciousness is clouded. Foam from the mouth, convulsions, involuntary defecation and urination. The skin is pale with a cyanotic tinge. Pulse 120 beats per minute, rhythmic, small filling, threadlike. ACT - 60/20 mm Hg. Heart sounds are muffled. In the lungs there is hard vesicular breathing, scattered dry wheezing. Formulate the diagnosis. Make an intensive care program, justify its appointment.

3. A 65-year-old man suffering from coronary artery disease: stable angina pectoris functional class III, extrasystolic arrhythmia, CHF I - severe, burning pain in the sternum, shortness of breath, loss of consciousness. Objectively: the general condition is severe, the skin is pale, covered with abundant cold sweat, pronounced acrocyanosis. Pulse -140 beats per minute by the type of atrial tachyarrhythmia, ACT - 70/40 mm Hg. Heart sounds are muffled. Anuria. On ECG - monophasic curve in leads III, AVR, V4 - V6.

Formulate the diagnosis, emergency therapy program. Justify the choice of drug

Test tasks for self-control:

1. A patient with hypertension took an antihypertensive drug for a long time, but suddenly stopped taking it. After that, the patient's condition worsened, a hypertensive crisis developed. What type of side effect did the patient develop?

A. Cumulation.
B. Withdrawal syndrome.
C. Tolerance.
D. Sensitization.
E. Dependence.

2. It is undesirable to combine Captopril with:

A. Veroshpiron
B. Hypothiazide
C. Furosemide
D. Torasemide
E. Indapamide

3. During the treatment of stable angina pectoris with a combination of antianginal drugs, the patient complained of headache, tinnitus, and dizziness. Which group of drugs can cause the listed side effects?

A. Calcium channel blockers.
B. Beta-blockers.
C. Anticoagulants.
D. Nitrates.
E. Antiplatelet agents.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/

2. National Scientific Medical Library of Ukraine http://library.gov.ua/

3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/

4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

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

6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua

7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org

8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Urgent conditions in case of impaired vascular tone, principles of pharmacotherapy"

Purpose:

To master the principles and algorithms of emergency care in case of hypertensive crises and acute hypotensive conditions.

Basic concepts (list of questions):

1. Uncomplicated hypertensive crisis.
2. Complicated hypertensive crisis.
3. Syncope (dizziness).
4. Collapse, orthostatic collapse.
5. Shock: classification.

Plan

1. Theoretical questions:

2Hypertensive crisis (HC) is an acute significant sudden increase in blood pressure (BP) by more than 30% of the initial level, which leads to the appearance of secondary clinical symptoms of impaired function of vital organs or neurovegetative disorders.

Criteria for hypertensive crisis:

• sudden onset;
• significant increase in blood pressure;
• appearance or intensification of symptoms from target organs.

The main feature of the crisis is an increase in blood pressure: systolic - by 20-100 mm Hg, diastolic - by 10-50 mm Hg. Some experts suggest setting a pressure level of 210/120 mm Hg as a diagnostic criterion, but a direct relationship between the level of blood pressure and the severity of the crisis has not been determined. The level of blood pressure significantly exceeds the normal level for an individual patient, that is, it exceeds the ability of cerebral blood flow to self-regulate or myocardial contractility and leads to acute encephalopathy, heart failure or other complications. GC can occur at any blood pressure value at any stage of arterial hypertension (AH) and for any duration.

Pathogenesis

The leading role in the development of clinical signs of crisis belongs to the interaction of systemic and local hemodynamic factors, which leads to an increase in blood pressure, the formation of systemic and local hemodynamic disorders, including cerebral, coronary, renal, peripheral, macro- and microcirculatory. The main consequence of this is the development of tissue and organ ischemia. Pathogenetic factors that contribute to the occurrence of GC:

• genetic predisposition to vasospasms (insufficient function of α- and β-receptors);
• high content of angiotensin II and noradrenaline circulating in the blood;
• lack of kininogen, kinin, prostacyclins;
• damage to the vascular endothelium and reduced production of vasodilator substances.

Violation of blood pressure regulation is caused by both exogenous and endogenous factors.

Exogenous factors:

• psycho-emotional stresses;
• meteorological influences;
• increased salt and water intake;
• excessive insolation;

• intercurrent diseases;
• smoking;
• contraceptives.

Endogenous factors:

• secondary aldosteronism;
• excessive renin formation due to decreased renal blood flow (especially pulse pressure);
• acute ischemia of the brain and heart;
• reflex effects from internal organs (prostate adenoma, nephroptosis, cholecystitis, pancreatitis);
• drug effects (sudden withdrawal of antihypertensive drugs);
• atherosclerosis of extracranial arteries with damage to the baroreflex apparatus;
• increased platelet aggregation and increased serotonin in the CNS;
• sleep apnea syndrome (episodes of asphyxia and alveolar hypoventilation during sleep);
• decreased oxygen content in tissues and stimulation of chemoreceptors of arteries and veins;
• increased activity of the sympathetic nervous system;
• increased intracranial pressure.

The direct causes of hypertension in patients with hypertension with reduced adaptive capabilities of the CNS are:

a) dysfunction (hyperreactivity) of the diencephalic region of the brain, which causes:

• increased antidiuretic activity and blood levels of adrenocorticotropic hormone (ACTH);
• increased production of antidiuretic hormone;
• increased aldosterone levels;
• fluid retention and hypervolemia;
• increased vascular reactivity with the occurrence of spasms;
• irritation of baro- and volume receptors;
• suppression of antidiuretic hormone secretion.

b) high variability of blood pressure (day and night) due to atherosclerosis of extracranial arteries and dysfunction of the baroreflex apparatus.

Classification

In Ukraine, it is proposed to use the classification of ACS according to the presence of complications for daily clinical practice.

Complicated ACS = emergency conditions with acute or progressive damage to target organs, pose a direct threat to the patient's life, require immediate lowering of blood pressure within the first hour of treatment.

Complicated ACS account for 20-25% of all patients with a significant increase in blood pressure. In the case of a complicated crisis, the course of the disease is characterized by signs of acute organic or functional damage to target organs:

• hypertensive encephalopathy;
• intracerebral or subarachnoid hemorrhage;
• ischemic stroke;
• transient ischemic attack;
• acute coronary syndrome;
• acute arrhythmic syndrome;
• acute left ventricular failure;
• acute dissecting aortic aneurysm;
• acute renal failure or hematuria;
• preeclampsia and eclampsia.

Uncomplicated HG = urgent emergencies pose a potential threat to the patient's life, are

characterized by a course without acute or progressive damage to target organs, require a decrease in pressure within several hours or days. Depending on which organs are predominantly affected, it is proposed to distinguish:

• cerebral crises;

• uncomplicated cardiac crises;

• hypothalamic paroxysm (diencephalic-vegetative crisis);

• a significant increase in blood pressure in the early postoperative period;

• an increase in systolic blood pressure to 240 mm Hg and above, diastolic blood pressure to 140 mm Hg and above even without symptoms of target organ damage.

Diagnostics

Symptoms that occur in patients can be conditionally divided into general and local. General symptoms (redness or pallor of the skin, sweating, dizziness, palpitations, dry mouth, tinnitus, fear, excitement, tremor) are not specific and are of little help in diagnosis.

Local symptoms are divided into cerebrovascular, cardiovascular, renal and ocular. Local symptoms also include nosebleeds.

The most important symptomatology of GC is determined by the nervous system, which may be due to the following reasons:

• acute violation of cerebral blood flow autoregulation as a result of the direct effect of high blood pressure on the vessels of the brain, which manifests itself in the form of acute hypertensive encephalopathy;

• hypertensive damage to small arteries and arterioles, which leads to cerebral hemorrhage, the formation of lacunar brain infarctions or the development of cerebral dementia.

The process of cerebral blood flow autoregulation is the narrowing and dilation of cerebral vessels in response to changes in systemic blood pressure. Direct measurements of cerebral blood flow in animals have confirmed that a decrease in systemic blood pressure is accompanied by dilation of cerebral arteries aimed at preventing tissue hypoperfusion. An increase in blood pressure leads to vasoconstriction, which prevents brain hyperperfusion. The mechanisms of autoregulation include myogenic activation of precapillary arterioles and metabolic regulation of blood flow.

Myogenic activation of arterioles is induced by an increase in their transmural pressure due to a systemic increase in blood pressure, which causes their narrowing.

Metabolic regulation is triggered by hypoxic changes under conditions of brain hypoperfusion. A decrease in perfusion pressure and blood flow causes hypoxia and enhances the release of vasodilator mediators (nitric oxide, prostacyclin, adenosine) from the endothelium of the vascular wall and surrounding tissues.

There are 2 theories of the development of hypertensive encephalopathy.

1. According to Strandgaard (1973), under certain threshold levels of blood pressure, spasmed arterioles cannot withstand, relax and blood enters the capillary bed, capillary permeability increases with subsequent cerebral edema and microinfarcts.

2. According to Finnerty (1974), an increase in blood pressure leads to a very strong spasm of arterioles, which causes ischemia, contributes to an increase in capillary permeability and rupture of their walls with subsequent cerebral edema and small hemorrhages.

Morphologically, with a significant increase in blood pressure, alternation of dilated and spasmed areas is observed in small arteries, so the arteries resemble sausages in shape. First, petechial hemorrhages appear, focal, and then diffuse cerebral edema with the development of the clinical picture of encephalopathy.

If the pressure cannot be quickly reduced, coma and death occur.

The clinic of hypertensive encephalopathy is due to a gradual increase in cerebral edema. Preclinical, clinical and paroxysmal forms are distinguished.

The preclinical stage is characterized by the presence of hypertension, memory and attention disorders, an increased level of self-doubt, detected during a special examination, and changes in such paraclinical indicators as:

• REG (increased tone, difficulty in venous outflow);

• sonodopplerography (decreased blood flow in the main arteries of the head);

• EEG (decreased amplitude of biopotentials, irregularity and disorganization of the alpha rhythm);

• fundus (narrowing, tortuosity of vessels).

At the clinical stage, intermittent headache and dizziness, deterioration of memory, attention and performance, poor sleep, irritability appear. The neurological status is determined by:

• anisocoria;

• somewhat sluggish pupillary reaction to light;

• oral automatism reflexes;

• erratic nystagmus;

• increased tendon reflexes;

• visual impairment - diplopia, nystagmus;

• increased muscle tone;

• mild hand tremor.

The paroxysmal stage of hypertensive encephalopathy is characterized by:

• the appearance of fainting episodes;

• cephalalgias;

• dizziness;

• vegetative-vascular crises of the sympatho-adrenal, vagoinsular and mixed types.

If treatment is not started at this time and blood pressure continues to rise, transient cerebral circulatory disorders occur, which, according to the WHO definition, are accompanied by the appearance of general and local symptoms with the reverse development of neurological signs within 24 hours. A feature of acute hypertensive encephalopathy is the reverse development of all symptoms under effective treatment, when blood pressure is reduced to the development of severe cerebral edema with wedging of the cerebellum into the foramen magnum or to the appearance of multiple hemorrhages.

The increase in symptoms occurs gradually over 24-48 hours, which helps to differentiate acute hypertensive encephalopathy from intracerebral hemorrhage, the symptoms of which develop suddenly, quickly and do not decrease during the day.

The diagnosis of hypertensive encephalopathy is established by excluding stroke, brain tumor, vasculitis, encephalitis and some other brain diseases.

Acute hypertensive encephalopathy occurs in the form of cerebrovascular crises, which neuropathologists divide into 3 degrees of severity (M.K. Bogolepov, P. Skochiy, 2000).

Mild form – angiodystonic crisis – is characterized by short-term disorders of brain functions without focal cerebral manifestations. Symptoms: headache or a feeling of heaviness in the head, dizziness, irritability, emotional instability (anxiety, fear), weakness, facial hyperemia, vasomotor disorders of the skin, sweating, shortness of breath, palpitations, fainting or short-term loss of consciousness, unclear thoughts. Sometimes the patient does not respond to addressing him, everything floats before his eyes, sounds are perceived as if from a distance, a feeling of stuffiness in the ears appears.

Moderate severity crisis – angiodystrophic – occurs with general cerebral symptoms and transient focal neurological symptoms. Patients develop a sharp headache, dizziness, impaired balance, staggering while walking, a feeling of fog before the eyes, nausea, vomiting, paleness of the face, trembling of the hands. On the fundus of the eye – signs of edema and varicose veins.

Severe form of acute hypertensive encephalopathy – dynamic disturbance of cerebral circulation. Unconsciousness lasts from several minutes to 2 hours and is replaced by stupor,

nausea, vomiting, paresthesias. Pathological reflexes appear for a short time, as well as disorders of motor, sensory, speech and other functions. There are muscle hypotension, mild nystagmus, convergence insufficiency, decreased abdominal reflexes, asymmetry or decreased tendon reflexes. Sometimes transient speech, visual, gnostic disorders, epileptic seizures occur. Local symptoms mostly disappear after a few hours, while general cerebral symptoms can persist for weeks.

Hypertensive damage to small arteries and arterioles leads to cerebral hemorrhage, formation of lacunar brain infarctions or development of cerebral dementia.

Stroke remains the main cause of death in patients with hypertension with various forms of cerebrovascular diseases, among them 120 thousand with cerebral strokes.

According to the definition of the WHO, cerebral stroke is the rapid onset of symptoms of focal or generalized impairment of cerebral functions of vascular genesis lasting 24 hours or more, or which causes the death of the patient.

This definition includes subarachnoid hemorrhage and excludes subdural hematoma and hemorrhage or infarction caused by infection or brain tumor.

Depending on the localization of hemorrhage in the substance and membranes of the brain, the following subtypes of hemorrhagic stroke are distinguished:

• parenchymal;

• subarachnoid;

• others (sub-, epidural, ventricular, parenchymatous-ventricular, parenchymatous-subarachnoid).

The neurological clinic of parenchymal hemorrhage is determined by the following factors:

• localization of irreversible damage to brain structures and impaired function of perifocal areas and pathways due to compression of them by a hematoma;

• development of intracranial hypertension, hydrocephalus, which are complicated by dislocation of the brain stem and subsequent wedging;

• breakthrough of blood into the ventricles of the brain or subarachnoid space.

Doctor's tactics

A feature of the doctor's tactics for GC is that therapy often has to begin before a complete examination of the patient is completed. Initial assessment includes:

1. Continuous monitoring of blood pressure (direct methods are preferred - intraarterial, indirect methods - cuff).

2. Rapid initial assessment of the history and physical examination with special attention to:

a) neurological, cardiac, pulmonary, real symptoms;

b) determination of the function of vital organs.

3. To clarify the degree of involvement of target organs in GC, a number of mandatory diagnostic measures are performed, in particular, determination of:

• complete blood count hemoglobin;

• blood glucose;

• electrolytes (serum potassium and sodium);

• serum creatinine, nitrogen;

• hematocrit.

Instrumental studies include: blood pressure monitoring, echocardiography and ECG, ultrasound of vessels and abdominal organs, computed tomography of the target organ (head, adrenal glands), angiography, fundus examination.

Treatment

Recommendations for the treatment of crises are based on the results of small uncontrolled studies.

When determining treatment, the doctor should answer the following questions:

• Is this complicated hypertensive crisis, i.e. an emergency?
• Is a rapid effect of therapy necessary?
• Is hypotension necessary only for a short time?
• Is there a high risk of drug-induced hypotension?
• Does the patient have ischemic heart disease, rhinovascular hypertension, cerebrovascular disease, dehydration?
• What antihypertensive therapy has the patient used recently?

Urgent measures should be aimed at:
• reducing increased left ventricular contractility;
• eliminating peripheral vasoconstriction and hypervolemia;
• eliminating cerebral ischemia (especially in the event of seizures);
• eliminating acute coronary or heart failure.

In patients with uncomplicated crises, whose condition is relatively stable, oral forms of drugs should be used that are well absorbed when taken under the tongue and reduce pressure after 15-20 minutes. Treatment of uncomplicated crises is carried out on an outpatient basis and does not require emergency hospitalization of patients.

The goal of treatment of complicated GC is to reduce blood pressure by 25% of the initial level within the first hour, but not lower than 160/100 mm Hg.

Treatment of complicated crisis is carried out only in intensive care units until the patient's condition is stabilized. Stabilization of the patient's condition is the patient's status when, against the background of reduced blood pressure, signs of progressive damage to target organs are eliminated and a safe level of blood pressure does not depend on parenteral administration of antihypertensive drugs.

For rapid reduction of blood pressure, short-acting drugs are used, which are administered parenterally under conditions of monitoring of blood pressure and hemodynamic indicators.

The choice of treatment tactics (drug, routes of administration, expected speed and magnitude of reduction in elevated blood pressure) depends on the severity and presence of complications.

The speed of reduction in elevated blood pressure in complicated hypertension:
• within 30-120 min -> decrease in blood pressure by 15-25%;
• within 2-6 h -> blood pressure level 160/100 mm Hg.;
• further -> oral antihypertensive drugs.

Features of treatment of complicated crises

Hypertension + encephalopathy

Rapid improvement of the patient's condition after the start of antihypertensive therapy can be a differential criterion for acute encephalopathy and stroke, since in a patient with a stroke, a decrease in blood pressure, on the contrary, leads to a deterioration in the patient's condition and an increase in neurological symptoms.

Recommended:

a) sublingual tablet preparation (for example, captopril, capoten, nifedipine), except for centrally acting agents (clonidine, methyldopa, reserpine);

b) infusions of sodium nitroprusside, labetalol, nicardipine, magnesium sulfate.

Sodium nitroprusside is a mixed ultrashort-acting vasodilator. It has an NO group (endothelium-dependent relaxing factor) in its molecule, which, when released, dilates arteries and veins. This leads to a decrease in blood flow to the heart, a decrease in peripheral resistance, and an increase in heart rate. Due to the redistribution phenomenon, it can cause a deterioration in coronary blood flow. The hypotensive effect appears immediately after the start of administration and ends a few minutes after the end of the infusion. The agent quickly decomposes under the influence of light, so its solution should be closed with darkened caps.

Dihydropyridine calcium antagonists - nifedipine and nicardipine - are comparable in

effectiveness to sodium nitroprusside, but they are better tolerated by patients.

Labetalol - a β-blocker with α-blocker properties begins to act after 5 minutes, the effect lasts for 3-6 hours. This drug is effective in any type of crisis, except for GC, complicated by acute left ventricular failure due to negative inotropic action.

Drugs with central depressant action and β-blockers without alpha-blocking ability should be avoided (they worsen cerebral blood flow). It should be remembered that in elderly patients with hypertensive encephalopathy, the decrease in pressure should be gradual - by 25% during the first hour (otherwise, cerebral hypoperfusion occurs, which is clinically manifested by dizziness, weakness and worsening of neurological symptoms).

GC + eclampsia

Eclampsia is a form of hypertensive encephalopathy, manifested by convulsions, oliguria, and syncope. It is a common cause of fetal death.

The main clinical features are hypertension and proteinuria, often combined with edema.

Precursors of eclampsia:

• visual impairment;
• headache;
• hyperreflexia;
• laboratory criteria for increased proteinuria (more than 3 g in daily urine), decreased albumin in blood plasma, increased creatinine concentration, thrombocytopenia.

Complications of eclampsia:

• pulmonary edema;
• loss of vision due to focal edema in the optic nerve area;
• cerebral hemorrhage;
• placental abruption;
• DIC syndrome;
• renal failure.

Treatment tactics. Mandatory hospitalization. The first issue in managing a pregnant woman with eclampsia and preeclampsia is delivery.

Recommended drugs: methyldopa, hydralazine, clonidine, labetalol and other β-blockers. Diuretics are not indicated.

It should be remembered that excessive lowering of blood pressure can worsen blood flow in the uterus and contribute to placental abruption.

Hydralazine is a direct arteriolar vasodilator that does not affect the capacitive veins. The decrease in total peripheral resistance under the influence of hydralazine activates baroreceptors, causes tachycardia and an increase in cardiac output. The drug can provoke a headache due to increased intracranial pressure.

A combination of hydralazine with a β-blocker (to prevent tachycardia) and a diuretic (causes fluid retention) is advisable.

GC + stroke

Stroke (ischemic or hemorrhagic) requires special caution when lowering blood pressure. In such patients, an acute increase in blood pressure can be both a cause of stroke and a response to acute ischemia, since cerebral perfusion in the affected areas occurs as a result of an increase in blood pressure.

Experts of the European Stroke Initiative in their recommendations (2000) consider it inappropriate to begin actively lowering blood pressure if its level does not exceed 220 mm Hg. It is recommended to maintain the blood pressure level of 160-180/90-100 mm Hg.

Recommended short-acting drugs:

• infusions of labetalol, sodium nitroprusside, enalaprilat;
• per os – clonidine, captopril.

It should be remembered that sodium nitroprusside can increase intracranial pressure due to the expansion of cerebral vessels, so it is better to combine it with osmotic diuretics.

Drugs that sharply and persistently lower blood pressure or have a central depressive effect (β-blockers, clonidine, methyldopa, reserpine) should be avoided.

Blood pressure level of 180/100 mm Hg is the limit for the administration of thrombolytics.

3. GK + acute left ventricular failure

Acute left ventricular failure can occur as a result of a significant increase in blood pressure. However, the opposite situation may occur when blood pressure increases due to acute left ventricular failure. Even a slight increase in afterload is excessive for the heart in conditions of insufficient function.

Recommended drugs that reduce afterload and preload: sodium nitroprusside, nitroglycerin, enalaprilat, trimetaphan, narcotic analgesics can also be used. Parenteral diuretics are mandatory.

Do not use - hydralazine, β-blockers, diazoxide.

Nitroglycerin is formed into a molecule of NO as a result of a series of enzymatic reactions. The drug does not cause a robbery syndrome. Nitroglycerin should be administered through special systems, because it binds to polyvinyl chloride and settles on the tubes of the system.

From the group of ACE inhibitors, enalaprilat is used, the indication for which is the absence of hypovolemia or high-renin hypertension.

It should be remembered that the combination of ACE inhibitors with thiazide diuretics causes a decrease in the level of uric acid in the blood, with furosemide - inactivation of furosemide, with β-blockers - increased action of ACE inhibitors and reduction of vasoconstriction caused by β-blockers.

GC + acute coronary insufficiency and myocardial infarction

Acute coronary syndrome can occur in response to increased pressure or itself provoke reflex high blood pressure. Increased pressure increases afterload, resulting in increased resistance to cardiac output. The tension of the left ventricular walls increases, which in turn leads to increased myocardial oxygen demand. In patients with GC and unstable angina, progression of angina and myocardial infarction are likely. Target pressure is < 160/100 mm Hg.

Recommended drugs: nitroglycerin and b-blockers in the absence of heart failure.

Diazoxide and calcium antagonists should not be used.

Nitroglycerin is also indicated for patients with GC after coronary artery bypass grafting.

GC + acute dissecting aortic aneurysm

Aortic dissecting aneurysm is the most dangerous complication of hypertension. Without treatment, 25% of patients die within the first day, 50% within a week.

Aortic dissection is caused by a sudden rupture of the intima, as a result of which blood enters the aortic wall and separates the intima from the adventitia at different depths. This is accompanied by necrosis of the media. The risk of dissecting aortic aneurysm is higher in patients with Marfan and Ehlers-Danlos syndromes, coarctation of the aorta, bicuspid aortic valve, and in pregnant women.

All patients with dissecting aortic aneurysm are treated with “controlled hypotension” when systolic pressure is maintained within 100-120 mm Hg.

Recommended drugs: sodium nitroprusside, adrenoreceptor inhibitors, labetalol.

Do not use direct vasodilators (hydralazine, diazoxide) due to activation of the sympatho-adrenal system.

The ganglion blocker trimetaphan blocks the autonomic nerve ganglia, dilating the vessels. It is the drug of choice in patients with dissecting aortic aneurysm due to negative isotropic action and reduced cardiac output. More toxic than sodium nitroprusside.

GC + catecholamine crises

Catecholamine crises occur in patients with pheochromocytoma, during withdrawal of clonidine or methyldopa, and overdose of sympathomimetics: amphetamines, cocaine, ephedrine. Catecholamine crises are accompanied by tachycardia, tremor, sweating, pallor, headache, and a feeling of fear.

For hypotension, α- and β-adrenergic blockers are recommended.

From the group of α-adrenergic blockers, phentolamine is used, which blocks both postsynaptic α-1 and presynaptic α-2 receptors, causing a block of adrenergic vasoconstrictor impulses, which leads to the relief of spasms and dilation of arterioles and precapillaries.

Reflex tachycardia can cause myocardial ischemia or the appearance of severe arrhythmias.

GC + intracerebral or subarachnoid hemorrhage

The drugs of choice are sodium nitroprusside or arfonad. Adrenoblockers should not be prescribed. With caution - diuretics (threat of hypokalemia) and centrally acting drugs (worsening of consciousness disorders).

4. GC + acute renal failure

Treatment drugs: sodium nitroprusside, diazoxide, hydralazine, methyldopa.

Doctor's tactics after withdrawal from GC and stabilization of the patient's condition

After lowering the blood pressure and achieving stabilization of the patient's condition, the following questions are resolved:

1. Did GC lead to the development of such dangerous complications as impaired cerebral or coronary circulation, decompensation of heart or kidney functions, exfoliative vascular lesions, retinal hemorrhages?

2. What caused the occurrence of GC (withdrawal syndrome, excessive salt intake)?

3. What permanent antihypertensive therapy should be used by the patient at home?

Complications of GC treatment:

• ricochet hypotension (too rapid infusion, prolonged effect of therapy, potentiation of the effect of various drugs, new heart diseases - myocardial infarction, tamponade - redistribution of blood plasma, unforeseen secondary nature of hypertension - renal artery stenosis);

• worsening of neurological status (cerebral ischemia due to too rapid a decrease in blood pressure, thiocyanide toxicity, drug side effects, increased intracranial hypertension, new metabolic disorders);

• increased AT (increased circulating blood volume, redistribution, unexplained secondary origin of AH, poor treatment regimen or compliance);

• metabolic acidosis (thiocyanide toxicity, tissue hypoperfusion secondary to inadequate blood pressure reduction);

• worsening of renal function (tissue hypoperfusion, fluid retention, acute tubular necrosis, do not temporarily discontinue therapy due to treatment).

In urgent hypotensive conditions caused by adrenal insufficiency, glucocorticoid replacement therapy is used - hydrocortisone at a dose of 100 mg intravenously, followed by a long-term infusion of hydrocortisone.

Collapse is one of the forms 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 inflow to the heart, a drop in arterial and venous pressure, brain hypoxia and suppression of the body's vital functions. Causes: acute infections (typhoid and typhus, meningoencephalitis, pneumonia, etc.), acute bleeding, diseases of the endocrine and nervous system (tumors, syringomyelia, etc.), exogenous intoxications (carbon monoxide poisoning, organophosphorus compounds, etc.), spinal and epidural anesthesia, orthostatic blood redistribution (overdose of some drugs - ganglioblockers, insulin, antihypertensive drugs,

etc.), acute diseases of the abdominal cavity (peritonitis). Collapse can be a complication of acute myocardial contractile dysfunction, which is combined by the concept of "small cardiac output syndrome", which occurs in the acute period of myocardial infarction, with pronounced tachycardia, with deep bradycardia, with sinus node dysfunction, etc.

Shock - a set of disorders of cardiac activity, respiration, metabolism and neuroendocrine regulation in response to excessive irritation. The most common form is traumatic shock (with multiple injuries and damage to the head, chest, abdomen, pelvic bones and limbs, with thermal and chemical burns, electric shock). The victim is initially in an excited state, cannot critically assess the severity of his condition, is restless, seeks to run somewhere. Later, excitement is replaced by lethargy, depression, indifference to the environment. The patient is pale, blood pressure drops, pulse increases, breathing is superficial, the skin is covered with sticky sweat. Shock can be a reaction to sharp pain in diseases of internal organs, for example, with myocardial infarction (cardiogenic shock) or a ruptured stomach ulcer, bacterial shock occurs with sepsis, toxic shock occurs when toxic substances are exposed. A special form is emotional shock, which is possible with severe mental trauma associated, for example, with a fire, flood, train accident, sudden news of great grief.

Treatment is aimed at the underlying disease; if possible, the factor that caused the shock is eliminated. Treatment of shock should be adequate to the mechanism of its occurrence. In cardiogenic shock, along with anesthesia, 1-2 ml of noradrenaline, dobutamine are administered intravenously drip, trying to maintain systolic blood pressure at 80-100 mm Hg; Korglikon is carefully administered (which should be used in smaller doses in 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. In case of hypovolemia, whole blood, plasma, isotonic sodium chloride solution and other fluids are transfused (under control of arterial and venous pressure). In case of anaphylactic shock, 1 ml of 0.1% adrenaline solution is administered intravenously, and then prednisolone 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 paramount importance.

2. Questions for self-control (list of questions):

1. Etiology, pathogenesis, classification of hypertensive crises and hypotensive states.
2. List the pathogenetic mechanisms of hypertensive crises and hypotensive states, which are the object of influence of hypotensive and hypertensive drugs.
3. List the main groups of hypertensive and hypotensive drugs.
4. Explain the mechanisms of action of the main groups of drugs.
5. Highlight the clinical and laboratory-functional criteria for therapeutic efficacy and safety of hypotensive and hypertensive drugs.
6. Formulate urgent drug therapy for uncomplicated and complicated hypertensive crisis.
7. Justify the appointment of captopril in hypertensive crisis and indicate the criteria for assessing the effectiveness and safety of its use.
8. Name the main undesirable effects of clonidine and the mechanisms of their occurrence, which must be taken into account during urgent and planned therapy of arterial hypertension.
9. Name and explain the mechanisms of hemodynamic changes in the body after the administration of adrenomimetics, analeptics, GCS and other hypertensive drugs.
10. What undesirable effects are inherent in hypertensive drugs?

3.Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for the main hypotensive and hypertensive drugs (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the choice and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize the development of a hypertensive crisis, acute hypotensive condition, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, select the drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 their detection at the early stages.

10. Substantiate the duration of basic and maintenance therapy.

B. Solving situational tasks.

1. A 33-year-old man complains of palpitations, ineffective inspiration, moderate heaviness in the heart area, pulsating headache, facial flushing, body tremors, sweating, nervous tension. The condition worsened sharply after psychoemotional stress. History: stage I hypertension. Episodic drug therapy. Objectively: facial skin is hyperemic. Normosthenic, somewhat overnourished. Pulse - 94 beats per minute, rhythmic, ACT - 198/96 mm Hg. The left border of the heart is shifted outward by 1.5 cm. The accent of the II tone is heard over the pulmonary artery. Specify the nature of the crisis. Select drugs for its treatment. Explain their mechanism of action.

2. A man, 58 years old, two days ago developed and increasing headaches, nausea, and vomited three times, which does not provide relief. He is worried about weakness, unsteadiness of gait, dizziness, and occasional difficulty speaking. The condition worsened after nervous overstrain. In the anamnesis: he has had arterial hypertension for the past 25 years. Regularly, for the past 2 years, he has been taking 1 tablet (0.000075 g) of clonidine before going to bed. Maximum ACT - 230/130 mm Hg, working - 170/100 mm Hg. His mother had hypertension, died of a cerebral vascular stroke. Objectively: the patient is drowsy, lethargic. Hypersthenic. Obesity of the II degree. Xanthelasma in the area of the upper eyelid of the right eye. Pulse - 54 beats. in 1 min, rhythmic. ACT - 220/154 mm Hg. Left ventricular hypertrophy. Accentuation of the II tone over the aorta. On the ECG - a decrease in the amplitude of the T wave in leads V3 - V6. Formulate the diagnosis. Indicate the drugs necessary for the treatment of this 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, periodic confusion of consciousness. The condition worsened sharply 50 min ago. History: hypertension for 10 years. Maximum ACT - 220/130 mm Hg, working -170 / 110-115 mm Hg. In the last 1.5 years, she often calls emergency doctors due to increased blood pressure. Objectively: general condition is severe. Consciousness is periodically clouded. Convulsive twitching in the limbs. Pulse - 82 beats per minute, rhythmic. ACT - 240/140 mm Hg. Left ventricular hypertrophy. Accentuation of the II tone and systolic murmur over the aorta. Formulate the diagnosis. Specify the nature of the attack. Justify the choice of drugs for the treatment of existing disorders.

4. A 56-year-old patient is hospitalized for hypertension. He was taking medications: capoten 25 mg three times a day, adverzuten - 1 mg 3 times a day. 30 minutes after taking the drugs, the patient fell and lost consciousness for a few seconds. Objectively: the skin is pale, moist. Pulse - 100 per minute, rhythmic. Blood pressure 60/20 mm Hg. What complication did the patient have? Indicate the drugs necessary for the treatment of this disease process.

5. A 34-year-old woman with acute bronchopneumonia, after an intradermal test for penicillin, after 5 minutes, suddenly developed cough, shortness of breath, fear, anxiety, headache, dizziness, tinnitus, nausea, vomiting, abdominal pain. Objectively: general condition is severe. Consciousness is clouded. Foam from the mouth, convulsions, involuntary defecation and urination. Skin is pale with a cyanotic tint. Pulse 120 beats per minute, rhythmic, small filling, threadlike. ACT - 60/20 mm Hg. Heart sounds are muffled. In the lungs there is hard vesicular breathing, scattered dry rales. Formulate a diagnosis. Make a program of intensive therapy, justify its appointment.

Test tasks for self-control:

1. A patient with arterial hypertension was prescribed one of the antihypertensive drugs. A/T normalized, but the patient began to worry about a constant dry cough. Which of the listed drugs has the following side effect?

A. Nifedipine.
B. Anaprilin.
C. Clophenin.
D. Reserpine.
E. Enalapril.

2. A patient with hypertension took an antihypertensive drug for a long time, but suddenly stopped taking it. After that, the patient's condition worsened, a hypertensive crisis developed. What type of side effect did the patient develop?

A. Cumulation.
B. Withdrawal syndrome.
C. Tolerance.
D. Sensitization.
E. Dependence.

7. It is undesirable to combine Captopril with:

A. Veroshpiron
B. Hypothiazide
C. Furosemide
D. Torasemide
E. Indapamide

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical pharmacology of antianginal drugs"

Purpose:

To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of antianginal drugs:

- slow calcium channel blockers: phenylalkylamines (verapamil, halopamil); benzothiazines (diltiazem);
- beta-blockers: - non-selective - nadolol, propranolol, timolol, pindolol; - beta-1-selective - bisoprolol, metoprolol, nebivolol, atenolol, betaxolol;
- nitrates: nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, isosorbide-5-nitrate;
- sydnonimines: molsidomine, advocard;
- sinus node f-channel inhibitors: ivabradine, coraxan.

Basic concepts (list of questions):

1. Acute ischemic heart disease.
2. Chronic ischemic heart disease.
3. Angina attack: definition, development factors.
4. Thrombosis, thromboembolism.
5. Antianginal drugs.

Plan

1. Theoretical questions:

Ischemic heart disease (IHD) is a pathological condition characterized by an absolute or relative disruption of the blood supply to the myocardium due to damage to the coronary arteries. IHD is myocardial damage caused by a disorder of coronary circulation, which occurs as a result of a disruption of the balance 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).

The variety of mechanisms that determine the nature and speed of development and progression of coronary artery disease explains the existence of numerous variants of clinical manifestations of this disease, the main of which are sudden cardiac death, angina pectoris, painless myocardial ischemia, myocardial infarction and post-infarction cardiosclerosis.

Classification of coronary artery disease

1. Sudden cardiac death (primary cardiac arrest).
2. Angina.

2.1. Stable angina pectoris (with indication of functional class from I to IV).

2.1.1. FC I: attacks occur during high-intensity exercise;

2.1.2. FC II: attacks occur when walking more than 500 m and climbing more than the first floor;

2.1.3. FC III: attacks occur when walking 100-500 m, climbing the first floor;

2.1.4. FC IV: attacks occur when walking less than 100 m and at rest.

2.2. Unstable angina:

2.2.1. First-time angina.

2.2.2. Progressive angina.

2.2.3. Early post-infarction or postoperative angina.

2.3. Spontaneous (vasospastic, variant, Prinzmetal) angina.

3. Painless myocardial ischemia.

4. Microvascular angina ("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. Post-infarction cardiosclerosis.

Risk factors for coronary heart disease are circumstances, the presence of which leads to the development of coronary heart disease. These factors are in many ways similar to risk factors for atherosclerosis, since the main link in the pathogenesis of coronary heart disease is atherosclerosis of the coronary arteries.

Biological determinants or factors: -old age; -male gender; -genetic factors contributing to the occurrence of dyslipidemia, hypertension, glucose tolerance, diabetes mellitus and obesity.

Anatomical, physiological and metabolic (biochemical) features: -dyslipidemia; -arterial hypertension; -obesity and the nature of fat distribution in the body; -diabetes mellitus.

Behavioral factors that can lead to exacerbation of coronary heart disease: -food habits; -obesity, as a factor in the development of coronary heart disease; -smoking; -insufficient physical activity, and physical exertion exceeds the adaptive capabilities of the body; -alcohol consumption; -behavior that contributes to coronary artery disease; -stress.

Pathogenesis

According to modern ideas, CHD is a pathology based on myocardial damage, which is caused by coronary insufficiency (insufficient blood supply). Disruption of the balance between the needs of the myocardium in blood supply and its actual blood supply can be caused by a number of reasons.

Intravascular causes: -thrombosis and thromboembolism of the coronary arteries; -atherosclerotic narrowing of the lumen of the coronary arteries; -spasm of the coronary arteries.

Extravascular causes: -myocardial hypertrophy; -tachycardia; -arterial hypertension.

CHD is a group concept that includes both acute and chronic conditions based on ischemia and the changes in the myocardium caused by it (sclerosis, dystrophy, necrosis), but only in cases where ischemia is caused by narrowing of the lumen of the coronary arteries, which is associated with atherosclerosis, or the cause of the mismatch of coronary blood flow to the needs of the myocardium is not established.

Clinical forms

To substantiate the diagnosis of CHD, its clinical form should be demonstrably established (according to the classification) according to the generally accepted criteria for the diagnosis of this disease. In most cases, the key to making a diagnosis is the recognition of myocardial infarction or angina pectoris - the most frequent and typical manifestations of CHD, other clinical forms of the disease are much less common, their diagnosis is difficult.

Sudden coronary death

Primary cardiac arrest is thought to be associated with electrical instability of the myocardium. It is classified as an independent form of coronary artery disease only if there is no evidence to diagnose another form of coronary artery disease or another disease. For example, death occurring in the early phase of myocardial infarction does not fall into this category and is considered a death resulting from myocardial infarction. If resuscitation measures were not performed or were ineffective, primary cardiac arrest is classified as sudden coronary death. The latter is defined as death occurring in the presence of witnesses immediately or no later than 6 hours after the onset of the heart attack.

Angina

As a manifestation of coronary artery disease, angina pectoris combines angina pectoris

of tension, which is divided into: - newly occurring; - stable; - progressive; - spontaneous ("angina at rest", one of the variants is Prinzmetal's angina).

Angina pectoris. This form of the disease is characterized by periodic attacks of 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, the retrosternal pain that appeared during emotional or physical stress (burning, heaviness, discomfort) radiates to the left arm and/or shoulder blade. Quite rarely, the localization and irradiation of pain are atypical. The duration of the tachycardia attack varies from 1 to 10 minutes, in some cases up to 30 minutes. As a rule, the pain quickly stops after stopping the load or within 2-4 minutes after sublingual (under the tongue) administration of nitroglycerin. The diagnosis of "stable angina pectoris" is established with a stable manifestation of the disease in the form of a regular occurrence of attacks of pain (which are preceded by ECG changes) at a certain load for a period of at least 3 months. The severity of stable angina pectoris is characterized by the threshold level of physical exertion that patients tolerate. The functional class of the severity of the disease is necessarily indicated when formulating the diagnosis.

Progressive angina pectoris is characterized by a relatively rapid increase in the severity and speed of pain attacks with a decrease in tolerance to physical exertion. Pain attacks occur at rest or with less than the previous load, are much more difficult to stop with nitroglycerin (most often an increase in a single dose is required), and in some cases are stopped only by the introduction of narcotic analgesics.

Spontaneous angina - this form of coronary heart disease differs from angina pectoris in 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 attacks can occur at rest, without an obvious cause, most often at night or in the early hours, in some cases have a pronounced cyclical nature. In terms of localization, duration and irradiation, as well as the effectiveness of nitroglycerin, attacks of spontaneous angina differ little from attacks of angina of exertion. Variant angina - under Prinzmetal's angina is defined as spontaneous angina, which is accompanied by transient elevations of the ST segment on the ECG.

Myocardial infarction

This diagnosis is established in the presence of clinical and/or laboratory (enzyme activity dynamics) and electrocardiographic data indicating the occurrence of a small or large focus of necrosis in the myocardium. If the patient is not hospitalized in the intensive care unit as quickly as possible when a heart attack occurs, there is a possibility of developing severe complications and a high probability of death.

Large-focal myocardial infarction. Transmural myocardial infarction is justified by pathognomonic ECG changes or a specific increase in the activity of enzymes in the blood serum (AST, lactate dehydrogenase, creatine phosphokinase, etc.) even with an atypical clinical picture. The enzymes listed above belong to the enzymes of redox reactions and are normally observed only inside the cell. If cell destruction occurs (for example, during necrosis), the enzymes are released and determined during laboratory tests. 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 there are 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.

Post-infarction cardiosclerosis. References to post-infarction cardiosclerosis as a complication of coronary artery disease are included in the diagnosis no earlier than two months from the date of myocardial infarction. As an independent clinical form of ischemic heart disease, post-infarction cardiosclerosis is established in the absence of angina pectoris and other forms of coronary artery disease provided for by the classification, with the

simultaneous presence of electrocardiographic and clinical signs of focal myocardial sclerosis (persistent conduction and rhythm disturbances detected on the ECG, signs of cicatricial changes in the myocardium, chronic heart failure). If during the remote period of examination of the patient there are no ECG signs of a previous infarction, the diagnosis can be substantiated 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 ruptures of the myocardium, intracardiac thrombosis, chronic cardiac aneurysm, dysfunction of the papillary muscles of the heart is necessarily indicated, and the nature of heart rhythm and conduction disorders is also determined, the stage and form of heart failure are indicated.

Arrhythmic form. Cardiac arrhythmia or signs of left ventricular heart failure (cardiac asthma, shortness of breath, pulmonary edema) occur as equivalents characteristic of spontaneous angina or angina of exertional attacks. Diagnosis of these forms of the disease is difficult, the diagnosis is finally formed on the basis of an analysis of the totality of ECG results in stress tests, or with selective coronary angiography data and monitor observation.

Diagnostics

In CHD, the most common complaints are: -retrosternal pain associated with physical exertion or stress; -severe shortness of breath; -signs of heart failure (swelling starting in the lower extremities, forced sitting position); interruptions in the work of the heart; -weakness; -feeling of a heart rhythm disturbance.

Of the anamnesis data, the duration and nature of pain, arrhythmia or shortness of breath, their relationship with physical exertion, the degree of physical exertion that the patient can withstand without an attack, the effectiveness of various medications during an attack (for example, the effectiveness of nitroglycerin). It is very important to find out the presence of risk factors.

During a physical examination, signs of heart failure may be detected (crepitation and moist rales in the lower parts of the lungs, hepatomegaly, "cardiac" edema). There are no objective symptoms specific to CHD that could be detected without instrumental or laboratory examination. An ECG should be performed if CHD is suspected.

Electrocardiography

ECG is an indirect method of research, which does not provide data on the number of dead myocardial cells, however, it allows to assess some of its functions. In the diagnosis of mostly 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 a pathological Q wave on the ECG; - in lead I: the presence of a pathological Q wave (> 0.03c, amplitude 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, amplitude more than a quarter of the amplitude of the R wave); - in lead III there is a pathological Q wave (> 0.03c, amplitude more than half the amplitude of the R wave); - in leads V1, V2 and V3 there is a QR or QS wave, and the T wave is negative; - in leads V4, V5 and V6 there is a pathological Q wave (> 0.04s), and the T wave is negative. The T wave makes it possible to determine the stage of the process in dynamics. For example, in lead II: sharply positive in the most acute stage of infarction ("cat's back", Pardee curve); negative in the acute stage (as a rule, with a smaller amplitude); rises to the isoline in the stage of scarring and the subacute stage, but in most cases (if there is a large focal infarction) does not reach it). A sign of scar tissue in the myocardial tissue is a weakly expressed negative T wave and a pathological Q wave. The data obtained during the ECG are an objective instrumental criterion that allows you to determine the presence of myocardial infarction, the duration and localization of the damage.

Echocardiography

The essence of this method is to irradiate tissues with ultrasound pulses of a fixed frequency and then receive the reflected signal. Based on the magnitude of the reflection, a

picture of the density of the tissues passed by the pulse is formed. Modern devices provide the output of graphic information in real time, in addition, there is the possibility of assessing blood flow due to the Doppler effect. In coronary artery disease, echocardiography makes it possible to assess the condition of the myocardium, as well as the preservation and contractile activity of the valvular apparatus of the heart.

Laboratory indicators

CHD is a combination of several diseases with different biochemical processes. The following changes may occur:

Changes characteristic of myocardial infarction: increased concentration of specific proteins (such as troponin, creatine phosphokinase, aminotransferases, myoglobin, lactate dehydrogenase). All proteins are contained exclusively inside the cell. As a result of necrosis and massive destruction of cells, these proteins enter the bloodstream and are determined during laboratory tests. Nonspecific reaction to myocardial damage: neutrophilic leukocytosis (3-7 days) as an inflammatory process, as a response to necrotic changes, increased ESR (7-14 days), which is a reflection of changes in the ratio of the number between different protein fractions (also occurring mainly due to the development of inflammation) and increased levels of ALT, AST - nonspecific markers of cytolysis. Changes characteristic of atherosclerosis include: triglyceride concentration, high- and low-density lipoprotein cholesterol, total cholesterol, apolipoprotein A1 and B concentrations, and the atherogenic index.

Functional tests

As a rule, functional tests are various types of physical exertion, which are accompanied by the registration of heart parameters (usually ECG). The purpose of such tests is to determine the pathology in the early stages of development, when at rest characteristic changes have not yet developed, and during exercise the person feels anxiety. Exercise tests are used to conduct a differential diagnosis and determine tolerance to physical exertion. This load can be provided in various ways: treadmill; bicycle ergometry; step test; climbing stairs; walking a certain distance.

Other instrumental diagnostic methods

Angiography and CT angiography of the coronary arteries are diagnostic methods in which a radiopaque substance is injected into the vascular bed. Against this background, a series of CT scans or X-rays are performed, which allows contrasting 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 100% safe, the development of allergic reactions and severe (up to anaphylaxis) complications is possible.

Intraesophageal electrocardiography It is used as an additional method, which allows assessing the absence or presence of additional foci of excitation that are not registered in standard leads. The essence of the technique is to introduce an active electrode into the esophageal cavity. The method makes it possible to assess in detail the electrical activity of the atrioventricular junction and atria.

Holter monitoring is a method of recording ECG during the day, used to detect disturbances in the work of the heart that occur periodically. It makes it possible to correlate the clinic with the data obtained. ECG recording is carried out using a Holter monitor - a special portable device that the patient wears on his belt or on a strap over his shoulder during the day. During the study, the patient leads a normal lifestyle, noting in a diary the exact time and circumstances of the occurrence of problems in the heart. After monitoring, the data are transferred to a computer, where they are processed. Some monitors have the ability to directly print the study data onto a cardiograph tape.

Treatment of ischemic disease involves the use of different groups of drugs that affect certain links in the pathogenesis of coronary heart disease.

Classification of coronary heart disease treatment agents:

1. Antianginal drugs.

2. Antithrombotic drugs.
3. Drugs that improve heart muscle metabolism (trimetazidine, thiotriazolin).
4. Lipid-lowering drugs.
5. Angiotensin-converting enzyme inhibitors (ACEIs).

Classification of antianginal agents

I. Agents that reduce myocardial oxygen demand:
• Nitrates.
• Sydnonimines.
• β-blockers.
• Calcium channel blockers (phenylalkylamine, benzothiazepine derivatives).
• Selective If-inhibitors.

II. Agents that improve oxygen delivery to the myocardium:
• Calcium channel blockers (dihydropyridine, benzothiazepine derivatives).
• Adenosine potentiators.

Nitrates.

Nitrates: nitroglycerin and its depot preparations; isosorbide dinitrate; isosorbide mononitrate.

A highly active vasodilator substance is formed in the vascular endothelium - endothelial relaxing factor (ERF). In terms of chemical structure, ERF is similar to nitric oxide (NO). It is believed that endothelial dysfunction, which accompanies the pathology of coronary and other vessels, may be due to insufficient synthesis of ERF.

Nitrates in the process of metabolism release NO, which activates guanylate cyclase and increases the content of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells. cGMP promotes dephosphorylation of myosin light chains, which leads to relaxation of smooth muscles and vasodilation.

Despite the fact that nitrates dilate 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 work and, accordingly, myocardial oxygen demand due to a decrease in 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 regulation of vascular tone and anticoagulant properties of blood, influence on leukocyte adhesion, proliferation of vascular smooth muscle elements, apoptosis. There is experimental evidence of the antiatherosclerotic effect of NO. In experiments, nitrates normalized endothelial function, reduced damage to the vascular intima, and prevented LDL oxidation.

Indications for the appointment of nitroglycerin:
• Angina pectoris (sublingually).
• Unstable angina pectoris (sublingually, intravenously).
• Acute period of myocardial infarction (usually intravenously).
• Coronary artery spasm during coronary angiography (intravenously).

The effect of sublingual administration occurs after 1-3 minutes, lasts 20-30 minutes.

It should be borne in mind that the shelf life of the drug in the original packaging is 1 year, and after opening the convalescent tube with proper storage, about 1-2 months, after which the convalescent tube should be replaced with a new one. Aerosol forms of nitroglycerin are more convenient in this regard, the medicinal substance in which does not have contact with air. Criteria for adequacy of the dose of nitroglycerin preparations when taken orally (sublingually):
• Decrease in blood pressure (BP) by 10-15 mm Hg.
• Increase in heart rate by 10-15 beats/min.
• Increase in load time on paired bicycle ergometry by 2 min or more (one test before taking, one at the maximum effect of the drug).

Isosorbide dinitrate, like nitroglycerin, has an antianginal effect due to the "hemodynamic unloading" of the myocardium as a result of a predominant (by 40%) decrease in venous tone. When taken sublingually (after chewing the tablet), the effect develops after 3-5 min and lasts up to 60 min. When taken orally, the speed and duration of the drug's action are 20-30 min and 2-3 hours, respectively, so nitrosorbide can be used both for the treatment of coronary artery disease and for the relief of an attack of angina. Prolonged forms of isosorbide dinitrate (isomac-retard) are prescribed 2-3 times a day. Izoket-retard and Kardiket-retard - longer-acting drugs - can be prescribed 1-2 times a day.

Isosorbide mononitrate (Mono Mac, Olikard-retard) differs significantly from other nitrates in its pharmacokinetic parameters. Its bioavailability is 100%; in addition, the drug has no first-pass effect, and the half-life is 4-5 hours, which allows it to be prescribed 2 or 3 times a day, even in conventional, non-prolonged forms. The drug is used to treat coronary artery disease, starting with angina pectoris of functional class II.

Side effects of nitrates

• Orthostatic hypotension, reflex tachycardia. It should be emphasized that the dilation of veins and arteries, which leads to a decrease in blood pressure, is the basis of 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 Hg, a collaptoid reaction may occur.

• Headaches due to dilation of cerebral vessels and increased intracranial pressure.

• Tolerance (habituation) to nitrates, which develops with prolonged, regular, frequent use of drugs (especially in high doses) or failure to observe a nitrate-free period.

Mechanisms of tolerance development:

• Decrease in the activity of adenylate cyclase and the level of cAMP.

• Decrease in the content of SH-groups, which ensure the conversion of nitrates into nitric oxide and nitrosothiols.

• Activation of the sympathoadrenal system and the renin-angiotensin-aldosterone system.

• Increased production of superoxides.

• Reduced biotransformation of nitrates.

Measures to prevent tolerance to nitrates:

• Increasing the dose of the drug. However, in most cases this method gives a temporary effect, since addiction also develops to a higher dose.

• Intermittent method of prescribing nitrates. It is based on restoring the body's sensitivity to drugs in the "nitrate-free period", the duration of which during the day should be at least 8-12 hours. At this time, antianginal drugs of other groups can be used.

• Combination of nitrates with ACE inhibitors - captopril, perindopril, zofenopril - to restore the content of SH-groups in the endothelium and reduce the activity of the RAAS.

• Combination of nitrates with β-blockers, calcium channel blockers, or antioxidant vitamins.

Nitrates are characterized by the phenomenon of "rebound", when, upon sudden cessation of taking the drugs after prolonged therapy, a significant deterioration in the course of the disease is noted (angina attacks become more frequent, pain syndrome intensifies). Prevention of the rebound phenomenon is carried out by gradually reducing the dose and frequency of taking the drugs.

Contraindications to the use of nitro drugs:

• Blood pressure below 100/60 mm Hg.

• Cardiogenic shock.

• Intracranial hemorrhages.

• Hypovolemia.

• Toxic pulmonary edema.

• Constrictive pericarditis.

• Hypersensitivity to nitro drugs.

Interaction of nitrates with other drugs. The interaction of nitro drugs with phosphodiesterase inhibitors, in particular with sildenafil (Viagra), is of fundamental importance, since such a combination creates the risk of potentially dangerous arterial hypotension. Sildenafil can be used only after at least a 24-hour break after taking nitrates, including nitroglycerin. Increased hypotensive effect is observed when nitrates are combined with barbiturates, opioid analgesics, tricyclic antidepressants, alcohol, and other drugs that lower blood pressure. Weakening of the vasodilating effect is possible with simultaneous use of nitrates with carbachol, alpha-adrenomimetics (noradrenaline, mezaton), histamine, angiotensin, corticosteroids, CNS stimulants, M-cholinoblokars (atropine).

Sydnonimines. The only drug used in this group is molsidomine (sydnofarm, corvaton). Its mechanism of action at the cellular and systemic levels is similar to that of nitrates, but unlike the latter, molsidomine increases the formation of cGMP without forming nitrosothiols. Therefore, tolerance to it practically does not develop. The onset of action of molsidomine when taken orally is 20 minutes, and its duration is up to 6 hours. When taken sublingually, the effect occurs after 5 minutes and lasts 6-7 hours. Retarded forms of the drug containing 8 mg of the active substance are more often used. Such forms of molsidomine are convenient to use in the "nitrate-free period", since the drug does not give cross-resistance with nitrates. The 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 nitrate-like action, which combines several mechanisms of action: the release of NO and an additional vasodilator effect due to the activation of potassium channels (this leads to hyperpolarization of the membranes of vascular smooth muscle cells, which leads to a decrease in the cytoplasmic concentration of calcium ions). The drug reduces the tone of arteries and veins, dilates coronary vessels.

Classification of β-blockers and mixed adrenoblockers

1. β-blockers

1.1. Non-selective (β1, β2) without intrinsic sympathomimetic activity

• Propranolol (anaprilin).
• Timolol (blokadren).
• Nadolol (corgard).

1.2. Non-selective (β1, β2) with intrinsic sympathomimetic activity

• Pindolol (visken)
• Oxprenolol (trazikor)

1.3. Selective (β1) without intrinsic sympathomimetic activity

• Talinolol (Cordanum).
• Bisoprolol (Concor).
• Metoprolol tartrate (Egilok).
• Metoprolol succinate (Betalok ZOK).
• Atenolol (Tenormin).
• Betaxolol (Lokren).
• Esmolol (Breviblok).

1.4. Selective (β1) with intrinsic sympathomimetic activity

• Acebutolol (Sectral).

1.5. Selective (β1) with vasodilating action

• Nebivolol (Nebilet).
• Celiprolol (Selectol).

2. Mixed adrenoblockers (β, α1)

• Labetalol (Trandate).
• Carvedilol (Dilatrend).

β-Adrenergic blockers (BABs) are one of the main groups of drugs used to treat

coronary artery disease. They are currently 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 BABs is reversible binding to β-adrenergic receptors and competitive blockade of adrenergic effects on various organs and tissues. It is the blockade of sympathetic effects that underlies the main beneficial effect of drugs in this group, namely the ability to reduce mortality from cardiovascular causes.

The pharmacological classification of BABs is based on several specific characteristics, such as cardioselectivity - the ability of drugs in therapeutic doses to selectively block β1-adrenoreceptors of the heart. Cardioselective drugs have fewer side effects associated with the blockade of β2-adrenoreceptors (bronchospasm, peripheral vascular spasm, increased contractile activity of the myometrium). Sometimes β1-adrenoblockers are called "cardioselective", but, unfortunately, cardioselectivity decreases or completely disappears with increasing dose, so the safety of these drugs, for example, in the treatment of patients with obstructive pulmonary diseases, is relative. Some drugs have intrinsic sympathomimetic activity. They, shielding β-adrenoreceptors from the action of catecholamines, at the same time maintain a certain level of activation of adenylate cyclase associated with receptors. These drugs reduce the strength and frequency of heart contractions to a lesser extent, less often cause bronchospasm and spasm of peripheral vessels, practically do not affect carbohydrate metabolism and blood lipid levels.

Of great clinical importance are such properties of β-blockers as lipophilicity and hydrophilicity. Based on this indicator, BABs are divided into three groups:

- lipophilic,
- hydrophilic;
- amphophilic.

Lipophilic β-blockers (betaxolol, metoprolol, propranolol, etc.) are quickly and fairly completely (up to 90%) absorbed in the gastrointestinal tract, metabolized in the liver (80-100%), penetrate well through the blood-brain barrier, which causes the development of central side effects. The dose of these drugs should be adjusted in patients with liver diseases, as well as when administered simultaneously with drugs that inhibit microsomal oxidation. The risk of accumulation of lipophilic β-blockers occurs when blood flow through the liver is reduced (elderly patients, cirrhosis of the liver, venous congestion). Hydrophilic β-blockers (atenolol, nadolol, etc.) are not completely (30-70%) and unevenly absorbed in the gastrointestinal tract. They are usually metabolized to a small extent in the liver and excreted by the kidneys either unchanged (40-70%) or as metabolites. As a result, when prescribing them, renal function should be taken into account, and in patients with low glomerular filtration (30-50 ml/min) the dose of drugs should be reduced. Hydrophilic β-blockers penetrate the blood-brain barrier worse than lipophilic ones, so it is generally believed that they cause less side effects from the CNS. Amphophilic β-blockers (acebutolol, celiprolol, bisoprolol), which are soluble in both lipids and water, have two main routes of elimination from the body - hepatic metabolism (40-60%) and renal excretion (unchanged).

Only lipophilic β-blockers (metoprolol, propranolol, timolol) and amphiphilic - bisoprolol have a cardioprotective effect regardless of the presence or absence of selectivity. These drugs, when used for a long time after myocardial infarction, reduce mortality by 20-50%.

A special group is represented by β-blockers with vasodilating properties. This property is realized in different ways. 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 - by increasing the content of ERF in the vascular endothelium, develops due to the antagonism of the G-isomer (RSSS) with N-monometal-G-arginine (Γ-NMMMA) - 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 cardiodepression), a natural decrease in blood pressure. Peripheral blood flow worsens due to a relative increase in peripheral vascular resistance (with prolonged use, the severity of this effect is less). Blood circulation in striated muscles worsens, cerebral blood flow does not change, and renal blood flow depends on the β-adrenergic blocker used; when treated with non-selective propranolol - it worsens, when treated with selective atenolol - it increases. Deterioration of bronchial patency under the influence of β-blockers can lead to severe respiratory disorders in patients with obstructive pulmonary diseases.

The mechanism of antianginal action of β-blockers is the blockade of β1-adrenoreceptors of the heart, which leads to a decrease in the frequency and strength of heart contractions, and accordingly, the work of the heart and the oxygen demand of the myocardium. In addition, BABs redistribute coronary blood flow in favor of ischemic subendocardial layers of the myocardium.

Indications for the use of β-blockers in coronary artery disease:

1. Treatment of stable angina, starting from functional class II.
2. Unstable angina.
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 better to prescribe β-blockers to patients suffering from coronary artery disease with concomitant diseases: arterial hypertension, supraventricular tachycardias, ventricular extrasystoles. Considering that the stability of the antianginal effect of β-blockers is determined not so much by the strength of the effect on β1-adrenoreceptors, but by the uniformity of neurohumoral blockade, for reliable suppression of angina attacks, drugs with a long half-life are better.

For patients with coronary artery disease who have suffered a myocardial infarction, it is more expedient to prescribe lipophilic β-blockers, for which it has been proven that they can reduce mortality in the long term after MI, - metoprolol, timolol, propranolol and the mixed BAB carvedilol. At the same time, metoprolol and timolol are the drugs of choice in patients with unchanged left ventricular ejection fraction (LVEF), and carvedilol and metoprolol succinate - in patients with reduced LVEF.

Therapy with β-blockers is started with minimal daily doses, with their subsequent increase after 4-5 days until the desired effect. The criterion for dose adequacy is considered to be a decrease in heart rate to 55-60 beats/min at rest. However, when selecting doses of drugs with intrinsic sympathomimetic activity, one should not focus on heart rate.

Side effects of β-blockers

1. Associated with blockade of β1-adrenoreceptors of the heart (cardiac): -bradycardia; -atrioventricular blockade; -decreased force of heart contractions - cardiodepression; -hypotension.

2. Associated with the blockade of β2-adrenergic receptors of smooth muscles (non-cardiac): -bronchospasm; -spasm of peripheral vessels; -increased contractile activity of the myometrium.

3. Others:

• β-blockers impair glucose tolerance, suppressing the mechanisms of counteraction to hypoglycemia in diabetes mellitus: in people with type 1 diabetes mellitus, these drugs can cause hypoglycemia. In addition, they mask some symptoms of hypoglycemia (tremor, tachycardia), without affecting the characteristic sweating.

• BABs have a proatherogenic 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 appointment of thiazide diuretics), and subsequently they weaken somewhat.

• Erectile dysfunction may develop in men. Selective β1-adrenergic blockers and β-adrenergic blockers with sympathomimetic activity cause these side effects to a lesser extent.

• Lipophilic β-adrenergic blockers can cause side effects from the CNS (weakness, apathy, drowsiness, nightmares, depression). BABs cause a "rebound" phenomenon, which can develop after 2-3 days (usually 3 months) of regular intake; it is associated with increased sensitivity and density of β-adrenergic receptors (irregulation). Clinical manifestations of the rebound syndrome include: the development of tachycardia or recurrence of tachyarrhythmia, the appearance, increase in frequency or severity of angina pectoris, the development of myocardial infarction, palpitations, tremor, anxiety. These symptoms appear on the 3rd-5th day after discontinuation of β-blockers and sometimes persist for a week or more (from 1 to 21 days). To prevent this complication, the drugs should be discontinued for 2 weeks, gradually reducing the dose.

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 sinus node cells, impulse conduction through the atrioventricular node, contraction of cardiomyocyte muscle fibers and vascular smooth muscle cells. Selective blockers of L-type calcium channels are verapamil, diltiazem, nifedipine, etc.

- T-type calcium channels are responsible for the automatism of the sinus node, impulse conduction through the atrioventricular node, contraction of smooth muscle cells, regulation of protein synthesis and cell proliferation. Selective blockers are mibefradil, cinnarizine, flunarizine.

- Through the N-, P- Q-type calcium channels, the release of some neurotransmitters and hormones occurs.

- R-type calcium channels are involved in the release of ERF.

The selective blocker is the drug isradipine. For the treatment of diseases of the cardiovascular system, L-type calcium channel blockers are mainly used.

The classification of calcium channel blockers is presented in Table. 5. Calcium channel blockers differ in the tropism of action on the myocardium and blood vessels. Phenylalkylamine derivatives act primarily on typical and atypical cardiomyocytes, dihydropyridine derivatives - on blood vessels. Benzothiazepine derivatives have approximately the same effect on vascular smooth muscle and the heart. Diphenylpiperazines and nimodipine (dihydropyridine, group IIb) have a predominant effect on cerebral vessels.

The mechanism of antianginal action of phenylalkylamines is associated with a decrease in calcium influx into typical cardiomyocytes, cells of the sinus node and the conduction system of the heart. Consequently, the force and frequency of heart contractions, cardiac work and myocardial oxygen demand are reduced. The antianginal effect of dihydropyridine derivatives is mainly due to a decrease in calcium influx into smooth muscle cells of both coronary and peripheral vessels, which leads to their expansion. The result 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 ino- and chronotropic effects.

• Indirect reduction in myocardial oxygen consumption, due to a decrease in pre- and afterload.

• Improved oxygen delivery to the myocardium due to dilation of coronary vessels.

• The presence of an antiplatelet effect.

• Indirect antiatherogenic effect.

Indications for the use of calcium channel blockers

1. Stable angina, starting from functional class II.

2. Variant angina of Prinzmetal.

Currently, short-acting nifedipine is not used for the systematic treatment of coronary heart disease and arterial hypertension, since prolonged use of the drug increases the mortality of patients with these diseases. This restriction does not apply to delayed-release forms of the drug.

II-III generation drugs have improved pharmacokinetic properties and cause fewer side effects.

Side effects

• The most characteristic of phenylalkylamine derivatives: - bradycardia; - atrioventricular block; - decreased force of heart contractions; - hypotension.

• The most characteristic of dihydropyridine derivatives: - compensatory tachycardia; - edema of non-cardiac origin; - flushing; - constipation; - hypotension.

Selective If inhibitors

• Ivabradine (Coraxan).

In recent years, selective If inhibitors (specific blockers of the inward ion flow through mixed Na+/K+ channels that are activated at the moment of hyperpolarization) have been intensively studied. The If ion flow plays an important role in pacemaker activity, since it is responsible for the occurrence of the phase of spontaneous slow diastolic depolarization in the cells of the sinus node, and therefore determines the heart rate. As a result of the blockade of If-channels in the sinoatrial node due to the decrease in heart rate, the myocardial oxygen demand decreases without a concomitant decrease in the strength of heart contractions (the effect is dose-dependent).

One of the drugs - If-channel blockers - is Ivabradine (Coraxan), which is prescribed at 5-10 mg 2 times a day. When using the usually recommended doses (7.5 mg 2 times a day), a decrease in heart rate by approximately 10 beats / min is noted at rest and during exercise. This reduces the work of the heart and oxygen consumption by the myocardium. The drug is comparable in antianginal activity to atenolol, but unlike β-blockers, it does not cause bronchospasm, AV-blockade and erectile dysfunction. Ivabradine is contraindicated in bradycardia (heart rate less than 50 beats/min), AV block II-III degree, sick sinus syndrome.

Side effects are mainly due to the effect of the drug on the h-channels of the retina related to f-channels, which is the cause of visual symptoms of varying severity in 10-15% of patients (photopsia, increased brightness in the visual field, blurred vision). These symptoms, as a rule, occur in the first 2 months of therapy, are moderately expressed, reversible and do not require special treatment.

2. Questions for self-control (list of questions):

1. Etiology, pathogenesis, classification of ischemic heart disease.
2. Pathogenetic mechanisms of coronary artery disease, which is the object of the influence of antianginal drugs.
3. List the main groups of antianginal drugs.
4. Explain the mechanisms of action of antianginal drugs, based on their pharmacodynamics.
5. Formulate the significance of the leading pharmacokinetic characteristics (T1/2el, plasma protein binding, Vd) in the individual selection of antianginal drugs.
6. Highlight the clinical and laboratory-functional criteria for therapeutic efficacy and safety of antianginal drugs.
7. What principles are the basis for the classification of antianginal drugs?
8. What hemodynamic changes occur in the body under the influence of slow calcium channel blockers? Indications and contraindications to their use.

3.Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for the main antianginal drugs (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the choice and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize vascular tone disorders, the development of coronary artery disease, write a clinical diagnosis of the disease.

5. Determine the group of drugs necessary for the patient; based on theoretical pharmacodynamic data and own observations, choose a drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 their detection at the early stages.

10. Substantiate the duration of basic and maintenance therapy.

B. Solving situational tasks.

1. A 52-year-old patient suffers from stage II hypertension. Smokes. Is not regularly treated. Objectively: BP - 175/105 mm Hg, HR - 92 beats per minute, scattered dry rales in the lungs against the background of weakened vesicular breathing. The liver protrudes 2 cm from the edge of the costal arch, edema in the ankle joints. Formulate the main and concomitant diagnosis. Make a program of combined therapy taking into account the concomitant disease. Give it a clinical and pharmacological justification.

2. A 65-year-old man suffering from coronary artery disease: stable angina pectoris functional class III, extrasystolic arrhythmia, CHF I - severe, burning pain behind the sternum, shortness of breath, loss of consciousness. Objectively: the general condition is severe, the skin is pale, covered with abundant cold sweat, pronounced acrocyanosis. Pulse - 140 beats per minute by the type of atrial tachyarrhythmia, ACT - 70/40 mm Hg. Heart sounds are muffled. Anuria. On ECG - monophasic curve in leads III, AVR, V4 - V6.

Formulate the diagnosis, emergency therapy program. Justify the choice of drugs

3. Patient Z., 62 years old, hospitalized with complaints of severe pain behind the sternum, which lasts 1 hour and is not relieved by nitroglycerin. Suffers from angina, previously the attack was relieved by nitrates. There are no concomitant diseases. Objectively: cyanosis of the lips. Heart sounds are muffled, activity is rhythmic. On ECG: acute phase of transmural infarction of the anterior wall of the left ventricle. Your actions.

Test tasks for self-control:

1. A patient with hypertension took an antihypertensive drug for a long time, but suddenly stopped taking it. After that, the patient's condition worsened, a hypertensive crisis developed. What type of side effect did the patient develop?

A. Cumulation.
B. Withdrawal syndrome.
C. Tolerance.
D. Sensitization.
E. Addiction.
2. Captopril is undesirable to combine with:
A. Veroshpiron
B. Hypothiazide
C. Furosemide
D. Torasemide
E. Indapamide
3. During the treatment of stable angina pectoris with a combination of antianginal drugs, the patient complained of headache, tinnitus, and dizziness. What group of drugs can cause the indicated side effects?
A. Calcium channel blockers.
B. Beta-blockers.
C. Anticoagulants.
D. Nitrates.
E. Antiplatelet agents.
4. During physical activity, the patient developed a squeezing pain in the sternum, accompanied by stiffness and a feeling of fear. What can be recommended for the relief of anginal attacks?
A. Nifedipine.
B. Nitroglycerin.
S. Anaprilin.
D. Verapamil.
E. Diltiazem.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

"Clinical pharmacology of drugs that affect the blood system (antithrombotic, coagulants) and lipid metabolism (hypolipidemic)"

Purpose:

1. To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of antithrombotic drugs:

- thrombolytics (streptokinase, alteplase, etc.);
- direct-acting anticoagulants (heparin, fraxiparine, enoxaparin, etc.);
- indirect-acting anticoagulants (warfarin, neodicoumarin, etc.);
- antiplatelet agents (acetylsalicylic acid, clopidogrel, etc.).

2. To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of coagulants:

- direct-acting (fibrinogen, thrombin);
- vitamin K analogues (kanavit, vikasol);
- fibrinolysis inhibitors (aminocaproic acid, tranexamic acid).

3. Learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of hypolipidemic drugs:

- statins (atorvastatin, rosuvastatin, etc.);
- fibrates (fenofibrate, tricor);
- inhibitors of cholesterol absorption in the intestine (ezetimibe).

Basic concepts (list of questions):

1. Mechanisms of thrombus formation.
2. Mechanisms of thromboembolism.
3. Atherosclerosis: pathogenesis.
4. Main clinical symptoms and syndromes associated with impaired hemocoagulation and atherogenesis.
5. Thrombolytic drugs.
6. Anticoagulants of direct and indirect action.
7. Antiplatelet agents.
8. Coagulants of direct and indirect action.
9. Hypolipidemic drugs that inhibit the synthesis of endogenous cholesterol in the liver.
10. Hypolipidemic drugs that inhibit the absorption of cholesterol in the intestine.

Plan

1. Theoretical questions:

One of the causes of the development of CHD is a change in platelet function (Tc), activation of thromboxane A2 synthesis and a decrease in the formation of prostacyclin. The general final mechanism of platelet activation is an increase in the expression of glycoprotein receptors (GP IIb/IIIa-R) on the platelet surface, which leads to the formation of interplatelet bonds, increased platelet aggregation and, as a result, the formation of a thrombus.

General indications for the appointment of antiplatelet agents:

• Stable angina pectoris of functional class II-IV.
• Unstable angina pectoris and myocardial infarction.

• Primary and secondary prevention of cardiovascular events.

• Post-infarction cardiosclerosis.

• Prevention of thrombosis during intracoronary interventions.

Acetylsalicylic acid is a non-selective irreversible inhibitor of COX1, which leads to a violation of the synthesis of cyclic endoperoxides and their metabolites (thromboxane and prostacyclin). Thromboxane (Thx-A2), which is one of the most powerful aggregation factors, is synthesized mainly in platelets, the lifespan of which is 7-10 days. When aspirin is administered, irreversible blockade of COX occurs, the resynthesis of which is impossible, since platelets are anucleate cells. In the vascular endothelium, under the influence of COX, the predominant synthesis of prostacyclin (PgI2), which is a functional antagonist of Thx-A2, occurs. Aspirin blocks this process in endothelial cells, but since they are nucleated cells, the enzyme is quickly resynthesized in them and prostacyclin production is restored. The antiplatelet effect of acetylsalicylic acid is achieved even in small doses (50-325 mg/day) and persists for several days.

With a stable course of coronary artery disease, aspirin is prescribed 75-125 mg orally once a day, with an exacerbation of the disease - 250-325 mg once a day. In the same doses, the drug is prescribed for cardiac surgery. It should be borne in mind that acetylsalicylic acid is less effective in women for primary and secondary prevention of myocardial infarction than in men.

The use of the drug is limited in:

• gastric ulcer and duodenal ulcer (due to a decrease in the production of cytoprotective prostaglandins in the gastrointestinal mucosa);

• bronchospastic conditions (due to activation of the lipoxygenase pathway of arachidonic acid metabolism and possible increased production of leukotrienes, including those that are part of the slowly reacting substance of anaphylaxis;

• increased bleeding;

• uncontrolled arterial hypertension or its crisis (due to an increased risk of fatal hemorrhagic complications).

In addition, some caution should be observed when prescribing aspirin for the purpose of primary prevention of myocardial infarction and ischemic stroke to patients over 70 years of age, in whom an increase in the number of cases of gastrointestinal bleeding and intracranial hemorrhages is noted against the background of the drug.

ADP (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, 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 that of aspirin 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 noted on the 8th-11th day and persists for 10 days after drug withdrawal. Ticlopidine is prescribed at 500 mg/day in 1-2 doses, with good tolerability the daily dose can be increased to 750 mg. It is the drug of choice for intolerance to acetylsalicylic xylot. Side effects include leuko- and neutropenia, dyspeptic disorders, allergic reactions and hepatotoxicity.

Clopidogrel, which is one of the metabolites ticlopidine, when used at a dose of 75 mg/day, is significantly superior in activity and safety to ticlopidine and aspirin, but has a higher cost. It can be used in combination with aspirin in acute coronary syndrome, including myocardial infarction, and percutaneous coronary interventions, when combination therapy with two antiplatelet agents is required. The dose of clopidogrel in this case is 75 mg/day (after a loading dose of 300 mg/day), and the duration of combination therapy reaches 12 months. In addition, combination therapy can be indicated for a long time for high-risk patients and ischemic stroke.

The new thienopyridine prasugrel, which at a loading dose of 60 mg (maintenance dose of 10 mg) allows for faster and more pronounced inhibition of platelet aggregation compared with taking clopidogrel in loading dose of 300 mg or higher - 600 mg (maintenance dose - 150 mg). Prasugrel is more effective than clopidogrel in preventing ischemic events after percutaneous coronary intervention (19% reduction in cardiovascular death, non-fatal MI, non-fatal stroke; 42% reduction in the risk of fatal MI, 34% reduction in the risk of repeated emergency revascularization of the target artery, 52% reduction in the risk of stent thrombosis). However, compared with clopidogrel, prasugrel therapy is accompanied by an increased risk of major bleeding (32%) and life-threatening hemorrhage, including fatal (52%).

GP IIb/IIIa receptor blockers - abciximab, monafram, eptifibatide, tirofiban - 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 Tc degranulation and Tc-dependent thrombin formation. Drugs of this group are much more effective than all known antiplatelet agents.

Indications for the use of GP IIb/IIIa receptor blockers:

• Endovascular interventions.

• "Acute" period in patients with unstable angina and myocardial infarction without a Q wave.

• As a means of secondary prevention in patients with a high risk of coronary and vascular events.

• In combination with thrombolytic and anticoagulant therapy in patients with transmural myocardial infarction to prevent rethrombosis.

Side effects of drugs in this group include thrombocytopenia and bleeding.

Contraindications to the use of GP IIb/IIIa receptor blockers:

• Internal bleeding, including recent (up to 6 weeks) or suspected.

• Extensive surgery (up to 6 weeks).

• Severe trauma (up to 6 weeks).

• Cerebrovascular accident (up to 2 years), residual effects after cerebral circulation, regardless of duration.

• Severe hypertension.

• Malignant neoplasms.

PDE blockers and adenosine potentiators

Dipyridamole is a PDE and adenosine deaminase blocker. 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 process of platelet aggregation decreases. In addition, blockade of PDE in vessels (including coronary vessels) leads to an increase in the level of cAMP, and, accordingly, their expansion. Inhibition of adenosine deaminase with 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 the level of cAMP (due to inhibition of adenylate cyclase) and the development of a cardiodepressive effect with a decrease in the need for myocardial oxygen. Activation of A2-adenosine receptors in the smooth muscle of vessels contributes to an increase in the activity of adenylate cyclase, the accumulation of cAMP and the expansion of vessels (including coronary vessels). Apparently, 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 blood circulation in the heart. Average daily doses of dipyridamole are 75-600 mg (in 3-4 doses). In terms of antiplatelet activity, the drug is significantly inferior to aspirin and thienopyridines. Side effects include tachycardia (due to PDE inhibition) and the phenomenon of "stealing" (redistribution of blood flow from the ischemic zone to the non-ischemic zone).

Drugs that improve heart muscle metabolism

The main category of patients in whom metabolic drugs can be used as part of the treatment of coronary artery disease is 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 III-IV functional class;
- It is not possible to apply any method of treatment of resistance.

It should be noted that metabolic therapy agents do not have a proven effect on the final hard points, but sometimes they can give a certain clinical effect.

Angiotensin-converting enzyme inhibitors

• Ramipril (Tritace).

• Perindopril (Prestarium).

One of the promising classes of drugs for improving the prognosis of life of patients with coronary artery disease is ACE inhibitors. Currently, the most studied for this indication are ramipril and perindopril, which have common properties that somewhat distinguish them from other ACE inhibitors (strong affinity for tissue components of the renin-angiotensin-aldosterone system (RAAS), long duration of action). The following mechanisms underlie the positive clinical effect of ACE inhibitors in coronary artery disease:

• Antianginal effect, which is mediated by peripheral vascular dilation (reduction of after- and preload), which is accompanied by a decrease in myocardial oxygen demand. In addition, there is a direct dilation of coronary vessels and improvement of coronary blood flow. Such 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, which develops due to the blockade of the secretion of tissue plasminogen activator inhibitor-1.

• Antiatherogenic effect, due to the normalization of endothelial function, antimitogenic, antioxidant and indirect profibrinolytic effects.

• Reduction of left ventricular hypertrophy regardless of the decrease in blood pressure, associated with a decrease in the activity of RAAS and SAS.

The inclusion of ACE inhibitors in the complex therapy of coronary heart disease allows for a positive effect on the heart, blood vessels, kidneys, improving long-term consequences (myocardial infarction, cardiovascular mortality). The recommended dose of perindopril is 8 mg/day, ramipril - 10 mg/day. The maximum effect of ACE inhibitors in patients with coronary artery disease will probably be observed in patients with moderate and high risk, who have uncontrolled risk factors (smoking, hypercholesterolemia) and other indications for 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 in the combination of coronary artery disease with diabetes mellitus and desirable in severe atherosclerotic lesions of the vessels of the lower extremities.

TREATMENT OF STABLE ANGINA

Treatment of angina has two main purposes.

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.

Drugs that improve the prognosis in patients with angina are recommended for all patients with angina attacks in the absence of contraindications. First of all, we are talking about antiplatelet agents (acetylsalicylic acid), β-blockers (as drugs of choice in patients with angina attacks or when diagnosing episodes of myocardial ischemia using instrumental methods) and hypolipidemic agents (in the presence of dyslipidemias), as well as ACE inhibitors. The following provisions are valid with respect to antianginal drugs in patients

with stable angina:

- antianginal drugs eliminate or reduce the symptoms of the disease;
- antianginal combination therapy is somewhat more effective than monotherapy;
- increasing life expectancy with the use of antianginal drugs requires additional evidence;
- the occurrence of acute ischemic episodes is prevented by acetylsalicylic acid, β-blockers, statins, ACE inhibitors.

Treatment of patients with stable angina should be carried out taking into account its functional class (FC). This involves stopping an attack of angina during heavy physical exertion in patients with FC I. As a rule, nitroglycerin is prescribed sublingually (intermittent use). Further therapy consists of measures related to the normalization of the work and rest regime, the elimination of psychoemotional stress, and risk factors. For the treatment of angina pectoris of FC I, antiplatelet agents and hypolipidemic agents (in the presence of dyslipidemia) may be prescribed. 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, as well as to use their various combinations. The drugs of choice in this case are β-blockers, with their ineffectiveness or pronounced side effects, nitrates or CCBs should be prescribed. If concomitant diseases are arterial hypertension or tachyarrhythmias, it is advisable to prescribe β-blockers or phenylalkylamine CCBs. In the presence of bronchial asthma, the drugs of choice are CCBs or nitrates. If stable angina occurs against the background of heart failure, preference should be given to β-blockers or nitrates, and the appointment of phenylalkylamine CCBs is not recommended. The presence of diabetes in patients with coronary artery disease makes it necessary to additionally introduce ACE inhibitors into therapy. In addition, antiplatelet therapy and the appointment of hypolipidemic agents (in the presence of dyslipidemia) are indicated for patients with FC II.

If monotherapy is ineffective, then combined antianginal therapy is used. Indications for its implementation are:

- ineffectiveness of monotherapy in patients with FC II;
- intolerance of standard doses of drugs;
- coronary artery disease with frequent cardiac arrhythmias (FC II-IV);
- coronary artery disease with heart failure (FC IV) or other concomitant diseases;
- correction of adverse hemodynamic changes that occur with monotherapy.

The following combinations are most often used:

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 better in patients with heart rhythm disorders and arterial hypertension. In addition, this combination can be used in patients with a combination of coronary artery disease and CHF.

2. Calcium channel blockers and nitrates. The results of the combined use of CCBs and nitrates are contradictory. According to a number of researchers, when adding CCBs to nitrates, a more pronounced antianginal effect can be obtained than with monotherapy. Along with this, it has been shown that the addition of nifedipine or verapamil to isosorbide dinitrate does not lead to an increase in the antianginal effect compared to monotherapy with these drugs. Additional administration of CCBs (phenylalkylamines and benzothiazepines) is certainly advisable for the prevention of nitrate resistance (in the nitrate-free period).

3. β-blockers and CCBs (dihydropyridine derivatives) - the combination of drugs is not superior to treatment with each of these drugs separately. Although the β-blocker in this combination is able to eliminate reflex tachycardia caused by dihydropyridine CCBs. The combination of β-blockers and CCBs - phenylalkylamine derivatives (verapamil) is practically not used due to 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, slowing 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. For this, antiplatelet agents, β-blockers, ACE inhibitors and statins are used.

Thus, the following conclusions can be drawn:

• Treatment of stable angina pectoris II-III FC should be carried out with one or more antianginal drugs, which the patient must take 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 angina pectoris.

• In addition to antianginal drugs, it is necessary to prescribe antiplatelet and hypolipidemic drugs, and in a significant part of patients - ACE inhibitors.

Treatment of variant angina

It has been established that in the genesis of Prinzmetal's variant angina, a leading role is played by local spasm of the epicardial coronary artery, which causes transmural ischemia in the corresponding zone of myocardial blood supply. There is an increased sensitivity of this area of the coronary artery to vasospastic stimuli (ergonovine, acetylcholine, leukotrienes, serotonin, etc.). Variant angina can occur both against the background of stenosing atherosclerosis of the carotid arteries (often the zone of spasm is in the area of the plaque), and in people with outwardly intact coronary arteries. The most effective means of stopping attacks of variant angina are nitrates (sublingual tablets or spray), and their prolonged forms can be successfully used for the prevention of attacks. A central role in the treatment of Prinzmetal's angina is played by calcium channel blockers, which are able to prevent and resolve the arising spasm of the arteries. Different points of application of the effect make the combination of BCC with nitrates advantageous - this is the basis of the therapy of variant angina. There is also information about the potential effectiveness of α-blockers (prazosin) in patients with Prinzmetal angina. In most patients, the symptoms of the disease regress spontaneously within 3-6 months, but relapses of the disease may occur, sensitive to previously performed treatment.

Atherosclerosis is a common disease of arteries of the elastic and muscular-elastic types (large and medium caliber), characterized by infiltration of atherogenic lipoproteins into the vessel wall with the subsequent development of connective tissue, atheromatous plaques, organ and general circulatory disorders, which is the main cause of many diseases of the cardiovascular system.

Cholesterol transport in the body is carried out as part of various fractions of lipoproteins, each of which has its own specific significance 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). The level of triglycerides (TG) in the blood is also important for predicting the risk of complications of atherosclerosis.

The most important aspect of the complex drug treatment of patients with atherosclerosis is the use of hypolipidemic agents. They are prescribed in cases where a strictly observed diet (with restriction of saturated fats) and lifestyle correction (weight loss, smoking cessation, increased physical activity) do not lead within 1.5-2 months to the target blood lipid indicators that are desirable for patients with cardiovascular diseases. The use of drugs of this group in CHD leads to a decrease in total and coronary mortality, major coronary events, the need for invasive cardiac interventions, and strokes. In this case, you should focus on the levels of LDL cholesterol, total cholesterol (C) and HDL cholesterol.

Doctors should realize that the time of doubts about the need for hypolipidemic therapy has passed. It is necessary to act in accordance with the call of leading European cardiologists M. Oliver and Poole-Wilson: "Lower your patient's cholesterol level now", meaning that it is

necessary to reduce the level of LDL-C. The main mechanisms that lead to an improvement in the course of coronary heart disease and other diseases under the influence of hypolipidemic therapy (with a decrease in the level of LDL-C) are: "stabilization" of the atherosclerotic plaque; improvement (restoration) of the functional state of the endothelium, which contributes to the expansion of the coronary arteries due to an increase in the production of vasodilating substances by the endothelium; improvement of blood fluidity; normalization of platelet function - reduction of their "thrombotic potential"; slowing down the formation of foam cells; reduction of the inflammatory reaction - reduction of macrophage activity; increase in the level of HDL and increase in the removal of lipids from the atherosclerotic plaque. It is known that acute coronary insufficiency (myocardial infarction, unstable angina) is to some extent associated with the "instability" of the atherosclerotic plaque - a violation of its integrity, subsequent contact of lipid content with blood, hemorrhage into the plaque, thrombosis. Hypolipidemic therapy allows you to stabilize the state of the atherosclerotic plaque, reduce the severity and progression of these changes. For this purpose, antiatherogenic (hypolipidemic) agents are used - these are drugs that reduce the pathologically high level of atherogenic lipoproteins in the blood, and, consequently, total cholesterol, low and very low density lipoprotein cholesterol, triglycerides.

Table . Target Lipid Levels
Target Blood Lipid Levels (General Population)
Total Cholesterol Below 5 mmol/L
LDL Cholesterol Below 3 mmol/L
HDL Cholesterol Above 1 mmol/L
Triglycerides Below 2 mmol/L

In addition to hyperlipidemia, “risk factors” are important in predicting complications. Individuals who have at least one of the risk factors are more likely to develop atherosclerosis than individuals who do not. The presence of several risk factors contributes to the development and progression of atherosclerosis to an even greater extent.

Risk factors for the development of atherosclerosis:

1. Uncontrollable:

• age (in most patients, atherosclerosis manifests itself at the age of 40-50 years and older);

• male gender (in men, atherosclerosis manifests itself more often and 10 years earlier than in women);

• genetic predisposition to the development of atherosclerosis.

2. Controlled:

• smoking;

• arterial hypertension (BP> 140/90 mmHg)

• obesity.

3. Potentially or partially reversible:

• hyperglycemia - hypercholesterolemia and/or hypertriglyceridemia;

• hyperglycemia and diabetes mellitus;

• low level of HDL (α-LP) in the blood (<0.9 mmol / l)

4. Other possible factors:

• low physical activity (hypodynamia);

• mental and emotional stress.

There is evidence that convincingly proves that "lifestyle modification", i.e. a combination of an almost completely vegetarian diet, intensive physical training and psychotherapy (relaxation), can cause regression of coronary artery stenosis. Strict diet, physical training and their combination cause a more pronounced regression of coronary artery stenosis than long-term use of hypolipidemic agents. Currently, the literature discusses

the role of viral and chlamydial infections in the development of atherosclerosis.

Increased plasma cholesterol content 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 in human blood plasma are cholesterol esters, triglycerides and phospholipids. The causes of hyperlipidemia can be both primary (genetic) and secondary (endocrine pathology - diabetes mellitus, hypothyroidism, somatotropic hormone deficiency; kidney pathology - chronic renal failure, nephrotic syndrome; gallstone disease, liver pathology, alcoholism; taking medications - thiazides, β-blockers, glucocorticoids, estrogens, vitamin A, diphenin).

Classification of hyperlipidemias (according to D. Frederikson)

Type Increased level of LP Cholesterol TG Atherogenicity Prevalence

I Chylomicrons Normal or ↑ ↑↑↑↑ Not proven ≤1%

IIa LDL ↑↑ Normal +++ 10%

IIb LDL, VLDL ↑↑ ↑↑ +++ 40%

III LDL ↑↑ ↑↑↑ +++ ≤1%

IV VLDL Normal or ↑ ↑↑ + 45%

V VLDL, chylomicrons Normal or ↑ ↑↑↑↑ + 5%

In clinical practice, this classification of hyperlipidemias is most often used:

Type I - associated with a large number of chylomicrons, occurs rarely (1% of cases). In this type of atherosclerosis does not occur, but there is a risk of developing severe destructive pancreatitis and pancreatic necrosis, so chylomicronemia increases the risk of thrombosis and embolism.

Clinical manifestations: weight gain, attacks of intestinal colic, enlarged liver and spleen, pancreatitis, xanthomatous rashes on the skin.

Type IIa - increased LDL in the blood, occurs in 10% of cases.

Type IIb - increased LDL and VLDL in the blood, occurs in 40% of patients.

Clinical manifestations: xanthomas of the Achilles tendon and quadriceps tendon, lipoid arc on the cornea, xanthomatosis of the eyelids, skin of the elbows and knees, coronary artery disease, arterial hypertension, hepatic steatosis, xanthomatosis and atherosclerosis of the semilunar valves.

Type III - increased LDL in the blood, occurs very rarely - less than 1%.

Clinical manifestations: palmar and plantar xanthomas, lipoid arc on the cornea, hepatic steatosis, weight gain, coronary artery disease, hypertension, pancreatitis, severe atherosclerosis of peripheral vessels.

Type IV - increased VLDL in the blood, occurs in 45% of cases.

Clinical manifestations: enlarged liver and spleen, hypertension, obesity (android type), hepatic steatosis.

Type V - increased VLDL and chylomicrons in the blood, occurs in 5% of cases, practically not atherogenic.

Clinical manifestations: attacks of intestinal colic, enlarged liver and spleen, weight gain, rarely - coronary artery disease.

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 a crucial 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-sized arteries.

HYPOLYPIDEMIC AGENTS:

- Statins: simvastatin (Zocor), rosuvastatin (Crestor), atorvastatin (Atoris);
- Nicotinic acid: (vitamin PP, niacin, enduracin);
- Fibrates: clofibrate (Miscleron), gemfibrozil (Normolip), fenofibrate (Lipantil);

• Bile acid sequestrants: cholestyramine (Questran), colestipol (Cholestid), guarem;
• Cholesterol absorption blockers: ezetimibe (Ezetrol);
• Antioxidants: probucol;
• HDL-raising drugs: Essentiale, Lipostabil.
• Polyunsaturated fatty acid drugs: ω-3 fatty acids (Omacor).

Hypolipidemic drugs must be used for a long time, so the effectiveness and safety of the drugs is of great importance. Currently, of all hypolipidemic drugs, statins meet these requirements to a greater extent. They are the most active hypocholesterolemic drugs.

Statins

 Natural: Lovastatin (Mevacor), Pravastatin (Lipostat), Simvastatin (Zocor).

 Synthetic:

I generation: Fluvastatin (Lescol, Lescol forte).

II generation: Atorvastatin (Liprimar).

III generation: Rosuvastatin (Crestor).

 Combined drugs: Vytorin (Simvastatin + Ezetimibe), Kaduet (Atorvastatin + Amlodipine), Advicor (Lovastatin + Niacin).

Pharmacodynamics. Statins are products of the life of the fungal microorganism Aspergillus terreus or their synthetic analogues. They are classified as a new class of antibiotics - monocalins. Their mechanism of action is associated with the blockade of the key enzyme of cholesterol synthesis - 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase). Statins, inhibiting the activity of the enzyme HMG-CoA reductase, reduce the formation of endogenous cholesterol. As a result of a decrease in the content of cholesterol in the liver, the activity of hepatocyte receptors that capture low-density lipoproteins (LDL) increases, which leads to a significant decrease in LDL-C and total cholesterol in the blood. At the same time, there is a moderate decrease in very low-density lipoproteins (LDL-C) and triglycerides (TG). Under the influence of statins, the lipid profile of blood plasma changes as follows: the level of total cholesterol decreases (↓ cholesterol and ↓ triglycerides). It should be noted that under the influence of statins, there is no synthesis in the body of potentially toxic sterols (isopentiniline, squalene). In addition, HMG-CoA, after inhibition of HMG-CoA reductase, is easily metabolized back into acetyl-CoA, which is involved in many biochemical reactions of the body.

It should be noted that a decrease in the level of total cholesterol by only 1% leads to a decrease in the risk of vascular catastrophes (CHD, strokes) by 2%. Another important effect of statins is also known - increasing the resistance of the endothelium to the influence of damaging factors, stabilizing atherosclerotic plaque, and inhibiting oxidative processes.

Pharmacokinetics. Statins are prescribed orally (before or after meals) in the evening, because the maximum synthesis of cholesterol in the liver occurs at night. All drugs are well absorbed and actively (70%) are taken up by the liver during the first pass. This is important, because all statins are inactive - they are prodrugs, and in the liver they are converted 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), the majority remains in the liver, where it mainly exerts its effect. The maximum concentration of drugs in the blood occurs approximately 1.5 hours later. The hypocholesterolemic effect develops 3 days - 2 weeks after the start of treatment. The maximum therapeutic effect occurs mainly after 4 weeks. Statins are prescribed once a day. Elimination is carried out mainly by the liver. In chronic kidney disease, dose adjustment is not required. Taking into account the biological rhythms of cholesterol synthesis in the body (its synthesis is carried out mainly at night), natural statins and synthetic drugs of the first generation are recommended to be taken once in the evening. For synthetic drugs of the II-III generations, this recommendation is not

mandatory.

Treatment with statins should be carried out continuously, because within a month after stopping the drug, the blood lipid level returns to the initial level. Usually, therapy with drugs of this group begins with small doses (for most drugs 5 - 10 mg / day) with a gradual increase to the dose that allows you to achieve the target level of LDL. Table 4 shows the doses of statins necessary to reduce LDL cholesterol by 20-55%. The magnitude of the relative (in percent) reduction of this level does not depend on the initial value of the indicator, but depends on the dose of the drug.

The dose of any statin should be increased at an interval of 1 month, since it is during this time that the greatest effect of the drug is usually achieved. Maximum doses of statins are prescribed for severe hyperlipoproteinemia, mainly for familial hypercholesterolemia.

The use of statins in the primary and secondary prevention of CHD reduces cardiovascular mortality, significantly reduces overall mortality, the number of strokes of any etiology, regardless of age, gender, previous medical history, and baseline cholesterol levels.

Synthetic statins today provide the most powerful hypolipidemic effect and have a high safety profile, which is 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, rosuvastatin is metabolized in the liver mainly by the cytochrome P450 isoform CYP2C9, which is associated with good drug tolerance and fewer drug interactions. Synthetic statins of I-II generations reduce LDL-C levels by an average of 30-35%, while drugs of the III generation (rosuvastatin) are able to reduce this indicator to 50-65% of the initial level, which is comparable to the effect of extracorporeal procedures. The maximum effect is noted already on the 7th-10th day. Triglyceride levels decrease by approximately 25-45%, and HDL increases by 5-10% (regardless of the drug and dose, with the exception of rosuvastatin). In addition, atorvastatin and rosuvastatin are able to cause regression of atherosclerosis, reducing the size of atherosclerotic plaques.

In addition to the main hypolipidemic action, statins have a number of additional (pleiotropic effects), due to which the morphological and functional state of the vascular wall improves in patients with atherosclerosis. The existence of pleiotropic effects is explained not only by the blockade of HMG-CoA reductase, as a result of which the formation of mevalonate metabolism products (isoprenoid family) is reduced, which are involved in the processes of proliferation, differentiation, migration, apoptosis of cells, and expression of endothelial NO synthetase. This allows statins to reduce the level of pro-inflammatory cytokines - tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, prevent oxidative modification of lipoproteins, and increase the level of endogenous antioxidants. There is data on the antagonism of statins to the 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 platelet membrane phospholipids). Statins are able to inhibit cell proliferation induced by platelet-derived growth factor in response to endothelial damage by various agents. The ability to inhibit migration and proliferation of smooth muscle cells is most pronounced in simvastatin and fluvastatin, and least in pravastatin. Favorable results of statin treatment may also be associated with stabilization of atherosclerotic plaques, reduction of their size (only atorvastatin and rosuvastatin) and ability to rupture, as well as elimination of endothelial dysfunction under the influence of drugs.

If the positive effects of statins, due to the hypocholesterolemic effect itself, develop relatively slowly (sometimes up to 3-5 years), then pleiotropic effects are realized quite quickly (from several days to several months). Statins increase life expectancy by six months for every year lost.

A new direction has become the creation of combined drugs. The use of two hypolipidemic agents in such formulations allows to achieve a pronounced potentiating effect not only in terms of reducing total cholesterol or LDL (Vytorin, Ezetimibe), but also to

significantly increase the level of HDL (Advicor).

All statins, in general, are well tolerated.

Undesirable effects. Hepatotoxicity. Rhabdomyolysis ("melting" of muscles), myositis, muscle weakness (constant monitoring of CPK! blood). Impotence. Dyspeptic syndrome. Thrombocytopenia, anemia. Skin rashes, photosensitization. Side effects include increased transaminase activity. When taking statins, it is necessary to monitor liver function tests and creatine phosphokinase activity. If the activity of creatine phosphokinase exceeds the norm by 2 times, the drug should be canceled.

Nicotinic acid (Vitamin B3, vitamin PP, Niacin, Enduracin).

Nicotinic acid (niacin) is a component of NAD and NADP, which are coenzymes of several hundred dehydrogenases involved in tissue respiration and metabolic processes, inhibits cAMP (triglyceride lipase activator), inhibits lipolysis (by blocking tissue lipases) and the mobilization of free fatty acids, from which VLDL is synthesized. As a result, the formation of VLDL in the liver decreases, from which dangerous atherogenic lipoproteins - LDL (↓ VFA, ↓ TG, ↓ LDL) are synthesized and the content of VLDL cholesterol and TG in the blood decreases. There is a decrease in the level of LDL cholesterol and total cholesterol. At the same time, the destruction of HDL slows down.

Pharmacodynamics. The drug 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 are reduced 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 levels by 25%, but it takes 3-6 weeks to achieve the maximum effect. In combination with bile acid secretion, it can reduce LDL levels by 40-60%. HDL levels increase by an average of 15-35%, but with an initially normal rate, the increase may be greater. 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 doses over a month. Large doses of the drug, in which it exhibits a hypolipidemic effect, and the associated unpleasant sensations (nausea, rashes, harmless skin vasodilation, a feeling of heat during the initial intake or dose increase) force many patients to abandon 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 uric acid levels, impaired liver function, exacerbation of gastric and duodenal ulcers. To a large extent, the disadvantages inherent in nicotinic acid are reduced in enduratsii, which is nicotinic acid applied to a wax matrix. This dosage form allows you to maintain fairly high concentrations of the active substance in the blood for a long time, so the dose usually does not exceed 1.5 g/day. The drug is prescribed in the first week at 500 mg 1 time per 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 LDL cholesterol, but more effectively reduces TG levels and increases HDL cholesterol. Therefore, it is more effective in ↑ TG (types IIb, III, IV) and less effective in IIa.

Pharmacological effects:

- Regulates tissue respiration; synthesis of proteins, fats; breakdown of glycogen;
- 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 ↑ incorporation of cholesterol into HDL;
- Stimulates the formation of reticulocytes and normochromic erythrocytes.

Pharmacokinetics. Nicotinic acid and its amide (nicotinamide) are administered parenterally and orally. They are well absorbed in the lower part of the stomach and in the upper parts of the duodenum. Therefore, in inflammatory diseases of the absorption zone, the process of its transportation may be disrupted. Biotransformation is carried out in the liver with the formation of its metabolites. Elimination of nicotinic acid is mainly with urine in

unchanged form. It should be noted that nicotinic acid can be synthesized by the liver and erythrocytes from tryptophan with the obligatory participation of vitamins 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, redness of the skin, urticaria, itching of the skin, increased secretion of gastric juice, severe burning during urination. At the same time, nicotinamide does not cause these effects. With prolonged use and overdose of nicotinic acid, there may be: diarrhea, anorexia, vomiting, hyperglycemia, hyperuricemia, ulceration of the gastrointestinal mucosa, impaired liver function, atrial fibrillation.

Indications. Hypovitaminosis B3. Pellagra (impaired CNS function, impaired motor function of the gastrointestinal tract - diarrhea or constipation, dry skin and mucous membranes - dermatitis, glossitis, stomatitis). Atherosclerosis (prescribed in very large doses - 3-9 g/day, the body's normal need for vitamin 30 mg/day). Obliterating endarteritis, Raynaud's disease, migraine, spasms of the biliary and urinary tracts (nicotinamide is not prescribed). Thrombosis. Prevention of type 1 diabetes (nicotinamide is used).

Ion exchange resins or bile acid sequestrants and agents that inhibit the absorption of cholesterol in the intestine:

I generation:

• Cholestyramine (Vazosan).

• Colestipol (Cholestipol).

• Huar resin (Guarem).

II generation:

• Colesevelam (Velchol).

• Colestimed (Cholebin).

Bile acid sequestrants (sorbents) are ion exchange resins that are insoluble in water and are not absorbed in the intestine.

Pharmacodynamics. These drugs are not absorbed from the gastrointestinal tract. They have the ability to bind bile acids in the intestinal lumen, which reduces the reabsorption of the latter and enhances their excretion from the body. To compensate for the loss of bile acids in the liver, their synthesis from cholesterol is activated. The result 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, a slight increase in the level of HDL cholesterol is observed. The triglyceride content either does not change or increases slightly with subsequent normalization.

The plasma lipid profile changes as follows: total cholesterol decreases, there is a slight decrease in TG. They are most effective in type IIa hyperlipidemia. The decrease in total cholesterol for these drugs (with long-term use) is on average 13%. LDL content decreases by 12-19% in average therapeutic doses and can reach 25% in maximum doses after 1-2 weeks. However, high doses of drugs are poorly tolerated by patients. In combination with statins or nicotinic acid, the decrease in LDL can reach 40-60%. HDL level increases by 3-8%.

Undesirable effects. Bile acid sequestrants are not absorbed in the intestine, therefore they do not cause systemic side effects. Dyspeptic syndrome (constipation, formation of fecal stones, nausea, flatulence); steatorrhea, which disrupts the absorption of fat-soluble vitamins, especially vitamin K. The second generation drugs are characterized by somewhat higher efficacy and better tolerability. The tolerability of bile acid sequestrants can be improved by gradually increasing the dose of the drugs. With prolonged regular use, the effect of the drugs decreases.

The indication for the appointment of anion exchange resins is severe hypercholesterolemia, refractory to the recommended dietary measures. Studies have proven that long-term use of these drugs as monotherapy, in combination with diet or other hypolipidemic agents slows down the progression of atherosclerosis and significantly reduces mortality from coronary heart disease. These drugs have a peculiar taste, consistency, so they

are recommended to be washed down with juices, syrups, milk. They are used for primary hypercholesterolemia 2-3 times a day, the therapeutic effect occurs after about 1 month.

Fibrates

Their division into generations is based on pharmacokinetic features, effectiveness of use and the frequency of complications.

I generation: • Clofibrate (miscleron).

II generation: • Gemfibrozil (Gevilon). • Bezafibrate (bezamidine).

III generation: • Fenofibrate (lipantil). • Ciprofibrate (Lipanor).

Fibric acid derivatives include hypolipidemic agents that mainly lower triglyceride levels in the blood. The ancestor of this group is clofibrate (miscleron), which was later replaced by other fibrates.

Pharmacodynamics. The mechanism of action of drugs in this group is associated with the activation of peroxisomal proliferators, which are activated in nuclear receptors (PPARa), 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, by activating PPARa receptors, located mainly in the liver and adipose tissue, contribute to an increase in the production of apoprotein apo-A-1 (the main protein of HDL) and lipoprotein lipase, which breaks down VLDL, which leads to a decrease in the content of VLDL in the blood and, accordingly, triglycerides. In addition, PPARa receptors probably regulate the expression of genes that affect monocyte renewal, adhesion and the formation of foam cells. In addition, fibrates, like statins, block the activity of HMG-CoA reductase, reducing cholesterol synthesis and somewhat reducing the content of LDL-C in the blood. However, this effect is much less pronounced than that of statins. Drugs in this group are able to reduce TG levels by 50% while increasing HDL by an average of 15% (up to 18-20%). At the same time, the level of LDL does not change or even increases (especially against the background of severe triglycerinemia during treatment with clofibrate or gemfibrozil) or decreases (during therapy with fenofibrate, bezafibrate or ciprofibrate). The main effect of fibrates is to ↓ TG and VLDL plasma, as well as to reduce the formation of LDL from them.

Pharmacokinetics. Fibrates are well absorbed from the intestine and appear in the blood in a deesterified form. Fibrates are prodrugs, converted to the active substance in the intestine, liver, kidneys. The maximum concentration in the blood, depending on the drug, occurs from 1.5 to 4 hours. All drugs are very well bound to albumin (more than 90%) and can displace other drugs from their binding. Biotransformation of fibrates occurs in the liver with the formation of glucuronic acid conjugates and are excreted mainly in the urine. Therefore, in chronic renal failure, their content in the body increases. Drugs of the 1st and 2nd generations are prescribed 3 times a day, and 3rd generations - 2 times a day.

Adverse effects. Occur frequently. When using 1st generation - 31%, 2nd generation - 20%, 3rd generation - 10% of cases.

- Hepatotoxicity (↑ transaminases, alkaline phosphatase).
- Violation of colloidal stability of bile (there is a risk of formation of stones in the gallbladder).
- Myositis, myasthenia, myopathy, rhabdomyolysis.
- Dyspeptic syndrome (eructation, nausea, vomiting, constipation, diarrhea, flatulence).
- Cardiac arrhythmias.
- Leukopenia, thrombocytopenia, anemia.
- Carcinogenesis !!! (rectal tumors)
- Rarely - alopecia, impotence, headache, dizziness, pancreatitis, rash, dermatitis, visual impairment, laryngeal edema.

Indications.

- Effective as an additional means of primary prevention of hyperlipidemia.
- Hyperlipidemia IV, V types; III type in combination with obesity and type II diabetes.

- Reducing the risk of developing coronary heart disease in patients with hyperlipidemia IIb type (↓ HDL).

Cholesterol absorption blockers - Ezetimibe (Ezetrol). Combined: Vytorin (Simvastatin + Ezetimibe).

A new group of hypolipidemic drugs are cholesterol absorption blockers, the main representative of which is ezetimibe. This drug, after entering the small intestine, is localized at the border of the marginal brush border of the villi and slows down the absorption of cholesterol (including cholesterol from vegetable fats), which leads to a decrease in its flow from the intestine to the liver and a compensatory increase in the activity of HMG-CoA reductase, a decrease in the level of LDL-C, TG and an increase in the concentration of HDL-C in the blood plasma. After 2 weeks of use of ezetimibe, the absorption of cholesterol in the intestine is reduced by 54% compared to placebo.

Drugs of this group can be used both as monotherapy and in combination with statins or enhance the secretion of bile acids. The dose of the drug in this case is 10 mg 1 time per day. When administered simultaneously with statins, ezetimibe exhibits an additive effect (at a dose of 10 mg/day in combination with any of the statins, it provides an additional reduction in LDL-C by 17-22%). It is assumed that for successful reduction of LDL-C and from a safety point of view, it is more expedient to add ezetimibe to low and medium doses of statins than to use statins alone in dangerous high doses.

Cholesterol absorption blockers are usually well tolerated. Side effects include headache and dyspeptic disorders, and when combined with statins, fatigue and myalgia may be added.

Antioxidants - Probucol (Fenbutol).

Pharmacodynamics. Free radical oxidation of lipids plays a certain role in the development of atherosclerosis. With its antioxidant effect, probucol protects lipoproteins from peroxidative modification, reduces their antigenicity and inhibits the formation of "foam" cells in the intima of blood vessels. This effect is very important, because the formation of "foam" cells is accompanied by the formation of oxygen free radicals. In addition, it is known that macrophages in atheroma produce free radicals that lead to the destabilization of atherosclerotic plaque. The drug has high lipophilicity, is included in the composition of LDL, modifies them and thus increases the non-receptor transport of LDL into liver cells. Probucol increases the synthesis of a protein that carries cholesterol esters from the cell. In the blood, the drug causes a decrease in LDL cholesterol, but at the same time reduces the level of HDL cholesterol. Probucol has practically no effect on the level of TG.

Pharmacokinetics. The drug is used orally during meals at 500 mg 2 times a day, preferably with products containing oil. It is poorly absorbed (approximately 20%) from the gastrointestinal tract. The maximum concentration in the blood occurs after a few hours. However, it should be emphasized that there is no relationship between the concentration of probucol and its antisclerotic effect. It penetrates very well into various tissues, where it accumulates and continues to be secreted into the blood after its withdrawal for another 6 months. Biotransformation in the liver occurs to a small extent, is excreted in the urine in unchanged and modified form. The hypocholesterolemic effect appears no earlier than 2 months from the start of treatment.

Adverse effects: prolongation of the QT interval on the ECG (which creates a risk of severe ventricular arrhythmias). Myopathies. Hyperuricemia. Hyperglycemia. Thrombocytopenia. Dyspeptic syndrome - diarrhea, flatulence, nausea, abdominal pain.

Indications. It is used as an additional means of primary prevention of hyperlipidemias that have arisen in patients with a homozygous form of hereditary hyperlipidemia, when LDL receptors are practically absent. Currently, the use of this drug is limited due to low efficacy and serious side effects.

Drugs that increase HDL levels, essential phospholipid preparations: lipostabil. essentiale.

A promising direction in hypolipidemic therapy is the creation of drugs that allow

increasing HDL levels in the blood, since even a slight increase in the concentration of this lipoprotein fraction can reduce the risk of coronary heart disease. Statins, effectively reducing LDL cholesterol levels, have a weak effect on HDL concentration, increasing it by only 5-10%. For fibrates and nicotinic acid derivatives, this figure does not exceed 25%.

Lipostabil, as a representative of phospholipid preparations, consists of essential phospholipids, represented mainly by polyunsaturated phosphatidylcholine and polyunsaturated fatty acids (linoleic, linolenic, oleic, arachidonic). The possibility of using drugs of this group is based on their ability to solubilize excess cholesterol in biological membranes (1 molecule of phospholipid dissolves up to 3 molecules of cholesterol). The main acceptor of exogenous phospholipids is HDL, which is the main antiatherogenic fraction in the body. In terms of hypolipidemic effect, the drug is inferior to the main classes of hypolipidemic drugs. Lipostabil is prescribed rarely, 2 capsules 3 times a day; the course of treatment is up to 6 months or more.

Pharmacodynamics. The composition of the drugs includes phosphatidylcholine, which activates the enzyme lecithin-cholesterol-acetyltransferase. This enzyme converts free cholesterol into cholesterol esters, which are not dangerous for the development of atherosclerosis. In addition, phosphatidylcholine is included in the composition of HDL, which helps to accelerate the transport of cholesterol from the membranes of the endothelium and platelets, preventing the aggregation and adhesion of the latter. These drugs do not lower LDL cholesterol and do not affect blood 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, and adenosine-5-monophosphate.

Indications. Used in combination with other hypolipidemic agents. They are used to improve peripheral circulation and liver function, especially in patients with diabetes.

Polyunsaturated fatty acid preparations: ω-3-fatty acids (Omakor).

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 (reduce VLDL levels), on hemostasis and blood pressure. The hypolipidemic effect is realized by delaying the synthesis of triglycerides in the liver by ω-3-PUFA, since EPA and DHA inhibit the esterification of other fatty acids. They reduce the level of TG and contribute to a decrease in the number of free fatty acids involved in their synthesis (due to an increase in peroxisomal β-oxidation of fatty acids). As a result, the level of VLDL decreases. In some patients with hypertriglyceridemia, the level of LDL increases at the same time. The content of HDL increases intermittently and very slightly (in terms of the effect on this indicator, ω-3-PUFA are significantly inferior to drugs of other classes). During treatment with the drug, the synthesis of thromboxane A2 decreases and blood clotting time increases slightly.

The appointment of ω-3-PUFA preparations (1 g/day) to patients with coronary heart disease allows to significantly reduce the combined indicator, which includes mortality from all causes, development of myocardial infarction, and attacks of angina without fatal outcome. When using ω-3-PUFA (Omakor) after primary myocardial infarction, total mortality is reduced by 20%, mortality from cardiovascular diseases by 30% and the risk of sudden death by 45%.

ω-3-PUFA preparations are currently considered as adjuvant therapy for secondary prevention after myocardial infarction, as well as in endogenous hypertriglyceridemia: type IV (monotherapy); types IIb/III (in combination with statins). The doses of the drug in this case are 2 g/day with a possible increase to 4 g/day in case of insufficient effectiveness.

2. Questions for self-control (list of questions):

1. List the pathogenetic mechanisms of thrombus formation and thromboembolism,

which are the object of influence of antithrombotic drugs.

2. List the main groups of antithrombotic drugs.

3. Explain the mechanisms of action of the main groups of antithrombotic drugs, based on their pharmacodynamics.

4. Formulate the significance of the leading pharmacokinetic characteristics (T1/2el, plasma protein binding, Vd) in the individual selection of antithrombotic drugs.

5. Highlight the clinical and laboratory-functional criteria of therapeutic efficacy and safety of antithrombotic drugs.

6. What principles are the basis for the classification of hypolipidemic drugs?

8. List the drugs and the main mechanisms that affect atherogenesis.

9. Provide a classification of hypolipidemic drugs.

10. Explain the mechanism of hypolipidemic action of statins. Formulate indications and contraindications for their appointment.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write prescriptions for the main antithrombotic and hypolipidemic drugs (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and the list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. To identify signs during subjective and objective examination of the patient that characterize hemocoagulation and atherogenesis disorders, to write a clinical diagnosis of the disease.

5. To determine the group of drugs needed by the patient; based on theoretical data on pharmacodynamics and own observations, to select drugs for the patient.

6. To choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. To identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. To justify the need for combined drug therapy and to suggest possible options for a safe combination of drugs.

9. To make a forecast of side effects of drugs prescribed to the patient and to outline a plan for their detection at the early stages.

10. To justify the duration of basic and supportive therapy.

B. Solving situational tasks.

1. A man named L., 39 years old, an office worker, was found to have an elevated serum total cholesterol level during a routine examination. He has no complaints. He has been smoking for 15 years. His family history is not burdened. Objectively: increased nutrition, PE - 76 beats per minute, ACT - 160/100 mm Hg. Art. Heart parameters are unchanged. Biochemical blood test: 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 myocardial changes.

What type of dyslipidemia is found in the patient? Your recommendations for non-drug management of the patient. Justify the differentiated choice of hypocholesterolemic drugs,

indicate their mechanism of action.

2. Patient E., 63 years old, has been observed for 12 years due to hypertension. 6 years ago he had a myocardial infarction. The maximum ACT figures are 180/115 mm Hg. He regularly takes Enap 10 mg/day. No complaints. Objectively: increased nutrition, PE - 74 beats per minute, ACT - 170/100 mm Hg. heart borders - shifted to the left by 2.5 cm from the left midclavicular line, accent 2 tones above the aorta, no peripheral edema. ECG: in III and aVF leads pathological Q wave, negative T wave (compared to 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, EF - 54%, akinesia of the posterior-basal parts of the left ventricle.

Formulate the diagnosis. Justify the differentiated choice of drugs for this patient.

Test tasks for self-control:

1. Acetylsalicylic acid is used in ischemic heart disease as an antiplatelet agent. Specify the daily dose of the drug:

A. 500 mg.

B. 3000 mg.

C. 100 mg.

D. 2000 mg.

E. 1000 mg.

2. A 49-year-old patient with ischemic heart disease and a history of duodenal ulcer requires the appointment of an antiplatelet agent. Which drug will you choose?

A. Aspirin-cardio.

B. Curantil.

C. Aspecard.

D. Plavix.

E. Warfarin.

3. The mechanism of antiplatelet action of aspirin is associated with:

A. Increased cyclooxygenase activity.

B. Inhibition of prostacyclin synthesis.

C. Normalization of adenosine synthesis.

D. Stimulation of prostaglandin synthesis E.

E. Inhibition of thromboxane A2 synthesis.

4. A 38-year-old patient, six months ago, during treatment in the clinic for duodenal ulcer, an increase in cholesterol level to 8.0 mmol/l was detected. After a hypocholesterolemic diet for 6 months and morning exercises, cholesterol decreased within 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. Objectively: height 175 cm, body weight - 78 kg, pulse - 80 beats per minute, blood pressure - 130/80 mm Hg. No changes were detected in the internal organs. What drug treatment is appropriate to prescribe to the patient for primary prevention of coronary heart disease?

A. Rosuvastatin.

B. Nicotinic acid.

C. Lipostabil.

D. Gemfibrozil.

E. Cholestyramine.

5. According to chronopharmacology data, it is possible to increase the hypocholesterolemic effect of statins by prescribing them at the following time of day:

A. Night.

B. Dawn.

C. Evening.

D. Morning.
E. Lunch.

6. A patient with signs of vascular atherosclerosis was prescribed one of the hypolipidemic drugs that reduces cholesterol synthesis by blocking the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase. Specify this drug:
A. Nicotinic acid.
B. Cholestyramine.
C. Clofibrate.
D. Probucol.
E. Atorvastatin.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Emergency conditions in ischemic heart disease, principles of treatment"

Purpose:
To learn the principles and algorithms of emergency care in ischemic heart disease.

Basic concepts (list of questions):
1. Acute coronary syndrome.
2. Unstable angina: classification, pathogenesis.
3. Acute myocardial infarction: classification, pathogenesis.
4. Acute thrombosis: pathogenesis.
5. Thromboembolism: pathogenesis.

Plan

1. Theoretical questions:

TREATMENT OF ACUTE CORONARY SYNDROME (UNSTABLE ANGINA AND MYOCARDIAL INFARCTION)

The main cause of the development of ACS is rupture of atherosclerotic plaque or erosion of the endothelium with subsequent thrombosis of the coronary artery and the occurrence of acute ischemia. As numerous studies have shown, the earlier the necessary treatment is started, the more hope 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 before the final diagnosis is clarified, and patients should be managed as patients with myocardial infarction or unstable angina. Acute myocardial ischemia may be a sign of developed MI, but does not always mean necrosis of cardiomyocytes (unstable angina). When determining treatment tactics, it is important to differentiate ACS with persistent ST segment elevation on the ECG and ACS without persistent ST segment elevation.

Patients with ACS with persistent ST elevation are patients with pain or discomfort in the chest and persistent ST segment elevation or "new" (presumably the first time) complete blockade of the left bundle branch block on the ECG. Persistent ST segment elevation suggests the presence of acute complete occlusion of the coronary artery by a thrombus. The main task of treatment in this situation is the rapid and stable restoration of the vessel lumen - reperfusion of the ischemic myocardium. For this, both pharmacological methods are used - the administration of thrombolytics, and surgical - percutaneous coronary intervention (PCI).

Patients with ACS without persistent ST elevation are patients with pain or discomfort in the chest and changes on the ECG indicating acute myocardial ischemia, but without ST segment elevations. These patients may have persistent or transient ST depression, inversion, smoothing or pseudonormalization of the T wave, although in some patients the ECG on admission may be normal. Thrombolytic agents are not used in the treatment of such patients. The main tasks of treatment are to maintain coronary artery patency by limiting and preventing intracoronary thrombosis and distal thromboembolism, and eliminating ischemia (conservatively or surgically).

The goal of treatment of ACS is to eliminate ischemia and its complications, prevent the

development of myocardial necrosis (or its further spread), and ultimately improve the prognosis. The main directions of drug therapy, based on the common pathogenesis of ACS:

• lysis of a thrombus occluding a coronary artery (for ACS with ST elevation);

• prevention of further thrombosis, microembolization and creation of conditions for spontaneous lysis of a thrombus that does not close the lumen of the vessel;

• elimination of ischemia and prevention of its occurrence;

• analgesia;

• prevention and treatment of complications (treatment of HF, shock, prevention and treatment of arrhythmias, etc.);

• initiation of secondary prevention measures.

The main groups of pharmacological agents used in the treatment of ACS:

• Antithrombotic agents (antiplatelet agents, anticoagulants, thrombolytics).

• Antiischemic agents (nitrates, β-blockers, calcium channel blockers).

• Drugs of other groups (analgesics, ACE inhibitors, statins, etc.).

Antithrombotic agents

1. Antiplatelet agents (see above).

2. Anticoagulants:

2.1. Direct acting:

2.1.1. Unfractionated: • heparin.

2.1.2. Low molecular weight: • dalteparin (fragmin); • nadroparin (fraxiparin); • enoxaparin (Clexane).

2.1.3. Heparinoids (parenteral factor Xa inhibitors): • fondaparinux (Arixtra).

2.1.4. Oral factor Xa inhibitors: • rivaroxaban (Xarelto).

2.2. Indirect action:

2.2.1. Coumarin derivatives:

2.2.1.1. Monocoumarins: • warfarin (Coumadin); • acenocoumarol (Sincoumar).

2.2.1.2. Dicoumarins: • ethyl biscum acetate (neodicoumarin).

2.2.2. Indandione derivatives: • phenindione (Phenyline).

2.2.3. Indirect thrombolytics:

I generation: • urokinase (Urokidan); • streptokinase (Streptoliase).

II generation:

• Acetylated plasminogen-streptokinase activator complex: • alteplase (actilize).

III generation (mutant): • tenecteplase (metalize); • reteplase (rapilisin).

In patients with non-ST elevation MI, treatment begins with the appointment of antiplatelet and anticoagulant drugs, while in patients with persistent ST segment elevation, therapy includes the use of thrombolytics. In patients with non-ST elevation MI, the use of thrombolytics is dangerous.

Principles of the use of antiplatelet drugs in ACS:

- antiplatelet drugs are an obligatory component of ACS therapy, they should be prescribed as early as possible, with treatment starting with loading doses;

- acetylsalicylic acid is prescribed to all patients with ACS in the absence of contraindications; in case of intolerance, the drug is replaced with clopidogrel;

- antiplatelet drugs are usually combined with the administration of heparin or its low molecular weight fractions;

- the activity of antiplatelet therapy is determined by the severity of the course of GCS and the patient's prognosis, it is advisable to combine antiplatelet agents with different mechanisms of action before planned CHB and in patients with a high risk of adverse prognosis.

The drug of choice among antiplatelet agents for GCS is acetylsalicylic acid in the first dose of 250 mg (it is advisable to chew a tablet of regular, not enteric-coated aspirin) and then 75-160 mg 1 time per day daily. The drug must be taken indefinitely (lifelong). For patients

who are planning to undergo thrombolytic therapy, it is safer to limit the first dose of aspirin to 160 mg.

In case of intolerance to acetylsalicylic acid, antiplatelet agents from the thienopyridine group are prescribed (clopidogrel in a loading dose of 300 mg once with 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 GCS (aspirin 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, fondaparinux or bivalirudin should be added to antiplatelet drugs (aspirin and/or thienopyridines). Long-term use of drugs from this group in addition to aspirin is undesirable, as it is accompanied by an increase in mortality.

Principles of prescribing direct anticoagulants for ACS:

 Direct-acting anticoagulants, primarily heparins, are an essential element of ACS treatment; heparin therapy is started immediately upon patient admission.

 Unfractionated heparin is used intravenously in the treatment of coronary thrombosis to maintain its stable concentration in the blood.

 Low-molecular-weight heparins, fondaparinux or bivalirudin can be used instead of unfractionated heparin for ACS without ST elevation.

 It is advisable to discontinue heparin gradually to prevent possible reactive hypercoagulation.

 It is not recommended to change the anticoagulant during ACS treatment.

 NFG is administered intravenously as a bolus of 60-70 U/kg (but not more than 5000 U) followed by a continuous intravenous infusion at an initial rate of 12-15 U/kg per hour (but not more than 1000 U/h). The duration of NFG administration 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 the acute period of MI: due to the slow onset of effect with ACS, they are prescribed only for the prevention of thrombosis and embolism in special cases (concurrent atrial fibrillation, implanted artificial heart valves, signs of intracardiac thrombosis, deep vein thrombosis, thromboembolism in history) after stabilization of the patient's condition. The mechanism of action of the drugs is associated with the blockade of the enzyme epoxide reductase in the liver, which leads to a decrease in the synthesis of II, VII, IX and X blood clotting factors, as a result of which the process of hydroxylation of γ-carboxyglutamic acid and, accordingly, the synthesis of vitamin K-dependent blood clotting factors is disrupted. The rate of decrease in the blood plasma levels of these factors is determined by their half-life, which is for factor II - 80-120 hours, for factor VII - 4-6 hours, for factor IX - 24 hours, for factor X - 48-72 hours. Thus, clinically significant changes in blood clotting after taking the first dose of an indirect anticoagulant are determined no earlier than after 8-12 hours, the maximum effect is manifested after 72-96 hours, and the duration of action of a single dose can be from 2 to 5 days.

Indirect anticoagulants can be used in combination with acetylsalicylic acid after several days of parenteral administration of direct anticoagulants in the early stages of the disease. When combining warfarin with aspirin, the dose of the latter should be 75 mg/day, while the dose of warfarin should be selected individually so that the MHO is equal to - 2. At the same time, it should be borne in mind that the combination of aspirin and warfarin increases the risk of major bleeding by 2 times, but prevents major cardiovascular complications more effectively than acetylsalicylic acid alone. An important role in the treatment of indirect anticoagulants is played by the interaction of drugs of this group with other pharmacological agents, which is 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 indirect anticoagulants: • amiodarone; • ciprofloxacin; •

co-trimoxazole; • fluconazole; • cimetidine; • clofibrate; • erythromycin, azithromycin, roxithromycin, clarithromycin; • metronidazole.

Drugs that reduce the effect of indirect anticoagulants: • barbiturates; • cholestyramine; • carbamazepine; • griseofulvin; • rifampicin; • vitamin K.

Indirect anticoagulants are contraindicated in bleeding, severe liver and kidney dysfunction, and uncontrolled arterial hypertension.

Thrombolytic therapy is now included in the list of standard treatment measures in patients with ST-segment elevation MI. Persistent ST-segment elevation suggests the presence of acute complete occlusion of a coronary artery by a thrombus. According to generalized clinical studies, more than 100,000 patients have shown that effective thrombolytic therapy reduces the risk of death by 10-50%.

Modern thrombolytics can be conditionally divided into three main groups.

I generation drugs, which activate plasminogen associated with fibrin and circulating in the blood to approximately the same extent.

II generation drugs, which have relative specificity for fibrin-associated plasminogen. These drugs are considered more effective than streptokinase, but their general disadvantage is the need for a fairly long intravenous infusion.

III generation drugs (mutant thrombolytics) have higher fibrinolytic activity, due to their modification using genetic engineering methods. For example, tenecteplase, compared with alteplase, has a longer duration of action, 14 times higher specificity for fibrin and 70 times higher resistance to tissue plasminogen activator inhibitor (ITAP-1). In addition, third-generation thrombolytics are much easier to use, since they can be administered as a bolus. In most controlled clinical studies, a linear relationship between the time from the start of MI treatment and mortality has been shown. This explains the need for the earliest possible start of thrombolytic therapy. It is believed that thrombolysis within the first hour from the onset of MI symptoms will not only reduce mortality, but in 40% of patients will interrupt the process of MI development, and will also prevent the development of irreversible myocardial damage, its dysfunction and sudden death, more than half of which cases occur in the first hours of MI. In the absence of contraindications, thrombolytic therapy should be started in the first hour from the onset of MI symptoms ("golden hour"). However, even in patients who received thrombolytics (in particular, streptokinase) late (12-24 hours after the onset of MI symptoms), a 19% reduction in mortality was also noted over a 5-week follow-up period. The mechanisms of mortality reduction with "late" thrombolysis are unclear. It should be noted that intracoronary administration of thrombolytics (in particular, drugs of the I and II generations) in the acute period of MI is significantly more effective than its intravenous administration.

General principles of thrombolytics in ACS

Thrombolytics should be used as early as possible after the first symptoms of thrombosis appear. The best results of thrombolysis are observed within the first 1-4 hours from the onset of clinical symptoms, so thrombolysis is started 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 admission of the patient to the start of the administration of thrombolytics 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, surgical intervention is sometimes preferable, if it is possible in a short time.

Thrombolytics are administered intravenously, without mixing with other drugs. Given the short half-life, a relatively long or repeated intravenous infusion of the drug is necessary to achieve the effect. The exception is drugs with a longer half-life (anistreplase, reteplase, tenecteplase), which can be administered as a single bolus, which is convenient in 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), simultaneous administration of antiplatelet agents (aspirin + clopidogrel) and antithrombin (heparin, LMWH (enoxaparin, fondaparinux) for several days is necessary. The positive effect of thrombolysis on the prognosis in ACS is significantly stronger in heavier patients, it increases in proportion to the risk of death. In 10-40% of patients with arterial thrombosis, thrombolytics may be ineffective. Among the possible reasons: non-thrombotic occlusion of the artery (hemorrhage into the plaque, dissection, occlusion by a piece of tissue after CHB, severe coronary spasm in cocaine poisoning), poor access of thrombolytics (perfusion disorders due to cardiogenic shock or poor collateral blood flow), some features thrombosis. The patient should be monitored continuously for at least 3, and preferably 24 hours after the start of thrombolysis to assess its effectiveness and timely recognition of complications.

The main complication of thrombolytic therapy is bleeding, including intracranial hemorrhage. Streptokinase is also characterized by allergic reactions and rarely - anaphylactic shock.

Indications for thrombolysis (in the absence of contraindications):

• ACS with ST segment elevation within the first 12 hours from the onset of clinical symptoms, provided that ST elevation is more than 1 mm in at least 2 adjacent chest leads or in at least 2 leads from the extremities;

• ACS within the first 12 hours from the onset of clinical symptoms with the appearance of a "new" or presumably "new" complete blockade of the left bundle branch block.

Thrombolysis is also advisable if there is:

• posterobasal (true posterior) infarction myocardial infarction within the first 12 hours from the onset of clinical symptoms, which is characterized by tall R waves in V1-2, ST segment depression in V1-3 and/or isolated ST elevation in posterior leads (V) and often tall, pointed T waves in V1-3;

• myocardial infarction with ST segment elevation (within 12-24 hours after the onset of symptoms) with persistent symptoms of ischemia and ST elevation of more than 1 mm in at least two adjacent thoracic or at least two limb leads. Despite the large number of thrombolytics studied in angiographic and clinical studies, in practice, preference is given to streptokinase, alteplase, and the more convenient tenecteplase and reteplase.

Absolute contraindications to the use of thrombolytics:

• Previous intracranial hemorrhage of any nature.
• Known structural abnormalities intracranial vessels.
• Known intracranial malignant tumor (primary or metastatic).
• Ischemic stroke within 3 months (excluding acute ischemic stroke up to 3 hours ago).
• Suspected aortic dissection.
• Active bleeding or hemorrhagic diathesis (except menstruation).
• Significant closed head injury or facial trauma within the previous 3 months.

Complications of thrombolytic therapy are uncommon, but sometimes very dangerous. They may be associated either with the main mechanism of action (bleeding, hypotension, chills, reperfusion arrhythmias), or with specific properties and features of the drug.

Some principles of using nitroglycerin and other nitrates in ACS

• Nitrates should be prescribed to all patients with ACS with persistent ischemia, heart failure or hypertension in the absence of contraindications.

• The appointment 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 administering nitrates are used: sublingually and inhaled, used in the prehospital and early hospital stages; intravenously - for persistent ischemia, left ventricular failure or uncontrolled hypertension; orally and transdermally - for the prevention of ischemia after relative stabilization of coronary blood

flow.

• Intravenous administration of nitrates should be started as soon as possible after the patient is admitted with ACS, the duration of continuous infusion is 24-48 hours, and then the risk of tolerance increases significantly.

• Control of the effect of intravenous administration of nitrates is carried out by assessing hemodynamic effects: the degree of decrease in blood pressure and increase in heart rate.

• To prevent absorption of nitroglycerin on the walls of the infusion system during its intravenous administration, it is advisable to use only glass bottles and connecting tubes made of polyethylene or polypropylene (but not polyvinyl chloride or polyurethane). Otherwise, nitroglycerin losses must be compensated by increasing the dose.

• Nitrates should be discontinued gradually due to the risk of withdrawal syndrome; after discontinuation of intravenous administration, it is advisable to transfer the patient to oral forms of nitrates, adhering to the regimen necessary for the prevention of tolerance (nitrate-free interval of 10-12 hours).

For intravenous administration, nitroglycerin is diluted in physiological sodium chloride solution or in 5% glucose solution to a concentration of 100 μg/ml (20 ml of 0.1% nitroglycerin solution per 200 ml of total solution). The effective dose (5-200 μg per min, usually 40-100 μg per min) depends on the individual sensitivity of the patient. The initial rate of intravenous infusion is 10-20 μg per min (2-4 drops per min), if necessary, the dose is increased by 10-20 μg per min every 3-5 min until a clinical effect is achieved or side effects appear. A decrease in blood pressure by 10-20% from the initial level is considered an indicator of the hemodynamic effect of nitrates. Nitroglycerin is administered intravenously for 24-48 hours, and after 24 hours of continuous administration of nitroglycerin, it may be necessary to increase the infusion rate due to the development of tolerance. After the end of intravenous administration, long-acting nitrates are taken.

Intravenous administration of nitroglycerin is especially indicated in cases of myocardial infarction complicated by acute heart failure. The use of nitroglycerin reduces the mortality rate 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 per minute) depends on the individual sensitivity of the patient. The initial rate of intravenous infusion is 15-20 mcg per minute (3-4 drops per minute), if necessary, the dose is increased by 10-15 mcg per minute (2-3 drops) every 5-15 minutes to a level of 200 mcg per minute (40 drops per minute). The criteria for the effective dose are the same as for nitroglycerin.

Beta-blockers

β-blockers help reduce pain, limit the size of the necrosis focus, and reduce the risk of developing severe arrhythmias. Early BAB therapy in patients with MI reduces overall mortality within 7 days by 14%, the frequency of reinfarction by 18%, and the frequency of cardiac arrest (ventricular fibrillation) by 15%. The greatest reduction in mortality is observed in the first 48 hours of the disease (on average by 25%), which indicates the importance of prescribing β-blockers in the first day of infarction. It has been established that limiting the area of necrosis in myocardial infarction is achieved only by β-blockers without VSMA, regardless of cardioselectivity, but there is no convincing evidence that any particular β-blocker is more effective than another.

Principles of β-blocker use in GCS - β-blockers should be prescribed as early as possible to all GCS patients in the absence of contraindications. If there are contraindications to the use of β-blockers in the acute period of GCS, they can be prescribed later, when the condition is stabilized (compensation of heart failure, elimination of hypotension and bradycardia, effective cardiac pacing). 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) than to completely abandon the use of β-blockers. Intravenous administration of β-blockers with subsequent transition to 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 non-ST-segment elevation ACS; the remaining patients are prescribed drugs orally. The target dose of β-blockers should provide a decrease in resting heart rate to 50-60 beats/min; with intravenous administration, continuous ECG monitoring, frequent blood pressure control, and lung auscultation are necessary. An important clinical criterion for the effectiveness of BAB treatment is a decrease in resting heart rate to 55-60 beats/min. Achieving these heart rate values is considered the goal of therapy, since the risk of reinfarction and death increases in parallel with an increase in heart rate, and an adequate decrease in pulse rate (regardless of thrombolytic therapy) contributes to an improvement in prognosis. β-blockers are not prescribed or their intravenous administration is stopped if the heart rate becomes lower than 50 beats/min, systolic pressure is lower than 100 mm Hg. Art., the PQ interval exceeds 0.22 s. It is undesirable to use these drugs against the background of acute heart failure, bradycardia and atrioventricular block (without an implanted pacemaker), bronchospasm.

Calcium channel blockers - reduce the slow transmembrane flow of calcium into the cell from the extracellular space, which reduces the contractility of the myocardium and vascular smooth muscle. Some CCBs also suppress the automatism of the sinus node and slow down AV conduction. All drugs of this class cause dilation of the coronary arteries. Thus, the anti-ischemic effect of calcium channel blockers includes:

- improvement of coronary blood flow due to the elimination of coronary spasm (dynamic stenosis of the coronary arteries);
- reducing myocardial oxygen demand by reducing afterload (peripheral vasodilation) and inhibiting myocardial contractility, as well as by reducing heart rate (some representatives).

Despite their high clinical efficacy, calcium channel blockers have not yet proven their ability to positively influence the prognosis in ACS, and some of them (short-acting nifedipine) may worsen treatment outcomes.

Principles 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. The main purpose of their appointment is to relieve symptoms. Drugs that slow down the rhythm (verapamil or diltiazem) are prescribed for persistent ischemia or to control the heart rate in atrial fibrillation-flutter, if BABs are ineffective or contraindicated (bronchial asthma, variant angina, vasospasm in cocaine intoxication). Dihydropyridine calcium channel blockers are used only in combination with BABs, as a reserve agent in case of ineffective treatment; nifedipine in a short-acting dosage form is contraindicated in ACS due to activation of the sympathetic system, tachycardia and possible hypotension.

Calcium channel blockers are contraindicated in patients with significant LV systolic dysfunction, chronic heart failure, and AV conduction disorders; their use is possible in patients with mild LV systolic dysfunction in a hospital setting.

During treatment with phenylalkylamine calcium channel blockers, one should not allow a decrease in heart rate to less than 50-60 beats/min, the occurrence of pauses and hypotension (BP <90/60 mm Hg). When prescribing dihydropyridine drugs, one should be wary of the development of hypotension and reflex tachycardia. Verapamil and diltiazem are contraindicated in heart rate less than 50 beats/min, BP less than 90/50 mm Hg, SA and AV block of the II-III degree. (without an implanted pacemaker), WPW syndrome, digitalis administration, severe heart failure (Killip class 2-4), bleeding, shock.

Analgesics

Opioid analgesics are used to treat pain syndrome in myocardial infarction. Morphine, which has a sufficient analgesic and sedative effect, slightly dilates the veins, reduces venous return to the heart, preload and, as a result, myocardial oxygen demand. However, morphine lowers blood pressure and, due to its vagotonic effect, causes bradycardia, atrioventricular block, especially in patients with inferior posterior myocardial infarction. In addition, the drug suppresses the respiratory center, causes nausea, vomiting, constipation. But the beneficial effect - pain relief - prevails over these side effects. Morphine is administered intravenously at a dose of 2-4 mg (0.2-0.4 ml of a 1% solution) for severe pain. In the future, repeated administration of 2-4 mg of the drug is possible until pain relief or the appearance of side effects. Complete analgesia when using the drug is usually achieved in 15-30% of cases, incomplete - in 40-60%. In addition to morphine, other opioid analgesics can be used (promedol, fentanyl, omnopon, pentazocine).

When using morphine, hypotension may occur (eliminated in a horizontal position or by administering 0.9% NaCl solution), bradycardia (reduced by intravenous administration of 0.5-1.0 mg of atropine), nausea and vomiting (relieved by intravenous administration of 5-10 mg of metoclopramide), respiratory depression (removed by intravenous administration of 0.1-0.2 mg of naloxone). Tramadol (tramal), which acts on opiate receptors, has greater safety and much lower narcotic potential compared to classical opioid analgesics. In MI, the average doses of tramadol that provide sufficient analgesia in 58.8% of cases are about 1.4 mg/kg.

In case of ineffectiveness of opioid analgesics and in the absence of hypotension in the patient, neuroleptanalgesia (NLA) can be used: intravenous administration of 1-2 ml of 0.005% solution of opioid analgesic fentanyl and 2-4 ml of 0.25% solution of neuroleptic droperidol. Ataractanalgesia (AA) is a method of combined use of opioid analgesics and benzodiazepine tranquilizers (for example, 2 ml of 0.005% solution of fentanyl and 2 ml of 0.5% solution of diazepam). In contrast to NLA, ataractanalgesia is characterized by less respiratory and hemodynamic disorders. Diazepam, which is part of AA, does not have a direct effect on the myocardium, but is able to briefly reduce the ventricular rate, which leads to some decrease in blood pressure and cardiac output.

If the effect of opioid analgesics, NLA or AA is insufficient, analgesia should be provided 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).

2. Questions for self-control (list of questions):

1. Etiology, pathogenesis, classification of acute coronary syndrome.
2. List the pathogenetic mechanisms of acute coronary syndrome, which is the object of the influence of hypotensive and hypertensive drugs.
3. List the main groups of antithrombotic drugs in acute coronary syndrome.
4. Explain the mechanisms of action of the main groups of drugs.
5. Highlight the clinical and laboratory-functional criteria for therapeutic efficacy and safety of thrombolytic and anticoagulant drugs.
6. Formulate urgent drug therapy for acute coronary syndrome.
7. Formulate urgent drug therapy for an attack of angina pectoris.
8. An attack of angina pectoris: risk factors, clinical picture.

3.Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for the main drugs prescribed in urgent cardiology (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for

prescription. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize the development of an attack of angina pectoris, acute coronary syndrome, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, select the drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 their detection at the early stages.

10. Substantiate the duration of basic and supportive therapy.

B. Solution of situational tasks.

1. A 62-year-old man was hospitalized in the intensive care unit with a prolonged attack of retrosternal pain that is not relieved by taking nitroglycerin. Objectively: BP - 80/60 mm Hg, HR - 106 per 1 min, BH - 22 per 1 min. During auscultation, the heart sounds are muffled, the rhythm is galloping. What explains the decrease in BP? Your recommendations for further examination and treatment of the patient.

2. A man N., 60 years old, complains of angina attacks while walking, climbing to the second floor. He has had coronary artery disease for many years. Objectively: vesicular breathing in the lungs, BH - 18 per min. Heart tones are muffled. HR - coincides with the pulse rate and is 90 per 1 min, BP - 140/70 mm Hg, the legs are pasty. On ECG: left ventricular hypertrophy.

Formulate a diagnosis. Make a treatment plan.

3. A 52-year-old man complains of angina attacks that occur when walking 500 meters, heart failure. He has been ill for about a year. Objectively: BH 16 in 1 min., heart borders shifted 1 cm to the left, tones are muffled, heart rate - 84 in 1 min, single extrasystoles, pulse - 78 per min, blood pressure - 150/70 mm Hg.

Formulate a diagnosis. Make a treatment plan. What drugs are indicated to improve the long-term prognosis?

4. A 47-year-old man has angina attacks in the early morning. During Holter monitoring at this time, an arcuate shift of the ST segment upwards in the chest leads is recorded, which persists for 15 min. Objectively: heart sounds are muffled, heart rate - 64 per minute, blood pressure - 140/80 mm Hg.

Test tasks for self-control:

1. During physical activity, the patient experienced a squeezing pain in the sternum, accompanied by stiffness and a feeling of fear. What can be recommended to relieve an angina attack?

A. Nifedipine.

B. Nitroglycerin.

C. Anaprilin.
D. Verapamil.
E. Diltiazem.

2. 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. Decrease in blood pressure.
B. Bradycardia.
C. Increase in blood pressure.
D. Atrioventricular block.
E. Extrasystole.

3. The mechanism of antiplatelet action of aspirin is associated with:

A. Increase in cyclooxygenase activity.
B. Inhibition of prostacyclin synthesis.
C. Normalization of adenosine synthesis.
D. Stimulation of prostaglandin synthesis E.
E. Inhibition of thromboxane A2 synthesis.

4. A patient with signs of vascular atherosclerosis was prescribed one of the hypolipidemic agents that reduces cholesterol synthesis by blocking the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase. Specify this agent:

A. Nicotinic acid.
B. Cholestyramine.
C. Clofibrate.
D. Probucol.
E. Atorvastatin.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky

http://www.nbuv.gov.ua/

4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

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

6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua

7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.or

TOPIC
"Clinical, biochemical, pathophysiological, pathomorphological definition of inflammation"

Purpose:

To learn the main factors of the inflammatory process, clinical and pathomorphological signs of inflammation, leading pathogenetic processes of inflammation, which are subsequently the points of destination of the corresponding pharmacotherapy.

Basic concepts (list of questions):

1. Inflammation: definition, phlogogenic factors of the development of the inflammatory process.
2. Stages of the inflammatory process.
3. Clinical signs of inflammation.
4. Prostaglandins, leukotrienes and other eicosanoids.
5. Pathogenesis of inflammation.
6. Phospholipase A2, cyclic oxygenases, lipoxygenases - biological and pathological role.
7. Main groups of anti-inflammatory drugs.

Plan

1. Theoretical questions:

Inflammation (Latin inflammatio) - the reaction of living tissues to local damage, which arose in the course of evolution. It consists of complex changes in the microcirculatory bed, blood system and connective tissue, aimed at isolating and eliminating the damaging agent and restoring (or replacing) damaged tissues.

Among the causes of inflammation, exogenous (external) factors (microorganisms, protozoa, chemicals, foreign bodies, pressure, ruptures, thermal effects, radiation energy, etc.) and endogenous (internal) factors that arise in the body itself as a result of another disease (stones in the gall bladder or bladder, blood clots, antigen-antibody complexes, foci of necrosis, hematoma, etc.). These manifestations of the inflammatory reaction of tissues to damage are realized at the level of cells, microcirculation and connective tissue. In the pathogenesis of inflammation, three stages are conventionally distinguished: alteration, exudation and proliferation.

Inflammation begins with cell damage - alteration. Primary and secondary alteration are distinguished. Primary alteration is the result of the damaging action of the inflammatory factor and depends mainly on its properties. Primary alteration is not yet a component of inflammation, since inflammation is a reaction to damage, that is, to primary alteration. Secondary alteration is the result of the effect on connective tissue, microvessels and blood of lysosomal enzymes released from cells and active oxygen metabolites. That is, secondary alteration is an integral part of the inflammatory process, since it is the body's reaction to damage. Cell alteration is accompanied by a violation of the structure and function of

intracellular formations. When mitochondria are damaged, respiration is limited or stopped, glycolysis is enhanced, the concentration of macroergic compounds, the activity of the plasma membrane ion pump are reduced, cells lose ions K, P, Mg, Ca, Zn. In the focus of inflammation, tissue hypoxia, metabolic acidosis, hyperoncemia develop, and as a result of an increase in the number of extracellular molecules, hyperosmia. The consequence of lysosomal damage is the release of lysosomal enzymes. Alteration of the vascular wall is accompanied by an increase in its permeability. Alteration of nerve formations with impaired impulse conduction through vasoconstrictors leads to neuroparalytic arterial hyperemia. Irritation of nerve elements, e.g. receptors, by the axon-reflex mechanism is also manifested by dilation of arterioles, relaxation of precapillary sphincters with the development of arterial hyperemia. Hypoxia and products of primary alteration initiate secondary alteration. Hypoxia, in turn, induces activation of lipid peroxidation, but lysosomal enzymes of neutrophils, macrophages and the contact ("guardian") polysystem of blood plasma proteins are of particular importance in the development of secondary alteration. Lysosomal enzymes (more than 60) destroy cell membranes and components of the supporting tissue both directly - through the action of phospholipase, collagenase, elastase, and exoglycosidase, and indirectly - through the release of mediators (biogenic amines) by mast cells, basophils, platelets, or through components of the "guardian" system of blood plasma proteins.

The stage of alteration is followed by the stage of exudation - the release of the liquid part of the blood, electrolytes, proteins and cells through the vascular wall into the inflamed tissue. The main mechanism of exudation is an increase in the permeability of the vascular wall, caused by the action of a number of pathogenetic factors. These include: destruction of the vascular wall during alteration; rounding of endothelial cells and the formation of folds in the plasma membrane of endothelial cells during cytoskeleton contraction; "spreading" of endothelial cells by leukocytes. The increase in permeability in the first, early, short-term (5–30 min) phase is mediated by the action of biogenic amines and acetylcholine on postcapillary venules. In the later phase (1–7 days), the increase in permeability is mediated by the action of polypeptide and lipid mediators of inflammation on venules and capillaries. Microcirculatory disorders and increased vascular permeability not only cause exudation, but also underlie leukocyte infiltration of the focus of inflammation, which sometimes reaches 50% of the daily production of phagocytes. The accumulation of neutrophils in the area of inflammation reaches a peak 2–4 hours after its onset. In the blood, leukocytes are in an unactivated state. Their activation occurs in the focus of inflammation, where they participate in phagocytosis. Neutrophils have the ability to absorb pathogenic microorganisms, as well as digest dead tissue, and support the cascade of the inflammatory and reparative process. If neutrophils die during phagocytosis, then macrophages remain, resorbing the products of cell decay and intercellular substance, clearing the field for regeneration. This process is implemented with the help of such lysosomal enzymes as collagenase and elastase. A mobile equilibrium is established between macrophages and fibroblasts - the main producers of collagen. Macrophages play an important role in the connection of the exudative and proliferative phases of inflammation. Proliferation is the process of reproduction of connective tissue cells. The proliferative phase of inflammation provides for the restoration of the tissue structure, including all elements of the organ-tissue functional complex. Macrophages stimulate the proliferation of fibroblasts through the secretion of a number of BAS (cytokinins and growth factors). Fibroblasts provide for the formation of the main elements of the stroma during proliferation. In parallel, vascular neoplasia occurs. Strands of cells formed from the endothelium are separated from the capillaries. Later, the lumen of newly formed capillaries appears in these strands.

Inflammation is classified according to the severity of the main local process (alterative, exudative and proliferative); reactivity of the organism (normergic, hypoergic and hyperergic); type of exudate (serous, purulent, hemorrhagic, fibrinous, mixed); course (acute, subacute, chronic). The main physicochemical changes in the focus of inflammation are

hyperosmia, hyperonchia, acidosis. Acidosis causes swelling of the connective tissue, increases exudation and local edema. An increase in osmotic pressure increases exudation. Acidosis and an increase in osmotic pressure create conditions for the appearance of a swelling (tumor) in the focus of inflammation. Redness (rubor) occurs as a result of vasodilation, an increase in the inflow of arterial blood containing bright red oxyhemoglobin, and the opening of capillaries that did not function before. The influx of warmer arterial blood into the tissue and increased metabolism can explain the increase in local temperature (calor). Pain (dolor) occurs as a result of irritation of sensitive nerve endings by various BAS - pain mediators (bradykinin, histamine, underoxidized metabolic products, e.g. lactic acid), as well as as a result of tissue tension during edema, which causes compression of sensitive nerve endings. A sharply expressed inflammatory process, accompanied by changes in metabolism, blood circulation, innervation in tissues, is usually manifested by a violation of the function of an organ or system (functio laesa). Along with local signs of inflammation, general changes occur in the body. A typical general sign of most inflammatory processes is an increase in the number of leukocytes per unit volume of peripheral blood (leukocytosis) and a change in the leukocyte formula. Quite often, inflammation is accompanied by fever. It develops under the influence of pyrogens formed by neutrophilic leukocytes. During inflammation, the ratio of blood protein fractions changes: the level of albumins decreases and the level of globulins increases. Due to changes in the composition of protein fractions of blood plasma and a decrease in the charge of erythrocytes, the erythrocyte sedimentation rate increases.

Inflammation is the most common pathological process. There is no direction of medicine that would not be associated with the prevention, diagnosis and treatment of the inflammatory process. In this regard, knowledge of the general mechanisms of the occurrence, development and consequences of inflammation is necessary for the doctor and pharmacist to resolve issues of their pharmacological correction. Anti-inflammatory effects are exhibited by glucocorticoid hormones, NSAIDs, a group of small immunosuppressants (heparin, chloroquine, D-penicillamine, gold preparations, etc.), some enzyme preparations (wobenzym, etc.); local action - astringents (ethyl alcohol, etc.). Inflammation of microbial etiology requires the use of chemotherapeutic, antiseptic drugs.

Inflammation (Latin inflammatio) - a typical pathological process, a complex protective reaction of the body to the action of harmful agents, which has developed over a long evolution and is a complex of tissue and vascular changes. This is one of the processes underlying many diseases, different in nature. The biological significance of inflammation is to prevent the spread of pathogenic agents in the body, sometimes the inflammatory process contributes to their destruction.

Inflammation is a local adaptive reaction of the body in response to damage. This cyclical reaction ends with the elimination of the pathogenic cause, tissue regeneration and restoration of organ function.

Inflammation is a complex local vascular-mesenchymal reaction to tissue damage caused by the actions of various agents. This reaction is aimed at the destruction of the agent that caused the damage and the restoration of damaged tissue. Inflammation is a reaction developed during phylogenesis, has a protective and adaptive nature and contains elements not only of pathology, but also of physiology.

The causes of inflammation can be both external (bacteria, their toxins, mechanical injuries, the action of chemicals, etc.) and internal (hematomas, salt deposits, tissue necrosis, etc.). Acute, subacute and chronic inflammation are also distinguished. Acute inflammation of the external integuments of the body is manifested by redness, edema, increased temperature at the site of inflammation and impaired function of the affected tissues. In chronic inflammation, as well as inflammation of internal organs, not all of these signs are observed.

According to morphogenesis, the following are distinguished:

1. Exudative inflammation - characterized by a predominance of vascular reaction and the formation of inflammatory exudate in the focus;

2. Productive (proliferative) inflammation - develops with prolonged tissue damage, characterized by a predominance of prolonged cell proliferation in the focus of inflammation with the formation of a cellular infiltrate.

Inflammation consists of a vascular reaction, alteration, exudation and proliferation.

The vascular reaction consists of a short-term narrowing of arterioles and capillaries, and then their increased expansion and filling (vascular hyperemia). Such vascular changes are caused by the accumulation of substances at the site of inflammation that affect the tone of the vascular wall (acetylcholine, histamine, adenine nucleotides). Due to the increased permeability of the vascular wall, plasma and leukocytes leak into the surrounding tissues (exudation). Alteration - tissue damage during inflammation is caused by a change in their function and structure, as a result of which various processes develop from dystrophy to necrosis, is the initial (initial) phase of inflammation. In this phase, biologically active substances are released - mediators of inflammation, which can be of plasma (humoral) and cellular (tissue) origin. Plasma-derived mediators are representatives of the kallikrein-kinin system, the coagulation and anticoagulation (factor XII, or Hageman factor, plasmin) and complement (components C3-C5) systems. Mediators of these systems increase microvascular permeability, activate chemotaxis of polymorphonuclear leukocytes, phagocytosis and intravascular coagulation.[6] Mediators of cellular origin are associated with effector cells - basophils, which release histamine, serotonin, a slowly reacting substance of anaphylaxis, etc.; platelets, which also secrete lysosomal enzymes; polymorphonuclear leukocytes, rich in leukokines, lysosomal enzymes, cationic proteins and neutral proteases.[6] In such tissue, accelerated metabolism occurs, in particular, excessive consumption of glucose in the absence of oxygen, which leads to acidosis. Metabolic disorders cause an increase in osmotic and oncotic pressure.

Exudation is a vascular reaction with the formation of exudate and inflammatory cellular infiltrate, which ends with the cleansing of the focus of inflammation from pathogens and destroyed cells. The nature of the exudative process is influenced by the nature of the pathogen. Exudate can be serous (blood plasma albumin), fibrinous (rich in fibrinogen), purulent (with a predominance of leukocytes), putrefactive (putrefactive transformation of exudate), hemorrhagic (increased number of erythrocytes), catarrhal (rich in mucus). Depending on the nature of the effusion, different types of exudative inflammation are distinguished (serous, purulent, etc.). The accumulation of exudate causes edema, which results in compression of nerve endings and pain. In the process of vascular changes, leukocytes leave the vascular bed and carry out phagocytosis. Disturbance of blood circulation at the site of inflammation leads to the formation of blood clots in the vessels, and compression of small vessels by edema, as a result of which the spread of harmful agents in the body is delayed. Inflammation localizes the infection in the area of penetration and limits its penetration into the body.

Against the background of exudation and alteration, proliferation begins - cell reproduction, most pronounced in the final stages of the inflammatory process. Then tissue regeneration begins. In the phase of cell proliferation and repair of damaged tissue, cell proliferation and the formation of cell proliferates are microscopically observed, at the end there is a restoration of the original structure of the tissue or the formation of a scar and reparative remodeling of damaged tissue.

Classification

• Exudative inflammation (inflammatio exsudativa) — characterized by the predominance of vascular reaction and the formation of inflammatory exudate in the focus

• Catarrhal inflammation (inflammatio catarrhalis) — inflammation of the mucous membranes, it is accompanied by abundant secretion of mucous exudate due to hypersecretion of mucous glands

• Purulent inflammation (inflammatio purulenta)

• Hemorrhagic inflammation (inflammatio haemorrhagica)

• Serous inflammation (inflammatio serosa)

• Fibrinous inflammation (inflammatio fibrinosa)

• Putrid inflammation, or gangrenous, ichorous (inflammatio putrida) — develops as a continuation of purulent, fibrinous or serous inflammation.

• Mixed inflammation

• Proliferative inflammation, or productive (inflammatio productiva, inflammatio proliferativa) — develops with prolonged tissue damage, is characterized by the predominance of prolonged cell proliferation in the focus of inflammation with the formation of a cellular infiltrate.

2. Questions for self-control (list of questions):

1. Give a definition of the inflammatory process.
2. Stages of inflammation: definition.
3. Nonspecific clinical signs of inflammation: definition.
4. Pathophysiology of inflammation.
5. Biochemical and pathogenetic features of the course of the inflammatory process.
6. The place and role of NSAIDs in the treatment of inflammation.
7. The place and role of GCS in the treatment of inflammation.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write prescriptions for basic anti-inflammatory drugs (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for prescription. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.
2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.
3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.
4. Highlight signs during subjective and objective examination of the patient that characterize the development of the inflammatory process, write a clinical diagnosis of the disease.
5. Determine the group of drugs necessary for the patient; based on theoretical data on pharmacodynamics and own observations, select drugs for the patient.
6. Choose the optimal dosage regimen of the drug, taking into account the characteristics of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.
7. Identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.
8. Justify the need for combined drug therapy and suggest 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 their detection at the early stages.
10. Justify the duration of basic and maintenance therapy.

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.

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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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.or

TOPIC
"Clinical pharmacology of nonsteroidal anti-inflammatory drugs"

Purpose:

1. To master the pharmacokinetics, pharmacodynamics and pharmacotoxicodynamics of the main groups of NSAIDs, presented in the theoretical part of the lesson. Indications for use. Undesirable effects. Contraindications to the appointment.

2. To master:

a) the main indications for the appointment of NSAIDs and control over their effectiveness and safety;

b) the main pathogenetic mechanisms that are the object of the drug effect of NSAIDs: phases of inflammation, inflammatory mediators, monocyte-macrophage systems, immune complexes and prostaglandin synthesis.

Basic concepts (list of questions):

1. Inflammation: definition, phlogogenic factors of the development of the inflammatory process.
2. Stages of the inflammatory process.
3. Clinical signs of inflammation.
4. Prostaglandins, leukotrienes and other eicosanoids.
5. Pathogenesis of inflammation.
6. Phospholipase A2, cyclic oxygenases, lipoxygenases - biological and pathological role.
7. Nonsteroidal anti-inflammatory drugs.
8. NSAIDs: pharmacological effects, mechanism of action.
9. NSAIDs: indications for use.
10. NSAIDs: main side effects, prevention and treatment.

Plan

1. Theoretical questions:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of drugs that have analgesic, antipyretic and anti-inflammatory effects, reduce pain, fever and inflammation. The use of the term "nonsteroidal" 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 their undoubted clinical effectiveness, NSAIDs belong to a group of drugs characterized by the so-called "pharmacological scissors", that is, in addition to the therapeutic effect, they have serious side effects. Even short-term use of

these drugs in small doses in some cases can lead to the development of side effects, which occur in approximately 25% of cases, and in 5% of patients can pose a serious threat to life. The risk of side effects is especially high in the elderly, who make up more than 60% of NSAID consumers. It should also be noted that many diseases require long-term use of NSAIDs. Therefore, every doctor is faced with the problem of rational choice of the drug and adequate treatment regimen, taking into account the effectiveness and safety of the anti-inflammatory drug.

Classification

NSAIDs are classified depending on 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 referred to as "non-narcotic analgesics" or "analgesics-antipyretics".

From a practical point of view, it is important that drugs belonging to the same group and even close in chemical structure differ slightly in both the strength of the effect and the frequency of development and nature of adverse reactions. Thus, among the NSAIDs of the first group, indomethacin and diclofenac have the most powerful anti-inflammatory activity, and ibuprofen has the least. Indomethacin, which is a derivative of indoleacetic acid, is more gastrotoxic than etodolac, which also belongs to this chemical group. The clinical efficacy 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 (Aspirin);
- Lysine monoacetylsalicylate (Aspizol);

B) Non-acetylated:

- Sodium salicylate;
- Dolobide (Diflunisal);

Pyrazolidines - Azapropazone (Raymox);

- Clofezone;
- Phenylbutazone (Butadione);

Indoleacetic acid derivatives - Indomethacin (Metindol);

- Sulindac (Clinoril);
- Etodalac (Lodin);

Phenylacetic acid derivatives - Diclofenac sodium (Ortofen, Voltaren);

- Diclofenac potassium (Voltaren – Rapid);
- Fentiazac (Donorest);
- Lonazalac calcium (Iriten).

Oxicams - Piroxicam

-Tenoxicam

-Lornoxicam

-Meloxicam

Propionic acid derivatives - Ibuprofen (Nurofen, Solpaflex);

- Naproxen (Naprosyn);
- Ketoprofen (Profenid);
- Flurbiprofen (Flugalin);
- Fenoprofen (Fenopron);
- Fenbufen (Lederlen);
- Tiaprofenic acid (Surgam).

Non-acidic derivatives

Alkanones - Nabumetone
Sulfonamide derivatives - Nimesulide
- Celecoxib
- Rofecoxib
NSAIDs with weak anti-inflammatory activity
Anthranilic acid derivatives - Mefenamic acid (Pomstal);
- Meclofenamic acid (Meclomet);
- Tolfenamic acid (Klotam).
Pyrazolones - Metamizole sodium (Analgin);
- Phenylbutazone (Butadione).
Paraaminophenol derivatives - Phenacetin;
- Paracetamol.
Heteroaryl acetic acid derivatives - Ketorolac;
- Tolmetin (Tolectin).

Classification of NSAIDs (by duration of action):
1. Short-acting (T1/2 = 2-8 hours):
- Ibuprofen; - Ketoprofen; - Indomethacin; - Fenoprofen; - Voltaren; - Tolmetin;
2. Medium-acting (T1/2 = 10-20 hours): - Naproxen; - Sulindac;
3. Long-acting (T1/2 = 24 hours or more): - Oxycodone; - Phenylbutazone.
Classification of NSAIDs by selectivity to different forms of cyclooxygenase
Selective COX-1 blockers Low doses of acetylsalicylic acid: Aspecard, Aspirin cardio, Cardiomagnyl, Magnicor.
Nonselective COX-1 and COX-2 blockers Ketoprofen, Diclofenac, Ibuprofen, Indomethacin and others.
Preferred COX-2 blockers Meloxicam, Movalis, Melox, Revmoxicam, Nimesil, Nise, Nimegesic, Nimesulide
Selective COX-2 blockers Celecoxib, Rofecoxib, Celebrex, Ranselex, Revmoxib, Flogoxib, Rofica, Denebol.
Selective COX-3 blockers Paracetamol

Classification of NSAIDs by effect on the processes of cartilage biosynthesis.
I. Suppress inflammation and are neutral to arthrosis - Piroxicam, diclofenac, sulindac;
II. Suppress inflammation and aggravate arthrosis - Acetylsalicylic acid, indomethacin, fenoprofen, phenylbutazone;
III. Suppress inflammation and contribute to the normalization of metabolic processes in cartilage tissue - benoxaprofen, tiaprofenic acid (surgam), paracetamol.

Pharmacodynamics
Despite their widespread use, the mechanism of action of NSAIDs remained unstudied for a long time. 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 drug concentrations much higher than therapeutic and were not associated with its anti-inflammatory, analgesic and antipyretic effects. The most important mechanism of NSAIDs is associated with the inhibition of the synthesis of cyclooxygenase (COX) and lipoxygenase (LOG) - key enzymes in the metabolism of arachidonic acid. Arachidonic acid is part of membrane phospholipids and is released under the influence of the enzyme phospholipase A2. COX and LOG catalyze the further transformation of arachidonic acid. The products of their metabolism include cyclic endoperoxides, prostaglandins (PG), thromboxane (TXA2), leukotrienes (LT), etc. PGs are produced by many cells and are among the most important paracrine and autocrine mediators.
PGs have diverse biological activities:

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 PGs are potentiated by the action of free radicals formed during the enzymatic oxidation of arachidonic acid. Activation of free radical oxidation (FRO) promotes the release of lysosomal enzymes, which leads to further destruction of cell membranes, sensitizes 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) formed in the body under the influence of microbes, viruses, toxins (mainly - PG-E2).

Thromboxane is a factor in platelet aggregation, narrows blood vessels. Prostacyclin, formed from the damaged vascular wall, reduces platelet aggregation and adhesion, dilates blood vessels.

The existence of two main isoforms of COX is known: COX-1 and COX-2.

COX-1 is a structural enzyme, synthesized in most cells of a healthy body (excluding erythrocytes) and catalyzes the formation of physiological PGs, thromboxane and prostacyclin, which play an important role in the regulation of a number of physiological processes in the body, such as protection of the gastrointestinal mucosa, ensuring renal blood flow, regulation of vascular tone, blood clotting, bone metabolism, growth of nervous tissue, pregnancy, regeneration and apoptosis processes. COX-2 is involved in the synthesis of prostaglandins during inflammation. Moreover, COX-2 is absent under normal conditions, but is formed under the influence of certain tissue factors that initiate an 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 the activity of NSAIDs 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 with respect to COX-2 and, therefore, the less toxic. For example, for meloxicam it is 0.33, diclofenac - 2.2, tenoxicam - 15, piroxicam - 33, indomethacin - 107. The existence of another COX isoform is also assumed - COX-3. The assumed COX-3 is expressed in the brain, also affects the synthesis of PG and plays a role in the development of pain and fever. However, unlike other isoforms, it does not affect the development of inflammation.

Different representatives of NSAIDs differ not only in chemical structure and pharmacodynamic features, but also in the degree of influence on different COX isoforms. For example, acetylsalicylic acid, indomethacin, ibuprofen inhibit COX-1 to a greater extent than COX-2. The most widely used NSAID diclofenac inhibits both isoenzymes to the same extent. Selective or selective COX-2 inhibitors include nimesulide, meloxicam, nabumetone. However, it must be taken into account that with increasing dose, their selectivity is significantly weakened. Highly selective or specific COX-2 inhibitors are coxibs: celecoxib, rofecoxib, valdecoxib, parecoxib, etoricoxib. COX-3 activity 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 may be associated with inhibition of lipid peroxidation, stabilization of lysosomal membranes (both of these mechanisms prevent damage to cellular structures), reduction of ATP formation (energy supply of the inflammatory reaction decreases), inhibition of neutrophil aggregation (release of inflammatory mediators from them is impaired), inhibition of rheumatoid factor production in patients with rheumatoid arthritis. The analgesic effect is to some extent associated with impaired conduction of pain impulses in the spinal cord (metamizole).

Some NSAIDs relieve pain and inflammation of articular cartilage, but at the same time

metabolic processes inside the joint are grossly disrupted, and ultimately destruction of articular cartilage occurs. Among these drugs, acetylsalicylic acid and indomethacin, widely used in rheumatology, should be put in the first place. These drugs, from the point of view of their effect on metabolic processes in articular cartilage, should be used in limited quantities. The next group of drugs are drugs that are indifferent to the metabolic processes in the cartilage itself, relieve pain and inflammation, but do not disrupt the metabolism of 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 to varying degrees, but not only do not disrupt the metabolism of articular cartilage, but also stimulate synthetic processes in articular cartilage. These are benoxaprofen, tiaprofenic acid and paracetamol. It should be noted that currently there are and are widely studied COX-independent aspects of the mechanism of action of NSAIDs, which will significantly expand the spectrum of their use. Thus, there is evidence that a number of NSAIDs are able to significantly stimulate the proliferative response of T-lymphocytes and the synthesis of interleukin-2. The latter is associated with an increase in intracellular calcium levels, inhibition of chemotaxis, increased neutrophil aggregation, and the formation of hypochlorous acid and superoxide radicals of oxygen. The ability of salicylates to inhibit the activation of transcription factors 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 cellular activation of leukocytes under the influence of chemotactic stimuli in the early stages of inflammation.

There are results on the effect of NSAIDs on central pain mechanisms that are not associated with COX inhibition. It is believed that the antinociceptive effect of NSAIDs is partially associated with the release of endogenous opioid peptides.

The antiproliferative effect of NSAIDs can also be mediated by various mechanisms: both by increasing the activity of natural killer cells when inhibiting PG synthesis, and by COX-2-dependent regulation of cell apoptosis. It has been established that the production of COX-2 precedes the 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 the activation of glial cells, an increase in the level of pro-inflammatory cytokines, and complement activation. COX-2 metabolites also contribute to the growth of tumor cells, so the ability to inhibit COX-2 will allow the use of NSAIDs in oncology in the treatment of a number of cancers.

Requirements for modern NSAIDs

- Anti-inflammatory action
- Predominant inhibitory effect on COX-2
- Analgesic action
- Chondroprotective action or lack of effect on articular cartilage metabolism; improvement of synovial fluid composition
- Normalizing effect on Ca2+ metabolism in bone tissue
- Myotropic antispasmodic action
- Immunomodulatory properties
- Minimum side effects
- Possibility of creating dosage forms (ointments, suppositories, tablets, etc.) based on the substance that meet biopharmaceutical requirements.

A very important aspect of the use of NSAIDs is safety, which is characterized by the benefit/risk ratio. When taking NSAIDs, the spectrum of side effects can be quite wide. The likelihood of developing undesirable effects is determined by the belonging of a particular

drug (dosage form) to the prescription or non-prescription group. It should be noted that the safety of the drug is significantly influenced by the characteristics of the dosage form and the production technology of the drug.

MAIN EFFECTS

Anti-inflammatory effect. NSAIDs mainly suppress the exudation phase. The most potent drugs - indomethacin, diclofenac, phenylbutazone - also act on the proliferation phase (reducing collagen synthesis and the associated tissue sclerosis), but weaker than on the exudative phase. NSAIDs have practically no effect on the alteration phase. All NSAIDs are inferior to glucocorticoids in terms of anti-inflammatory activity.

Analgesic effect. It is more pronounced in mild and moderate pain localized in muscles, joints, tendons, nerve trunks, as well as in headache or toothache. In severe visceral pain, most NSAIDs are less effective and are inferior in analgesic effect to the morphine group (narcotic analgesics). At the same time, a number of controlled studies have shown a fairly high analgesic activity of diclofenac, ketorolac, ketoprofen, metamizole in colic and postoperative pain. The effectiveness of NSAIDs in renal colic, which occurs in patients with urolithiasis, is largely associated with inhibition of PG-E2 production in the kidneys, a decrease in renal blood flow and urine formation. This leads to a decrease in pressure in the renal pelvis and ureters above the site of obstruction and provides a long-term analgesic effect. The advantage of NSAIDs over narcotic analgesics is that they do not suppress the respiratory center, do not cause euphoria and drug dependence, and for colic, it is also important that they do not have a spasmogenic effect.

Antipyretic effect. NSAIDs are effective only for fever. They do not affect normal body temperature, which is how they differ from "hypothermic" agents (chlorpromazine and others).

Antiaggregation effect. As a result of inhibition of COX-1 in platelets, the synthesis of the endogenous proaggregant thromboxane is suppressed. The strongest and longest-lasting antiaggregation activity is possessed by aspirin, which irreversibly inhibits the ability of platelets to aggregate for the entire duration of its life (7 days). The antiaggregation effect of other NSAIDs is weaker and is reversible. Selective COX-2 inhibitors do not affect platelet aggregation.

Immunosuppressive effect. Moderately expressed, manifested with prolonged use and has a "secondary" nature: by reducing capillary permeability, NSAIDs complicate the contact of immunocompetent cells with the antigen and the contact of antibodies with the substrate.

PHARMACOKINETICS

All NSAIDs are well absorbed in the gastrointestinal tract. They are almost completely bound to plasma albumin, displacing some other drugs, and in newborns - bilirubin, 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 and excreted through the kidneys.

INDICATIONS FOR USE

1. Rheumatic diseases: rheumatism (rheumatic fever), rheumatoid arthritis, gouty and psoriatic arthritis, ankylosing spondylitis (Bechterew's disease), Reiter's syndrome.

It should be borne in mind that in rheumatoid arthritis, NSAIDs have only a symptomatic effect, without affecting the course of the disease. They are not able to stop the progression of the process, cause remission and prevent the development of joint deformity. At the same time, the relief that NSAIDs bring to patients with rheumatoid arthritis is so significant that none of them can do without these drugs. In large collagenoses (systemic lupus erythematosus, scleroderma, and others), NSAIDs are often ineffective.

2. Non-rheumatic diseases of the musculoskeletal system: osteoarthritis, myositis, tendovaginitis, trauma (domestic, sports). Often, in these conditions, the use of local dosage forms of NSAIDs (ointments, creams, gels) is effective.

3. Neurological diseases: neuralgia, radiculitis, sciatica, lumbago.

4. Renal, hepatic colic.

5. Pain syndrome of various etiologies, including headache and toothache, postoperative pain.

6. Fever (usually at a 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 hyperproduction of PG-F2a. In addition to the analgesic effect, NSAIDs reduce blood loss. Especially when using naproxen and its sodium salt, diclofenac, ibuprofen, ketoprofen. NSAIDs are prescribed at the first appearance of pain in a 3-day course or on the eve of menstruation.

ADVERSE REACTIONS

Gastrointestinal tract. It has now been established that against the background of the use of NSAIDs, lesions of any parts of the gastrointestinal tract can develop - from the lower third of the esophagus (in the presence of gastroesophageal reflux) to the distal parts of the large intestine, enteropathy. But the most common lesions are in the antrum of the stomach and the duodenal bulb. When treated with drugs of this group, dyspeptic disorders are observed in 30-40% of patients, erosions and ulcers of the stomach and duodenum in 10-20%, bleeding and perforation in 2-5%. A separate syndrome has now been identified - NSAIDs-gastropathy. Its appearance, on the one hand, is associated with the local damaging effect of drugs on the mucous membrane of the stomach and intestines, increased permeability of cell membranes, and a decrease in the biosynthesis of gastric mucus. On the other hand, it is caused by inhibition of COX-1 and inhibition of the synthesis of physiological PGs, 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 occurs in 3 stages:

1) inhibition of prostaglandin synthesis in the mucosa;

2) reduction of prostaglandin-mediated production of protective mucus and bicarbonates;

3) the appearance of erosions and ulcers, which can be complicated by bleeding or perforation.

The damage is more often localized in the stomach, mainly in the antral or prepyloric department. Clinical symptoms in NPLZ-gastropathies are absent in almost 60% of patients, especially the elderly, therefore the diagnosis is established in many cases during fibrogastroduodenoscopy. At the same time, in many patients with dyspeptic complaints, mucosal damage is not detected. The absence of clinical symptoms in NSAID gastropathies is associated with the analgesic effect of the drugs. Therefore, patients, especially the elderly, who do not experience any adverse effects from the gastrointestinal tract during long-term use of NSAIDs, are considered a group at increased risk of developing serious complications of NSAID gastropathies (bleeding, severe anemia) and require particularly careful monitoring, including endoscopic examination. Risk factors for the development of NSAID gastropathies are: age over 60 years, female gender, smoking, alcohol abuse, history of gastrointestinal diseases, concomitant use of glucocorticoids, immunosuppressants, anticoagulants, long-term NSAID therapy, high doses or simultaneous use 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 diseases are strictly contraindicated to use these drugs. In order to improve tolerability and minimize the ulcerogenic effect of NSAIDs, it is recommended to combine their administration with proton pump inhibitors, H2-histamine blockers or gastroprotectors; change the dosing tactics of NSAIDs (dose reduction), use of enteric-coated dosage forms of drugs or prodrugs (for example, sulindac), as well as switch to parenteral, rectal or local administration of NSAIDs.

However, since NSAID gastropathy is not so much a local as a systemic reaction, these approaches have not become a solution to the problem. It is recommended to use selective NSAIDs that selectively block COX-2 and in therapeutic doses do not significantly affect COX-1. Thus, the preferred COX-2 inhibitors meloxicam, etodolac, nabumetone and nimesulide have a favorable gastrotoxicity profile. Currently, specific COX-2 inhibitors, such as celecoxib and rofecoxib, are widely used in clinical practice, which have practically no negative effect on the gastrointestinal tract. A synthetic analogue of PG-E2, misoprostol, is highly effective, the use of which allows you to prevent the development of ulcers, both in the stomach and in the duodenum. Combined drugs are available, which include NSAIDs and misoprostol.

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 have been identified.

I. By blocking the synthesis of PG-E2 and prostacyclin in the kidneys, NSAIDs cause vasoconstriction and deterioration of renal blood flow. This leads to the development of ischemic changes in the kidneys, a decrease in glomerular filtration and diuresis. As a result, water and electrolyte metabolism disorders may occur: water retention, edema, hypernatremia, hyperkalemia, increased serum creatinine, and increased blood pressure. Indomethacin and phenylbutazone have the most pronounced effect on renal blood flow.

II. NSAIDs can have a direct effect on the renal parenchyma, causing interstitial nephritis (the so-called "analgesic nephropathy"). The most threatening in this regard are phenacetin, paracetamol. Serious kidney damage is possible, up to the development of severe renal failure. The development of acute renal failure when using NSAIDs as a consequence of acute allergic interstitial nephritis has been described.

Risk factors for nephrotoxicity are age over 65 years, cirrhosis of the liver, renal pathology, decreased circulating blood volume, gout, atherosclerosis, long-term use of NSAIDs, concomitant use of diuretics, congestive heart failure, arterial hypertension. The greatest nephrotoxicity among NSAIDs is possessed by paracetamol, indomethacin, phenylbutazone, ibuprofen, fenoprofen, 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 may be recommended, for example, sulindac, meloxicam, nimesulide.

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 advanced age, impaired renal function, alcohol consumption, and the use of other hepatotoxic drugs. Hepatotoxic effects are most often observed against the background of taking diclofenac, nimesulide, phenylbutazone, sulindac, paracetamol, and indomethacin, which limits the use of these drugs in patients with a history of liver disease. For these patients, the rational use of coxibs, meloxicam, and ketoprofen is appropriate.

Hematotoxicity: manifested by aplastic anemia, thrombocytopenia, agranulocytosis, and methemoglobinemia (paracetamol). The most pronounced inhibitory effect on the hematopoietic system is exerted by paracetamol, indomethacin, acetylsalicylic acid, metamizole sodium, fenoprofen.

Coagulopathies: manifest as gastrointestinal bleeding (most NSAIDs inhibit platelet aggregation and have a moderate anticoagulant effect by inhibiting 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, clofezone. Patients with a clinical triad including vasomotor rhinitis, nasal polyposis, and bronchial asthma are at high risk of developing hypersensitivity reactions to NSAIDs.

Bronchospasm: "aspirin" asthma (or Vidal's syndrome) develops most often with the use

of acetylsalicylic acid and its derivatives. The causes of 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.

Ototoxicity is caused by salicylates.

Prolongation of pregnancy and delay in labor. 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 for use during pregnancy, the greatest teratogenic effect is possessed by indomethacin, salicylates, aminophenazone.

Retinopathies and keratopathies - as a result of indomethacin deposition in the retina and cornea.

Mutagenicity and carcinogenicity are possible. NSAIDs penetrate the placenta and can cause the development of congenital pathological changes 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 natriuresis due to inhibition of filtration and increased proximal tubular reabsorption of sodium ions; an increase in renal resistance due to inhibition of the synthesis of PGs that provide renal blood flow; an increase in the release of noradrenaline from nerve endings; a decrease in glomerular filtration and renal blood flow, activation of the renin-angiotensin system, damage to the renal parenchyma ("analgesic nephropathy"); an increase in endothelin secretion; mineralocorticoid activity of a number of NSAIDs (for example, phenylbutazone).

Development of cardiovascular diseases and hemostasis disorders - caution should be exercised when prescribing specific COX-2 inhibitors (especially rofecoxib), since in recent years this group of NSAIDs has been shown to have the ability to cause cardiovascular and cerebrovascular complications. This is due to inhibition of prostacyclin synthesis in the vascular endothelium. Thromboxane production does not decrease, and an imbalance occurs 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 phenomena, congestive heart failure, cerebrovascular bleeding, and others. It is considered advisable to refuse the use of specific COX-2 inhibitors in patients prone to thrombosis, who have a history of myocardial infarction, cerebral circulation disorders. Risk factors for the hypertensive effect of NSAIDs are advanced age, congestive heart failure, renovascular hypertension, cirrhosis of the liver. Piroxicam, phenylbutazone, indomethacin, rofecoxib should not be used in such patients; ketoprofen, ibuprofen, meloxicam are recommended.

Neurological and psychiatric disorders - indomethacin, phenylbutazone can cause headache, dizziness, attention disorders, hand tremor, depression and even psychosis, so they are not recommended for people whose profession requires increased attention and quick reactions. When using ibuprofen, sulindac, especially in patients with lupus erythematosus, aseptic meningitis may develop. There is evidence that long-term use of NSAIDs can lead to memory impairment.

CONTRAINDICATIONS

NSAIDs are contraindicated in erosive-ulcerative lesions of the gastrointestinal tract, especially in the acute stage, severe liver and kidney dysfunction, cytopenias, individual intolerance, 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 to persons whose professions require increased attention.

WARNING

NSAIDs should be prescribed with caution to patients with bronchial asthma, as well as to persons who have previously had adverse reactions when taking any other NSAIDs. For

patients with hypertension or heart failure, those NSAIDs should be chosen that have the least effect on renal blood flow. In the elderly, it is necessary to strive to prescribe the minimum effective doses and short courses of NSAIDs.

RULES FOR PRESCRIBING AND DOSAGE

Individualization of the choice of drug. For each patient, the most effective drug with the best tolerability should be selected. Moreover, it can be any NSAID, but as a countermeasure to inflammation, it is necessary to prescribe a drug from group I. The sensitivity of patients to NSAIDs of even one chemical group can vary widely, so the ineffectiveness of one of the drugs does not yet indicate the ineffectiveness of the group as a whole. When using NSAIDs in rheumatology, it is necessary to take into account that the development of the anti-inflammatory effect lags behind the analgesic effect. The latter is noted in the first hours, while the anti-inflammatory effect - after 10-14 days of regular intake, and when prescribing naproxen or oxicams even later - for 2-4 weeks.

Dosage. Any new drug for a given patient should be prescribed initially in the lowest dose. With good tolerability, the daily dose is increased after 2-3 days. 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, ibuprofen), while maintaining restrictions on 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 administration. With long-term course administration (for example, in rheumatology), NSAIDs are taken after meals. But to obtain a rapid analgesic or antipyretic effect, it is better to prescribe them 30 minutes before or 2 hours after meals, washed down with 1/2-1 glass of water. After taking it, it is advisable not to lie down for 15 minutes in order to prevent the development of esophagitis. The time of taking NSAIDs can also be determined by the time of maximum severity of symptoms of the disease (pain, stiffness in the joints), i.e. taking into account the chronopharmacology of the drugs. In this case, it is possible to deviate from the generally accepted schemes (2-3 times a day) and prescribe NSAIDs at any time of the day, which often allows to achieve a greater therapeutic effect with a smaller daily dose. With severe morning stiffness, it is advisable to take quickly dissolved NSAIDs as soon as possible (immediately after waking up) or prescribe long-acting drugs at night. The highest absorption rate in the gastrointestinal tract and, therefore, a faster onset of effect are naproxen, diclofenac potassium, water-soluble ("effervescent") aspirin.

Monotherapy. The simultaneous use of two or more NSAIDs is inappropriate for the following reasons:

- the effectiveness of such combinations has not been 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 adverse reactions increases. The exception is the possibility of using paracetamol in combination with some other NSAID to enhance the analgesic effect.

In some patients, two NSAIDs may be prescribed at different times of the day, for example, those that are rapidly absorbed - in the morning and afternoon, and long-acting - in the evening.

DRUG INTERACTIONS

Often, patients receiving NSAIDs are prescribed other drugs. In this case, it is imperative to take into account the possibility of their interaction with each other. Thus, 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 antibiotics - aminoglycosides, digoxin and some other drugs, which has significant clinical significance and entails a number of practical recommendations. It is necessary, if possible, to

avoid the simultaneous appointment of NSAIDs and diuretics, on the one hand, weakening the diuretic effect and, on the other, the risk of developing renal failure. The most dangerous is the combination of indomethacin with triamterene.

Many drugs that are prescribed simultaneously with NSAIDs, in turn, can affect their pharmacokinetics and pharmacodynamics:

- aluminum-containing antacids (almagel, maalox) and cholestyramine reduce the absorption of NSAIDs in the gastrointestinal tract. Therefore, the concomitant administration of such antacids may require an increase in the dose of NSAIDs, and intervals of at least 4 hours are required between taking 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 sedatives.

Effect of NSAIDs on the effect of other drugs

Pharmacokinetic interaction

Indirect anticoagulants + all NSAIDs, especially aspirin → Displacement from plasma protein binding, increased anticoagulant effect → Avoid NSAIDs, if possible, or strictly monitor.

Oral hypoglycemic drugs (sulfonylurea derivatives) + phenylbutazone → Inhibition of metabolism in the liver, increased hypoglycemic effect. Avoid NSAIDs, if possible, or strictly monitor blood glucose levels.

Oral hypoglycemic drugs + all NSAIDs, especially aspirin → Displacement from plasma protein binding, increased hypoglycemic effect.

Digoxin + all NSAIDs → Inhibition of renal excretion of digoxin in impaired renal function (especially in young children and the elderly), increased blood concentration, increased toxicity. With normal renal function, the interaction is less likely. Avoid NSAIDs if possible, or strictly monitor creatinine clearance and digoxin concentration in the blood.

Antibiotics, aminoglycosides + all NSAIDs → Inhibition of renal excretion of aminoglycosides, increasing their concentration in the blood. Strict control of aminoglycoside concentration in the blood.

Methotrexate (high "non-rheumatological" doses) + all NSAIDs → Inhibition of renal excretion of methotrexate, increasing its concentration in the blood and toxicity (interaction with the "rheumatological" dose of methotrexate is not determined) Simultaneous administration is contraindicated. The use of NSAIDs is permissible in intervals between chemotherapy.

Pharmacodynamic interaction

Antihypertensive drugs - beta-blockers, diuretics, ACE inhibitors + all NSAIDs - to the greatest extent - indomethacin, phenylbutazone, to the least - sulindac → Weakening of the hypotensive effect due to inhibition of PG synthesis in the kidneys (sodium and water retention) and vessels (vasoconstriction). Use sulindac and, if possible, avoid other NSAIDs in hypertension. Strict blood pressure control. Increased antihypertensive therapy may be required.

Diuretics + all NSAIDs - to the greatest extent - indomethacin, phenylbutazone, to the least - sulindac → Weakening of the diuretic and natriuretic effect, worsening of the condition in heart failure. Avoid NSAIDs (except sulindac) in 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.

Combinations of increased risk!

Diuretics + all NSAIDs (to a lesser extent - sulindac) → Increased risk of developing renal failure - the combination is contraindicated.

Triamterene + 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 monitor the level of potassium in the plasma.

2. Questions for self-control (list of questions):

1. Explain the classification of NSAIDs by chemical structure.
2. Describe the classification of modern NSAIDs taking into account the pharmacodynamic effect, the degree of its expression, and the chemical structure.
3. List the pharmacodynamic effects of NSAIDs and explain their clinical significance.
4. Explain the process of formation and functional purpose of prostaglandins.
5. Describe the general mechanism of development of pharmacodynamic effects of NSAIDs.
6. Define free oxygen radicals and explain their clinical significance.
7. Explain the mechanism of anti-inflammatory action of NSAIDs.
8. Name the phases of inflammation and make a differentiated selection of NSAIDs for each of them.
9. Explain the mechanism of antipyretic action of NSAIDs.
10. Describe the mechanism of the analgesic effect of NSAIDs and compare it with the mechanism of action of narcotic analgesics.
11. Explain the mechanism of the irritating effect of NSAIDs on the mucous membranes of the stomach and intestines. Indicate the drugs that prevent the negative effect.
12. Indicate the mechanism of development of the bronchospastic effect of NSAIDs and ways to prevent it.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for basic NSAIDs (tablets and/or ampoules), indicate possible use, the spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.
2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.
3. Write a protocol for independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.
4. Identify signs during subjective and objective examination of the patient that characterize the development of the inflammatory process, write a clinical diagnosis of the disease.
5. Determine the group of drugs needed by the patient; based on theoretical data on pharmacodynamics and own observations, select the drug for the patient.
6. Choose the optimal dosage regimen of the drug, taking into account the characteristics of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.
7. Identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.
8. Justify the need for combined drug therapy and suggest 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 their detection at early stages.
10. Justify the duration of basic and supportive therapy.

B. Solution of situational tasks.

1. A 36-year-old patient has a diagnosis of rheumatism, active phase of stage I, regurgitant carditis, mitral heart disease with predominance of insufficiency, circulatory failure of stage IIB. Treatment is prescribed: cardiac glycosides, diuretics, metabolic agents. What anti-inflammatory drug is indicated for the patient? Justify the choice of drug.

2. A 42-year-old patient went to the clinic with complaints of minor pain in the knee joints after work. He works as a loader. There are no visible changes in the joints during objective examination, a rough crunch is detected during movement. X-rays show narrowing of the joint space, exacerbation of the intercondylar elevation, osteophytes at the edges of the tibial epiphysis. The diagnosis is: degenerative osteoarthritis of the knee joints. Your treatment plan for the patient.

Test tasks for self-control:

1. Highly selective COX-2 inhibitors include:
A. Acetylsalicylic acid.
B. Celecoxib.
C. Ibuprofen.
D. Diclofenac sodium.
E. Mefenamic acid.

2. 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 protein binding.
B. Reduction of prothrombin activity by NSAIDs.
C. Inhibition of platelet aggregation.
D. Inhibition of oxidative liver enzymes by some NSAIDs.
E. All of the above mechanisms.

3. The combined use of NSAIDs and hypoglycemic drugs leads to:
A. Increased blood sugar levels.
B. Decrease in blood sugar levels.
C. Decrease in the amount of low-density lipoproteins.
D. Increase in the amount of low-density lipoproteins.
E. Increase in the level of high-density lipoproteins.

4. Name which pathogenetic link of the inflammatory process is influenced by NSAIDs?
A. Decrease in capillary permeability.
B. Stabilization of lysosomes.
C. Inhibition of the synthesis of macroergic phosphates.
D. Inhibition of the synthesis and release of inflammatory mediators.
E. All of the above.

5. Choose from the listed NSAIDs with the most pronounced anti-inflammatory effect:
A. Paracetamol.
B. Analgin.
C. Indomethacin.
D. Acetylsalicylic acid.
E. Piroxicam

6. Selective COX-2 inhibitor:
A. Paracetamol.
B. Nimesulide.
C. Butadione.
D. Indomethacin.
E. Acetylsalicylic acid.

7. NSAID with the least pronounced ulcerogenic effect.
A. Paracetamol.
B. Meloxicam.
C. Butadione.
D. Indomethacin.
E. Acetylsalicylic acid.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical pharmacology of steroid anti-inflammatory drugs"

Purpose:

To learn: - glucocorticosteroid drugs:

- short-acting: cortisone, hydrocortisone;
- medium-acting: prednisolone, methyl prednisolone;
- long-acting: triamcinolone (polcortolone, kenacort, kenalog); dexamethasone (dexone); betamethasone (celeston); paramethasone (monocortin).
- inhaled corticosteroids: beclomethasone, budesonide, fluticasone, flunisolide.
- corticosteroids for cutaneous use:

= highly active (betamethasone dipropionate, clobetasone propionate, halobetasol propionate);

= medium-active (triamcinolone acetonide, fluticasone propionate);

= weakly active (hydrocortisone, prednisolone, flumethasone pivalate);

- basic, slow-acting anti-inflammatory drugs: methotrexate, sulfasalazine, chloroquine, auronofin.

To learn: a) the main indications for the appointment of GCS and control over their effectiveness and safety;

b) the main pathogenetic mechanisms that are the object of the pharmacological effect of GCS;

c) the main types of hormone therapy (replacement, stimulating, inhibiting, pharmacodynamic);

d) the principles of hormone therapy, the choice of a specific drug and its routes of administration;

e) the pharmacodynamics of the main groups of GCS and their synthetic analogues used for the purpose of anti-inflammatory, anti-allergic, immunosuppressive and anti-shock therapy;

e) the pharmacokinetics of GCS;

g) undesirable effects of GCS and methods of their correction;

h) the principles of combining GCS with other drugs;

i) comparative characteristics of steroidal and nonsteroidal anti-inflammatory drugs;

j) chronopharmacology of GCS and their synthetic analogues;

Basic concepts (list of questions):

1. Inflammation: definition, phlogogenic factors of the development of the inflammatory process.
2. Stages of the inflammatory process.
3. Clinical signs of inflammation.
4. Prostaglandins, leukotrienes and other eicosanoids.
5. Pathogenesis of inflammation.
6. Phospholipase A2, cyclic oxygenases, lipoxygenases - biological and pathological

role.

7. Steroidal anti-inflammatory drugs (GCS).
8. GCS: pharmacological effects, mechanism of action.
9. GCS: indications for use.
10. GCS: main side effects, prevention and treatment.

Plan

1. Theoretical questions:

STEROID ANTI-INFLAMMATORY DRUGS (GLUCOCORTICOSTEROIDS).

Glucocorticosteroids (GCS) are synthetic drugs (analogs of endogenous hormones produced by the adrenal cortex) that have anti-inflammatory, desensitizing, immunosuppressive, anti-shock and antitoxic effects.

This group includes drugs: Betamethasone (Diprospan, Celeston), Beclomethasone dipropionate (Bezlazon Eco, Beclojet, Bekotide), Budesonide (Pulmicort, Symbicort Turbuhaler), Flumethasone (Lorinden S, Seretide), Hydrocortisone (Hydrocortisone, Cortef, Laticort, Oxycort), Dexamethasone (Polydexa), Methylprednisolone (Advantan, Metipred, Solu-Medrol), Mometasone furoate (Momat, Nasonex, Elocom), Prednisolone (Aurobin, Dermozolon, Rectodelt), Triamcinolone acetonide (Kenalog, Polcortolon, Fluorocort), Fluticasone propionate (Flixonase, Flixotide), Flucortolone (Ultraproct).

REGULATION OF GLUCOCORTICOSTEROID RELEASE

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 hormone is secreted in pulses - 8-10 pulses/day. The level of cortisol secretion does not remain constant throughout the day (the maximum concentration in the blood is reached by 7-8 am, the minimum - by midnight). During stress (infection, surgery, hypoglycemia), the synthesis and secretion of GCS increases approximately 10 times (up to 250 mg/day).

Regulation of GCS secretion is controlled by the hypothalamic-pituitary mechanism. When the concentration of free cortisol decreases, the hypothalamus secretes corticotropin - a releasing factor that stimulates the release of adrenocorticotropic hormone (corticotropin) in the anterior pituitary. Adrenocorticotropic hormone, 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 influence 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 substances of lipid nature (derivatives of cholesterol) and can dissolve in cell membranes. Penetration of the hormone into the cell is possible not only in bound form (using a carrier protein), but also passively. Steroid receptors (GCR) are located in the cytoplasm of cells. However, their density in different cells is different: from 10 to 100 steroid-sensitive receptors, which may cause different sensitivity of tissues to GCS. In addition, GCS can have different tropisms for GCS. Thus, the endogenous glucocorticosteroid cortisol mainly binds to the GCS of the cytoplasmic membrane, while the synthetic GCS - dexamethasone, to a greater extent, binds to cytosolic GCS. The number of glucocorticosteroid receptors can differ significantly and change during GCS therapy.

The next stage is the movement of the hormone receptor complex (HRC) into the cell

nucleus. The penetration of HRC into the nucleus is possible after restructuring their structure (activation), which leads to the appearance of their ability to bind to nuclear components.

Activated HRC binds in the nucleus to a certain section of DNA. The HRC - DNA complex contributes to an increase in RNA synthesis. Recent studies have shown that the effect of glucocorticosteroid hormones on the biosynthesis of messenger RNAs (mRNA) is a key step in the implementation of the biological effects of GCS in 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, perhaps, 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 proteins of chromatin, which leads to a change in their structure, has been described. The anti-inflammatory effect of steroids is mediated through specific GCRs, changes in the activity of GCRs and the synthesis of RNA and proteins (nuclear pathway).

PHARMACODYNAMIC EFFECTS OF GLUCOCORTICOSTEROIDS

1. The anti-inflammatory effect of glucocorticoids 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 due to:

 membrane-stabilizing effect and, as a consequence, a decrease in the permeability of cellular and subcellular membranes (mitochondria and lysosomes);

 a decrease in the permeability of the vascular wall, in particular, capillaries and vasoconstriction in the focus of inflammation. Vasoconstriction is a specific effect of GCS 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 the suppression of the release of lipid mediators and activators of the kinin system, a decrease in the activity of hyaluronidase;

 inhibition of the synthesis of some cytokines involved in inflammatory reactions, as well as blockade of the synthesis of cytokine receptor proteins;

 reduction in 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, transcription or reducing the half-life of messenger RNA;

 inhibition of the migration of mast cells and eosinophils into the focus of inflammation. It is known that glucocorticosteroids reduce the number of eosinophils by suppressing the production of GM-CSF and IL-5;

 inhibition of mast cell degranulation and release of biologically active amines (histamine, serotonin, kinins and prostaglandins) from mast cells;

 reduction in the intensity of energy production processes in the focus of inflammation;

 inhibition of neutrophil migration into the focus of inflammation, disruption of their functional activity (chemotactic and phagocytic). GCS cause peripheral leukocytosis both after a single administration (for 4-6 hours) and with long-term 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.

Currently, there is a hypothesis that in the mechanism of anti-inflammatory action of GCS, their ability to induce the synthesis of some (lipomodulin) and inhibit the synthesis of others (collagen) proteins in cells is important. The mediator of the anti-inflammatory effect of GCS is most likely lipomodulin (lipocortin), the synthesis of which occurs under the influence of small concentrations of these hormones in various cell types. Lipomodulin blocks

phospholipase A2 of cell membranes and, thereby, disrupts the release of phospholipid-bound arachidonic acid, which is then converted into prostaglandins, leukotrienes and thromboxane. The latter take an active part in the inflammatory processes. Inhibition of leukotriene B4 reduces the chemotaxis of leukocytes, and leukotrienes C4 and D4 (slowly reacting substances) reduces the contractile ability of smooth muscles, vascular permeability and mucus secretion in the airways.

The decrease in cytokine production, in particular IL-1, caused by GCS, also inhibits the activity of phospholipase A2 and, to a large extent, cyclooxygenase-2 (COX-2). Currently, nitric oxide (NO) is also considered as the most important initiator of the inflammatory reaction. Glucocorticosteroids reduce the production of nitric oxide by inhibiting the activity of the enzyme NO synthetase (NOS), which has been shown in an experiment on monocytes.

Increased expression of neutral endopeptidase is important in the implementation of the anti-inflammatory effect of glucocorticosteroids in neurogenic inflammation. Neutral endopeptidase plays a role in the cleavage of tachykinins, the latter being released from sensitive nerve endings. Endopeptidases, as shown by the conducted studies, are also responsible for the degradation of bronchoconstrictor peptides, such as bradykinin, tachykinin and endothelin-1.

The antiproliferative effect of GCS is associated with:

o inhibition of nucleic acid synthesis;

o impaired differentiation of fibrocytes from fibroblasts;

o a decrease in their functional activity, which leads to inhibition of sclerosing processes in the focus of inflammation.

INFLUENCE OF GLUCOCORTICOSTEROIDS ON THE 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 to the tissues, primarily to the bone marrow and spleen. In this case, GCS 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 reactions belongs to cytokines. The key cytokine is IL-2, which is involved in the induction of immune reactions that occur after the interaction of a T-cell 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 inhibition 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 inhibit 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. At the same time, T-helpers are more sensitive to glucocorticosteroids than T-suppressors.

The inhibitory effect of GCS on B-cells is weak. 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 GCS 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, reduction of bactericidal activity of cells, inhibition of the secretion of collagenase, elastase and plasminogen activators, and impaired release of macrophage factors that cause mucus formation.

IMMUNODEPRESSIVE EFFECT OF GLUCOCORTICOSTEROIDS

Mechanisms underlying this effect:

o reduction in the number of lymphocytes in the peripheral blood (lymphopenia), due to the transition of circulating lymphocytes (mainly T-cells) to the lymphoid tissue, possibly their accumulation in the bone marrow;

o increased apoptosis of immature or activated T- and B-lymphocytes;

o inhibition of T-cell proliferation;

o reduction in the 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 reduction in the level of immunoglobulins (high doses of glucocorticoids);

o inhibition of the delayed-type hypersensitivity reaction (type IV allergic reactions), in particular the tuberculin test;

o impaired cooperation between T - and B - lymphocytes;

o impaired synthesis of immunoglobulins and antibodies, including autoantibodies;

o decreased number of monocytes in the vascular bed.

In the immune inflammatory process, as well as in the development of the stress response, the hypothalamus - pituitary - adrenal cortex system plays a significant role. Many cytokines stimulate the functional hypothalamus - pituitary - adrenal system.

INFLUENCE OF GLUCOCORTICOSTEROIDS ON TISSUE METABOLISM

The effect of GCS on carbohydrate metabolism consists in stimulating the processes of gluconeogenesis, i.e. the synthesis of glycogen from the products of protein and nitrogen metabolism. At the same time, the rate of glucose utilization by tissues is disrupted due to a decrease in its penetration into the cell. As a result, transient hyperglycemia and glucosuria may be observed in some patients. Prolonged hyperglycemia leads to depletion of the insular apparatus of the pancreas and the development of "steroid" diabetes mellitus.

The effect of GCS on protein metabolism is manifested by increased protein breakdown in most organs and tissues and, above all, in muscle tissue. The consequence of this is an increase in the content of free amino acids and products of nitrogen metabolism in blood plasma. In the future, the products of protein and nitrogen metabolism are used in the processes of gluconeogenesis. The breakdown of muscle tissue proteins causes weight loss, muscle atrophy, muscle weakness, impaired growth of cartilage and bone tissue. Inhibition 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 dystrophy, skin atrophy (striae).

Increased protein catabolism is observed when using medium therapeutic doses of GCS. The use of small doses of GCS, on the contrary, stimulates the synthesis of albumins in the liver from free amino acids in the blood plasma. This is especially important in patients with impaired protein-synthetic function of the liver.

The effect of GCS on fat metabolism is manifested in the form of their lipolytic and simultaneously lipogenetic action. The lipolytic effect is observed in the subcutaneous adipose 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 Cushingoid (moon-shaped face, pituitary-type obesity, impaired glucose tolerance, etc.). The effect of glucocorticoids 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 the rate of glomerular filtration, the excretion of sodium and water from the body. At the same time, in patients with severe heart failure, GCS can

stimulate the synthesis of aldosterone, which leads to sodium and fluid retention and the development of edematous syndrome. The breakdown of proteins in the tissues is accompanied by an increase in potassium and calcium in the blood plasma. Hypokalemia gradually develops, which contributes to the intensification of dystrophic processes in the tissues and, first of all, in the heart muscle, which can cause cardiac arrhythmias, cardialgia and lead to an increase in the severity of heart failure. GCS inhibit the absorption of calcium in the intestine, increase its excretion in the urine. As a result, the release of calcium from bone tissue increases, 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 some patients who take GCS for a long time. Calcium deficiency in bones can contribute to 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 GCS leads to an increase in the production of hydrochloric acid and pepsin in the stomach;

o the effect of GCS on endocrine organs is manifested in the suppression of the secretion of ACTH and gonadotropin in the anterior pituitary, a decrease in the function of the gonads with the development of secondary amenorrhea and infertility, suppression of the secretion of thyroid hormones;

o GCS in the CNS can increase the excitability of the cortical structures of the brain and reduce the seizure threshold. They have a euphoric effect in a number of patients, and under certain conditions cause the development of depression.

PHARMACOKINETICS OF GLUCOCORTISTERODS

When taken orally, GCS 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 15-60 mg of cortisol and 1-4 mg of corticosterone daily. 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 capacity of transcortin is small and is completely exhausted when the plasma cortisol concentration increases above 20 μg/100 ml. In this case, the drug is transported by plasma albumins (from 40 to 90% of GCS in blood plasma are in an albumin-bound state). At the same time, only the unbound (free) fraction of GCS is physiologically active, which exerts its pharmacological effect on target cells. Side effects in patients receiving corticosteroids are determined by the amount of the free fraction of GCS. 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 suppression 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 prednisolone, to 300 minutes for dexamethasone.

Interestingly, the maximum pharmacological activity of GCS occurs during 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 after about 6 hours. This gives reason to believe that the effects of GCS depend to a greater extent on their induction of enzymatic activity inside 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 - from 4 to 8 days. Normally, the level of cortisol begins to increase at 2 am with a peak at 8 am and returns to the basal level by 12 noon. Symptoms of rheumatoid arthritis (stiffness, inflammatory activity) usually decrease a few

hours after awakening at the peak of cortisol synthesis. Until recently, it was believed that taking GCS in the morning hours suppresses the synthesis of ACTH and cortisol to a lesser extent than at night and in the evening. Recently, data have appeared that a circadian increase in IL-6 levels may also be associated with an increase in arthritis activity in the morning hours. Diurnal fluctuations in IL-6 are observed in normal and in patients. Normally, the peak concentration of IL-6 occurs slightly earlier than ACTH and cortisol between 1-4 am. However, in arthritis, the peak of IL-6 is delayed and occurs between 2-7 am and the concentration of IL-6 is significantly higher than normal. Therefore, the appointment of GCS (5-7.5 mg) at night (approximately 2 am) is more preferable in terms of inhibiting IL-6 secretion and is associated with a significantly more pronounced decrease in the duration of morning stiffness and joint pain.

The different activity of GCS is also determined by the different degree of binding to plasma proteins. Thus, most of the natural cortisol is in the bound state, while only 3% of methylprednisolone and less than 0.1% of dexamethasone binds to corticosteroid-binding globulin. Liver enzymes metabolize GCS to inactive compounds, which are then excreted by the kidneys. Metabolites are excreted in the 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 is enhanced in hyperthyroidism and is induced by phenobarbital and ephedrine. Hypothyroidism, cirrhosis, concomitant treatment with erythromycin leads to a decrease in hepatic clearance of GCS. In patients with hepatocellular insufficiency and low serum albumin levels, the concentration of the free fraction of prednisolone in plasma increases, which contributes to a more rapid development of side effects.

CLASSIFICATION OF GLUCOCORTICOSTEROIDS

Depending on the duration of ACTH suppression after a single dose of GCS, they are divided into: a) short-acting GCS - suppress ACTH activity for up to 24-36 hours, b) medium-acting GCS - up to 48 hours and c) long-acting GCS - over 48 hours.

I. NATURAL - Cortisol, Cortisone (Hydrocortisone), Cortisone acetate - suppress ACTH activity for up to 24-36 hours.

II. Semi-synthetic

1. Short-acting drugs - Prednisolone, Prednisone, Methylprednisolone (Urbazone, Metipred) - suppress AGTH activity for up to 24-36 hours.

2. Medium-acting drugs - Triamcinolone (Polcortolone) - suppress ACTH for up to 48 hours.

3. Long-acting drugs - Betamethasone, Dexamethasone - suppress ACTH for more than 48 hours.

USE OF GLUCOCORTICOSTEROIDS

The classic area of therapeutic use of GCS is such general pathological processes as inflammation, allergy, sclerosis and degeneration of connective tissue derivatives. GCS are used as anti-inflammatory, antiallergic and immunosuppressive agents, as well as as replacement therapy for adrenal insufficiency.

The following options for GC therapy are distinguished:

1. Systemic:
o medium therapeutic doses
o alternating therapy
o pulse therapy
o "mini-pulse" therapy
o combined (primarily with cytostatics)
2. Local (intra-articular, inhalation, rectal administration, etc.);
3. Local (ointments, drops, aerosol).

Systemic GC therapy 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 GC, the following phases are conditionally distinguished:

o Induction: short-acting GCs (prednisolone or methylprednisolone) are used in a dose approximately corresponding to 1 mg/kg of body weight per day with an 8-hour interval.

o Consolidation: involves switching to a single dose of the entire GC dose in the morning.

o Reduction: the rate of decrease in GCS depends on the dose. It is possible to switch to alternating therapy.

o Supportive treatment: use of the minimum effective dose of drugs.

o Prevention of complications of GCS therapy: begins with the induction phase.

When conducting systemic GCS therapy, it is necessary to take into account several general principles of pharmacotherapy, compliance with which allows to increase the effectiveness and safety of treatment, as well as reduce the frequency of undesirable side effects.

GCS therapy should be started only in the presence of strict indications and as early as possible, without trying to apply initially more "milder" methods of treatment. In this case, hormonal therapy should be used together with conventional therapy, and not prescribed instead of it. Rational therapy involves the use of short-acting GCS in the optimal dose and, if possible, for the period necessary to control the activity of the process. GCS should be prescribed only under medical supervision over their use for the purpose of early detection of side effects and their correction. When prescribing hormone therapy, not only the doctor, but also the patient must be informed in detail about the possibilities and complications of this treatment method.

 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 doses of GCS in terms of prednisolone are 0.5-1 mg per kg of body weight.

 When prescribing GCS, the principle of equivalent doses should be followed in order to obtain the same anti-inflammatory effect. Equivalent doses are prednisolone - 5 mg: triamcinolone - 4 mg: methylprednisolone - 4 mg: dexamethasone - 0.5 mg; betamethasone - 0.75 mg; hydrocortisone - 25 mg. In this case, the calculation is always made for prednisolone. 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 an 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 switched to a single dose of the drug in the morning hours (consolidation phase).

 The selection of the initial dose of GCS, 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 GCS therapy, attention should be paid to the following:

- the required daily dose should be selected individually, starting with the minimum average therapeutic doses, usually recommended for this disease;

- in chronic diseases, GCS should not be prescribed in large doses and for a long course, and when remission occurs, GCS treatment should be stopped;

- in life-threatening conditions, large doses of corticosteroids should be prescribed immediately.

 In the process of hormone therapy in the peripheral blood, there is a decrease in the number of eosinophils, lymphocytes, erythrocytes, a decrease in hemoglobin levels with a

simultaneous increase in the content of leukocytes due to neutrophils (up to 12,000). Such a hemogram can be mistakenly interpreted as a continuation of the exacerbation of the process. At the same time, these changes should be considered favorable and indicate a sufficient dosage of GCS.

 The rate of reduction of the dose of corticosteroids. After achieving a clinical effect, one should be able to reduce the dose of GCS to a maintenance dose. For this, the initial dose of GCS is gradually reduced to the minimum level at which the obtained positive effect is maintained. If the daily dose of the course of treatment is within 15-40 mg/day in terms of prednisolone, then the cancellation should be carried out by 2.5-5 mg every 5-7 days until the physiological dose is reached. When prescribing GCS in doses of 40 mg and more, the dose reduction may occur more quickly (5 mg and even in some cases 10 mg per week) to the level of 40 mg, and then as indicated above. In these cases, the rate of reduction in the dose of corticosteroids is determined by the duration of their use. The shorter the duration of the course of treatment, the faster the withdrawal of corticosteroids is possible. However, the lower the dose of GCS, the longer the periods between successive reductions in the dose of the drug should be. This tactic allows you to create conditions for restoring the functional capabilities of the hypothalamic-pituitary-adrenal system already during drug withdrawal.

 In case of relapse of the disease, hormone therapy is resumed. The dose of GCS is increased to that at which the patient had stabilization of the process. In the future, the cancellation should be carried out more carefully and gradually. Determination of the duration of therapy and the rate of dose reduction should be carried out not 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 GCS therapy: stabilization of ESR within 7 days, reduction in the level of C-reactive protein, fibrinogen.

 Cancellation of glucocorticosteroids. Problems associated with the cancellation of glucocorticosteroids arise after a long course of therapy. In this case, a more abrupt withdrawal of drugs threatens the development of complications of two types. First, these are manifestations of adrenal insufficiency associated with suppression of the hypothalamic-pituitary-adrenal system. Secondly, this is a relapse of the inflammatory process underlying 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 prednisolone in the range of 10-15 mg gives a full replacement effect and is considered physiological. In this regard, the cessation of the drug to a physiological dose can be carried out quite quickly. Further reduction of the dose of corticosteroids should be much slower.

 During treatment, it must be remembered that suppression of the hypothalamic-pituitary-adrenal axis persists in patients who have received even small doses of corticosteroids (more than 10 mg/day for three or more weeks) for a long time (up to 1 year) after drug withdrawal.

 Rapid drug withdrawal (within 1-2 days) is extremely rare, only in the case of acute steroid psychosis, or with generalization of herpesvirus infection.

 In cases where it is not possible to completely avoid glucocorticosteroid therapy, patients should be transferred to maintenance doses of hormones, individual for each patient and corresponding, as a rule, to replacement doses at the rate of 5-15 mg of prednisolone per day. Hormones should be taken in the morning hours (from 6 to 9 am) taking into account the natural biorhythm of their secretion.

 There is evidence of the absence of significant suppression of the hypothalamic-pituitary-adrenal axis if the dose of prednisolone does not exceed 10 mg per day. Against the background of GCS treatment, the occurrence of adverse reactions is significantly more

common in patients who received more than 10 mg of prednisolone per day. The risk of side effects is lower when the total dose of prednisolone is reduced and the drug is taken at a certain time. At the same time, treatment with low doses of GCS can reduce the potential risk of osteoporosis due to inhibition of IL-6 synthesis.

 In order to reduce the dose of GCS, it is recommended to combine them with NSAIDs, basic therapy. However, the likelihood of developing ulcerative lesions of the gastrointestinal tract increases. To stimulate the production of own hormones, in some cases, ACTH (corticotropin) may be prescribed against the background of gradual withdrawal of corticosteroids.

 When using GCS as replacement therapy for primary adrenal insufficiency (Addison's disease), simultaneous administration of glucocorticosteroids and mineralocorticosteroids is indicated. Cortisone acetate or hydrocortisone in combination with deoxycorticosterone acetate or fludrocortisone are recommended as GCS.

In secondary adrenal insufficiency, in most cases, the use of one GCS is possible. In adrenogenital syndrome, patients should receive maintenance doses of corticosteroids 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 in doses 5-10 mg higher than those that patients take constantly.

MAIN INDICATIONS FOR THE PRESCRIPTION OF GLUCOCORTICOSTEROIDS

1. Rheumatic diseases:

- rheumatic fever of 2-3 stages. activity in the presence of rheumatic carditis, especially in combination with polyarthritis and polyserositis - medium therapeutic doses;

- systemic lupus erythematosus during the period of exacerbation (pulse therapy), in chronic forms - medium therapeutic doses of corticosteroids or as maintenance therapy;

- systemic dermatomyositis during the period of exacerbation - pulse therapy of corticosteroids or as maintenance therapy;

- nodular periarteritis during the period of exacerbation - pulse therapy of corticosteroids or as maintenance therapy;

- rheumatoid arthritis in combination with visceritis (febrile syndrome, carditis, nephritis, serositis); in rapidly progressive articular forms of rheumatoid arthritis and high titer of rheumatoid factor - pulse therapy, then, often, maintenance therapy; in case of ineffectiveness of previous NSAID therapy and basic therapy - medium therapeutic doses of GCS, in case of monoarthritis - intraarticular administration of GCS;

- juvenile rheumatoid arthritis.

2. Systemic vasculitis - systemic GCS therapy.

3. Carditis (infectious-allergic myocarditis, Abramov-Fidler myocarditis, subacute septic endocarditis - immunological phase) - systemic GCS therapy.

4. Diseases of the musculoskeletal system:

- post-traumatic osteoarthritis - for short-term use in the acute period or for intra-articular administration;

- ankylosing spondylitis (Bechterew's disease);

- subacute gouty arthritis - for short-term use in the acute period or for intra-articular administration;

- acute and subacute bursitis;

- acute nonspecific tendosynovitis;

- psoriatic arthritis.

5. Kidney disease (chronic nephritis with nephrotic syndrome - the appointment of GCS is most indicated in membranous and membranous-proliferative variants; in lupus nephritis) - systemic GCS therapy.

6. Gastrointestinal tract disease (nonspecific ulcerative colitis, Crohn's disease) -

systemic GCS therapy.

7. Liver disease (autoimmune hepatitis) - systemic GCS therapy.

8. Diseases of the bronchopulmonary system (obstructive bronchitis, allergic bronchial asthma, sarcoidosis - systemic therapy and inhaled corticosteroids).

9. Hematological diseases: acquired (autoimmune) hemolytic anemia, thrombocytopenic purpura - systemic therapy with corticosteroids.

10. Allergic conditions: treatment of allergic conditions in case of ineffectiveness of conventional means: seasonal or chronic allergic rhinitis, nasal polyps, bronchial asthma (including asthmatic status), contact dermatitis, atopic dermatitis (neurodermatitis), hypersensitivity to drugs and serum sickness (anaphylactic shock, Quincke's edema, Lyell's syndrome, Stevens-Johnson, drug or food agranulocytosis, thrombocytopenia, giant urticaria).

11. Eye diseases: severe acute and chronic allergic reactions and inflammatory processes in the eyes and adjacent structures, such as allergic conjunctivitis, keratitis, corneal herpes, iritis and iridocyclitis, chorioretinitis, anterior segment inflammation, retrobulbar neuritis.

12. Skin diseases: eczema (chronic dermatoses), in the treatment of keloids and localized hypertrophic infiltrative inflammations, lichen planus, psoriasis, granuloma annulare, lichen simplex chronicus (neurodermatitis), discoid lupus erythematosus, diabetic lipoid necrobiosis, alopecia areata, psoriasis, erythema nodosum and others - local therapy with corticosteroids.

13. Tumor diseases: palliative treatment of leukemias and lymphomas in adults, acute childhood leukemia.

14. Endocrine disorders: primary or secondary adrenal insufficiency, acute adrenal insufficiency, bilateral adrenectomy, congenital adrenal hyperplasia, acute thyroiditis and thyrotoxic crisis, hypercalcemia associated with cancer.

15. Shock states: hemodynamic, traumatic, endotoxic, cardiogenic (infarction).

16. Cerebral edema (increased intracranial pressure) - GCS are necessary as adjuncts to reduce the intensity or prevent cerebral edema associated with surgical or other brain trauma, strokes, primary or metastatic malignant brain tumors.

17. Prevention of renal transplant rejection. The drugs are used in combination with commonly used immunosuppressants.

Indications for the use of intranasal glucocorticoids:

- seasonal (intermittent) allergic rhinitis;
- persistent allergic rhinitis;
- nasal polyposis;
- non-allergic rhinitis with eosinophilia;
- idiopathic (vasomotor) rhinitis.
- inhaled glucocorticoids 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, gastric or duodenal ulcer, thromboembolism, arterial hypertension, severe renal failure, mental illnesses with productive symptoms, systemic mycoses, herpes infection, tuberculosis (active form), syphilis, vaccination period, purulent infections, viral or fungal eye diseases, corneal diseases combined with epithelial defects, glaucoma, lactation period.

Intranasal administration of glucocorticoids is contraindicated in the following cases: hypersensitivity, hemorrhagic diathesis, repeated nosebleeds in history, side effects.

The term "pulse therapy" refers to rapid (within 30-60 min) intravenous administration of large doses of GC (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 it to be considered as the means of choice when conducting pulse therapy. The level of MP in plasma during intravenous administration reaches a maximum within 1 h and rapidly decreases over the next 6-7 hours. After 4 days, only trace amounts of active MP are detected in the peripheral blood, but it actively accumulates in various tissues, especially in erythrocytes, the brain, and some visceral organs. Pulse therapy is accompanied by adrenal suppression, but their function is restored within approximately 4 weeks.

Indications for pulse therapy:

• SLE (fever, arthritis, serositis, myositis, hematological disorders, CNS lesions), with lupus nephritis in combination with cytostatics (cyclophosphamide).

• Systemic vasculitis (except giant cell arteritis) in combination with cytostatics.

• Polymyositis/Dermatomyositis (in case of life-threatening complications).

• RA (rheumatoid vasculitis in combination with cytostatics).

The assumption that the anti-inflammatory effect of GCS lasts longer than the undesirable metabolic effects has led to the emergence of alternating GCS therapy - a treatment method in which short-acting GCS without pronounced mineralocorticoid activity are administered once in the morning every 48 hours. At the same time, therapeutic efficacy is maintained, but the severity of side effects is reduced. The positive properties of alternating therapy are manifested only with long-term treatment of GCS. It is not used with short-term administration of GCS, as well as in the initial stage of treatment or during the period of 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 GCS therapy: RA (in adults or juvenile), microcrystalline arthropathies (gout and pseudogout), arthritis in diffuse connective tissue diseases, seronegative spondyloarthropathies, osteoarthritis, synovitis of the knee joint, other diseases that occur with inflammation of the joints, periarthritis of the shoulder joint (adhesive capsulitis, frozen shoulder).

For intra-articular administration of GCs, short- and long-acting preparations are used. The question of the need for repeated injections of GCS should be decided individually. Unreasonable frequent administration can lead to GCS dependence, to the progression of secondary osteoarthritis. If after 1-2 injections there is no clinical improvement or it is expressed to a minimal degree, then further local GCS therapy is inappropriate. To increase the effectiveness of local therapy, provide rest to the joints into which GCS was injected for a period of at least 48-72 hours.

SYSTEMIC SIDE EFFECTS OF GLUCOCORTICOSTEROIDS:

From the central nervous system: increased nervous excitability, insomnia, euphoria, depression, psychosis.

From the cardiovascular system: myocardial dystrophy, increased blood pressure, deep vein thrombosis, thromboembolism.

From the digestive system: steroid ulcers of the stomach and intestines, gastrointestinal bleeding, pancreatitis, fatty liver.

From the sensory organs: posterior subcapsular cataract, glaucoma.

From the endocrine system: suppression of function and atrophy of the adrenal cortex, diabetes mellitus, obesity, Cushing's syndrome.

From 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.

Reproductive system: menstrual cycle disorders, sexual dysfunction, delayed sexual development, hirsutism.

Laboratory parameters: hypokalemia, hyperglycemia, hyperlipidemia, hypercholesterolemia, neutrophilic leukocytosis.

Others: sodium and water retention, edema, exacerbation of chronic infectious and inflammatory processes.

Local side effects of inhaled glucocorticosteroids: candidiasis of the mouth and pharynx, dystonia, cough.

Intranasal corticosteroids: nasal itching, sneezing, dryness and burning of the nasal and pharynx mucosa, epistaxis, perforation of the nasal septum.

Hypothalamic-pituitary-adrenal axis (HPA) suppression

HPA suppression is one of the most dangerous consequences of steroid use. The ability to respond to global physiological stress (e.g., surgery or trauma) may be impaired, placing the patient at risk for hypotension and hypoglycemia. Signs include behavioral disturbances, nausea, postural hypotension, and hypoglycemia. The risk is related to the dosage, duration, and regimen of therapy, although other factors may also be important. There is considerable individual variation in the effects of steroid therapy. Some patients have had HPA axis suppression with 15 milligrams of prednisolone taken daily for several weeks, while others have shown no evidence of HPA axis suppression despite higher daily doses for longer periods. Thus, it is difficult to predict the risk of HPA axis suppression in an individual patient based solely on dosage and duration of therapy. Dose scheduling influences the degree of HPA axis suppression. Physiological doses of corticosteroids (5-7.5 mg prednisolone) taken in the morning do not cause HPA axis suppression, but when the same doses are given at night, normal daytime cortisol secretion is suppressed. Doses above physiologic levels begin to have a predominant effect after about a month. Alternate-day therapy (a two-day dose taken at 8 a.m. every other day) does not produce clinically significant HPA axis suppression. Cyclic 5-day regimens of daytime therapy lasting 2 to 4 weeks also do not produce HPA axis suppression. However, a 2-week cycle of therapy followed by a 2-week rest period does produce HPA axis suppression. A daily pharmacologic dose of glucocorticoids taken in the morning produces less HPA axis suppression than the same dose divided and taken throughout the day. HPA axis recovery may occur within 12 months. Hypothalamic-pituitary function returns first 2-5 months after cessation of therapy, as evidenced by the appearance of normal plasma levels of adrenocorticotropic hormone (ACTH). Signs of adrenal recovery will begin to appear after 6-9 months, with the return of normal cortisol levels. The maximum adrenal response to ACTH may not occur until 9-12 months after cessation of therapy. There is no proven method for accelerating the return of normal HPA function. Increasing ACTH levels does not appear to accelerate adrenal recovery. It is very difficult to estimate how long a clinically important lack of adrenal response will last. Because of the considerable individual variability in patients, it has not been possible to establish a reliable correlation between the degree of HPA suppression and blood cortisol concentrations. To address this uncertainty, HPA axis testing becomes an important tool for decision-making. Of the various tests (insulin-induced hypoglycemia, etc.), the ACTH test is the most widely used, as its results correlate well with cortisol levels measured during stress after surgery. Cortisol concentrations are determined, and then one ampoule (250 mg) of synthetic ACTH (cosyntropin) is administered intravenously. Cortisol concentrations are measured in blood samples taken 30 and 60 minutes later. Although this test has a certain percentage of false positives, many consider it to be much more convenient and safer than insulin-induced hypoglycemia, the test considered the "gold standard" for HPA testing.

Precautions

In patients with hypothyroidism, cirrhosis of the liver, hypoalbuminemia, as well as in elderly and senile 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 in the fetus (in the third trimester of pregnancy).

Infectious diseases such as measles, chickenpox may be severe in children and adults taking glucocorticoids. The administration of live vaccines is contraindicated in patients taking immunosuppressive doses of corticosteroids.

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 on the background of treatment with glucocorticosteroids can be asymptomatic or asymptomatic, manifesting as bleeding and perforation. Therefore, patients who receive oral glucocorticosteroids for a long time should periodically undergo fibroesophagogastroduodenoscopy and stool analysis for occult blood.

In various inflammatory or autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus and intestinal diseases), cases of steroid resistance may be observed.

Interaction

With the simultaneous use of glucocorticosteroids with other drugs, the following effects may be observed:

• With antacids - reduced absorption of glucocorticosteroids.

• With barbiturates, 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 - 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 ethacrynic acid - hemorrhagic complications.

• With indomethacin and salicylates - ulcerative lesions of the digestive tract.

• With paracetamol - increased toxicity of this drug.

• With azathioprine - increased risk of myopathy, cataracts.

• With mercaptopurine - possible increase in uric acid concentration in the blood.

• With hingamine - possible increase in undesirable effects of this drug (dermatitis, myopathy, corneal opacity).

• With methandrostenolone - increased therapeutic and undesirable effects of glucocorticosteroids.

• With androgens and iron preparations - increased erythropoiesis due to increased synthesis of erythropoietin.

• With hypoglycemic drugs - reduced effectiveness of these drugs.

Inhaled glucocorticoids and long-acting β-2-adrenomimetics have complementary effects and synergism. Theophylline can enhance the anti-inflammatory activity of inhaled glucocorticosteroids.

Principles of therapy

When using corticosteroids, it is necessary to obtain maximum therapeutic benefit with a minimum of adverse effects. In most cases, steroids do not cure the disease, but rather suppress or modify the inflammatory and immune response and reduce the signs of the disease. Therefore, it is necessary to carefully weigh the expected therapeutic benefit and

potential risks. The risk is insignificant with short-term treatment (7-14 days), even with the use of high doses, which can be very effective in some situations (for example, in 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 consideration of the risks described above.

Choice of drug. Corticosteroids differ mainly in duration and degree of action. Rapid-acting agents are less likely to lead to HPA axis suppression, especially when used in the morning with a low dose as part of an every-other-day regimen. Slow-acting agents are preferred for situations where large doses must be used. Mineralocorticoid activity is desirable in adrenal insufficiency but not in significant inflammation or immunoreactivity. Regardless of the agent chosen, nonsteroidal therapy should be continued if minimal doses of corticosteroids are allowed.

Prednisolone is the most widely used of the glucocorticosteroids. Its short half-life and low cost make it the most useful agent for immunosuppressive and anti-inflammatory effects. Prednisolone is the active hepatic metabolite of prednisone and is used in cases of liver problems. Dexamethasone is about seven times more potent than prednisone and has a half-life of 24 hours. This makes it useful for testing the HPA axis. Hydrocortisone (cortisone), a drug about four times less potent than prednisone, is used primarily in pharmacological doses as adjunctive therapy in patients with HPA suppression. Theoretically, the use of ACTH would seem attractive because it would help to avoid HPA axis suppression, but ACTH also stimulates an undesired mineralocorticoid and androgenic response. In addition, it is not known what glucocorticoid response will be obtained from the administered dose. These inconveniences limit the use of ACTH.

Choice of regimen: daily or every other day

In the treatment of most diseases requiring corticosteroid therapy (asthma, sarcoidosis, etc.), the every other day regimen has been used successfully, although often the therapy must be daily initially. The important advantages of the every other day regimen are the prevention of significant HPA axis suppression and the minimization of the risk of Cushingoid without a significant loss of anti-inflammatory activity. The risk of most of the side effects mentioned above is reduced or completely eliminated with the use of the every other day regimen.

The every other day regimen alone cannot prevent HPA axis suppression if, for example, dexamethasone is used for therapy. In addition, the therapy regimen must be strictly adhered to. Failure to adhere to the dosing schedule or to vary the dose on the first day does not prevent HPA suppression.

Daily therapy is used for exacerbations of the disease and for the treatment of some diseases that can only be controlled with a daily regimen (e.g., temporal arteritis, pemphigus vulgaris). In cases where the use of a daily regimen is unavoidable, HPA suppression can be minimized if the full daily dose is taken at once in the morning, in the lowest possible dose. A daily regimen with a single dose is almost as effective as a regimen with divided doses. However, unlike the every-other-day regimen, the risk of developing Cushing's syndrome is greater.

Switching from a daily to an every-other-day regimen

Most patients who have a positive dynamic with daily therapy are candidates for switching to an every-other-day regimen. This allows for a transition to a less painful regimen without loss of control of the disease. Unlike a dose reduction, the total dose taken does not change. The transition is made by gradually increasing the dose on the first day and decreasing the dose on the second day, until a double dose is taken every other day, with no additional drugs on the intervening day. The speed of the 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 is to increase the dose on the first day and reduce the dose on 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 changes ranges from 1 day to several weeks and is determined empirically based on the patient's clinical response. It is important to keep in mind that most patients who have taken GCS on a daily regimen for more than 2-4 weeks have HPA suppression.

Dosage reduction and discontinuation

Abrupt discontinuation of corticosteroid therapy for more than one month at a dose of more than 20-30 milligrams of prednisone per day may result in a sudden exacerbation of the underlying disease or lead to withdrawal syndrome. There are no proven methods to accelerate HPA recovery. Disease manifestations should be monitored and dosage reduction should be empirically determined, observing for sudden exacerbation of the disease or signs of adrenal insufficiency (postural hypotension, weakness, and gastrointestinal disturbances).

An empirical approach to reducing dosage to physiologic levels is to make adjustments in increments of 10 milligrams of prednisone or its equivalent every 1-3 weeks if the initial dose was more than 40 milligrams per day. If the dosage was less than 40 milligrams, in increments of 5 milligrams. Once a physiologic dose of prednisone (5-7.5 mg) is reached, the patient can be switched to 1-milligram prednisone tablets or an equivalent dose of hydrocortisone so that further dosage reductions can be made in smaller increments. Subsequent weekly or biweekly reductions can then be made in 1-milligram increments.

During the tapering process, some patients develop a withdrawal syndrome characterized by depression, myalgia, arthralgia, anorexia, headaches, and nausea. Studies have failed to establish a relationship between these signs and cortisol or 17-hydroxycorticosteroid levels. In most cases, the 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 appear to be related to the rate at which the dosage is tapered.

Identification of Adrenal Insufficiency Induced by Steroid Therapy

When anticipating stress (including surgery), it is important to know the status of the HPA axis and whether additional steroid therapy will be required. As previously noted, the onset and duration of HPA suppression is very difficult to predict, making HPA axis testing useful in deciding whether a patient will require additional steroid therapy. In this case, a test using cosyntropin (synthetic ACTH) is a convenient, safe, and effective way to test the HPA axis. If the cortisol concentration at 60 minutes is greater than 18 mug/dL or there is an increase from baseline of at least 10 mug/dL, then the adrenal response is sufficient to allow the patient to 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 therapy should be given to overcome the acute stress. Hydrocortisone is commonly used. Depending on the severity of the stress, 100 to 400 milligrams of hydrocortisone per day in divided doses is used. The lower end of the dose range (100 milligrams) corresponds to stress from gastrointestinal upset, influenza, or tooth extraction. In cases of severe stress (trauma or surgery), the patient should be given 100 milligrams of hydrocortisone parenterally every 6 to 8 hours. A pre-prepared syringe containing 4 milligrams of dexamethasone should be used for parenteral use in the critical condition 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 status or intelligence may be affected because of the risk of HPA axis suppression. Patients taking corticosteroids on an alternate-day schedule should be instructed on the importance of adhering to the schedule and taking the drug before 8 a.m. to minimize the risk of HPA suppression. Patients should be informed of the need to increase the dosage if there is stress or illness throughout the course of corticosteroid therapy. Patients should understand the need to contact their physician and increase the dosage if they are exposed to physical or psychological stress. Many patients are

afraid to stop steroid therapy or refuse to reduce the dose of steroids for fear of relapse of the underlying disease. A detailed review of the side effects of long-term therapy should be conducted to explain the need for dose reduction and the desirability of ultimately stopping corticosteroids. In cases where daily therapy with high doses is required, adverse psychiatric effects (including Cushing's syndrome) can be reduced by informing the patient of their likelihood and reversibility.

Basic, slow-acting anti-inflammatory drugs: methotrexate, sulfasalazine, chloroquine, auronofin.

Methotrexate, concentrate for injection, lyophilisate for injection, injection solution, tablets, film-coated tablets - antineoplastic agent - antimetabolite.

Mechanism of action. An antitumor, cytostatic agent of the antimetabolite group, inhibits dihydrofolate reductase, which is involved in the reduction of dihydrofolic acid to tetrahydrofolic acid (a carrier of carbon fragments necessary for the synthesis of purine nucleotides and their derivatives).

Inhibits DNA synthesis, repair and cell mitosis. Rapidly proliferating tissues are especially sensitive to the action: malignant tumor cells, bone marrow, embryonic cells, epithelial cells of the intestinal mucosa, urinary bladder, and oral cavity. Along with the antitumor effect, it has an immunosuppressive effect.

Pharmacokinetics. Absorption when taken orally depends on the dose: when taken at 30 mg/sq m, it is well absorbed, the average bioavailability is 60%. Absorption decreases when taken in doses exceeding 80 mg/sq m (it is believed that this is due to saturation).

In children with leukemia, absorption ranges from 23 to 95%. TCmax is 40 min-4 g when taken orally and 30-60 min - when administered intramuscularly. Food slows down absorption and reduces Cmax. Binding to plasma proteins is about 50%, mainly to albumin. The volume of distribution is 0.18 l/kg.

When administered in therapeutic doses, regardless of the route of administration, it practically does not penetrate the blood-brain barrier (high concentrations are achieved in the cerebrospinal fluid after intrathecal administration). Penetrates into breast milk. After oral administration, it is partially metabolized by the intestinal flora, the main part in the liver (regardless of the route of administration) with the formation of a pharmacologically active polyglutamine form, which also inhibits dihydrofolate reductase and thymidine synthesis.

T1/2 in patients receiving less than 30 mg/m2 of the drug in the initial phase is 2-4 g, and in the final phase (which is long) - 3-10 h when using small and 8-15 g - when using large doses of the drug. In chronic renal failure, both phases of drug excretion can be significantly longer.

It is excreted mainly by the kidneys in unchanged form by glomerular filtration and tubular secretion (with intravenous administration 80-90% is excreted within 24 hours), with bile up to 10% is excreted (with subsequent reabsorption in the intestine). The excretion of the drug in patients with impaired renal function, pronounced ascites or transudate is significantly slowed down. With repeated administration, it accumulates in the tissues in the form of polyglutamate.

Indications. Breast cancer, epidermoid carcinoma of the head and neck, lung cancer (small cell and non-small cell), trophoblastic tumors (chorionepithelioma of the uterus, cystic fibrosis), cervical cancer, ovarian cancer, bladder cancer, colorectal cancer, esophageal cancer, gastric cancer, pancreatic cancer, testicular cancer, acute lymphoblastic leukemia, leukemic infiltration of the meninges (prevention and treatment), acute myeloblastic leukemia, non-Hodgkin lymphomas (primarily lymphosarcoma, especially in children, and Burkitt lymphoma), lymphogranulomatosis, mycosis fungoides, non-metastatic osteosarcoma, soft tissue sarcoma, meningeal cancer.

Severe forms of psoriasis, psoriatic arthritis, rheumatoid arthritis, dermatomyositis, SLE, ankylosing spondylitis.

Contraindications. Hypersensitivity, immunodeficiency, pregnancy, lactation.

In the treatment of psoriasis and rheumatic diseases (additionally): severe suppression of bone marrow hematopoiesis, severe hepatic/renal failure.

With caution. Ascites, dehydration, obstructive diseases of the gastrointestinal tract, pleural or peritoneal effusion, chronic renal failure, parasitic and infectious diseases of a viral, fungal or bacterial nature - the risk of developing a severe generalized disease (currently or recently transferred, including recent contact with a patient) - herpes simplex, herpes zoster (viremic phase), chickenpox, measles; amebiasis, strongyloidiasis (established or suspected); gout (including a history) or urate nephrourolithiasis (including a history), infections and inflammation of the oral mucosa, vomiting, diarrhea (fluid loss due to severe vomiting and diarrhea may lead to increased toxicity of methotrexate), gastric ulcer and duodenal ulcer, ulcerative colitis preceding chemotherapy or radiation therapy, asthenia.

Dosage. Inside, in/m, in/in, in/a or intrathecally (the drug with a preservative containing benzyl alcohol is prohibited for intrathecal administration and high-dose therapy).

Tablets are taken orally before meals, without chewing. Doses and treatment periods are set individually depending on the chemotherapy regimen, indications, treatment regimen, patient "response" and tolerability, are calculated based on body surface area or body weight.

Doses above 100 mg/sq m are administered only intravenously drip (the solution or concentrate is previously diluted with 5% glucose solution (10 mg - 0.5-1 l of glucose solution) and under the cover of calcium folinate.

In rheumatoid arthritis: the initial dose is usually 7.5 mg once a week in one go or 2.5 mg every 12 hours (3 times a week in total). To achieve the optimal effect, the weekly dose can be increased (not more than 20 mg), then the dose should be reduced to the lowest effective dose.

In psoriasis, the initial doses are orally, intramuscularly or intravenously, 7.5-25 mg/week, once, or 2.5 mg at intervals of 12 hours 3 times a week until an adequate effect is achieved, but not more than 30 mg/week. The dose is usually increased gradually, when the optimal effect is achieved effect, the dose is reduced to the lowest effective dose.

Side effects. From the side of the blood-forming 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-ulcerative lesions and bleeding from the gastrointestinal tract (including melena, hematemesis), hepatotoxicity (acute hepatitis, fibrosis and cirrhosis of the liver, liver failure, hypoalbuminemia, increased activity of "hepatic" transaminases), pancreatitis.

From the side of the nervous system: headache, drowsiness, dysarthria, aphasia, hemiparesis, paresis, convulsions; with when used in high doses - transient cognitive impairment, emotional lability; unusual cranial sensitivity, encephalopathy (including leukoencephalopathy).

From the skin: erythematous rash, skin itching, urticaria, photosensitivity, skin pigmentation disorders, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme (including Stevens-Johnson syndrome), toxic epidermal necrolysis.

From the respiratory system: rarely - pulmonary fibrosis, respiratory failure, alveolitis, interstitial pneumonitis (including fatal), COPD.

From the cardiovascular system: pericarditis, pericardial effusion, decreased blood pressure, thromboembolism (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, pulmonary embolism).

From the genitourinary system: severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria, impaired spermatogenesis and oogenesis, transient oligospermia, decreased libido, impotence, dysmenorrhea, vaginal discharge, gynecomastia, infertility, miscarriage, fetal death, fetal developmental defects.

From the musculoskeletal system: arthralgia, myalgia, osteoporosis, 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).

Others: vasculitis, diabetes mellitus, lymphoma, anaphylactic reactions.

In the treatment of rheumatoid arthritis: more than 10% - increased activity of "liver" transaminases, nausea, vomiting; 3-10% - stomatitis, thrombocytopenia; 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, joint pain, chest pain, cough, dysuria, eye discomfort, nosebleeds, fever, increased sweating, ringing in the ears, 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 dysfunction (11%), including nausea, vomiting, diarrhea, stomatitis (2%), leukopenia (2%), headache (1.2%), alopecia (0.5%), dizziness (0.2%), skin rash (0.2%).

Overdose. Treatment: administration of a specific antidote - calcium folinate, if possible immediately, preferably within the first hour, in a dose equal to or exceeding the dose of methotrexate; subsequent doses are administered as needed, depending on the concentration of this drug in the blood serum. To prevent precipitation of methotrexate and/or its metabolites in the renal tubules, hydration of the body and alkalinization of urine are carried out, which accelerates the excretion of methotrexate.

Interaction. Increases the anticoagulant activity of coumarin or indandione derivatives and/or increases the risk of bleeding by reducing the synthesis of 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, there may be a need to adjust the dose of antigout drugs (allopurinol, colchicine, sulfinpyrazone); The use of uricosuric antigout drugs may increase the risk of nephropathy associated with increased uric acid formation against the background of methotrexate treatment (allopurinol is preferable).

Simultaneous administration of salicylates, phenylbutazone, phenytoin, sulfonamides, sulfonylurea derivatives, aminobenzoic acid, pyrimethamine or trimethoprim, a number of antibiotics (penicillin, tetracycline, chloramphenicol), indirect anticoagulants and hypolipidemic drugs (cholestyramine) increases toxicity due to displacement of methotrexate from albumin binding and/or a decrease in tubular secretion, which in some cases may lead to the development of severe toxic effects, sometimes even fatal.

NSAIDs in combination with 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 for 7-12 days, piroxicam for 10 days, diflunisal and indomethacin for 24-48 hours, ketoprofen and NSAIDs with a short T1/2 for 12-24 hours before the infusion of methotrexate in moderate and high doses and for at least 12 hours (depending on the concentration of this drug in the blood) after its end. Caution should be exercised when combining NSAIDs with low doses of methotrexate (possible reduction in 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 gastrointestinal tract (tetracycline, 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 developing hepatotoxicity.

Folate-containing drugs (including multivitamins) reduce the toxic effect of methotrexate on the bone marrow.

L-asparaginase reduces the severity of the antitumor effect of methotrexate by inhibiting cell replication.

Acyclovir for parenteral use against the background of intrathecal administration of methotrexate increases the risk of developing neurological disorders.

Hematotoxic drugs increase the risk of developing hematotoxicity of methotrexate.

Combination with radiation therapy may increase the risk of bone marrow suppression.

Methotrexate may reduce the immune response to vaccination, so the interval between administration of live and inactivated viral vaccines varies from 3 to 12 months.

Auronofin

Pharmacological action. Gold preparation for oral administration (contains 29% Au), has anti-inflammatory effect. The mechanism of action is not fully understood: it is believed that the suppression of cellular immunity is due to the absorption of Au3 + by monocytes and polymorphonuclear leukocytes, which leads to inhibition of phagocytosis and blockade of lysosomal enzymes. Reduces the activity of sulfhydryl systems and enzyme complexes of leukocytes and lymphocytes, which leads to a decrease in the concentrations of Ig and rheumatoid factor, inhibits the synthesis of collagen and prostaglandins.

The therapeutic effect develops gradually and is noted after 3-4 months (sometimes 6 months) from the moment of taking the drug.

Pharmacokinetics. Absorption after oral administration - 25%. Binding to plasma proteins - 60%. Css is noted 3 months after the start of treatment, at a dose of 6 mg/day is 68 μg/ml.

Rapidly metabolized in the liver (unchanged auranofin is practically not detected in the blood). T1/2 in the blood - 21-31 days, in tissues - 42-128 per day. Excreted by the kidneys (60%) and with bile.

Indications. Rheumatoid arthritis (treatment and prevention in the detection of early radiological changes in the joints), psoriatic arthritis, Felty's syndrome.

Contraindications. Hypersensitivity, CHF, chronic renal failure, hepatitis (active phase), suppression 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 treatment is ineffective for 4 months and is well tolerated, the dose may be increased to 9 mg/day in 3 divided doses for adults, to 0.2 mg/kg/day for children. If the treatment is ineffective for the next 3 months, the drug is discontinued.

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 and constipation, stomach pain, gastritis, necrotizing enteritis, 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, skin itching, eosinophilia, dermatitis, hyperthermia.

Interaction. Incompatible with penicillins, levamisole, chloroquine; compatible with nonsteroidal anti-inflammatory drugs. Side effects are enhanced by cytostatics, hepato- and nephrotoxic drugs, penicillamine.

Special instructions. Before and during therapy, it is necessary to monitor the peripheral blood picture (Hb content, platelet count), kidney function (urea, creatinine concentration, protein content in the urine), liver function (activity of "liver" transaminases) during the first year of treatment - monthly, the second - every 2-3 months. In case of proteinuria more than 1 g/day, therapy should be discontinued.

Sulfasalazine, enteric-coated tablets.

Pharmacological group - antimicrobial and anti-inflammatory intestinal agent.

Pharmacological action. Antimicrobial intestinal agent, sulfonamide, also has anti-inflammatory effect. The possibility of use in the treatment of nonspecific colitis 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.

Acts on diplococci, streptococci, gonococci, Escherichia coli.

Pharmacokinetics. Absorption - 10%, undergoes cleavage by intestinal microflora with the formation of sulfapyridine - 60-80 and 25% 5-ASA. The connection with plasma proteins of sulfasalazine - 99%, sulfapyridine - 50%, 5-ASA - 43%.

Sulfapyridine is metabolized in the liver by hydroxylation with the formation of inactive metabolites, 5-ASA - by acetylation. T1/2 sulfasalazine - 5-10 hours, sulfapyridine - 6-14 hours, 5-ASA - 0.6-1.4 hours. Excreted through the intestines - 5% of sulfapyridine and 67% of 5-ASA, by the kidneys - 75-91%.

Indications. Nonspecific ulcerative colitis.

Contraindications. Hypersensitivity, hepatic and/or renal failure, anemia, porphyria, congenital deficiency of glucose-6-phosphate dehydrogenase; lactation period, children's age (up to 5 years).

Dosage. Inside, 1 g 4-6 times a day, for 2-3 weeks, with a subsequent reduction in the 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, over 7 years old - 0.5 g 3-6 times a day.

Side effect. Headache, dizziness, dyspepsia: nausea, vomiting, diarrhea, abdominal pain, decreased appetite; blood impurities in feces, interstitial pneumonitis, drug-induced hepatitis, photosensitization, urine coloration in orange-yellow color, agranulocytosis, leukopenia, thrombocytopenia, hemolytic anemia, allergic reactions: toxic epidermal necrolysis (Lyell's syndrome), malignant exudative erythema (Stevens-Johnson syndrome), 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 suppress bone marrow hematopoiesis increase the risk of myelosuppression.

Chloroquine (delagil), tablets. Pharmacological group - antimalarials.

Pharmacological action. Antiprotozoal agents, also has immunosuppressive and anti-inflammatory effects. Causes the death of asexual erythrocytic forms of all types of plasmodia. Has a gametocidal effect, except for Plasmodium falciparum. Due to inhibition of nucleic acid synthesis, it has a moderately pronounced immunosuppressive and nonspecific anti-inflammatory effect.

Pharmacokinetics. After oral administration, it is rapidly and almost completely absorbed from the gastrointestinal tract. Cmax is achieved after 2-6 hours. 55% binds to plasma albumin. Rapidly distributed throughout the organs and tissues of the body (liver, kidneys, spleen, lungs). Easily penetrates the blood-brain barrier and placenta.

Metabolized in small quantities (25%). Excreted by the kidneys (70% - in unchanged form) slowly. T1/2 - 1-2 months.

In renal failure, it may accumulate. With an acidic urine reaction, the elimination rate increases, with an alkaline reaction - it increases.

Indications. Malaria (prevention and treatment of all types), extraintestinal amebiasis, amoebic liver abscess, SLE (chronic and subacute forms), rheumatoid arthritis, scleroderma,

photodermatosis, porphyria cutanea tarda.

Contraindications. Hypersensitivity, hepatic and/or renal failure, suppression 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. Malaria treatment is carried out according to the following scheme: 1 day once 1 g, after 6-8 hours - 0.5 g, on the 2nd and 3rd day of treatment - 0.75 g daily in 1 dose. With amebiasis - 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 - 0.25-0.5 g daily.

Side effect. From the digestive system: nausea, vomiting, stomach pain.

From the nervous system: dizziness, headache, sleep disturbances, psychosis, epileptic seizures.

From the side of the cardiovascular system: myocardial damage with changes in the ECG, decreased blood pressure.

From the sensory organs: with prolonged use - corneal clouding, retinal damage, visual impairment, tinnitus.

Allergic reactions: dermatitis, photosensitization.

Others: muscle pain, leukopenia, skin and hair color change.

2. Questions for self-control (list of questions):

1. Modern classification of GCS.
2. Explain the mechanisms of the anti-inflammatory action of GCS.
3. Explain the mechanisms of the effect of GCS on carbohydrate metabolism and indicate what indications and contraindications may be in this regard.
4. Indicate the features of the effect of GCS on lipid metabolism.
5. Explain the mechanisms of water-electrolyte metabolism disorders that occur against the background of the use of GCS and the complications associated with them, indications and contraindications to their use.
6. Indicate the general properties and individual differences of natural GCS from their synthetic analogues in terms of the degree of anti-inflammatory effect and the characteristics of metabolic disorders in the body.
7. Indicate GCS that have the most pronounced anti-shock effect, explain the mechanism of this action.
8. Explain the mechanism and measures for the prevention of the ulcerogenic effect of GCS.
9. Explain the mechanisms and measures for the prevention of hormone resistance, tolerance and "withdrawal syndrome".
10. Explain the tactics of use and dosing regimen of GCS in conditions of asthmatic status. In what other conditions is pulse therapy of GCS indicated.
11. What advantages and disadvantages are characteristic of inhaled glucocorticosteroids. What is the tactic of their use against the background of hormone-dependent bronchial asthma.
12. Define the concept of "rational hormone therapy" of GCS. What chronopharmacological features must be taken into account in conditions of long-term administration of GCS.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for basic GCS (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for prescription. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize the development of the inflammatory process, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, choose a drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 their detection at the early stages.

10. Substantiate the duration of basic and maintenance therapy.

B. Solution of situational tasks.

1. The patient takes prednisolone at a dose of 2 tablets per day. Indicate equivalent doses of triamcinolone. What other drugs can be replaced with prednisolone?

2. Choose corticosteroids for congestive heart failure: prednisone, dexamethasone, triamcinolone, prednisolone. Give a justification for the choice.

3. Which anti-inflammatory drugs cause osteoporosis: acetylsalicylic acid, butadione, prednisolone, ibuprofen, indomethacin.

4. A 36-year-old patient has a diagnosis of rheumatism, active phase I degree, regurgitant carditis, mitral heart disease with predominance of insufficiency, circulatory failure IIb stage. Treatment is prescribed: cardiac glycosides, diuretics, metabolic agents. What anti-inflammatory drug is indicated for the patient? Justify the choice of drug.

5. A 42-year-old patient went to the clinic with complaints of minor pain in the knee joints after work. He works as a loader. On objective examination, there are no visible changes in the joints, a rough crunch is detected during movement. On radiographs, there is a narrowing of the joint space, aggravation of the intercondylar elevation, osteophytes at the edges of the tibial epiphysis. The diagnosis is: deforming osteoarthritis of the knee joints. Your treatment plan for the patient.

6. Choose a drug for a 39-year-old patient with a diagnosis of Bechterew's disease, mixed course, activity II, FN II: voltaren, prednisolone, indomethacin, acetylsalicylic acid.

7. A 63-year-old patient has been receiving maintenance therapy with prednisolone at a dose of 2 tablets per day for bronchial asthma for a year. What complication do you expect from the use of corticosteroids?

8. A patient with pulmonary tuberculosis and concomitant bronchial asthma was prescribed rifampicin treatment on the background of prednisolone, which has been used for a long time. After 5 days of treatment, the patient had a sharp exacerbation of bronchial asthma, which was stopped only after 2 weeks by the use of large doses of corticosteroids. Explain the situation that has developed.

Test tasks for self-control:

1. Prevention of the catabolic effect of glucocorticosteroids is carried out by one of the listed drugs:

A. Potassium orotate.
B. Famotidine.
C. Panangin.
D. Potassium chloride.
E. Hypothiazide.

2. A 32-year-old patient was urgently admitted to the hospital with a lupus crisis. Choose the most effective dose of prednisolone.

A. 50-60 mg.
B. 10-20 mg.
C. Pulse therapy 500-1000 mg.
D. 100-120 mg.
E. 5-10 mg.

3. It is known that triamcinolone has less pronounced mineralocorticoid properties than prednisolone. What undesirable effects are more pronounced in triamcinolone than in other glucocorticoids?

A. Muscle atrophy.
B. Gastroduodenal ulcers.
C. Vasomotor syndrome
D. Sensation of blood rush to the head.
E. All of the above effects.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical pharmacology of antibiotics"

Purpose: To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of antibiotics:

- penicillins;
- cephalosporins;
- carbapenems;
- monobactams;
- macrolides;
- aminoglycosides;
- tetracyclines;
- amphenicols;
- glycopeptides.

Basic concepts (list of questions):

1. Antibiotics.
2. Antibacterial therapy.
3. Antibiotic resistance.
4. Beta-lactam antibiotics.
5. Antibiotics of other groups.
6. Criteria for the effectiveness of antibiotic therapy.
7. Criteria for the safety of antibiotic therapy.

Plan

1. Theoretical questions:

Antimicrobial drugs are a group of drugs that are very often used in clinical medicine. Antibiotics, fluoroquinolones and nitroimidazoles are mainly used in the treatment of infectious pathologies.

Basic rules for rational antibacterial therapy

I. Antibacterial therapy is considered rational if it is etiotropic, and this involves the following stages:

 isolation of the pathogen;

 determination of the number of microbial bodies per unit volume of the delivered material (if the number of microbial bodies of a particular microorganism exceeds the critical level, such a pathogen is considered etiologically significant);

 determination of the sensitivity of the etiologically significant pathogen to the spectrum of antibiotics (taking into account the localization of the infectious process and the

predominant accumulation in therapeutic concentrations of the drug in individual organs and tissues).

II. It is necessary to ensure the administration of the drug in a dosage regimen that provides a constant therapeutic concentration in organs and tissues:

 adhere to the dosage regimen specified in the instructions for the drug;

 assess the possibility of pharmaceutical (physicochemical) or pharmacokinetic interaction, which can significantly reduce the effectiveness of therapy.

III. If there is a choice between several drugs, preference is given to the most effective and least toxic, taking into account:

 the patient's age;

 medical history (allergy to medications in history);

 the presence of concomitant diseases that affect the absorption, distribution, biotransformation and excretion of the antibacterial drug;

 pregnancy and breastfeeding.

Classification of antibacterial drugs

There are several classifications of antibacterial drugs, but the most appropriate is the distribution of drugs according to the ATC (Anatomical Therapeutic Chemical (ATC) classification, WHO Collaborating Centre for Drug Statistics Methodology), namely: broad-spectrum penicillins, cephalosporins, carbapenems, aminoglycosides, tetracyclines, amphenicols, macrolides, lincosamides, glycopeptide antibiotics and antibacterial chemotherapeutic agents such as quinolines, fluoroquinolones, imidazole derivatives, nitrofuran derivatives, sulfanilamides. Antifungal drugs are divided into antibiotics (amphotericin B), imidazole derivatives (ketoconazole), triazole derivatives (fluconazole, intraconazole).

Clinical pharmacology of penicillins

Penicillins are among the most commonly used groups of antibiotics. The mechanism of action of penicillins is to bind to PBG-1 (penicillin-binding protein) and PBG-3. Since PBG-1 ensures the stability of the cell wall in all directions, inhibition of this protein leads to rapid destruction associated with the inhibition of the biosynthesis of mucoproteins of the outer membrane and the death of microorganisms. As a result, the drugs have a bactericidal effect on gram-positive and some gram-negative pathogens.

Classification of penicillins

I. Penicillins sensitive to the action of beta-lactamases: benzylpenicillin, phenoxymethylpenicillin, benzathine benzylpenicillin.

II. Penicillins resistant to the action of beta-lactamases: oxacillin, methicillin.

III. Broad-spectrum penicillins: ampicillin, amoxicillin, piperacillin, ticarcillin.

IV. Combinations of penicillins with beta-lactamase inhibitors: ampicillin/sulbactam (ampisulbin, unazine); amoxicillin/clavulanic acid (augmentin, amoxiclav); piperacillin/tazobactam (tazocin); ticarcillin/clavulanic acid (timentin).

When prescribing penicillins, it is necessary to pay attention to the fact that penicillins of the 2nd group affect mainly gram-positive pathogens, penicillins of the III group are destroyed under the influence of beta-lactamases.

Penicillins have significant differences in pharmacokinetic parameters. A number of diseases affect the absorption of penicillins from the gastrointestinal tract. For example, slowing down the absorption of ampicillin occurs in celiac disease, reducing absorption is

possible after selective proximal vagotomy, dysentery in children, and in gastric ulcer and duodenal ulcer without stenosis, the absorption of ampicillin increases, and in stenosis it decreases. A decrease in the absorption of phenoxymethylpenicillin occurs in pancreatitis and achlorhydria. Clavulanic acid has a beta-lactam structure and is able to inactivate beta-lactamase enzymes. In particular, clavulanic acid is active against plasmid beta-lactamases, which are often responsible for the occurrence of cross-resistance to antibiotics. The presence of clavulanic acid in the composition of the drug protects it and adds activity against lactamase-producing strains. After administration of the combined drug, about 35-45% of clavulanic acid is excreted in the urine unchanged within the first hours.

When prescribing penicillins, it is necessary to take into account the possibility of complications of therapy, among which allergic reactions are the most common. In order to prevent allergic reactions, it is necessary to: - carefully collect and evaluate the medical history; - do not use penicillins topically; - do not use penicillin derivatives in case of allergy to penicillin; - conduct a sensitivity test; - after using penicillins, observe the patient for 30 minutes.

Cephalosporins

Cephalosporins are broad-spectrum antibiotics. Their superior spectrum of action against certain groups of pathogens allows them to be classified into the appropriate generation. The most well-known classification of cephalosporins is as follows:

Generation Features of the spectrum of action International name Commercial name

I Broad spectrum with predominant action on gram-positive pathogens Cephalexin Lexin, Sporidex

Cefazolin Kefzol, Reflin

II Broad spectrum with predominant action against enterobacteria Cefaclor Vercef

Cefamandol Cefamabol

Cefuroxime Zinacef, Kymocef

Cefuroxime axetil Zinnat

Cefoxitin Mefoxin

III Broad spectrum with enhanced action against pseudomonads Cefixime Loprax

Ceftibuten Cedex

Cefotaxime Claforan

Ceftriaxone Rocefin, Oframax, Medaxon

Cefoperazone Cefobid, Medocef

Ceftazidime Fortum

IV Broad spectrum with action against bacteroids Cefpirom Cefrom

Cefepime Maxipim

Cephalosporins have a bactericidal effect on pathogens. The mechanism of action is the initial binding to PZB-3 (penicillin-binding protein), which causes the release of a large amount of endotoxin when gram-negative bacteria die, and cephalosporins also bind to the enzyme endopeptidases (this leads to a violation of the integrity of the mucopeptide shell) and to glycosidases (this disrupts the synthesis of polysaccharide chains in the cell wall of microorganisms), which contributes to the release of autolytic enzymes and ensures the death of the pathogen. In addition to taking into account the features of the antibacterial spectrum of each of the representatives of the cephalosporin class, one should take into account their

ability to accumulate in individual organs and tissues. Thus, cefotaxime, cefuroxime, ceftazidime, ceftriaxone accumulate in the cerebrospinal fluid, but this is possible only in meningitis; a high concentration of almost all cephalosporins is detected in bile; in the lung tissues, cefotaxime, cefoperazone, cefpirome, cefoxitin accumulate in the highest concentrations; cefazolin enters the pancreas and retains its activity there; cefazolin, cefotaxime, ceftazidime, cefamandole, cefuroxime accumulate in the heart muscle and heart valves. The ability to diffuse into a blood clot is inherent in cefazolin and cefamandole. The course of the disease can change the pharmacodynamic and pharmacokinetic properties, as well as the safety of cephalosporin therapy. Cephalexin, cefoxitin, cefuroxime can be used without changing the dosage regimen in liver diseases. Cefotaxime, ceftriaxone, ceftazidime, cefoperazone can be prescribed subject to correction of their dose in diseases of the hepatobiliary system.

The pharmacokinetic properties of cephalosporins also determine the effectiveness and safety of therapy. Thus, protein binding determines the duration of drug circulation in the blood, however, in dysproteinemia, which accompanies many acute and chronic diseases, it is drugs with a high percentage of protein binding that change pharmacokinetic parameters and also cause symptoms of relative overdose of the drug. At the same time, a high percentage of protein binding ensures a long stay of the cephalosporin in the focus of inflammation and destruction. Each of the cephalosporins undergoes biotransformation to varying degrees, usually due to acetylation processes. The vast majority of cephalosporins are excreted in the urine unchanged. Therefore, when renal filtration function decreases to 10% of normal and below, the following dosage regimen can be used: cefazolin, cefamandole ¼ of the usual dose; cefaclor, cephalexin, cefoxitin 1/3 of the usual dose.

Cephalosporins are used for infections of the skin, soft tissues, brain, eyes, respiratory organs, heart muscle, hepatobiliary system, intestines, urinary and reproductive systems, bones, peritonitis, sepsis.

All complications of therapy can be divided into the following groups:

1. Allergic reactions;

2. Pharmacotoxic reactions (dyspepsia syndrome, hematotoxicity, hepatotoxicity, neurotoxicity, nephrotoxicity);

3. Immunobiological reactions (dysbiosis of organs and systems). Cephalosporins do not have a proven embryo- or fetotoxic effect, although all of them are determined in the tissues of the fetus. Their use during pregnancy is possible only according to vital indications on the part of the woman. During lactation, for the period of breastfeeding, their use must be discontinued.

Aminoglycosides

Aminoglycosides belong to bactericidal antibiotics of a broad spectrum of action. The mechanism of their antibacterial action is associated with irreversible binding to the 30S subunits of ribosomes, which leads to defects in reading the mRNA code and the inclusion of unusual amino acids in the peptide chain. The drugs affect aerobic gram-negative and some gram-positive pathogens. There are significant differences in the spectrum of action between individual antibiotics of this group. Aminoglycosides are not active against "atypical" microorganisms, fungi, viruses and the vast majority of anaerobic bacteria.

In clinical practice, three generations of aminoglycosides are distinguished:

I generation: streptomycin, neomycin, kanamycin;

II generation: gentamicin;

III generation: amikacin, tobramycin, netilmicin, sisomycin.

From the 1st generation to the 3rd, the antibacterial effect on gram-negative flora increases and the probability of oto- and nephrotoxic action decreases. Resistance to aminoglycosides in clinical strains of microorganisms is partially cross-linked. Resistance to aminoglycosides in microorganisms is due to the ability to produce specific enzymes (aminoglycoside acetyltransferase, N-phosphate transferase, O-nucleotide transferase), which inactivate these antibiotics. All drugs of this group have a short half-life, they are mainly not metabolized and are excreted in the urine in an active state. This feature of pharmacokinetics determines the high probability of nephrotoxic effect and the ability to cumulate in case of impaired renal function.

When using aminoglycosides as part of combination therapy, the possibility of physicochemical interaction should be taken into account. It is especially necessary to take into account the impossibility of mixing aminoglycosides with other antibiotics in one syringe. The likelihood of nephrotoxic action increases with simultaneous use with nephrotoxic drugs of other drug groups.

Complications of therapy are of a general nature. The most likely are oto- and nephrotoxicity of drugs. Ototoxicity is associated with the death of the auditory nerve endings, it is irreversible and can manifest itself in the form of cochlear or vestibular variants. Nephrotoxicity is caused by necrosis of epithelial cells of the renal tubules. Its first signs are polyuria, then protein in the urine and an increase in the level of blood creatinine appear. In order to detect these complications of therapy in a timely manner, it is necessary to record an audiogram every 10 days and monitor kidney function.

The dosage regimen for aminoglycosides must be adjusted in patients with renal impairment. The dose is adjusted based on creatinine clearance or blood creatinine levels.

Macrolides

Macrolides are antibiotics with a bacteriostatic effect, but in high concentrations under certain conditions (relatively low microbial density, growth phase of the microorganism) they can have a bactericidal effect on β-hemolytic streptococcus group A and pneumococcus. The mechanism of action of macrolides is to bind to the catalytic peptidyltransferase center of the ribosomal 50S subunit, which leads to inhibition of protein synthesis.

Macrolides are classified depending on the number of carbon atoms in the lactone ring:

I. 14-membered macrolides: erythromycin, roxithromycin, clarithromycin;

II. 15-membered macrolides: azithromycin;

III. 16-membered macrolides: spiramycin (rovamycin), josamycin, midecamycin.

Macrolides accumulate in the tonsils, middle ear, paranasal sinuses, lungs, bronchopulmonary secretion, pleural and peritoneal fluid, lymph nodes, genitals. The drugs penetrate well into cells, which is noticeable for the treatment of infections caused by intracellular pathogens (Mycoplasma spp., Chlamydia spp., Legionella spp., etc.). Due to the ability to enter phagocytic cells, the drugs are transported to the focus of inflammation.

When using macrolides orally, it is necessary to take into account the effect of food on

their bioavailability. Thus, food slows down the absorption of erythromycin and azithromycin, so they are taken 1 hour before meals or 2-3 hours after, roxithromycin is used before meals. Clarithromycin is taken with meals, and food does not affect the bioavailability of rovamicin. A feature of the pharmacokinetics of macrolides is the presence of two peaks of concentration in the blood, which is associated with the initial deposition in the gallbladder and subsequent release into the intestine and absorption from it. Roxithromycin is most bound to plasma proteins (92-96%), and rovamycin is least bound (10-18%).

Macrolides are metabolized in the liver with the participation of cytochrome P450 (CYP3A4 isoform) with the formation of inactive metabolites and compounds with antibacterial activity. Metabolites are excreted in bile and urine. In case of impaired renal function, dose adjustment of clarithromycin and roxithromycin is necessary, and in case of liver cirrhosis, the half-life of erythromycin and josamycin is prolonged. The main indications for the use of macrolides are: respiratory tract infections (including those caused by "atypical" pathogens), ear, skin and soft tissue infections, sexually transmitted infections, gastrointestinal infections, toxoplasmosis, opportunistic infections in patients with AIDS, Lyme disease, odontogenic infections.

When carrying out combination therapy, the possibility of pharmacokinetic interaction at the stage of biotransformation should be taken into account. After all, due to competition for cytochrome P 450, macrolides can change the safety and effectiveness of drugs used simultaneously with them. For example, inhibition of biotransformation of antihistamines of the second generation leads to an increase in their concentration in the blood with subsequent increased cardiotoxicity (development of the "pirouette" syndrome).

Complications of therapy with macrolides include: allergic reactions, pharmacotoxic reactions, among which the most common are dyspeptic syndrome and hepatotoxicity, manifested by increased levels of bilirubin and hepatic transaminases in the blood serum. Like all other antibacterial agents, macrolides can cause dysbacteriosis.

Carbapenems

Carbapenems are antibiotics of the beta-lactam structure. They have an ultra-broad spectrum of action and have a bactericidal effect. The mechanism of action is associated with the interaction with the PZB-2 type of the inner wall of the bacterial membrane and, thus, the synthesis of the cell wall is disrupted. Carbapenems have resistance to plasmid lactamases of the broad and extended spectrum and unique resistance to chromosomal beta-lactamases. The pharmacokinetic parameters of imipenem/cilastatin (thienam) and meropenem (meronem) are similar. They have a weak connection with protein, are excreted mainly in the urine. The presence of cilastatin in the composition of thienam prevents damage to imipenem by the enzyme dehydropeptidase-1 in the kidneys. Cilastatin is a highly specific inhibitor of this enzyme. Meropenem has a higher stability against renal dehydropeptidase-1 due to the introduction of a methyl group into its molecule at position C1 of the carbapenem nucleus, the absence of cilastatin reduces the nephrotoxicity of the drug. Carbapenems are used in the treatment of the vast majority of severe infectious diseases, nosocomial infections. The dosage regimen is given.

The side effects of both drugs are somewhat similar, but meropenem does not cause seizures. When administering drugs, only approved solvents should be used, and the possibility of pharmacokinetic interactions should be taken into account.

Glycopeptides

The mechanism of action of glycopeptide antibiotics is to inhibit the biosynthesis of cell membranes of microorganisms, change their permeability and disrupt RNA synthesis. The drugs always have a bactericidal effect. The following are sensitive to the action of glycopeptides: S. aureus (including MRSA), S. epidermidis, Streptococeus spp., Enterococeus spp., Corynebacterium jeikeium and other diphtheroids, Listeria monocytogenes, Actinomyces spp., Clostridium perfringes and Clostridium difficile, Peptostreptococcus spp., Propionibacterium spp., Neisseria gonorrhoea, Prevotella spp., Porphyromonas spp. Resistant to glycopeptide antibiotics: gram-negative bacilli (except gonococci), mycobacteria, atypical bacteria, Pediococcus spp., Leuconostoc spp., Lactobacillus spp., Erysipelotrix spp., Nocardia spp. When comparing the strength of antibacterial action, it should be noted that teicoplanin is 2-4 times stronger than vancomycin against S. aureus, Stereptoccus spp. and Enterococcus spp. 4-8 times, Peptosoreptococcus spp., Clostridium, Propionibacterium spp. 2-8 times. The pharmacokinetics of the drugs differ significantly, but none of them is absorbed when administered orally.

Glycopeptide antibiotics can be used orally (vancomycin) to treat patients with pseudomembranous colitis caused by C. difficile or staphylococcal enterocolitis. Teicoplanin can be administered intraperitoneally in patients on chronic hemodialysis. Glycopeptide antibiotics are used to treat severe infections caused by susceptible Gram-positive bacteria, including strains resistant to methicillin and cephalosporins. Typically, these are infections of the respiratory tract, urinary tract, skin and soft tissue, bones and joints, sepsis/septicemia, endocarditis, and peritonitis.

When using glycopeptide antibiotics, it is necessary to take into account the possibility of allergic reactions, especially when using vancomycin ("red man" syndrome, which is associated with the release of histamine and is accompanied by redness and itching in the neck and upper chest, chest pain, hypotension, angioedema). The development of hematotoxic reactions (eosinophilia, thrombocytopenia, leukopenia) is also possible. From the gastrointestinal tract, nausea, vomiting, diarrhea, increased enzyme activity (transaminases and/or alkaline phosphatase), transient increase in serum creatinine are possible. In some cases, dizziness, headache, asthenia, edema, increased serum uric acid content, vasculitis occur. Pain and phlebitis were observed at the site of drug administration. The drugs have oto- and nephrotoxicity, which are enhanced when used with neuro- and nephrotoxic drugs (furosemide, amphotericin B, aminoglycosides, bacitracin, polymyxin B). Simultaneous use of vancomycin and anesthetic drugs may be accompanied by skin hyperemia, the development of histamine-like and anaphylactic reactions.

Tetracyclines

Tetracyclines are broad-spectrum drugs; they have a bacteriostatic effect on microorganisms. The mechanism of action of this group of drugs is associated with binding to the 70S and, to a lesser extent, the 30S subunits of bacterial ribosomes, specifically inhibiting enzymes that participate in the binding of aminoacyl-t-RNA to ribosome acceptors. The drugs are well absorbed when administered orally. The high percentage of tetracyclines binding to plasma proteins makes the use of hemodialysis ineffective for removing drugs from the body. Tetracyclines are excreted mainly in the urine, to a lesser extent, in the bile.

Tetracyclines are used in adults and children over 14 years of age in the treatment of rare diseases caused by pathogens sensitive to them. The dosage regimen depends on the pharmacokinetic parameters of the drug and the severity of the disease.

When using tetracyclines, allergic reactions and gastrointestinal disorders may develop: nausea, vomiting, diarrhea, glossitis, dysphagia, esophagitis, esophageal erosion; hematotoxicity is manifested in the form of hemolytic anemia, thrombocytopenia, neutropenia, eosinophilia, in some cases superinfection occurs; tetracycline also causes liver and kidney damage, pancreatitis, dizziness, pigmentation of the skin, mucous membranes and tooth enamel in children, increased intracranial pressure, hypovitaminosis, photosensitization.

When conducting combination therapy, it should be taken into account that antacids, calcium, magnesium, iron salts, cholestyramine reduce the absorption of tetracycline from the gastrointestinal tract. Tetracycline reduces the effectiveness of oral contraceptives and increases the risk of uterine bleeding, increases the nephrotoxicity of methoxyflurane. When used simultaneously with retinol, the risk of developing intracranial hypertension increases.

Amphenicols

Chloramphenicol (chloramphenicol) and thiamphenicol are broad-spectrum drugs with a bacteriostatic effect. The mechanism of action is associated with a violation of the process of protein synthesis in the microbial cell at the stage of transferring amino acids from t-RNA to ribosomes.

After oral administration, the bioavailability of chloramphenicol is 80%, and after intramuscular administration - 70%. 50-60% of chloramphenicol binds to plasma proteins, the volume of distribution is 0.6-1 l / kg. It is metabolized in the liver, excreted mainly in the urine in the form of inactive metabolites, partially excreted in the bile (30%).

Chloramphenicol is prescribed for infections caused by pathogens sensitive to it, including such diseases as typhoid fever, paratyphoid fever, generalized salmonellosis, yersiniosis, brucellosis, tularemia, rickettsiosis, chlamydia, psittacosis, trachoma. Orally, the drug is prescribed 30 minutes before meals, adults 0.25 - 0.5 g 3-4 times a day (the maximum daily dose is 4 g). Parenterally (in / m, in / in) administered 0.5 - 1 g 2-3 times a day.

Among the most frequent complications of therapy are: hematotoxicity (granulocytopenia, reticulocytopenia, erythropenia, decreased hemoglobin level, aplastic anemia), neurotoxicity (psychomotor disorders, confusion, visual and auditory hallucinations, decreased hearing and vision acuity), gastrointestinal tract damage (nausea, vomiting, diarrhea), allergic reactions and suppression of intestinal microflora are also possible. When conducting combination therapy, chloramphenicol should not be prescribed with drugs that suppress hematopoiesis (sulfonamides, pyrazolone derivatives, cytostatics), do not use together with phenytoin, neodicoumarin, tolbutamide, barbiturates.

2. Questions for self-control (list of questions):

1. List the mechanisms of action of antibiotics.
2. Name the main classifications of antibiotics.
3. List the main groups of antibiotics that have a bactericidal or bacteriostatic effect.
4. Give the classification of penicillins, cephalosporins, aminoglycosides, tetracyclines.
5. Name the criteria that determine the choice of an antibiotic for the treatment of an

infectious process.

6. List the criteria for the effectiveness of antibiotics.

7. What organs and systems are involved in the elimination of antibiotics and the significance of this process?

8. List the undesirable effects of antibiotic therapy, methods of their prevention and treatment.

9. Indicate the features of the pharmacokinetics and pharmacodynamics of lincomycin.

10. In what diseases are macrolides the drug of first choice?

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for the main representatives of different groups of antibiotics (tablets and/or ampoules), indicate the possible application, the spectrum of diseases (syndromes) indicated for the appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize the presence of an infectious inflammatory process, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, choose a drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 their detection at the early stages.

10. Substantiate the duration of basic and supportive therapy.

B. Solution of situational tasks.

1. A 42-year-old patient was brought to the department with complaints of an increase in body temperature to 39.8 ° C, cough with a small amount of sputum, sweating. On objective examination: in the lungs on the right below the scapula there is a zone of dullness of percussion sound, harsh breathing, moist wheezing. Your diagnosis? Prescribe therapy, name the 1st line drug. The doctor on duty prescribed the patient (see Task 1) penicillin 250 thousand units 4 times a day. Give an assessment of pharmacotherapy.

2. A 23-year-old patient with acute right-sided pneumonia, who is being treated with benzylpenicillin at a dose of 6 million units per day, has a subfebrile temperature on the third day, dullness of percussion sound in the lower lobe of the lung, moist sonorous wheezing. Tactics of patient management.

3. In the urological clinic, a 67-year-old patient was prescribed carbenicillin after prostatectomy. What do you think is the reason for this? What other antibiotic can replace carbenicillin, taking into account its specific action?

4. A 3-year-old child who had pneumonia developed jaundice. The parents emphasized that the child was not given tetracycline. Upon further clarification of the medical history, it was found that the child had received ascorutin, rondomycin, calcium chloride, aspirin, and analgin. Explain the cause of jaundice. Your conclusions?

5. The doctor on duty is called to a 27-year-old patient who was in the ward for pneumonia. He complains of weakness and dizziness. Objectively - covered in cold sweat, cyanotic lips, pulse - 93 beats per minute, rhythmic, weak filling, ACT - 90/55 mm Hg. The voice is slightly hoarse. The nurse reported that 40 minutes ago the patient had another injection of penicillin. Your diagnosis? Specify the variant and severity of the patient's condition. Treatment plan. Prevention.

6. A 38-year-old patient has rheumatism, active phase, I degree of activity, reversible rheumatic carditis, mitral stenosis, I degree of heart failure. In the hospital, pharmacotherapy is successfully carried out: benzylpenicillin, voltaren, riboxin, panangin, ranitidine. What antibiotic should be prescribed to the patient in outpatient settings to prevent recurrence of rheumatism?

7. A 19-year-old patient complains of dry cough, muscle pain, increased body temperature to 39°C. During the week, he was bothered by sore throat and subfebrile temperature. Objectively: labored breathing. In the blood: L. - 7.0 • 109/l, leukocyte formula is normal. ESR - 26 mm/h. Chest X-ray data: increased pulmonary pattern, focal shadows of weak intensity in the lower parts of the right lung. Formulate a diagnosis. Treatment plan. Give a clinical and pharmacological assessment of the prescribed treatment.

Test tasks for self-control:

1. The effectiveness of antibacterial therapy is assessed after:
A. 48-72 hours
B. 6-12 hours
C. 2-4 hours
D. 84-96 hours
E. 2 hours
2. The causative agents of erysipelas and scarlet fever are always:
A. Pneumococcus
B. Staphylococcus
C. Streptococci
D. Friedendler's bacillus
E. Viruses
3. Among the side effects of penicillin treatment, the following are in the foreground:
A. Dysbacteriosis, candidomycosis

B. Alcohol intolerance
C. Neurotoxicity
D. Nephro- and hepatotoxicity
E. Allergic reactions
4. Tetracyclines should be avoided in children, as it is known that they:
A. Deposited in calcium-rich tissues
B. Cause liver damage
C. Increase cerebrospinal fluid pressure
D. Irritate the gastrointestinal mucosa, suppress intestinal flora.
E. Cause superinfections (staphylococcal enteritis)
5. Name the antibiotic used for penicillin allergy:
A. Imipenem.
B. Ampicillin
C. Cefoperazone
D. Azithromycin
E. Cefazolin
6. Cholecystitis, cholangitis, biliary sepsis require the appointment of:
A. Vancomycin and imipenem
B. Erythromycin and tetracycline
C. Ampicillin and chloramphenicol
D. Cephalosporins
E. Antibiotics are not needed

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical pharmacology of synthetic antimicrobial drugs: fluoroquinolones, nitroimidazoles, nitrofurans, sulfonamides"

Purpose: To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of synthetic antimicrobial groups:

- fluoroquinolones;
- nitroimidazoles;
- nitrofurans;
- sulfonamides.

Basic concepts (list of questions):

1. Antibacterial therapy.
2. Criteria for the effectiveness of antibacterial therapy.
3. Criteria for the safety of antibacterial therapy.
4. Fluoroquinolones.
5. Nitroimidazoles.
6. Nitrofuran derivatives.
7. Sulfonamides.

Plan

1. Theoretical questions:

Sulfonamides

Sulfonamide drugs are broad-spectrum antibacterial agents. They are derivatives of sulfanilic acid, similar in chemical structure to para-aminobenzoic acid. These drugs have competitive antagonism with para-aminobenzoic acid and prevent its use by microorganisms for the synthesis of dihydrofolic acid, which, through several stages, participates in the synthesis of pyrimidine bases of DNA and RNA. Thus, the bacteriostatic effect of sulfonamides is realized.

Sulfonamides are classified according to the characteristics of pharmacokinetics, in particular absorption in the gastrointestinal tract and the duration of excretion from the body:

I. Drugs that are well absorbed in the digestive tract:

- drugs of short duration of action (T½ - 8 hours): etazol, norsulfazole;
- drugs of medium duration of action (T½ - 8-20 hours): sulfasin;
- drugs of long duration of action (T½ - 24-48 hours): sulfapyridazine, sulfadimethoxin, sulfamonomethoxin;
- drugs of ultra-long duration of action (T½ - 65 hours): sulfalen.

II. Drugs that are practically not absorbed in the gastrointestinal tract (phtazine, phthalazole, sulgin).

III. Drugs of local action (streptocide, sulfacyl-sodium).

IV. Combined drugs containing sulfonamides (co-trimoxazole).

The duration of action of sulfonamides is due to labile reverse binding to albumin. By binding to protein, sulfonamides can displace other drugs or endogenous compounds such as bilirubin from the protein complex. Sulfanilamides can be displaced from the protein complex by salicylates and other NSAIDs. Sulfanilamides penetrate well from the blood into various fluids and tissues of the body. They can accumulate in tissues with impaired blood circulation. They pass well through the placental barrier and can cause methemoglobinemia and hyperbilirubinemia, primarily in newborns. They are metabolized in the liver by acetylation and glucuronidation (sulfadimethoxine) with the formation of inactive metabolites. If the drug undergoes insignificant acetylation, then it is excreted from the body in an active state and can have an antimicrobial effect in the urinary tract (etazol, urosulfan). Sulfanilamides and their metabolites are removed from the body mainly by filtration. Lipid-soluble sulfonamides are reabsorbed in the renal tubules after glomerular filtration, which, together with their ability to bind to plasma proteins, causes a longer effect. Acetylated compounds are not reabsorbed by the kidneys, but under conditions of neutral or acidic pH of urine are able to form a precipitate (crystalluria) in the urinary tract. Glucuronides of sulfonamides are well soluble in water, do not form a precipitate.

The sensitivity of microorganisms to sulfonamides decreases at high concentrations of PABA (pus, detritus), in the presence of folic acid, purine and pyrimidine bases.

Sulfonamides cause the following adverse reactions: allergic reactions (erythema, urticaria, photodermatosis, glossitis, conjunctivitis, anaphylactic shock), pharmacotoxic reactions (dyspepsia, nephrotoxicity due to crystalluria, granulocytopenia, thrombocytopenia, megaloblastic anemia, intravascular hemolysis with the development of kernicterus, methemoglobinemia, nonhemolytic jaundice) and immunobiological reactions (intestinal dysbacteriosis). Contraindications to the use of sulfonamides include: hypersensitivity to sulfonamides, diseases of the blood system, renal failure, thyrotoxicosis, pregnancy, breastfeeding, children under 2 years of age.

Nitrofurans

These are synthetic drugs that have either a bactericidal or bacteriostatic effect on certain gram-positive and gram-negative pathogens: sensitive to them are Escherichia coli, dysentery bacillus, paratyphoid pathogens, salmonella, cholera vibrio, Giardia, Trichomonas, staphylococci, large viruses, and gas gangrene pathogens. Nitrofurans have some antifungal activity. The quality of the effect, i.e. bacteriostatic or bactericidal, depends on the concentration of nitrofurans in the medium. The mechanism of action of the drugs is to inhibit the respiratory chain (NADH block), the tricarboxylic acid cycle (Krebs) and other biochemical processes in the microbial cell, which leads to the destruction of the microbial wall or cytoplasmic membrane.

After oral administration, they are well absorbed from the gastrointestinal tract (nitrofurantoin) or not absorbed (nifuroxazide). They are distributed unevenly in the body. In high concentrations, they accumulate in lymph, bile, and saliva. Nitrofurans cross the placental barrier. The drugs are partially metabolized to form inactive metabolites. Elimination of nitrofurans occurs mainly by the kidneys through tubular secretion. Alkalinization of urine accelerates excretion, since nitrofurans are weak acids. On the contrary, acidification of urine (for example, simultaneous use of ascorbic acid, calcium chloride) promotes their reabsorption and accumulation in the body, which increases the risk of toxic effects.

Indications for the use of nitrofurans are: diarrhea of infectious genesis, chronic colitis, enterocolitis, bacillary dysentery, giardiasis, paratyphoid, urinary tract infections. Locally, in the form of washes, it is used to treat purulent wounds, infected burns, fistulas, conjunctivitis, bronchial sanitation during bronchoscopy, and to wash cavities (peritonitis, pleural empyema).

Complications of therapy caused by nitrofurans are as follows: dyspeptic phenomena (loss of appetite, nausea, vomiting), allergic reactions, possible development of neurotoxic manifestations (headache, dizziness, polyneuropathy, optic nerve damage), hematotoxic manifestations (eosinophilia, leukopenia, hemoglobinemia, hyperchromic anemia), in newborns the development of methemoglobinemia is possible (due to the presence of easily oxidized fetal hemoglobin and insufficiency of reducing enzymes in erythrocytes).

When conducting therapy with nitrofurans, the possibility of interactions should be taken into account. Thus, nitrofurans cannot be prescribed with sulfonamides and nalidixic acid because this leads to antagonism. It should be borne in mind that furazolidone is an MAO antagonist, and this increases the pharmacological activity of noradrenaline, adrenaline, isadrine, mezaton, dopamine, for this reason it cannot be used with MAO inhibitors, indirect adrenomimetics, alcohol and cheese should not be consumed during treatment. In addition to furazolidone, alcohol toxicity is increased by nifuroxazide. Contraindications to the use of nitrofurans are the following: hypersensitivity to nitrofurans, impaired renal function (does not apply to nifuroxazide), pregnancy, children in the neonatal period, nifuroxazide is contraindicated in children under 2 months.

Fluoroquinolones

Fluoroquinolones are derivatives of nalidixic acid, in which a fluorine atom is present in position 6 of the heterocyclic cycle of the quinolone or analogue. The change in the chemical

structure causes pharmacokinetic and pharmacodynamic differences compared to quinolones. The most significant clinical advantages of fluoroquinolones are:

- Broad spectrum of action;
- Always bactericidal effect on gram-positive pathogens that are in the division stage and gram-negative pathogens that are both in the resting and multiplying stages;
- Activity in a wide pH range;
- Minor negative effect on the immunological indicators of the body and intestinal microflora after prolonged use;
- The ability to penetrate into phagocytes, macrophages, neutrophils and into the abscess cavity and have an antibacterial effect there.

The mechanism of action of fluoroquinolones is associated with inhibition of the A-subunits of bacterial DNA gyrase (topoisomerase II) and, some fluoroquinolones also inhibit topoisomerase IV (levofloxacin), thus suppressing the vital functions of bacteria, which leads to the death of microorganisms.

There are several classifications of fluoroquinolones, according to one of them, monofluoroquinolones (norfloxacin, pefloxacin, ofloxacin, levofloxacin, ciprofloxacin, moxifloxacin), difluoroquinolones (lomefloxacin, sparfloxacin), trifluoroquinolones (fleroxacin) are distinguished.

Fluoroquinolones are broad-spectrum drugs. The vast majority of strains of Neisseria spp., Haemophillus spp., B. Catarrhalis, E. Coli, Shigella and Salmonella spp., Acinetobacter spp. are highly sensitive to them. The sensitive ones include Klebsiella spp., Proteus spp., Providencia spp., Bordetella spp., Enterobacter spp., Legionella spp., Yersinia spp., Serratia spp., Campylobacter spp., Staphylococcus spp. Among Pseudomonas strains, including P. aeruginosa, as well as S. aureus, Streptococcus spp (including S. pneumoniae), Legionella, Listeria, Providencia, Serratia, there are both sensitive and moderately sensitive strains. As a rule, moderately sensitive are: Brucella spp., Corynebacterium spp., Yardnerella, Chlamydia spp., Mycobacterium tuberculosis, anaerobic streptococci. Fluoroquinolones are inactive against treponemas, fungi and viruses. In addition to taking into account the sensitivity of the pathogen to the drug, when prescribing fluoroquinolones, it is necessary to take into account their different ability to accumulate in organs and tissues.

All fluoroquinolones are metabolized in the body, to a lesser extent this applies to ofloxacin, levofloxacin and moxifloxacin. Usually the drugs are excreted in the urine in an active state - it is advisable to use them for urinary tract infections. The main indications for the use of fluoroquinolones are: infections of the respiratory tract, middle ear, paranasal sinuses, eyes, digestive tract, gallbladder and biliary tract, kidneys and urinary tract, skin and soft tissues, bones and joints, genitals, gonorrhea, peritonitis, sepsis, prevention and treatment of infections in patients with immunodeficiency states, including those treated with immunosuppressants and in neutropenia.

Fluoroquinolones, like other antibacterial agents, can cause the following complications of therapy: allergic reactions (itching, skin hyperemia, urticaria, bronchospasm, angioedema, shock, photosensitivity, Stevens-Johnson syndrome, Lyell syndrome, exudative polymorphic erythema); pharmacotoxic reactions (nausea, diarrhea, pseudomembranous colitis, hypoglycemia, porphyria, headache, dizziness, drowsiness, sleep disorders, paresthesias, tremor, anxiety, fear, convulsions, confusion, visual, hearing, taste disorders, tactile sensitivity disorders, psychotic reactions, hallucinations, depression, impaired coordination of

movements, tachycardia, arterial hypotension, collapse, muscular weakness, tendon damage, myalgia, arthralgia, increased activity of hepatic transaminases, bilirubin and creatinine in serum, hepatitis, interstitial nephritis, eosinophilia, leukopenia, thrombocytopenia, agranulocytosis, hemolytic anemia, pancytopenia, phlebitis, vasculitis, pneumonitis), immunobiological (dysbacteriosis, superinfection).

Fluoroquinolones are contraindicated in cases of hypersensitivity, epilepsy, children under 18 years of age, pregnant women, and women during breastfeeding.

Nitroimidazole derivatives

The drugs of this group easily penetrate into anaerobic microorganisms, where they are reduced (under the influence of nitroreductase) to form a substance that destroys bacterial DNA. Bacillus fragilis converts them into metabolites that inhibit certain aerobic microorganisms. Therefore, metronidazole, tinidazole, ornidazole are effective agents for the treatment of mixed infections. Due to the possibility of affecting anaerobic microorganisms and protozoa, the drugs are used in the treatment of amebiasis, urogenital trichomoniasis, nonspecific giardiasis, surgical infections caused by sensitive strains, for the prevention of anaerobic infections during surgical interventions in patients at risk, brain infections (brain abscess, meningitis), abscessing pneumonia, lung abscess, peritonitis, liver abscess, infectious complications after operations on the large intestine, endometritis, infectious complications after hysterectomy, Simakovsky-Plaut-Vincent angina, osteomyelitis, endocarditis, gas gangrene, septicemia, infections of the oral cavity, teeth, and jaw.

After oral administration, the absorption of metronidazole, tinidazole, ornidazole is about 90%. The plasma protein binding of metronidazole is 10%, tinidazole is 12%, ornidazole is 13%. They are metabolized in the body, their main metabolites are hydroxylated compounds, which also inhibit anaerobic microorganisms. The half-life of metronidazole is 8-10 hours, ornidazole is 13 hours, and tinidazole is 12-14 hours. They are excreted from the body mainly with urine and to a lesser extent with feces. The dosage regimen for the use of drugs depends on the severity of the infection and the nosological form.

Among the most frequent complications of therapy should be mentioned: decreased appetite, metallic taste in the mouth, nausea, vomiting, diarrhea, ataxia, dysarthria, dizziness, headache, cramps, numbness of the extremities, paresthesia, suppression of leukopoiesis, intestinal dysbacteriosis, allergic reactions, dark urine color.

When using imidazole derivatives, one should take into account their ability to increase the toxicity of alcohol (except ornidazole), ornidazole and metronidazole potentiate the effect of oral anticoagulants of the coumarin series, ornidazole increases the duration of the muscle relaxant effect of vecuronium bromide. Simultaneous use of metronidazole and barbiturates or phenytoin leads to a decrease in the effectiveness of metronidazole. Contraindications include: I trimester of pregnancy (in the II and III trimesters, metronidazole can be prescribed only for vital indications), organic lesions of the CNS, blood diseases, hypersensitivity, breastfeeding.

2. Questions for self-control (list of questions):

1. Clinical and pharmacological characteristics of sulfonamides.

2. Principles of classification of sulfonamides.

3. Clinical and pharmacological characteristics of fluoroquinolones.

4. Clinical and pharmacological characteristics of nitrofurans.

5. Principles of classification of nitrofurans.

6. Clinical and pharmacological characteristics of nitroimidazoles.

7. Name the criteria that determine the choice of an antimicrobial agent for the treatment of an infectious process.

8. List the criteria for the effectiveness of antibacterial therapy.

9. List the safety criteria for the use of different groups of synthetic antibacterial drugs.

10. Principles of antibacterial therapy during pregnancy.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for basic drugs - synthetic antimicrobial drugs (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for prescription. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize the presence of an infectious inflammatory process, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, choose a drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 detecting them at the early stages.

10. Substantiate the duration of basic and supportive therapy.

B. Solving situational tasks.

1. A 27-year-old man complains of cough with rusty sputum, chest pain during breathing, an increase in body temperature to 39°C. He became acutely ill after hypothermia. Objectively: BH 30 in 1 min, HR - 92 in 1 min, BP - 130/80 mm Hg. In the lungs on the right from the IV rib down - increased voice tremor, dullness of percussion sound, bronchial breathing. Formulate the diagnosis. Treatment plan. Give a clinical and pharmacological assessment of the prescribed treatment.

2. A 46-year-old man was diagnosed with pneumonia with multiple cavities of decay in both lungs. Treatment with penicillin was ineffective. When examining the bronchial lavage contents, Staphylococcus aureus was cultured, which is resistant to methylpenicillin. Treatment plan for the patient. Prescribe the most optimal antibacterial drug.

3. A 34-year-old patient was admitted with complaints of pain in the lumbar region, dysuric phenomena, an increase in body temperature to 37.5 - 38°C, chills. In addition, headaches, dizziness, fatigue are disturbing. On examination: ACT - 180/110 mm Hg. art., in urine - proteinuria - 0.5 g / l, leukocytes - 25 - 30 in the field of view, bacteriuria, cylindruria. In the blood - leukocytosis with a shift of the leukocyte formula to the left, ESR -18 mm / h. Substantiate the diagnosis of the disease. Make a plan for further examination and treatment of the patient.

4. A 43-year-old patient was admitted with complaints of pain in the lower abdomen radiating to the perineum, accompanied by tenesmus, frequent urination with cuts, weakness, sleep disorders, appetite. Body temperature is normal. In the anamnesis, severe hypothermia. In the general analysis of urine - leukocytes 20 - 25 in the field of view, erythrocytes - 8 -12 in the field of view, bacteria - completely in the field of view, oxalates in a small amount. Make a diagnosis of the disease. What additional tests are necessary for this? Select the range of drugs that are effective in this pathology, their dosage regimen and routes of administration.

5. A patient came to the emergency department with complaints of severe weakness, pain in the lower abdomen, nausea, vomiting, frequent loose stools. The stools are watery with a dirty-greenish tint. On examination - the skin is pale, the tongue is dry, covered with a dirty-white coating. Body temperature is 38.5°C, pulse - 96 beats per minute, ABP - 95/60 mm Hg. The abdomen is painful on palpation in the umbilical region, rumbling and splashing are noted. To clarify the diagnosis, outline a plan for examining the patient. Write a plan for comprehensive treatment. What groups of antibacterial agents are most effective for this pathology?

Test tasks for self-control:

1. Nitroimidazole derivatives are effective in the treatment of infections:
A. Caused by non-spore-forming anaerobes
B. Caused by Escherichia coli
C. Skin and mucous membranes
D. Sexually transmitted
E. Caused by Pseudomonas aeruginosa
2. The most common side effects of nitrofurans are:
A. Dyspeptic disorders (nausea, vomiting, abdominal pain)
B. Hematopoietic disorders (aplastic anemia, thrombocytopenia)
C. Allergic reactions (anaphylactic shock, Quincke's edema)

D. Candidiasis of the skin and mucous membranes, oral candidiasis.
3. Choose the correct statement:
A. Pefloxacin affects chlamydia
B. Fluoroquinolones can affect the growth of cartilage tissue
C. Fluoroquinolones are well absorbed when taken orally
D. Fluoroquinolones can interfere with the action of antifungal agents
E. Gyrase inhibitors have a "post-antibiotic effect"
against gram-negative bacteria
4. Among the side effects caused by sulfonamides is
Lyell's syndrome (toxic epidermal necrolysis). It ends
fatally in:
A. 40% of cases
B. 100%
C. 1%
D. 5%
E. 70-80%

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical pharmacology of antiviral and antifungal drugs"

Purpose:

To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of antiviral and antifungal drugs:
- antiherpetic drugs (acyclovir, valacyclovir);
- anticytomegalovirus drugs (ganciclovir);
- antiinfluenza drugs (remantadine, oseltamivir);
- interferons;
- polyenes (amphotericin B, nystatin, levorin);
- azoles (ketoconazole, miconazole, fluconazole, itraconazole);
- allylamines (terbinafine);
- other antifungal drugs (griseofulvin, potassium iodide).

Basic concepts (list of questions):

1. Viruses, classification, features of vital activity.

2. Main diseases caused by viruses.
3. Main classes of antiviral drugs.
4. Fungi, classification, features of life.
5. Main classes of antifungal drugs.
6. Diseases caused by fungal infection.
7. Helminths, features of life.
8. Diseases caused by different classes of helminths.
9. Main groups of anthelminthic drugs.

Plan

1. Theoretical questions:

Antiviral drugs

Antiviral drugs are classified depending on the chemical structure and mechanism of action. Nucleosides and nucleotides include acyclovir, ribavirin, ganciclovir, valacyclovir. Their mechanism of action is to interact with the DNA polymerase of the virus and integrate into DNA, resulting in the formation of defective DNA. Rimantadine belongs to cyclic amines and prevents the inclusion of the virus into host cells. It is used as a prophylactic against influenza A (especially A2) and B viruses. Neuraminidase inhibitors (zanamivir, oseltamivir) affect type A and B viruses, disrupting their aggregation and exit from cells. The drugs are used in the complex treatment of influenza. Protease inhibitors (saquinavir, indinavir, ritonavir, nelfinavir) inhibit HIV-1 and HIV-2 proteases, which leads to the synthesis of immature parts of HIV that are unable to support the further development of the infection.

Nucleotide and nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, stavudine, lamivudine), entering cells under the influence of cellular kinases, undergo phosphorylation to triphosphate, which acts as an inhibitor and simultaneously as a substrate for reverse transcriptase of retroviruses, including HIV. Due to this, the further formation of viral DNA is blocked due to the incorporation of triphosphate into the corresponding chains of its molecule.

Non-nucleoside reverse transcriptase inhibitors (nevirapine, efavirenz) bind directly to the enzyme and block the RNA- and DNA-dependent activity of DNA polymerase and, thus, cause the destruction of the catalytic center of the enzyme. The activity of drugs in this group is not associated with triphosphate.

Features of the kinetics of individual antiviral drugs are given in Table 30. Acyclovir is practically not absorbed when applied to the skin and mucous membranes. After intravenous or oral administration, the pharmacokinetic parameters in children over 1 year of age correspond to those in adults. Ribavirin binds poorly to plasma proteins, but accumulates in erythrocytes. It is excreted in the urine by glomerular filtration in unchanged form and in the form of metabolites. The half-life is about 2 weeks. Saquinavir is metabolized in the liver by the cytochrome P 450 isoenzyme - SUZA4.

Ritonavir is metabolized by the cytochrome P-450 system to hydroxylated inactive metabolites with their subsequent glucuronidation. Nelfinavir is partially metabolized by cytochrome P-450 isoenzyme CYP3A. Lamivudine is metabolized in the liver to a small extent (5-10% of the dose). Nevirapine is extensively metabolized by cytochrome P-450.

Efavirenz has different effects on cytochrome P-450 isoenzymes: it inhibits CYP2C9, CYP2C19, CYP3A4 and stimulates CYP2E1. Oseltamivir does not affect cytochrome P-450, but is metabolized by esterases. Inositol pranobex is metabolized in the body with the formation of uric acid.

Combination therapy with antiviral agents may result in physicochemical and/or pharmacokinetic interactions. Probenecid, when used with acyclovir, increases the level of the latter in the blood. Simultaneous administration of acyclovir and mycophenolate mofetil leads to an increase in the concentration of both drugs. Neuro- and nephrotoxicity may increase when acyclovir is used with other drugs that have the same toxicity. Probenecid increases the half-life of ganciclovir.

With simultaneous use of zidovudine and ganciclovir, the likelihood of neutropenia and anemia increases. Ganciclovir may increase the AUC of didanosine. With simultaneous administration of ganciclovir and imipenem/cilastatin, generalized seizures may occur. Drugs that inhibit the replication of dividing cells may enhance the toxic reactions of ganciclovir. These drugs include: dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B. Drugs metabolized by the CYP3A4 isoenzyme may alter the pharmacokinetics of saquinavir. The AUC was affected by concomitant administration of saquinavir and/or nelfinavir, ritonavir, and clarithromycin. Saquinavir increases the AUC of terfenadine, which is accompanied by cardiotoxicity. Saquinavir should not be used concomitantly with cisapride and astemizole. Saquinavir increases the concentration of ketoconazole. The AUC of saquinavir increases delavirdine and decreases nevirapine. Rifampicin, ifavirenz decrease the concentration of indinavir in the blood, and ketoconazole, delavirdine increase it. The concentration of indinavir, ritonavir, nelfinavir is also reduced by phenobarbital, phenytoin, carbamazepine, dexamethasone. With simultaneous use of indinavir with atorvastatin, lovastatin, simvastatin, the risk of myopathy, including rhabdomyolysis, increases. Ritonavir increases the blood concentration of amiodarone, astemizole, itraconazole, ketoconazole, bepridil, cisapride, clozapine, dihydroergotamine, ergotamine, piroxicam, propafenone, clonidine, terfenadine. Simultaneous use of ritonavir with clorazepam, diazepam, midazolam, trizolam, zolpidem increases the risk of respiratory disorders, asthenia. Ritonavir reduces the effectiveness of oral contraceptives, theophylline, increases the AUC of saquinavir, nelfinavir, indinavir, clarithromycin, trimethoprim, rifabutin, reduces the AUC of zidovudine, theophylline, ethinyl estradiol, sulfamethoxazole. Concomitant use with analgesics, antihistamines, antiarrhythmics and sedatives, antidepressants, antipsychotics, calcium antagonists is not recommended.

Rifampicin reduces the AUC of nelfinavir. Concomitant use of nelfinavir and terfenadine leads to an increase in the concentration and cardiotoxicity of the latter. Nelfinavir prolongs the sedative effect of triazolam and midazolam.

With simultaneous use with zidovudine, the level of diphenin in the blood decreases. Taking paracetamol during treatment with zidovudine increases the risk of neutropenia. Probenecid increases the half-life of zidovudine. Zidovudine metabolism is slowed down by: acetylsalicylic acid, codeine, morphine, indomethacin, ketoprofen, oxazepam, lorazepam, clofibrate. Zidovudine increases the nephro- and hematotoxicity of other drugs.

Didanosine should not be used simultaneously with tetracycline antibiotics; when used with ganciclovir, the risk of hemoglobin reduction in the blood increases. Simultaneous use of trimethoprim/sulfamethoxazole increases the concentration of lamivudine in the blood

plasma. Lamivudine inhibits intracellular phosphorylation of zalcetibine.

Ifavirenz inhibits the metabolism of terfenadine, astemizole, cisapride, midazolam, triazolam, which can lead to the development of dangerous side effects. Ifavirenz reduces the blood concentration of indinavir and increases the concentration of saquinavir, and also affects the pharmacokinetics of clarithromycin and increases the toxicity of ritonavir.

When using antiviral agents, the possibility of such side effects as damage to the gastrointestinal tract (nausea, vomiting, diarrhea), changes in the hepatobiliary system (increased activity of liver enzymes), hematotoxicity, manifestations of CNS lesions (headache, increased fatigue, drowsiness, confusion, hallucinations, tremor, psychosis, coma), allergic reactions and increased levels of creatinine and urea in the blood are also possible.

Antifungals

Antifungals are divided into three main groups:

1) drugs used in dermatology, this subgroup includes the following drugs for topical use:

a) antibiotics (nystatin, natamycin, griseofulvin);

b) imidazole and triazole derivatives (clotrimazole, miconazole, econazole, ketoconazole);

c) other antifungal drugs for topical use (salicylic acid, ciclopirox, terbinafine, tolciclate, naftifine).

For systemic use in dermatology, griseofulvin, terbinafine can be recommended.

2) drugs used in gynecology:

a) antibiotics (nystatin, natamycin);

b) imidazole derivatives (clotrimazole, miconazole, econazole, isoconazole);

3) antifungal agents for systemic use:

a) antibiotics (amphotericin B);

b) imidazole derivatives (ketoconazole);

c) triazole derivatives (fluconazole, itraconazole).

Antifungal agents have a different spectrum of action. Nystatin affects fungi of the genus Candida, and the antibiotic amphotericin B affects the following types of fungi: Asperigillus, Cryptococcus, Blastomycetes, Sporotrichum, Mucoromycetes, Coccidiomycetes, Histoplasma.

When administered orally, nystatin, amphotericin B are poorly absorbed from the gastrointestinal tract, ketoconazole, fluconazole, itraconazole are well absorbed. Amphotericin B after administration enters the peritoneal, synovial fluid. Therapeutic concentrations in almost all tissues, including cerebrospinal fluid, are created by fluconazole, itraconazole. Fluconazole is not biotransformed and is excreted unchanged in the urine.

Indications for the use of antifungal drugs are superficial (localized) or deep (systemic) mycoses. Doses of drugs for systemic use are prescribed taking into account kidney function.

When conducting combination therapy, it should be taken into account that the vast majority of antifungal drugs (fluconazole, ketoconazole, and others) are inhibitors of liver cytochrome P-450, which slows down metabolism and increases the toxicity of many drugs (theophylline, cisapride, astemizole, midazolam, triazolam, cyclosporine, oral contraceptives), or reduces the effectiveness, for example, of terfenadine. Antifungal drugs increase the toxicity of indirect anticoagulants, antiviral drugs.

Among the complications of therapy when using systemic drugs, gastrointestinal and liver disorders, as well as neuro- and hematotoxicity, are more common. The development of allergic reactions is possible.

2. Questions for self-control (list of questions):

1. Classification of antifungal drugs by chemical structure.
2. Features of the classification of antiviral drugs. What is the basis for their classification?
3. What are the main pharmacodynamic effects of antifungal drugs? Explain their clinical significance.
4. What is the general mechanism of development of pharmacological effects of antiviral drugs characterized by?
5. What are the main mechanisms of action of antiviral drugs?
6. What are the basic principles of choosing antiviral and antifungal drugs?
7. What criteria for assessing the effectiveness are the basis for their use?
8. What criteria and methods for assessing the safety of antiviral and antifungal drugs are you aware of?

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write prescriptions for the main antiviral, antifungal, anthelmintic drugs (tablets and/or ampoules), indicate the possible use, the spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.
2. Study the working medical history (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.
3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.
4. Identify signs during subjective and objective examination of the patient that characterize the development of a viral, fungal process, write a clinical diagnosis of the disease.
5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, select the drug for the patient.
6. Choose the optimal dosage regimen of the drug, taking into account the characteristics of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.
7. Identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.
8. To justify the need for combination drug therapy and to suggest possible options for a safe combination of drugs.
9. To make a forecast of side effects of drugs prescribed to the patient and to outline a

plan for their detection at the early stages.

10. To justify the duration of basic and maintenance therapy.

B. Solution of situational tasks.

1. Patient L., 20 years old, with acute respiratory viral infections (pharyngitis, rhinitis) and an increase in body temperature to 390C was prescribed biseptol to prevent bacterial complications.

Evaluate the correctness of the medical tactics. Your advice.

2. A 42-year-old patient was brought to the department with complaints of an increase in body temperature to 39.8oC, cough with a small amount of sputum, sweating. On objective examination: in the lungs on the right below the scapula there is a zone of dullness of percussion sound, hard breathing, moist wheezing, fungi of the genus Candida were found in the analyte of sputum.

Your diagnosis? Prescribe therapy, name the 1st line drug, what antifungal drugs do you suggest.

3. A 23-year-old patient with community-acquired right-sided pneumonia, treated with benzylpenicillin at a dose of 12 million units per day, has a subfebrile temperature on the third day, dullness of percussion sound in the lower lobe of the lung, and moist rales.

In complex therapy, prescribe the optimal antifungal drug

4. A 32-year-old woman was admitted to the therapeutic department with complaints of an increase in body temperature to 38.50 C, cough with a small amount of yellow sputum, and sweating. Objectively: in the lungs on the left below the angle of the scapula, there is a zone of dullness of percussion sound, weakened vesicular breathing, and moist rales. The doctor on duty prescribed the patient benzylpenicillin sodium i/m 4 times a day at 2,500,000 units.

Formulate a preliminary diagnosis. Assign the necessary additional examination of the disease. Evaluate the treatment tactics of the doctor on duty. If necessary, correct the pharmacotherapy. Indicate the methods of monitoring the effectiveness of the treatment carried out in the hospital. Prescribe an antifungal drug.

Test tasks for self-control:

1. Among the listed drugs, the following have antifungal action:

A. Kefzol

B. Fluconazole

C. Rifampicin

D. Streptomycin

E. Lincomycin

2. After long-term use of the drug prescribed for an acute respiratory disease, the

patient developed the following symptoms: headache, dizziness, tinnitus, nausea, pain in the epigastric region. Which drug could cause a similar clinical picture?

A. Vitamin C.

B. Acetylsalicylic acid.

C. Naphthyzinum.

D. Bromhexine.

E. Midantan.

3. Myelosuppression is a very serious side effect of all drugs, except:

A. –vinblastine

B. –cyclophosphamide

C. –cytarabine

D. –acetylsalicylic acid

E. Acyclovir

4. Antiviral drugs of plant origin:

A. Flavozid

B. Ganciclovir.

C. Famciclovir.

D. Ribamidil.

E. Zidovudine.

5. Onychomycosis is a disease that manifests itself:

A. Fungal infection of the nail plates of the fingers

B. Candida infection of the inguinal folds

C. Black dots in places of broken hair

D. Erosions and cracks in the corners of the mouth

E. Dry cough, headache, hyperthermia.

6. Choose a drug for the treatment of candidal lesions of the mucous membranes of the genital organs:

A. Nystatin

B. Fluconazole

C. Metronidazole

D. Tetracycline

E. Linex

7. A 26-year-old patient with disseminated herpes. Choose a drug for the treatment of this patient:

A. Acyclovir

B. Fluconazole

C. Levofloxacin

D. Metronidazole

E. All of the above drugs are used for complex therapy

8. Which of the listed drugs is used for helminthiasis?

A. Amikacin

B. Diacarb

C. Amphotericin B

D Levamisole

E. Nitroxoline

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

"Clinical and pharmacological characteristics of drugs that affect the functions of the gastrointestinal tract"

Purpose:

To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of drugs that normalize the functions of the gastrointestinal tract:

- antisecretory (proton pump inhibitors, H2-histamine blockers, M-cholinoblockers);
- antacids (systemic and non-systemic);
- prokinetics (metoclopramide, domperidone);
- gastrocytoprotectors (sucralfate, misoprostol);

- antihelicobacter (amoxicillin, clarithromycin, tetracycline, metronidazole, colloidal bismuth);

- probiotics, prebiotics, symbiotics.

Basic concepts (list of questions):

1. Functions of the gastrointestinal tract.

2. Anatomical and physiological features of the hollow organs of the gastrointestinal tract.

3. Physiological regulation of secretory and motor-evacuation functions of the gastrointestinal tract.

4. Main symptoms and syndromes, diseases of the gastrointestinal tract: etiology, pathogenesis.

5. Helicobacter pylori and other bacteria that cause infectious and inflammatory processes of the gastrointestinal tract: microbiology.

6. Antisecretory drugs.

7. Antihelicobacter drugs.

8. Antacid drugs.

9. Prokinetics, antiemetics, antiemetics.

10. Means for correction and restoration of microbiocenosis of various parts of the gastrointestinal tract.

Plan

1. Theoretical questions:

Diseases of the esophagus, stomach, duodenum, small and large intestines, as a rule, are accompanied by a violation of their physiological functions. Correct assessment of the nature and degree of functional disorders is the basis for their effective drug correction. In the complex of therapeutic measures, the leading role belongs to drugs that normalize secretory and motor functions, regulate appetite, restore intestinal flora, accelerate reparative processes, etc. Effective correction of these functions is a necessary condition for positive dynamics of the disease, faster recovery or remission, restoration of working capacity.

Pharmacotherapy of digestive tract dysfunctions

A large arsenal of drugs is used for various diseases of the gastrointestinal tract - GERD, gastritis, peptic ulcer, enteritis, colitis. Let's consider the main groups of drugs used to treat digestive tract dysfunctions.

Drugs used for disorders of the secretory function of the stomach

Drugs used for reduced secretory function of the stomach - replacement therapy.

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

In case of insufficient secretion of gastric juice to improve food digestion, the following are prescribed as replacement therapy: natural gastric juice, pepsin, diluted

hydrochloric acid.

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

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

Acidin-pepsin (betacid) is available in tablets of 0.25 and 0.5 g, each of which contains one part of pepsin and four parts of acidin, the latter, when hydrolyzed, releases free hydrochloric acid. The drug is used for the same indications as pepsin and natural gastric juice. The acidin-pepsin tablet is dissolved in 1/3 cup of water. The drug is prescribed 3-4 times a day during or after meals. The course of treatment is 30-45 days.

Drugs used for increased secretory function of the stomach.

With increased secretion of the gastric glands, a syndrome develops associated with an increase in the production of hydrochloric acid by parietal cells, resulting in an increase in the activity of pepsin - an excreta of the chief cells of the gastric mucosa. An increase in the production of hydrochloric acid and an increase in the activity of pepsin leads to a decrease in the production of mucin - the main component of mucus covering the mucous membrane of the stomach and intestines. Hyperacidity, increased pepsin activity and mucin deficiency lead to damage to the mucous membrane of the stomach and duodenum (inflammation, erosion, ulcers) and contribute to the development of a syndrome of increased activity of the acid-peptic factor.

Three subgroups of agents are used for pathogenetic therapy of patients with this syndrome:

1. Agents that reduce the function of the gastric glands or inhibitors of gastric secretion: a) M-holinoblockers; b) ganglioblockers; c) tranquilizers; d) H2-histamine blockers; e) proton pump blockers.

2. Antacids, or drugs that neutralize hydrochloric acid.

3. Agents that protect the gastric and duodenal mucosa from acid-peptic action and improve reparative processes (film-forming agents).

Agents that reduce the secretory function of the stomach include, first of all, M-holinoblockers. As a rule, these are drugs of non-selective action: atropine and atropine-like drugs (platifillin, metacin). These drugs reduce the basal and nocturnal secretion of gastric juice and hydrochloric acid. However, it should be said that M-holinoblockers of non-selective action reduce gastric contractions and tone to a greater extent than they affect the secretion of the glands. The limitation of the use of M-holinoblockers is also due to the wide range of effects that they cause, in addition to the effect on the gastrointestinal tract (tachycardia, dryness of the mucous membranes, visual impairment). Therefore, M-holinoblockers of non-selective action are currently assigned a secondary role in the treatment of patients with peptic ulcer disease, gastritis, erosions; they are used only in combination

with other drugs. At the same time, drugs created in the 80s that selectively block mainly M-1-holinoreceptors of the stomach, in particular pirenzepine (gastrocepinum; in tab. 0.025 g). This tricyclic compound is a derivative of benzodiazepine. All effects of pirenzepine have a peripheral effect, since the blood-brain barrier is impermeable to it. Pharmacodynamics of the drug: blocking M-1-holinoreceptors of the parasympathetic ganglia of the stomach. In addition, pirenzepine selectively blocks M-1-cholinoreceptors of parietal cells (G-cells), which produce gastrin (the strongest stimulator of hydrochloric acid secretion). Unlike atropine, pirenzepine (gastrocepin) does not have atropine-like effects on the heart, smooth muscles of the stomach, gastrointestinal tract, gallbladder, and blood vessels; inhibits basal and pentagastrin- and insulin-stimulated gastric secretion; has a cytoprotective effect on the gastric mucosa. The drug is prescribed at 50 mg 2 times a day.

Ganglion blockers (benzohexonium, pyrylene, pentamine) reduce both the total volume of gastric secretion and the content of hydrochloric acid in gastric juice, but the non-selectivity of their action on vegetative ganglia creates a lot of side effects. Therefore, ganglion blockers are used only in extremely severe cases of peptic ulcer disease.

Tranquilizers (diazepam) can also reduce nocturnal secretion of gastric glands, however, this group is rarely used for this purpose, the exception being the stress mechanism of ulcer formation.

A new word in the treatment of peptic ulcer disease is the creation by English pharmacologists in the late 70s of new antisecretory drugs called H2-histamine blockers, that is, drugs that block H2 histamine receptors. Histamine, as has been shown recently, plays a key role in the production of hydrochloric acid. Under its influence, the secretion of hydrochloric acid increases sharply.

H2-receptor blockers are one of the strongest known drugs that suppress the secretory function of the stomach. As is known, there are three types of histamine receptors. H1-histamine receptors, which are localized in small arterial vessels, bronchi, smooth muscles of the intestine, and heart. Drugs that block these receptors (diphenhydramine, tavegil, etc.), eliminate the effects of histamine on the corresponding organs. H2-histamine receptors are located in the parietal cells of the gastric mucosa, in the myometrium, and also in some vessels. Agents that block this type of receptor reduce the secretion of gastric juice. To a greater extent, H2-histamine blockers inhibit basal and nocturnal secretion. The third type of histamine-sensitive receptors is located in the vestibular apparatus; agents that block them are close to betaserc.

Five generations of H2-histamine blockers are distinguished. A representative of the I generation is cimetidine, synthesized in 1975. Cimetidine is more effective in duodenal ulcer than gastric ulcer. In 1979, another drug of this class, belonging to the II generation of H2-histamine blockers, was released abroad - ranitidine (zantak, ranisan; Ranitidini hydrochloridum; in tab. 0.15 and 0.3). The drug is similar in its pharmacological effects to cimetidine, but without antiandrogenic action, and is also more active (5-10 times) and has a high blocking activity and selectivity of action against H2-histamine receptors than cimetidine. Ranitidine is also less toxic. There are drugs of H2-histamine blockers of the III generation, in particular, famotidine (kvamatel, gastrosidine, ulfamide), synthesized in 1984. In 1987, nizatidine appeared - a representative of the IV generation of H2-histamine blockers, later - the V generation - roxatidine.

H2-blockers are the most common drugs used in the treatment of peptic ulcer disease.

This is due, first of all, to their ability to reduce the secretion of hydrochloric acid. In addition, H2 blockers inhibit pepsin production, increase gastric mucus production, increase prostaglandin synthesis in the gastric mucosa, increase bicarbonate secretion, improve microcirculation, normalize motor function of the stomach and duodenum. H2 blockers are also used in the treatment of a wide range of diseases of the gastrointestinal tract, including: gastroesophageal reflux disease, acute and chronic pancreatitis, dyspepsia, respiratory reflux-induced diseases, including reflux-induced bronchial asthma, Zollinger-Ellison syndrome, chronic gastritis and duodenitis, Barrett's esophagus and other acid-dependent diseases. Ranitidine has fewer side effects typical of cimetidine, and subsequent generation drugs have even fewer. At the same time, the activity of famotidine is 20-60 times higher than that of cimetidine and 3-20 times higher than that of ranitidine. Compared with ranitidine, famotidine more effectively increases pH and reduces the volume of gastric contents. The duration of antisecretory action of ranitidine is 8-10 hours, and famotidine is 12 hours. The 4th and 5th generation H2 blockers nizatidine and roxatidine in practice differ little from famotidine and do not have significant advantages over it, and roxatidine is even slightly inferior to famotidine in acid-suppressing activity. Due to side effects, cimetidine is not currently used. Ranitidine, whose acid-suppressing ability is slightly inferior to famotidine (or at least does not exceed it), has a wider range of side effects. Other single-component H2 blockers also do not have noticeable advantages over famotidine and, forced, in addition, to compete with proton pump inhibitors, have not become widespread in the pharmacotherapy of gastrointestinal diseases. Therefore, today, from the point of view of practical gastroenterology, only famotidine and ranitidine are relevant among H2 blockers.

H+,K+-ATPase inhibitors - Omeprazole (0.02 capsules) - is a racemic mixture of two enantiomers, reduces acid secretion by specific inhibition of the acid pump of parietal cells. With a single administration, the drug acts quickly and provides reversible inhibition of acid secretion. Omeprazole is a weak alkali, concentrates and converts into an active form in the acidic environment of the tubular cells of the parietal layer of the gastric mucosa, where it is activated and inhibits the H+,K+-ATPase of the acid pump. The drug has a dose-dependent effect on the last stage of acid synthesis, inhibits both basal and stimulated secretion regardless of the stimulating factor. Intravenous administration of omeprazole provides dose-dependent inhibition of hydrochloric acid in humans. To achieve a rapid decrease in intragastric acidity, intravenous administration of 40 mg of omeprazole is recommended, after which a rapid decrease in intragastric secretion occurs, which is maintained for 24 hours.

The degree of inhibition of acid secretion is proportional to the area under the curve (concentration-time AUC) of omeprazole and not proportional to the actual concentration of the drug in the blood at a given time. Tachyphylaxis has not been observed during treatment with omeprazole. A decrease in gastric acid secretion under the action of proton pump inhibitors or other acid-inhibiting agents leads to an increase in the growth of normal intestinal microflora, which in turn may lead to a small increase in the risk of developing intestinal infections caused by bacteria such as Salmonella and Campylobacter.

The volume of distribution in healthy subjects is 0.3 l/kg, a similar figure is determined in patients with renal failure. In elderly patients and in patients with renal insufficiency, the volume of distribution is somewhat reduced. The binding of omeprazole to plasma proteins is about 95%. After administration, the mean terminal elimination half-life is 0.3 to 0.6 l/min. There is no change in the half-life during treatment. Omeprazole is

completely metabolized by cytochrome P-450 (CYP) in the liver. The metabolism of the drug depends mainly on the specific isoenzyme CYP2C19 (S-mephine hydroxylase), which is responsible for the formation of the main metabolite hydroxyomeprazole. The metabolites affect gastric acid secretion. About 80% of an intravenously administered dose is excreted as metabolites in the urine, and the rest in the feces. In patients with impaired renal function, the excretion of omeprazole did not undergo any changes. An increase in the half-life is determined in patients with impaired liver function, however, omeprazole does not accumulate. Indications for use: duodenal ulcer, peptic ulcer, reflux esophagitis, treatment of Zollinger-Ellison syndrome.

Side effects - omeprazole is generally well tolerated. Side effects have been reported, however, in most cases a true relationship between the effect and treatment has not been established.

Skin - skin rashes and itching of the skin. In some cases, photosensitivity reaction, erythema multiforme, alopecia. Musculoskeletal system - in some cases, arthralgia, muscular weakness, muscle pain. Central and peripheral nervous systems: headache, hyponatremia, dizziness, paresthesia, drowsiness, insomnia. In some cases, patients with severe concomitant diseases may experience depression, agitation, aggressiveness and hallucinations. Gastrointestinal tract: diarrhea, constipation, abdominal pain, nausea, vomiting, flatulence. In some cases, dry mouth, stomatitis, gastrointestinal candidiasis. Liver system: in some cases, increased activity of liver enzymes, encephalopathy may develop in patients with severe liver diseases. Endocrine system: in some cases, gynecomastia. Hematopoietic system: in some cases, leukopenia, thrombocytopenia, agranulocytosis and pancytopenia. Others: general malaise, hypersensitivity reaction in the form of urticaria (rarely), in some cases, angioedema, fever, bronchospasm, interstitial nephritis, anaphylactic shock.

Antacids. This group includes agents that neutralize hydrochloric acid and those that reduce the acidity of gastric juice. These are antacids. Usually these are chemical compounds with the properties of weak alkalis, they neutralize hydrochloric acid in the lumen of the stomach. Reducing acidity is of important therapeutic importance, since the activity of pepsin and its digestive effect on the gastric mucosa depend on its amount. The optimal pH value for pepsin activity is in the range from 1.5 to 4.0. At pH = 5.0, pepsin is active. Therefore, it is desirable that antacids raise the pH no higher than 4.0 (it is optimal that when taking antacids, the pH of gastric juice is 3.0 - 3.5), which does not disrupt the digestion of food. Usually, the pH of gastric contents normally fluctuates within 1.5 - 2.0. The pain syndrome begins to subside when the pH becomes more than 2.

There are systemic and non-systemic antacids. Systemic antacids are drugs that are able to be absorbed, and therefore have effects not only in the stomach, but can also lead to the development of alkalosis in the body as a whole. Non-systemic antacids are not absorbed, and therefore are able to neutralize acidity only in the stomach, without affecting the acid-base state of the body. Antacids include sodium bicarbonate (baking soda), calcium carbonate, aluminum and magnesium hydroxide, magnesium oxide. Usually these substances are used in various dosage forms and in various combinations. Systemic antacids include sodium bicarbonate and sodium citrate, all other drugs listed above are non-systemic.

Sodium bicarbonate (baking soda) is a compound that is readily soluble in water and reacts quickly in the stomach with hydrochloric acid. The reaction occurs with the formation of sodium chloride, water and carbon dioxide. The drug acts almost instantly. Despite the fact

that sodium bicarbonate acts quickly, its effect is short and weaker than that of other antacids. The carbonic acid formed during the reaction stretches the stomach, causing bloating, belching. In addition, taking this drug may be accompanied by a "rebound" syndrome. The latter is that a rapid increase in pH in the stomach leads to the activation of parietal G-cells of the central part of the stomach, which produce gastrin. Gastrin stimulates the secretion of hydrochloric acid, which leads to the development of hyperacidity after the antacid is discontinued. Usually, the "rebound" syndrome develops after 20-25 minutes. As a result of good absorption from the gastrointestinal tract, sodium bicarbonate can cause systemic alkalosis, which is clinically manifested by decreased appetite, nausea, vomiting, weakness, abdominal pain, spasms and muscle cramps. This is a rather dangerous complication that requires immediate discontinuation of the drug and assistance to the patient. Given the severity of these side effects, sodium bicarbonate is used extremely rarely as an antacid.

Non-systemic antacids, as a rule, are insoluble, act in the stomach for a long time, are not absorbed, and act more effectively. When they are used, the body does not lose either cations (hydrogen) or anions (chlorine), and there are no changes in the acid-base state. The action of non-systemic antacids develops more slowly, but lasts longer.

Aluminum hydroxide (aluminium hydroxide; Aluminii hydroxydum) is a drug with moderate antacid action, acts quickly and effectively, a significant effect is manifested after about 60 minutes. The drug binds pepsin, reduces its activity, inhibits the formation of pepsinogen and increases mucus secretion. One gram of aluminum hydroxide neutralizes 250 ml of decinormal hydrochloric acid solution to pH = 4.0. In addition, the drug has an astringent, enveloping and adsorbing effect. Side effects: not all patients tolerate the astringent effect of the drug well, which may manifest as nausea, taking aluminum drugs is accompanied by constipation, therefore aluminum-containing drugs are combined with magnesium drugs. Aluminum hydroxide helps to remove phosphates from the body. The drug is indicated for diseases with increased secretion of gastric juice (hydrochloric acid): ulcer, gastritis, gastroduodenitis, food poisoning, flatulence. Aluminum hydroxide is prescribed orally in the form of a 4% aqueous suspension, 1-2 teaspoons per dose (4-6 times a day).

Magnesium oxide (Magnesii oxydum; powder, gel, suspension) - burnt magnesia - a strong antacid, more active than aluminum hydroxide, acts faster, longer and has a laxative effect. Each of the listed antacids has both advantages and disadvantages. In this regard, their combinations are used. The combination of aluminum hydroxide in the form of a special balanced gel, magnesium oxide and D-sorbitol made it possible to obtain one of the most common and effective, at present, antacid drugs - Almagel (Almagel; 170 ml; the drug got its name from the words al-aluminum, ma-magnesium, gel-gel). The drug has antacid, adsorbing and enveloping effect. The gel-like dosage form contributes to the uniform distribution of ingredients over the surface of the mucous membrane and prolongation of the effect. D-sorbitol promotes bile secretion and laxative effect. Indications for use: gastric and duodenal ulcers, acute and chronic hyperacid gastritis, gastroduodenitis, esophagitis, reflux esophagitis, Zollinger-Ellison syndrome, heartburn in pregnancy, colitis, flatulence. There is a drug Almagel-A, in which anesthesin is also added to the composition of Almagel, which provides both a local anesthetic effect and inhibits gastrin secretion. Almagel is usually used 30-60 minutes before meals, as well as within an hour after meals. The drug is prescribed individually depending on the localization of the process, the acidity of gastric juice, etc. Similar drugs to Almagel: - Gastrogel; - Phosphalugel contains aluminum phosphate and

colloidal gels of pectin and agar-agar, which bind and absorb toxins and gases, as well as bacteria, reduce the activity of pepsin; - Megalak; - Mylanta contains aluminum hydroxide, magnesium oxide and simethicone; - Gastal - tablets, which include: 450 mg of aluminum hydroxide - magnesium carbonate gel, 300 mg of magnesium hydroxide.

Currently, one of the most popular drugs from the group of antacids is the drug Maalox (Maalox). The drug contains aluminum hydroxide and magnesium oxide. Maalox is available in the form of a suspension and in tablets; 5 ml of Maalox suspension contains 225 mg of aluminum hydroxide, 200 mg of magnesium oxide and neutralizes 13.5 mmol of hydrochloric acid; the tablets contain 400 mg of aluminum hydroxide and magnesium oxide, so they have a higher acid-neutralizing activity (up to 18 mmol of hydrochloric acid). Even more active is Maalox-70 (up to - 35 mmol of hydrochloric acid). The drug is indicated for gastritis, duodenitis, gastric ulcer and duodenal ulcer, reflux esophagitis.

Drugs that protect the gastric mucosa from acid-peptic action and improve reparative processes

1. Bismuth preparations (Vicalin, De-Nol).
2. Sucralfate (Venter).
3. Prostaglandin preparations.
4. Dalargin.

Bismuth preparations are used as astringents and antiseptics in the treatment of patients with peptic ulcer disease. Most often these are combined tablets - Vicalin (bismuth basic nitrate, sodium bicarbonate, powder of calamus rhizome, buckthorn bark, rutin). In recent years, drugs have entered medical practice that more strongly protect the mucous membrane from acid-peptic action. These are second-generation colloidal bismuth preparations, one of which is De-nol (De-nol; 3-potassium dicitrate bismuthate; each tablet contains 120 mg of colloidal bismuth subcitrate). This drug envelops the mucous membrane, forming a protective colloidal-protein layer on it. It does not have antacid action, but exhibits antipeptic activity by binding pepsin. The drug also has an antimicrobial effect, it is much more effective than bismuth-containing antacids and increases the resistance of the mucous membrane. De-nol cannot be combined with antacids. The drug is used for any localization of ulcers, it is highly effective for: gastric and duodenal ulcers that do not heal for a long time; peptic ulcer in smokers; prevention of relapses of peptic ulcer disease; chronic gastritis. Prescribe 1 tablet three times a day half an hour before meals and 1 tablet before bedtime. De-nol is contraindicated in severe renal failure.

Venter (sucralfate; in tab. 0.5 g) is a basic aluminum salt of sucrose octasulfate. The antiulcer effect is based on binding to proteins of necrotic tissue, into complex complexes that form a strong barrier. Locally neutralizes gastric juice, slows down the action of pepsin, the drug also absorbs bile acids. At the site of the ulcer, the drug is fixed for six hours. Venter and de-nol cause scarring of duodenal ulcers after three weeks. Sucralfate is used 1.0 g four times a day before meals, as well as before bedtime. Side effect: constipation, dry mouth.

Solcoseryl - a protein-free extract from the blood of cattle. Protects tissues from hypoxia and necrosis. Used for trophic ulcers of any localization. Apply 2 ml 2-3 times a day, administered intravenously and intramuscularly, until the ulcer heals.

Prostaglandin preparations: misoprostol (cytotec). Under the influence of these preparations, the acidity of gastric juice decreases, the motility of the stomach and intestines increases, and favorable effects on the ulcer niche in the stomach are determined. The

preparations have a reparative, hypoacid (by increasing mucus formation), and hypotensive effect. Misoprostol (Misoprostol; in tab. 0.0002) is a prostaglandin E2 preparation obtained from plant raw materials. Synonym - cytotec. Prostaglandin preparations are indicated for acute and chronic gastric and duodenal ulcers. Side effects: transient diarrhea, mild nausea, headache, abdominal pain.

Dalarginum (Dalgarginum; in amp. and flak. 0001) - a drug of peptide nature, which promotes the healing of gastric and duodenal ulcers, reduces the acidity of gastric juice, has a hypotensive effect. The drug is indicated for exacerbation of gastric and duodenal ulcers.

Drugs that have a specific antibacterial effect on Helicobacter pylori: de-nol, metronidazole, amoxicillin, clarithromycin, tetracycline.

The drug metronidazole has a wide spectrum of action against protozoa (trichomonads, amoeba, giardia), is effective on anaerobic microflora (in diseases of the chest, urinary tract), as well as on Helicobacter pylori. The most effective antibacterial effect is observed when metronidazole and de-nol are combined.

Drugs that affect intestinal motility

Drugs that reduce intestinal motility

In spastic conditions of the intestine, the following drugs are used to reduce its tone and motor activity:

1) M-cholinoblockers (drugs of the atropine group): - atropine; - metacin; - scopolamine; - platifillin. Drugs of this subgroup eliminate excessive activity of the vagus nerve.

2) Ganglioblockers: - pyrylene; - benzohexonium.

3) Myotropic antispasmodics - papaverine (Papaverini hydrochloridum; in tab. 0.04 and in amp. 2 ml of 2% solution) - eliminates painful intestinal spasms; - no-spa (Nospanum; in tab. 0.04 and in amp.) - a modified papaverine molecule. In essence, the last two drugs have the same effects. Depending on the degree of pain syndrome, tablet or injection forms of drugs are used.

The following agents that reduce intestinal peristalsis (antidiarrheals) are also distinguished: 1) adsorbents (activated carbon, cholestyramine), 2) astringents (tannin), 3) enveloping, 4) antidiarrheal agents that eliminate increased vagal activity (reasec, imodium). This subgroup of agents is an antagonist of acetylcholine stimulation of the intramural nerve plexuses of the intestine.

Imodium does not have a central effect, since it does not penetrate the blood-brain barrier. The active substance of the drug is a haloperidol derivative loperamide. It is available in two dosage forms, namely, in capsules of 0.002 and in the form of a solution for oral administration (vials of 100 ml). The pharmacological action of Imodium is associated with direct stimulation of the opioid receptors of the intestine, which leads to a pronounced decrease in the tone and motility of the latter. At the same time, the drug increases the tone of the anal sphincter. The effect of Imodium develops quickly and lasts 4-6 hours. The indication for use is acute diarrhea ("travelers' diarrhea"). A single dose is 2-4 mg, the daily dose should not exceed 16 mg. Side effects: from the gastrointestinal tract, dry mouth, abdominal pain, bloating and discomfort, nausea, constipation may develop; from the central nervous system, sometimes patients note a feeling of fatigue, drowsiness, dizziness and headache. Allergic reactions are possible.

Means that enhance intestinal motility

In this subgroup, first of all, it should be said about the means that enhance intestinal motility by affecting its receptors. At the same time, the stimulating effect can be provided by means that act on afferent and efferent innervation.

Means that increase the tone of cholinergic nerves: - M-cholinomimetics (aceclidine) and anticholinesterase agents (proserin). These drugs are successfully used for hypotension or atony of the intestine. Sometimes vasopressin is used, which has a stimulating myotropic effect.

Means that enhance the contractile activity of the intestine include laxatives. Laxatives are agents that accelerate intestinal emptying by increasing intestinal peristalsis and increasing the excretion of water with feces. The latter is a consequence of impaired absorption of water from the intestinal lumen, or increased secretion. Currently, a large number of laxative drugs have been created, hence the many classifications of drugs in this group.

I. Laxatives that affect the entire intestine: saline laxatives: magnesium (Epstein-Barr) and sodium (Glauber's salt) sulfates. When they are taken, the osmotic pressure in the intestinal lumen increases, which prevents the absorption of the liquid part of the chyme and juices. The volume of intestinal contents increases, this leads to a violation of mechanoreceptors and increased peristalsis. Saline laxatives act on the entire intestine, the effect occurs 1-3 hours after administration. Saline laxatives are prescribed for acute poisoning, for acute constipation, before surgery to cleanse the intestines, before proctological examinations, and also together with some anthelmintic drugs to expel worms. Saline laxative is diluted in a quarter cup of water and washed down with two cups of water. These are the strongest laxatives, they act the fastest and stop further absorption of poisons from the intestines.

II. Laxatives that act mainly on the small intestine: castor oil (Oleum Ricini; in caps. 1.0 and in flak. 30.0 and 50.0) in the duodenum under the action of pancreatic lipase is hydrolyzed with the release of glycerin and ricinolic acid. The latter irritates the cells of the intestinal mucosa, inhibits the process of active absorption of water and electrolytes, which leads to increased motility and accelerates intestinal emptying. Polyhydric alcohol - glycerin, enveloping the mucous membrane, facilitates the movement of the contents. The effect manifests itself after 2-6 hours, sometimes there are moderate spastic abdominal pain. Indications for use are the same as for saline laxatives, and in addition, during X-ray examination of the intestine (they act more gently than saline laxatives), as well as in complex stimulation of labor and, earlier, in the treatment of enteritis (old method). Preparations of this group are contraindicated in acute poisoning with fat-soluble poisons (kerosene, gasoline).

III. Laxatives that act on the large intestine. Preparations that act mainly on the large intestine are of great practical importance. In this group of drugs, the following preparations are distinguished: - of plant origin; - synthetics; - various medicines.

Of the preparations of plant origin containing the so-called anthraglycosides (consisting of sugars and anthracene derivatives, for example, emodin and chrysophanic acid), preparations of rhubarb root, senna leaves and roots, Alexandrian leaves, buckthorn root, licorice root, figs, plums are used. Laxatives of plant origin are used in the form of powders, tablets, dry extracts, tinctures, drops, suppositories. In the small intestine, anthraglycosides (emodin, chrysophanic acid) are absorbed, enter the blood, and in the colon, on the contrary, they are released from the blood into its lumen and irritate the receptors of the colon, which

causes muscle contraction of this entire section of the intestine. The tone of the colon increases. Some of these compounds enter the intestine in an undigested form. Due to the action of the drugs, the reduced evacuation function (slow defecation) is normalized. Diarrhea usually does not occur, but a calm restoration of the act of defecation occurs.

Synthetic agents include phenolphthalein in the form of tablets (purgen), isaphenin, bisacodyl, picosulfate (guttalax). The laxative effect develops after 6-8-12 hours. There are also standardized drugs: califig (fig, senna - extracts, clove oil and oil of Alexandria leaf, mint), regulax (senna - leaves and fruits, fig and plum puree, liquid paraffin), kafiol. The main indications for the use of these drugs: chronic constipation; acute constipation before and after operations; to facilitate defecation in hemorrhoids, to facilitate defecation in rectal fissures; intestinal atony caused by stress, malnutrition, dietary disorders, a sedentary lifestyle. These drugs are taken once a day, usually before bedtime, depending on the habit of the act of defecation. When prescribing these drugs, digestion and absorption in the small intestine are not disturbed. The drugs are usually well tolerated, but with prolonged use of some of them (rhubarb preparations), chronic severe liver dysfunction sometimes occurs. Such drugs should not be prescribed to nursing mothers, since, being excreted in milk, they can cause diarrhea in a child. There may also be individual intolerance to the drugs. It should be remembered that with prolonged use, electrolyte losses, especially potassium, as well as albuminuria, hematuria are possible.

Synthetic drugs are also used for chronic constipation - phenolphthalein (purgen) in the form of tablets, isaphenin, bisacodyl, picosulfate (guttalax).

Laxatives of any mechanism of action should not be prescribed for a long time, since there is an intensive loss of cations, especially potassium. Hypokalemia, hypokalemia develop, and the synthesis of acetylcholine in general and in the intestine in particular is disrupted. This is accompanied by constipation, anorexia, muscle weakness, inhibition of reflexes, and bladder paresis.

Emetics and antiemetics

Emetics

Vomiting: 1) a protective act (liberation of the stomach from poisons and toxins), a physiological process, 2) a concomitant process, worsening the condition of the body (toxicosis, cytostatic and radiation therapy, seasickness). Vomiting is controlled by the corresponding center of the medulla oblongata, the stimulation of which causes the act of vomiting.

Drugs that cause vomiting act: 1) centrally (morphine and other narcotic analgesics, apomorphine, antitumor drugs) 2) reflexively, irritating the receptors of the gastric mucosa (copper sulfate, zinc sulfate). As the main medicinal emetic, apomorphine (Apomorphini hydrochloridum; in ampoules of 1.5 and 10 ml of 1% solution) is used - a specific agonist of D-receptors, a semi-synthetic alkaloid. This drug has some properties of morphine (weak analgesic activity, inhibition of the respiratory center). However, the drug most pronouncedly acts on the chemoreceptor zone of the medulla oblongata (trigger zone), which determines its pronounced effect. Apomorphine, like morphine, directly inhibits the vomiting center. In recent years, the effect of apomorphine on neurobehavioral (stereotypes, aggressiveness) functions due to the effect on D-receptors has been established. Neuroleptics are antagonists of apomorphine.

Indications for the use of apomorphine as an emetic: 1) when it is necessary to quickly

remove toxic substances and poor-quality products from the stomach, especially if it is not possible to wash the stomach. With subcutaneous administration (0.2 - 0.5 ml), the effect develops after a few minutes; 2) rarely as an expectorant in a mixture for adults at 0.001; 3) in narcology in the treatment of patients with chronic alcoholism.

Antiemetics

Antiemetic effect can be provided by drugs that act on different links of nervous regulation of the act of vomiting:

1) if vomiting is caused by local irritation of the stomach, then after removal of the irritating substance, enveloping (flax seed preparations, rice, starch, etc.), astringent (tannin, tanalbin, bird cherry fruits) agents can be used, and better - a combined antacid drug - Almagel-A;

2) if vomiting is caused by excitation of neurons of the vomiting center (or trigger zone), then other agents are used. Previously, sedatives and hypnotics were used, but now modern neurotropic drugs have been created. These drugs can be divided into the following subgroups:

- M-holinoblockers, which are used mainly for the prevention and treatment of sea and air sickness, as well as for Meniere's disease. This is a disease in which vomiting is caused by irritation of the vestibular apparatus. As a rule, M-cholinoblockers such as scopolamine and hyoscyamine are used. The above alkaloids, along with atropine, are contained in blekot, dope, scopolia.

- Antihistamines - H1-histamine blockers (diphenhydramine, diprazine - the most active and even effective for vomiting of any origin, including vestibular vomiting).

Very effective antiemetics are neuroleptics. This is the third subgroup of neurotropic antiemetics.

- Neuroleptics and, above all, phenothiazine derivatives: aminazine, triphthazine, etaperazine, fluorophenazine, thiethylperazine (torecan). Thiethylperazine (torecan) is considered the best due to its strong selective action and lack of side effects. In addition, neuroleptics are used - butyrophenone derivatives (haloperidol, droperidol), which are also effective in vomiting of central genesis.

The antiemetic domperidone (motilium; in tab. 0.01) - is structurally close to the butyrophenone group of drugs (droperidol, pimozide), and its action is similar to metoclopramide. It is a D2 receptor antagonist, does not penetrate the blood-brain barrier (unlike metoclopramide - cerucal) and does not cause extrapyramidal disorders. The drug is indicated for functional disorders of the gastrointestinal tract, gastric hypotension, reflux esophagitis. The drug alleviates biliary dyskinesia. Side effects: increased prolactin levels, headache, dry mouth, dizziness. The antiemetic effect of neuroleptics is mainly associated with their inhibitory effect on D-receptors (dopamine) chemoreceptor trigger zone of the vomiting center.

In addition to D-receptor blockers, drugs that block serotonin receptors have an antiemetic effect.

- Serotonin 5-HT 3 (or S3 -) receptor blockers (5-HT - from the words 5-Hydroxy Tryptophan, S - from Serotonine): tropisetron, ondansetron (osetron).

Subtypes of serotonin receptors: - 5-HT 1 - (or S1) receptors are represented mainly in the smooth muscles of the gastrointestinal tract; - 5-HT 2 - (or S2) in the smooth muscles of blood vessels, bronchi, on platelets; - 5-HT 3 - (or S3) in peripheral tissues and in the CNS.

One of the new antiemetics used to prevent vomiting during chemotherapy in cancer patients is the drug tropisetron (Tropiseptronum; synonym - Navoban; available in capsules of 0.005 and in amp. of 5 ml of 0.1% solution). The duration of action of the drug is 24 hours. Tropisetron is indicated for the prevention of vomiting during chemotherapy in cancer patients, the course is 6 days. The daily dose is 0.005, which is prescribed before meals. Side effects: dyspepsia, dizziness, constipation, increased blood pressure.

Finally, there are drugs that have antiemetic activity, but have a mixed nature of action.

- Metoclopramide (Metoclopramidum; synonyms - reglan, cerucal; in tab. 0.01 and 2 ml (10 mg) in amp.) - a drug, is a specific blocker of dopamine (D2), as well as serotonin (5-HT 3) receptors. It is significantly more active than other drugs (for example, aminazine). The drug has an antiemetic and antihypoxic effect. In addition, it regulates the function of the gastrointestinal tract, normalizes its tone and motility; promotes the healing of gastric and duodenal ulcers. As an antiemetic, metoclopramide is indicated for: - intoxication with cardiac glycosides; for the prevention of side effects of cytostatics and antiblastoma antibiotics; dietary disorders; complex therapy of ulcer patients, patients with gastritis; dyskinesia of the abdominal organs, flatulence; vomiting of pregnant women. Side effects: rarely possible parkinsonism (caffeine must be administered), as well as drowsiness, tinnitus, dry mouth. The drug is prescribed after meals.

2. Questions for self-control (list of questions):

1. Explain modern ideas about the etiology, pathogenesis, classification of peptic ulcer disease.
2. List the main groups of drugs used to treat gastric and duodenal ulcers.
3. Give the classification of drugs that normalize the motor and secretory functions of the gastrointestinal tract.
4. Indicate the pathways of pharmacological action in hypoacid conditions.
5. Determine the mechanisms of the therapeutic effect of antisecretory drugs.
6. Highlight the clinical and laboratory-functional criteria for the therapeutic efficacy and safety of drugs in disorders of the gastrointestinal tract.
7. Give a clinical and pharmacological characteristic of drugs used in the urgent practice of treating disorders of the gastrointestinal tract: atropine, aminazine, magnesium sulfate, no-shpi, benzohexonium, cerucal, baralgin, sodium bicarbonate, almagel.
8. What principles are the basis for the classification of antiulcer drugs?
9. Justify the value of atropine in hepatic, intestinal colic, increased secretory activity of the stomach and indicate possible side effects when using it.
10. H2-histamine blockers: mechanism of action, indications for use, contraindications, side effects.
11. Explain the need for prescribing drugs that affect the functions of the CNS in the complex treatment of peptic ulcer disease. Mechanism of action, indications, side effects.
12. Give a clinical and pharmacological characteristic of drugs used in intestinal dysbacteriosis.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for the main groups of drugs used in gastrointestinal diseases (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize disorders of the gastrointestinal tract, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, choose a drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 their detection at the early stages.

10. Substantiate the duration of basic and maintenance therapy.

B. Solution of situational tasks.

1. A 26-year-old patient was admitted to the therapeutic department with a diagnosis of exacerbation of duodenal ulcer with severe pain and dyspeptic syndrome. As part of the complex therapy, the patient was prescribed atropine 0.1% solution, 0.5 ml subcutaneously 2 times a day. After a week, the pain syndrome and heartburn significantly decreased, while dryness appeared in the mouth and nose, and vision deteriorated somewhat. Give an assessment of the pharmacodynamics of atropine. What is the further tactics of using this drug?

2. A 32-year-old patient was admitted for treatment with a diagnosis of peptic ulcer with localization of the ulcer in the duodenal bulb. Functional examination of the gastric contents revealed increased gastric secretion (basal and stimulated), high acidity. Endoscopy revealed the presence of a chronic ulcer and a bleeding vessel. Determine the effective drugs for the treatment of this disease, their dose, time and frequency of administration, and duration of treatment.

3. A 43-year-old patient is being treated in the gastroenterology department for an exacerbation of duodenal ulcer. The study revealed a moderate increase in the acidity of

gastric contents, the presence of H. pylori. Select the drug or drugs that cause scarring of the duodenal ulcer, indicate their effective dose, time and frequency of administration, and duration of treatment.

4. A 42-year-old patient with gastrointestinal bleeding was brought to the surgical department. During endoscopic examination, an acute gastric ulcer was detected. In the anamnesis: rheumatoid arthritis. Pharmacotherapy of arthritis was carried out. Which drug caused the development of a gastric ulcer and bleeding.

5. A doctor prescribed an antacid to a man suffering from a duodenal ulcer. While taking the drug, nausea and abdominal pain appeared. The examination revealed a violation of acid-base balance in the direction of alkalosis. What drug could have caused this violation?

Test tasks for self-control:

1. A drug from the group of anticholinesterases, which poorly penetrates the blood-brain barrier, which enhances motility and secretion of the gastrointestinal tract.

A. Bromocriptine.

B. Proserin.

C. Pancreatin.

D. Gastrocepin.

E. Galantamine.

2. Specify the group of drugs that suppress the secretory function of the stomach.

A. H +, K + -ATPase inhibitors of the first and second generations.

B. H2-histamine receptor blockers of the first, second, third generations.

C. M1-cholinoblockers.

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

E. All of the above groups.

3. Drugs for the etiological treatment of gastric ulcer.

A. Famotidine + Almagel.

B. Pantoprazole + Eglonil.

C. De-nol + metronidazole.

D. Gastrotsepin + Elenium.

E. Omeprazole + Misoprostol.

4. A child is diagnosed with duodenal ulcer, a fresh ulcer with increased acid-forming function of the stomach, in the exacerbation phase. Helicobacter pylori was detected. What is the minimum period of anti-helicobacter therapy?

A. 3 days.

B. 7 days.

C. 14 days.

D. 12 days.

E. 10 days.

5. For hypersalivation, the following is used:

A. Bromocriptine.

B. Proserin.

C. Pancreatin.

D. Gastrocepin.

E. Atropine.

6. For eradication of Helicobacter pylori, the following should be included in the combination therapy of chronic gastritis:

A. Gastrocepin.

B. Clarithromycin.

C. Almagel.

D. Ceftriaxone.

E. Furosemide

7. What is the most rational scheme for using Almagel for exacerbation of duodenal ulcer? The drug should be used:

A. During meals and before bedtime.

B. During the day for pain and before bedtime.

C. Immediately before each meal and before bedtime.

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

E. Immediately after each meal and before bedtime.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/

2. National Scientific Medical Library of Ukraine http://library.gov.ua/

3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/

4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

5. Interregional Society of Evidence-Based Medicine Specialists:

http://www.osdm.org/index.php

6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua

7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org

TOPIC

"Clinical and pharmacological characteristics of drugs that affect the functions of the hepatobiliary system and pancreas"

Purpose:

To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of drugs that normalize the functions of the hepatobiliary system:

- hepatoprotectors (vitamins of group B, ascorbic acid, lipoic acid, silibor, silymarin, legalon, karsil, essentiale, ademetionine (heptral);
- choleretics, cholekinetics (alohol, cholenzym, liobil, chologoum (dehydrocholic acid), ursodeoxycholic acid, oxaphenamide, tsikvalon, nicodin, dry immortelle extract, flamine, liquid corn stigma extract, holosas, hofitol, galstena; atropine, platifillin);
- enzyme and antienzyme drugs ((pancreatin, panzinorm, creon; contrical, gordox)

Basic concepts (list of questions):

1. Functions of the liver, gallbladder, pancreas.
2. Anatomical and physiological features of the parenchymal digestive organs.
3. Physiological regulation of secretory and motor-evacuation functions of the gastrointestinal tract.
4. Main symptoms and syndromes, diseases of the hepatobiliary system and pancreas: etiology, pathogenesis.
5. Hepatoprotective drugs.
6. Choleretic and cholekinetic drugs.
7. Enzyme and antienzyme drugs.
8. Means for the treatment of colic.

Plan

1. Theoretical questions:

Pathology of the hepatobiliary system

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

Chemical damage

A fairly large number of substances are known - detergents, uncouplers of oxidative phosphorylation and free respiration, carcinogens, drugs, etc. Chemical damage to the liver can be caused by natural substances and xenobiotics, including drugs. It is known that the liver is a target for the manifestation of toxicity of a number of drugs, since it is in this organ

that the metabolism of xenobiotics occurs. Hepatocytes function in conditions of high concentrations of reactive and toxic forms of drugs. The latter can be toxic in their native form or become so during their metabolism. In the process of neutralizing xenobiotics, two phases are described: 1) metabolism, i.e. the introduction of polar groups using the P450 hydroxylase system; 2) conjugation of molecules with water-soluble ligands. Both processes serve to eliminate foreign components of their internal environment of the organism. Conjugation processes are most often catalyzed by UDP-glucuronyltransferase, glutathione-S-transferase. Glucuronidation is the main type of conjugation in the detoxification of substances. Sulfation, as a rule, provides a decrease in toxicity and acceleration of the clearance of xenobiotics. The glutathione-S-transferase reaction is important for unstable electrophilic molecules. Microsomal glutathione-S-transferase is closely associated with the cytochrome P450 system, which serves for the rapid inactivation of active metabolites formed during the metabolism of xenobiotics. Drug metabolism is localized not only in hepatocytes, but also in sinusoidal endothelial cells capable of transforming xenobiotics. A number of drugs exhibit selective toxicity towards these cells compared to hepatocytes. This selectivity is associated with weaker protective mechanisms of sinusoidal endothelial cells to the action of xenobiotics.

Currently, 5 main mechanisms are known that lead to cell death: 1) damage to the plasma membrane and disruption of the cytoskeleton; 2) dysfunction of mitochondria; 3) loss of intracellular ion homeostasis; 4) activation of enzymes of substance degradation; 5) oxidative stress as a result of a mismatch between prooxidant and antioxidant resources of the cell.

Immune mechanisms of hepatotoxicity

There are several main mechanisms of liver damage through molecular mechanisms related to immune reactions: the functioning of killer lymphocytes and cell cooperation, the formation of neoantigens and autoantibodies, the action of mediators (cytokines, nitric oxide), activation of the complement system.

1. Immunoallergic hepatotoxicity

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

2. Cytotoxic lymphocytes

Lymphocyte cytotoxicity plays a prominent role in the pathogenesis of various liver diseases. At least two main mechanisms of lymphocyte cytotoxicity are distinguished. First, T-lymphocytes are able to find antigens of target cells and become activated when interacting with them. At the same time, cytotoxic agents are released that cause cytolysis of target cells. Secondly, it is suggested that lymphocyte-mediated cell death is a process that does not depend on the presence of calcium ions. It is suggested that changes in the permeability of the plasma membrane of target cells during intercellular interaction are preceded by endonuclease hydrolysis.

3. Cytokines

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

4.Complement system

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

5. Cellular cooperation

It has been shown that Kupffer cells play an important role in the development of liver damage. The following sequence of events can be described: an increase in the concentration of endotoxin entering through the portal vein - activation of Kupffer cells and their release of chemoattractants, including interleukins, leukotriene B4, and C5-component of complement - influx of neutrophils from the circulation - activated neutrophils with adhesion molecule receptors adhere to sinusoidal endothelial cells, and the adhesion molecule promotes leukocyte migration into the liver parenchyma - activated neutrophils produce free radical oxygen species that cause various types of damage, for example, activation of membrane peroxidation - liver macrophages produce toxic mediators and cause platelet aggregation, leading to microthrombosis - local hypoxia develops - lobular necrotic lesions appear.

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

Basic principles of treatment of liver diseases

According to modern principles of treatment of liver diseases, the program of complex therapy of such pathology includes two main directions. The first represents etiotropic therapy aimed at suppressing the pathological pathogen, its elimination and sanitation of the

organism. In clinical practice, etiotropic therapy is used only in viral hepatitis with a parenteral mechanism of infection. The second direction corresponds to pathogenetic therapy, which aims at adequate pharmacological correction of universal, multifactorial and different-time links of pathogenesis. It should be noted that the universality of the main links of pathogenesis of various liver lesions allows, despite the polyetiological nature of this pathology, to use a fairly close pathogenetic therapy, the basis of which can be drugs with a directed effect on liver cells. When using pathogenetic treatment, the identity of clinical manifestations in a variety of liver diseases allows the use of the same drugs. Currently, about 1000 drugs are presented on the pharmaceutical market that are used in liver therapy.

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

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

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

3) choleretic agents;

4) antiviral and antimicrobial agents;

5) immunomodulators;

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

7) inhibitors and inducers of microsomal systems that carry out the metabolism of xenobiotics;

8) hepatoprotectors;

9) antioxidants.

In general, the range of drugs used in the complex therapy of liver and biliary tract diseases includes more than 1000 names. This classification is rather conditional, since many drugs can be attributed to several groups of drugs highlighted here. However, among such a variety of drugs, a relatively small group is distinguished that has a selective effect on the liver - hepatoprotectors. Their action is aimed at restoring homeostasis in the liver, increasing the organ's resistance to the action of pathogenic factors, normalizing functional activity and stimulating reparative and regenerative processes in the liver. Hepatoprotectors today make up 10% of the total number of drugs. The main requirements for an ideal hepatoprotector were formulated by R.Preisig:

- The effect of the "first entry" of the drug into the body through the liver.
- Quite complete absorption in the body.
- Pronounced ability to bind or prevent the formation of highly active damaging compounds.
- Ability to reduce excessive inflammation.
- Ability to inhibit fibrogenesis.
- Ability to stimulate liver regeneration.
- Ability to restore natural metabolism (protein, carbohydrate, lipid) in liver pathology.
- Natural metabolism in liver pathology.
- Extensive enterohepatic circulation.
- The substance must be non-toxic to the liver.

Unfortunately, today none of the so-called hepatoprotectors used in medical practice

fully meets these requirements, although in recent years the arsenal of modern hepatoprotective agents has expanded due to the emergence of new natural and synthetic agents. In general, today hepatoprotective agents are mainly of plant origin (54%), while phospholipid preparations account for 16%, and other agents, including synthetic, organoleptic and amino acid preparations - 30% of the total number of "real" hepatoprotective drugs.

Modern classification of hepatoprotectors

 Drugs containing natural or semi-synthetic milk thistle flavonoids: hepabene, legalon, karsil, hepatofalk-planta, silibor.

 Preparations containing natural or semi-synthetic flavonoids of other plants: hofitol, cathergen (cyanidanol), Liv-52 (hepaliv).

 Organopreparations of animal origin: sirepar, hepatosan.

 Preparations containing essential phospholipids: essentiale, phosphogliv, enerliv.

 Preparations of different groups: ademethionine (heptral), lipoic acid (thioctacid), hepa-merz (ornithine), ursodeoxycholic acid (ursofalk), non-steroidal anabolics (methyluracil, pentoxyl, sodium nucleinate).

 Amino acids or their derivatives (ademethionine, ornithine aspartate) and antioxidant vitamins and vitamin-like compounds (vitamins C and E, lipoic acid).

In reality, the methods of "evidence-based medicine" have confirmed to one degree or another the clinical effectiveness of a very small number of drugs that are positioned on the market as hepatoprotectors. These include drugs containing phospholipids (Essentiale, Enerliv), amino acid drugs (ornithine aspartate, ademetionine), ursodeoxycholic acid.

Drugs containing an extract (or a mixture of flavonoids) of milk thistle, the main component of which is silymarin. Silymarin itself is a mixture of 3 main isomeric compounds - silibinin, silychristin and silydianin (in Legalon, for example, their ratio is 3:1:1). All isomers have a phenylchromanone structure (flavolignans). Silibinin is the main component not only in content, but also in clinical effect. The main effects of silymarin (silybinin) are: membrane protective, antioxidant and metabolic. Silibinin stabilizes the membranes of liver cells. At the same time, membrane permeability increases and the loss of cell components decreases. In addition, silibinin blocks PDE, which contributes to the slow decay of cAMP, and therefore stimulates a decrease in the concentration of intracellular calcium in hepatocytes and reduces calcium-dependent activation of phospholipases. The antioxidant and metabolic properties of silibinin are also important for membrane stabilization.

Silibinin is able to block the corresponding binding sites of a number of toxic substances and their transport systems. This is the mechanism of action of silibinin in poisoning with one of the toxins of the pale toadstool - alpha-Amantin. Especially for liver protection in this case, a readily soluble form for intravenous administration (sodium dihydrosuccinate (legalon-sil)) has been developed. Silibinin is able to bind radicals due to its phenolic structure and interrupt the processes of lipid peroxidation. At the same time, it inhibits both the formation of malondialdehyde and increased oxygen absorption. Silibinin contributes to a significant increase in the content of reduced glutathione in the liver, thereby increasing the organ's protection from oxidative stress, supporting its normal detoxification function. The metabolic effect of silibinin is to stimulate protein synthesis and accelerate the regeneration of damaged hepatocytes. Silibinin stimulates RNA polymerase I in the cell

nucleus and activates transcription and the rate of RNA synthesis, and, consequently, protein in liver cells. Silibinin does not affect the rate of reduplication and transcription in altered cells, which excludes the possibility of a tumor-proliferating effect. In cirrhosis of the liver, fibrosis of the organ is slowed down under the influence of the drug.

Also of interest are studies demonstrating the immunomodulatory activity of silymarin derivatives in patients with alcoholic cirrhosis of the liver. Long-term therapy with legalon (about 6 months) contributes to the reduction of initially elevated CD8 + lymphocytes and increases blast transformation of lymphocytes. The level of gamma globulins decreases. Silymarin derivatives should be used in patients with liver diseases with clinical and biochemical signs of activity. Caution should be exercised in patients with cholestasis, since there is information that cholestasis may be aggravated by the drugs. The duration of the course should not exceed 4 weeks, after which, if necessary, it is advisable to change the drug, for example, to prescribe a drug of essential phospholipids. This drug and legalon are used for acute and chronic hepatitis, cirrhosis of the liver, toxic-metabolic liver lesions, including xenobiotics. A feature of the drug Hepatofalk-Planta is that, along with the extract of milk thistle, its composition includes extracts from celandine and Javanese turmeric. Due to this, along with hepatoprotective, the drug has choleretic, antispasmodic and anti-inflammatory effects, reduces the saturation of bile with cholesterol, and has antibacterial properties. It is used for acute and chronic hepatitis, fatty hepatosis, and cirrhosis of the liver.

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

Preparations containing natural or semi-synthetic flavonoids of other plants

Cyanidanol-3 (catergen) is a tetra-hydroxy-5,7,3-4-flavanol-3. It is a semi-synthetic flavonoid derivative of plant origin and is very close in chemical structure to quercetin and rutin, as well as to silibinin. It is believed that the mechanism of hepatoprotective action is due to the binding of toxic free radicals and the stabilization of cell membranes and lysosomes (which is also characteristic of other flavonoids). In addition, under the influence of catergen, ATP biosynthesis is stimulated in the liver, thereby facilitating the course of biochemical reactions associated with energy expenditure and phosphorylation in the liver. Catergen has a membrane-stabilizing effect, reducing the permeability of cell membranes for low-molecular water-soluble compounds transported by free and exchange diffusion.

Clinical use of catherine in the treatment of acute and chronic liver diseases of various etiologies indicates the effectiveness of the drug not only in reducing the level of cholestasis, but also in reducing the activity of transaminases. It is used for acute and chronic hepatitis, cirrhosis of the liver, including alcoholic liver damage. When using catherine in patients with chronic parenchymal liver diseases, the effect of the drug may be insufficient. The drug is used for a long time (course duration is about 3 months). Hofitol is a drug, one ampoule of which contains 0.1 g of purified artichoke leaf extract in saline. The main hepatoprotective and choleretic effect is due to the presence of the phenolic compound cynarin in the extract in combination with phenolic acid. In addition, it contains carotene, vitamins C, B1, B2, inulin. It affects the functional activity of liver cells, stimulates the production of enzymes; This explains the effect of the drug on lipid and fat metabolism, increasing the antitoxic function of the liver. Hofitol reduces blood cholesterol levels in initial hypercholesterolemia, has a

choleretic effect due to a moderate choleretic and weak cholekinetic effect. It is used for toxic hepatitis, cirrhosis of the liver.

Liv-52 (Gepadif) contains a number of medicinal plants widely used in traditional Indian medicine. It is believed that Liv-52 protects the liver parenchyma from toxic agents. It acts as a therapeutic or prophylactic agent. It enhances intracellular metabolism and stimulates regeneration. At the same time, there is evidence that the use of the drug in acute liver pathology can increase the severity of cytolytic and mesenchymal-inflammatory syndromes. Therefore, the drug can be recommended at a time when the severity of the inflammatory syndrome in the liver is minimal and the phenomena of synthetic organ failure prevail.

Organopreparations of animal origin

Sirepar is a hydrolysate of bovine liver extract, containing 10 mg of cyanocobalamin in 1 ml. The reparative effect of the drug is apparently due to the presence of amino acids, low-molecular metabolites, and possibly fragments of liver growth factors in its composition. The drug promotes the regeneration of the liver parenchyma, has a detoxifying effect. Sirepar should not be prescribed to patients with active forms of liver diseases, as in this case the phenomena of cytolytic, mesenchymal-inflammatory and immunopathological syndromes may increase. It is prescribed for chronic hepatitis and cirrhosis of the liver, toxic and drug-induced lesions of the liver parenchyma. Before starting treatment, sensitivity to the drug must be determined.

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

Preparations containing essential phospholipids

Remembering that in all liver diseases, damage to hepatocyte membranes is noted, it is pathogenetically justified to prescribe therapy that has a restorative and regenerative effect on the structure and functions of cell membranes and provides inhibition of the process of cell destruction. The means of such directed action are preparations containing essential phospholipids (EPL). The EPL substance is a highly purified extract from soybeans and contains mainly phosphatidylcholine (PC) molecules with a high concentration of polyunsaturated fatty acids. The main active ingredient of EPL is 1,2 - dilinoleoyl - phosphatidylcholine, the synthesis of which by the human body is impossible. The presence of two essential (necessary) fatty acids determines the advantage of this special form of phospholipids in comparison with endogenous phospholipids.

The membrane-stabilizing and hepatoprotective effect of EFL is achieved by directly incorporating EFL molecules into the phospholipid structure of damaged liver cells, replacing defects and restoring the barrier function of the lipid bilayer of membranes. Unsaturated fatty acids of phospholipids contribute to increasing the activity and fluidity of membranes,

reducing the density of phospholipid structures, and normalizing permeability. Exogenous EFL contribute to the activation of phospholipid-dependent enzymes and transport proteins located in the membrane, which, in turn, has a supporting effect on metabolic processes in liver cells, contributing to an increase in its detoxification and excretory potential. The hepatoprotective effect of EFL is apparently also based on the inhibition of lipid peroxidation (LPO) processes, which are considered one of the leading pathogenetic mechanisms of the development of liver lesions. However, it is obvious that we should not overestimate the antioxidant properties of EFLs, since they themselves can be involved in lipoperoxidation processes.

The prototype of compounds containing the EFL substance is the drug Essentiale, which includes essential phospholipids, unsaturated fatty acids and vitamins. Not so long ago, Essentiale H appeared on the market, which contains only the highly purified EFL substance. In clinical practice, Essentiale is used in 3 main areas: in liver diseases and its toxic lesions; in pathology of internal organs complicated by liver damage; as a method of "drug cover" when using drugs that cause liver damage (tetracycline, rifampicin, paracetamol, indomethacin, etc.). In hepatology, Essentiale is prescribed for chronic hepatitis, cirrhosis of the liver, fatty dystrophy, hepatic coma. It is also used for radiation syndrome and toxicosis of pregnant women, for the prevention of recurrence of cholelithiasis, for preoperative preparation and postoperative treatment of patients, especially in cases of surgical interventions on the liver and biliary tract. At the same time, the use of Essentiale in active hepatitis requires some caution, because in some cases it can contribute to increased cholestasis and inflammatory activity. Usually the effectiveness of Essentiale is estimated as quite high, but there are also a number of reports of the lack of convincing data in favor of the expressed clinical activity of Essentiale in acute and chronic liver lesions. Close in composition and properties to Essentiale is the drug Esliver, which contains, in addition to the substance of essential phospholipids, therapeutic doses of vitamins (B1, B2, B6, B12, tocopherol and nicotinamide), which provides the drug with a wide range of therapeutic properties. The action of the components of the drug is aimed at restoring homeostasis in the liver, increasing the organ's resistance to the action of pathogenic factors, normalizing the functional activity of the liver, stimulating reparative and regenerative processes. The drug is used for acute and chronic hepatitis, cirrhosis of the liver, alcoholic, drug intoxication and other forms of poisoning, radiation syndrome, psoriasis.

Of particular interest is the domestic drug Phosphogliv, consisting of 0.1 g of phosphatidylcholine and 0.05 g of trisodium salt of glycyrrhizic acid. Due to EFL, which is part of the drug, the normalization of subjective symptoms of liver diseases, their clinical manifestations and laboratory indicators is improved or accelerated. Inflammatory reactions during necrosis of liver cells, their fatty infiltration are reduced. Glycyrrhizic acid has an immunostimulating effect, causing stimulation of phagocytosis and increased activity of IKK cells, induction of gamma interferon. In addition, it has an antiviral effect, blocking the penetration of viruses into cells, exhibits antioxidant properties. It is used for acute hepatitis, for stopping alcohol withdrawal syndrome, in the pre- and postoperative period of cholecystectomy. However, it should be noted that improvement of the liver condition and reduction of symptoms of intoxication are not observed in all patients. In addition, when using the drug, very careful monitoring of patients with autoimmune aggression is necessary.

Drugs of different groups

S-adenosyl-L-methionine (heptral) plays a central role in the biochemical reactions of transmethylation (biosynthesis of phospholipids), transsulfation (synthesis and turnover of glutathione and taurine, conjugation of bile acids with an increase in their hydrophilicity, detoxification of bile acids and many xenobiotics) and aminopropylation (synthesis of such polyamines as putrescine, spermidine and spermine, which play an important role in the formation of the ribosome structure and regeneration processes), where it serves either as a donor of groups or as a modulator of a number of enzymes. When using ademetionine, the elimination of free radicals and other toxic metabolites from hepatocytes increases. The experiment showed the antifibrotic activity of ademetionine. The drug also has an antineurotoxic and antidepressant effect. Ademetionine is quite effective in liver pathology accompanied by hepatic encephalopathy. It should be noted, however, that the hepatoprotective effect reaches its maximum expression only if the drug is administered parenterally. Ademetionine has a predominant effect on the manifestations of toxemia and to a much lesser extent affects the indicators of cytolysis and cholestasis. The drug is taken between meals. It is used for acute and chronic hepatitis, cirrhosis of the liver.

L-ornithine-L-aspartate (hepa-merz) is a fairly new drug for the treatment of liver diseases, which regulates metabolism in liver cells. In the intestine, the drug dissociates into its constituent components - the amino acids ornithine and aspartate, which participate in subsequent biochemical processes:

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

• 2) ornithine is a stimulator of carbamoylphosphate synthetase I (the first enzyme of the urea cycle);

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

• 4) aspartate is a substrate for the synthesis of glutamine, participating in the binding of ammonia in perivenous hepatocytes, brain and other tissues.

Thus, ornithine aspartate enhances ammonia metabolism, both in the liver and in the brain. A positive effect of Hepa-Merz on hyperammonemia and the dynamics of encephalopathy in patients with cirrhosis of the liver has been revealed. It contributes to the normalization of the body's KLS, the production of insulin and somatotropic hormone. It is used for fatty dystrophy, hepatitis, cirrhosis, liver damage as a result of alcoholism and drug addiction, for the treatment of brain disorders that arise as a result of liver dysfunction. The duration of the course of treatment is determined by the dynamics of the concentration of ammonia in the blood and the patient's condition. The course of treatment can be repeated every 2-3 months.

Ursodeoxycholic acid (UDCA) is a hydrophilic, non-toxic, tertiary bile acid. Its composition in the natural pool of human bile acids is only 4%. Taking UDCA leads to a decrease in the enterohepatic circulation of hydrophobic bile acids that have a hepatotoxic effect, thereby preventing their toxic effect on hepatocyte membranes and bile duct epithelium, inhibits the production of immunoglobulins, normalizes HLA-DR antigens on the surface of cell membranes, which reduces their autoimmune, reduces cholestasis-mediated immunosuppression. A certain influence is also exerted by the positive choleretic effect of UDCA, which, due to increased bile passage, also causes enhanced excretion of toxic substances from the liver. UDCA has an antioxidant effect, reducing the oxidative activation

of Kupffer cells by hydrophobic bile acids. Currently, the appointment of UDCA is considered justified in liver diseases accompanied by or caused by cholestasis, regardless of etiology. There is a single opinion about the dosage of UDCA, which is that the daily doses of the drug, effective in cholestasis, do not differ from the doses used to dissolve gallstones, and are 8-15 mg / kg of the patient's body weight. The drug is used for acute and chronic hepatitis (including autoimmune), toxic (including alcoholic) liver damage, non-alcoholic steatohepatitis, primary biliary cirrhosis (before the formation of pronounced cirrhotic transformation of the liver), hepatopathy of pregnant women.

Alpha-lipoic acid (lipamide, thioctacid) is a coenzyme involved in the oxidative decarboxylation of pyruvic acid and alpha-ketoacids, plays an important role in the bioenergetics of liver cells, participates in the regulation of carbohydrate, protein, lipid metabolism, and has a lipotropic effect. It participates as a coenzyme in multienzyme complexes of mitochondria:

- in pyruvic acid dehydrogenase, which ensures the conversion of PVA into acetyl-CoA (formation of NAD through the respiratory chain-ATP);

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

- in branched-chain amino acid dehydrogenase.

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

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

Drugs that affect motor function in dysfunctional biliary disorders:

- anticholinergic drugs; - nitrates; - myotropic antispasmodics; - intestinal hormones (HCG, glucagon); - choleretics; - cholekinetics.

Anticholinergic drugs - by reducing the concentration of intracellular calcium ions, lead to muscle relaxation. The intensity of relaxation depends on the initial tone of the parasympathetic nervous system, but when using drugs of this group, a wide range of undesirable effects are observed: dry mouth, difficulty urinating, visual impairment, which greatly limits their use. They can be used to stop an attack.

Nitrates (nitroglycerin, nitrosorbide) - cause relaxation of smooth muscles due to the formation of free radicals NO in them, which contributes to an increase in the content of cGMP. Their use, however, is accompanied by the development of pronounced cardiovascular effects and other side effects. In addition, the development of tolerance makes nitrates unsuitable for long-term therapy. Their use can be recommended as an initial stage of stopping an attack, and course administration can be justified in the combination of coronary artery disease and biliary dysfunction (mutually provoking and supporting the "clinical situation").

Myotropic antispasmodics

Calcium channel blockers (divided into non-selective and selective). Non-selective calcium channel blockers are able to relax smooth muscles, including those of the biliary tract, but this effect requires the use of high doses, which practically excludes their use due to pronounced cardiovascular effects. Selective calcium channel blockers (panaverium bromide, etilonia bromide) act mainly at the level of the colon, where they are mainly metabolized. About 5-10% of the dose of these drugs, which enter the bloodstream and are metabolized in the liver, can work at the level of the biliary tract - normalizing the functioning of the gallbladder. However, there is no certainty about their direct effect on the biliary tract. Perhaps their effect is associated with the normalization of the colon, reducing intra-abdominal pressure and restoring the pressure gradient, which normalizes the flow of bile. Their use is indicated in patients with dyskinetic disorders of the colon (IBS) and, at the same time, biliary tract dysfunction.

Sodium channel blocker - dyspatalin (mebeverine hydrochloride). In terms of chemical structure, it is a derivative of methoxybenzamine. Duspatalin blocks the sodium channels of the cell membrane, due to which the entry of sodium ions into the cell, and therefore calcium, becomes impossible, while the force of muscle contraction is significantly reduced. In addition, the drug blocks the filling of calcium depots from the extracellular space, thereby limiting the exit of potassium from the cell and preventing the development of hypotension. The drug is largely metabolized in the intestinal wall and partially in the liver, is excreted in the urine, no cumulation is observed. Duspatalin provides an effective antispasmodic effect, quickly eliminates the symptoms of hypertensive disorders of the biliary tract - pain in the right hypochondrium, nausea, flatulence. The drug was used in patients with biliary tract dysfunction and its effectiveness was noted after 2 weeks of treatment in 90% of patients. The effectiveness was assessed not only according to clinical data, but also according to changes in the contractile ability of the gallbladder and sphincter of Oddi (according to ultrasound). It is believed that the mechanism of action is double: direct - through the effect on muscle tone and indirect - through a decrease in intraintestinal pressure with "facilitation" of bile discharge when the pressure gradient changes. In the treatment of gallbladder hypofunction, drugs are used that enhance its motility. For this purpose, choleretics can be used, which include drugs containing bile and bile acids (allohol, dehydrocholic acid, liobil, cholenzym); synthetic drugs (oxamide, tsikvalon), some phytopreparations (hofitol, flamin, cholagogue, corn stigmas, etc.), as well as cholecystokinetic agents, such as magnesium sulfate, olive oil and other oils, sorbitol, xylitol, cholas, etc. Drugs that stimulate choleresis or contain bile acids simultaneously have the function of replenishing chronic biliary insufficiency, restoring impaired digestion of fats.

Drugs with prokinetic action can also be used (for example, domperidone, trimebutin). This group includes selective calcium channel blockers (pinaverium bromide, otilonium bromide) and myotropic antispasmodics (mebeverine). It should be remembered that the action of these drugs is largely indirect (either the tone of the sphincter of Oddi decreases, which is the pressure in the intestine and duodenum). The effect is always dose-dependent, therefore, the selection of an effective individual dose is necessary. Sometimes, in the absence of effect, it is possible to use drugs that reduce inflammation and visceral hyperalgesia (nonsteroidal anti-inflammatory drugs, tricyclic antidepressants in small doses). The choice of drug is very important, if not the main issue. It, in particular, depends on the required speed of

obtaining the effect. If the effect should be fast, then it is better to use cholekinetics (the dose of the drug also matters), and if the speed of the effect is not of primary importance, then preference should be given to "bile-containing" drugs. In cases where it is necessary to provide an anti-inflammatory effect at the same time, the choice should be made in favor of synthetic drugs, but the course of treatment should be long. In the presence of concomitant liver pathology, biliary dysfunction and chronic biliary insufficiency - the drug of choice is hofitol, which has a protective effect, choleretic effect and at the expense of this normalizes motor disorders. The data confirm its high effectiveness and in addition it has the effect of lowering cholesterol levels, while not blocking its synthesis, but enhancing its metabolism and the synthesis of bile acids; in the presence of stones in the gallbladder, the drug of choice is odestone, as well as in patients after cholecystectomy.

In case of exacerbation of chronic cholecystitis and a protracted course, treatment is usually carried out in a hospital, in the remission phase - in a polyclinic, dispensary, sanatorium. Treatment is aimed at eliminating pain and dyskinetic disorders, suppressing infection and the inflammatory process, eliminating digestive and metabolic disorders. Diet therapy, antispasmodics, analgesics (painkillers), antibacterial agents, antiparasitic drugs, choleretics and cholekinetics (drugs that improve the tone of the gallbladder), physiotherapy and balneotherapy (treatment with mineral water), and, if indicated, surgical treatment. To eliminate pain syndrome, parenteral antispasmodics are used from the first days: no-shpa, papaverine, galidor, atropine, metacin, platifillin. With severe pain syndrome, analgin or promedol are administered. Often, the combined drug baralgin is used for this purpose. In some cases, according to special indications, the combined drug Talomanal is used to relieve pain. Nitroglycerin drugs have a good antispasmodic effect on the sphincters of Oddi and Lutkens. As a rule, pain syndrome in chronic acalculous cholecystitis is relieved in the first 1-2 weeks from the start of complex treatment and cannot be resumed against the background of prolonged therapy. Usually, therapy with these drugs lasts at least 3-4 weeks. Pain syndrome in cholecystitis, as is known, depends not only on the severity of dyskinetic disorders of the gallbladder, sphincters of the biliary tract, but also on the nature and intensity of the inflammatory process in the biliary tract. In this regard, early and sufficiently long-term use of antibacterial and, if indicated, anti-parasitic agents in chronic acalculous cholecystitis can be quite effective and, in combination with other therapeutic measures, contributes to the elimination of the inflammatory process in the gallbladder and the development of remission. It is advisable in such a situation to use broad-spectrum antibacterial agents that enter the bile in a sufficiently high concentration. Based on this, the following are prescribed orally:

- azithromycin (0.5 g 1 time per day);
- doxycycline (0.05-0.1 g 2 times per day);
- ampicillin (0.5 g 4-6 times per day);
- furazolidone (0.05 g 4 times per day), etc.

Treatment with antibacterial agents is carried out on average for 8-10 days. After a 2-3-day break, taking into account the microflora isolated from the duodenum (during duodenal sounding), it is advisable to repeat the treatment with antibacterial agents for another 8-10 days. Some drugs (erythromycin, furazolidone) have an anti-giardiasis effect.

Choleretic agents are widely used in the treatment of patients with chronic acalculous cholecystitis. They are divided into two groups:

- choleretics (agents that stimulate the formation of bile);

- cholekinetics (drugs that enhance the muscular contraction of the gallbladder and thereby promote the secretion of bile into the intestines).

Choleretics include drugs containing bile and bile acids (allochol, dehydrocholic acid, decholine, liobil, cholenzym), a number of synthetic substances (oxaphenamide, tsikvalon, nicodine), preparations of plant origin (flamin, cholagone, corn stigmas, etc.), as well as conditionally some enzyme preparations containing bile acids - festal, digestal.

Cholekinetic agents include cholecystokinin, magnesium sulfate, Karlovy Vary salt, sea buckthorn and olive oil, sorbitol, xylitol, mannitol, cholasas.

Most choleretic agents have a combined effect, enhancing the secretion of bile and facilitating its entry into the intestines. Some drugs have both an anti-inflammatory (tsikvalon) and antibacterial (nicodine) effect.

The use of choleretics is contraindicated in severe inflammatory processes in the gallbladder and bile ducts, hepatitis and hepatosis, and cholekinetics also in liver failure. Taking into account the listed contraindications, choleretics should be used only in the remission phase of chronic cholecystitis and in combination with enzymes, and with hypotension of the gallbladder - with cholekinetics.

2. Questions for self-control (list of questions):

1. Etiology, pathogenesis, classification of hepatitis, cholecystitis, biliary dyskinesia, acute and chronic pancreatitis.

2. Formulate the main clinical and laboratory symptoms of biliary colic.

3. Formulate the main clinical and laboratory symptoms of insufficiency (exocretic) of the pancreas - the first stage (initial, latent), the second stage - pronounced pancreatic insufficiency (frequent or constant diarrhea, steatorrhea, creatorrhea, amylorrhea), the third - dystrophic.

4. List the pathogenetic mechanisms of hepatitis, cirrhosis of the liver, which is the object of the influence of hepatotropic drugs.

5. Describe the pathogenesis of bile secretion disorders and the pathways of pharmacological influence, taking into account the indicated factors.

6. What pharmacokinetic processes do you expect to improve when using hepatotropic drugs?

7. Explain the features of the pharmacodynamics of essentiale. Choose and justify the method of administration.

8. In case of cholelithiasis, a conservative treatment method is possible. Explain its pathogenetic mechanisms, name the corresponding drugs.

9. The choice of cholekinetic drugs depends on the clinical and pathogenetic features of biliary dyskinesia. Justify the choice of cholekinetic drugs in each variant of the course of the disease.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for the main groups of drugs used in diseases of the hepatobiliary system (tablets and/or ampoules), indicate possible use, spectrum of diseases

(syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize dysfunction of the hepatobiliary system and pancreas, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, select the drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 detecting them at the early stages.

10. Substantiate the duration of basic and maintenance therapy.

B. Solution of situational tasks.

1. Patient A., 34 years old, was admitted to the clinic with complaints of pain in the left hypochondrium, which appeared after a violation of the diet. The pain is girdling in nature, accompanied by nausea, vomiting, diarrhea alternates with constipation, general weakness is noted. Palpation of the abdomen reveals tenderness in the left hypochondrium. Attacks are accompanied by increased blood amylase and urine diastase, leukocytosis and increased ESR. What disease does the described clinical picture most likely correspond to? Your recommendations for the tactics of examination and treatment of this patient. Write out prescriptions.

2. A 38-year-old female patient, weighing 65 kg, was admitted to the therapeutic department due to exacerbation of chronic cholecystitis-pancreatitis. The patient is concerned about epigastric pain, repeated vomiting with bile, severe weakness, dizziness. Objectively: pale, cold, sticky sweat. Breathing is frequent, superficial. ACT - 100/50 mm Hg. Art.; Heart rate - 92 in 1 min. The abdomen is painful in the upper half, there are no symptoms of peritoneal irritation, peristalsis is preserved. The doctor on duty prescribed treatment with anticholinergics, antispasmodics, non-narcotic analgesics (all drugs are administered parenterally), in addition, 200 ml of 4% sodium bicarbonate solution is administered intravenously. Contrary to the doctor's expectations, after the measures taken, the patient's condition worsened. Nausea, vomiting, weakness, dizziness intensified, ACT - 90/50 mm Hg. Art.; Heart rate - 106 in 1 min. Explain the reason for the deterioration of the condition. What did the doctor on duty not take into account? Treatment tactics

3. A 20-year-old patient, a student, suffered from Botkin's disease a year ago,

complains of attacks of pain in the right hypochondrium. Objectively: sharply expressed soreness during palpation of the gallbladder. Cholecystography revealed an enlargement of the gallbladder and delayed evacuation. Ultrasound of the abdominal organs showed that after a trial breakfast the gallbladder was emptied by 20% of its original volume. Your diagnosis? Variant of the disease. What drugs that affect the function of the gallbladder are indicated for the patient?

4. A 59-year-old woman was admitted to the surgical department with acute pain syndrome on the background of exacerbation of pancreatitis. What analgesic should be prescribed to stop the attack?

5. A 55-year-old patient complains of dull pain in the right hypochondrium, bitterness in the mouth. She has suffered from chronic cholecystitis since the age of 35. A year ago, during an ultrasound examination, single concrements of 4-5 mm were found in the gallbladder. What cholekinetic drug is contraindicated for the patient? Your opinion on the further tactics of treating the patient.

Test tasks for self-control:

1. A 20-year-old patient, who is examined and treated in the gastroenterology department, has been diagnosed with autoimmune hepatitis. What group of drugs is included in the basic therapy of this disease?

A. Glucocorticoids and cytostatics.

B. Anabolic steroid drugs.

C. Antibacterial drugs.

D. Hepatoprotective drugs.

E. Vitamins.

2. The patient has small-nodular cirrhosis of the liver. Over the past 2 years, shortness of breath, swelling of the lower extremities, ascites have appeared. The patient took hepatoprotectors and glucocorticoids. What combination of drugs is most appropriate to additionally prescribe?

A. Veroshpiron + ascorutin.

B. Nerobol + furosemide.

C. Lidocaine + hypothiazide.

D. Albumin + ascorutin.

E. Veroshpiron + furosemide.

3. A patient was admitted to the surgical department of the hospital with symptoms of acute pancreatitis: vomiting, diarrhea, severe girdling abdominal pain, weakness, hypotension, dehydration. What drug with antienzyme activity is indicated for the patient?

A. Adrenaline

B. Analgin

C. Atropine sulfate

D. Kontrykal

E. Sodium bicarbonate

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

"Control of practical skills and theoretical knowledge. Credit lesson - test"

LIST OF QUESTIONS FOR PREPARATION FOR THE CREDIT CLASS - TEST

1. Clinical pharmacodynamics, definition, place and role in the choice of pharmacotherapy.
2. Clinical pharmacokinetics, definition, basic concepts, role in the choice of pharmacotherapy.
3. Classification of hypolipidemic drugs. Classification of dyslipidemias. Differentiated approach to the use of hypolipidemic drugs.
4. Mechanism of action, pharmacokinetics and pharmacodynamics, indications and contraindications for the appointment of statins.
5. Groups of drugs related to antianginal and antiischemic drugs.
6. Mechanism of action, pharmacological effects, indications and contraindications for the appointment of nitrates.
7. Mechanism of action, pharmacological effects, indications and contraindications for the appointment of beta-blockers.
8. Classification, mechanism of action, pharmacological effects, indications and contraindications for the appointment of calcium channel blockers.
9. Classification of beta-blockers. Features of use. Dosage.
10. Antiplatelet drugs. Classification. Mechanisms of action. Dosage methods.
11. Thrombolytic agents. Indications and contraindications for thrombolysis. Prescription regimens.
12. Anticoagulants. Classification. Mechanisms of action. Side effects.
13. Principles of drug selection for the treatment of angina pectoris, acute myocardial infarction.
14. Classification of antihypertensive drugs.
15. Mechanism of antihypertensive action, side effects when prescribing calcium channel blockers. Principles of dosing.
16. Mechanism of antihypertensive action, side effects when prescribing beta-blockers. Principles of dosing.
17. Mechanism of antihypertensive action, pharmacological effects, indications and contraindications, side effects when prescribing angiotensin-converting enzyme inhibitors. Principles of dosing.

18. Principles of combined use of antihypertensive drugs.
19. Differentiated choice of drugs for the treatment of hypertensive crises.
20. Classification of antiarrhythmic drugs. Differentiated approach to the prescription of antiarrhythmic drugs.
21. Classification of cardiac glycosides. Principles of dosing. Cardiac and noncardiac effects of cardiac glycosides. Indications for prescription. Clinical and ECG signs of cardiac glycoside intoxication. Principles of treatment of cardiac glycoside intoxication.
22. Differentiated choice of drugs for the treatment of cardiac asthma, pulmonary edema.
23. Non-glycoside positive inotropic drugs. Indications for use.
24. Classification of diuretic drugs.
25. Mechanism of action, pharmacokinetics and pharmacodynamics, indications and contraindications for the appointment of loop diuretics.
26. Mechanism of action, pharmacokinetics and pharmacodynamics, indications and contraindications for the appointment of thiazide and thiazide-like diuretics. Principles of dosing.
27. Classification of drugs that affect bronchial patency.
28. Mechanism of action, pharmacokinetics, indications and contraindications for the appointment of short- and long-acting beta-2-agonists. Dosage principles.
29. Methylxanthines, mechanism of action, pharmacological effects, side effects. Dosage principles.
30. Glucocorticosteroids. Pharmacokinetics and pharmacodynamics. Advantages of the use of inhaled glucocorticoids. Dosage regimens. Side effects that occur with long-term use of glucocorticosteroids.
31. Drug interactions. Types. Clinical examples.
32. Types of side effects when using drugs.
33. Clinical and pharmacological classification of nonsteroidal anti-inflammatory drugs.
34. Mechanism of action, pharmacological effects of nonsteroidal anti-inflammatory drugs. Indications and contraindications. Side effects of nonsteroidal anti-inflammatory drugs, their prevention and treatment.
35. Modern principles of choosing antimicrobial drugs.
36. Undesirable effects of antibacterial therapy, their prevention and treatment.
37. Classification, spectrum of activity, mechanism of action, features of clinical use of penicillins. Dosage principles.
38. Classification, spectrum of activity, mechanism of action, features of clinical use of cephalosporins. Dosage principles.
39. Classification, spectrum of activity, mechanism of action, features of clinical use of aminoglycosides. Dosage principles.
40. Classification, spectrum of activity, mechanism of action, features of clinical use of macrolides. Dosage principles.
41. Classification, spectrum of activity, mechanism of action, features of clinical application of fluoroquinolones. Principles of dosage.
42. Spectrum of activity, mechanism of action, features of clinical application of nitroimidazoles and nitrofurans. Principles of dosage.
43. Classification of drugs with antisecretory activity.
44. Clinical and pharmacological characteristics of proton pump inhibitors. Principles of dosage.
45. Clinical and pharmacological characteristics of H2-blockers of histamine receptors. Principles of dosage.
46. Antacids. Classification, pharmacokinetics and pharmacodynamics. Principles of clinical application and dosage.
47. Hepatoprotectors. Classification. Pharmacokinetics and pharmacodynamics. Indications and contraindications for use. Principles of dosage.

48. Choleretics and cholekinetics. Clinical and pharmacological features. Indications and contraindications for use. Dosage principles.
49. Enzymes and antienzymes. Classification. Pharmacological features. Indications for use. Dosage principles.
50. Classification, mechanism of action, pharmacokinetics, indications and contraindications for use, side effects of antiallergic drugs. Dosage principles.
51. Symptoms and laboratory methods for diagnosing coronavirus infection: advantages, informativeness in choosing pharmacotherapy.
52. Modern world and state protocols for providing medical care to patients with coronavirus infection, taking into account the main pathogenetic mechanisms of the disease.
53. Main groups of drugs for pharmacotherapy of coronavirus infection and its complications, their clinical and pharmacological characteristics. Immuno- and vaccine prophylaxis.

TOPIC
"Clinical and pharmacological characteristics of cardiac glycosides and non-glycoside positive inotropic drugs"

Purpose:

To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of glycoside and non-glycoside cardiotonics:
- cardiac glycosides (strophanthin, corglycon, digoxin, celanide, adonizide);
- non-glycoside cardiotonics (milrinone, levosimendan, dobutamine).

Basic concepts (list of questions):

1. Mechanical functions of the heart.
2. Anatomical and physiological features of the heart.
3. Heart failure: definition, classification, etiology, pathogenesis, clinical manifestations.
4. Cardiac glycosides: classification, effects, side effects.
5. Non-glycoside cardiotonics: classification, pharmacology, side effects.

Plan

1. Theoretical questions:

Medicines used to treat acute and chronic heart failure are a large group of drugs from different groups. Heart failure accompanies many acute and chronic heart diseases: coronary artery disease, myocarditis, valvular defects, myocardial dystrophy, etc. Today, the tactics of managing such patients have changed in many ways. Cardiotonics of a non-glycoside structure have appeared, new classes of cardiotropic drugs, however, cardiac glycosides still remain for the treatment of this pathology.

Cardiac glycosides

Cardiac glycosides are a group of herbal medicines that have a cardiotonic and antiarrhythmic effect in therapeutic doses. Cardiac glycosides are complex nitrogen-free compounds of plant origin that have a selective effect on the heart, which is realized mainly

through a pronounced cardiotonic effect. As a result, the use of these drugs for the treatment of patients with heart failure of various etiologies is justified.

Plants containing cardiac glycosides (there are about 400 of them in total) include, first of all, various types of digitalis. This plant got its name because of the flowers that resemble a foxglove. There are many digitalis containing cardiac glycosides, but to date, the chemical structure of 13 cardiac glycosides from 37 varieties of digitalis has been studied. In medical practice, the most widely used preparations of cardiac glycosides are those obtained from the following plants of this genus:

- Digitalis purpurea (red), Digitalis purpurea - cardiac glycoside - digitoxin.
- Foxglove, Digitalis lanata - preparations of cardiac glycosides - digoxin, celanide.

In addition, cardiac glycosides can be obtained from other plants:

- from the seeds of African perennial vines, Strophanthus gratus and Strophanthus Kombe) strophanthin is obtained;
- from the lily of the valley (Convallaria majalis) the preparation corglycon is obtained;
- from the spring adonis (Adonis vernalis) preparations (adoniside, infusion of adonis herb) are obtained.

All cardiac glycosides are chemically related to each other: they are complex organic compounds, the molecule of which consists of a non-sugar part (aglycone) and sugars (glycone). The basis of the aglycone is the steroid cyclopentaneperhydrophenanthrene structure, connected in most glycosides with an unsaturated lactone ring. Glycone can be represented by various 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 effect of cardiac glycosides is the steroid skeleton of the aglycone, 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 (CG), their permeability through the cell membrane, affinity for plasma and tissue proteins, as well as the degree of activity and toxicity depend on it. However, only the entire molecule of cardiac glycosides causes a clear cardiotropic effect.

When choosing CG for therapeutic use, not only its activity is important, but also the speed of onset of the effect, as well as the duration of action, which, to a large extent, depends on the physicochemical properties of the glycoside, as well as the methods of its administration. According to the physicochemical properties, CGs are divided into two groups: polar and non-polar. Belonging to a particular CG group is determined by the number of polar (ketone and alcohol) groups contained in the aglycone molecule.

1. Polar glycosides (strophanthin, corglycon) contain from four to five such groups.
2. Relatively polar (digoxin, celanide) - 2-3 groups each.
3. Non-polar (digitoxin) - no more than one group.

The more polar the CG molecule, 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 corglycon, are poorly soluble in lipids, and therefore poorly absorbed from the gastrointestinal tract. This determines the parenteral (intravenous) method of administration of polar glycosides. Polar glycosides are excreted by the kidneys (hydrophilic), and therefore, in case of impaired renal excretory function, their dose (to avoid cumulation) should be reduced.

Nonpolar SGs are easily soluble in lipids (lipophilic); they are well absorbed in the intestine, quickly bind to plasma proteins, mainly albumins. The main representative of nonpolar glycosides is digitoxin. The main amount of digitoxin enters the liver and is excreted in the bile, then absorbed again. Therefore, the half-life of nonpolar glycosides (for example, digitoxin) is on average 5 days, and the effect stops completely after 14-21 days. Nonpolar glycosides are prescribed orally, and if their administration per os is impossible (vomiting), they can be prescribed rectally (suppositories).

Relatively polar CGs (digoxin, celanide) occupy an intermediate position. Therefore, these drugs can be administered both per os and intravenously, which is done in practice.

Mechanism of therapeutic action of cardiac glycosides. Almost all cardiac glycosides are characterized by four main pharmacological effects:

I. Systolic action of CG.

The clinical and hemodynamic effect of CG is due to their primary cardiotonic effect and consists in the fact that under the influence of cardiac glycosides, systole becomes stronger, more powerful, and shorter. Cardiac glycosides, by enhancing the contraction of a weakened heart, lead to an increase in stroke volume. At the same time, they do not increase the consumption of oxygen by the myocardium, do not deplete it, and even increase its energy resources. This effect is called a positive inotropic effect. The biochemical molecular mechanisms of action of CG are associated with their complex effect on the bioenergetics of the myocardium (myocardiocytes). Cardiac glycosides are able to bind to special receptors both in the myocardium and in other tissues. In the myocardium, such a receptor for cardiac glycosides is the membrane sodium-potassium ATPase. By binding to the receptor and inhibiting this enzyme, cardiac glycosides change the conformation of the protein and phospholipid parts of both the outer membrane of cardiomyocytes and the membrane of the sarcoplasmic reticulum. This facilitates the influx of calcium ions from the extracellular environment and promotes the release of ionized calcium from intracellular storage sites (sarcoplasmic reticulum, mitochondria). As a result, SGs increase the concentration of biologically active calcium ions in the cytoplasm of myocardial cells. Calcium ions eliminate the inhibitory effect of modulating proteins - tropomyosin and troponin, promote the interaction of actin and myosin, activate myosin ATPase, which splits ATP. The energy necessary for myocardial contraction is generated. In addition, in the mechanism of the positive inotropic action of SGs, it is likely that they increase the function of adrenergic structures of the myocardium. On the ECG, the positive inotropic effect is manifested by an increase in voltage and a shortening of the QRS interval.

II. Diastolic action of CG.

This effect is manifested by the fact that when cardiac glycosides are administered to patients with heart failure, a decrease in the heart rate is noted, that is, a negative chronotropic effect is registered. The mechanism of the diastolic effect is multifaceted, but the main thing is that it is a consequence 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 rhythm of heart contractions slows down. Thus, when using therapeutic doses of cardiac glycosides, enhanced systematic contractions of the myocardium are replaced by sufficient periods of "rest" (diastole), which contribute to the restoration of

energy resources in cardiomyocytes. Prolongation 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, the prolongation of diastole will manifest itself as 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 using the exchange mechanism in its membrane.

III. Negative dromotropic action.

The next effect of cardiac glycosides is associated with their direct inhibitory effect on the conduction system of the heart and tonic effect on the vagus nerve. As a result, the conduction of excitation through the myocardial conduction system is slowed down. This is the so-called negative dromotropic effect. The slowing of conduction occurs throughout the conduction 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 is prolonged. In toxic doses, cardiac glycosides cause atrioventricular block. On the ECG, the slowing of conduction of excitation will be reflected in the lengthening of the PR interval.

IV. Positive bathmotropic effect.

In therapeutic doses, cardiac glycosides reduce the excitability of the sinus node pacemakers (negative bathmotropic effect), which is mainly associated with the activity of the vagus nerve. Toxic doses of drugs of this group, on the contrary, increase the excitability of the myocardium (positive bathmotropic action), which leads to the emergence 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, thanks to the work of 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 a decrease in potassium, which causes an electrically unstable state of myocardiocytes.

In a healthy person, under the influence of therapeutic doses of SG, the described changes will not occur (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, with myocardial infarction. In these conditions, cardiovascular failure occurs. Under the influence of cardiac glycosides in these conditions, an increase in the force of heart contractions and its minute blood volume improves hemodynamics throughout the body and eliminates the consequences of its disorders in patients with heart failure:

- first of all, venous stasis decreases, which contributes to the resolution of edema;
- impaired functions of internal organs (liver, gastrointestinal tract, kidneys) are restored;
- diuresis increases as a result of a decrease in sodium reabsorption and potassium loss with urine;
- the volume of circulating blood decreases.

As a result, the conditions for the heart's work are facilitated. Improved blood supply

to the lungs contributes to increased gas exchange. Oxygen delivery to tissues improves, tissue hypoxia and metabolic acidosis are eliminated. All this leads to the disappearance of cyanosis, shortness of breath in the patient, to the normalization of blood pressure, sleep, processes of inhibition and excitation in the CNS.

Pharmacokinetics of cardiac glycosides

The less polar the glycoside molecule, the better it dissolves in lipids and is absorbed from the gastrointestinal tract and vice versa. Therefore:

- strophanthin is practically not absorbed from the intestine;
- digoxin and celanide are absorbed by 30%;
- digitoxin - is absorbed by 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;
- nonpolar cardiac glycosides are administered orally;
- relatively polar - enterally and parenterally.

In blood plasma, drugs of this group can be bound to albumins or circulate in a free state. Polar glycosides are practically not bound to plasma proteins, and non-polar ones are almost completely bound to them (digitoxin, for example, binds to proteins by 97%). The bound fraction of glycosides does not enter the tissues, but its value may be lower than normal with a decrease in the protein content in blood plasma (liver, kidney diseases), in the presence of endogenous (free fatty acids) or exogenous (butadione, sulfonamides) agents in the blood.

Polar cardiac glycosides do not penetrate the connective tissue, therefore the concentration of strophanthin, digoxin in the blood is increased in obese individuals, as well as in the elderly (the maintenance dose should be much lower). The free fraction of SG enters almost all tissues, but especially in the myocardium, liver, kidneys, skeletal muscles, and brain. The drugs accumulate especially intensively in the myocardium. The main direction of action of cardiac glycosides is explained by the high sensitivity of 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 speed of development of the effect depends on both the ease of penetration of active substances through cell membranes and binding to blood plasma proteins. The effect of strophanthin develops 5-10 minutes after administration, digoxin - 30-40 minutes (with intravenous administration). After oral administration, the effect of digoxin is noted after 1.5-2 hours, and digitoxin - after 1-1.5 hours. The more and stronger the cardiac glycosides bind to proteins (especially digitoxin, very easily - strophanthin and corglycon), 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 in an unchanged form, while non-polar ones undergo biotransformation in the liver.

Not the entire dose of cardiac glycoside is eliminated from the body per day:

- strophanthin and corglycon - 45-60%;
- digoxin and celanide - 30-33%;
- digitoxin (at the beginning of treatment) - 7-9%.

A large part of the administered dose (different volumes for different glycosides) remains in the body, which is the reason for their cumulation - accumulation in the body with repeated administrations. At the same time, the longer the cardiac glycosides act, the greater the cumulation (material cumulation, i.e. accumulation of the cardiac glycoside itself in the body). The most pronounced cumulation is observed when using digitoxin, which is associated with the slow processes of inactivation and elimination of digitoxin from the body (the half-life is 160 hours). Approximately 7/8 of the administered dose of strophanthin is excreted in the first 24 hours, so cumulation is slightly expressed when using it.

Indications for use:

1. As an emergency aid for acute heart failure. For this purpose, it is best to prescribe intravenously fast-acting glycosides (strophanthin, corglycon).

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 some types of atrial (supraventricular) arrhythmias (as a second-choice agent for supraventricular tachycardia, atrial fibrillation and paroxysmal tachycardia, as well as for atrial flutter). In this case, the effect of SG on the conduction system is used, as a result, the speed of impulse conduction through the AV node decreases.

4. For prophylactic purposes, SG is used in the compensation stage in patients with heart disease before the upcoming major surgical operation, before childbirth, etc.

Principles of prescribing cardiac glycosides

SG cannot be prescribed spontaneously. This is a special section of patient treatment. Cumulation of the drug can lead to intoxication with cardiac glycosides. Thus, for the treatment of patients with chronic heart failure, CG is used in doses that ensure the creation of a stable therapeutic concentration of the drug in the blood. At the same time, in the first phase of treatment, compensation of cardiac activity is achieved in a particular patient. To do this, at the beginning of treatment, a dose is prescribed that allows achieving the maximum therapeutic effect (saturation dose or full dose of digitalization). After reaching the saturation dose, the treatment proceeds to the second phase ("maintenance"), when cardiac glycoside drugs 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 maintenance dose compensates for the amount of the drug that is 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 (achieving a saturation dose):

1. Rapid digitalization.

With this method of treatment of CG, a saturation dose is prescribed, which is achieved quickly, during the first 24-36 hours. This method is rarely used, only in a hospital setting, since there is a risk of drug overdose. Rapid digitalization is used in patients with severe acute heart failure with great caution, since they have reduced tolerance to cardiac glycosides, so the drug is easy to overdose (strophanthin is prescribed 1/4 of the volume of the ampoule every hour intravenously slowly).

2. Moderately rapid digitalization. This method involves the use of medium doses with

the achievement of the effect after 2-5-7 days. The drug is prescribed in parts, gradually adjusting the dose. This method is used most often.

3. Slow digitalization.

With this method, the patient's treatment begins with small doses of cardiac glycosides, almost equal to the maintenance dose. This method can also be used in outpatient settings.

Rapid digitalization should be carried out in a hospital, controlling possible toxic effects, slow - during outpatient treatment.

Interaction of cardiac glycosides with other drugs.

The inotropic effect of SG is enhanced by adrenomimetics (isoprenaline, noradrenaline, adrenaline), and the arrhythmogenic effect is eliminated by antiarrhythmic drugs of groups I (quinidine, procainamide) and II (lidocaine, phenytoin).

Interaction with other drugs leads to a weakening of the main action of cardiac glycosides or to an increase in their toxic effect:

- a decrease in the absorption of SG is caused by antacids (increased gastrointestinal motility) and hypolipidemic agents (cholestyramine);

- an increase in absorption is observed under the influence of anticholinergic agents that weaken intestinal peristalsis (atropine);

- bradycardia increases with simultaneous administration of beta-blockers, reserpine, quinidine, verapamil;

- atrioventricular conduction is slowed to a greater extent under the influence of beta-blockers, quinidine and other antiarrhythmic drugs of group I;

- an increase in arrhythmogenic properties is possible when interacting with diuretics, beta-adrenomimetics, reserpine, clonidine, calcium antagonists.

Toxic effect of cardiac glycosides

CGs are potentially one 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 SG drugs has symptoms of poisoning. The reasons for this may be:

1) low therapeutic index;

2) non-compliance with the existing principles of using cardiac glycosides;

3) combination with other drugs:

- when using cardiac glycosides together with diuretics, potassium loss occurs, which contributes to hypokalemia, which significantly reduces the threshold of excitability of cardiomyocytes, and as a result, cardiac arrhythmia (extrasystole) occurs;

- joint use of cardiac glycoside drugs with glucocorticoids also leads to potassium loss with a corresponding violation of the rhythm of heart contractions;

4) severe liver and kidney damage (sites of biotransformation and excretion of glycosides);

5) individual high sensitivity of the patient to cardiac glycosides, especially in myocardial infarction.

The mechanism of development of intoxications with cardiac glycosides is 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) disruption of the return of potassium ions to the cell, as well as the accumulation of

sodium ions in it, which contributes to increased cell excitability and the development of arrhythmias;

b) increased entry and impaired exit of calcium ions, which is realized by hypodiastole, which leads to a decrease in cardiac output.

Symptoms of intoxication are divided into:

I. Cardiac symptoms of intoxication:

1. Bradycardia.

2. Atrioventricular block (partial, complete, transverse).

3. Extrasystole.

II. Extracardiac (extracardiac) symptoms of intoxication:

1. From the gastrointestinal tract: decreased appetite, nausea, vomiting, abdominal pain. These are the earliest symptoms of intoxication from the gastrointestinal tract.

2. Neurological symptoms (associated with excessive bradycardia that occurs with an overdose of cardiac glycosides): adynamia, dizziness, weakness, headache, confusion, aphasia, impaired color perception, hallucinations, "tremor of objects" when viewed, decreased visual acuity.

Measures of assistance in case of intoxication with cardiac glycosides:

1. Immediately cancel SG drugs with simultaneous administration of activated charcoal, gastric lavage, saline laxatives should also be prescribed.

2. Temporarily cancel drug combinations. If the patient's condition is severe, use antiarrhythmic drugs. In a hospital setting, you can prescribe (4-5%) potassium chloride solution, intravenously, drip, under ECG control.

3. Prescribe the patient diphenin - a drug that stimulates liver enzymes and has a good antiarrhythmic effect. Currently, this is one of the best drugs for ventricular tachycardia caused by digitalis intoxication. Lidocaine (xikain) is less effective than diphenin in intoxication with cardiac glycosides. 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 drugs (fragments of monoclonal antibodies to cardiac glycosides) are, in fact, antidotes.

Prevention of cardiac glycoside intoxication:

1. Compliance with the principles of prescribing cardiac glycosides and individualization of patient treatment.

2. Rational combination of cardiac glycosides with other drugs.

3. Constant ECG monitoring (prolongation of the PQ interval, the appearance of arrhythmias).

4. Diet rich in potassium (dried apricots, raisins, bananas, baked potatoes); prescription of potassium preparations: panangin (potassium asparaginate in combination with magnesium asparaginate).

Contraindications to the prescription of cardiac 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 block;

3) hypokalemia;

4) ventricular paroxysmal tachycardia. Sometimes a positive inotropic effect can

determine contraindications to the appointment of cardiac glycosides - subaortic and isolated mitral stenosis in sinus rhythm.

Non-glycoside non-adrenergic synthetic cardiotonics

Due to the high toxicity of cardiac glycosides, a search was conducted for synthetic cardiotonics with a greater breadth of action, effectiveness in various types of heart failure, and the presence of other positive qualities. Thus, a number of drugs that meet these conditions were created - Amrinone and Milrinone.

Mechanisms of action:

- inhibition of phosphodiesterase;
- increase in the concentration of cAMP;
- activation of protein kinase;
- increase in the influx of calcium ions into the cell;
- stimulation of muscle contraction.

The first synthetic cardiotonic drug of a non-steroidal structure is Amrinone (Amrinone; ampoules of 20 ml of solution containing 100 mg of the active substance). The drug has a positive inotropic effect, vasodilator effect, increases cardiac output, reduces pressure in the pulmonary artery system, reduces peripheral vascular resistance. Indications 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.

Milrinone is similar in structure and action. It is more active than amrinone and, apparently, does not cause thrombocytopenia.

2. Questions for self-control (list of questions):

1. Classification of acute and chronic heart failure.
2. Etiology and pathogenesis of acute (cardiac asthma, pulmonary edema) and chronic heart failure.
3. Classification of diseases of the heart muscle.
4. Characteristics of the main functions of the heart: electrophysiological - automatism, excitability, conductivity, refractoriness; mechanical - contractility, tonicity.
5. Classification of cardiac glycosides.
6. Absolute and relative indications and contraindications for the appointment of cardiac glycosides.
7. Cardiac and non-cardiac effects of cardiac glycosides.
8. Tactics of individual dosing of cardiac glycosides.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for the main groups of cardiotonics (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for appointment.

Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working medical history (data from laboratory and instrumental studies, consultants' conclusions) and the prescription list.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize the presence of heart failure, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, select the drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the characteristics of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Justify the need for combined drug therapy and suggest possible options for a safe combination of drugs.

9. Make a forecast of the side effects of drugs prescribed to the patient and outline a plan for their detection at the early stages.

10. Justify the duration of basic and supportive therapy.

B. Solution of situational tasks.

1. A patient, 42 years old, is in a therapeutic hospital with a diagnosis of: rheumatism of the active phase, II stage. activity, reverse carditis, aortic valve insufficiency, CHF-II B stage. For one month he takes digitoxin 1 tab. (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, edema in the legs, decreased daily diuresis, increased liver size. What caused the deterioration of the patient's condition? What SG should be prescribed to reduce the severity of decompensation?

2. A 65-year-old patient complains of shortness of breath at rest, irregular heartbeat, swelling of the legs, abdominal enlargement, heaviness in the right hypochondrium, daily diuresis - 0.6 l. History: suffered a large-focal myocardial infarction 5 years ago. Periodic attacks of angina pectoris after nervous stress, climbing to the 2nd floor. Shortness of breath and swelling of the legs have been noted for the last 2 years. Periodically took digoxin (1 t. 2 times a day, 5 days a week) in "courses" of 2 months with a 1-month break (on the recommendation of the district therapist). The real deterioration occurred 3 weeks ago and is progressing. Objectively: general condition of moderate severity, orthopnea. Cyanosis of the lips, acrocyanosis, swelling of the neck veins, pulse - 118 beats. in 1 min, arrhythmic in the type of atrial fibrillation. HR - 144 in 1 min. ACT - 120/90 mm Hg. Hypertrophy of both ventricles. Accent of the II tone over the pulmonary artery, systolic murmur over the aorta. BH - 26 in 1 min. Breathing is hard, in the lower lateral parts there are rales. The tongue is

dry. The abdomen is round, free fluid is determined in the lateral parts. The liver protrudes 12 cm from the edge of the costal arch along the right midclavicular line, dense, smooth. Edema of the legs, lumbosacral spine. ECG - atrial fibrillation, tachysystolic form (HR - 156 in 1 min), hypertrophy of both ventricles. Scarring changes of the myocardium in the posterolateral part of the left ventricle.

Formulate a clinical diagnosis. Justify the choice of SG, its dose, saturation rate in the period of initial digitalization. Indicate the clinical and electrocardiographic criteria for the effectiveness of this stage of glycoside therapy.

3. A 52-year-old patient developed an attack of cardiac asthma. On examination, the pulse is 78 beats per minute, rhythmic. ACT - 170/100 mm Hg. Heart sounds are muffled. There is an enlarged liver, moderate swelling of the lower legs. The doctor prescribed intravenous administration of corglycon.

Evaluate the tactics of managing the patient. Make a plan for correcting the patient's treatment.

4. A patient is in the cardiology department who was brought in with an acute extensive myocardial infarction. The patient's condition is of moderate severity, pulse - 100 beats per minute, rhythmic. Heart sounds are muffled. Breathing over the lungs is vesicular. The liver is not enlarged, there is no edema. The patient was prescribed strophanthin. After the introduction of the minimum dose (0.25 ml - 0.05% solution), single extrasystoles appeared, after the second introduction of the same dose, bigeminia developed.

Evaluate the tactics of managing the patient. Explain the cause of the complication.

Test tasks for self-control:

1. Intoxication with cardiac glycosides is promoted by:
A. Old age
B. Late stages of chronic heart failure
C. Electrical impulse defibrillation
D. Hypokalemia and hypomagnesemia
E. All of the above factors
2. Contraindications to the appointment of cardiac glycosides are:
A. Progressive AV blockade
B. Wolff-Parkinson-White syndrome
C. Severe bradycardia
D. Subaortic stenosis
E. All of the above factors
3. In acute heart failure, the following are used for intravenous administration:
A. Strophanthin, digitoxin.
B. Celanid, corglycon, adonizide.
C. Strophanthin, corglycon.
D. Mezaton, digitoxin, strophanthin.

E. Fenoterol, strophanthin, corglycon.

4. The mechanism of cardiotonic action of cardiac glycosides is:

A. Inhibition of Na +, K + - ATPase of myocardial cells

B. Inhibition of prostaglandin synthesis

C. Inhibition of the enzyme phospholipase A2

D. Activation of platelets from phospholipids of cell membranes

E. Calcium ions accumulated in the cytoplasm of myocardial cells, which in turn inhibits the excretion of sodium.

5. Indications for the appointment of cardiac glycosides are:

A. Ventricular paroxysmal tachycardia

B. Isolated mitral stenosis on the background of sinus rhythm

C. Acute inflammatory and dystrophic changes in the myocardium

D. Acute and chronic heart failure

E. Ischemic heart disease

6. Choose the drug that has the most powerful cardiotonic effect:

A Digoxin.

B. Strophanthin

C. Digitoxin

D. Amiodarone

E. Propranolol

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical and pharmacological characteristics of antiarrhythmic drugs"

Purpose:

To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of antiarrhythmic drugs:

- For tachyarrhythmias:

Class I - sodium channel blockers (membrane stabilizing agents):

IA - prolong the effective refractory period (ERP): quinidine, novocainamide, disopyramide;

IV - shorten the ERP: lidocaine, mexiletine, diphenin;

IC - have different effects on the ERP: propafenone, etacizin.

Class II - beta-blockers:

Class III - potassium channel blockers: amiodarone, sotalol, bretylium.

Class IV - calcium channel blockers: cardiotropic - verapamil, gallopamil, diltiazem.

For bradyarrhythmias: M-cholinoblockers (atropine, platifillin), beta-adrenomimetics (izadrine, dobutamine).

Basic concepts (list of questions):

1. Electrophysiological functions of the heart.
2. Pathogenesis of tachyarrhythmias.
3. Pathogenesis of bradyarrhythmias.
4. Drugs for the treatment of tachyarrhythmias.
5. Drugs for the treatment of bradyarrhythmias.

Plan

1. Theoretical questions:

Cardiac arrhythmias combine a large number of various disorders of the origin and spread of electrical excitation in the heart. The classification of arrhythmias is quite extensive and complex, but from a clinical point of view, those rhythm disorders that can lead either to a critical slowdown in the rhythm up to the cessation of cardiac activity (bradyarrhythmias) or to a life-threatening acceleration of the heart rhythm (tachyarrhythmias) are especially important.

Classification of cardiac arrhythmias

1. Violations of automaticity: • Sinus tachycardia. • Sinus bradycardia. • Sinus arrhythmia.

2. Extrasystoles:

2.1. Supraventricular extrasystoles. 2.2. Ventricular extrasystoles.

3. Tachyarrhythmias:

3.1. Supraventricular tachycardias (paroxysmal and chronic): 3.1.1. Atrial tachycardias; 3.1.2. Tachycardias from AV connection; 3.1.3. Atrioventricular (AV) reciprocal tachycardias (presence of additional conduction pathways); 3.1.4. Atrial fibrillation and flutter.

3.2. Ventricular tachycardias: 3.2.1. Ventricular tachycardia; 3.2.2. Ventricular fibrillation and flutter.

4. Blockades, sinus node arrest.

5. Ventricular preexcitation syndromes: 5.1. WPW phenomenon.

6. Parasystoles.

Antiarrhythmic drugs (AADs) are used for the treatment and prevention of tachyarrhythmias, although non-pharmacological (electrical and surgical) methods of treatment have made fundamental changes in this area. Treatment of severe bradyarrhythmias is carried out mainly by methods of electrical cardiostimulation.

The formation and orderly conduction of an electrical impulse through the myocardium are provided by the structures of a specialized conduction system, the cells of which, unlike ordinary cardiomyocytes, normally possess not only excitability and conductivity, but also the ability to spontaneously generate rhythmic impulses - automatism.

The source of automatism, which allows for the sequential excitation of all parts of the heart, is the sinus (sinoatrial) node - the primary pacemaker. The impulse from the sinus node causes excitation (depolarization) of the atrial myocardium, spreading along the Bachmann, Wenkebach and Torel tracts; passes to the ventricles through the atrioventricular node (AVB), in which the movement of the excitation wave is significantly slowed down. Next, the

excitation spreads along the trunk of the atrioventricular bundle (bundle of His), its left and right legs and, finally, along the smallest Purkinje fibers, branching in the ventricular myocardium. Depolarization of the myocardium, thanks to a specialized conduction system, occurs quickly, in a strict sequence, and goes in the direction from the endocardium to the epicardium of the ventricles. Repolarization - the return of cells to the original unexcited state - occurs more slowly and moves in the direction from the epicardium to the endocardium.

On a normal ECG, the excitation of the structures of the conduction system is not reflected; atrial depolarization is manifested by a P wave, atrial repolarization is usually not visible; ventricular depolarization is manifested by a QRS complex; and ventricular repolarization is manifested by a T wave; the PQ interval reflects the time required for the conduction of excitation from the sinoatrial node to the ventricular myocardium - AV conduction (through the atria, AVB and the His-Purkinje system); the QT interval covers the depolarization and repolarization of the ventricles, therefore it is called electrical systole; the PP and RR intervals normally reflect the automatism of the sinus node.

The electrical properties of cells of the excitable tissue of the heart are determined by the nature of their transmembrane action potential (AP). AP occurs when the depolarization of the cell membrane reaches a certain threshold, according to the principle of "all or nothing". AP itself is the result of active transmembrane ion flows through specific channels.

AP of a cardiomyocyte consists of the following phases:

0 - depolarization phase (rapid entry of Na+ ions into the cell);

1 - initial repolarization phase (beginning of the exit of K+ ions from the cell);

2 - slow repolarization phase or "plateau": (entry of Ca2+ ions into the cell, which balances the exit of K+ ions);

3 - fast repolarization phase (exit of K+ ions, restoring the initial potential of the cell);

4 - complete repolarization phase (restoration of ion balance: exchange of K+ for Na+ and Na+ for Ca2+).

Most AADs block certain ion channels, causing corresponding changes in PD and, consequently, changes in the electrical properties of the myocardium and the conduction system.

MAIN MECHANISMS OF ARRHYTHMIA FORMATION

M. S. Kushakovsky (2004) combines all possible causes of arrhythmias into three classes:

I. Disturbances in the regulation of electrical processes in specialized and contractile cells of the myocardium of a neurogenic or endocrine (humoral) nature.

II. Organic changes in the myocardium: diseases of the myocardium, its anomalies, congenital or hereditary defects with damage to electrogenic membranes or destruction of cellular structures.

III. Combined regulatory and organic causes.

Electrophysiological mechanisms of arrhythmias are generally represented by disorders of impulse formation, disorders of impulse conduction, combined disorders of impulse formation and conduction.

Among the numerous and constantly performed mechanisms of tachyarrhythmias, the following are of greatest importance in clinical practice: changes in automatism, trigger rhythms and re-entry.

Acceleration of the rhythm due to increased automatism of the sinus node, atria, AV junction or ventricles causes the so-called automatic tachycardias. Their frequency is less than 10%, the main cause is metabolic and neuroendocrine regulation disorders (myocardial ischemia, hypoxemia, electrolyte disorders - hypokalemia, hypomagnesemia, acid-base balance disorders, hypersympathicotonia, hypercatecholaminemia). Typical examples of such disorders are atrial tachycardia during exacerbation of chronic lung diseases (hypoxemia), ventricular arrhythmias in the first hours of myocardial infarction (ischemia, hypercatecholaminemia). As a rule, automatic arrhythmias occur in acute conditions and resolve as they are stopped due to the elimination of the etiological factor. Usually, specific antiarrhythmic therapy is not required.

Trigger rhythms. If abnormal automatism is a consequence of partial membrane depolarization, then trigger rhythms are the result of incomplete repolarization. Late depolarizations are provoked by an increase in the rhythm, therefore they are called catechol-dependent, the amplitude of late depolarizations is increased by a high concentration of calcium in the cells. It is believed that supraventricular and ventricular arrhythmias in case of intoxication with cardiac glycosides, as well as atrial tachycardias against the background of hypercatecholaminemia are caused by this trigger mechanism.

Treatment of trigger arrhythmias most often consists in eliminating provoking factors (elimination of pauses, cancellation of antiarrhythmic drugs of classes IA, 1C and III - for brady-dependent forms; cancellation of cardiac glycosides and appointment of β-blockers - for tachy-dependent forms).

Re-entry, or re-entry of the impulse with its subsequent circular movement, is the mechanism of most clinically significant tachyarrhythmias. The condition of occurrence is the electrical heterogeneity of the myocardium, in which two conditionally parallel conductive paths (connected proximally and distally through conductive tissue) have different refractory periods and conduction velocities. Tachyarrhythmias based on re-entry are called reciprocal, this is the mechanism of both supraventricular and most ventricular arrhythmias, including fibrillation and flutter of the atrium and ventricles.

AADs can effectively suppress reciprocal arrhythmias by equalizing the refractory periods or conduction velocities of the antero- and retrograde paths of the loop, since its existence is possible only with a certain ratio of these parameters. Electrical effects on re-entry (cardioversion, defibrillation) or surgical destruction, which interrupts the pulse circulation circle, are no less effective.

ANTIARRHYTHMIC DRUGS

Classification of antiarrhythmic drugs

Classification of antiarrhythmic drugs (Vaughan-Williams E., 1969, with amendments and additions):

Agents used to treat tachyarrhythmias:

Class I - agents that block sodium channels - slow down depolarization:

IA - moderate slowing of depolarization and repolarization:

• Quinidine, procainamide, disopyramide, ajmalin.

IB - minimal slowing of depolarization, shortening of repolarization:

• Lidocaine, trimecaine, mexiletine, diphenylhydantoin.

IC - pronounced slowing of depolarization, minimal - repolarization:

• Flecainide, propafenone, etmosin, etacisin.

Class II - β-adrenergic receptor blockers without sympathomimetic activity:

• Propranolol, metoprolol, atenolol, esmolol, nadolol.

Class III - potassium channel blockers - slow repolarization:

• Amiodarone, sotalol, ibutilide, bretylium.

Class IV - calcium channel blockers - slow automaticity and AV conduction:

• Verapamil, diltiazem, bepridil, gallopamil.

Drugs with antiarrhythmic properties that are not included in the classification of E. Vaughan-Williams:

I. Drugs with primary antiarrhythmic action:

• Adenosine and adenosine triphosphate (ATP) - potassium channel activators.

• Alindine - chloride current blocker.

• Ivabradine - inhibitor of If-channels (slow sodium and potassium current).

• Cardiac glycosides (digoxin, strophanthin).

• Electrolytes (potassium, magnesium preparations).

II. Drugs with secondary antiarrhythmic action:

• Angiotensin-converting enzyme inhibitors (captopril, enalapril, etc.).

• Statins (simvastatin, atorvastatin, etc.).

• Polyunsaturated fatty acids (Omakor).

Drugs for the treatment of bradyarrhythmias (not intended for the treatment of organic dysfunctions of the SAV and AVV):

• M-cholinoblockers: - Atropine, belladonna preparations.

• Dihydropyridine calcium channel blockers: - Nifedipine, amlodipine, felodipine.

• Phosphodiesterase inhibitors: - Theophylline.

• Beta-1-agonists: - Isadrin, astmopent.

Non-pharmacological methods of treatment of arrhythmias:

Electrical influence:

• Cardioversion - defibrillation (external, transesophageal, intracardiac).

• Implantation of a cardioverter-defibrillator.

• Electrocardiostimulation (temporary and permanent).

Physical influence (radiofrequency ablation, cryolaser destruction, excision of the arrhythmia focus):

• Destruction of arrhythmogenic zones (re-entry loop channels, arrhythmia foci).

• Isolation of the arrhythmogenic focus (AVB ablation, atrial isolation, etc.).

• Excision of the arrhythmogenic area of the myocardium (aneurysm plastic).

Characteristics of individual antiarrhythmic drugs

Class I antiarrhythmic drugs

The unifying property of this class is the blockade of fast sodium channels, which is manifested by a decrease in the rate of depolarization and, consequently, a decrease in the rate of conduction in the atria and ventricles, inhibition of abnormal automatism of cardiomyocytes (inhibition of sodium-mediated spontaneous diastolic repolarization), and a decrease in the threshold of myocardial excitability. The reason for the division of class I AADs into three subclasses is the nature of the effect on repolarization - the duration of the PD. Class IA drugs moderately prolong the PD, class IB drugs - shorten the PD, class IC drugs - do not affect it.

Class IA antiarrhythmic drugs

General properties:

• Blockade of sodium and potassium channels (moderate).

• Slowing of depolarization (phase 0) and repolarization (phases 1-3) - prolongation of the PD.

• Prolongation (widening) of the QRS complex and the QT interval.

• Slowing of conduction (moderate) and increasing myocardial refractoriness (moderate).

• Suppression of abnormal automatism (weak).

• Ambiguous effect on the function of the AV and AVB: usually - an increase in the AV automaticity and conduction velocity in the AVB (vagolytic effect), with initial dysfunction of the AVB or AVB - direct inhibition of their function.

• Typical proarrhythmias - ventricular torsades de pointes (a consequence of QT prolongation) and reciprocal AV (a consequence of conduction disturbances).

• Efficacy in supraventricular and ventricular tachyarrhythmias - moderate.

Quinidine is prescribed for the relief and prevention of atrial fibrillation (AF) and atrial flutter (AT), relief of supraventricular tachycardias (SVT) and ventricular tachycardias (VT). When stopping AF and TP, quinidine is usually combined with verapamil to eliminate a sharp increase in ventricular rhythm (quinidine sulfate 200 mg 3-4 times a day or quinidine bisulfate 250 mg 2-3 times a day + verapamil 40-80 mg 3-4 times a day). When quinidine is first used to exclude idiosyncrasy, a test dose is given (1 tablet orally) and observation is carried out for several hours. The drug causes a vagolytic effect on the SAB and AVB, which may manifest as an increase in sinus rhythm (medium doses of quinidine), accelerated conduction through AVB with an increase in the frequency of ventricular contractions in atrial fibrillation or TP. Alpha-adrenolytic effect (hypotension, reflex tachycardia) and mild cardiodepression are observed with intravenous administration (rarely used due to poor hemodynamic control).

Procainamide (novocainamide) has a vagolytic effect on SAB and AVB, which is less pronounced than quinidine. Alpha-adrenolytic effect (vasodilation with hypotension) and cardiodepression are observed only with intravenous administration. Procainamide causes sudden death less often than quinidine. Increases the threshold for ventricular fibrillation (VF). The drug is used for the same indications as quinidine. As a second-line agent, procainamide is used for the relief of VT resistant to other AADs, with persistent VT.

Disopyramide (ritmylene) has a pronounced systemic vagolytic effect, including in relation to SAB and AVB (superior to quinidine), and significantly inhibits myocardial contractility. In patients with myocardial infarction, the drug does not increase mortality, but increases the incidence of CHF. Disopyramide is used for the treatment and prevention of ventricular arrhythmias in patients without severe organic myocardial lesions.

Class IV antiarrhythmics

General properties:

• Blockade of sodium channels (inactivated) is weak, but pronounced in damaged or ischemic arrhythmogenic tissue, with an increase in the rhythm.

• Slowing of depolarization, mainly in the focus of arrhythmia.

• Shortening of repolarization (phases 1-3) - shortening of PD.

• Absence of significant changes in P, PQ, QRS; QT shortens or does not change.

• Slowing of conduction in the arrhythmogenic zone in ventricular arrhythmias (significant).

• No effect on SAV, AVV and atrial myocardium due to shorter PD in the atria.

• Suppression of normal and abnormal automatism in the ventricles (moderate).

• Reduction of ventricular myocardial refractoriness (weak).

• Suppression of late afterdepolarizations (weak).

• Suppression of trigger rhythms in Purkinje fibers due to shortening of PD.

• High efficacy in reciprocal ventricular tachycardias.

• Low efficacy in supraventricular tachyarrhythmias (except for arrhythmias in glycoside intoxication).

• Low probability of proarrhythmias and absence of cardiodepression.

Lidocaine (xylocaine) - is an amide local anesthetic. It does not cause a slowdown in depolarization and, accordingly, the conduction velocity in normal tissue, but in ischemia, hypokalemia, and a frequent rhythm, it slows down conduction and shortens the refractory period, mainly in the ventricles (a consequence of the blockade of inactivated sodium channels), suppresses automatism in the ventricles (which can cause asystole in a slipping ventricular rhythm). It suppresses not only late but also early postdepolarizations. At the same time, it is hemodynamically neutral and does not cause cardiodepression. Lidocaine is used to stop ventricular arrhythmias in patients with myocardial infarction and during heart surgery. The drug prevents recurrence of VT/VF in myocardial infarction, but does not reduce mortality with prophylactic administration.

Mexiletine (mexitil) is a derivative of lidocaine for oral administration. It is close in effectiveness to class IA AAS in the treatment of ventricular arrhythmias in patients after myocardial infarction, but does not affect mortality after MI (possibly increases it). Mexiletine is used for the prevention and treatment of ventricular arrhythmias, mainly - the treatment of symptomatic ventricular extrasystole and unstable ST.

Phenytoin (diphenin, diphenylhydantoin) is used mainly as an anticonvulsant. Its antiarrhythmic properties resemble lidocaine, but there is a feature - an indirect central antiadrenergic effect. The drug is indicated for ventricular arrhythmias in patients with epilepsy, ventricular arrhythmias during operations for congenital heart defects.

Side effects of the AAZ subgroup: hypotension, dizziness, rarely - arrhythmias, gastrointestinal disorders, central neurotoxicity (ataxia, nystagmus, convulsions, apnea), myelodepression, individual intolerance.

Class IC antiarrhythmics

General properties:

• Sodium channel blockade is pronounced.

• Slowing of depolarization (phase 0), repolarization does not change (phases 1-3).

• On the ECG, the following are possible: expansion of the P wave, lengthening of the PQ interval, expansion of the QRS complex; the QT interval does not change or is slightly lengthened (due to the expansion of the QRS complex).

• Slowing of conduction in the myocardium of the atria, ventricles and the conduction system (significant).

• High efficiency in supraventricular and ventricular tachyarrhythmias.

• Suppression of myocardial contractility - cardiodepression.

• High arrhythmogenic potential - provocation of reciprocal ST.

• Increase mortality in the treatment of arrhythmias in patients with post-infarction cardiosclerosis, significant dilatation of the heart chambers, intraventricular blockades.

Flecainide (tambocor) slows down the conduction in the myocardium of the atria, ventricles and cells of the conduction system (at any heart rate) with a dose-dependent prolongation of PQ and QRS. It has little effect on the automatism of the sinus node, but slows down the time of restoration of its function. The drug is used for the relief and prevention of AF and TP in patients without severe heart disease, relief of dangerous ventricular arrhythmias resistant to treatment with other agents. At the same time, the appointment of flecainide should be avoided in patients who have suffered a myocardial infarction, with a pronounced decrease in myocardial contractility, dilatation of the heart chambers, severe CHF. This is due to the ability of flecainide, like other group IC drugs, to reduce myocardial contractility, and with prolonged use, to convert episodes of myocardial ischemia into episodes of ventricular fibrillation, increasing the risk of sudden death in patients who have had myocardial infarction.

Propafenone (Rythmonorm), like all class IC drugs, slows down the conduction in the myocardium of the atria, ventricles and cells of the conduction system, lengthening PQ and QRS. The degree of blockade increases with increasing heart rate. However, propafenone prolongs the effective refractory period of the atria, AVB to a lesser extent. In addition, it has weak properties of a β-blocker and calcium channel blocker. Reduces myocardial contractility to a lesser extent than flecainide and disopyramide. It is considered relatively safer than flecainide. Propafenone is used for the same indications as flecainide, it is often used to stop AV-reciprocal (WPW syndrome) and AV-nodal reciprocal tachycardias.

Side effects: about arrhythmias, gastrointestinal disorders, myelodepression, autoimmune disorders, dizziness, insomnia, paresthesia.

Class II antiarrhythmics (β-blockers)

The antiarrhythmic effect of β-blockers is due to the blockade of the arrhythmogenic effects of catecholamines. With a moderate ability to suppress arrhythmias, BABs have proven to be very effective in preventing life-threatening rhythm disturbances and preventing sudden death in a wide range of patients. This is the only class of AADs that has unconditionally proven its ability to improve the prognosis of ventricular arrhythmias in patients with and without severe myocardial damage. Unlike other classes of AADs, all representatives of BABs have the same mechanism of antiarrhythmic action.

The electrophysiological effects of BABs are expressed where adrenergic receptors are most abundant. These are SAV and AVV, in which inhibition of the 4th phase of the PD (spontaneous diastolic depolarization) leads to a slowdown in automatism, conduction and lengthening of refractory periods, which is manifested on the ECG by slowing the rhythm and AV conduction (PQ prolongation). In a normal heart, conduction in SAV is little susceptible to the action of BABs, but in pathology these agents can cause SA blockade. BABs have little effect on the conduction velocity and refractoriness of the atrial and ventricular myocardium, but they exhibit pronounced effects in ischemic or damaged myocardium. Thus, reducing ischemia under the influence of BABs reduces the risk of subsequent arrhythmias; in addition, BABs increase the threshold of VF and prevent the formation of re-entry by smoothing regional differences in the autonomic innervation of the myocardium. Some BABs have membrane-stabilizing properties, but they are detected outside the therapeutic doses and are not relevant in clinical practice. BABs are especially effective in arrhythmias provoked by

ischemia, physical exertion, stress and hypercatecholaminemia (administration of adrenomimetics, thyrotoxicosis).

General indications for the appointment of β-blockers in arrhythmias:

• Ventricular tachyarrhythmias: - treatment and prevention of sinus tachycardia, paroxysms of sinus reciprocal, AV reciprocal and AV nodal reciprocal tachycardia; - control of heart rate in chronic focal tachycardias, AF and TP; - prevention of FT and TP provoked by increased sympathotonus.

• Ventricular arrhythmias: - prevention of ventricular extrasystole and VT caused by physical exertion; - prevention of sudden death (VT and VSH) during and after myocardial infarction; - prevention of sudden death in patients with hypertrophic cardiomyopathy; - prevention of sudden death in people with congenital long QT interval; - treatment of supraventricular and ventricular arrhythmias in digitalis intoxication.

BABs increase the survival of patients with ventricular arrhythmias.

General properties of class II AADs - β-adrenergic blockers:

• Blockade of β-adrenergic receptors.

• Slowing of spontaneous diastolic depolarization (phase 4) and increasing the refractory period in SAV and AVV.

• On the ECG - prolongation of the PQ interval.

• Inhibition of SAV and AVV automaticity.

• Inhibition of conduction in AVV (SAV).

• Increase in effective refractory periods of SAV and AVV.

• Absence of ventricular proarrhythmias (bradyarrhythmias are possible).

• Effectiveness in supraventricular and ventricular tachyarrhythmias.

• Ability to prevent ventricular tachyarrhythmias and sudden death, including in patients with organic myocardial lesions (CHD, CHF, etc.).

Side effects: bronchospasm, cough, hypotension, bradyarrhythmias, increased tone of smooth muscles of the uterus, peripheral vessels, decreased libido.

Class III antiarrhythmics

The unifying property of this class is the blockade of potassium channels, which is manifested by a slowdown in repolarization (phases 1-3 of the PD), therefore, an increase in effective refractory periods in the myocardium and the conduction system. On the ECG, this effect is manifested by a prolongation of the QT interval. The effect of class III AADs is characterized by "inverse frequency dependence" - the effect is enhanced with a rarer rhythm and weakened with a more frequent rhythm. Meanwhile, most class III drugs are not such in their pure form, they differ significantly from each other in additional properties, the degree of inverse frequency dependence, spectrum of action and safety. Due to the peculiarities of action (QT prolongation and inverse frequency dependence), this class of AADs can provoke attacks of VT of the pirouette type. The only representative of class III AADs that has proven its safety in patients with severe heart disease (in the absence of an effect on overall mortality) is amiodarone. It has become a first-line agent in the treatment and prevention of ventricular arrhythmias in this category of patients.

General properties of class III AADs:

• Pronounced potassium channel blockade.

• Slowing of repolarization (phase 1-3 of PD) - increased duration of PD.

• On the ECG - prolongation of the QT interval.

• Increase in effective refractory periods in the conduction system, atria and ventricles (moderate).

• Suppression of automatism (from weak to moderate).

• Inverse frequency dependence.

• Proarrhythmia: torsades de pointes (a consequence of QT prolongation).

• Effectiveness in supraventricular and ventricular tachyarrhythmias (depends on the drug used).

Amiodarone (Cordarone) has the effects of all four classes of AADs. The main action is the blockade of potassium channels, hence the increase in myocardial refractoriness and the conduction system. In addition, the drug causes a slight blockade of fast sodium channels (a property of class I AAD), non-selective non-competitive blockade of β-adrenoceptors (a property of class II AAD) and blockade of calcium channels (a property of class IV AAD). The result of the last two effects is: inhibition of SAV automatism (bradycardia) and slowing of AV conduction (PQ prolongation). Expansion of resistive arteries - a decrease in peripheral resistance and afterload, as well as coronary dilation - a consequence of calcium channel blockade. The main action of amiodarone develops slowly, as the drug accumulates, so intravenous administration of the drug from this point of view does not have significant advantages over rapid oral loading. Meanwhile, with intravenous administration, the β-adrenergic blocking effect of amiodarone is more pronounced - inhibition of conduction in the AV node and hypotension, which is useful for arrhythmias induced by catecholamines, but may be undesirable in patients with hypovolemia.

Among other features of the action of amiodarone, it should be noted the minimal inverse frequency dependence and low probability of developing ventricular proarrhythmias, as well as the absence of significant cardiodepression. These properties, as well as the pronounced antifibrillatory effect, allow the drug to be safely used in patients with organic myocardial changes and severe CHF.

Amiodarone is the most powerful and universal antiarrhythmic drug. It is effective for both ventricular and supraventricular tachyarrhythmias. It may reduce the incidence of sudden cardiac death in patients with LV dysfunction after myocardial infarction and in patients with dilated cardiomyopathy, but probably has little effect on overall mortality in patients with CHF, inferior in this to implantable cardioverter-defibrillators. The onset of action of amiodarone when taken orally is 2-3 days (sometimes 2-3 months), the duration of action is from 2 weeks to several months. With intravenous administration, blockade of β-adrenergic receptors develops rapidly, but the main effect is at the same speed as with rapid oral loading.

The drug is used to stop and prevent life-threatening tachyarrhythmias: rate control, cardioversion and prevention of arrhythmia recurrence in patients with AF and TP; stop and prevention of ventricular tachyarrhythmias.

The side effects of amiodarone are numerous and dose-dependent: hypotension, bradycardia, photosensitivity, lipodystrophy, thyroid damage, central neurotoxicity, dyspepsia, hepatotoxicity, etc.

Sotalol (Sotagexal) as a pharmacological drug is a racemic mixture of two isomers: D-sotalol (class III AAD) and L-sotalol (with the properties of a non-selective β-adrenoblocker). The drug prolongs PD in the atria, ventricles and in the conduction system by blocking potassium channels, which is manifested by a lengthening of the effective refractory period and a dose-dependent prolongation of QT on the ECG. The additional β-adrenoblocking effect

of sotalol is approximately 1/3 of the effect of propranolol. The drug has a negative inotropic effect and has a significantly pronounced inverse frequency dependence.

In terms of antiarrhythmic effect, sotalol is somewhat inferior to amiodarone, but surpasses it in terms of the frequency of proarrhythmias (pirouette-type tachycardia). There is a direct dependence of the effectiveness (degree of QT prolongation) and simultaneously the frequency of proarrhythmias on the dose. Sotalol does not reduce mortality when used prophylactically in patients after myocardial infarction. The use of sotalol is indicated for the relief and prevention of ventricular tachyarrhythmias, reciprocal AV and AV nodal paroxysmal tachycardias, prevention of arrhythmia recurrences in patients with AF and TP; relief of supraventricular and ventricular tachyarrhythmias in patients with thyrotoxicosis.

When treating with sotalol, strict control of the QT interval is necessary. The corrected QT should not exceed 500 ms (it is advisable to evaluate it in sinus rhythm due to the inverse frequency dependence of the drug effect). Hypokalemia should be avoided (prolongs QT).

Class IV antiarrhythmic drugs - calcium channel blockers

Calcium channel blockers (CCBs) block slow calcium channels responsible for the depolarization of the SAH and AVH. Thus, automatism and conduction in SAV and AVV are suppressed, which is accompanied by a moderate slowing of the rhythm and prolongation of the PQ interval. BCCs have little effect on the electrophysiological properties of the myocardium of the atria and ventricles, but in pathology they are able to affect hypopolarized Purkinje fibers. In addition, BCCs suppress trigger activity in the myocardium, mediated by slow calcium channels, reduce myocardial contractility and vascular smooth muscle, causing cardiodepression and vasodilation. It is the expansion of blood vessels that causes a decrease in blood pressure, characteristic skin hyperemia and increased diuresis (due to dilation of the renal arteries) in patients treated with BCCs.

CCBs are effective in supraventricular arrhythmias, as they affect the conduction in the AV node, which allows you to effectively control the frequency of conducted atrial impulses, break the re-entry loops, capturing the AV node (reciprocal tachycardia in WPW syndrome and longitudinal dissociation of the AV node into fast and slow channels).

General indications for the appointment of CCBs in arrhythmias:

- Stopping paroxysms of AV-reciprocal and AV-nodal reciprocal tachycardia.
- Control of heart rate in AF and TP, atrial tachycardia.
- Stopping multi-source atrial tachycardia (in individual patients).
- Certain rare forms of VT (VT sensitive to verapamil).

Non-dihydropyridine CCBs are used for the treatment of arrhythmias - verapamil and diltiazem. Verapamil slows AV conduction more than diltiazem, but reduces the heart rate less due to reflex sympathetic activation of the SA node in response to sharp vasodilation. The pronounced dilation of the arteries is the cause of side effects of CCB: this is the steal syndrome - paradoxical exacerbation of ischemia due to redistribution of blood flow in favor of non-ischemic tissue; pasty legs and ankles due to redistribution of blood to the lower extremities. Some patients, especially elderly men with prostatic hyperplasia, have difficulty tolerating increased diuresis and increased frequency of urination. Among the nonvascular effects of CCB, one can note a decrease in the tone of the lower esophagus and cardiac pulp, intestinal smooth muscle - constipation. CCBs do not have a significant effect on bronchial patency, lipid and carbohydrate metabolism, and blood clotting.

BCC should not be used for AF in patients with WPW syndrome due to the risk of

acceleration of conduction through additional conduction pathways (increased rhythm, transition to VF), as well as in the treatment of arrhythmias in patients with severe CHF or LV dysfunction due to a possible negative impact on the prognosis.

General properties of class IV antiarrhythmic drugs:

• Blockade of calcium channels in SAV and AVV.

• Slowing of depolarization of SAV and AVV cells.

• Suppression of automatism, impaired conduction in SAV and AVV.

• On the ECG - slowing of the rhythm, prolongation of the PQ interval.

• Suppression of myocardial contractility (dangerous in severe LV dysfunction).

• Proarrhythmias are not characteristic, but bradyarrhythmias and acceleration of impulse conduction to the ventricles are possible in the presence of additional conduction pathways.

• Effectiveness in supraventricular reciprocal and focal tachyarrhythmias (trigger and automatic).

Verapamil (Isoptin, Finoptin) is a phenylalkylamine BCC, which is a racemate. In this case, the L-isomer is more active than the D-isomer, but the bioavailability of the latter is 2.5 times higher. Verapamil reduces heart rate, prolongs AV conduction, reduces myocardial contractility, reduces or does not change cardiac output, lowers blood pressure, often causes a reflex increase in sympathetic activity, which is masked by the main effect of the drug. When administered intravenously, verapamil can cause paradoxical acceleration of conduction along additional conduction pathways, sharply increasing the frequency of ventricular contractions. A similar antiarrhythmic effect is provided by halopamil and diltiazem.

Unclassified antiarrhythmic drugs

Digoxin - a typical representative of cardiac glycosides - a blocker of Na+/K+-ATPase. Increases intracellular calcium content during muscle contraction (increased contractility) and increases vagal tone - inhibition of SAV automatism, inhibition of conduction and prolongation of the effective refractory period in AVV, as well as shortening of the refractory period and moderate inhibition of conduction in the atrial myocardium. In toxic doses, digoxin increases automatism, increases myocardial excitability by increasing critical activity due to calcium overload (late afterpotentials) and reducing diastolic potential. Causes a slowdown in the rhythm, prolongation of the PQ interval, shortening of the QT interval and characteristic trough-like depression of the ST segment on the ECG.

As an antiarrhythmic agent, digoxin is used to control heart rate in AF and TP in patients with CHF, stopping supraventricular tachycardias.

Adenosine and adenosine triphosphate (ATP), metabolized when administered to adenosine, have a similar mechanism of action, which consists in activating adenosine A1 (purine P1) receptors. As a result, acetylcholine-dependent potassium channels open in cardiomyocytes of the atria, CAV, AVV, which leads to a reduction in the action potential, hyperpolarization and a decrease in the frequency of discharges of pacemaker cells. In high concentrations, adenosine causes inhibition of the function of CAV and AVV (slowing down automaticity and conduction) and vasodilation. The effect of the drug is pronounced, but short-lived due to a very short half-life (about 10 s). The effect is characterized by pronounced AV blockade and bradycardia. Adenosine is effective in reciprocal supraventricular tachycardias, if the re-entry loop passes through CAV or AVV, in patients

with additional conduction pathways. Severe vasodilation and coronary dilation can lead to the phenomenon of "robbery", provoking coronary insufficiency in patients with coronary artery disease.

Potassium preparations are available in many dosage forms - potassium chloride in the form of tablets: 1000 mg (Kaliy-normin), 750 mg tablets with delayed release (Kalypoz prolongatum); in the form of a 4% solution in ampoules; in combination with magnesium salts (Asparkam, Panangin) 140 mg of potassium asparaginate and 158 mg of magnesium asparaginate.

Potassium salts are used to compensate for its deficiency. In hyperkalemia (potassium level > 8 mmol/l), excitability and conduction in the myocardium and the conduction system are suppressed (bradycardia, sino-ventricular conduction, AV blocks, asystole). Potassium preparations are used for hypokalemia, intoxication with cardiac glycosides. Magnesium preparations are also presented in many dosage forms (Magne B6 tablets contain 500 mg of magnesium lactate (48 mg of magnesium); Magnerot tablets contain 500 mg of magnesium orotate (38.2 mg of magnesium); they are part of the preparations "Asparkam" and "Panangin"). Mg^{2+} ions activate Na^+/K^+-ATP-ase, increasing the content of intracellular potassium - antagonism with the effect of digoxin. Magnesium inhibits conduction along the AV and inhibits early postdepolarizations (they are considered the cause of torsades de pointes), which may be the reason for its effectiveness in stopping torsades de pointes even with normal magnesium content in the body. Magnesium salts also compensate for its deficiency (deficiency in food, impaired absorption in the intestine, loss through the kidneys in acute renal failure, hyperaldosteronism, hypercalcemia, hyperthyroidism, taking diuretics, aminoglycosides, cyclosporine and methotrexate, alcoholism, treatment with digitalis). Magnesium deficiency is manifested by tachycardia, QT prolongation, flattening of T with the appearance of a high U wave, and finally, arrhythmias. Magnesium preparations are used to treat torsades de pointes, cardiac glycoside intoxication, hypokalemia, hypomagnesemia. It should be noted that oral magnesium preparations do not have an antiarrhythmic effect in an acute situation due to unpredictable absorption.

GENERAL PRINCIPLES OF ANTIARRHYTHMIC THERAPY

The best way to treat arrhythmia is to eliminate its cause (reducing hypoxia in multi-source atrial tachycardia, eliminating myocardial ischemia in ventricular arrhythmias against the background of coronary insufficiency, treating thyrotoxicosis, replenishing electrolyte losses of various nature, ablation of additional conduction pathways in people with WPW syndrome, etc.).

It is necessary to “avoid prescribing antiarrhythmic drugs whenever possible” (Fogoros R. N., 2002). Only those rhythm disturbances that pose a risk to the patient’s life or are accompanied by pronounced symptoms are subject to treatment. For example, there is no need to treat frequent asymptomatic ventricular extrasystoles in a patient without structural heart pathology. The aggressiveness of antiarrhythmic therapy should correspond to the potential danger of arrhythmia to the patient’s life and health. Specific treatment of arrhythmias involves not only the appointment of AADs, but also the cancellation of drugs with proarrhythmic action and the use of non-pharmacological methods of treatment: electropulse therapy (EIT), implantation of cardioverter-defibrillators (ICD) and pacemakers (ECS); catheter ablation and cardiac surgery. When choosing between pharmacological and non-

pharmacological methods of treatment of arrhythmia, it is necessary to compare their effectiveness, the nature of the impact on the prognosis, as well as safety and accessibility for a particular patient. Often, a combination of both methods of influence is required to achieve the result.

Before prescribing an antiarrhythmic drug, the potential benefit and risk of its use should be weighed, and during treatment, the likelihood of side effects and complications of therapy should be minimized. The most dangerous complication is ventricular proarrhythmia: pirouette type VT (a consequence of QT prolongation in the treatment of AADs of classes IA and III); monomorphic VT (a consequence of QRS expansion - AAD class IC) and persistent polymorphic VT (drugs of classes I and III). The risk of proarrhythmia is especially high in patients with severe myocardial lesions, initial conduction or repolarization disorders (blockades, long QT), electrolyte disorders, chronic cardiac, renal or hepatic insufficiency.

Treatment of arrhythmias consists of two stages: stopping acutely occurring arrhythmia and prevention of recurrent arrhythmias or correction of existing subacute arrhythmias. Often, different treatment methods and different AADs are used at each stage.

For long-term treatment (prevention) of arrhythmias, only those drugs that have proven their safety or ability to improve the prognosis in a specific category of patients can be recommended. Thus, class I AADs are contraindicated in patients with severe organic myocardial lesions and CHF, while class II AADs (BABs) and some class III AADs (amiodarone) can be successfully used in these patients.

Treatment of certain types of tachyarrhythmias.

Treatment of focal atrial tachycardia (PT)

Relief of sympathicotonic paroxysmal forms of focal PT:

BABs (propranolol 1 mg intravenously for 1 min, if necessary - repeat the administration of the same dose after 5 min).

In case of ineffectiveness or contraindications - BCC (verapamil 5-10 mg intravenously for 2-3 min, if necessary, repeat the administration after 5 min - total dose up to 15 mg).

In case of ineffectiveness (in patients without gross myocardial pathology): propafenone 450-600 mg in 2-3 doses or flecainide 100 mg 2 times a day and other AAZ IA and IS classes.

Prevention of paroxysms of focal PT and treatment of chronic focal PT:

Surgical methods of treatment (catheter radiofrequency ablation).

In case of unavailability (ineffectiveness) of surgical treatment: BAB (propranolol 120-240 mg/day in 3 doses, metoprolol - 50-150 mg/day); BCC (verapamil 120-240 mg/day, diltiazem 120-180 mg/day orally).

Treatment of atrial tachycardia with AV block of the second degree

Often this arrhythmia is a sign of digitalis intoxication, therefore it is necessary:

- Cancellation of cardiac glycosides;

- Intravenous administration of potassium chloride preparations (0.8-1 g of KCl per injection - 20 ml of 4-5% solution in 200-400 ml of 5% glucose solution).

Electropulse therapy is contraindicated due to the risk of VF with digitalis intoxication.

The most relevant are AV-reciprocal tachycardias associated with the presence of additional conduction pathways (for example, WPW syndrome) and AV-nodal reciprocal

tachycardias, caused by longitudinal dissociation of the AV node into fast and slow channels. In WPW syndrome, the development of tachycardia is due to the circulation of excitation between the atria and ventricles (the impulse is conducted anterogradely through the AV node, retrogradely through additional pathways - orthodromic reciprocal AV tachycardia, or anterogradely through additional pathways, retrogradely through the AV node - antidromic reciprocal AV tachycardia). With dissociation of the AV node, the impulse makes a circular motion antegradely - along the slow pathway, retrogradely - along the fast one. Common to the described variants of PNST is the participation of the AV node in the implementation of the re-entry mechanism. Therefore, in the treatment of these NSTs, general approaches related to slowing down the conduction in the AVV can be used to stop re-entry.

Cupping:

- Vagus techniques (Valsalva maneuver, cough provocation, vomiting, immersion of the face in ice water, sinocarotid test, intense pressure on the abdomen in the abdominal aorta, pressure on the eyeballs);

- If ineffective, adenosine triphosphate at a dose of 10 mg (1 ml of 1% solution) intravenously as a bolus, if necessary - another 20 mg, and then 30 mg sequentially with an interval of 2 minutes;

- If ineffective after 2 minutes - verapamil intravenously slowly 5-10 mg over 2-3 minutes (repeat if necessary after 5 minutes - total dose up to 15 mg);

- If ineffective after 30 min - procainamide intravenously slowly at a rate of 50 mg/min (15 mg/kg);

- If hemodynamic instability, collapse or ineffectiveness of previous measures - EIT (electrical cardioversion with a synchronized discharge of 50-100 J).

Prevention:

- Surgical treatment: transvascular catheter radiofrequency ablation (destruction) of additional pathways or slow AV canal (efficiency > 90%);

- If surgical treatment is unavailable (ineffective): BCC (verapamil), amiodarone orally.

Treatment of atrial fibrillation and flutter

AF is the most common reason for seeking medical help for heart rhythm disorders. According to international and Ukrainian recommendations for the diagnosis and treatment of AF, the following forms are distinguished:

- Paroxysmal AF - a tendency to spontaneous rhythm recovery within 7 days from the moment of arrhythmia onset (usually within the first day);

- Persistent AF - no tendency to spontaneous rhythm recovery, duration of rhythm disturbances 7 days or more;

- Permanent AF - long-standing AF (more than 1 year), if cardioversion was not performed or was ineffective.

Clinically, AF can occur in the following variants: vagal form (more often in middle-aged women (40-50 years old), attacks at night, after meals, alcohol, with previous progressive bradycardia, AF with a relatively low frequency of ventricular contractions, rarely becomes chronic); adrenergic form (has no gender differences, occurs less often, usually occurs during the day, is provoked by physical exertion, stress, often accompanied by polyuria). Hemodynamic consequences of AF - lack of contribution of the atria to filling the ventricles and tachysystole, which, if left untreated, lead to heart failure and the formation of

arrhythmogenic cardiomyopathy in some patients. The most dangerous complication of AF is thromboembolism (stroke, myocardial infarction, kidney, intestine, spleen, etc.). Therefore, the main tasks of AF treatment are: - arrhythmia control; - thromboembolism prevention.

Arrhythmia control

There are two alternative ways to treat AF:

- Stopping an AF attack and maintaining sinus rhythm;
- Controlling the frequency of ventricular contractions while maintaining AF.

It is believed that restoration and maintenance of sinus rhythm is advisable in paroxysmal AF, in young patients, in people who do not tolerate paroxysms of AF, as well as in patients with rigid, usually hypertrophied LV myocardium, since the absence of atrial systole will greatly affect ventricular filling and hemodynamics. It is also obvious that stopping AF is necessary if it is accompanied by uncontrolled ischemia, hypotension, or acute heart failure. The tactic of controlling heart rate is more justified in elderly people with a mildly symptomatic course of AF, a poor prospect of maintaining sinus rhythm (atrial dilation, often recurrent course of persistent AF), as well as in paroxysmal AF and stable hemodynamics. Restoration of rhythm (cardioversion) in patients with AF and TP is always associated with the risk of embolism. It increases significantly with paroxysm duration of more than 48 hours and in the absence of prior anticoagulant treatment.

Cardioversion without prior anticoagulant preparation can be performed with AF/TP duration of less than 48 hours:

- Patients with low risk of embolism;
- Patients with hemodynamic instability (ischemia, myocardial infarction, cardiogenic shock, pulmonary edema).

Cardioversion with prior anticoagulant preparation (taking indirect anticoagulants - warfarin or phenylin for at least 3 weeks before cardioversion and 4 weeks after it in doses necessary to maintain MHO at 2.0-3.0) should be performed:

- With AF/TP duration > 48 hours (or unknown duration) in hemodynamically stable patients;
- With AF/TP duration < 48 h in patients with a high risk of embolism (history of embolism - stroke, transient ischemic attacks, etc.; mitral stenosis; prosthetic heart valves) or with a combination of two or more moderate risk factors for embolism (age > 75 years; concomitant CHF or EF < 35%; arterial hypertension; diabetes mellitus);
- In the presence of a thrombus in the left atrium or left atrial appendage.

Cardioversion with simultaneous initiation of anticoagulant therapy (heparin bolus 5000 IU intravenously before cardioversion with subsequent continuous intravenous infusion of heparin in doses that provide prolongation of APTT by 1.5-2.0 times (or subcutaneous administration of low molecular weight heparins in therapeutic doses) until the moment when the administration of indirect coagulants provides the level of MHO > 2.0 with subsequent administration of indirect anticoagulants for 4 weeks) can be performed:

- With the duration of AF/TP > 48 h in patients with hemodynamic instability (ischemia, myocardial infarction, cardiogenic shock, pulmonary edema);
- As an alternative to preliminary preparation with indirect anticoagulants in the absence of a thrombus in the left atrium or in the left atrial appendage during transesophageal echocardiography (!)

Transesophageal echocardiography allows with a high probability to exclude left atrial

thrombosis and, thus, to accelerate the performance of cardioversion.

AF can be stopped with the help of drugs (pharmacological cardioversion) or with an electric discharge (electrical cardioversion).

Electrical cardioversion is generally more effective than pharmacological, especially when the duration of AF is more than 7 days, but requires special conditions - premedication and preparation of the patient.

Electrical cardioversion is indicated:

- Patients with unstable hemodynamics (ischemia, myocardial infarction, hypotension, heart failure) with ineffective pharmacological control of high ventricular rate;

- Patients with AF on the background of ventricular preexcitation (for example, WPW syndrome) with a very high ventricular rate or hemodynamic instability - immediate cardioversion;

- Patients with stable hemodynamics, when subjective symptoms of AF are unacceptable to the patient;

- When restoring rhythm in the case of long-standing AF;

- If the patient has a preference (if cardioversion is required infrequently).

The effectiveness of electrical cardioversion increases the prior administration of amiodarone, flecainide, propafenone or sotalol, which is especially important when early recurrences of AF are observed after previously successful cessation of arrhythmia. Other AADs have an ambiguous effect on the cardioversion threshold, and cardiac glycosides increase the risk of VF (they should be canceled at least a day before the planned rhythm restoration).

Pharmacological cardioversion is easier to implement, but its effectiveness is lower (especially when the duration of AF is more than 7 days), and proarrhythmic complications develop more often than with electrical impulse exposure. Class IC and III drugs have proven high efficacy in stopping AF/TP: flecainide, propafenone, amiodarone; the efficacy of class IA drugs quinidine and procainamide is considered insufficiently established, and digoxin and sotalol are not recommended for these purposes. It should be noted that there is no information on the safety of using class IA, IC and III drugs for cardioversion in patients with organic heart damage and CHF (the exception is amiodarone), therefore, in these patients, amiodarone remains the drug of choice.

Thromboembolism prevention

Antithrombotic therapy is indicated for all patients with AF (regardless of its form: paroxysmal, persistent or chronic), with the exception of patients with isolated AF and patients with contraindications. In patients with a low risk of thromboembolism, aspirin is used, in patients with an increased risk - indirect anticoagulants (warfarin, phenylin, etc.). Thromboembolism prevention in patients with TP is carried out according to the same principles as in patients with AF.

2. Questions for self-control (list of questions):

1. Functions of the heart that regulate heart rhythm disturbances.

2. Automatism, conductivity, excitability, refractoriness: definition.

3. Pathophysiology of tachyarrhythmias.

4. Pathophysiology of bradyarrhythmias.

5. Symptoms of heart rhythm disturbances.

6. Laboratory and instrumental methods for diagnosing arrhythmias.

7. Clinical and pharmacological evaluation of drugs that normalize heart rhythm and conduction: quinidine; procainamide; lidocaine; verapamil; propranolol; amiodarone; atropine; isoprenaline; orciprenaline; glucagon.

8. Stopping paroxysmal supraventricular and ventricular tachycardia, atrial fibrillation and flutter.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write prescriptions for the main groups of anti-arrhythmic drugs (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for the appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize cardiac arrhythmias, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, choose a drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 detecting them at the early stages.

10. Substantiate the duration of basic and supportive therapy.

B. Solution of situational tasks.

1. A 61-year-old patient complained of an irregular pulse with a frequency of 56-58 beats per minute, shortness of breath during moderate physical exertion. The above phenomena occurred 2 weeks ago, on the 15th day of taking the following drugs: adelphan 1/2 tab. and apressin 1 tab. (0.01 g) at 2300; isodinite - 10 mg 3 times a day. History: hypertension for 10 years; inherent bradycardia (HR 52-54 in 1 min), extrasystolic arrhythmia was recorded - for 8 years and blockade of the left bundle branch block, during the last 3

years - periodic sinoauricular blockade 2: 1. Previous treatment of hypertension: adelphan - 1 tab. before bedtime; clonidine (0.000075 g) - 1 tab. at three o'clock in the morning (time of maximum daily activation of ACT). Objectively: general condition is satisfactory. Arteries in the frontotemporal regions are tortuous, dilated, and compacted. Pulse - 54 beats per minute, arrhythmic in the type of atrial fibrillation. Pulse deficit - 0. ACT - in the morning and during the day 130/80 - 120/70 - 114/64 mm Hg, at 3 am - 130/70 mm Hg. Left ventricular hypertrophy. Accentuation of the II tone over the aorta. Over the apex and aorta there is a rough systolic murmur. Breathing over the lungs is vesicular. The liver protrudes 1 cm from under the edge of the costal margin. There are no edemas. ECG - atrial fibrillation, bradycardia (HR -56 beats per minute), left ventricular extrasystoles (4-5 per minute), left bundle branch block. Formulate a clinical diagnosis. Assess the correctness of the therapy. Explain the mechanism of atrial fibrillation development; could the therapy have caused it? Justify the therapy of the existing disorders.

2. The doctor on duty is called to the department of pregnancy pathology to a patient, 27 years old. Diagnosis: pregnancy 35 weeks. Rheumatism: inactive phase, mitral stenosis. Complains of attacks of suffocation, cannot lie down. Breathing is hard in the lungs, wet rales in the lower parts. There is no edema.

Your diagnosis? Your urgent appointments?

3. A patient, 52 years old, has developed an attack of cardiac asthma. On examination, the pulse is 78 beats per minute, rhythmic. ACT - 170/100 mm Hg. Heart sounds are muffled. There is an enlarged liver, moderate edema of the lower legs. The doctor prescribed intravenous administration of strophanthin.

Evaluate the tactics of managing the patient. Make a plan for correcting the patient's treatment.

4. A patient is admitted to the cardiology department with an acute extensive myocardial infarction. The patient's condition is of moderate severity, pulse - 100 beats per minute, rhythmic. Heart sounds are muffled. Breathing over the lungs is vesicular. The liver is not enlarged, there is no edema. The patient was prescribed strophanthin. After the administration of the minimum dose (0.25 ml - 0.05% solution), single extrasystoles appeared, after the second administration of the same dose, bigeminia developed.

Evaluate the tactics of managing the patient. Explain the cause of the complication.

5. A patient was admitted to the cardiology department with an acute myocardial infarction complicated by an attack of paroxysmal tachycardia. The attack was stopped by intravenous drip administration of lidocaine. After the attack: pulse - 80-88 beats. in 1 min, rhythmic, ACP - 100/70 mm Hg, heart sounds are muffled. In the lungs there is a small amount of moist rales on both sides. A few hours after the end of the administration of lidocaine, the attack recurred, was stopped by novocainamide, but resumed again.

Explain the reason for the ineffectiveness of typical antiarrhythmic drugs. Correct the treatment. Make a list of drugs that cannot be used together with strophanthin.

Test tasks for self-control:

1. Choose 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. Choose the correct statement:

A. Highly polar glycosides are not absorbed in the gastrointestinal tract

C. Low-polar glycosides are poorly absorbed in the gastrointestinal tract, are not metabolized in the liver

C. The choice of the rate of digitalization does not depend on their concentration in the blood

D. High efficiency of glycosides is noted in acute myocardial infarction

E. Due to the large number of side effects, digitoxin is used only parenterally

3. All drugs of class 1A:

A. Effective for restoring sinus rhythm in atrial fibrillation and flutter.

B. Used to treat sinus bradycardia

C. Indicated in severe heart failure

D. Cause atrioventricular block when administered intravenously

E. Contraindicated in ventricular extrasystole

4. Novocainamide can be administered intravenously in the absence of:

A. Ventricular fibrillation

B. Sustained ventricular tachycardia

C. Signs of circulatory failure

D. Arterial hypertension

E. Increased creatinine in the blood

5. The most dangerous side effect of quinidine sulfate:

A. Development of ventricular tachycardia of the "pirouette" type

B. Orthostatic hypotension

C. Thrombocytopenia

D. Widening of the QRS complex by more than 40%

E. Jarisch-Herxheimer syndrome

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

"Clinical and pharmacological characteristics of drugs that affect bronchial patency"

Purpose:

To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of drugs:

a) bronchodilators: epinephrine (adrenaline), ephetonin (ephedrine), orciprenaline (alupent, astmopent), isadrin (euspirana, novodrin), terbutaline (brikanil), salbutamol (ventolin), fenoterol (berotek), clenbuterol, formoterol (foradil), salmeterol (serevent), euphyllin (aminophyllin, euphyllong, teopek), ipratropium bromide (atrovent, traventol), tiotropium bromide (spiriva);

b) glucocorticosteroids: hydrocortisone (cortef), prednisolone (prednisone), dexamethasone (dexone), triamcinolone (polcortolone, berlicort), betamethasone (celeston), beclamethasone (bekotid, bekodisk), budesonide (pulmicort);

c) mast cell membrane stabilizers: ketotifen (zaditen), cromolyn sodium (intal), nedocromil (tailed mint);

d) mucolytic and expectorant agents: mucaltin, acetylcysteine (ACC), carbocysteine (fluditec), ambroxol (lasolvan), bromhexine (bronchotil), althea, thermopsis, licorice; combined drugs: sinupret, terpincode, sinecod.

e) leukotriene receptor modifiers (montelukast, zafirlukast).

Basic concepts (list of questions):

1. Bronchial obstruction syndrome.
2. Bronchial asthma.
3. Chronic obstructive pulmonary disease.
4. The influence of the autonomic nervous system on the state of bronchial patency.
5. Broncholytic drugs.
6. Anti-inflammatory drugs in diseases of the respiratory system.
7. The place and role of antihistamine drugs in SBO.
8. Symptomatic treatment in diseases of the respiratory system.

Plan

1. Theoretical questions:

The use of drugs that change the state of the bronchial tree has a multifunctional purpose, due to their influence on the pathophysiological mechanisms of vascular tone disorders, edematous syndrome, syndromes of heart rhythm and conduction disorders, etc. The use of these drugs in combined pathology with the indicated syndromic disorders is of great importance. The ability to correctly navigate the mechanisms of action of drugs, scientifically substantiated use them to correct the etiopathogenesis of diseases, to apply drug therapy as a method of verifying the diagnosis - forms the clinical thinking of the future doctor.

Bronchial asthma - a chronic inflammatory disease of the respiratory tract with the

participation of various cellular elements. The key link is bronchial obstruction (narrowing of the lumen of the bronchi), caused by specific immunological (sensitization and allergy) or nonspecific mechanisms, which is manifested by repeated episodes of wheezing, shortness of breath, a feeling of chest congestion and cough. Bronchial obstruction is reversible partially or completely, spontaneously or under the influence of treatment. The prevalence in the world is from 4 to 10%. For treatment, symptomatic drugs are used, intended for stopping the attack, basic therapy drugs that affect the pathogenetic mechanism of the disease. A formidable complication of the disease is asthmatic status.

According to the GINA 2006 global strategy, bronchial asthma is "a chronic inflammatory disease of the airways, in which many cells and cellular elements are involved. Chronic inflammation causes the development of bronchial hyperresponsiveness, which leads to recurrent episodes of wheezing, shortness of breath, chest tightness and cough, especially at night and in the early morning. These episodes are usually associated with widespread, but variable in severity, airway obstruction in the lungs, which is often reversible either spontaneously or under the influence of treatment". According to the definition of WHO experts, bronchial asthma is "a chronic disease, the basis of which is an inflammatory process in the airways with the participation of a variety of cellular elements, including mast cells, eosinophils and T-lymphocytes. In susceptible individuals, this process leads to the development of generalized bronchial obstruction of varying degrees of severity, fully or partially reversible spontaneously or under the influence of treatment. The inflammatory process also causes a concomitant increase in the response of the respiratory tract in the form of bronchial obstruction to various external and internal stimuli.

Etiology. There are a number of risk factors that contribute to the occurrence and development of bronchial asthma in certain individuals: heredity, professional factors (exposure to biological and mineral dust, harmful gases, fumes), environmental factors (exhaust gases, smoke, high humidity, harmful fumes), nutrition (consumption of animal products rich in fats, proteins, refined easily digestible carbohydrates), respiratory infections, household allergens (pet hair, dust, mushrooms, mites, cockroaches), use of certain drugs (NSAIDs, beta-blockers). Pathogenesis. The key link in bronchial asthma of any genesis is increased reactivity of the bronchial tree. It is caused by a violation of the autonomic regulation of smooth muscle tone and the action of inflammatory mediators and leads to periodic reversible obstruction of the bronchi, which is manifested by increased airway resistance, lung overstretching, hypoxemia caused by focal hypoventilation and a mismatch between ventilation and perfusion of the lungs, hyperventilation.

The role of the autonomic nervous system. On smooth muscle cells are β1-, β2- and α-adrenoreceptors. β2-adrenoreceptors predominate, compared to them β1-adrenoreceptors are 3 times less. Stimulation of β2-adrenoreceptors reduces bronchial reactivity in patients with bronchial asthma, however, blockade of β-adrenoreceptors in healthy individuals does not cause a noticeable change in bronchial reactivity, stimulation of α-adrenoreceptors has almost no effect on the tone of bronchial smooth muscles. Normally, the tone of bronchial smooth muscles is regulated mainly by parasympathetic fibers of the vagus nerve. The use of drugs that block the conduction of excitation along parasympathetic fibers leads to bronchial dilation, and stimulation of these fibers causes bronchospasm. The tone of bronchial smooth muscles also changes under the influence of afferent fibers that come from bronchial receptors and are part of the vagus nerve. The sympathetic nervous system normally plays a minor role

in the regulation of bronchial muscles, but in bronchial asthma its role increases. Stimulation of unmyelinated fibers (type C afferent fibers located in the wall of the bronchi and alveoli) by inflammatory mediators leads to the release of neuropeptides, such as substance P, which cause bronchial narrowing, mucosal edema, and increased mucus secretion.

Biochemical factors. Calcium plays an important role in the contraction of bronchial muscles, since the ATP-dependent calcium pump, which removes calcium from the cell, is involved in maintaining the resting membrane potential of smooth muscle cells. An increase in the concentration of calcium inside the cell leads to contraction, and a decrease leads to relaxation of smooth muscle cells. In addition, an increase in the intracellular concentration of calcium causes the release of histamine, anaphylactic factor of eosinophil chemotaxis and anaphylactic factor of neutrophil chemotaxis from stem cells. It is assumed that adrenoreceptors are involved in the regulation of calcium levels in mast cells.

Cyclic nucleotides (cAMP and cGMP) are involved in the regulation of the contraction of bronchial smooth muscle cells and the degranulation of mast cells. The release of mediators by mast cells under the influence of M-cholinesterases and prostaglandin F2α is mediated by an increase in the level of cGMP. Stimulation of α-adrenoceptors leads to a decrease in cAMP levels, which also causes mast cell degranulation. Stimulation of β-adrenoceptors leads to an increase in cAMP levels and, as a result, to inhibition of mast cell degranulation. It is believed that blockade of adenosine receptors also inhibits degranulation. Heparin, thromboxanes, serotonin, free oxygen radicals, kinins, neuropeptides, proteases and cytokines are also involved in the pathogenesis of exogenous bronchial asthma.

Involvement of inflammatory cells

Mast cells. Mast cell activation occurs when allergens interact with IgE fixed on the surface of mast cells in exogenous bronchial asthma. In the case of endogenous asthma, mast cell activation can occur under the influence of osmotic stimuli, such as in exercise-induced asthma. When activated, they release mediators (histamine, leukotrienes, prostaglandin D2), which cause bronchospasm. In parallel, arachidonic acid and platelet activation factor are formed from the phospholipids of the mast cell membrane. Leukotrienes and prostaglandins are formed from arachidonic acid, in turn.

Eosinophils. The number of eosinophils in the respiratory tract is increased. These cells secrete the main proteins that damage the bronchial epithelium, and also participate in the release of growth factors and airway remodeling.

T-lymphocytes. Their number in the respiratory tract is also increased. They release specific cytokines (IL-4, IL-5, IL-9 and IL-13, etc.) that affect the process of eosinophilic inflammation and the production of IgE by B lymphocytes. Regulatory T cells suppress Th2 lymphocytes, so an increase in the activity of Th2 cells can occur with a decrease in the number of regulatory T cells. An increase in the number of inKT cells that secrete Th1 and Th2 cytokines in large quantities is possible.

Dendritic cells capture allergens from the surface of the bronchial mucosa and bring them to the regional lymph nodes, where, interacting with regulatory T cells, they stimulate the differentiation of T lymphocytes into Th2 cells.

Macrophages. The number of macrophages, like eosinophils and T lymphocytes, is increased in the respiratory tract. They can be activated when allergens interact with low-affinity IgE, resulting in the release of inflammatory mediators and cytokines.

Neutrophils. Their number in the respiratory tract and sputum is increased in patients

with severe asthma and smokers. The role of these cells in pathogenesis is not clear. A possible increase in their number is a consequence of glucocorticosteroid therapy.

Mediators of inflammation

Histamine and leukotrienes are mediators of the early phase of the immediate allergic reaction. As a result of the action of histamine, instant and short-term bronchospasm occurs, while leukotrienes cause delayed and more prolonged bronchospasm. The mediators of the late phase of the immediate allergic reaction include chemotaxis factors and platelet activation factor. The latter cause chemotaxis, activation of inflammatory cells in the bronchial mucosa and stimulate the synthesis of leukotrienes in these cells. The bronchospasm caused by them occurs 2-8 hours after the onset of the allergic reaction and can last for several days.

Involvement of airway structural cells

The airway structural cells also contribute to the development of inflammation. Thus, bronchial epithelial cells, when recognizing their mechanical environment, express various proteins and release cytokines, chemokines, and lipid mediators. Similar inflammatory proteins are produced by smooth muscle cells. Endothelial cells participate in the migration of inflammatory cells into the airways. Fibroblasts and myofibroblasts, through the production of collagen, proteoglycans, and other connective tissue components, participate in airway remodeling.

Bronchial obstruction

Pathological changes leading to bronchial obstruction affect the mucous membrane, submucosal layer and muscular layer of the bronchial tree. The pathological process extends from the trachea and large bronchi to the terminal bronchioles. The following reasons are given for bronchial narrowing:

Formation of mucous plugs. In asthma, thick, viscous mucus is formed, which contains exfoliated bronchial epithelium, eosinophils, Charcot-Leyden crystals. The mucus can partially or completely block the lumen of the bronchi. With the duration and severity of the attack, the mucus becomes viscous due to dehydration.

Changes in the bronchial wall. In asthma, the number of ciliated epithelial cells decreases, and goblet cells secreting mucus increase in number and undergo hyperplasia. Eosinophilic infiltration, edema and thickening of the basement membrane also occur, in the submucosal layer there is infiltration by eosinophils, neutrophils, lymphocytes and macrophages, hypertrophy and swelling of the glands. The muscular membrane of the bronchi hypertrophies. Spasm of the smooth muscles of the bronchi is the most likely cause of acute short-term attacks. The duration of attacks and resistance to treatment are due to blockage of the bronchi with mucous plugs and edema of the bronchial mucosa. Obstruction increases on exhalation, since in this case there is a dynamic narrowing of the airways. Due to bronchial obstruction, part of the air is retained in the alveoli, which leads to overstretching of the lungs and lengthening of exhalation. Excessive resistance of the airways leads to an increase in the work of breathing, which leads to the inclusion of accessory muscles, shortness of breath. The process can involve large and medium bronchi, but more often obstruction of small bronchi comes to the fore. Noisy, wheezing breathing is a sign of obstruction of large bronchi, and attacks of shortness of breath and cough more often occur with obstruction of small bronchi. Obstruction leads to an increase in residual volume, a decrease in vital capacity and an increase in total lung capacity. As a result of obstruction of the respiratory tract, their ventilation decreases. Normally, perfusion of poorly ventilated areas decreases, but in asthma

this does not always happen, the balance between ventilation and perfusion is disturbed, which leads to a decrease in paO2. In mild and moderate attacks of bronchial asthma, hyperventilation occurs, which leads to a decrease in paCO2 and respiratory alkalosis. In severe and prolonged attacks, hypoventilation develops, paCO2 increases and respiratory acidosis occurs. Lung overdistension and decreased paO2 in the alveoli cause alveolar capillarospasm and increased pressure in the pulmonary artery.

Research on the function of external respiration

To determine the function of external respiration in patients over 5 years of age, spirometry (which allows you to detect the forced expiratory volume in 1 second (FEV1) and forced vital capacity of the lungs (FVC)) and peak flowmetry (which allows you to detect the peak expiratory velocity (PEV)) are widely used.

There are appropriate indicators of FEV1, FVC and PEV, which were obtained as a result of population studies. They depend on the age, sex and height of the subject. These indicators are constantly revised. The indicators obtained in a particular patient are expressed as a percentage of the appropriate values. PEV is characterized by very wide ranges of fluctuations of the appropriate values.

The term "reversibility" refers to an increase in FEV1 (or less often PSV) a few minutes after inhalation of a rapid-acting bronchodilator (200-400 mcg of salbutamol or berotec). Sometimes reversibility is understood as an improvement in lung function that develops a few days or weeks after the appointment or correction of basic therapy. Spirometry is the method of choice for assessing the severity and reversibility of bronchial obstruction. FEV1 and FVC are measured using a spirometer during forced exhalation. The generally accepted criterion for diagnosing bronchial asthma is an increase in FEV1 by 12% or more compared to the value before inhalation of a bronchodilator. The sensitivity of the test is low, especially when the patient is receiving some (broncholytic or basic) therapy. Patients need to be taught how to perform a forced exhalation correctly, the breathing maneuver should be performed three times and the best of the results should be recorded. To differentiate bronchial obstruction from other lung diseases accompanied by changes in FEV1, it is important to determine the ratio of FEV1/FVC, called the Tiffno index (TI). Normally, TI is > 0.75-0.80, and in children it can be > 0.9. A decrease in this ratio below these values allows suspicion of bronchial obstruction, characteristic of COPD and bronchial asthma.

Peak flowmetry, which allows determining the peak expiratory flow rate, is an important method of diagnosis and assessment of the effectiveness of treatment. Modern peak flow meters are inexpensive, portable, and are an ideal choice for daily assessment of the severity of bronchial obstruction by patients at home. Measurement of PSV can replace the determination of other indicators of lung function; when determining PSV without FEV1, the severity of obstruction may be underestimated, especially with increasing severity of bronchial obstruction and the appearance of “air traps”. Since the use of different peak flow meters can lead to differences in PSV values (also taking into account that the range of appropriate PSV values is very wide), it is preferable to compare the PSV results of a particular patient with his own best indicators using the patient's personal peak flow meter. The best indicator is usually recorded during the period of remission of the disease. Since the results depend on the patient's expiratory efforts, the patient should be carefully instructed. PSV is usually measured in the morning (after waking up and before taking medication) and in the evening (before going to bed). The higher the PSV variability, the worse the asthma is

controlled. The ratio of the difference in PSV per day to the average PSV for 1-2 weeks is also determined. Another way to determine PSV variability is to determine the minimum PSV for 1 week as a percentage of the best indicator during the same period. This method is perhaps the best for assessing the lability of the bronchial lumen in clinical practice, since the obtained indicator is easier to calculate, and it correlates better with bronchial hyperreactivity than other parameters, and requires measuring PSV only once a day. Determination of PSV and various variants of its variability are used to evaluate the therapy, identify provoking factors, and predict exacerbations.

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 that cause attacks, there are:

- exogenous bronchial asthma - attacks are caused by exposure to the respiratory tract of an allergen coming from the external environment (plant pollen, mold fungi, animal hair, the smallest mites found in house dust). A special variant is atopic bronchial asthma, caused by a genetic predisposition to allergic reactions;
- endogenous bronchial asthma - attacks are caused by factors such as infection, physical exertion, cold air, psychoemotional stimuli;
- bronchial asthma of mixed genesis - attacks can occur both when an allergen acts on the respiratory tract and when exposed to the above factors.

Stratification of severity

When assessing the severity of the disease, the following are taken into account:

- The number of night symptoms per month, week, day;
- The number of daytime symptoms per week, day;
- Severity of physical activity and sleep disorders;
- Best FEV1 and PSV indicators per day;
- Daily fluctuations in FEV1 and PSV.

In the stratification of asthma by severity, there is the concept of a stage that corresponds to certain gradations of signs of the asthma symptom complex. There are four stages, if the patient does not take basic medications, then each of these stages corresponds to one of the four stages of severity:

Stage 1. Intermittent asthma

Attaches of the disease occur rarely (less than once a week)

Short exacerbations

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

FEV1 or PSV more than 80% of normal

PSV variation less than 20%

Stage 2. Mild persistent asthma

Symptoms of the disease occur more often than once a week, but less often than once a day

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

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

FEV1 or PSV more than 80% of normal

PSV variation 20-30%

Stage 3. Moderate persistent asthma

Asthma attacks occur almost daily

Exacerbations disrupt the patient's sleep, reduce physical activity activity

Nocturnal attacks occur very often (more often than once a week)

FEV1 or PSV decreases to 60% to 80% of normal

PSV variation more than 30%

Grade 4. Severe persistent asthma

Attacks occur daily

Nocturnal attacks occur very often

Limited physical activity

FEV1 and PSV are about 60% of normal

PSV variation more than 30%

Asthma exacerbation severity classification

Exacerbation of bronchial asthma is episodes of progressive increase in shortness of breath, cough, wheezing, feeling of chest tightness. At this time, the lumen of the bronchi narrows, which is accompanied by a decrease in peak expiratory velocity (PEV), forced expiratory volume in 1 second (FEV1), forced vital capacity of the lungs (FVC). To assess the severity of the exacerbation, a physical examination, a study of the function of external respiration, a study of arterial blood gases, an ECG, and a chest X-ray are performed.

Special forms of bronchial asthma

There are several separate clinical and pathogenetic variants: reflux-induced bronchial asthma, aspirin-induced bronchial asthma, exercise-induced bronchial asthma, occupational asthma, and nocturnal asthma.

Reflux-induced bronchial asthma

An attack of suffocation associated with aspiration of gastric contents was first described by the Canadian physician William Osler (1849-1919) in 1892. Later, the term reflux-induced asthma was given. Of particular interest is pathological gastroesophageal reflux (GER), which is considered to be the cause of asthma attacks, most often at night. Gastroesophageal reflux is present in 50-60% of children and more suffering from bronchial asthma. According to modern ideas, the pathogenesis of pulmonary diseases, including bronchial asthma, arising against the background of GERD, is associated with two mechanisms. The first is aspiration, when the development of bronchospasm occurs as a result of the throwing of gastric contents into the lumen of the bronchial tree; the second is reflex, when aggressive components of the refluxate, entering the esophagus during reflux, stimulate the vagus receptors of the esophagus, inducing, as a result, attacks of suffocation.

Microaspiration as a result of GER can cause the development of such conditions as chronic bronchitis, recurrent pneumonia, pulmonary fibrosis, episodes of suffocation, sleep apnea. Microaspiration of acidic contents leads to the formation of inflammatory processes in the bronchial tree, damage to the mucous membrane of the respiratory tract, which leads to the development of bronchospasm, increased secretion of the bronchial tree.

If the reflux nature of bronchial asthma is suspected, GERD diagnostics (daily pH-metry) and, if the diagnosis is confirmed, GERD treatment are performed.

TREATMENT

For the treatment of bronchial asthma, basic therapy drugs are used that affect the mechanism of the disease, with the help of which patients control asthma, and symptomatic

drugs that affect only the smooth muscles of the bronchial tree and relieve the attack.

Symptomatic therapy drugs include bronchodilators:

- Beta-2-adrenomimetics
- Xanthines.

Basic therapy drugs include:

- Cromones
- Inhaled glucocorticosteroids
- Leukotriene receptor antagonists
- Monoclonal antibodies.

If basic therapy is not used, the need for inhaled bronchodilators (symptomatic agents) will increase over time. In this case and in case of insufficient doses of basic drugs, the increase in the need for bronchodilators is a sign of an uncontrolled course of the disease.

Cromones

Cromones include sodium cromoglycate (Intal), sodium nedocromil (Tayled), and ketotifen (Zaditen). These agents are indicated as basic therapy for intermittent and mild bronchial asthma. Cromones are inferior in effectiveness to ICS. Since there are indications for the appointment of ICS even in mild bronchial asthma, cromones are gradually being replaced by more convenient ICS. Switching from ICS to cromones is also unjustified if symptoms are fully controlled with minimal doses of ICS.

Glucocorticosteroids

Inhaled glucocorticosteroids are used in asthma, which do not have most of the side effects of systemic steroids. If inhaled corticosteroids are ineffective, systemic glucocorticosteroids are added. ICCS are the main group of drugs for the treatment of bronchial asthma.

Classification of inhaled glucocorticosteroids depending on the chemical structure:

Non-halogenated:

- Budesonide (Pulmicort, Benacort)
- Ciclesonide (Alvesco)
- Chlorinated:
- Beclomethasone dipropionate (Becotide, Beclojet)
- Mometasone furoate (Asmonex)
- Fluorinated:
- Flunisolide (Ingacort)
- Triamcenolone acetonide
- Fluticasone propionate (Flixotide)

The anti-inflammatory effect of ICSs is associated with inhibition of the activity of inflammatory cells, reduction of cytokine production, interference with the metabolism of arachidonic acid and the synthesis of prostaglandins and leukotrienes, reduction of the permeability of microvascular vessels, prevention of direct migration and activation of inflammatory cells, and increased sensitivity of β-receptors of smooth muscles. ICs also increase the synthesis of the anti-inflammatory protein lipocortin-1, by inhibiting interleukin-5 they increase the apoptosis of eosinophils, thereby reducing their number, leading to the stabilization of cell membranes. Unlike systemic glucocorticosteroids, ICs are lipophilic, have a short half-life, are quickly inactivated, have a local (topical) effect, due to which they have minimal systemic manifestations. The most important property is lipophilicity, due to which

ICs accumulate in the respiratory tract, their release from tissues is slowed down and their affinity for the glucocorticoid receptor increases. Pulmonary bioavailability of ICs depends on the percentage of drug entry into the lungs (which is determined by the type of inhaler used and the correctness of the inhalation technique), the presence or absence of a carrier (inhalers that do not contain Freon have the best indicators) and on the absorption of the drug in the respiratory tract.

Until recently, the dominant concept of prescribing ICS was the concept of a step approach, which means that higher doses of ICS are prescribed for more severe forms of the disease. The basis of therapy for long-term control of the inflammatory process are ICS, which are used in persistent bronchial asthma of any severity and to this day remain the first-line means of bronchial asthma therapy. According to the concept of a step approach: "The higher the severity of the course of BA, the higher doses of inhaled steroids should be used." A number of studies have shown that patients who started treatment with ICS no later than 2 years from the onset of the disease have significant advantages in improving control of asthma symptoms, compared with those who started such therapy after 5 years or more.

Combinations of ICS and prolonged β2-adrenomimetics

There are fixed combinations of ICS and prolonged β2-adrenomimetics, which combine a basic therapy agent and a symptomatic agent. According to the GINA global strategy, fixed combinations are the most effective basic therapy agents for bronchial asthma, as they allow to relieve an attack and are at the same time a therapeutic agent. The most popular are two such fixed combinations:

salmeterol + fluticasone (Seretide 25/50, 25/125 and 25/250 mcg / dose, Seretide Multidisk 50/100, 50/250 and 50/500 mcg / dose)

formoterol + budesonide (Symbicort Turbuhaler 4.5 / 80 and 4.5 / 160 mcg / dose)

The composition of the drug Seretide includes salmeterol at a dose of 25 mcg / dose in a metered aerosol inhaler and 50 mcg / dose in the Multidisk device. The maximum permissible daily dose of salmeterol is 100 mcg, i.e. the maximum frequency of use of Seretide is 2 inhalations 2 times for a metered inhaler and 1 inhalation 2 times for the Multidisk device. This gives Symbicort an advantage when it is necessary to increase the dose of ICS. Symbicort contains formoterol, the maximum permissible daily dose of which is 24 mcg, which makes it possible to use Symbicort up to 8 times a day. The SMART study revealed a risk associated with the use of salmeterol compared to placebo. In addition, the undoubted advantage of formoterol is that it begins to act immediately after inhalation, and not after 2 hours, like salmeterol.

Systemic glucocorticosteroids

Systemic glucocorticosteroids or systemic glucocorticosteroids (GCS) can be used intravenously in small doses for asthma exacerbations, orally in short courses or long-term. Intravenous administration of large doses of GCS (pulse therapy) is much less commonly used. GCS can be used long-term if inhaled glucocorticosteroids are ineffective. At the same time, bronchial asthma is characterized as steroid-dependent and is assigned a severe course of the disease.

Side effects of GCS include osteoporosis, arterial hypertension, diabetes mellitus, suppression of the functional activity of the hypothalamic-pituitary-adrenal system, cataracts, glaucoma, obesity, thinning of the skin with the formation of striae and increased capillary permeability, muscle weakness. From the moment of prescribing GCS, osteoporosis

prevention therapy should be started. Prednisone, prednisolone, methylprednisolone, hydrocortisone are used for oral administration. These drugs have less mineralocorticoid activity than other GCS, a mild effect on striated muscles and a relatively short half-life. Long-term use of the drug triamcinolone can result in side effects such as the development of muscular dystrophy, weight loss, weakness, and damage to the gastrointestinal tract. Dexamethasone is not used orally for long-term treatment of bronchial asthma due to pronounced suppression of the function of the adrenal cortex, the ability to retain fluid and low affinity for pulmonary GCS receptors.

Antileukotriene drugs

Currently, the following leukotriene antagonists are known:

- Zafirlukast (Acolate)
- Montelukast (Singular)

Drugs of this group quickly eliminate the basal tone of the respiratory tract, created by leukotrienes due to chronic activation of the 5-lipoxygenase enzyme system. Due to this, this group of drugs has been widely used in aspirin-induced bronchial asthma, the pathogenesis of which involves increased activation of the 5-lipoxygenase system and increased sensitivity of receptors to leukotrienes. Leukotriene antagonists are especially effective in this form of asthma, the therapy of which often causes difficulties.

Zafirlukast significantly improved FEV1, PSV1, and symptom relief compared with placebo when added to ICS. The use of montelukast in combination with ICS and long-acting β2-agonists, especially in the presence of allergic rhinitis, allows for faster improvement of disease control and reduction of ICS dose.

A recent study conducted in the UK showed that leukotriene receptor antagonists are as effective as inhaled corticosteroids. Antileukotriene drugs were randomized controlled trials in a group of 650 patients with bronchial asthma for 24 months. The results of the study were published in the New England Journal of Medicine. The authors of the study believe that the use of antileukotriene drugs is possible in 4 out of 5 patients with bronchial asthma, especially in those patients who do not want to use ICS due to their side effects or because of steroid phobia.

Monoclonal antibodies

A new drug, Omalizumab (produced by Novartis under the trade name Xolair), has been developed relatively recently, which is a concentrate of antibodies to IgE. Xolair binds free IgE in the blood, thereby preventing degranulation and the release of biologically active substances that trigger early allergic reactions.

Xolair can be used in people over 12 years of age with moderate to severe forms of persistent bronchial asthma, with allergic asthma, the triggers of which are year-round allergens, confirmed by skin tests or a study of specific IgE.

The drug was studied in Study 1 and Study 2 with a total of one thousand seventy-one patients aged 12 to 76 years who received beclomethasone dipropionate, divided into 2 groups (received subcutaneous Xolair or placebo). Adding Xolair to existing ICS therapy allows for a significant reduction in ICS dose while maintaining asthma symptom control. In Study 3, which used fluticasone propionate as the ICS, allowed the addition of long-acting bronchodilators, and included more severe patients, no difference was found between Xolair and placebo.

Long-acting β2-adrenomimetics

Currently, long-acting β2-adrenomimetics include:

- Formoterol (Oxis, Foradil)
- Salmeterol (Serevent)
- Short-acting β2-adrenomimetics

The range of short-acting β2-adrenomimetics is represented by the following drugs:

- Fenoterol (Berotec)
- Salbutamol (Ventolin)
- Terbutaline (Bricanil)

They are the most effective of the existing bronchodilators, and therefore they take first place among drugs for the relief of acute asthma symptoms at any age. The preferred inhalation route of administration is as it provides a faster effect at a lower dose and fewer side effects. Inhalation of a β2-agonist provides pronounced protection against bronchospasm during physical exertion and other provoking factors, for 0.5-2 hours.

Xanthines

Xanthines include euphylline, which is used for emergency relief of an attack, and theophylline with a long action, which is taken orally. These drugs were used before β2-adrenomimetics and are used in some situations at the present time. Theophylline has been shown to be effective as monotherapy and additional therapy to ICS or even SGCS in children over 5 years of age. Euphylline eliminates daytime and nighttime symptoms and improves lung function, and maintenance therapy provides them with a protective effect during exercise. The addition of theophylline in children with severe asthma allows for improved control and a reduction in the dose of GCS. Preference is given to slow-release drugs with studied absorption and full bioavailability regardless of food intake (Teopek, Teotard). Currently, therapy with xanthine derivatives has an auxiliary value as a method of stopping attacks with low effectiveness or absence of other groups of drugs.

Drugs of other groups

Expectant drugs improve sputum discharge. They, especially when used through a nebulizer, reduce the viscosity of sputum, help loosen mucous plugs and slow down their formation. To enhance the effect with viscous sputum, it is recommended to take 3-4 liters of fluid per day. Postural drainage, percussion and vibration massage of the chest are effective after taking expectorant drugs through a nebulizer. Iodine preparations, guaifenesin, N-acetylcysteine, ambroxol are used as the main expectorant drugs.

Allergen-specific immunotherapy (ASIT)

One of the traditional methods of treating bronchial asthma, which affects its immunological nature. ASIT has a therapeutic effect that extends to all stages of the allergic process and is absent in known pharmacological drugs. The action of ASIT covers the immunological phase itself and leads to a switch in the immune response from Th2-type to Th1-type, inhibits both the early and late phases of the IgE-mediated allergic reaction, suppresses the cellular picture of allergic inflammation and nonspecific tissue hyperreactivity. It is performed on patients from 5 to 50 years old with exogenous bronchial asthma. At certain intervals, the allergen is injected subcutaneously, gradually increasing the dose. The duration of the course is at least 3 months. ASIT with house mite allergens is most effective, while ASIT with house dust allergens is ineffective. The simultaneous use of no more than 3 types of allergens is allowed, which are administered with an interval of at least 30 minutes. In addition to allergens, the administration of histaglobulin is also used to treat bronchial asthma.

Over the past decade, nasal and sublingual methods of allergen administration have been introduced into practice.

Use of nebulizers

In bronchial asthma, an important point in the implementation of successful therapy is the delivery of the drug to the focus of inflammation in the bronchi, to achieve this result, it is necessary to obtain an aerosol of a given dispersion. For this purpose, special devices called nebulizers are used, which are essentially an inhaler that produces an aerosol with particles of a given size. The general principle of operation of the device is to create a finely dispersed aerosol of the substance introduced into it, which, due to the small size of the particles, will penetrate deep into the small bronchi, which mainly suffer from obstruction.

The 2 most common types of nebulizers are ultrasonic and compressor. Each of them has both its advantages and disadvantages. Ultrasonic, more compact and quiet, suitable for carrying with you, but with their help you cannot enter oil solutions and suspensions. Compressor ones are relatively large due to the air pump, they require a stationary power supply from the AC network, and are quite noisy due to the operation of the same compressor, but they have an important advantage: they can be used to introduce suspensions and oil solutions, and they are approximately 40-50% cheaper than similar ultrasonic models.

2. Questions for self-control (list of questions):

1. Etiology, pathogenesis, classification of bronchial asthma.
2. Pathophysiological and pathochemical mechanisms of SBO development.
3. Outline the main clinical manifestations of SBO.
4. Indicate the pathways of pharmacological action in different variants of SBO.
5. List the groups of drugs that improve bronchial patency.
6. Explain the mechanisms of bronchospasmolytic and anti-inflammatory action of representatives of the main groups of drugs, based on their pharmacodynamics.
7. Formulate the significance of the leading pharmacokinetic indicators in the individual selection of drug doses.
8. Highlight the clinical and laboratory and instrumental criteria for therapeutic efficacy and safety of the drugs used.
9. The role of glucocorticoids in the treatment of patients with SBO, the rules for their appointment and cancellation, taking into account pharmacodynamic and pharmacokinetic features.
10. Formulate urgent medical care for asthmatic conditions, bronchospasm on the background of systemic anaphylaxis.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write prescriptions for the main groups of drugs for SBO (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for prescription. Indicate and explain possible effective and undesirable drug combinations.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and the list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. To identify the signs during subjective and objective examination of the patient that characterize bronchial patency disorders, to write a clinical diagnosis of the disease.

5. To determine the group of drugs needed by the patient; based on theoretical data on pharmacodynamics and own observations, to select the drug for the patient.

6. To choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. To identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. To justify the need for combined drug therapy and to suggest possible options for a safe combination of drugs.

9. To make a forecast of side effects of drugs prescribed to the patient and to outline a plan for their detection at the early stages.

10. To justify the duration of basic and maintenance therapy.

B. Solution of situational tasks.

1. A patient, 23 years old, was admitted to the department with a diagnosis of right-sided lower lobe bronchopneumonia. From the anamnesis it is known that the patient has been suffering from infectious-allergic bronchial asthma since the age of 8. Attacks are provoked by book and house dust. To stop the attacks, he uses theofedrine, which he takes 10 tablets per day. Against the background of the clinical picture of the underlying disease, the patient has signs of severe bronchial obstruction syndrome and an overdose of theofedrine. Suggest a treatment plan for the underlying and concomitant diseases, indicating specific drugs, their doses, and route of administration.

2. A patient, 53 years old, has been suffering from bronchial asthma of infectious-allergic genesis and chronic bronchitis for 10 years. She notes 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, whistling. Over the lungs - multiple dry whistling rales. Percussion - box sound. Cardiac activity is rhythmic, heart rate and BP - 110 in 1 min., ACT - 140/80 mm Hg., heart sounds are muffled. Mucous membranes are cyanotic, legs are pasty. Suggest a specific treatment plan for this patient, indicating the drugs, their doses, route and mode of administration.

3. A 30-year-old patient, after a bee sting in the area of the spinous process of the 7th cervical vertebra, developed facial edema, severe difficulty breathing, agitation, and then unconsciousness. Heart rate - 120 in 1 min., ACT - 80/40 mm Hg. Dry wheezing rales are heard over the lungs against the background of expiratory dyspnea. Formulate the diagnosis. Provide a plan for providing urgent medical care.

4. A 55-year-old patient suffers from stage II hypertension, ischemic heart disease, atherosclerotic cardiosclerosis with stage I circulatory failure, chronic obstructive bronchitis. She was self-medicated: she took oxprenolol 80, adelphan, and euphyllin. She was taken to the department due to loss of consciousness that occurred against the background of increasing bronchospasm. During examination, there were no neurological symptoms. On

ECG, no acute focal changes in the myocardium were detected, ACT - 140/80 mm Hg, heart rate - 82 in 1 min. Name the probable cause of bronchospasm and fainting, against the background of the absence of clinical signs of exacerbation of chronic obstructive bronchitis and signs of acute coronary pathology. Give specific recommendations for further pharmacotherapy of the patient.

5. A 48-year-old patient has bronchial asthma. In connection with attacks of suffocation, he uses inhalations of isadrine. The drug caused palpitations in the patient. Note the stimulation of which receptors caused tachycardia and palpitations in the patient, what is the tactic for further management of the patient?

6. 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 in her condition - bronchorrhea decreased sharply. However, after 10 days the condition worsened again: fever (up to 380C), shortness of breath, cough with sputum, heart rate - 90 beats per minute appeared. What are the reasons for such changes in the patient's condition? List all the undesirable effects of the drug that caused this condition? Prevention of complications, first aid.

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

8. A 52-year-old patient suffering from bronchial asthma was prescribed a drug to improve the drainage function of the bronchi and sputum discharge. 24 hours after starting the drug, the patient developed a sore throat, runny nose, and lacrimation. Note which drug the patient received?

9. A 56-year-old patient is inpatient in the therapeutic department with an exacerbation of bronchial asthma. The combination therapy includes intravenous jet administration of 10 ml of 2.4% euphyllin at 10 am. What are the safety criteria for euphyllin therapy in this case?

Test tasks for self-control:

1. A 68-year-old patient with persistent bronchial asthma regularly uses astmopent (inhalation). The drug causes tachycardia and palpitations in the patient. What is the mechanism of the indicated side effect?

A. Excitation of beta1-adrenoreceptors.

B. Excitation of beta2-adrenoreceptors.

C. Excitation of alpha2-adrenoreceptors.

D. Excitation of alpha1-adrenoreceptors.

E. Excitation of M-cholinoreceptors.

2. Specify the selective short-acting beta2-agonist for relieving attacks of suffocation:

A. Salmeterol.

B. Clenbuterol.

C. Fenoterol.

D. Tiotropium bromide.

E. Atrovent.

3. Name the selective beta2-agonist of prolonged action for the permanent 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, stage 3. Additional studies revealed reduced sensitivity of adreno- and cholinergic receptors of the bronchi to drugs. What drugs are the drugs of choice for the treatment of the patient?

A. Salbutamol by inhalation.

B. Beclomethasone by inhalation.

C. Berodual by inhalation.

D. Spiriva by inhalation.

E. Formoterol by inhalation.

5. A 62-year-old patient with concomitant pathology: coronary artery disease, angina pectoris of the III degree of exertion, chronic obstructive pulmonary disease, sought help to correct pharmacotherapy. As a result of the measures taken, the patient developed an attack of suffocation, expiratory shortness of breath. What drug could have caused these complications?

A. Salbutamol.

B. Ambroxol.

C. Nifedipine retard.

D. Propranolol.

E. Eufilong.

6. A patient with asthmatic status is being treated in the intensive care unit. The first-choice drug is:

A. Lazolvan intravenously.

B. Hydrocortisone intravenously.

C. Sodium bicarbonate intravenously.

D. Euphyllin intravenously.

E. Beclomethasone inhalation.

7. For the treatment of bronchoobstructive syndrome, a patient with bronchial asthma is prescribed a drug that reduces the activity of phosphodiesterase. Specify the drug that meets these conditions:

A. Izadrin.

B. Euphyllin.

C. Salbutamol.

D. Spiriva.

E. Salmeterol.

8. A 49-year-old patient with bronchial asthma is prescribed Berotec as a bronchodilator. The mechanism of action of the drug is associated with an increase in the enzymatic activity of the receptor apparatus. Specify the name of the enzyme:

A. Phospholipase A2.

B. Phosphodiesterase.

C. Adenylate cyclase.

D. Cyclic oxygenase 1.

E. Cyclic oxygenase 2.

9. Glucocorticosteroids are prescribed for the treatment of persistent bronchial asthma of the II degree of severity. What route of administration of these drugs 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 to take oral euphyllin. What safety criteria of the drug will you monitor first?

A. Palpitations, tachycardia.

B. Mental agitation.

C. Tremor of the hands.

D. Anorexia, nausea, epigastric pain.

E. Insomnia.

11. A patient with bronchial asthma developed oral candidiasis on the background of long-term bronchodilator therapy. Which of the listed drugs can cause this side effect first of all?

A. Beclomethasone.

B. Berotec.

S. Teopek.

D. Berodual.

12. While performing physical work in the garden, a patient with bronchial asthma developed increased shortness of breath, breathing worsened, cough and dry wheezing appeared. What group of drugs would you recommend for stopping such attacks?

A. Beta2-blockers.

B. Methylxanthines.

C. Beta2-agonists.

D. Oral glucocorticoids.

E. Mast cell membrane stabilizers.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com

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

6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua

7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org

8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical and pharmacological characteristics of antiallergic drugs"

Purpose:

To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of antiallergic drugs:

- Type 1 histamine blockers;
- Mast cell membrane stabilizers;
- Nonspecific antihistamine drugs.

Basic concepts (list of questions):

1. Allergy: definition, etiology, pathogenesis.
2. Immediate type 1 allergic reactions.
3. Delayed type 2 allergic reactions.
4. Type 1 histamine blockers: classification, mechanism of action, features of action by generation, side effects.
5. Mast cell membrane stabilizers (cromones): mechanism of action, indications, side effects.

Plan

1. Theoretical issues:

When Pirquet first introduced the term "allergy" in 1906, he meant a specific change in the body's ability to respond to an antigen acquired by the organism and attributed both hyper- and hyporeactivity to it. An example of the latter was immunity (immunodeficiencies). Currently, allergy is understood only as hyperreactivity of the body to various environmental influences, to any substance, most often with antigenic properties (A. D. Ado, 1980). It has

now been proven that true, specific allergic reactions are reactions whose development is based on immunological mechanisms, since only with their participation is a specific, selective increase in sensitivity to certain substances possible. Thus, the common thing that unites immunity and allergy is the fundamental similarity of the mechanisms involved in both types of reactions - that is, in immune and allergic, and a protective, beneficial character for the body (to limit the spread of the antigen at the individual level). What is the difference between immune and allergic reactions? To answer this, it is necessary to recall the features of the course of an allergic reaction. Among these features, the following processes are most often found:

1) inflammation, which is hyperergic in nature;
2) edema;
3) bronchospasm;
4) skin itching;
5) cytotoxic and cytolytic effects;
6) shock.

What do these processes have in common? There is only one thing in common - the presence at the time of damage, that is, all these clinical signs of an allergic reaction are a manifestation, a realization of damage caused by the immune mechanism. This is the boundary that distinguishes an immune reaction from an allergic one. Pure damage, and we call this reaction to an antigen immune, is damage - and we classify the same reaction as allergic. Thus, an allergic reaction is both protection and damage at the same time, it is both useful and harmful to the body.

According to the simplest classification, allergic reactions are of two types:

 immediate-type hypersensitivity reactions (ITRs)
 delayed-type hypersensitivity reactions (DTRs).

ITRs develop very quickly - a few minutes after the allergen enters the sensitized organism and last for hours.

In DTRs, the reaction develops after 8-12 hours and lasts for several days and even weeks. The mechanism of development of GTRs and DTRs is the same - immune, but its variants are different.

In the development of ITRs, humoral immunity reactions (reactions of B-lymphocytes, plasma cells) are of primary importance.

At the same time, in the development of immediate-type allergic reactions, the most important role is played by the interaction of allergen and antibodies, especially those belonging to the immunoglobulins of the IgE and IgG4 classes, on the surface (membrane) of mast cells, which occupy a strategic position around blood vessels, and basophils, with the subsequent opening of calcium channels, the influx of calcium ions into the cell and the exit, the release (release) of various biologically physiologically active substances through them, such as histamine, heparin, serotonin, bradykinin, leukotrienes (LTD4, LTS4, LTE4 or slowly reacting substance of anaphylaxis), prostaglandins (Pg I-2 - prostacyclin, Pg D-2 and all others), platelet activation factor (platelet aggregation).

Due to the fact that antibodies of the Ig and IgG4 classes are called reagins (ge + agere (lat.) - to act, to enter), this type of allergic reaction damage is called the reagin type of tissue damage or the anaphylactic type of RGNT.

Immediate-type allergic reactions in humans include anaphylactic shock, serum

sickness, atopic bronchial asthma, hay fever, urticaria, Quincke's edema. As we can see, these are life-threatening reactions, often leading to the death of the patient.

The development of delayed-type hypersensitivity is characterized by tissue reactions and is associated with cellular immunity reactions, namely with the activity of T-lymphocytes, macrophages. Therefore, the following mediators of allergy have been identified in RGUT:

- a factor inhibiting the migration of macrophages or lymphocytes;
- a lymphokine, increasing the number of these cells in the focus of inflammation;
- a factor activating macrophages;
- factor, complement stimulating factor and other lymphokines.

The listed lymphokines provide tissue lymphocyte-monocyte reactions. In RGUT, autoimmune diseases of the liver, kidneys, heart, joints, rejection of transplanted tissues, contact dermatitis and eczema, late reactions to microbial toxins (bacterial allergy), mycoses occur.

Classification of antiallergic agents

According to the two types of allergic reactions, antiallergic agents are divided into two groups:

A. Agents used in immediate-type hypersensitivity reactions;

B. Agents used in delayed-type hypersensitivity reactions.

In turn, group 1 is divided into 4 subgroups, and group B is divided into 2 subgroups. The following 4 subgroups of drugs are used in RGNT:

1. Drugs that prevent the release of histamine and other BAS from mast cells and basophils:

a) glucocorticoids (prednisolone, dexamethasone);

b) beta-adrenomimetics (adrenaline, isadrin, orciprenaline, salbutamol, berotec);

c) xanthines (euphyllin);

d) cromolyn sodium (intal);

e) heparin;

f) M-cholinoblockers (atropine, atrovent).

2. Drugs that prevent the interaction of free histamine with tissue receptors (H1 - blockers - the dimedrol group: dimedrol, diprazine, diazolin, tavegil, etc.)

3. Drugs that reduce tissue damage (steroidal anti-inflammatory drugs - glucocorticoids);

4. Agents that reduce (eliminate) the general manifestations of allergic reactions such as anaphylactic shock:

a) adrenomimetics;

b) bronchodilators of myotropic action;

c) glucocorticoids.

The four groups mentioned are agents that mainly affect the anaphylactic variant.

In case of RGUT, 2 groups of agents are used:

1. Agents that suppress immunogenesis, which suppress mainly cellular immunity (immunosuppressants):

a) glucocorticoids (prednisolone, dexamethasone, triamcinolone, etc.);

b) cytostatics (cyclophosphamide, azathioprine, mercaptopurine);

c) antilymphocyte serum, antilymphocyte globulin and human antiallergic

immunoglobulin;

d) slow-acting antirheumatic agents (hingamine, penicillamine);

e) antibiotics (cyclosporine A).

2. Agents that reduce tissue damage:

a) glucocorticoids (prednisolone, dexamethasone, triamcinolone, etc.)

b) NSAIDs (voltaren, piroxicam, indomethacin, naproxen, etc.).

Drugs used in RGNT

1. Drugs that prevent the release of histamine and BAS from mast cells and basophils.

a) Adrenomimetics and to a greater extent beta-adrenomimetics, primarily adrenaline, orciprenaline, isadrin, salbutamol, as well as selective beta-2-adrenomimetics such as fenoterol (beroteca).

These drugs have common mechanisms of action. First of all, it should be said that the antiallergic effect of beta-adrenomimetics is due to the activation of the membrane enzyme adenylate cyclase and an increase in the level of cAMP in the smooth muscle cell and basophils.

This prevents the opening of calcium channels and the entry of calcium ions into the cell, the release of calcium from intracellular depots, which inhibits the increase in the concentration of free calcium in the cytoplasm of cells and the development of subsequent reactions (release of BAS).

At the same time, such alpha- and beta-adrenomimetics as adrenaline and ephedrine have a dual effect. In addition to the specified pharmacological effect, these adrenomimetics also reduce the systemic manifestations of an immediate allergic reaction (reduce bronchial spasm, increase vascular tone, stimulate cardiac activity). In connection with the specified pharmacological effects and depending on the clinical situation, adrenomimetics are used for the following indications:

1) Adrenaline and ephedrine injections are indicated for the development of anaphylactic shock (intravenously, with cardiac arrest - intracardiac); the effect of ephedrine administration occurs more slowly (30-40 minutes), but also longer; adrenaline and ephedrine are also administered subcutaneously (0.3 ml) - for the relief of attacks of bronchial asthma of atopic genesis. A new dosage form of adrenaline (oil solution) has been recently created, which when administered intramuscularly lasts for 16 hours, but aseptic abscesses are possible. A racemic mixture of L- and D-adrenaline in a 2.25% solution is used in aerosols (the drug Adnephrin - 2-3 inhalations 3-4 times a day).

2) Beta-adrenomimetics, especially selective beta-2-adrenomimetics (fenoterol) in the form of aerosols can be used both for stopping an attack of bronchial asthma and for its prevention (before going outside).

Due to the limited duration of action of the above dosage forms of beta-adrenergic drugs (up to 5 hours), in recent years selective beta-2-adrenomimetics with a duration of action of about 10 hours have been created. These are the so-called prolonged beta-adrenomimetics, or retarded (retain (English) to keep) beta-adrenomimetics. They are available in tablet and inhalation dosage forms:

- formoterol (foradil), the duration of action of which is about 9 hours, taken 2 times a day; - bigolterol - duration of action of about 8-9 hours;

- salmeterol - duration of action of about 12 hours.

The listed preparations of retarded beta-adrenomimetics are used mainly for one

indication - prevention of nocturnal attacks of atopic bronchial asthma.

Xanthines - the next group of drugs that prevent the release of histamine and other mediators of immediate-type allergy from mast cells. The most typical representative is theophylline and its preparations, in particular, euphylline. Theophylline itself has a pronounced antiallergic effect and directly affects the tone of the smooth muscles of the bronchi (spasmolytic of myotropic action), is water-insoluble. The latter significantly limits the possibilities of its use only in the form of tablets and powders. In connection with the above, a theophylline-based drug was created, which has good water solubility. This drug was called euphyllinum. It is a mixture of 80% theophylline and 20% ethylenediamine. It is the latter substance that gives euphyllin the properties of water solubility. It is available in powders, tablets of 0.15; there are dosage forms for parenteral administration of solutions in ampoules of 10 ml of 2.4% concentration (intravenously), ampoules of 1 ml - 24% concentration (intramuscularly).

The drug has:

1) a pronounced antiallergic effect;

2) a direct spasmolytic effect (myotropic).

The antiallergic effect is associated with both the presence of an inhibitory effect on the process of releasing BAS from mast cells and other mechanisms inherent in this drug. In addition to the fact that the drug eliminates spasm of bronchial smooth muscles (broncholytic direct effect), it

3) eliminates bronchial circulatory insufficiency;

4) dilates coronary vessels, which helps to improve blood supply to these organs;

5) stimulates myocardial contractile activity;

6) increases diuresis (facultative diuretic);

7) reduces pressure in the pulmonary artery system, which is very significant in the development of pulmonary edema.

Euphyllin is used in injectable form to relieve attacks of bronchial asthma and to relieve asthmatic status, and in tablets it is used to prevent attacks of bronchial asthma. In the antiallergic action of xanthines (theophylline, in tablets, powders) two more points are important. The first is that xanthines are antagonists of adenosine - a mediator of the purinergic system, and this means that prolonged intake of xanthines leads to an increase in the concentration of catecholamines in the blood and, therefore, contributes to their bronchodilating effect. The second. Prolonged intake of xanthines contributes to the induction of the formation of T-suppressors, cells that suppress the synthesis of reagin antibodies IgE and IgG4). According to some ideas, it is believed that allergy is a partial immunodeficiency in terms of the content and functioning of T-suppressors. The rational use of drugs of this group requires compliance with one condition of mandatory control of the concentration of theophylline in the patient's blood. The constant concentration of the drug in the blood should be in the range of 10-20 μg / ml. Loading dose - 5.6 mg / kg, then every 6 hours 3 mg / kg.

Short-acting theophylline preparations are used when it is necessary to quickly achieve a high concentration of the drug in the blood.

With long-term treatment, prolonged-acting preparations are preferred. 3 generations of prolonged-acting theophylline preparations have already been created:

I generation - theophylline, diprofillin;

II generation - theophylline-retard;

- teotard (2 times);
- durophyllin (2 times);
- teo-dur - the best drug;

III generation - teonova;

- armophyllin;
- euphylon, etc.

The first domestic prolonged-acting theophylline preparation - teopek (tablets of 0.2, 2 times a day).

The group of drugs that limit the release of BAS from mast cells due to the membrane-stabilizing effect also includes the following two drugs - Cromolyn-Sodium (sodium cromoglycate) or Intal (Cromolyn-Sodium (Intalum) is available in capsules containing 0.02 of a metallic-looking powder. These capsules are not for oral use, but for placement in a special inhaler called a spinhaler. Placing the capsule in the inhaler, the patient crushes it and immediately takes 4 deep breaths, inhaling particles of Intal powder. The drug, having a pronounced membrane-stabilizing effect on the smooth cells of the mucous membranes of the respiratory tract, significantly limits the realization of the phenomenon of mast cell degranulation, preventing their reaction to the allergen. But there is one feature of this effect. This effect develops slowly, gradually, and a pronounced bronchodilator effect occurs only after 2-4 weeks of constant administration of the drug. Therefore, Intal is used only for the following indications:

1) to reduce the frequency of attacks of bronchial asthma;

2) to prevent attacks of bronchial asthma, attacks of suffocation in asthmatic bronchitis, pneumosclerosis and other conditions with bronchospasm.

Mast cells can be divided into 2 types according to the content of certain enzymes in them:

1) contain tryptase and are localized mainly in the mucous;

2) contain tryptase and chymase and are localized in the submucosal and mesentery of the intestine.

It turned out that the membrane-stabilizing effect of Intal is most pronounced only in relation to mast cells of the first type (containing only tryptase).

- Optikorm (from the words optics and sodium cromolyn), which is used to treat patients with allergic diseases (lesions) of the eye; the drug
- Lomuzol - for stopping allergic lesions of the nose, by insufflation into the nasal passages;
- Nalcrom - for the treatment of patients with food allergies;
- Sodium Nedocromil (tailed). Tailed is very active against bronchial hyperreactivity syndrome, that is, it has a pronounced bronchodilating effect.

The drug has no side effects, it significantly reduces the need for patients to use beta-adrenomimetics, which can lead to a deterioration in the patient's condition.

- Ketotifen (zaditen) - Ketotifenum - is available in capsules and tablets of 0.001 for oral use, as well as syrup (pediatrics), 1 ml of which contains 0.2 mg of the drug. This is one of the best drugs for the chronic treatment of patients with bronchial asthma. It also, having a membrane-stabilizing effect, like Intal, reduces the reaction of mast cells to an allergen, limiting the release of BAV (allergy mediators) from them. In addition, the drug directly blocks H1 - histamine receptors on the smooth muscles of the bronchi, which limits the

reaction of the latter to histamine. In addition, ketotifen also has sedative and potentiating effects. The last three pharmacological effects (H1-histamine blocking, sedative, hypnotic) are inherent in diphenhydramine, and therefore ketotifen can be simply described as a drug that has the properties of intal and diphenhydramine. As a rule, ketotifen tablets and capsules are used for chronic treatment of adult patients with bronchial asthma, and syrup is used for treatment (prevention of attacks) of children with bronchial asthma. The effect is observed after 2 weeks.

The first subgroup of drugs also includes glucocorticoid hormones: cortisone, hydrocortisone - preparations of natural hormones, but there are also their synthetic analogues - prednisolone, dexamethasone, beclomethasone, etc.

The mechanism of action of glucocorticoid hormones is multifaceted. The antiallergic and anti-inflammatory effects of glucocorticoids are associated with their stabilizing effect on membranes (membrane stabilizing), including smooth cell lysosomes. This prevents the interaction of Fc-receptors of mast cells with the Fc-site of IgE. The latter significantly reduces the release of various mediators from the cell (histamine, heparin, serotonin), which protects tissues from destructive processes. In addition, glucocorticoids in the pathochemical stage of allergic reactions significantly inhibit the release of IL-2 due to inhibition of IL-1 secretion by macrophages and a direct effect on T-cells.

The drugs inhibit the activity of phospholipase-A2, that is, they prevent the formation of arachidonic acid metabolism products. In addition, glucocorticoids in fairly high doses inhibit lymphopoiesis, cooperation of T and B cells, inhibit the proliferation of fibroblasts and their function, somewhat inhibit antibody formation and the formation of immune complexes.

Of the glucocorticoids in atopic asthma, the use of beclomethasone or becotide is of importance. It is prescribed by inhalation, so it does not have a systemic effect, that is, it acts locally.

The group of drugs that limit the release of mediators of allergic reactions from mast cells also includes heparin. In certain quantities, heparin is found in mast cells and its main biological role is that it binds histamine and serotonin. Given this fact, it is administered for this purpose in the treatment of patients with allergic diseases, in particular, patients with bronchial asthma. In addition, heparin disrupts the cooperation of T and B lymphocytes, inhibits the activity of the complement system, reduces the formation of anaphylotoxins, releases histamine from mast cells, prevents the interaction of antibodies with antigens, as well as the formation of CEC. As a rule, heparin in this case is prescribed in the form of inhalations.

Sometimes for the same purpose, M-cholinoblockers are used, which block M-cholinoreceptors on mast cells, reduce the activity of guanylate cyclase and the level of cGMP in them and thereby prevent the opening of calcium channels, and therefore, the launch of the entire cascade cytochemical process. It is mainly used for bronchial asthma.

In this regard, Atrovent, which is available in the form of a patented aerosol inhaler, is beneficial. Due to the fact that it is a quaternary amine, it is less absorbed, does not penetrate the CNS, and has less effect on the gastrointestinal tract.

Atrovent, adsorbing mainly on the surface of the bronchial mucosa, suppresses excessive secretion and bronchospasm. Children under 7 years of age are inhaled 3-4 times a day.

The second subgroup of drugs used in DNT reactions are drugs that prevent the

interaction of released histamine, i.e. H1-blockers (antihistamines).

In 1968, P. Gell, R. Coombs, taking into account the peculiarities of the mechanisms of development of various allergic reactions, proposed a classification of types of allergic reactions. Thus, from a pathogenetic perspective, there are 4 types of allergic reactions:

1) anaphylactic or reagin type of reactions, where the immune mechanism of the reaction is associated with the production of IgE and IgG4 (reagin antibodies);

2) cytotoxic type of reactions, in which the immune mechanism is associated with antibodies of the IgG and IgM classes that react with antigenic determinants of cell membranes;

3) Arthus phenomenon - immune complex type, tissue damage by immune complexes (IgG and IgM);

4) delayed hypersensitivity (sensitized lymphocytes).

H1-blockers are effective only in the first type of allergic reactions - in reaginic.

Histamine, this most important 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 following functions were determined: gastric secretion, neurotransmitter function of the CNS, allergic reactions, inflammation, etc. Almost 20 years later, 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 proven and three of their subtypes were identified: H1, H2 and H3, which differ in structure, localization and physiological effects that occur during their activation and blockade. From this time, an active period of synthesis and clinical testing of various antihistamine drugs began.

Histamine, acting on the receptors of the respiratory system, eyes and skin, causes characteristic symptoms of allergies, and antihistamines, selectively blocking the H1-type receptors, are able to prevent and treat them.

Most of the antihistamines used have a number of specific pharmacological properties that characterize them as a separate group. These include the following effects: antipruritic, antiedematous, antispastic, anticholinergic, antiserotonin, sedative and local anesthetic, as well as the prevention of histamine-induced bronchospasm. Some of them are due not to histamine blockade, but to structural features.

H-1-RECEPTORS

and the effects of histamine H-2-RECEPTORS

and the effects of histamine

-smooth muscle of the intestine;

--smooth muscle of the bronchi;

--smooth muscle of the urinary bladder;

--capillaries, blood vessels;

--nasal mucosa. --gastric glands;

--salivary glands;

--uterine musculature.

--intestinal musculature contraction;

--bronchial musculature contraction;

--bladder contraction;

--vasodilation, capillaries, decreased blood pressure; increased vascular permeability, edema, hyperemia, feeling of fever, itching;

--rhinorrhea, nasal edema, sneezing. --increased secretion of gastric juice;

--increased salivation;

--decreased uterine tone.

Antihistamines block the action of histamine on H1 receptors by the mechanism of competitive inhibition, and their affinity for these receptors is much lower than that of histamine. Therefore, these drugs are not able to displace histamine bound to the receptor, they only block unoccupied or released receptors. Accordingly, H1-blockers are most effective for preventing immediate-type allergic reactions, and in the event of a developed reaction, they prevent the release of new portions of histamine.

According to their chemical structure, most of them belong to fat-soluble amines, which have a similar structure. The nucleus (R1) is represented by an aromatic and/or heterocyclic group and is connected by a nitrogen, oxygen or carbon (X) molecule to an amino group. The nucleus determines the severity of antihistamine activity and some of the properties of the substance. Knowing its composition, you can predict the strength of the drug and its effects, for example, the ability to penetrate the blood-brain barrier.

There are several classifications of antihistamines

According to one of the most popular classifications, antihistamines have been divided into first- and second-generation drugs since their creation. First-generation drugs are also commonly called sedatives (by dominant side effect) in contrast to non-sedative second-generation drugs. Currently, it is customary to distinguish the third generation: it includes fundamentally new drugs - active metabolites, which, in addition to the highest antihistamine activity, exhibit the absence of a sedative effect and the cardiotoxic effect characteristic of second-generation drugs (see table). In addition, according to their chemical structure (depending on the X-bond), antihistamines are divided into several groups (ethanolamines, ethylenediamines, alkylamines, derivatives of alphacarboline, phenothiazine, piperazine and piperidine).

Three generations of antihistamines (trade names are given in brackets)

I generation II generation III generation

• Diphenhydramine (Diphenhydramine)

• Clemastine (Tavegil)

• Chloropyramine (Suprastin)

• Mebhydrolin (Diazolin)

• Quifenadine (Fencarol)

• Sequifenadine (Bikarfen)

• Promethazine (Diprazine, Pipolfen)

• Cyproheptadine (Peritol) • Acrivastine (Semprex)

• Astemizole (Gismanal)

• Dimetinden (Fenistil)

• Azelastine (Allergodil)

• Loratadine (Claritin) • Cetirizine (Zyrtec)

• Fexofenadine (Telfast)

Comparative effectiveness of antihistamines by the degree of blockade of histamine H1 receptors.

Drug Degree of blockade of histamine H1 receptors

Diphenhydramine +

Promethazine ++

Chloropyramine +++

Clemastine ++++

Cetirizine, loratadine +++++

Acrivastine, ebastine ++++++

First-generation antihistamines (sedatives). All of them are well soluble in fats and, in addition to H1-histamine receptors, also block cholinergic, muscarinic and serotonin receptors. Being competitive blockers, they reversibly bind to H1-receptors, which necessitates the use of fairly high doses. The following pharmacological properties are most characteristic of them.

• Sedative effect is determined by the fact that most first-generation antihistamines are easily soluble in lipids, penetrate well through the blood-brain barrier and bind to H1-receptors of the brain. Perhaps their sedative effect consists of blocking 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 is enhanced when combined with alcohol and psychotropic drugs. Some of them are used as hypnotics (doxylamine). Rarely, instead of sedation, psychomotor agitation occurs (more often in medium therapeutic doses in children and in high toxic doses in adults). Due to the sedative effect, most drugs cannot be used during work that requires attention. All first-generation drugs potentiate the effects of sedatives and hypnotics, narcotic and non-narcotic analgesics, monoamine oxidase inhibitors and alcohol.

• The anxiolytic effect inherent in hydroxyzine may be due to inhibition of activity in certain areas of the subcortical region of the CNS.

• Atropine-like reactions associated with the anticholinergic properties of drugs are most characteristic of ethanolamines and ethylenediamines. They are manifested by dryness in the mouth and nasopharynx, urinary retention, constipation, tachycardia and disturbances vision. These properties ensure the effectiveness of the discussed funds in non-allergic rhinitis. At the same time, they can increase obstruction in bronchial asthma (due to increased sputum viscosity), cause exacerbation of glaucoma and lead to infravesical obstruction in prostate adenoma, etc.

• The antiemetic and antispasmodic effect is also probably associated with the central cholinolytic action of the drugs. Some antihistamines (diphenhydramine, promethazine, cyclizine, meclizine) reduce the stimulation of vestibular receptors and inhibit the function of the labyrinth, and therefore can be used for motion sickness.

• A number of H1-histamine blockers reduce the symptoms of parkinsonism, which is due to central inhibition of the effects of acetylcholine.

• The antitussive effect is most characteristic of diphenhydramine, it is realized due to a direct effect on cough center in the medulla oblongata.

• The antiserotonin effect, especially characteristic of cyproheptadine, determines its use in migraine.

• The α1-blocking effect with peripheral vasodilation, especially characteristic of phenothiazine antihistamines, can lead to a transient decrease in blood pressure in susceptible individuals.

Local anesthetic (cocaine-like) action is characteristic of most antihistamines (arises due to a decrease in the permeability of membranes for sodium ions). Diphenhydramine and promethazine are stronger local anesthetics than novocaine. At the same time, they have systemic quinidine-like effects, manifested by a prolongation of the refractory phase and the development of ventricular tachycardia.

• Tachyphylaxis: a decrease in antihistamine activity with prolonged use, which confirms the need to alternate drugs every 2-3 weeks.

• It should be noted that first-generation antihistamines differ from the second generation in their short duration of action with a relatively rapid onset of clinical effect. Many of them are available in parenteral forms. All of the above, as well as their low cost, determine their wide use.

Moreover, many of the qualities discussed have allowed the "old" antihistamines to occupy their niche in the treatment of certain pathologies (migraines, sleep disorders, extrapyramidal disorders, anxiety, motion sickness, etc.) not related to allergies. Many first-generation antihistamines are part of combination drugs used for colds, as sedatives, hypnotics, and other components.

Some 1st generation drugs may also be effective in the following situations:

1. For ARVI (drugs with anticholinergic action have a "drying effect on the mucous membranes):

o Pheniramine (Avil);

+ paracetamol + ascorbic acid (Fervex).

o Promethazine (Pipolphen, Diprazin);

+ paracetamol + dextromethorphan (Coldrex Nite).

o Chloropyramine (Suprastin).

o Chlorphenamine; + paracetamol + ascorbic acid (Antigrippin);

+ biclotimol + phenylephrine (Hexapneumine);

+ phenylpropanolamine (CONTAC 400);

+ phenylpropanolamine + acetylsalicylic acid (HL-cold).

o Diphenhydramine (Dimedrol).

2. For cough suppression:

Diphenhydramine (Dimedrol)

Promethazine (Pipolphen, Diprazin)

3. For the correction of sleep disorders (improve falling asleep, depth and quality of sleep, however, the effect lasts no more than 7-8 days):

Diphenhydramine (Dimedrol);

+ paracetamol (Efferalgan Nightcare).

4. For appetite stimulation:

Cyproheptadine (Peritol);

Astemizole (Hismanal).

5. For the prevention of nausea and dizziness caused by labyrinthitis or Meniere's disease, as well as to reduce the manifestations of motion sickness:

Diphenhydramine (Dimedrol)

Promethazine (Pipolphen, Diprazin)

6. For the treatment of vomiting in pregnant women:

Diphenhydramine (Dimedrol)

7. For potentiation of the action of analgesics and local anesthetics (premedication, component of lytic mixtures):

Diphenhydramine (Dimedrol)

Promethazine (Pipolphen, Diprazin)

The most commonly used chloropyramine, diphenhydramine, clemastine, cyproheptadine, promethazine, phencarol, and hydroxyzine.

H1-antagonists of the first generation have advantages in the following cases:

1. Treatment of acute allergic reactions (urticaria, angioedema), when parenteral administration of drugs is required;

2. Treatment of itchy dermatoses (atopic dermatitis, eczema, chronic recurrent urticaria, etc.). Painful itching of the skin is often the cause of insomnia and a decrease in the quality of life. In these cases, the sedative effect of antihistamines of the first generation is useful. A number of drugs produced in the form of a gel (dimetindene) are effective for stopping local allergic reactions;

3. Premedication before diagnostic and surgical interventions to prevent the release of histamine of non-allergic genesis;

4. Symptomatic therapy of acute respiratory viral infections (local and oral administration as part of combination drugs) eliminates itching in the nose, sneezing;

Indications for the use of H1 antagonists of the first generation:

1. allergic diseases:
2. seasonal allergic rhinitis, conjunctivitis;
3. perennial allergic rhinitis, conjunctivitis;
4. acute urticaria and angioedema;
5. chronic recurrent urticaria;
6. food allergy;
7. drug allergy;
8. insect allergy;
9. atopic dermatitis;
10. hypersensitivity of non-allergic origin caused by histamine liberation or prophylactic use with the introduction of histamine liberators (reactions to radiocontrast agents, to the introduction of dextrans, drug, food, etc.);
11. prophylactic use with the introduction of histamine liberators;
12. insomnia;
13. vomiting of pregnant women;
14. vestibular disorders;
15. colds (ARVI).

Side effects

Classical H1-antagonists can have:

 a hypnotic effect associated with the penetration of drugs through the blood-brain barrier and blockade of H1-receptors in the CNS, which is facilitated by their lipophilicity, and other effects on the CNS: impaired coordination, lethargy, dizziness, decreased ability to concentrate.

 the antiemetic effect of AGLS (ethanolamines), which is associated both with the H!-antagonistic effect and partly with anticholinergic and sedative activity. This effect of

AGLS is used for medicinal purposes.

 from the digestive system (increased or decreased appetite, nausea, vomiting, diarrhea, discomfort in the epigastric region).

 with prolonged use of classical H1-antagonists, a decrease in the therapeutic efficacy of the drugs (tachyphylaxis) often develops.

 Some drugs have local anesthetic properties.

 In rare cases, a cardiotoxic effect is possible (prolongation of the QT interval).

Contraindications and precautions

Contraindications to the use of antihistamines

1. generation, in addition to hypersensitivity to the drug, are:
2. pregnancy;
3. breastfeeding;
4. work requiring high mental and motor activity, concentration of attention;
5. urinary retention.

Given the presence of an atropine-like effect, drugs of this group should not be prescribed to patients with bronchial asthma, glaucoma and prostate adenoma. Caution is required when prescribing first-generation antihistamines for asthenodepressive conditions and cardiovascular diseases.

Interactions

First-generation antihistamines potentiate the anticholinergic effect of M-holinoblockers, synthetic anticonvulsants, neuroleptics, tricyclic antidepressants, MAO inhibitors, and drugs for the treatment of parkinsonism.

Antihistamine drugs enhance the central depressive effect of hypnotics (general anesthetics), sedatives and hypnotics, tranquilizers, neuroleptics, centrally acting analgesics, and alcohol.

Chloropyramine (suprastin) is one of the most widely used sedative antihistamines. It has significant antihistamine activity, peripheral anticholinergic and moderate antispasmodic effect. Effective in most cases for the treatment of seasonal and year-round allergic rhinoconjunctivitis, angioedema, urticaria, atopic dermatitis, eczema, itching of various etiologies; in parenteral form - for the treatment of acute allergic conditions requiring emergency care. Provides a wide range of therapeutic doses used. Does not accumulate in the blood serum, therefore does not cause overdose with prolonged use. Suprastin is characterized by a rapid onset of effect and short duration (including side) action. 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 due to the proven high efficiency, controllability of its clinical effect, the availability of various dosage forms, including injectable ones, and low cost.

Diphenhydramine, best known in our country under the name diphenhydramine, is one of the first synthesized H1-blockers. It has a fairly high antihistamine activity and reduces the severity of allergic and pseudoallergic reactions. Due to its significant anticholinergic effect, it has an antitussive, antiemetic effect and at the same time causes dryness of the mucous membranes, urinary retention. Due to its lipophilicity, diphenhydramine gives pronounced sedation and can be used as a hypnotic. It has a significant local anesthetic effect, as a result of which it is sometimes used as an alternative for intolerance to novocaine and lidocaine. Diphenhydramine is available in various dosage forms, including parenteral, which has

determined its widespread use in emergency therapy. However, a significant range of side effects, unpredictability of consequences and effects on the central nervous system require increased attention when using it and, if possible, the use of alternative agents.

Clemastine (tavegil) is a highly effective antihistamine drug, similar in action to diphenhydramine. It has high anticholinergic activity, but penetrates the blood-brain barrier to a lesser extent. It also exists in injectable form, which can be used as an additional agent for anaphylactic shock and angioedema, for the prevention and treatment of allergic and pseudoallergic reactions. However, hypersensitivity to clemastine and other antihistamines with a similar chemical structure is known.

Cyproheptadine (peritol) along with antihistamine has a significant antiserotonin effect. In this regard, it is mainly used for some forms of migraine, dumping syndrome, as an appetite stimulant, for anorexia of various genesis. It is the drug of choice for cold urticaria.

Promethazine (pipolfen) - a pronounced effect on the central nervous system has 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 for potentiation of anesthesia.

Quifenadine (phencarol) - has less antihistamine activity than diphenhydramine, but is also characterized by less penetration through the blood-brain barrier, which determines the lower severity of its sedative properties. In addition, fencarol not only blocks histamine H1 receptors, but also reduces the content of histamine in tissues. It can be used when tolerance to other sedative antihistamines develops.

Hydroxyzine (Atarax) — despite the existing antihistamine activity, it is not used as an antiallergic agent. It is used as an anxiolytic, sedative, muscle relaxant and antipruritic agent.

Thus, first-generation antihistamines, which affect both H1- and other receptors (serotonin, central and peripheral cholinergic receptors, a-adrenoreceptors), have different effects, which determined their use in many conditions. But the severity of side effects does not allow them to be considered as first-choice drugs in the treatment of allergic diseases. The experience gained in their use has allowed the development of single-acting drugs — the second generation of antihistamines.

Second-generation antihistamines (non-sedating).

Unlike the previous generation, they have almost no sedative and anticholinergic effects, but are distinguished by the selectivity of action on H1-receptors. However, they have a cardiotoxic effect to varying degrees.

The most common for them are the following properties.

• High specificity and high affinity for H1 receptors in the absence of effects 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 slow excretion.

• Minimal sedative effect when using drugs in therapeutic doses. It is explained by the weak passage of the blood-brain barrier due to the peculiarities of the structure of these drugs. Some particularly sensitive individuals may experience moderate drowsiness, which is rarely the reason for drug withdrawal.

• Absence of tachyphylaxis with prolonged use.

• The ability to block potassium channels of the heart muscle, which is associated with

prolongation of the QT interval and heart rhythm disturbances. The risk of this side effect increases when combining antihistamines with antifungals (ketoconazole and intraconazole), macrolides (erythromycin and clarithromycin), antidepressants (fluoxetine, sertraline and paroxetine), when consuming grapefruit juice, and in patients with severe liver dysfunction.

• Lack of parenteral forms, but some of them (azelastine, levocabastine, bamipin) are available in forms for topical use.

The advantages of 2nd generation antihistamines include a wider range of indications for use. However, the idea of the clinical effectiveness of 2nd generation antihistamines in the treatment of bronchial asthma and atopic dermatitis is based on a small number of uncontrolled studies. The action of the drug develops rather slowly (within 4-8 weeks), and the pharmacodynamic effects of 2nd generation drugs have been proven only mainly in vitro.

Below are second-generation antihistamines with their most characteristic properties.

Terfenadine is the first antihistamine drug that does not have a depressing effect on the central nervous system. Its creation in 1977 was the result of research into both the types of histamine receptors and the features of the structure and action of existing H1-blockers, and marked the beginning of the development of a new generation of antihistamines. Currently, terfenadine is used less and less, which is due to its increased ability to cause fatal arrhythmias associated with prolongation of the QT interval (torsade de pointes).

Astemizole is one of the longest-acting drugs in the group (the half-life of the active metabolite is up to 20 days). It is characterized by irreversible binding to H1-receptors. It has practically no sedative effect and does not interact with alcohol. Since astemizole has a delayed effect on the course of the disease, its use is inappropriate in acute processes, but may be justified in chronic allergic diseases. Since the drug has the property of accumulating in the body, the risk of developing heart rhythm disorders, sometimes fatal, increases. Due to these dangerous side effects, the sale of astemizole in the USA and some other countries has been discontinued.

Acrivastine (Semprex) is a drug with high antihistamine activity with minimal sedative and anticholinergic effects. A feature of its pharmacokinetics is the low level of metabolism and the absence of cumulation. Acrivastine is preferable in cases where there is no need for constant antiallergic treatment due to the rapid achievement of the effect and short-term action, which allows the use of a flexible dosing regimen.

Dimetendene (fenistil) is the closest to first-generation antihistamines, but differs from them in significantly less pronounced sedative and muscarinic effects, higher antiallergic activity and duration of action.

Loratadine (Claritin) is one of the most popular second-generation drugs, which is quite understandable and logical. Its antihistamine activity is higher than that of astemizole and terfenadine, due to the greater strength of binding to peripheral H1 receptors. The drug is devoid 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 bloodstream in small quantities and does not have undesirable effects on the central nervous and cardiovascular systems.

Azelastine (allergodil) is a highly effective agent for the treatment of allergic rhinitis and conjunctivitis. It is used in the form of a nasal spray and eye drops, azelastine is practically devoid of systemic action.

Another topical antihistamine is bamipin (soventol) in the form of a gel intended for use in allergic skin lesions accompanied by itching, insect bites, jellyfish burns, frostbite, sunburn, as well as 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 affect the QT interval. Currently, they are represented by two drugs - cetirizine and fexofenadine.

Cetirizine (Zyrtec) is a highly selective antagonist of peripheral H1 receptors. It is an active metabolite of hydroxyzine, which has a much less pronounced sedative effect. Cetirizine is almost not metabolized in the body, and the rate of its excretion depends on kidney function. Its characteristic feature is its high ability to penetrate the skin and, accordingly, its effectiveness in skin manifestations of allergies. Cetirizine did not show any arrhythmogenic effects on the heart either in the experiment or in the clinic, which determined the area of practical use of metabolite drugs and determined the creation of a new drug - fexofenadine.

Fexofenadine (telfast) is an active metabolite of terfenadine. Fexofenadine is not transformed in the body and its kinetics do not change with impaired liver and kidney function. It does not enter into any drug interactions, does not have a sedative effect and does not affect psychomotor activity. In this regard, the drug is allowed for use by persons whose activities require increased attention. The study of the effect of fexofenadine on the QT interval showed both in the experiment and in the clinic a complete absence of cardiotropic action when using high doses and with prolonged use. Along with maximum safety, this drug demonstrates the ability to relieve symptoms in the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria. Thus, the pharmacokinetic features, safety profile and high clinical efficacy make fexofenadine the most promising antihistamine drug at present.

So, the doctor's arsenal has a sufficient number of antihistamines with different properties. It must be remembered that they provide only symptomatic relief for allergies. In addition, depending on the specific situation, both different drugs and their various forms can be used. It is also important for the doctor to remember the safety of antihistamines.

Recently, 3rd generation antihistamines have been created that have significant selectivity and do not cause side effects from the CNS. The use of 3rd generation antihistamines is more justified in long-term therapy of allergic diseases:

• perennial allergic rhinitis;

• seasonal allergic rhinitis (conjunctivitis) with a duration of seasonal exacerbations > 2 weeks;

• chronic urticaria;

• atopic dermatitis;

• allergic contact dermatitis;

• early atopic syndrome in children.

The pharmacokinetic properties of antihistamines vary significantly. Modern 3rd generation antihistamines have a long duration of action (12-48 hours). The maximum half-life is astemizole (about 10 days), which suppresses skin reactions to histamine and allergens

for 6-8 weeks. Serious cardiotoxic side effects in the form of severe heart rhythm disturbances have been described for two 3rd generation antihistamines (terfenadine and astemizole).

Topical antihistamines, in particular, acelastine (allergodil) have a rapid (within 20-30 minutes) symptomatic effect, improve mucociliary clearance, and have no significant systemic side effects.

The most promising oral antihistamines are loratadine and cetirizine.

Loratadine (Claritin) is an antihistamine that does not have a sedative effect or significant drug interactions, and is recommended for use by patients of all age groups. Claritin's excellent safety profile allowed the drug to be included in the list of over-the-counter drugs.

Cetirizine (Zyrtec) is a basic antihistamine, especially in young children, when the inhalation route of drug administration is difficult. It has been shown that long-term administration of cetirizine to children with early atopic syndrome reduces the risk of progression of atopic conditions in the future.

Criteria for choosing antihistamines

The need to choose a drug that has an additional antiallergic effect:

• year-round allergic rhinitis;

• seasonal allergic rhinitis (conjunctivitis) with a duration of seasonal exacerbations of up to 2 weeks;

• chronic urticaria;

• atopic dermatitis;

• allergic contact dermatitis;

• early atopic syndrome in children.

Indicated for use in children:

Children under 12 years of age:

• loratadine (Claritine)

• cetirizine (Zyrtec)

• terfenadine (Trexyl)

• astemizole (Hismanal)

• dimetinden (Fenistil)

Children 1-4 years of age with early atopic syndrome:

• cetirizine (Zyrtec)

• loratadine (Claritine)

• desloratadine (Erius)

Indicated for use in women during pregnancy and lactation:

• loratadine (Claritine)

• cetirizine (Zyrtec)

• desloratadine (Allergostop, Delot, Dezal, Claramax, Clarinex, Larynex, Loratec, Lordestin, NeoClaritin, Eridez, Erius, Eslotin, Ezlor)

• fexofenadine (Telfast, Allegra)

• pheniramine (Avil)

The presence of specific problems:

patients with renal failure:

• loratadine (Claritine)

• astemizole (Hismanal)
• terfenadine (Trexyl)
patients with liver dysfunction:
• loratadine (Claritine)
• cetirizine (Zytrec)
• fexofenadine (Telfast)

The second large group of drugs is drugs used in delayed-type hypersensitivity reactions.

With the development of RGUT, contact dermatitis, autoimmune diseases, transplant rejection reactions, bacterial allergies, mycoses, and many viral infections occur. In these processes, cellular immunity reactions mainly develop and T-lymphocyte sensitization is noted.

There are two groups of drugs used in this type of allergy: -

 drugs that suppress immunogenesis (immunodepressants);

 drugs that reduce tissue damage.

The drugs of the first group include, first of all, slow-acting antirheumatic drugs (chingamin, penicillamine):

a) Chingamin (delagil) (Chingaminum); available in tablets of 0.25) - was introduced into medicine as an antimalarial drug, but due to the fact that it was able to suppress inflammatory reactions in which HRT is involved, it is used as a remedy for HRT. Mechanism of action: hingamine stabilizes cellular and subcellular membranes, limits the release of hydrolases from lysosomes that damage cells, counteracting the emergence of clones of sensitized cells in tissues, activation of complement systems, killers. As a result, the focus of inflammation is limited, that is, the drug has an anti-inflammatory effect. It is used for long-term relapsing rheumatism, RA, SLE and other diffuse connective tissue diseases. The effect develops slowly over 10-12 weeks, treatment continued for 6-12 months.

Penicillamine is a product of penicillin metabolism, containing a sulfhydryl group capable of binding heavy metals (iron, copper), eliminating free oxygen radicals. It is used for actively progressive RA. The effect occurs after 12 weeks, improvement after 5-6 months.

b) Glucocorticoids (mainly prednisolone) inhibit the response of cells to lymphokines, thereby limiting the clone of sensitized cells; reduce tissue infiltration by monocytes, stabilize cell membranes, reduce the number of T-cells, reduce cooperation of T - and B-cells and the formation of immunoglobulins. It is used for diffuse connective tissue diseases - SLE, scleroderma, RA, etc.

c) Cytostatics (cyclophosphamide, azathioprine): Azathioprine (Azathioprinum; in tablets of 0.05). They inhibit cell division, especially lymphoid tissue, limit the formation of immunocompetent cells (T-sensitized lymphocytes) and the development of the above immunopathological mechanisms in RA, SLE, etc. Usually they are used only in particularly severe cases, therefore they are used as a reserve. Serious complications are possible when using cytostatics.

d) ALS and antilymphocyte globulin are biological preparations obtained by immunizing animals with appropriate antigens (T-lymphocytes, mononuclear cells). They are used for the same indications as the previous group of drugs.

e) Cyclosporine (Cyclosporin A, Sandimmun); an aqueous solution is available - 100

mg in 1 ml; solution for oral use in 50 ml bottles; soft capsules (25, 50, 100 mg of active ingredient) - a cyclic polypeptide consisting of 11 amino acids; from the fungus Tolypocladium inflatum Gams. Has an immunosuppressive effect in the form of inhibition of the secretion of interleukins and interferons and other lymphokines activated by T-lymphocytes. Inhibits the secretion of these mediators during the activation of T-lymphocytes by antigen. It is used in transplantology, for the treatment of skin diseases (psoriasis). Thus, the group of antiallergic drugs is a developing group of drugs that has significant practical importance.

Most emergencies in allergology are related to type I allergic reactions, a manifestation of anaphylaxis.

ANAPHYLAXIS

is an acute systemic reaction of a sensitized organism to repeated contact with an antigen, which develops in type I allergic reactions and is manifested by acute peripheral vasodilation.

The extreme manifestation of anaphylaxis is anaphylactic shock.

MAIN PROVISIONS

1. If an anaphylactic reaction is suspected, epinephrine should be administered as soon as possible.

2. All patients who have previously suffered anaphylactic shock should have a syringe-tube with epinephrine. Domestic allergists recommend that patients with reactions to stings by hymenoptera insects carry a syringe-pack containing, in addition to epinephrine, systemic antihistamines [for example, chloropyramine (suprastin□), clemastine (tavegil□)] and systemic glucocorticoids (for example, dexamethasone, prednisolone).

3. Rooms where vaccination, allergy tests and allergen-specific immunotherapy or X-ray contrast studies are performed should be fully equipped with the necessary means to provide emergency medical care in the event of the development of anaphylactic or anaphylactoid reactions.

ETIOLOGY

1. Allergens during allergen-specific immunotherapy.

2. Medicines and vaccines:

- antibiotics (for example, penicillins);
- nonsteroidal anti-inflammatory drugs;
- adrenocorticotropic hormone, insulin, etc.

3. Insect bites:

- wasps, bees, mosquitoes.

4. Food:

- nuts (e.g. peanuts), fish, shellfish, kiwi, eggs, milk, etc.

5. Radiopaque substances.

6. Natural rubber (latex):

- gloves, catheters, condoms, etc.

7. Physical exercise, chills, cold.

CLINICAL PICTURE

1. Primary symptoms:

- weakness, dizziness, tremor, possible shortness of breath;

- erythema, burning sensation of the skin;
- itching of the palate and external auditory canal;
- feeling of an approaching attack;
- possible nausea.

2. Secondary symptoms:
- swelling of the skin, especially of the eyelids and lips;
- urticaria;
- laryngeal edema, hoarseness, shortness of breath;
- abdominal pain, nausea, vomiting, diarrhea;
- arterial hypotension, collapse;
- in severe cases, laryngospasm, loss of consciousness, involuntary urination and defecation, shock, respiratory arrest and cardiac activity are possible.

DIFFERENTIAL DIAGNOSIS

1. Acute attack of bronchial asthma.
- Skin manifestations are absent.
- A/T is normal or increased.

2. Fainting.
- Signs of skin and respiratory system involvement are absent.
- Bradycardia.

3. Hereditary angioedema.
- Urticaria is uncharacteristic.
- Epinephrine administration is ineffective.

TREATMENT

1. Epinephrine:
- epinephrine (adrenaline□) 0.1% solution (1 mg/ml) intramuscularly at a dose of 0.1 ml/10 kg; injected deep into the thigh or shoulder;
- adrenaline injection can be repeated after 10-30 minutes;
- epinephrine (adrenaline□) 0.01% solution (0.1 mg/ml) can be administered at a dose of 1-3 ml intravenously to adults in deep shock or 0.1 - 0.5 ml to a child. Rarely prescribed outside the hospital.

2. Necessary conditions:
- the patient should lie on a flat surface with raised legs;
- you should make sure that the patient is breathing. If possible, start oxygen inhalation.

3. Intravenous administration of glucocorticoids:
- methylprednisolone 80-125 mg for adults or 2 mg/kg for children. Alternatively, intravenously administered hydrocortisone 250-500 mg for adults and 10 mg/kg for children or dexamethasone 8-24 mg;
- additionally administered orally prednisolone in an initial dose of 30-50 mg/day.

4. Intravenous administration of fluids:
- Ringer's solution* or isotonic sodium chloride solution should be started immediately intravenously. Adults should be given 500-1000 ml of fluid within the first hour.

5. Aminophylline:
- if symptoms of bronchial asthma appear, it is necessary to administer aminophylline at a dose of 5 mg/kg (adults 4-6 ml, i.e. 200 - 300 mg) intravenously for 5-10 minutes when

signs of bronchospasm appear.

6. Antihistamines:

- oral preparations, for example hydroxyzine (atarax□):

- the dose for adults is 25-50 mg:

- in children, solutions of the medicinal substance with a concentration of 2 mg/ml are used, and depending on age, different volumes of the solution are prescribed:

◊ up to 1 year - 2.5 ml;

◊ from 1 to 5 years - 5 ml;

◊ from 6 to 10 years - 10 ml;

- domestic experts recommend intravenous administration of antihistamines.

ANAPHYLACTIC SHOCK

• T78.2 Anaphylactic shock unspecified.

• T78.0 Anaphylactic shock caused by a pathological reaction to food.

• T80.5 Anaphylactic shock associated with the introduction of serum.

• T88.6 Anaphylactic shock caused by a pathological reaction to an adequately prescribed and correctly used drug.

Definition

Anaphylactic shock is a life-threatening, acutely developing condition accompanied by a violation of hemodynamics,

which leads to circulatory failure and hypoxia in all vital organs.

Anaphylactic shock develops after the patient contacts an allergen that is intolerable to him (foreign proteins during blood transfusion; medications; allergens introduced during seasonal immunotherapy; hymenoptera venom, etc.). Like all types of shock, anaphylactic shock has 4 degrees of severity.

A distinctive feature of anaphylactic shock is the possible development of skin manifestations in the form of urticaria, erythema, edema, as well as the development of bronchospasm before or simultaneously with the appearance of hemodynamic disturbances. Other manifestations are similar to those in any other form of shock.

Before admission to the intensive care unit

1. Stop the administration of the intended drug - allergen.

2. If possible, apply a tourniquet above the site of drug administration or prick the site of drug administration with a 0.1% solution of adrenaline or noradrenaline in a dose of 0.3-0.5 ml with 4-5 ml of saline.

3. Perform venipuncture or venesection and begin intravenous administration of drugs:

- if necessary, intravenously drip: dopamine (individual dose) from 300 to 700 μg/ml (max. 1500 μg/ml) with a gradual decrease, the duration of administration is determined by hemodynamic indicators;

- administration of glucocorticoids (hydrocortisone 250 mg intravenously drip, prednisolone 90-120 mg intravenously jet, dexamethasone 8-32 mg, etc.);

- with systolic blood pressure above 90 mm Hg. antihistaminic drugs [clemastine (tavegil*) 2.0 ml] can be administered;

- plasma-replacing drugs intravenously drip or jet;

- in case of bronchoobstructive syndrome - aminophylline (euphyllin□) 2.4% 10 ml intravenously in saline.

4. Administration of pressor amines (0.1% solution of epinephrine (adrenaline*)

subcutaneously at intervals of 5-10 min).

5. Oxygenation.

6. Correction of acid-base status (KOS).

7. Treatment of acute respiratory failure, transfer to mechanical ventilation and transportation of the patient to intensive care.

8. Symptomatic therapy.

If treatment is ineffective, continue treatment in the intensive care unit

Terms of hospitalization

• The duration of hospitalization is from 1 to 10 days. Requirements for treatment results

• Full recovery or restoration of working capacity.

ACUTE TOXICO-ALLERGIC REACTIONS TO MEDICATIONS

Definition

Acute toxic-allergic reactions (OTAR) to medications are

a systemic reaction of the body that occurs in response to the administration of a therapeutic dose of a medication, which is based on both immune and non-immune mechanisms of development and occurs with a clinical picture of generalized exudative erythema multiforme (L51.8, 77090), bullous dermatosis (L13.8, 77080), toxic epidermal necrolysis (L53.0, 77100).

The main pathogenetic mechanism of OTAR is the development of nonspecific generalized vasculitis (from serous to necrotic), which determines 4 degrees of severity of the disease.

Hospitalization: I and III degrees of severity - in the allergological, therapeutic and dermatological department, III and IV degrees of severity - in intensive care units or intensive care units.

Examination

1. Mandatory laboratory tests (table 189):

- clinical blood test detailed, daily, until the condition stabilizes, then if necessary;
- coagulogram; at III-IV degrees of severity - in dynamics;
- biochemical blood test (total protein and protein fractions, creatinine, bilirubin, ALT, AST, fibrinogen, CRP, glucose, electrolytes);
- at III-IV degrees of severity, dynamic control of the level of total protein, creatinine, blood sugar, transaminases, electrolytes;
- glycemic profile;
- determination of blood group and Rh factor;
- Wasserman reaction (RW), HIV;
- general urine analysis daily until the condition stabilizes, if necessary, urine analysis according to Nechiporenko;
- skin and mucous membrane cultures for III-IV degree of severity, multiplicity according to indications;
- bacteriological examination of sputum;
- bacteriological examination of feces;
- bacteriological examination of bronchoscopy;
- COS during mechanical ventilation.

2. Instrumental examination methods.

- Required:

- electrocardiography;

- chest X-ray examination.

- Additional:

- esophagogastroduodenoscopy when stabilizing the condition and after epithelialization of the mucous membranes of the oral cavity;

- bronchoscopy according to indications;

- ultrasound examination of the abdominal cavity, thyroid gland at I-II degree of severity upon admission, at III-IV degree of severity upon stabilization of the condition.

3. Consultations of specialists.

- Required:

- allergist-immunologist;

- dentist;

- ophthalmologist;

- ENT;

- dermatologist.

- Additional:

- other specialists - according to indications.

4. Allergy examination.

- Carried out at the degree of severity after recovery; at III-IV degree of severity - after 3-4 months. The scope of the allergy examination is determined by the allergist-immunologist.

5. Immunological examination.

- Required:

- determination of the level of total IgE, IgA, IgM, IgG, lymphocyte subpopulations;

- determination of specific IgE and IgG antibodies.

- Additional:

- determination of LE cells, anti-DNA, CEC, CRP, antistreptolysin O, acantholytic cells.

Care for patients with acute toxic-allergic reactions to drugs of III-IV degree of severity

Treatment of patients with OTAR to drugs of III-IV degree of severity must be carried out in specially created sterile conditions in an open manner (use of sterile wards or aerotherapeutic installations with the supply of heated sterile air) with individual fasting. In the case of an exudative component, the skin must be dried and disinfected with solutions, without using ointment bases; as epithelialization progresses, solutions can gradually be replaced with creams and ointments.

Treatment of the mucous membranes of the eyes at III-IV degrees of severity should be carried out 6 times a day (three massages with eye hydrocortisone ointment in combination with collargol*, three instillations of dexamethasone eye drops).

Treatment of the oral cavity after each meal (rinsing with rheopoliglyukin*, freshly brewed tea, treatment with hydrogen peroxide, disinfectant solutions); at the beginning of epithelialization and in the absence of contraindications, it is possible to use rosehip seed oil and sea buckthorn oil.

Characteristics of therapeutic measures

1. Nonspecific hypoallergenic diet, at III-IV degrees of severity - a wiped table or parenteral nutrition.

2. Glucocorticoids: parenteral administration, individual dose from 4 to 32 mg of dexamethasone or betamethasone per day based on the minimum necessary, especially in III-IV degree of severity, with a gradual decrease when the condition stabilizes until complete withdrawal.

3. All patients with OTAR are shown intensive transfusion therapy aimed at detoxification and removal of the causative allergen-drug. The daily volume of transfusion exposure in patients with OTAR of III-IV degree of severity can reach 6000-8000 ml/day under the control of central hemodynamics, diuresis, KOS:

- electrolyte solutions;
- plasma-replacing solutions;
- saline solutions.

4. Replacement therapy with blood products:

- albumin;
- native plasma;
- immunoglobulins (sandoglobulin□, pentaglobin□, octagam*, etc.);
- transfusion of fresh donor blood in patients of III-IV degree of severity with the development of leukopenia and agranulocytosis.

5. Symptomatic treatment:

- antihistamines;
- anticoagulants;
- disaggregants;
- diuretics;
- vasopressor amines (in case of hemodynamic disturbances);
- analgesics (according to indications);
- protease inhibitors;
- cardiac glycosides;
- sedatives.

6. Additional detoxification methods can be used with stable hemodynamics and adequate replacement therapy:

- therapeutic plasmapheresis;
- hemosorption;
- hemodialysis.

7. Antibacterial action - broad-spectrum antibiotics taking into account the pharmacological history and the results of bacteriological examination. The use of penicillin antibiotics and their derivatives is strictly prohibited, if necessary, other antimicrobial and antifungal drugs are prescribed.

8. Additional method of immunocorrection - extracorporeal immunopharmacotherapy.

9. Correction of dysbacteriosis (eubiotics in combination with enzyme preparations).

10. If necessary, mechanical ventilation, therapeutic bronchoscopy.

ALLERGIC URTICARIA

Allergic urticaria is a disease of the allergic gene, characterized by the appearance of urticaria elements on the skin. The main allergens are medications, food products, hymenoptera venom, plant pollen, house dust. In this category of patients, urticaria is often

combined with respiratory manifestations of allergy (allergic rhinitis, bronchial asthma). Patients with allergic urticaria are characterized by a clear relationship between exposure to the allergen and the development of an exacerbation of the disease. Acute and chronic (more than 6 weeks) urticaria are distinguished. Rashes are characterized by severe itching and complete reversibility.

Standard of medical care for patients with angioedema and urticaria

1. Patient model.

• Age category: adults and children.

• Ideological form: urticaria, angioedema.

• Phase: acute condition.

• Stage: first visit.

• Complications: regardless of complications.

• Conditions for provision: emergency medical care.

Treatment of exacerbation of allergic urticaria

(standard)

Severe course

• Carrying out elimination measures.

• First-generation antihistamines parenterally: clemastine (tavegil□) 0.1% 2 ml intramuscularly or intravenously in isotonic sodium chloride solution or chloropyramine (suprastin*) 2.5% for 5-7 days. If ineffective - systemic glucocorticoids: dexamethasone 4-12 mg intramuscularly or intravenously prednisolone 30-90 mg intramuscularly, intravenously for 2-3 days. Then second-generation antihistamines - loratadine (claritin*) 10 mg 1 time per day, astemizole (gismanal)□ 10 mg 1 time per day. Duration of administration up to 1 month. It is possible to use antihistamines with a stabilizing effect on mast cell membranes: ketotifen (zaditen*) 0.001 g 2 times a day for 3 months.

2. Questions for self-control (list of questions):

1. What indications and contraindications (absolute and relative) to the use of antiallergic drugs do you know?

2. What are the main groups of the most active and well-studied antiallergic drugs?

3. How are antiallergic drugs classified?

4. What effects do antiallergic drugs have? What is their clinical significance?

5. What provisions should be followed when choosing an antiallergic drug?

6. What clinical and laboratory indicators indicate the achievement of a therapeutic effect?

7. What are the features of the action of antiallergic drugs when combining them with drugs of other groups?

8. What measures should be taken to prevent allergic reactions?

9. What are the main stages of providing emergency care for immediate-type allergic reactions?

10. What treatment measures should be included in the provision of emergency care for bronchial obstruction syndrome caused by an allergen?

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write prescriptions for the main groups of antiallergic drugs (tablets and/or ampoules), indicate possible use, the spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. To identify the signs during the subjective and objective examination of the patient that characterize the development of allergic reactions, to write a clinical diagnosis of the disease.

5. To determine the group of drugs needed by the patient; based on theoretical data on pharmacodynamics and own observations, to select the drug for the patient.

6. To choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. To identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. To justify the need for combined drug therapy and to suggest possible options for a safe combination of drugs.

9. To make a forecast of the side effects of drugs prescribed to the patient and to outline a plan for their detection at the early stages.

10. To justify the duration of basic and maintenance therapy.

B. Solution of situational tasks.

1. A woman, 30 years old, every year for the last 4 years in August complains of nasal congestion and mucous discharge from it, cough, itching of the eyelids, lacrimation. After using Suprastin, these symptoms disappear. What type of allergic reaction is taking place? What are the features of clinical observation and management of this patient?

2. A woman, 32 years old, who suffers from bronchial asthma, is scheduled for cholecystectomy. What are the features of premedication for this patient? List the basic drugs that will help prevent an attack of bronchial asthma. Which antiallergic drugs will be preferred?

3. A 10-year-old boy, on the background of ampicillin, acutely developed a drug allergy in the form of generalized urticaria, massive angioedema. The child's condition is serious. What is your tactic? What is the sequence of the doctor's actions? What drugs should be used to start intensive care?

4. The doctor prescribed penicillin intramuscularly to the patient. In the prescription letter, he also prescribed an intradermal test for sensitivity to penicillin and novocaine. The nurse asked the patient if he had previously received penicillin and had previously had allergic reactions to penicillin and novocaine. The patient replied that he had previously received penicillin and had repeatedly undergone local anesthesia during surgical interventions and allergic reactions. The nurse made an independent decision and, without

conducting a test for sensitivity to penicillin and novocaine, was going to inject benzylpenicillin to the patient. What is the main mistake of the nurse? What can the first injection in this patient lead to?

1. Patient P., 34 years old, with community-acquired pneumonia, 5 minutes after an intradermal test for penicillin, suddenly developed cough, shortness of breath, anxiety, dizziness, tinnitus, nausea, abdominal pain. Objectively: serious condition, confused consciousness, convulsions, involuntary urination, pale skin, PP - 120 beats per minute, weak filling, ACD - 60/20 mm Hg. st., heart sounds are muffled.

Formulate the diagnosis. Make a plan for intensive therapy, justify its choice.

7. An antihistamine used for motion sickness was advertised on TV. A father, about to fly on a business trip, asked his son, a medical student, to choose this remedy from the list of antihistamines: 1) astemizole, 2) terfenadine, 3) loratadine, 4) cimetidine, 5) diphenhydramine (diphenhydramine), 6) meclizine. Choose the remedy and justify your answer.

8. A woman, 23 years old, suddenly developed an attack of suffocation, skin itching, hoarseness, and swelling of the lips after a bee sting. Objectively: the condition is serious, consciousness is not impaired, BH - 30 in 1 minute, PP - 102 beats in 1 minute, ACD - 100/60 mm Hg. st., heart sounds are muffled, dry rales in the lungs.

What is the probable diagnosis in this case? What is the treatment strategy for this patient? Justify your answer.

Test tasks for self-control:

1. For conduction anesthesia, a 35-year-old man with no history of illness was administered 2 ml of 1% lidocaine solution. A few minutes later, the patient developed profuse sweating, general weakness, visual impairment, severe pallor, nausea, and difficulty breathing. The pulse was weak and tense, heart rate was 118 per minute, blood pressure was 60/20 mm Hg, and heart rate was 28 per minute. Which drug is most effective in the treatment of this patient?

A. Atropine sulfate.

B. Norepinephrine hydrotartrate.

C. Prednisolone.

D. Adrenaline hydrochloride.

E. Dimerol or suprastin.

2. A 60-year-old patient was taken to the intensive care unit with a diagnosis of wasp sting, anaphylactic shock. Which of the following drugs is the first-line and most effective for providing emergency care for anaphylactic shock?

A. Suprastin.

B. Prednisolone.

C. Calcium chloride.

D. Diphenhydramine.

E. Ephedrine hydrochloride.

3. A 12-year-old girl who has had bronchial asthma for 6 years has an attack of suffocation. What drugs should be prescribed to the patient first?

A. Mucolytics.

B. Antibiotics.

C. Inhaled β2-agonists.

D. Corticosteroids.

E. Antihistamines.

4. A 12-year-old child has had atopic dermatitis since infancy. Which group of drugs is least suitable for the treatment of this disease?

A. Hyposensitizing.

B Nonsteroidal anti-inflammatory drugs.

C. Immunomodulators.

D. Sedatives.

E. Antihistamines.

5. A 10-year-old boy developed an acute drug allergy in the form of generalized urticaria and massive angioedema after taking ampicillin. The child's condition is serious. What drugs should be used to start intensive therapy?

A. Sedatives.

B. Calcium gluconate.

C. Corticosteroids.

D. Antihistamines.

E. Diuretics.

6. The patient has anaphylactic shock. Name the drug of choice.

A. Fenoterol

B. Adrenaline

C. Ephedrine

D. Mezaton

E. Noradrenaline

7. After vaccination, the doctor prescribed an antihistamine to the trolleybus driver to prevent an allergic reaction. Name it.

A. Diphenhydramine.

B. Tavegil.

C. Diprazine.

D. Suprastin.

E. Loratadine.

8. Diphenhydramine was prescribed to the patient for the treatment of urticaria to eliminate an itchy rash on the skin. What mechanism ensures its effectiveness in this case?

A. Suppression of histamine release

B. Inhibition of histamine synthesis

C. Independent antagonism with histamine

D. Acceleration of histamine destruction

E. Competitive blockade of H1 receptors

9. To prevent an attack of bronchial asthma, the doctor prescribed cromolyn sodium to the patient. Which of the following mechanisms is characteristic of this agent?

A. Blockade of histamine receptors

B. Decrease in immunoglobulin concentration

C. Binding of free histamine

D. Stabilization of mast cell membranes

E. Inactivation of histamine

10. A 45-year-old woman suffers from seasonal allergic rhinitis associated with

ragweed flowering. Which of the following medications can be used to prevent this disease?

A. Tavegil
B. Diazolin
C. Fenkarol
D. Ketotifen
E. Diphenhydramine

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC

"Clinical and pharmacological characteristics of drugs that affect the condition of the CNS"

Purpose:

To master the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of drugs:

- Sedative drugs;
- Tranquilizers;
- Neuroleptics;
- Antidepressants;
- Nootropics.

Basic concepts (list of questions):

1. Central nervous system.
2. Peripheral nervous system.
3. Stroke: classification, principles of pharmacotherapy.
4. Inflammatory diseases of the CNS and PNS: etiology, pathogenesis, pharmacotherapy.
5. Characteristics of the main groups of drugs in neurology.

Plan

1. Theoretical questions:

Psychotropic drugs have recently been increasingly used by doctors of various specialties. On the one hand, this is due to the constant increase in the number of neuropsychiatric diseases, on the other - frequent secondary disorders of the CNS in many diseases of a somatic nature. In addition, rational pharmacotherapy, based on the effective and safe use of drugs, must take into account the possible negative impact of non-psychotropic drugs on the CNS, which is not always taken into account by practicing doctors. Studying this topic will allow students to more fully navigate the mechanisms of action of psychotropic drugs, reasonably use them to manage the pathogenesis of the disease, which will ultimately increase the effectiveness of prevention and treatment of CNS disorders.

SUBSTANCES THAT AFFECT THE CENTRAL NERVOUS SYSTEM

These are drugs that can affect human mental functions (memory, behavior, emotions, etc.), and therefore they are used for disorders of mental activity, for neurotic and neurosis-like disorders, states of internal tension, fear, anxiety, and restlessness.

CLASSIFICATION OF PSYCHOTROPIC DRUGS

1) Sedatives.
2) Tranquilizers.
3) Neuroleptics.
4) Antimanic.
5) Antidepressants.

Sometimes some authors call nootropic drugs (nootropics) as the sixth (6) group of psychotropic drugs.

Let's start the analysis of this group of drugs with sedatives.

Sedatives are sedatives. Sedatives (sedatives) include:

1) small doses of barbiturates,

2) bromine and magnesium salts,

3) herbal preparations (valerian, dog nettle, passionflower herb, etc.).

All of them, causing a moderately sedative effect, have an indiscriminate, depressant effect on the cerebral cortex. In other words, sedatives enhance the inhibitory processes in the neurons of the cerebral cortex.

Of the bromine salts, SODIUM BROMIDE and POTASSIUM BROMIDE are most often used. Valerian preparations in the form of infusions, tinctures, extracts are widely used.

Sedatives are also preparations of motherwort herb. Infusions and tinctures of motherwort are used. A passionflower preparation is Novopassit. Infusions of common hops, Quater's mixture (valerian, bromides, menthol, etc.), magnesium ions (magnesium sulfate).

Indications for use: sedatives are used for neurasthenia, hysteria, mild forms of neurosis, increased irritability, insomnia associated with this.

The second group of psychotropic drugs is the group of TRANQUILISERS. Tranquilizers are modern sedatives with a selective effect on the emotional sphere of a person. The term tranquilizers comes from the Latin tranquillium - peace, tranquility. The psychotropic effect of tranquilizers is mainly associated with their effect on the limbic system of the brain. In particular, tranquilizers reduce the spontaneous activity of hippocampal neurons. At the same time, they have a depressing effect on the hypothalamus and activate the reticular formation of the brainstem. Acting in this way, tranquilizers are able to reduce the state of internal tension, anxiety, fear.

Based on this, this group of drugs is also called ANXIOLYTICS. The fact is that the Latin term anxius - or the English "anxious" is translated as "anxious, full of fear, fear", and the Greek lysis - dissolution.

Therefore, in the literature, the term anxiolytics is used as a synonym for the concept of tranquilizers, that is, drugs that can reduce the state of internal tension.

Due to the fact that these drugs are mainly used to treat patients with neuroses, they have their third main name, namely, anti-neurotic drugs.

Thus, we have three equivalent terms: tranquilizers, anxiolytics, anti-neurotic drugs, which we can use as synonyms. You can also find synonyms in the literature: small tranquilizers, psychosedatives, ataractics.

Of the tranquilizers used in medical practice, benzodiazepine derivatives are most widely used, as they have a wide range of therapeutic effects and are relatively safe.

SIBAZON diazepam (Sibazonum; in tablets 0.005; in ampoules 0.5% solution 2 ml); synonyms - diazepam, seduxen, relanium, valium. Drugs of this group: chlozepid (elenium), phenazepam, nozepam, mezapam (rudotel).

The mechanism of action of benzodiazepine tranquilizers: in the body, in the territory of the specified zones of the CNS, benzodiazepines interact with the so-called benzodiazepine receptors, which are closely related to GABA receptors (GABA - gamma-aminobutyric acid - inhibitory CNS mediator; glycine - also an inhibitory CNS mediator; L-glutamic acid - an excitatory mediator). When benzodiazepine receptors are stimulated, activation of GABA receptors is observed. Therefore, the interaction of benzodiazepines with the receptors of the same name manifests itself in the form of a GABA-mimetic effect.

All benzodiazepines, eliminating the feeling of emotional tension, have similar

properties, but differ in pharmacokinetics. Diazepam or sibazone are used more often than other drugs.

PHARMACOLOGICAL EFFECTS OF TRANQUILIZERS

1) The main one is their tranquilizing or anxiolytic effect, which is manifested in the ability to reduce the state of internal tension, anxiety, mild fear. They reduce aggression and cause a state of calm. At the same time, they eliminate both situational (associated with any event, specific action) and non-situational reactions. In addition, they have a pronounced sedative effect.

2) The next effect is their muscle relaxant effect, although the muscle relaxant effect of tranquilizers is weak. This effect is realized mainly due to the central action, but they cause inhibition of polysynaptic spinal reflexes.

3) By increasing the threshold of a convulsive reaction, tranquilizers have anticonvulsant activity. It is believed that the anticonvulsant and muscle relaxant activity of tranquilizers is associated with GABAergic action.

4) All benzodiazepine tranquilizers have a mild hypnotic effect, and the benzodiazepine tranquilizer NITRAZEPAM has such a powerful hypnotic effect that it rightfully belongs to the group of hypnotics on this basis.

5) Potentiate the effect (enhance the effect of CNS depressants and analgesics). Benzodiazepines lower blood pressure, reduce respiratory rate, and stimulate appetite.

INDICATIONS FOR USE:

1) as a means for the treatment of patients with primary neuroses (anti-neurotic agents);

2) for neuroses on the basis of somatic diseases (myocardial infarction, peptic ulcer);

3) for premedication in anesthesiology, as well as in the postoperative period; in dentistry;

4) for local spasms of skeletal muscles ("tic");

5) sibazon in injections (iv, im); for convulsions as an anticonvulsant of various genesis and for status epilepticus, muscle hypertonus;

6) as a mild hypnotic for some forms of insomnia;

7) for alcohol withdrawal syndrome in people suffering from chronic alcoholism.

SIDE EFFECTS

1) Benzodiazepines cause daytime drowsiness, lethargy, adynamia, mild inhibition, decreased attention, inattention. Therefore, they should not be prescribed to drivers, operators, pilots, and students. Tranquilizers are best taken at night (at least 2/3 of the daily dose at night, and 1/3 of the dose during the day).

2) Benzodiazepine tranquilizers can cause muscle weakness, ataxia.

3) Tolerance and physical dependence may develop.

4) Withdrawal syndrome may develop, characterized by insomnia, agitation, and depression.

5) Drugs can cause allergies, photosensitivity, dizziness, headache, sexual dysfunction, menstrual cycle, and accommodation.

6) Tranquilizers have a cumulative effect.

Habituation and the development of dependence are the reason for the abuse of tranquilizers. This is their main drawback and a great misfortune.

Considering the above-mentioned undesirable effects, the so-called "daytime

tranquilizers" have now been created, which have a much less pronounced muscle relaxant and depressant effect. These include MESAPAM (Rudotel, Germany). They act weaker in their tranquilizing effect, but most importantly, they cause side effects to a lesser extent. They have a sedative, anticonvulsant, muscle relaxant effect. They are used to treat patients with neuroses, alcoholism. Therefore, they are considered as "daytime" tranquilizers, which are less disruptive to performance during the day (Table 0, 01).

Another drug - FENAZEPAM (tablets of 2.5 mg, 0.0005, 0.001) - a very strong drug, as an anxiolytic, as a tranquilizer it surpasses other drugs. In terms of duration of action, it is in 1st place among the above-mentioned benzodiazepines, in terms of action it is even close to neuroleptics. For phenazepam, it has been shown that its decrease in blood plasma by 50% occurs after 24-72 hours (1-3 days). It is prescribed for very severe neuroses, which brings it closer to neuroleptics.

Indicated for neurosis-like, psychopathic and psychopath-like conditions, which are accompanied by anxiety, fear, emotional lability. Indicated for obsessions, phobias, hypochondriacal syndromes. Used to relieve alcohol withdrawal.

Similar properties to benzodiazepines have a derivative of propanediol - MEPROBAMATE or MEPROTAN. It is inferior to the tranquilizer phenazepam. It exhibits a sedative, muscle relaxant and anticonvulsant effect. It enhances the depressing effect of anesthetics, sleeping pills, ethyl alcohol, narcotic analgesics. It is well absorbed from the gastrointestinal tract. It suppresses fast-wave sleep, causes a strong aftereffect, is toxic, depresses the respiratory center, disrupts coordination. It affects the blood, causes allergies.

The third group of psychotropic drugs is NEUROLEPTICS or ANTIPSYCHOTIC DRUGS (neuron - nerve, leptos - gentle, thin - Greek.). Synonyms: major tranquilizers, neuroplegics. These are drugs for the treatment of patients with psychosis.

PSYCHOSIS - a condition characterized by a distortion of reality (i.e. delusions, hallucinations, aggressiveness, hostility, affective disorders). In general, this fits into the concept of productive symptoms.

Psychoses can be ORGANIC or ENDOGENOUS (schizophrenia, manic-depressive psychosis) and REACTIVE, that is, they are not independent diseases, but a condition that arose in response to shocks. For example, during the earthquake in Armenia - mass psychoses. The basis of psychoses is of great importance a sharp increase in the sympathetic tone of the CNS, that is, an excess of catecholamines (noradrenaline, dopamine or dopamine).

The discovery and introduction into practice in the middle of the century of active psychotropic drugs of the neuroleptic group is one of the greatest achievements of medicine. This fundamentally changed the strategy and tactics of treating many mental illnesses. Before the advent of these drugs, the treatment of patients with psychosis was very limited (electroshock or insulin coma). In addition, neuroleptics are currently used not only in psychiatry, but also in border areas of medicine, neurology, therapy, anesthesiology, surgery. The introduction of these drugs contributed to the development of fundamental research in the field of psychopharmacology, physiology, biochemistry, pathophysiology in order to learn the mechanisms of various manifestations of mental disorders.

The MECHANISM of the antipsychotic action of neuroleptics is not sufficiently understood. It is believed that the antipsychotic effect of neuroleptics is due to the inhibition of dopamine receptors (D-receptors) of the limbic system (hippocampus, lumbar gyrus, hypothalamus).

The blocking effect on dopamine receptors is manifested by antagonism with dopamine and dopamine mimetics (apomorphine, phenamine) both in behavioral reactions and at the level of individual neurons.

On preparations of neuronal membranes it has been established that neuroleptics inhibit the binding of dopamine by its receptors.

In addition to blocking receptors sensitive to dopamine and noradrenaline, neuroleptics reduce the permeability of presynaptic membranes, disrupting the release of these biogenic amines and their reverse neuronal uptake (D-2 receptors). For some neuroleptics (phenothiazine derivatives), their blocking effect on serotonin receptors and M-cholinoreceptors of the brain may be important in the development of psychotropic effects. Thus, the main mechanism of action of neuroleptics is considered to be the blockade of D-receptors.

By chemical structure, neuroleptics belong to the following groups:

1) phenothiazine derivatives - aminazine, etaperazine, triphazine, fluorophenazine, thioproperazine or nazeptyl, etc.;

2) butyrophenone derivatives - haloperidol, droperidol;

3) dibenzodiazepine derivatives - clozapine (leponex);

4) thioxanthene derivatives - chlorprothixene (truxal);

5) indole derivatives - carbidin;

6) rauwolfia alkaloids - reserpine.

Phenothiazine derivatives are the most widely used agents in the treatment of major psychoses.

The most typical representative of phenothiazine derivatives is AMINAZIN or largactyl (international name: chlorpromazine). Aminazinum (pills of 0.025; 0.05; 0.1; amp. of 1, 2, 5 and 10 ml - 25% solution).

Aminazine was the first drug of this group, synthesized in 1950. In 1952 it was introduced into clinical practice (Delay and Deniker), which marked the beginning of modern psychopharmacology. Phenothiazines have a three-ring structure in which 2 benzene rings are connected by sulfur and nitrogen atoms.

Since other neuroleptics of the phenothiazine group differ from aminazine only in the strength of action and some features of the psychotropic effect, aminazine should be discussed in detail.

MAIN PHARMACOLOGICAL EFFECTS OF AMINAZIN

1) Pronounced effect on the CNS. First of all, it is a neuroleptic effect, which can be characterized as a deep sedative effect (supersedative) or an overly pronounced tranquilizing effect. In this regard, it is clear why this group of drugs was previously called "major tranquilizers".

In patients with major psychoses and agitation, Aminozin causes a decrease in psychomotor activity, a decrease in motor-protective reflexes, emotional calm, a decrease in initiative and agitation, without providing a hypnotic effect (neuroleptic syndrome). The patient sits silently, he is indifferent to the surrounding and what is happening around him, minimally reacting to external stimuli. Emotional dullness. Consciousness is preserved during this period.

This effect develops quickly, for example, with parenteral administration (iv, im) after 5-10 minutes and lasts for 6 hours. It is explained by the blockade of adrenoreceptors and

dopamine receptors in the brain.

2) The antipsychotic effect is realized by reducing productive symptoms and affecting the emotional sphere of the patient: reducing delusions, hallucinations, reducing productive symptoms. The antipsychotic effect does not manifest itself immediately, but gradually, after many days, mainly after 1-2-3 weeks after daily administration. It is believed that this effect is due to the blockade of D-2 receptors (dopamine presynaptic).

3) Aminazine, like all phenathiazine derivatives, has a pronounced antiemetic effect associated with the blockade of chemoreceptors of the trigger zone (critical zone located at the bottom of the IV ventricle. But it is not effective in vomiting caused by irritation of the vestibular apparatus or gastrointestinal tract. It eliminates the effect of apomorphine (dopamine receptor stimulator) on the trigger zone in the medulla oblongata brain.

4) Aminazine inhibits the thermoregulation center. The final effect depends on the ambient temperature. Most often, due to increased heat loss, slight hypothermia is observed.

5) A decrease in motor activity (myorelaxant effect) is typical for aminazine. At sufficiently high doses, a state of catalepsy develops, when the body and limbs remain in the position they were given for a long time. This state is due to the suppression of the descending facilitating effects of the reticular formation on spinal reflexes.

6) One of the manifestations of the effect of aminazine on the CNS is its ability to potentiate the effect of analgesics, anesthetics, and hypnotics. This effect is also partly due to the inhibition of the biotransformation processes of these drugs by aminazine.

7) In large doses, aminazine has a hypnotic effect (light, superficial sleep).

Aminazine, like all phenothiazines, also affects peripheral innervation.

1) First of all, aminazine has pronounced alpha-blocker properties, as a result of which it eliminates some of the effects of adrenaline and noradrenaline. Against the background of aminazine, the compressor response to adrenaline decreases sharply or a "perversion" of the effect of adrenaline occurs and blood pressure drops.

2) In addition, aminazine is characterized by some M-cholinoblocking (i.e. atropine-like) properties. This is manifested by a slight decrease in the secretion of the salivary, bronchial and digestive glands.

Aminazine affects not only the efferent, but also the afferent innervation. With local action, it has a pronounced local anesthetic activity. In addition, it has a pronounced antihistamine activity (blocks H-1 histamine receptors), which leads to a decrease in vascular permeability, and is also a myotropic antispasmodic.

Aminazine is characterized by its effect on the cardiovascular system. This is primarily manifested by a decrease in blood pressure (both systolic and diastolic), mainly due to its alpha-adrenoblocking effect. Cardiodepressive effects, antiarrhythmic effect are noted.

Aminazine, in addition to its above-mentioned effects on the nervous system and executive organs, has pronounced pharmacological effects on metabolism.

First of all, it affects the endocrine system. In women, it causes amenorrhea and lactation. It reduces libido in men (blocking D-receptors in the hypothalamus and pituitary gland). Aminazine blocks the release of growth hormone.

Aminazine is administered enterally and parenterally. With a single administration, the duration of action is 6 hours.

INDICATIONS FOR USE

1) It is used as an emergency aid for acute psychoses. For this indication, it is

administered parenterally. Aminazine and its analogues are most effective in the patient's agitation, anxiety, tension and other productive psychotic symptoms (hallucinations, aggressiveness, delusions).

2) Previously used in the treatment of patients with chronic psychoses. Currently, there are more modern means, in the absence of which it can be used.

3) As an antiemetic for vomiting of central genesis (with irradiation, for example, with vomiting of pregnant women). Also with persistent hiccups, during treatment with antitumor drugs.

4) Due to the alpha-adrenoblocking effect, it is used to relieve hypertensive crisis. In neurology: in conditions with increased muscle tone (after a cerebral stroke), sometimes in status epilepticus.

5) In the treatment of drug addiction to narcotic analgesics and ethyl alcohol.

6) In the treatment of patients with manic states.

7) During heart and brain operations (hypothermic effect), during premedication, the same effect is used to eliminate hyperthermia in children.

SIDE EFFECTS

1) First of all, it should be noted that with prolonged use of aminazine, patients develop profound inhibition. This effect is so strongly expressed that as it increases, the patient eventually turns into an emotionally "dull" person. Aminazine can change behavioral reactions, accompanied by drowsiness, impaired psychomotor functions. Lethargy, apathy develop.

2) Almost 10-14% of patients receiving aminazine develop extrapyramidal disorders, extrapyramidal symptoms of parkinsonism: tremor (tremor paralysis), muscle rigidity. The development of these symptoms is due to a deficiency of dopamine in the black nuclei of the brain, which occurs under the influence of a neuroleptic.

3) Frequent side effects of aminazine are nasal congestion, dry mouth, and palpitations. Due to their anticholinergic effects, phenothiazines (aminazine, etc.) cause blurred vision, tachycardia, constipation, and ejaculation inhibition.

4) Hypotensive crises may develop, especially in the elderly. Intravenous administration may even be fatal.

5) Blood disorders develop in 0.5% of patients: agranulocytosis, thrombocytopenia, aplastic anemia. In a number of patients (up to 2%) there is cholestatic jaundice, various hormonal disorders (gynecomastia, lactation, menstrual disorders), exacerbation of diabetes, impotence.

6) Phenothiazines can cause either an increase or decrease in body temperature.

7) In psychiatric practice, tolerance can develop, especially to the sedative and antihypertensive effects. The antipsychotic effect is preserved.

As already mentioned, aminazine belongs to phenothiazine derivatives. It was the first drug of this series. Subsequently, a number of compounds of this class and series were synthesized (meterazine, etaperazine, triftazyl, thioproperazine or mazheptil, fluorophenazine, etc.). In general, they are similar to aminazine and differ from it only in the expressiveness of individual properties, lower toxicity and fewer side effects. Therefore, aminazine is gradually being replaced from clinical practice by the above-mentioned drugs.

In the last 10 years, the drug THIORIDAZINE (sonapax) has been widely used. In terms of antipsychotic activity, it is inferior to aminazine. The drug has an antipsychotic

effect combined with a sedative effect without pronounced inhibition, lethargy, emotional indifference. It very rarely causes extrapyramidal disorders. It is indicated for mental and emotional disorders, feelings of fear, tension, excitement.

Butyrophenone derivatives are of great interest as antipsychotics. Of this series of compounds, HALOPERIDOL (halophene) is mainly used for the treatment of patients with mental illnesses.

Haloperidolum (tablets of 0.0015, 0.005; vials of 10 ml of 0.2% - intravenously; amp. - 1 ml - 0.5% solution). Its action begins relatively quickly. When the drug is administered intravenously, the maximum concentration in the blood occurs after 2-6 hours and remains at a high level for 3 days.

It has a less pronounced sedative effect and an effect on the autonomic nervous system (alpha-adrenoblocking, atropine-like and ganglioblocking effects are less). However, it has stronger antipsychotic activity than aminazine, therefore it is of interest in patients with very strong excitement and mania.

The frequency of extrapyramidal reactions in the treatment of this drug is very high, so it does not have significant advantages over phenothiazines in the treatment of schizophrenia. It is used in the treatment of patients with acute mental illnesses with hallucinations, delusions, aggression; with intractable vomiting of any origin or with resistance to other neuroleptics, as well as with hypnotics, analgesics as a premedication agent.

DROPERIDOL belongs to the same group of drugs.

Droperidolum (amp. 5 and 10 ml 0.25% solution, Hungary). It differs from haloperidol in its short-term (10-20 minutes) potent action. It has antishock and antiemetic effects. It lowers blood pressure, has an antiarrhythmic effect. Droperidol is used mainly in anesthesiology for neuroleptic analgesia. In combination with the synthetic analgesic fentanyl, it is part of the drug talamonal, which exhibits a rapid neuroleptic and analgesic effect, leads to muscle relaxation, drowsiness. It is used in psychiatry for the treatment of reactive states. In anesthesiology: premedication during and after surgery. With endotracheal anesthesia. Contraindications: parkinsonism, hypotension, when prescribing antihypertensive drugs.

Currently, new neuroleptics have been created that practically do not cause extrapyramidal disorders. In this regard, one of the latest drugs, CLOZAPIN (or leponex), is of interest. It has a strong antipsychotic effect with a sedative component in the absence of symptoms of parkinsonism. When using the drug, there is no such sharp general oppression as with aminazine. The sedative effect develops at the beginning of treatment, which then passes. Clozapine belongs to dibenzodiazepine derivatives. It has high antipsychotic activity. It is used in psychiatry to treat patients with manic-depressive psychosis and schizophrenia, with psychopathies.

It is believed that clozapine and classical neuroleptics (phenothiazines and butyrophenones) interact with different types of D-receptors. In addition, clozapine has a pronounced blocking activity against M-cholinoreceptors of the brain.

Clozapine is well tolerated, but it is necessary to monitor the blood, since there is a risk of developing agranulocytosis, tachycardia, and collapse are possible. It should be prescribed with caution to drivers, pilots and other categories of persons.

SULPIRIDE (eglonil) - a moderate neuroleptic. It has an antiemetic, moderate antiserotonin effect, no sedative effect, no anticonvulsant activity, has an antidepressant effect, some stimulating effect. It is used in psychiatry (lethargy, lethargy, anergy), in therapy

in the treatment of peptic ulcer, migraine, dizziness.

The fourth group of psychotropic drugs, which we will consider very briefly, are ANTIMANICAL DRUGS.

MANIA - a painfully elevated excited state, usually accompanied by an increase in mood, a desire to make speeches, etc.

From the Greek - mania - madness.

Mania is usually observed as one of the phases of manic-depressive syndrome (MDS).

In the treatment of patients with mania, the following are used:

1) neuroleptics;

2) lithium salts.

Neuroleptics are effective not only in mania, but also in general in agitated (severe excitement, agitation) states of various genesis. Their effect is manifested in general depression, the development of apathy and drowsiness.

Lithium salts have a more specific effect. They have a pharmacotherapeutic effect only in mania, without causing general inhibition.

Lithium salts are used for the treatment and prevention of mania.

The mechanism of action of lithium salts is not well understood. It is believed that they reduce the release of norepinephrine from nerve endings by increasing intracellular oxidative deamination and more active neuronal reuptake of the mediator. In addition, it is believed that lithium displaces sodium from cells, and as is known, sodium provides depolarization, i.e. excitation of cells (neurons).

When lithium salts are administered enterally, they are well absorbed from the small intestine. Lithium is excreted by the kidneys by filtration. The rate of lithium elimination can be slightly increased by increasing the sodium content in the chloride diet. When the intake of table salt is reduced or its excessive excretion is increased, lithium is retained in the body and this leads to intoxication (salt-free diet, use of diuretics).

Various lithium salts are used: carbonate, chloride, iodide, acetate, nitrate. Lithium carbonate is most often used.

Lithii carbonatus (tablets in a shell of 0.3). Lithium carbonate has been used in the treatment of mental illnesses since 1949 (Cade). Lithium carbonate is administered only enterally.

As noted above, one of the most important indications for the use of lithium salts is the treatment of patients with mania. Lithium salts differ from neuroleptics in:

1) a slower development of the effect (after 2-3 weeks), which dictates the use of neuroleptics at the beginning of treatment in severe manic states;

2) the difference in the action of lithium salts from neuroleptics is that they have a more selective effect on mania, the absence of a sedative effect (does not cause lethargy or apathy in patients).

The effectiveness of lithium salts for the prevention of mania, as well as depression in TID, is of great importance.

SIDE EFFECTS

It is necessary to take into account the small therapeutic latitude of lithium salts. This leads to the fact that the toxicity of these drugs is proportional to their content in serum. In this regard, when using them, regular monitoring of their content in the blood is necessary (no

more than 1.6-2 mEq/l).

Moderate toxicity is manifested by diarrhea, dyspeptic disorders, drowsiness, muscle weakness, tremor, ataxia, polyuria, thirst. Lithium carbonate can cause allergic reactions, blurred vision. Non-toxic goiter, hypothyroidism, and ECG changes may develop.

Lithium salts are contraindicated in cases of impaired renal excretory function, thyroid diseases, and the drug should be used with caution in peptic ulcer disease and cholecystitis.

ANTIDEPRESSANTS.

Used for pathologically depressed mood. Antidepressants with a sedative effect are also called TYMOLEPTICS (from the Greek - thymos - soul, spirit; leptos - gentle, thin), and with a stimulating effect - TYMORETICS (Greek - ereto - to irritate).

Successful correction of depression with the help of medications is one of the most important achievements of psychopharmacology in recent years.

The cause of depression is a violation of the normal transmission of serotonin and noradrenaline

CLASSIFICATION OF ANTIDEPRESSANTS

It can be briefly presented by two main groups of drugs, most often used in the clinic.

1) Drugs that potentiate the action of monoamines (monoamines - tyrazine, serotonin).

Serotonin and noradrenaline reuptake inhibitors. In this group, we will analyze two drugs: imizin, amitriptyline.

Reuptake inhibitors of only serotonin - fluoxetine

Reuptake inhibitors of only noradrenaline - maprotiline

2) Monoamine oxidase inhibitors A and B - nialamide (nuredal).

The most widespread drugs of the first group, which are usually designated as

TRICYCLIC ANTIDEPRESSANTS due to their structure.

IMIZIN (Imizinum; in tablets of 0.025; in ampoules of 1.25% solution of 2 ml) is a typical representative of the drugs of this group and is used very often.

Other drugs: desipramine (norpramin), trimipramine, amitriptyline, nortriptyline or (sensivan), protriptyline (vivactyl), nitroxazepine, etc.

Imizin has pronounced antidepressant properties, combined with a weak sedative effect. Sometimes, however, imizine may also have a psychostimulating effect (euphoria, excitement, insomnia).

THE MECHANISM OF ACTION by which tricyclic antidepressants act in humans is unknown. There are only hypotheses. One of them associates the antidepressant effect of imizine with its ability to inhibit the reverse neuronal uptake of norepinephrine. This leads to a large accumulation of this mediator in the receptors, which enhances the adrenergic effects. Imizine does not affect the activity of monoamine oxidase (MAO). In addition, imizine may activate serotonin receptors, which is due to the violation of its neuronal and extraneuronal uptake. Strengthening the inhibitory effect of serotonin on the limbic system (amygdala complex) may be one of the important mechanisms of the antidepressant effect of imizine.

In addition, the central M-holinoblokiruyuschee action of tricyclic antidepressants also plays an important role.

PHARMACOLOGICAL EFFECTS

1) Tricyclic antidepressants have a pronounced effect on behavior. Imisin has an antidepressant effect. Improves mood, eliminates longing, unmotivated anxiety, suicidal thoughts, increases activity, desire for activity. In addition, it has a certain sedative effect.

2) Along with the central effects, Imisin has some peripheral M-holinoblokiruyuschee (atropine-like), papaverine-like (spasmodic myotropic) and pronounced antihistamine action.

When using Imisin for depression, the therapeutic effect occurs after 2-3 weeks, and when using amitropyline somewhat faster. It is excreted by the kidneys, 90% bound to plasma proteins.

SIDE EFFECTS

Most often, side effects are associated with: 1) atropine-like properties (dry mouth, accommodation disorders, tachycardia, constipation, delayed diuresis). There may be phenomena: 2) orthostatic hypotension, collapse. In case of overdose - tachycardia, arrhythmias. There may also be undesirable effects on the psyche: either excessive sedative effect or excitement, hallucinations, insomnia.

There may be headache, allergic reactions, tremor, jaundice, leukopenia.

THE PREPARATION IS CONTRAINDICATED in glaucoma, prostate adenoma. It cannot be used together with MAO inhibitors.

AMITRIPTYLINUM (Amitriptylinum; in tab. 0.025; in amp. 1% solution 2 ml) - in pharmacodynamics and pharmacokinetics similar to imizin.

Along with high antidepressant activity, amitriptyline has pronounced psychosedative properties. It has no stimulating effect. It surpasses imizin in M-holinoblokiruyuschemu and protivogistaminnymu action.

Amitriptyline is the most active antidepressant. Its therapeutic effect is manifested after 10-14 days.

Side effects: constipation, tremor, muscle rigidity, dry mouth.

The second group of drugs INHIBITORS - MAO (IMAO - nialamide). Currently, they are used quite rarely due to high hepatotoxicity. Therefore, when choosing, preference is given to tricyclic antidepressants. But sometimes MAOIs are also useful.

THE MECHANISM OF ACTION OF MAOIs is due to the fact that these agents inhibit the process of oxidative deamination of norepinephrine and serotonin, which leads to the accumulation of the latter in brain tissue in significant quantities. Most drugs in this group block MAO irreversibly. Therefore, to restore MAO, it must be synthesized anew, which requires a certain time (up to 2 weeks).

MAO inhibitors have hypotensive activity, which is associated with the inhibition of the release of norepinephrine from the presynaptic endings of adrenergic fibers. Reduce pain in angina (blocking the central links of reflex pathways to the heart).

They are well absorbed from the gastrointestinal tract, eliminated by the kidneys.

SIDE EFFECTS

The drugs are relatively toxic. This is manifested mainly by a hepatotoxic effect (severe hepatitis). In addition, they excite the CNS (insomnia, euphoria, convulsions).

Antidepressants have found wide application in the treatment of patients with the depressive phase of manic-depressive psychosis, as well as with neurotic and reactive depressions. They are used in child psychiatry to correct the behavior of children in case of their mental underdevelopment, as well as to treat enuresis.

There is a possibility of developing orthostatic collapse. They should be used with

caution together with other neurotropic agents (narcotic analgesics, indirect adrenomimetics, tricyclic antidepressants).

It is necessary to exclude foods containing tyrazine (cheese) from the patient's diet.

A large number of hydrazine derivatives have been synthesized as MAO inhibitors. But currently, few are used, in particular - NIALAMID. This is one of the least effective antidepressants (effect in 12-14 days). But low-toxic, which is its advantage. Of the non-hydrazine MAOIs - TRANSAMINE (a strong MAO inhibitor - effect in 7-9 days). These drugs are contraindicated in liver and kidney diseases, cerebral circulation disorders, and mental agitation.

Another group of drugs, recently increasingly popular serotonin reuptake inhibitors - fluoxetine

CENTRAL NERVOUS SYSTEM STIMULATORS

Stimulants are conventionally divided into 4 large groups:

1. PSYCHOSTIMULATORS

a) psychomotor:

- caffeine; phenamine; sydnocarb.

b) psychometabolic (nootropics):

- nootropil (piracetam); cerebrolysin; gamalon, etc.

2. ANALEPTICS

a) direct action:

- bemegrid; etimizol, etc.

b) reflex action:

- cytiton, etc.

c) mixed action:

- cordiamine, etc.

3. SPINAL CORD STIMULATORS

- strychnine;

- securenin, etc.

4. GENERAL TONIZING MEDICINES (ADAPTOGENS)

a) of plant origin: preparations of ginseng, eleutherococcus, aralia, golden root, maral root, Bittner balm, etc.

b) of animal origin: pantocrine, etc.

PSYCHOSTIMULATORS and NOOTROPICS

PSYCHOSTIMULATORS

Psychostimulants (or psychotonics, psychoanaleptics, psychomotor stimulants) improve mood, the ability to perceive external stimuli, and psychomotor activity. They reduce the feeling of fatigue, increase physical and mental performance (especially when tired), and temporarily reduce the need for sleep (drugs that invigorate a tired body are called "doping" - from the English word to dope - to give drugs).

Unlike drugs that depress the CNS, stimulants are of less importance, since they lack selectivity of action. In addition, stimulation of the CNS is accompanied by its further suppression.

CLASSIFICATION OF PSYCHOSTIMULATORS

1) Agents that act directly on the CNS:

a) stimulate mainly the cerebral cortex (xanthine alkaloids, phenamine, sydnocarb,

methylphenamine, meridol, etc.);

b) stimulate mainly the medulla oblongata (corazol, cordiamine, bemegrid, camphor, carbon dioxide);

c) stimulate mainly the spinal cord (strychnine).

2) Agents that act on the CNS reflexively (lobeline, veratrum, nicotine).

It should be remembered that such a division is conditional and when used in large doses they can stimulate the CNS as a whole.

A typical representative of psychostimulants is PHENAMINE (amphetamine sulfate; tab. 0.005; drops in the nose, in the eye 1% solution). Chemically, it is a phenylalkylamine, i.e. similar in structure to adrenaline and noradrenaline.

MECHANISM OF ACTION is associated with the ability to release NORADRENALINE and DOPAMINE from presynaptic endings. In addition, phenamine reduces the reuptake of noradrenaline and dopamine.

Phenamine stimulates the ascending activates the reticular formation of the brain stem.

PHARMACOLOGICAL EFFECTS

EFFECT ON THE CNS

A powerful CNS stimulant. It increases mental and physical performance, improves mood, causes euphoria, insomnia, tremor, anxiety. In therapeutic doses, it has an awakening effect, eliminates fatigue, increases physical capabilities. Stimulates the respiratory center and in this regard acts as an analeptic.

EFFECT ON THE CARDIOVASCULAR SYSTEM

Increases both systolic and diastolic blood pressure. Tachyphylaxis is known in relation to the hypertensive effect of phenamine.

SMOOTH MUSCLE

Phenamine increases the tone of the sphincter of the urinary bladder and relaxes the bronchial muscles, but only at high doses. Phenamine reduces appetite (on the hypothalamus), has some anticonvulsant effect (with Petit mal).

SIDE EFFECTS

An undesirable effect is stimulation of the sympathetic nervous system (tachycardia, anxiety, headache, tremor, excitement, confusion, paranoid psychosis, angina attacks).

The drug causes drug dependence, mainly mental, accumulates. Tolerance may develop.

INDICATIONS FOR USE:

1) neurotic subdepression;

2) for narcolepsy, for catalepsy, for the prevention of pathological drowsiness (narcolepsy);

3) obesity;

4) as analeptics for poisoning with narcotic analgesics.

Similar to phenamine are pyridrol and meridol, which act on the CNS. They do not have undesirable peripheral adrenomimetic effects.

In addition to phenamine, the active psychostimulant sidnocarb (mesocarb) also belongs to the group of phenylalkylsyndnonimines. This is an original domestic drug, somewhat different in chemical structure from phenamine. In Russian clinics, sidnocarb is currently the main psychostimulant. Compared to phenamine, it is much less toxic and does not exhibit a pronounced peripheral sympathomimetic effect. The psychostimulant effect

develops gradually, but it is longer, is not accompanied by euphoria and motor excitement. As a rule, tachycardia and a sharp increase in blood pressure are absent. After the drug is taken, the patient does not feel general weakness and drowsiness. The drug is used for various types of asthenia, which occur with inhibition and lethargy, apathy, decreased performance, hypochondria, increased drowsiness.

The drug is used as a psychostimulant for asthenic and neurasthenic disorders in patients who have suffered intoxications, infections and brain injuries, in some forms of psychosis.

In addition, sydnocarb is used to relieve asthenic manifestations after the use of neuroleptics, tranquilizers, as well as in the treatment of patients with alcoholism (relief of asthenoneurotic reactions during the period of "alcohol withdrawal", to reduce the phenomenon of withdrawal).

Sydnocarb is also used in the treatment of children with oligophrenia, which is accompanied by adynamia, aspontaneity, lethargy, inhibition, asthenia.

Side effects. In case of overdose, increased irritability, anxiety, decreased appetite are possible. In patients with psychosis, increased delusions and hallucinations are possible. Sometimes a moderate increase in HELL is noted.

The drug is available in tablets of 0.005; 0.01; 0.025.

The industry produces a combined drug Sidnogluton, containing 0.025 sidnocarb and 0.1 glutamic acid. The latter potentiates the psychostimulating effect of Sidnocarb.

The agents that stimulate mainly the cerebral cortex include XANTHINE ALKALOIDS (purine derivatives; metalxanthines), a typical representative of which is CAFFEINE.

Xanthine alkaloids are found in several plants that grow all over the world. Three natural xanthine alkaloids have been found in these plants: caffeine, theobromine, theophylline, which are purine bases. When heated with nitric acid, they form a yellow precipitate, from which the term xanthine (Greek - xanthos - yellow) originated. Caffeine is found in tea leaves (Thea sinensis - 2%), in coffee seeds (Coffea arabica - 1-2%), in cocoa seeds (Theobroma acuminata), etc.

PHARMACOLOGICAL EFFECTS

Caffeine has the most pronounced effect on the CNS, followed by theophylline and theobromine. The effect of caffeine on higher nervous activity depends on the dose and type of nervous system. In small doses, caffeine increases the activity of the cortex, in large doses it inhibits it. In small doses, it helps to accelerate the thinking process and makes it clearer, brings clarity to the train of thought, reduces drowsiness, fatigue and adds the ability to perform intellectually complex tasks. It reduces reaction time, increases motor activity and consolidates conditioned reflexes. These effects can be observed after 1-2 cups of coffee. One cup contains about 1500 mg of caffeine.

Higher doses cause increased excitability, confusion, insomnia, headache, tremor. Theophylline in large doses can even cause convulsions.

MEDITATION OF THE True, in large doses tachycardia and arrhythmias occur, that is, its peripheral effect prevails (cardiac output increases).

SPINAL CORD

Very large doses increase the reflex excitability of the spinal cord and can lead to clonic seizures.

BLOOD VESSELS

Xanthines have a myotropic effect on blood vessels, but this vasodilating effect is short-lived. It cannot be used to treat diseases of peripheral vessels.

Xanthines have an ambiguous effect on various vascular areas. The latter helps with migraines. Caffeine has a weak myotropic spasmolytic effect on smooth muscle organs (bronchi, biliary tract). This is of great importance for the clinic. It has long been known that theophylline eliminates bronchospasm in anaphylactic shock, stimulates skeletal muscles, increases their metabolism, and eliminates their fatigue.

Caffeine increases BASIC METABOLISM. Increases glycogenolysis, causing hyperglycemia. Increases lipolysis, releases adrenaline from the adrenal medulla.

DIURESIS

Xanthines increase diuresis. The strongest in this regard is theophylline, followed by theobromine and caffeine.

Xanthines increase the volume, acidity and pepsin content in gastric juice.

MECHANISM OF ACTION is associated with two directions:

1) xanthines inhibit cyclic nucleotide phosphodiesterase and prevent the transition of cAMP to 5-AMP;

2) cause changes in calcium distribution at the level of intracellular processes.

SIDE EFFECTS

1) Confusion, tremor, headache, insomnia. Tinnitus, headache, tachycardia, shortness of breath, arrhythmias. With these reactions, sedatives should be prescribed.

2) Xanthines are indicated orally for patients with peptic ulcer disease and gastritis.

3) Xanthines develop addiction, to a greater extent - mental dependence, which, however, is not dangerous.

INDICATIONS FOR USE

To stimulate mental activity. With fatigue, with symptoms of asthenia, with migraine, hypotension. With inattention, impaired attention, exhaustion.

Caffeine is a part of many combined preparations with non-narcotic and narcotic analgesics: citramone, panadol extra, solpadeine, as well as with ergot alkaloids - the drug cofetamine.

NOOTROPICS, NOOTROPIC MEDICINES

The term is formed from the Greek - noos - thinking, tropos - aspiration, affinity. Means that have a special effect on the higher integrative functions of the brain, stimulate memory, learning, improve mental activity.

Improving mental, mental activity is the main effect of this group of drugs. This is manifested in mental deficiency associated with organic brain lesions.

Mechanisms of action of nootropics at the neurophysiological level: influence on transchannel and other types of polysynaptic evoked potentials, recorded on EEG.

The direction of action of nootropic drugs indicates their significant influence on the integrative activity of the brain and the processes of information transmission in the brain. Probably, under the influence of nootropics, tuning to the theta rhythm of various brain formations and processes of information transmission in the brain occurs. The ability of nootropics to improve learning and memory processes is based on the process of increasing the level of spatial synchronization of brain biopotentials.

It should be noted that these drugs do not affect the higher nervous system of healthy

animals and the psyche of a healthy person. Normally, they do not change many behavioral reactions, conditioned reflexes, bioelectric activity of the brain, motor activity.

The pharmacotherapeutic action of nootropics at the molecular level in conditions of pathology is based on a beneficial effect on neurometabolism and brain energy. Therefore, this group of drugs is also called psychometabolic stimulants. The main nootropic agents used in practice imitate the metabolic effects of -aminobutyric acid (GABA).

The first drug synthesized abroad in the late 60s in the research laboratory of the UCB company (Belgium) was called NOOTROPIL. In our country there is an analogue - PIRACETAM (Piracetamum; in tablets of 0.2; in ampoules of 20% solution of 5 ml; capsules - 0.4). It is a classic nootropic agent, therefore it is used by doctors of various specialties most often.

PHARMACOLOGICAL EFFECTS

Piracetam (nootropil) is a cyclic derivative of GABA. Nootropics improve the metabolism of brain cells and, above all, the metabolism of glucose and oxygen in them, increase the resistance of cells to hypoxia, improve blood supply to the brain, and the connection between the hemispheres. Nootropics improve memory, reduce fatigue. But the effects appear gradually, not immediately after administration. Piracetam has anticonvulsant activity, and in recent years its immunomodulatory effects, immunopotentiating effect have also been described.

INDICATIONS FOR USE:

- in conditions after concussion;
- in mentally retarded children, with varying degrees of oligophrenia; in children with impaired memory, attention, speech;
- in the elderly, elderly people, in geriatrics to improve memory, mood;
- in chronic treatment of drug addicts, alcoholics;
- in patients after a stroke;
- nootropics are indicated for enuresis in young children.

In addition, they are prescribed to potentiate the effects of immunostimulants.

AMINALON - a GABA preparation. Obtained synthetically. GABA is an inhibitory mediator that plays an important role in the metabolic processes of nervous tissue. The drug stimulates tissue respiration, activates Krebs cycle enzymes, improves glucose utilization by neurons.

Indications for use: vascular diseases of the brain, mental retardation in children.

Side effects of nootropics: brain stimulation can lead to irritability, sleep disturbances, mood swings, anxiety in children, increased blood pressure, sexual arousal. Therefore, they are used in courses (2-3 weeks).

In recent years, the group of nootropics has expanded significantly. This includes the Hungarian drug Cavinton (Gedeon Rihter), Cerebrolysin, etc.

CAVINTON (tablets of 0.005; ampoules of 0.5% solution of 2 ml). Ethyl ester of apovincaminovy acid (preparation of alkaloid of periwinkle).

Cavinton has the following effects:

1) dilates the vessels of the brain;

2) increases cerebral blood flow, improves oxygen supply to the brain;

3) improves glucose utilization by neurons, promotes the accumulation of cAMP,

ATP;

4) reduces platelet aggregation;

5) increases the content of catecholamines in the CNS.

It is used primarily in neurology for:

1) neurological and mental disorders associated with cerebral circulation disorders (stroke, trauma, sclerosis);

2) memory disorders;

3) dizziness;

4) aphasia;

5) hypertensive encephalopathy;

6) atherosclerosis of retinal vessels, i.e. in ophthalmology, etc.;

7) hearing loss of toxic genesis.

ANALEPTIC AGENTS (ANALEPTICS)

Analeptic agents (from the Greek analeptikos - restores, strengthens) are understood as a group of drugs that primarily excite the vital centers of the medulla oblongata - vascular and respiratory. In large doses, these drugs can disrupt the motor zones of the brain and cause convulsions.

In therapeutic doses, analeptics are used for weakening vascular tone, respiratory depression, infectious diseases, in the postoperative period, etc.

Currently, the group of analeptics can be conditionally divided into three subgroups by localization of action:

1) Drugs that directly activate (restore) the respiratory center:

- bemegrid; etimizol.

2) Drugs that reflexively stimulate the respiratory center:

- cytiton; lobeline.

3) Mixed-type agents, have both direct and reflex action:

- cordiamine; camphor; corazole; carbonic acid.

Bemegrid (Bemegridum; in ampoules of 10 ml of 0.5% solution) is a specific antagonist of barbiturates and has a "reviving" effect in intoxication caused by drugs of this group. The drug reduces the toxicity of barbiturates, relieves respiratory and circulatory depression. The drug also stimulates the CNS, therefore it is effective not only in barbiturate poisoning.

Bemegrid is used in acute barbiturate poisoning, to restore breathing upon exit from anesthesia (ether, fluorotan, etc.), to remove the patient from a severe hypoxic state. The drug is administered intravenously, slowly until breathing, blood pressure, and pulse are restored.

Side effects: nausea, vomiting, convulsions.

In the line of direct-acting analeptics, a special place is occupied by the drug ethimizol.

Ethimizol (Aethimizolum; in tablets of 0, 1; in ampoules of 3 and 5 ml of 1% solution). The drug activates the reticular formation of the brain stem, increases the activity of neurons of the respiratory center, enhances the adrenocorticotropic function of the pituitary gland. The latter leads to the release of additional portions of glucocorticoids. At the same time, the drug differs from bemegrid in a mild depressing effect on the cerebral cortex (sedative effect), improves short-term memory, and promotes mental work. Due to the fact that the drug promotes the release of glucocorticoid hormones, it has an anti-inflammatory effect.

Indications for use. Ethimizol is used as an analeptic, a respiratory stimulant in case of poisoning with morphine, non-narcotic analgesics, in the recovery period after anesthesia, and in case of atelectasis of the lung. In psychiatry, its sedative effect is used in anxiety states. Given its anti-inflammatory effect, it is prescribed for the treatment of patients with polyarthritis and bronchial asthma, as well as as an antiallergic agent.

Side effects: nausea, dyspepsia.

Reflexively acting stimulants are H-cholinomimetics. These are the drugs cytiton and lobeline. They excite the H-cholinorceptors of the sinocorotid zone, from where afferent impulses enter the medulla oblongata, thereby increasing the activity of the neurons of the respiratory center. These drugs act quickly, within a few minutes. Clinically, there is an increase in the frequency and depth of breathing, an increase in blood pressure. The drugs are administered only intravenously. They are used for the only indication in carbon monoxide poisoning.

In mixed-type agents, the central effect (direct excitation of the respiratory center) is supplemented by a stimulating effect on the chemoreceptors of the carotid glomerulus (reflex component). As noted above, these are cordiamine and carbon dioxide. In medical practice, carbogen is used: a mixture of gases - carbon dioxide (5-7%) and oxygen (93-95%). It is prescribed in the form of inhalations, which increase the respiratory volume by 5-8 times.

Carbogen is used in case of overdose of general anesthetics, carbon monoxide poisoning, and asphyxia of newborns.

Cordiamine is a neogalenic drug (prescribed as an officinal drug, but is a 25% solution of nicotinic acid diethylamide) as a respiratory stimulant. The action of the drug is realized by stimulating the respiratory and vasomotor centers.

It is prescribed for heart failure, shock, asphyxia, and intoxication.

PREPARATIONS THAT STIMULATE MAINLY THE FUNCTIONS OF THE SPINAL CORD

In this group, two drugs are essentially used: strychnine and securinine.

Strychnine (Strichninum; powder; in ampoules of 1 ml of 0.1% solution) is the main alkaloid of chilibuhi seeds (vomiting nut).

In medical practice, the nitric acid salt - strychnine nitrate is used.

In addition to strychnine, dry chilibuhi extract and chilibuhi tincture are also used.

Convulsions caused by strychnine

Strychnine and other chilibuhi preparations excite the CNS and, first of all, increase reflex excitability. The patient's reflex reactions become more generalized. Strychnine improves the activity of the sense organs (sight, taste, hearing, tactile sensations), excites the vasomotor and respiratory centers, tones the skeletal muscles, myocardium.

Strychnine preparations are used as tonics for a general decrease in metabolic processes, rapid fatigue, hypotonic disease. weakening of cardiac activity due to intoxications and infections, for some functional disorders of the visual apparatus, for paresis and paralysis (of diphtheria origin, for example), for gastric atony.

Side effects occur with overdose and are manifested by tension of muscle groups (facial, occipital), difficulty breathing, convulsions.

The drug securinin, obtained from the herb securenega, is similar in nature to strychnine, but less active (10 times). Used for asthenic conditions, paresis and paralysis, hypo - and asthenic form of neurasthenia, impotence due to functional disorders.

GENERAL TONIZING MEDICINES (ADAPTOGENS)

The drugs of this group can be divided into plant and animal origin. The most commonly used are herbal remedies, namely various galenic preparations of plants (ginseng root extracts, levzeya extract, rhodiola rosea or golden root, eleutherococcus, tinctures of zamanikha, lemongrass, Transbaikal skullcap, aralia). Of the animal origin drugs, one can name the drug pantocrine, obtained from reindeer antlers, and is available as a neogalenic preparation for oral (in drops) and parenteral administration.

The pharmacological action of these drugs is due to the content of salonin glycosides-ginsenoids, essential oils, sterols, peptides and minerals. These biologically active substances have a stimulating effect on the central nervous system, increase performance, regulate the work of the endocrine glands, moderately reduce blood pressure, the level of atherogenic lipids (cholesterol) and glucose in the blood, activate the activity of the adrenal glands, The use of these drugs leads to a decrease in the incidence of acute respiratory infections, an increase in the patient's resistance to viral and other infections, an improvement in well-being and appetite.

These drugs are indicated for mental and physical overstrain during the period of convalescence after long and severe diseases, in particular, infectious nature (dysentery, typhoid and viral infections, etc.). The drugs are also prescribed to cancer patients in the rehabilitation period, after courses of chemotherapy and radiation exposure.

As a rule, drugs are prescribed for a long time, for 1-2 months. It is advisable to take adaptogens in the morning, after breakfast. The appointment of these funds in the afternoon is not indicated, since sleep disturbance in the form of difficulty falling asleep is possible. In some individuals, hypersensitivity to certain drugs may occur.

NARCOSIS is a condition characterized by reversible general depression of the CNS, manifested by loss of consciousness, decreased sensitivity (primarily pain), reflex reactions, muscle tone while maintaining vital functions (breathing, blood circulation, metabolism).

MECHANISMS OF ACTION of anesthetics are associated with the fact that they inhibit interneuronal (synaptic) transmission of excitation in the CNS. There is a violation of the transmission of afferent impulses, a change in cortical-subcortical relationships. Functional disintegration of the CNS occurs, associated with impaired synaptic transmission, causing the development of anesthesia.

The sequence of action of anesthetics on the CNS is as follows:

- cerebral cortex (consciousness);
- spinal cord (skeletal muscles);
- medulla oblongata (vital centers of respiration, blood circulation).

Synaptic formations of different levels of the CNS and different morphofunctional organization have different sensitivity to anesthetics. For example, synapses of the activating reticular formation of the brain stem are especially highly sensitive to anesthetics, while synapses of the medulla oblongata centers are most resistant to them. The difference in the sensitivity of synapses of different levels of the CNS explains the presence of certain stages in the action of general anesthetics.

CERTAIN STAGES OF ANESTHESIA ARE DISTINGUISHED, which are observed when using most anesthetic agents.

1st stage of analgesia, stunning, rausch-narcosis. Analgesia - loss of pain sensitivity. From the Greek. "an - denial, algos - pain. The stage of analgesia begins from the moment of

inhalation (if this is the route of administration) of the drug and continues until the patient loses consciousness. Thus, consciousness is preserved at this stage. Sensitivity is reduced, reflexes and muscle tone are preserved. Only superficial operations are possible at this stage: opening of a felon, abscess, tooth extraction, some obstetric operations (interventions).

2nd stage - the stage of excitement (delirium). It begins with loss of consciousness to the state of surgical anesthesia. At this stage, excitement, screaming, increased muscle activity, breath holding, tachypnea, hyperventilation may be observed. Consciousness is absent, reflexes and tone are all enhanced (there is a removal of the inhibitory function of the cerebral cortex).

The undesirable effects of this stage (motor excitement, increased tone of skeletal muscles, vomiting) can be minimized by correct premedication.

3rd stage - the stage of surgical anesthesia. There are 4 levels of this stage: 1st - superficial; 2nd - light; 3rd - deep; 4th - super-deep surgical anesthesia. As the dose of the drug increases, anesthesia deepens. Anesthesia during extensive surgical interventions is carried out at the 2nd-3rd levels of the 3rd stage. This stage is characterized by a gradual loss of reflexes, rhythmic breathing and relaxation of skeletal muscles. Lost reflexes. Practically the loss of the eyelid reflex and the development of rhythmic breathing indicate the beginning of surgical anesthesia. Finally, the 4th stage is the stage of paralysis or agonal stage. It is characterized by pronounced depression of the centers of the medulla oblongata. Gradually, complete paralysis of the respiratory muscles and diaphragm develops, breathing stops, which is accompanied by vasomotor collapse, - palpitations are stopped.

CLASSIFICATION OF ANESTHESIA MEDICINES

From the point of view of practical application, anesthetics are divided into 2 large groups:

1) agents for inhalation (through the lungs) anesthesia;

2) agents for non-inhalation anesthesia.

In turn, inhalation anesthetics are divided into:

- inhalation volatile liquids, this includes ether for anesthesia, fluorothane;

- gaseous anesthetics - nitrous oxide, cyclopropane.

Non-inhalation anesthetics include: thiopental sodium, sodium oxybutyrate, ketamine, propanidide, diprivan.

Let's analyze one of the main agents from the group of inhalation liquids - ether for anesthesia (Aether pro narcosi - 100 ml, 150 ml bottle).

The first inhalation general anesthetic - nitrous oxide - was discovered by Priestley in 1776, who accurately described effects caused by it. In 1846, Morton proved the possibility of using nitrous oxide for general anesthesia and demonstrated surgery under anesthesia (USA). In 1847, N. I. Pirogov widely used ether anesthesia in surgical practice. By chemical structure, it is diethyl ether. It is a colorless volatile liquid with a pungent odor and a boiling point at t = 35 degrees. Ether for anesthesia has a pronounced activity, a sufficient breadth of therapeutic action, and relatively low toxicity. It is one of the safest agents for anesthesia. It is an excellent general anesthetic with a wide range of action.

Advantages of the drug as a general anesthetic:

1) Ether for anesthesia has a pronounced activity, being a fairly strong anesthetic. When using ether, the stages of anesthesia are clearly expressed. The stage of analgesia is characterized by a decrease in pain sensitivity, which is associated with the suppression of

interneuronal transmission of excitation in afferent pathways and a decrease in the functional activity of neurons of the cerebral cortex; consciousness is preserved, orientation is impaired. Being an excellent general anesthetic, it allows some surgical manipulations to be performed even when using concentrations that do not provide complete surgical anesthesia (dislocation, exercise, childbirth, etc.).

2) Ether for anesthesia provides deep anesthesia. Causes surgical anesthesia without premedication.

3) Ether for anesthesia causes good muscle relaxation in the stage of surgical anesthesia, facilitates the operation. Myorelaxation is associated not only with the effect of ether on the central mechanisms of muscle tone regulation, but also with some of its suppressive effects on the neuromuscular structure. Causing a curarising effect on skeletal muscles, it provides sufficient muscle relaxation.

4) Possessing sufficient activity, ether, at the same time, has a wide range of action. From this it follows that ether is relatively safe for anesthesia even when used by inexperienced specialists.

5) Under the influence of ether, HELL does not change at levels 1 and 2 of stage 1 of surgical anesthesia and does not sensitize the myocardium to adrenaline, and therefore the drug does not provoke cardiac rhythm disturbances.

6) Slightly, in comparison with other general anesthetics, it suppresses breathing.

7) Ether is devoid of pronounced hepato- and nephrotoxicity.

8) Ether does not require the use of complex equipment (mask anesthesia).

9) Economically, ether is a cheap means of anesthesia.

DISADVANTAGES OF ETHER AS A MEANS OF ANESTHESIA

1) Ether anesthesia is characterized by a long stage of excitation (up to 20-30 minutes). Anesthesia under its influence occurs slowly and is sometimes accompanied by strong excitation and increased motor activity.

2) Unpleasant occurrence, namely suffocation, an unpleasant smell increase salivation and secretion of the bronchial mucosa, which is accompanied by coughing and laryngospasm, vomiting. There may even be reflex respiratory arrest, and the possibility of baroreceptor sensitization during ether anesthesia sometimes leads to reflex cardiac arrest.

3) After operations under ether anesthesia, atelectasis and pneumonia may develop (irritation, cooling of the lungs, dissolution of surfactant).

4) By activating the central links of the sympathoadrenal system and releasing adrenaline, it increases the heart rate (tachycardia).

5) The n. vagus is reflexively stimulated, which, in addition to cardiac arrest, can reduce the motor activity of the gastrointestinal tract.

6) Slow recovery (awakening) from anesthesia. In people suffering from alcoholism, tolerance to ether is observed, as a result of which anesthesia can be difficult.

7) The drug is unstable in light, so it is stored in dark glass; explosive.

INDICATIONS FOR USE:

1) mono-anaesthesia during operations on the abdominal organs;

2) mixed anesthesia (anaesthesia with a mixture: ether plus flurotan);

3) combined anesthesia (introductory anesthesia plus ether, plus muscle relaxants plus analgesics).

PHTHOROTHANUM (Phthorothanum) in orange glasses of 50 ml

ADVANTAGES:

1) high activity as a general anesthetic (3-4 times more than ether) ensures the achievement of the surgical stage of anesthesia;

2) anesthesia occurs quickly (3-5 minutes), with a short stage of excitation, which is weakly expressed;

3) anesthesia is easily controlled;

4) the patient wakes up after 5-10 minutes;

5) a significant breadth of action of Phthorothanum;

6) satisfactory muscle relaxation;

7) does not irritate the mucous membranes;

8) inhibits the function of the salivary, bronchial, gastric glands, relaxes the tone of the bronchi.

DISADVANTAGES: stimulates n. vagus, causes bradycardia (atropine is required). Special equipment is required. HELL reduces (inhibits the vasomotor center and sympathetic ganglia. Increases bleeding, and also has a direct myotropic effect on vessels. Causes cardiac arrhythmias, as it sensitizes the myocardium to adrenaline (noradrenaline, adrenaline, ephedrine, i.e. catecholamines cannot be administered; mezaton is required - alpha-adrenomimetic). In the postoperative period, it causes chills.

INDICATIONS FOR USE:

1) mononarcosis during operations on the organs of the thoracic and bronchial cavities;

2) combined anesthesia;

3) mixed anesthesia.

GASEOUS AGENTS

These include nitrous oxide, cyclopropane.

NITROUS OXIDE (laughing gas) is a practically non-toxic agent, does not have irritating properties. Does not have a negative effect on parenchymal organs. There are practically no side effects.

The disadvantage, in essence, is one - low activity. Causes anesthesia, surgical stage, only in concentrations of 94-95 percent in inhaled air. It is impossible to use such concentrations (hypoxia develops). In practical anesthesiology, therefore, a mixture of 80 percent nitrous oxide and 20% oxygen is used. There is no necessary depth of anesthesia, there is also no sufficient muscle relaxation. Only the initial level of the surgical anesthesia stage is achieved. Therefore, nitrous oxide is combined with other drugs, for example, flurotan, thereby obtaining an azeotropic mixture (an inseparable boiling mixture), as well as with muscle relaxants. Rapid awakening is noted.

INDICATIONS FOR USE:

1) pure nitrous oxide gas is prescribed for rausch anesthesia, i.e. for anesthesia during transportation (hip fracture, myocardial infarction, abscess opening);

2) and in combination with flurotan, as the main anesthesia for various major operations, with the addition of muscle relaxants for combined anesthesia (nitrous oxide plus flurotan plus muscle relaxant);

3) labor pain relief;

4) induction anesthesia.

MEDICINES FOR NON-INHALINGAL ANESTHESIA

These agents are usually used parenterally, rarely enterally. The most common route of

administration is intravenous.

By duration of action, drugs for intravenous anesthesia are classified as follows:

1) short-acting drugs (duration of anesthesia up to 15 minutes) - propanidide (sombrevin), ketamine (ketalar, calypsol), propofol (diprivan);

2) medium-acting drugs (duration of action - 20-50 minutes) - thiopental sodium, predion (viadril);

3) long-acting drugs (duration of action - 60 minutes or more) - sodium oxybutyrate.

1. PROPANIDIDE (epontol, sombrevin: in ampoules of 10 ml - 5% solution) very rapid onset of anesthesia (after 30-40 seconds) without an excitation stage. The stage of surgical anesthesia with a single injection of the drug into a vein lasts approximately 3 minutes, consciousness is restored after another 2-3 minutes. The short duration of action of the drug is explained by its hydrolysis by blood plasma cholinesterase. If administered intravenously, the time of surgical anesthesia can be significantly increased.

There are few side effects, most often these are allergic reactions. There is a moderate irritating effect, which is usually manifested by hyperemia and pain along the vein. Hyperventilation, slight tachycardia, slightly reduced blood pressure, muscle twitching may occur. Used for induction anesthesia and short-term operations. Convenient in outpatient practice, in dentistry (tooth extraction, acute pulpitis, especially if several teeth - drip intravenously), for taking a biopsy, setting dislocations, repositioning fragments, removing sutures, during catheterization, bronchoscopy, etc.).

2. KETAMIN (Ketaminum, bottles of 10 ml, 20 ml (synonyms: ketalar, calypsol) - solutions are used for IV and IM administration. Ketamine causes only general anesthesia and a mild hypnotic effect with partial loss of consciousness (a state similar to neuroleptanalgesia). It is very important that surgical anesthesia does not develop under the influence of ketamine. This condition is called "dissociative anesthesia". This means that substances such as ketamine inhibit some formations of the CNS and do not affect others, that is, there is a dissociation of their action.

Advantages:

1) wide therapeutic range;

2) rapid onset;

3) good analgesia.

With intravenous administration, the effect occurs after 30-60 seconds and lasts 5-10 minutes, and with intramuscular administration - after 2-6 minutes and lasts 15-30 minutes.

There is no muscle relaxation, involuntary movements of the limbs may be observed. Pharyngeal, laryngeal, cough reflexes are preserved. Blood pressure increases, pulse increases. Hypersalivation, laryngospasm may occur.

In the postoperative period, vivid but unpleasant dreams, psychomotor reactions, hallucinations are common (it is necessary to administer sibazon intravenously).

Used for:

1) induction of anesthesia (introductory);

2) for short-term painful manipulations (treatment of burn surfaces, cardiac catheterization and bronchoscopy), removal of foreign bodies, in dentistry (pulpitis, opening of phlegmon, etc.);

3) anesthesia during mass admission (in / m);

4) combined (fluorotan plus muscle relaxants), when performing a cesarean section.

Increases intraocular pressure, intracranial pressure.

DIPRIVAN (Diprivanum); international name - propofol. White aqueous isotonic emulsion for intravenous administration, 0.01 in 1 ml. Ultra-short-acting agent.

Pharmacological effects: this is an ultra-short-acting anesthetic with a rapid onset of effect (30 sec.) and rapid recovery from anesthesia.

Indications: a means for induction anesthesia, but also for maintenance (4-12 mg / kg / hour). It is necessary to combine with analgesics (low analgesic activity).

Side effects:

1) hypotension;

2) temporary apnea;

3) when recovering from anesthesia - nausea, vomiting, headache, urine color change, bronchospasm;

4) thrombosis, phlebitis.

Contraindications: intolerance, epilepsy (carefully!), with impaired cardiovascular system, kidneys, liver. Cannot be mixed with anything except dextrose and lidocaine.

3. THIOPENTAL-SODIUM - hypnotic and narcotic effects. When administered intravenously, it causes anesthesia in about 1 minute without an excitation stage. Duration of action - 20-30 minutes, quickly destroyed in the liver. Accumulates in large quantities in adipose tissue, insufficient muscle relaxation.

Since the IV route of administration, there is little opportunity to influence the nature of the action after administration, that is, such anesthesia is poorly controlled. The drug has a small therapeutic range, depresses breathing (barbiturate), a strong analgesic, weak muscle relaxation. Disadvantages: muscle twitching, laryngospasm, violation of the vagus nerve, increased secretion of glands.

Thiopental sodium should be administered very slowly, as there may be a sharp depression of the respiratory and vasomotor centers, as well as the heart (apnea, collapse).

Used for: 1) induction anesthesia and 2) short-term surgical interventions (as an independent agent). Premedication with atropine is necessary. Bemegrid is a thiopental antagonist.

4. PREDION or VIADRIL is a steroid, but does not have hormonal properties. Used for induction anesthesia, as its activity is low. Anesthesia in 5-15 minutes without the stage of excitation. Duration - 20-30 minutes. Good muscle relaxation. Non-toxic. The main side effect of predion is an irritating effect (damage to the vascular endothelium, thrombosis, thrombophlebitis).

5. SODIUM OXYBUTYRATE - (in ampoules of 10 ml of a 20% solution) a synthetic analogue of a natural metabolite of the CNS. GABA is a natural inhibitory mediator, and GHB, i.e. sodium oxybutyrate is its analogue (instead of the amino group there is a hydroxyl group). It exhibits a sedative, hypnotic, antihypoxic effect and causes anesthesia. The surgical stage of anesthesia occurs 30-40 minutes after intravenous administration. Therefore, it is well used in the form of rectal suppositories. When combined with other anesthetics and analgesics (weak analgesic activity), it increases their activity. Causes pronounced muscle relaxation. Its activity is insufficient, so it is administered in large doses (2.0-4.0). The stage of surgical anesthesia occurs after 30-40 minutes. The duration of anesthesia is 1.5-3 hours. Can be used enterally (orally and rectally). Used for induction and combined anesthesia, for labor pain relief, for hypoxic cerebral edema, as an antishock agent.

ANALGESIC (PAIN RELIEF)

These drugs selectively reduce and suppress pain sensitivity, without significantly affecting other types of sensitivity and without disturbing consciousness (analgesia - loss of pain sensitivity; an - denial, algos - pain). Doctors have long tried to relieve the patient from pain. Hippocrates 400 years BC wrote: "... the removal of pain is a divine work." Based on the pharmacodynamics of the corresponding drugs, modern painkillers are divided into 2 large groups:

I-I - narcotic analgesics or morphine group. This group of drugs is characterized by the following points (conditions):

1) have strong analgesic activity, which allows them to be used as highly effective painkillers;

2) these drugs can cause drug addiction, that is, addiction, drug dependence associated with their specific effect on the CNS, as well as the development of a painful condition (withdrawal) in people with developed addiction;

3) in case of overdose, the patient develops a deep sleep, which gradually passes into anesthesia, coma and, finally, ends with the cessation of the respiratory center. That is why they got their name - narcotic analgesics.

The second group of drugs is non-narcotic analgesics, the classic representatives of which are: aspirin or acetylsalicylic acid. There are many drugs here, but they are not addictive, since they have different mechanisms of action.

Let's analyze the first group of drugs, namely drugs of the morphine group or narcotic analgesics.

Narcotic analgesics have a pronounced depressing effect on the central nervous system. Unlike drugs that depress the CNS indiscriminately, it has an analgesic, moderately hypnotic, antitussive effect, and suppresses the respiratory centers. In addition, most narcotic analgesics cause drug (mental and physical) dependence.

The most prominent representative of this group of drugs, from which this group got its name, is MORPHINE.

Morphini hydrochloridum (tablet 0.01; amp. 1% - 1 ml). The alkaloid morphine is isolated from opium (Greek - opos - juice), which is the frozen, dried juice of unripe pods of the sleeping poppy (Papaver somniferum). The homeland of the poppy is Asia Minor, China, India, Egypt. Morphine got its name from the name of the ancient Greek god of dreams Morpheus, who is, according to legend, the son of the god of sleep Hypnos.

Morphine in opium contains 10-11%, which is almost half of all the alkaloids present in it (20 alkaloids). They have been used in medicine for a long time (5000 years ago as: an analgesic, antidiarrheal). Despite the synthesis of morphine by chemists in 1952, it is still obtained from opium, which is cheaper and easier.

According to the chemical structure, all pharmacologically active opium alkaloids belong either to PHENANTHREN derivatives or to ISOQUINOLINE derivatives. The alkaloids of the phenanthrene series include: morphine, codeine, thebaine, etc. It is the phenanthrene alkaloids that are characterized by a pronounced depressing effect on the CNS (analgesic, antitussive, hypnotic, etc.).

Isoquinoline derivatives are characterized by a direct antispasmodic effect on smooth muscles. A typical isoquinoline derivative is papaverine, which has no effect on the CNS, but affects smooth muscles, especially in a state of spasm. Papaverine acts in this case as an

antispasmodic.

PHARMACOLOGICAL PROPERTIES OF MORPHINE

1. The effect of morphine on the CNS

1) Morphine primarily has an analgesic or analgesic effect, while the analgesic effect is exerted by doses that do not significantly change the functions of the CNS.

Analgesia caused by morphine is not accompanied by slurred speech, impaired coordination of movements, touch, vibration sensitivity, and hearing are not weakened. The analgesic effect is the main one for morphine. In modern medicine, it is one of the strongest painkillers. The effect is noticeable a few minutes after injection. More often, morphine is administered intramuscularly, subcutaneously, but it can also be administered intravenously. The effect lasts 4-6 hours.

As is known, pain consists of 2 components:

a) perception of pain, which depends on the threshold of pain sensitivity of a person;

b) mental, emotional reaction to pain.

In this regard, it is important that morphine sharply suppresses both components of pain. First, it increases the threshold of pain sensitivity, thus reducing the perception of pain. The analgesic effect of morphine is accompanied by a feeling of well-being (euphoria).

Secondly, morphine changes the emotional reaction to pain. In therapeutic doses, it may not even completely eliminate the feeling of pain, but patients perceive it as something extraneous.

How and in what way does morphine exert these effects?

MECHANISM OF ACTION OF NARCOTIC ANALGESIC DRUGS.

In 1975, Hughes and Kosterlitz discovered specific "opiate receptors of several types in the nervous system of humans and animals, with which narcotic analgesics interact.

Currently, 5 types of these opiate receptors are distinguished: mu, delta -, kappa, sigma, epsilon.

It is with these opiate receptors that various endogenous (produced in the body itself) peptides with high analgesic activity normally interact. Endogenous peptides have a very high affinity for these opiate receptors. The latter, as it became known, are located and function in various parts of the CNS and peripheral tissues. Due to the fact that endogenous peptides have high affinity, they are also called LIGANDS in the literature in relation to opiate receptors, that is, (from the Latin - ligo - bind) they directly bind to receptors.

There are several endogenous ligands, they are all oligo-peptides containing different numbers of amino acids and united under the name "ENDORPHINS" (i.e. endogenous morphines). Peptides, which include five amino acids, are called enkephalins (methionine-enkephalin, lysine-enkephalin). Currently, this is a whole class of 10-15 substances that have from 5 to 31 amino acids in their molecule.

Enkephalin, Hughes, Kosterlitz - these are "substances in the head".

Pharmacological effects of enkephalins:

- release of pituitary hormones;
- change in memory;
- regulation of breathing;
- modulation of the immune response;
- analgesia;
- a state similar to catatonia;

- convulsive attacks;
- regulation of body temperature;
- control of appetite;
- reproductive functions;
- sexual behavior;
- reactions to stress;
- lowering blood pressure.

MAIN BIOLOGICAL EFFECTS OF ENDOGENIC OPIATES

The main effect, role, biological function of endorphins is the inhibition of the release of "pain neurotransmitters" from the central endings of afferent unmyelinated C-fibers (including noradrenaline, acetylcholine, dopamine).

As is known, these pain mediators can be, first of all, substance P (a peptide of amino acids), cholecystokinin, somatostatin, bradykinin, serotonin, histamine, prostaglandin. Pain impulses spread along C - and A-fibers (A-delta fibers) and enter the posterior horns of the spinal cord.

When pain occurs, a special system of enkephalinergic neurons is normally stimulated, the so-called antinociceptive (anti-pain) system is released neuropeptides, which have an inhibitory effect on the pain system (nociceptive) of neurons. The final result of the action of endogenous peptides on opiate receptors is an increase in the pain threshold.

Endogenous peptides are very active, they are hundreds of times more active than morphine. Currently, they are isolated in pure form, but in very small quantities, are very expensive, while they are mainly used in experiments. But there are already results in practice. For example, the domestic peptide DALARGIN has been synthesized. The first results have been obtained, and already in the clinic.

In case of insufficiency of the antinociceptive system (antipain enkephalinergic), and this happens with excessively pronounced or prolonged harmful effects, pain sensations have to be suppressed with the help of painkillers - analgesics. It turned out that the site of action of both endogenous peptides and exogenous narcotic drugs is the same structures, namely opiate receptors of the nociceptive (pain) system. In this regard, morphine and its analogues are agonists of opiate receptors. Certain endo - and exogenous morphines affect various opiate receptors.

In particular, morphine acts mainly on mu-receptors, enkephalins on delta-receptors, etc. ("responsible" for analgesia, respiratory depression, reduction of the heart rate, immobilization).

Thus, narcotic analgesics, in particular morphine, playing the role of endogenous opiate peptides, being essentially imitators of the action of endogenous ligands (endorphins and enkephalins), increase the activity of the antinociceptive system and enhance the inhibitory effect on the pain system.

In addition to endorphins, serotonin and glycine function in this antinociceptive system, they are synergists of morphine. Acting mainly on mu receptors, morphine and other drugs of this group mainly suppress aching, pulling pain associated with the summation of nociceptive impulses coming from the spinal cord along a nonspecific path to the nonspecific nuclei of the thalamus, disrupting its spread to the upper frontal, parietal gyri of the cerebral cortex (i.e., pain perception), as well as to other parts of it, in particular, to the hypothalamus, amygdala complex, in which vegetative, hormonal, emotional reactions to pain are formed.

Suppressing this pain, drugs inhibit the emotional reaction to it, as a result of which narcotic analgesics prevent dysfunction of the cardiovascular system, the emergence of fear, suffering associated with pain. Strong analgesics (fentanyl) are able to suppress the conduction of excitation along a specific nociceptive pathway.

Exciting enkephalin (opiate) receptors in other brain structures, endorphins and narcotic analgesics affect sleep, wakefulness, emotions, sexual behavior, and epileptic convulsive reactions, vegetative functions. It turned out that almost all known neurotransmitter systems are involved in the implementation of the effects of endorphins and morphine-like drugs.

Hence the various other pharmacological effects of morphine and its drugs. So, the 2nd effect of morphine, a sedative and hypnotic effect. The sedative effect of morphine is very clearly expressed. Morpheus is the son of the god of sleep. The sedative effect of morphine consists in the development of drowsiness, some darkening of consciousness, impaired ability to logical thinking. Patients wake up easily from sleep caused by morphine. The combination of morphine with hypnotics or other sedatives makes the CNS depression more pronounced.

The 3rd effect is the effect of morphine on mood. Here the effect is twofold. In some patients, and more often in healthy individuals, after a single administration of morphine, a feeling of dysphoria, anxiety, negative emotions, no pleasure, and a decrease in mood occurs. As a rule, this occurs in healthy individuals who have no indications for the use of morphine.

With repeated administration of morphine, especially in the presence of indications for the use of morphine, the phenomenon of euphoria usually develops: an increase in mood occurs with a feeling of bliss, lightness, positive emotions, and pleasantness throughout the body. Against the background of drowsiness, reduced physical activity, difficulty concentrating develops, and a feeling of indifference to the surrounding world arises.

A person's thoughts and judgments lose their logical consistency, imagination becomes fantastic, bright colorful pictures and visions appear (the world of dreams, "high"). The ability to engage in art, science, and creativity is lost.

The occurrence of the listed psychotropic effects is due to the fact that morphine, like other analgesics of this group, directly interacts with opiate receptors located in the cerebral cortex, hypothalamus, hippocampus, and amygdala.

The desire to experience this state again is the cause of a person's mental dependence on the drug. Thus, it is euphoria that is responsible for the development of drug addiction. Euphoria can occur even after a single injection.

The 4th pharmacological effect of morphine is associated with its effect on the hypothalamus. Morphine suppresses the thermoregulation center, which can lead to a sharp decrease in body temperature in case of morphine poisoning. In addition, the effect of morphine on the hypothalamus is also associated with the fact that it, like all narcotic analgesics, stimulates the release of antidiuretic hormone, which leads to urinary retention. In addition, it stimulates the release of prolactin and somatotropin, but delays the release of luteinizing hormone. Under the influence of morphine, appetite decreases.

5th effect - morphine, like all other drugs of this group, has a pronounced effect on the centers of the medulla oblongata. This action is ambiguous, since it excites a number of centers, and inhibits a number.

Suppression of the respiratory center occurs most easily in children. Suppression of the respiratory center is associated with a decrease in its sensitivity to carbon dioxide.

Morphine inhibits the central links of the cough reflex and has a pronounced inherent antitussive activity.

Narcotic analgesics, like morphine, can contribute to the stimulation of neurons of the chemoreceptor trigger zone of the bottom of the IV ventricle, causing nausea and vomiting. Morphine itself suppresses the vomiting center in large doses, so repeated administration of morphine does not cause vomiting. In this regard, the use of emetics in morphine poisoning is useless.

6th effect - the effect of morphine and its preparations on blood vessels. Therapeutic doses have a slight effect on the HELL and heart, toxic doses can cause hypotension. But morphine causes dilation of peripheral blood vessels, especially capillaries, partly due to direct action and partly due to the release of histamine. Thus, it can cause redness of the skin, an increase in its temperature, swelling, itching, sweating.

EFFECT OF MORPHINE ON THE GASTROINTESTINAL Tract and OTHER SMOOTH MUSCLE ORGANS

The effect of narcotic analgesics (morphine) on the gastrointestinal tract is attributed mainly to their increased activity of neurons of the center n. vagus, and to a lesser extent due to a direct effect on the nerve elements of the wall of the gastrointestinal tract. In this regard, morphine causes a strong spasm of the smooth muscles of the intestine, imocecal and anal sphincters and simultaneously reduces motor activity, reducing peristalsis (gastrointestinal tract). The spasmogenic effect of morphine is most pronounced in the duodenum and colon. The secretion of saliva, hydrochloric acid of gastric juice and the secretory activity of the intestinal mucosa are reduced. The passage of feces is slowed down, the absorption of water from them increases, which leads to constipation (morphine constipation - an increase in the tone of all 3 muscle groups). Morphine and its analogues increase the tone of the gallbladder, contribute to the development of spasm of the sphincter of Oddi. Therefore, although the analgesic effect alleviates the patient's condition with biliary colic, during the pathological process itself it intensifies.

THE EFFECT OF MORPHINE ON OTHER SMOOTH MUSCLE FORMATIONS

Morphine increases the tone of the uterus and bladder, ureters, which is accompanied by "urinary urgency". At the same time, the visceral sphincter is reduced, which, with insufficient response to urges from the bladder, leads to urinary retention.

Morphine increases the tone of the bronchi and bronchioles.

INDICATIONS FOR THE USE OF MORPHINE

1) Acute pain that threatens the development of pain shock. Examples: severe trauma (fractures of tubular bones, burns), relief of the postoperative period. In this case, morphine is used as an analgesic, anti-shock agent. For the same purpose, morphine is used for myocardial infarction, pulmonary embolism, acute pericarditis, spontaneous pneumothorax. To relieve suddenly occurring pain, morphine is administered intravenously, which quickly reduces the risk of developing shock.

In addition, morphine is used as an analgesic for colic, for example, intestinal, renal, hepatic, etc. However, it is important to remember that in this case, morphine is administered together with the antispasmodic atropine, and only when the doctor is absolutely sure of the correctness of the diagnosis.

2) Chronic pain in hopeless dying patients with a humane purpose (example: hospices - hospitals for hopeless cancer patients; admission by the hour). In fact, chronic pain is a

contraindication to the use of morphine. Only in hopeless, dying tumor patients, doomed, is the administration of morphine mandatory.

3) As a means of premedication during anesthesia, before anesthesia, that is, in anesthesiology.

4) As an antitussive for cough that threatens the patient's life. According to this indicator, morphine is prescribed, for example, for major operations, chest injuries.

5) In acute left ventricular failure, that is, for cardiac asthma. In this case, the effect is due to a decrease in the excitability of the CNS and pathological shortness of breath. It causes peripheral vasodilation, resulting in a redistribution of blood from the pulmonary artery system to the dilated peripheral vessels. This is accompanied by a decrease in blood flow and a decrease in pressure in the pulmonary artery and CVT. Thus, the work of the heart decreases.

6) In acute pulmonary edema.

SIDE EFFECTS OF MORPHINE

The breadth of pharmacological effects of morphine also determines its numerous side effects. These are, first of all, dysphoria, constipation, dry mouth, confusion, dizziness, nausea and vomiting, respiratory depression, headache, increased fatigue, paresthesia, bradycardia. Sometimes intolerance in the form of tremor and delirium, as well as allergic reactions, occurs.

CONTRAINDICATIONS TO THE USE OF MORPHINE

There are no absolute ones, but there is a whole group of relative contraindications:

1) early childhood (up to 3 years old) - the risk of respiratory depression;

2) in pregnant women (especially at the end of pregnancy, during childbirth);

3) with various types of respiratory failure (emphysema, bronchial asthma, kyphoscoliosis, obesity);

4) with severe head injuries (increased intracranial pressure; in this case, morphine, further increasing intracranial pressure, causes vomiting; vomiting, in turn, increases intracranial pressure and thus a vicious circle is formed).

In our country, a very powerful analgesic with a long-lasting effect has been created based on morphine - MORPHILONG. It is a new drug containing morphine hydrochloride and narrowly fractionated polyvinylpyrrolidone. As a result, Morphilong acquires a long duration of action (its analgesic effect lasts 22-24 hours) and a greater intensity of the effect. Side effects are less pronounced. This is its advantage over morphine (its duration is 4-6 times greater than the duration of morphine). It is used as a prolonged analgesic:

1) in the postoperative period;

2) with severe pain syndrome.

OMNOPON (Omnoponum in ampoules of 1 ml - 1% and 2% solution). Omnopon is a new galenic preparation of opium in the form of a mixture of 5 opium alkaloids. It contains 48-50% morphine and 32-35% other alkaloids of both the phenanthrene and isoquinoline series (papaverine). In this regard, omnopon has a less spasmogenic effect. In principle, the pharmacodynamics of omnopon is similar to that of morphine. However, omnopon is still used together with atropine. The indications for use are practically the same.

In addition to morphine, omnopon has been used in medical practice by many synthetic and semi-synthetic drugs. These drugs were created with 2 goals:

1) to get rid of poppy plantations;

2) so that patients do not develop addiction. But this goal was not achieved, since all narcotic analgesics have common mechanisms of action (through opiate receptors).

Of considerable interest is PROMEDOL, which is a synthetic drug, a derivative of piperidine.

Promedolum (tablet - 0.025; amp. 1 ml - 1% and 2% solution). In terms of analgesic activity, it is inferior to morphine by 2-4 times. Duration of action is 3-4 hours. It causes nausea and vomiting less often, and suppresses the respiratory center to a lesser extent. Unlike morphine, promedol reduces the tone of the urinary tract and bronchi, relaxes the cervix and slightly increases the contraction of the uterine wall. In this regard, promedol is preferred for colic. In addition, it can be used during childbirth (according to indications, since it suppresses fetal breathing to a lesser extent than morphine, and also relaxes the cervix). In 1978, a synthetic analgesic appeared - MORADOL, which is a derivative of phenanthrene in its chemical structure. A similar synthetic drug is TRAMAL. MORADOL (butorphanol tartrate) when administered intramuscularly and intravenously provides a high degree of analgesic efficacy, while analgesia occurs faster than with morphine administration (after 30-60 minutes, morphine - after 60 minutes). The effect lasts 3-4 hours. At the same time, it has significantly fewer side effects and, most importantly, a very low risk of developing physical dependence even with prolonged use, since moradol rarely causes euphoria (it acts mainly on other opiate delta receptors). In addition, it has limited respiratory depression, even in large doses. Use: for the same indications as morphine, but in cases of prolonged need for use. In therapeutic doses, it does not suppress the respiratory center, safe for the mother and fetus. Another synthetic representative of piperidine-phenanthrene derivatives is FENTANYL. Fentanyl has a very high analgesic activity, surpassing morphine in activity (100-400 times). A distinctive feature of fentanyl is the short duration of the pain relief it causes (20-30 minutes). The effect develops after 1-3 minutes. Therefore, fentanyl is used for neuroleptanalgesia together with the neuroleptic droperidol (talomonal).

This type of analgesia is used when the patient must be conscious, for example, with myocardial infarction. The form of analgesia itself is very convenient, since the patient does not react to painful irritation (analgesic effect) and is completely indifferent to everything that happens (neuroleptic effect, consisting of supersedative and strong tranquilizer).

The opium alkaloid CODEINE stands out (Codeinum in tab. 0.015). As an analgesic, it is much weaker than morphine. It has a weak affinity for opiate receptors. The antitussive effect of codeine is weaker than that of morphine, but quite sufficient for practice.

Advantages of codeine:

1) unlike morphine, it is well absorbed when taken orally;

2) codeine is less depressant of breathing;

3) causes less drowsiness;

4) has less spasmogenic activity;

5) addiction to codeine develops more slowly.

INDICATIONS FOR THE USE OF CODEINE:

1) for dry, hacking, unproductive cough;

2) the second stage of combating chronic pain in cancer patients (WHO), according to the three-stage scheme. Codeine (50-150 mg after 5 hours) plus a non-narcotic analgesic, plus adjuvants (glucocorticoids, antidepressants, anticonvulsants, psychotropics, etc.).

ACUTE POISONING WITH MORPHINE AND MORPHINE-LIKE DRUGS

Acute poisoning with morphine can occur with an overdose of the drug, as well as with accidental intake of large doses in patients with addiction. In addition, morphine can be used for suicidal purposes. For adults, the lethal dose is 250 mg.

In acute morphine poisoning, the clinical picture is characteristic. The patient's condition is very serious. Sleep develops first, passes into the stage of narcosis, then coma, leading to paralysis of the respiratory center.

The clinical picture consists primarily of respiratory depression, its reduction. The skin is pale, cold, cyanotic. There is a decrease in body temperature and urination, at the end of poisoning - a decrease in blood pressure. Bradycardia develops, a sharp narrowing of the pupil (point size of the pupil), at the end from hypoxia the pupil expands. Death occurs due to respiratory depression or shock, pulmonary edema and secondary infection.

TREATMENT of patients with acute morphine poisoning is based on the same principles as the treatment of acute barbiturate intoxication. Assistance measures are divided into specific and non-specific.

SPECIFIC ASSISTANCE MEASURES are associated with the administration of specific morphine antagonists. The best antagonist is NALOXONE (narcan). In our country, there is practically no naloxone, and therefore a partial antagonist - NALORPHINE is more often used.

Naloxone and nalorphine eliminate the effect of morphine and its preparations on opiate receptors and restore normal CNS function.

Nalorphine, a partial antagonist of morphine, in its pure form (monodrug) acts like morphine (causes an analgesic effect, but weaker, depresses breathing, causes bradycardia, constricts the pupils). But against the background of the administered morphine, nalorphine manifests itself as its antagonist. Nalorphine is usually used intravenously in a dose of 3 to 5 mg, repeating the injection after 30 minutes if necessary. Its effect literally occurs at the "tip of the needle" - within the first minute of administration. In case of an overdose of these drugs, a person poisoned by morphine may quickly develop withdrawal syndrome.

NON-SPECIFIC MEASURES OF AID are associated with the removal of unabsorbed poison. Moreover, gastric lavage should be performed even with parenteral administration of morphine, since partial secretion of the gastrointestinal mucosa into the intestinal lumen occurs. The patient must be warmed, and if convulsions occur, anticonvulsants are used.

In case of deep respiratory depression, artificial ventilation of the lungs is performed.

CHRONIC MORPHINE POISONING is usually associated with the development of dependence on it. The development of addiction and drug addiction is naturally accompanied by repeated administration of narcotic analgesics. Physical and mental dependence are distinguished.

Manifestations formed ADDICTION to narcotic analgesics is the occurrence of withdrawal syndrome or abstinence when stopping repeated administration of morphine. The withdrawal syndrome consists of a number of characteristic signs: 6-10-12 hours after the last injection of morphine, the morphine user experiences rhinorrhea, lacrimation, terrible yawning, chills, goosebumps, hyperventilation, hypothermia, mydriasis, muscle pain, vomiting, diarrhea, tachycardia, weakness, sweating, sleep disorders, hallucinations, anxiety, restlessness, aggressiveness. These symptoms last for 2-3 days. To prevent or eliminate these phenomena, the addict is ready to do anything, even a crime. Constant use of the drug leads a person to physical and mental degradation.

The mechanism of development of abstinence is connected with the fact that narcotic analgesics, activating opiate receptors on the principle of feedback (as in endocrinology), inhibit the release, and perhaps the synthesis of endogenous opiate peptides, gradually replacing their activity. As a result of the abolition of analgesics, a deficiency occurs and an analgesic and endogenous peptide are introduced earlier. The abstinence syndrome develops.

Mental dependence develops earlier than physical dependence. The basis of the emergence of mental dependence is euphoria, a sedative effect and an indifferent attitude to the disturbing effects of the external environment. In addition, repeated administration of morphine causes very pleasant sensations in the abdominal cavity for the morphine user, a feeling of unusual warmth in the epigastric region and lower abdomen, reminiscent of those during intense orgasm.

In addition to mental and physical dependence, there is a 3rd sign of drug addiction - the development of tolerance, resistance, and habituation. In this regard, the addict is constantly forced to increase the dose of the analgesic.

Treatment of morphine addiction is fundamentally no different from the treatment of alcohol or barbiturate addiction. Treatment of drug addicts is carried out in special institutions, but the results are not yet encouraging (a few percent). The development of withdrawal syndrome (abstinence), relapses of addiction are frequent.

There is no special remedy. General tonics and vitamins are used. It is easier to prevent drug addiction than to treat it. The danger of drug addiction is the main reason for limiting the use of these drugs in medicine. They are dispensed from pharmacies only by special prescriptions, the drugs are stored on list "A".

NON-NARCOTIC ANALGESIC - these are painkillers, analgesia drugs that do not have a significant effect on the central nervous system, do not cause drug addiction and anesthesia. In other words, unlike narcotic analgesics, they do not have a sedative and hypnotic effect; euphoria, addiction and drug dependence do not occur when they are used.

Currently, a large group of drugs has been synthesized, among which the so-called:

1) old or classic non-narcotic analgesics

2) new, more modern and to a greater extent possessing anti-inflammatory action - the so-called non-steroidal anti-inflammatory drugs - NSAIDs.

2. Questions for self-control (list of questions):

1. Explain the pathogenesis of the harmful effects of stress on the CNS, cardiovascular system and internal organs.

2. Identify ways of protection and pharmacological correction of the psychosomatic reaction of a person during acute and chronic stress.

3. Formulate the main pathogenetic mechanisms of the development of mental disorders in patients with severe vascular and somatic pathology.

4. Name the drugs used in the treatment of somatogenic psychoses and depressions.

5. List the drugs that increase the memory functions and adaptive capabilities of the brain.

6. List the indications for the appointment, the rules for choosing and determining the dosage regimen of sedatives, tranquilizers, neuroleptics, antidepressants and nootropics.

7. What are the basic principles of treating patients with psychoneurological disorders.

8. What are the principles of classifying psychotropic drugs?

9. Why are neuroleptics used mainly for psychoses, and tranquilizers are used more often for neuroses? Which of them have antiarrhythmic and muscle relaxant effects?

10. What drugs are used for neuroleptanalgesia, premedication before anesthesia?

11. Why are MAO inhibitors incompatible with some foods?

12. What classes of drugs can be classified as hypnotics?

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for basic drugs that affect the functions of the nervous system (tablets and/or ampoules), indicate possible use, the spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable combinations of drugs.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and a list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. Identify signs during subjective and objective examination of the patient that characterize damage to the nervous system, write a clinical diagnosis of the disease.

5. Determine the group of drugs needed by the patient; based on theoretical pharmacodynamic data and own observations, choose a drug for the patient.

6. Choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. Highlight clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. Substantiate the need for combined drug therapy and suggest 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 their detection at the early stages.

10. Substantiate the duration of basic and maintenance therapy.

B. Solution of situational tasks.

1. A 31-year-old patient, weighing 72 kg, suffers from neurocirculatory dystonia of a mixed cerebral-cardiac, hypertensive type. Complaints of increased irritability, insomnia, frequent headaches, feeling of lack of air, pain in the heart area, tachycardia. Objectively: HR - 90 in 1 min, ACD - 140/90 mm Hg, extremities pale, cold. Laboratory and instrumental examination data allow to exclude organic lesions of the CNS and cardiovascular system.

Prescribe a drug from the class of psychotropic drugs, justify your choice and administration regimen.

2. A patient, 47 years old, weighing 82 kg, suffers from stage II hypertension. Against the background of a hypertensive crisis with ACD - 240/140 mm Hg and HR - 98 in 1 min, an acute violation of coronary circulation in the anterior wall of the left ventricle developed. The

patient is excited, not adequate.

Assign correction of psychomotor agitation of this patient, indicating the drug, its dose and route of administration.

3. A 58-year-old patient, weighing 53 kg, suffers from a hypertensive form of chronic pyelonephritis. Against the background of chronic alcoholism, a subarachnoid hemorrhage occurred. On the second day of hospitalization, delirium developed. The patient is excited, gets up, resists attempts to examine and continue treatment, and curses.

Which of the PLZs would you choose to stop delirium in this patient? Specify the dose and route of administration.

4. A patient, 80 years old, is being treated in the neurological department for severe widespread atherosclerosis with predominant damage to the cerebral vessels, dyscirculatory encephalopathy of the II degree. In the complex of therapeutic measures, he receives therapy: Cavinton 2 ml intravenously drip in the morning, Piracetam 400 mg 3 times a day (at 9.00, 14.00 and 21.00), Cerebrolysin 1.0 ml intramuscularly - in the afternoon. The patient complains of worsening night sleep.

Which of the prescribed drugs can be associated with insomnia? Make a correction to the therapy.

5. A 13-year-old girl, after a quarrel with her parents, took 30 tablets of Relanium with suicidal intent. She was taken to the hospital 2 hours after the incident in a state of deep stupor.

Give a prognosis for the clinical course of poisoning. What vital functions should be monitored first? Make a complete plan of treatment measures to save the teenager's life.

6. A patient with manic-depressive psychosis receives haloperidol (0.0015 g 2 times a day), aminazine (0.025 g 3 times a day), azafen (0.025 1 time a day) as part of complex therapy. 2 weeks after the start of treatment, he developed abdominal pain, body temperature 370C, and yellow skin.

Your opinion regarding this patient's condition. Your recommendations. Justify your answer.

7. A 48-year-old unemployed man was treated for alcohol-induced depression for a long time. Then he developed hypertension and was prescribed one of the traditional antihypertensive drugs that act slowly. During the treatment, he developed a persistent long-term deterioration in mood (feelings of sadness, hopelessness, despair). One day he committed suicide. Could the medication he was taking have caused these symptoms? If so, which one?

8. Opioids: agonists and antagonists. It was decided to prescribe an opioid analgesic to a woman for labor pain relief. Which substance would be best in this case? What measures should be taken? What should be prescribed in case of an accidental overdose of an opioid analgesic?

9. Patient S., 40 years old, had a complication during surgery for gallstone disease under halothane anesthesia - malignant hyperthermia. What is the best remedy for weakening muscle rigidity, characteristic of this syndrome?

10. The patient is undergoing inpatient treatment for schizophrenia. He receives haloperidol. By the end of the 1st month of treatment, the patient's condition has noticeably improved, delusional-hallucinatory symptoms have practically disappeared, but there have been complaints of tremor, stiffness of movements. An objective examination shows

increased skeletal muscle tone. What complication has developed in the patient, the mechanism of its development? The doctor's tactics? Which drugs from this group practically do not cause this complication?

11. The patient is undergoing inpatient treatment for depression, receives amitriptyline. As a result of treatment, the condition has improved somewhat, but there have been complaints of dry mouth, visual impairment (difficulty in viewing nearby objects), constipation, urinary retention. What is the cause of these symptoms? What drugs from this group of antidepressants could be offered as an alternative to amitriptyline? Representatives of some other subgroups of antidepressants practically do not cause these side effects?

12. A patient was admitted to the hospital with cirrhosis of the liver. The history includes chronic alcoholism and hospitalization for alcohol-related seizures. 1) What should the doctor prescribe to prevent possible seizures caused by alcohol withdrawal syndrome?

Test tasks for self-control:

1. A patient was admitted to the hospital with cirrhosis of the liver. The history includes chronic alcoholism and hospitalization for alcohol-related seizures. Choose from the following drugs:

A. phenytoin (diphenin),

B. teturam,

C. chlordiazepoxide (elenium),

D. phenobarbital,

E. thiopental.

2. A 50-year-old man was hospitalized in the intensive care unit with acute transmural myocardial infarction of the posterior diaphragmatic region of the left ventricle. Which drug is least indicated for administration?

A. Nifedipine.

B. Nitroglycerin.

C. Propranolol.

D. Fentanyl.

E. Morphine.

3. A sixty-year-old patient suffering from hypertension and obesity feels weakness in the right limbs, which increases during the day. The previous three days were observed short-term speech disorders. Objectively: partial motor and sensory aphasia, right-sided spastic hemiparesis. What group of drugs should be prescribed to the patient to prevent the development of ischemic stroke?

A. Group B vitamins.

B. Lipotropic drugs.

C. Anticonvulsants.

D. Vasodilators.

E. Tranquilizers.

4. A 2-year-old boy, who has been ill with acute pneumonia with toxic syndrome for 3 days, developed tonic-clonic convulsions against the background of an increase in body temperature to 40oC. What first aid measure should be carried out first?

A. Mannitol 20% solution intravenously drip.

B. Magnesium sulfate 25% solution intravenously.

C. Hexenal 5% solution intravenously.

D. Seduxen 0.5% solution intramuscularly.

E. Droperidol 0.25% solution intravenously or intramuscularly.

5. Drug addicts develop severe mental, neurological and somatic disorders after the drug has stopped working. What is this symptom complex called?

A. Idiosyncrasy

B. Cumulation

C. Sensitization

D. Withdrawal syndrome

E. Tolerance

6. A patient receiving clonidine for the treatment of hypertension developed signs of severe central nervous system depression while drinking alcohol. What could this be due to?

A. Idiosyncrasy

B. Summation of effects

C. Cumulation

D. Potentiation of effects

E. Intoxication

7. In complex therapy for chronic heart failure, the patient was prescribed an analeptic, which also has a direct cardiostimulating and expectorant effect. This drug can also be used externally for rubbing in arthritis. Identify this drug.

A. Bemegrid

B. Cordiamin

C. Ethimizol

D. Caffeine

E. Camphor

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

TOPIC
"Clinical and pharmacological characteristics of drugs used to treat endocrine diseases"

Purpose:

To learn the pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics of the main groups of drugs used in endocrinology:

- insulin preparations;
- sulfonylurea derivatives;
- biguanides;
- thyroid and antithyroid drugs.

To learn the principles of pharmacotherapy of diabetic complications and urgent conditions in thyroid diseases (thyrotoxic crisis).

Basic concepts (list of questions):

1. Pancreas: anatomical and physiological features.
2. Thyroid gland: anatomical and physiological features.
3. Pancreatic hormones: physiology and pathology.
4. Thyroid hormones: physiology and pathology.
5. Diabetes mellitus: classification, approaches to pharmacotherapy.
6. Hypo- and hyperfunction of the thyroid gland: classification, approaches to pharmacotherapy.
7. The main groups of drugs used in endocrinology, their clinical and pharmacological characteristics.

Plan

1. Theoretical questions:

The World Health Organization reports that currently 6% of the world's population has diabetes mellitus, which is approximately 284.7 million people, it is somewhat less common in children, determining the average figures within 0.3%. Forecasts for the future are disappointing, according to experts, the number of patients will grow, and by 2030 there will be 438.4 million. The number of patients with diabetes mellitus increases by approximately 6-10% annually. Thus, it can be argued that approximately every 15 years the number of patients with diabetes mellitus doubles.

Diabetes predisposition

The main cause of diabetes is considered to be genetic predisposition. If at least one of the parents has diabetes, the child automatically falls into the risk group. " In such a situation, no preventive measures against the disease will save, but you can recognize its development in time and immediately choose the right tactics to prevent it from going into a more severe stage.

This problem is certainly one of the most urgent, because diabetes firmly occupies its place in the "top three" - diseases that most often cause human death. Only cancer and atherosclerosis are not inferior to it in the palm of the hand. Doctors are sounding the alarm and urging all people to be more attentive to their health in order to prevent the disease, or to have time to start fighting it at an early stage. Diabetes mellitus is characterized by a chronic increase in blood sugar levels, which determines a condition called hyperglycemia, which occurs due to insufficient insulin secretion or due to a decrease in the sensitivity of the body's cells to it.

ETIOLOGY AND PATHOGENESIS OF DIABETES

Type 1 diabetes mellitus (insulin-dependent) is a polyetiological disease. The factors that cause its development often act in a complex on a genetically predisposed organism. Several genes are involved in the implementation of the action and only a certain combination of them leads to a predisposition to diabetes. The relationship between the development of diabetes and HLA antigens DR3; DR4; Dw3; Dw4; B8; B18, Bw15; DQB10302; DQA10301

has been proven, in the presence of which the risk of developing diabetes increases by 7-14 times (the greater the number of antigens, the higher the risk of developing diabetes). According to modern ideas, type 1 diabetes mellitus is considered an autoimmune disease. Against the background of genetic predisposition, b-cells are affected by various diabetogenic factors of the external environment - viruses (Coxsackie, retroviruses, mumps, hepatitis A), toxins, nutritional factors (excessive amounts of nitrates and nitrites in food, etc.), drugs (cimetidine, glucocorticoids, indomethacin, etc.), which lead to the destruction of β-cells. The antigens formed affect the multinucleated phagocytic system, including it in immune and inflammatory processes, modulate the immune response by T and B lymphocytes (B lymphocytes produce antibodies, and T lymphocytes produce the growth factor - interleukin (IL, g-interferon, tumor necrosis factor). As a result, the production of autoantibodies to b cells in macrophages increases, which leads to their destruction and the continuation of the autoimmune reaction. With the duration of type 1 diabetes up to 5-6 years, b cells in the islets of Langerhans disappear almost completely. The clinic of diabetes manifests itself when more than 2/3 of b cells are destroyed.

The justification for this theory:

a) the development of the disease is associated with the HLA antigen system;

c) there is a close connection between diabetes and other autoimmune diseases

h) antibodies to b cells are detected in the blood of patients with diabetes;

e) histological examination shows infiltration of islets by lymphocytes (mononuclear cells)

e) insulitis is observed in islets.

Due to the action of diabetogenic factors, an increase in free radical oxidation is also observed. Under the influence of free radicals (O2-, NO -), the membrane proteins of β-cells are denatured and become autoantigens, which enhances the autoimmune reaction.

Insulin resistance is important in the pathogenesis of type 2 diabetes.

Its causes may be: the presence of antibodies to insulin, increased levels of counterinsular hormones, free fatty acids (FFA), ketone bodies.

Insulin resistance is distinguished into hepatic and peripheral. When treated with insulin, after 3-6 months, restoration of insulin sensitivity in the liver is observed and, as a result, a decrease in glucose production by the liver, however, glucose utilization in peripheral tissues remains reduced.

Type 2 diabetes is also a polyetiological disease, but the causes of its occurrence and pathogenesis differ from type 1 diabetes.

1. Genetic factor (heredity).

The presence of the above HLA antigens creates a predisposition to the development of diabetes.

2. Decreased sensitivity to insulin of the liver and peripheral tissues. This can be congenital or acquired (increased levels of counterinsular hormones in Itsenko-Cushing's disease, acromegaly, chronic stress, etc.) defects that lead to the development of peripheral insulin resistance. Factors that contribute to the development of insulin resistance are obesity, arterial hypertension, hyperlipidemia, hyperuricemia, a sedentary lifestyle, increased levels of hormones: glucocorticoids, somatotropin, catecholamines, thyroxine, etc.

3. Impaired insulin secretion. In the initial stages, hyperinsulinemia is noted, but later hypoinsulinemia is observed. A decrease in the sensitivity of β-cells to glucose leads to

impaired insulin secretion (phase 1). In combination with insulin resistance in the periphery (to endogenous and exogenous insulin), this leads to constant postprandial hyperglycemia, which ultimately leads to depletion of β-cells.

4. Obesity. Normally, there are about 50,000 insulin receptors on lipocytes. In obesity, not only the sensitivity of receptors to insulin decreases, but also their number. In the initial stages of hyperinsulinemia, there is an increase in glucose absorption by adipose tissue, which leads to an increase in obesity. However, over time, the number and sensitivity of receptors on adipocytes decreases and, as a result, glucose absorption decreases and hyperglycemia increases.

5. Hyperproduction of counterinsular hormones - impaired insulin secretion and hyperglycemia occur according to the mechanisms of action inherent in individual hormones (glucocorticoids enhance gluconeogenesis, glycolysis in the liver, reduce the permeability of glucose through tissue membranes, etc.).

6. Decreased glycogen synthetase activity in the muscles is accompanied by an increase in the amount of free glucose in the blood. This leads to hyperinsulinemia and depletion of β-cells.

7. Increased formation of amylin (discovered in 1989, is formed in secretory granules together with insulin as a result of intracellular degradation of the granules).

In diabetes, there is:

a) amyloid deposition in the islets of Langerhans as a result of the action of antibodies to amylin;

b) hyperinsulinemia leads to increased formation of anilin, dysfunction of β-cells and a decrease in insulin production.

Amylin is an insulin antagonist in the muscles: it reduces glucose absorption, reduces glycogen synthesis, enhances gluconeogenesis, glycogenolysis, glucagon synthesis, insulin promotes the development of resistance.

8. Toxicity of hyperglycemia. As a result of chronic hyperglycemia, the function of β-cells (insulin secretion) decreases. With normoglycemia, insulin synthesis improves, which explains the "honeymoon" phenomenon (improvement of the course and reduction of the insulin dose in the debut of type 1 diabetes). As a result of hyperglycemia:

a) resistance of insulin receptors is observed. A decrease in glycemia is accompanied by a decrease in hyperinsulinemia and an increase in the sensitivity of insulin receptors;

b) the level of glycosylated proteins increases, which leads to tissue damage and an increase in their immunogenicity.

9. Toxicity of hyperinsulinemia. Hyperinsulinemia enhances the proliferation of smooth muscles, increases the synthesis of cholesterol, LDL, and reduces the activity of Na-dependent ATPase. These actions contribute to the development of atherosclerosis.

10. Autoimmune factors. Hyperglycemia, hyperinsulinemia change the immunogenicity of tissues, which leads to damage and triggers autoimmune processes.

Several factors act simultaneously, which often reinforce each other. As a result, there is:

- Peripheral insulin resistance
- Impaired β-cell function
- Increased glucose production in the liver
- Metabolic disorders in patients with diabetes

The main role in the pathogenesis of diabetes and its complications belongs to impaired carbohydrate metabolism. Due to insulin deficiency, the permeability of membranes in muscles and adipose tissue for glucose and its intracellular metabolism decreases, and glucose production in the liver increases. The hyperglycemia present in diabetes leads to increased glycosylation of cell membrane proteins, primarily vessels. As a result of an increase in the level of glycosylated hemoglobin (HbA1c) and a decrease in diphosphate in erythrocytes, tissue hypoxia occurs in the periphery. Violation of the membrane of capillaries, erythrocytes, platelets leads to impaired hemostasis and blood rheology. An increase in the polyol pathway of glucose metabolism is of great importance. If in healthy individuals about 2% of glucose is metabolized in the pentose cycle, then in patients with diabetes this figure can increase to 6% or more.

Increased activity of aldose reductase and the sorbitol pathway of glucose metabolism also leads to increased secretion of GH.

Risk factors for diabetes mellitus

An important manifestation of carbohydrate metabolism disorders in patients with diabetes mellitus is glucosuria. In healthy individuals, glucose is practically absent in the urine, since it is reabsorbed from primary urine in the renal tubules. This process is provided by the enzymes hexokinase and phosphatase. Hyperglycemia leads to increased enzyme activity, but only to a certain limit (8.9 mmol / l). In insulin deficiency, glucose reabsorption decreases and glucosuria can occur even with relatively low hyperglycemia, i.e. there is a discrepancy between the degree of hyperglycemia and the severity of glucosuria.

Hyperglycemia, an increase in the osmotic pressure of the blood and its effect on the CNS, also leads to tissue dehydration. As a result of tissue dehydration, cellular metabolism is disrupted, thirst (polydipsia) occurs and diuresis (polyuria) increases. One of the causes of polyuria is also an increase in urine osmotic pressure due to glucosuria, and with decompensation and excretion of protein and fat metabolism products (ketone bodies, etc.) in the urine.

Disturbance of fat metabolism is a consequence of insulin deficiency and carbohydrate metabolism disorders, as well as the action of counterinsular hormones. Inhibition of lipogenesis processes leads to hyperlipidemia and dyslipidemia. An increase in the content of NFE in the blood of patients with diabetes is a compensatory reaction to impaired carbohydrate metabolism. Hyperlipidemia is one of the factors of fatty infiltration of the liver. The influx of fat into the liver, depleted in glycogen, is a manifestation of its adaptation in energy metabolism: due to the depletion of glycogen as an energy source, another, easily utilized substrate is formed in it from fat - ketone bodies. Thus, fatty infiltration of the liver and ketosis are a consequence of insulin deficiency. The development of fatty infiltration is promoted, in addition to the depletion of the liver with glycogen, by a diet rich in fats and a lack of lipotropic nutritional factors, excessive production of GH and other factors.

A manifestation of decompensation of fat metabolism is ketosis. As a result of hyperketonemia and ketonuria, a violation of water-salt metabolism occurs, the enzyme systems of the brain are suppressed with the subsequent development of coma.

Violation of fat metabolism is also manifested by hypercholesterolemia - a consequence of increased cholesterol formation in the liver and a decrease in its breakdown. Its degree depends on the compensation of diabetes and with decompensation, the cholesterol level can increase to 40 mmol / l.

One of the manifestations of dyslipidemia is an increase in the amount of low and very low density lipids (LDL and VLDL), which are highly atherogenic. This creates conditions for the development of atherosclerosis in patients with diabetes. An active role in this is also played by increased lipid peroxidation (LPO), which leads to a violation of the structure and function of cell membranes.

Changes in protein metabolism are mainly manifested by impaired synthesis and increased protein breakdown. In case of glycogen deficiency, glucose is formed from non-carbohydrate substances: glycerol, lactic acid, amino acids, citric, oxalic-acetic, ketoglutaric acid. This process is called gluconeogenesis. As a result of protein metabolism disorders, dysproteinemia occurs (the amount of albumin decreases, the amount of a2-, b- and g-globulins increases), the formation of ammonia, urea and other protein breakdown products increases, which, in the case of decompensation of diabetes, leads to hyperazotemia and hyperazoturia (ketonuria).

Clinical classification of diabetes mellitus (A. S. Efimov, 1998)

I. Clinical forms:

1. Primary: essential, genetic (with or without obesity)

2. Secondary (symptomatic): pituitary, steroid, thyrogenic, adrenal, pancreatic (inflammation, tumors or removal of the pancreas). bronze (with hemochromatosis).

3. Gestational diabetes (gestational).

4. Impaired carbohydrate tolerance (latent).

5. Risk factors (prediabetes).

II. Types of diabetes with course:

1. Type I - insulin-dependent

2. Type II - insulin-independent

III. Severity: mild, moderate, severe.

IV. Compensation state: compensated, subcompensated, decompensated.

B. Presence of angiopathies (stages I - II - III) and neuropathies:

1. Microangiopathy - retinopathy, nephropathy, angiopathy (capillaropathy) of the lower extremities or other localization.

2. Macroangiopathy - damage to the vessels of the heart, brain, lower extremities or other localization.

3. Universal micro- and macroangiopathy.

4. Neuropathy (peripheral, autonomic, visceral, encephalopathy).

V. Damage to other organs and systems: hepatopathy, dermopathy, enteropathy, cataract, osteoarthropathy and others.

VI. Acute complications of diabetes:

1. Ketonemic (ketoacidotic) coma

2. Hyperosmolar coma

3. Hyperlactacidemic coma

4. Hypoglycemic coma.

Clinical characteristics of individual types of diabetes mellitus

DIAGNOSIS OF DIABETES

1. Determination of fasting blood glucose and its repeated determinations during the day are the main (key) method for diagnosing diabetes.

The diagnosis of diabetes can be made if:

With two determinations, fasting blood glucose is more than 6.1 mmol / l (110 mg%);

With arbitrary determination between days, blood glucose is more than 11.0 mmol / l

This is supplemented by the determination of glucosuria per day or fractionally in separate portions.

Indications for conducting a standard glucose tolerance test

1. Temporary disorders of carbohydrate metabolism:

• glucosuria in pregnant women

• hyperglycemia after eating up to 9.9 mmol / l;

• reactive hypoglycemia.

2. The presence of risk factors for diabetes:

• hereditary predisposition;

• excess body weight;

• pathological pregnancy and childbirth: miscarriages, polyhydramnios, stillbirth, toxicosis of pregnant women, newborn weight more than 4 kg;

• peripheral vascular disease, arterial hypertension;

• chronic infection;

• Dermopathy, retinopathy and neuropathy of unknown cause;

• hyperlipidemia, hyperuricemia.

Conditions for conducting a standard glucose tolerance test

1. The test is not performed in case of various intercurrent diseases, liver and kidney damage.

2. The subject is on a normal diet (at least 150 g of carbohydrates) for three days before the test and performs usual physical work.

3. At least 3 days before the test, medications that affect the test results (corticosteroids, estrogens, saluretics, salicylates), as well as sugar-lowering drugs, should be canceled.

4. The test is performed after a night's fasting of 10 - 14 hours. Drinking water is allowed.

5. A fasting blood sample is taken from the subject, after which he takes 75 g of glucose dissolved in 250 - 500 ml of water for 5 - 10 minutes. A second blood sample is taken after 60 minutes, and then after 1 hour. (According to the recommendations of the WHO Expert Committee on Diabetes, the main diagnostic criterion for interpreting the oral glucose tolerance test is the fasting glucose level and after 2 hours. After loading).

Determination of the level of glycosylated hemoglobin (HbA1c)

In healthy people, the amount of HbA1c is 4-6% of the total amount of hemoglobin. In patients with diabetes, its amount increases significantly depending on the level of hyperglycemia. Allows you to detect early stages of diabetes (preclinical), since it is possible to diagnose hyperglycemia during the last month. The level of HbA1c> 6.5% approximately corresponds to fasting glycemia> 6.1 mmol / l, and 7.5% - glycemia> 7.0 mmol / l.

DIABETES CLINIC

In its development, DM usually goes through 3 stages, which are more clearly distinguished in patients with type 2 diabetes.

1. Prediabetes - a state (period of the patient's life) preceding the disease. Laboratory indicators do not go beyond the normal range. Patients often have risk factors for diabetes:

• the presence of DM in relatives (if both relatives have DM, the risk of developing it

in children increases to 50%)

• obesity (the risk increases with increasing obesity)

• hyper- and dyslipoproteinemia

• birth of a child with a large (more than 4 kg) body weight - both for the child and for the mother (the risk increases with increasing weight)

• in women, glucosuria during pregnancy; miscarriages and stillbirths

• viral diseases

• acute and chronic stress

• atherosclerosis, hypertension

• acute and chronic intoxications

• acute and chronic diseases of the liver and pancreas

• iatrogenic factors (thiazide diuretics, glucocorticoids, etc.)

2. Impaired glucose tolerance (latent diabetes) - a condition in which there is no clinical course of diabetes, fasting normoglycemia and aglucosuria. Violations are detected when performing a TSH. Patients during this period may experience the so-called "minor symptoms" of diabetes:

• chronic gingivitis, stomatitis, periodontitis, tooth loss

• chronic pustular skin diseases, furunculosis

• itching of the skin, genitals

• skin trophic disorders, skin wounds that do not heal for a long time

• unmotivated sexual weakness, menstrual cycle disorders

• polyneuritis

• cataracts

3. Overt (manifest) diabetes mellitus - a condition when clinical symptoms become manifest, changes in laboratory parameters, primarily hyperglycemia and glycosuria. Clinical symptoms of diabetes mellitus, primarily complaints of patients, are due to the disease itself, the degree of its compensation and complications.

Patients have:

• polydipsia, thirst, dry mouth;

• polyuria, frequent urination, which leads to dehydration:

• muscle weakness, increased fatigue;

• weight loss (type 1 diabetes), weight gain (type 2 diabetes);

• loss of appetite (polyphagia is initially possible)

• leg pain, paresthesia, loss of sensitivity;

• itching (local - perineum, scalp or generalized);

• visual impairment, sexual dysfunction;

• chronic pustular or fungal skin lesions

Depending on the clinic and laboratory indicators, there are 3 degrees of severity of diabetes: mild, moderate and severe

Criteria for the severity of diabetes

According to the degree of compensation of metabolic processes, diabetes can be compensated, subcompensated and decompensated.

Compensation is understood as a satisfactory general condition of the patient, preserved working capacity, absence of complications, normoglycemia, aglucosuria and normal biochemical indicators, achieved under the influence of treatment.

Diabetes is considered subcompensated when the patient's condition is satisfactory, but working capacity is reduced, complications are not pronounced, against the background of treatment, glycemia is 8-10 mmol / l, glucosuria is 20-30 g / l, metabolic disorders are insignificant, ketoacidosis is absent.

Decompensated diabetes - a pronounced clinical course of the disease, the patient's condition is moderate or severe, complications are pronounced, hyperglycemia and glycosuria are high, significant metabolic disorders, ketoacidosis, ketonuria. Patients are unable to work.

Insulin (from the Latin insula - island) is a protein-peptide hormone produced by the β-cells of the islets of Langerhans of the pancreas. Under physiological conditions, insulin is formed in β-cells from preproinsulin - a single-chain precursor protein consisting of 110 amino acid residues. After transfer through the membrane of the rough endoplasmic reticulum, a signal peptide of 24 amino acids is cleaved from preproinsulin and proinsulin is formed. The long chain of proinsulin in the Golgi apparatus is packed into granules, where as a result of hydrolysis four basic amino acid residues are cleaved off with the formation of insulin and the C-terminal peptide (the physiological function of the C-peptide is unknown).

The insulin molecule consists of two polypeptide chains. One of them contains 21 amino acid residues (chain A), the second - 30 amino acid residues (chain B). The chains are connected by two disulfide bridges. The third disulfide bridge is formed inside the chain A. The total molecular weight of the insulin molecule is about 5700. The amino acid sequence of insulin is considered conservative. In most species there is one insulin gene, encoding one protein. The exceptions are rats and mice (they have two insulin genes each), they produce two insulins, differing in two amino acid residues of the B-chain.

The primary structure of insulin in different biological species, including and in different mammals, it varies somewhat. The closest to the structure of human insulin is porcine insulin, which differs from human by one amino acid (in its B chain instead of the amino acid threonine residue, it contains an alanine residue). Bovine insulin differs from human by three amino acid residues.

Historical background. In 1921, Frederick R. Banting and Charles R. Best, working in the laboratory of John J. R. Macleod at the University of Toronto, isolated from the pancreas an extract (later found to contain amorphous insulin) that lowered blood glucose levels in dogs with experimental diabetes. In 1922, the pancreatic extract was administered to the first patient, 14-year-old Leonard Thompson, a diabetic, and thereby saved his life. In 1923, James B. Collip developed a method for purifying the extract secreted from the pancreas, which subsequently made it possible to obtain active extracts from the pancreases of pigs and cattle that gave reproducible results. In 1923 Banting and Macleod were awarded the Nobel Prize in Physiology or Medicine for their discovery of insulin. In 1926, J. Abel and C. Du Vigneault obtained insulin in crystalline form. In 1939, insulin was first approved by the FDA (Food and Drug Administration). Frederick Sanger completely deciphered the amino acid sequence of insulin (1949-1954). In 1958, Sanger was awarded the Nobel Prize for his work on deciphering the structure of proteins, especially insulin. In 1963, artificial insulin was synthesized. The first recombinant human insulin was approved by the FDA in 1982. An ultra-short-acting insulin analogue (insulin lispro) was approved by the FDA in 1996. Mechanism of action. In the implementation of the effects of insulin, the leading role is played by its interaction with specific receptors localized on the plasma membrane of the cell,

and the formation of the insulin-receptor complex. In complex with the insulin receptor, insulin penetrates the cell, where it affects the processes of phosphorylation of cellular proteins and triggers numerous intracellular reactions.

Pharmacological effects of insulin. Insulin affects almost all organs and tissues. However, its main targets are the liver, muscle and adipose tissue.

Endogenous insulin is the most important regulator of carbohydrate metabolism, exogenous is a specific hypoglycemic agent. The effect of insulin on carbohydrate metabolism is due to the fact that it enhances the transport of glucose through the cell membrane and its utilization by tissues, promotes the conversion of glucose into glycogen in the liver. Insulin also inhibits endogenous glucose production by inhibiting glycogenolysis (the breakdown of glycogen to glucose) and gluconeogenesis (the synthesis of glucose from non-carbohydrate sources, such as amino acids and fatty acids). In addition to hypoglycemic effects, insulin has a number of other effects.

The effect of insulin on fat metabolism is manifested in the inhibition of lipolysis, which leads to a decrease in the supply of free fatty acids in the blood. Insulin prevents the formation of ketone bodies in the body. Insulin enhances the synthesis of fatty acids and their subsequent esterification.

Insulin is involved in protein metabolism: it increases the transport of amino acids across the cell membrane, stimulates peptide synthesis, reduces protein consumption by tissues, and inhibits the conversion of amino acids to ketoacids.

The action of insulin is accompanied by the activation or inhibition of a number of enzymes: glycogen synthetase, pyruvate dehydrogenase, hexokinase are stimulated, lipases are inhibited (both hydrolyzing lipids of adipose tissue and lipoprotein lipase, which reduces the "cloudiness" of blood serum after taking a meal rich in fats).

In the physiological regulation of insulin biosynthesis and secretion by the pancreas, the concentration of glucose in the blood plays a major role: when its content increases, insulin secretion increases, and when it decreases, it slows down. In addition to glucose, insulin secretion is influenced by electrolytes (especially Ca2+ ions), amino acids (including leucine and arginine), glucagon, and somatostatin.

Pharmacokinetics. Insulin preparations are administered s/c, s/m or s/n (only short-acting insulins are administered s/n and only in diabetic precoma and coma). Insulin suspensions cannot be administered s/n. The temperature of the injected insulin should correspond to room temperature, since cold insulin is absorbed more slowly. The most optimal method for continuous insulin therapy in clinical practice is s/n administration.

The completeness of absorption and the onset of the insulin effect depend on the injection site (usually insulin is injected into the abdomen, thigh, buttocks, upper arms), dose (volume of injected insulin), insulin concentration in the preparation, etc.

The rate of insulin absorption into the blood from the s/n injection site depends on a number of factors - the type of insulin, the injection site, the speed of local blood flow, local muscle activity, the amount of insulin injected (it is recommended to inject no more than 12-16 U of the preparation into one place). Insulin enters the blood most quickly from the subcutaneous tissue of the anterior abdominal wall, more slowly from the shoulder area, on the anterior surface of the thigh, and even more slowly from the subscapular region and buttocks. This is due to the degree of vascularization of the subcutaneous fat of the listed areas. The profile of insulin action is subject to significant fluctuations both in different

people and in the same person. In the blood, insulin binds to alpha and beta globulins, normally 5-25%, but binding may increase during treatment due to the appearance of serum antibodies (the production of antibodies to exogenous insulin leads to insulin resistance; when using modern highly purified drugs, insulin resistance rarely occurs). T1/2 from the blood is less than 10 minutes. Most of the insulin entering the blood undergoes proteolytic degradation in the liver and kidneys. Rapidly excreted from the body by the kidneys (60%) and liver (40%); less than 1.5% is excreted unchanged in the urine.

Insulin preparations currently used differ in a number of characteristics, including source of origin, duration of action, pH of the solution (acidic and neutral), presence of preservatives (phenol, cresol, phenol-cresol, methylparaben), insulin concentration - 40, 80, 100, 200, 500 U/ml

Classification. Insulins are usually classified by origin (bovine, porcine, human, as well as human insulin analogues) and duration of action.

Depending on the sources of production, there are insulins of animal origin (mainly pig insulin preparations), semi-synthetic human insulin preparations (obtained from pig insulin by enzymatic transformation), genetically engineered human insulin preparations (DNA-recombinant, obtained by genetic engineering).

Insulin activity is determined by a biological method (by the ability to reduce blood glucose in rabbits) or by a physicochemical method (by electrophoresis on paper or by chromatography on paper). One unit of action, or international unit, is taken to be the activity of 0.04082 milligrams of crystalline insulin. The human pancreas contains up to 8 mg of insulin (approximately 200 U).

CLASSIFICATION OF INSULIN PREPARATIONS

1) by origin;

2) by the speed of onset of effects and their duration;

3) by the method of purification and degree of purity of the preparations.

I. By origin, there are:

a) natural (biosynthetic), natural, insulin preparations made from the pancreas of cattle, for example, insulin tape GPP, ultralente MS and more often pigs (for example, actrapid, insulrap SPP, monotard MS, semilente, etc.);

b) synthetic or, more precisely, species-specific, human insulins. These preparations are obtained using genetic engineering methods by recombinant DNA technology, and therefore they are most often called DNA recombinant insulin preparations (actrapid NM, homophane, isophane NM, humulin, ultratard NM, monotard NM, etc.).

II. According to the method of purification and purity of the preparations, the following are distinguished:

a) crystallized (poorly purified), but not chromatographed - these are the majority of the so-called "traditional" insulin preparations previously produced in our country (insulin for injection), but discontinued;

b) crystallized and filtered through gels ("molecular sieve") - the so-called single monopeak insulins (actrapid, insulrap, etc.);

c) crystallized and purified using a "molecular sieve" and ion-exchange chromatography - the so-called monocomponent insulins (actrapid MS, semilente MS, monotard MS, ultralente MS).

Crystallized, but not chromatographed insulins are, as a rule, insulin preparations of

natural origin. They contain various impurities in the form of molecules of proinsulin, glucagon, C-peptide (binds A and B chains of proinsulin), somatostatin and other proteins. In these preparations, the content of proinsulin is more than 10,000 parts per million.

Highly purified insulin preparations (by filtration through gels), called monopeak, since only one peak is visible on the chromatogram, contain impurities of less than 3,000 (from 50 to 3,000), and even more improved - monocomponent - less than 10 parts per million parts of insulin. Monocomponent preparations are gaining increasing importance.

III. According to the speed of onset of effects and their duration, the following are distinguished:

a) fast-acting short-acting preparations (actrapid, actrapid MS, actrapid NM, insulrap, homorap 40, insuman rapid, etc.). The onset of action of these drugs is 15-30 minutes, the duration of action is 6-8 hours;

b) drugs of medium duration of action (onset of action in 1-2 hours, the total duration of the effect is 12-16 hours); - semilente MS; - humulin H, humulin tape, homophane; - tape, tape MS, monotard MS (2-4 hours and 20-24 hours, respectively);

• iletin I NPH, iletin II NPH;

• insulong SPP, insulin tape GPP, SPP, etc.

c) drugs of medium duration in a mixture with short-acting insulin: (onset of action 30 minutes; duration - from 10 to 24 hours);

• actraphane NM;

• humulin M-1; M-2; M-3; M-4 (duration of action up to 12-16 hours);

• insuman comb. 15/85; 25/75; 50/50 (effective for 10-16 hours).

d) long-acting drugs:

• ultralente, ultralente MS, ultralente NM (up to 28 hours);

• insulin superlente SPP (up to 28 hours);

• humulin ultralente, ultratard NM (up to 24-28 hours).

Insulin preparations are divided into short- and ultra-short-acting preparations based on the duration of action, imitating the normal physiological secretion of insulin by the pancreas in response to stimulation, medium-acting preparations and long-acting preparations - imitating basal (background) secretion of insulin, as well as combined preparations (combining both actions). Currently, human insulin (Humulin - human) is produced semi-synthetically from pig insulin or biosynthetically using specially grown bacteria or yeast fungi (genetically engineered), which has become available to patients only in the last 20 years.

The following groups are distinguished:

Ultra-short-acting insulins (the hypoglycemic effect develops 10-20 minutes after s/c injection, the peak of action is reached on average after 1-3 hours, the duration of action is 3-5 hours):

- insulin lispro (Humalog);

- insulin aspart (NovoRapid Penfill, NovoRapid FlexPen);

- insulin glulisine (Apidra).

- Short-acting insulins (the onset of action is usually after 30-60 minutes; the maximum action is after 2-4 hours; the duration of action is up to 6-8 hours):

- soluble insulin [human genetically engineered] (Actrapid NM, Gensulin R, Rinsulin R, Humulin Regular);

- soluble insulin [human semi-synthetic] (Biogulin R, Humodar R);

- soluble insulin [porcine is monocomponent] (Actrapid MS, Monodar, Monosuinsulin MK).

Long-acting insulin preparations - include medium-acting and long-acting preparations.

Medium-acting insulins (onset in 1.5–2 hours; peak in 3-12 hours; duration 8-12 hours):

- insulin-isophane [human genetically engineered] (Biosulin N, Hansulin N, Gensulin N, Insuman Basal GT, Insuran NPH, Protafan NM, Rinsulin NPH, Humulin NPH);
- insulin-isophane [human semisynthetic] (Biogulin N, Humodar B);
- insulin-isophane [porcine is monocomponent] (Monodar B, Protafan MS);
- insulin-zinc suspension component (Monotard MS).

Long-acting insulins (onset in 4-8 hours; peak in 8-18 hours; total duration 20-30 hours):

- insulin glargine (Lantus);
- insulin detemir (Levemir Penfill, Levemir FlexPen).

Combined-acting insulin preparations (biphasic preparations) (hypoglycemic effect begins 30 minutes after s/c injection, reaches a maximum in 2-8 hours and lasts until 18-20 hours):

- insulin biphasic [human semi-synthetic] (Biogulin 70/30, Humodar K25);
- insulin biphasic [human genetically engineered] (Gansulin30R, Gensulin M 30, Insuman Comb 25 GT, Mixtard 30 NM, Humulin M3);
- insulin aspart biphasic (NovoMix 30 Penfill, NovoMix 30 FlexPen).

Ultra-short-acting insulins are human insulin analogues. It is known that endogenous insulin in β-cells of the pancreas, as well as hormone molecules in short-acting insulin solutions produced, are polymerized and represent hexamers. With subcutaneous administration, hexameric forms are absorbed slowly and it is impossible to create a peak hormone concentration in the blood, similar to that in a healthy person after a meal. The first short-acting insulin analogue, which is absorbed from the subcutaneous tissue 3 times faster than human insulin, was insulin lispro. Insulin lispro is a derivative of human insulin obtained by rearranging two amino acid residues in the insulin molecule (lysine and proline at positions 28 and 29 of the chain). Modification of the insulin molecule disrupts the formation of hexamers and ensures rapid entry of the drug into the blood. Almost immediately after subcutaneous administration, insulin lispro molecules in the tissues in the form of hexamers quickly dissociate into monomers and enter the blood. Another insulin analogue, insulin aspart, was created by replacing proline at position 28 with negatively charged aspartic acid. Like insulin lispro, it also quickly dissociates into monomers after subcutaneous administration. In insulin glulisine, the replacement of the amino acid asparagine of human insulin at position B3 with lysine and lysine at position B29 with glutamic acid also contributes to faster absorption. Ultra-short-acting insulin analogues can be administered immediately before or after meals.

Short-acting insulins (also called soluble) are solutions in a buffer with neutral pH values (6.6–8.0). They are intended for subcutaneous, less often intramuscular administration. If necessary, they are also administered intravenously. They have a rapid and relatively short-term hypoglycemic effect. The effect after subcutaneous injection occurs after 15-20 minutes, reaches a maximum after 2 hours, the total duration of action is approximately 6 hours. They

are used mainly in the hospital during the establishment of the required dose of insulin for the patient, as well as when a rapid (urgent) effect is required - in diabetic coma and precoma. With intravenous administration, T1/2 is 5 minutes, therefore, in diabetic ketoacidotic coma, insulin is administered intravenously drip. Short-acting insulin preparations are also used as anabolic agents and are prescribed, as a rule, in small doses (4-8 units 1-2 times a day).

Medium-acting insulins are less soluble, more slowly absorbed from the subcutaneous tissue, and as a result have a longer effect. The long-lasting effect of these drugs is achieved by the presence of a special prolongator - protamine (isophane, protaphane, basal) or zinc. The slowing of insulin absorption in drugs containing zinc as a component of insulin suspension is due to the presence of zinc crystals. NPH insulin (neutral protamine Hagedorn, or isophane) is a suspension consisting of insulin and protamine (protamine is a protein isolated from fish milk) in a stoichiometric ratio. Long-acting insulins include insulin glargine - an analogue of human insulin obtained by recombinant DNA technology - the first insulin drug that does not have a pronounced peak of action. Insulin glargine is produced by two modifications of the insulin molecule: substitution of glycine at position 21 of the A chain (asparagine) and addition of two arginine residues at the C-terminus of the B chain. The drug is a clear solution with a pH of 4. The acidic pH stabilizes the insulin hexamers and provides a long and predictable absorption of the drug from the subcutaneous tissue. However, due to the acidic pH, insulin glargine cannot be combined with short-acting insulins that have a neutral pH. A single injection of insulin glargine provides 24-hour peak-free glycemic control. Most insulin preparations have a so-called "peak" of action, which occurs when the concentration of insulin in the blood reaches a maximum. Insulin glargine does not have a pronounced peak, since it is released into the bloodstream at a relatively constant rate.

Long-acting insulin preparations are available in various dosage forms that provide a hypoglycemic effect of varying duration (from 10 to 36 hours). The prolonged effect allows you to reduce the number of daily injections. They are usually produced in the form of suspensions that are administered only subcutaneously or intramuscularly. In diabetic coma and precomatose states, prolonged preparations are not used.

Combined insulin preparations are suspensions that consist of neutral soluble short-acting insulin and isophane insulin (medium-acting) in certain ratios. Such a combination of insulins of different durations of action in one preparation allows the patient to avoid two injections when using the preparations separately.

These are combined preparations that are a mixture of short-acting and medium-acting insulins. Their feature is a two-peak effect, in particular, the first peak is due to short-acting insulin, the second is due to medium-acting insulin. Ready-made stable mixtures are produced in cartridges (penfills) for syringe pens, but you can choose the proportions of the mixture yourself for maximum adaptation to the patient's needs. The numbers in the names of insulins mean concentration.

Humulin MZ (France)

Mixtard 10-50 NM Penfill (Denmark)

Insuman Comb (France/Germany)

Leading manufacturers of modern insulin preparations: Eli Lilly (USA), Novo Nordisk (Denmark), Aventis (Hochst Marion Roussel) (France/Germany).

For the convenience of patients with diabetes, in addition to insulin in vials, syringe pens are produced, into which cartridges-penfills are inserted and changed after use (the

names of insulins contain the composition "pen"), and ready-made syringes in the form of disposable pens (thrown away after use). The needles on syringe pens are much thinner and have double laser sharpening, which makes injections almost painless. Penfills contain thermostable insulin (stable for 30 days), so the patient can carry it in his pocket. Penfills free patients from the need to carry syringes and sterilizers, which significantly improves the quality of life.

Many scientific laboratories are conducting research on the creation of insulin preparations for non-parenteral administration. In particular, in 1998, a report appeared on the inhalation form of insulin ("diabetic inhalation system"). Also, since 1999, oral insulin preparations - hexylinsulin - have been used in the experiment.

ACTRAPIDE, obtained from beta cells of the islets of the pancreas of pigs, is available as an official drug in 10 ml vials, most often with an activity of 40 U in 1 ml. It is administered parenterally, most often under the skin. This drug (like all drugs of the subgroup of rapid-short-acting insulins) has a rapid hypoglycemic effect. The effect develops after 15-20 minutes, and the peak of action is noted after 2-4 hours. The total duration of the hypoglycemic effect is 6-8 hours in adults, and up to 8-10 hours in children.

Advantages of rapid-short-acting insulin drugs (actrapide):

1) act quickly;

2) give a physiological peak concentration in the blood;

3) act for a short time.

4) The main disadvantage is the short duration of action, which requires repeated injections.

Indications.

The main indication for the use of insulin is type 1 diabetes mellitus, however, under certain conditions it is prescribed for type 2 diabetes mellitus, including resistance to oral hypoglycemic agents, severe concomitant diseases, in preparation for surgical interventions, diabetic coma, and diabetes in pregnant women. Short-acting insulins are used not only for diabetes mellitus, but also for some other pathological processes, for example, for general exhaustion (as an anabolic agent), furunculosis, thyrotoxicosis, for stomach diseases (atony, gastroptosis), chronic hepatitis, initial forms of liver cirrhosis, and also for some mental diseases (administration of large doses of insulin - the so-called hypoglycemic coma); sometimes it is used as a component of "polarizing" solutions used to treat acute heart failure.

Indications for the use of rapid-acting insulin preparations:

 Treatment of patients with insulin-dependent diabetes mellitus. The drug is administered subcutaneously.

 In the most severe forms of non-insulin-dependent diabetes mellitus in adults.

 In diabetic (hyperglycemic) coma. In this case, the drugs are administered subcutaneously, as well as intravenously.

 Very rarely, the drugs are used as an anabolic agent in children with poor nutrition. In this case, the drug is administered subcutaneously to increase appetite. According to this indicator, the drugs are used in patients with general malnutrition, exhaustion, furunculosis, thyrotoxicosis, vomiting, chronic hepatitis

 The drugs can be part of a polarizing mixture (potassium, glucose and insulin) to support the work of the myocardium in cardiac arrhythmias (when the phenomenon of hypokalemia is recorded, for example, in case of intoxication with cardiac glycosides).

 In a psychiatric clinic, the drugs were previously used in shock therapy for patients with schizophrenia (by achieving a hypoglycemic coma). Now there is practically no such evidence, since there are a lot of good psychotropic drugs.

 The drugs are indicated for patients with non-insulin-dependent diabetes mellitus during pregnancy, since sugar-lowering drugs do not have a teratogenic effect

 For individuals with non-insulin-dependent diabetes mellitus during abdominal and other major surgical interventions, with infectious diseases

Dosing insulin is an extremely complex issue, since individual selection of doses is required.

One of the most primitive ways to calculate the dose of insulin is to administer 1 U of insulin per gram of sugar in the patient's urine. It is advisable to carry out the first insulin injections and the selection of the optimal dose in a hospital. At the same time, they try to choose not an abstract dose, but a specific one. The patient is prescribed the entire diet for a week in advance.

Insulin is the main specific means of diabetes therapy. Diabetes treatment is carried out according to specially developed schemes using insulin preparations of different duration of action. The choice of the drug depends on the severity and characteristics of the course of the disease, the general condition of the patient and the speed of onset and duration of the hypoglycemic effect of the drug.

All insulin preparations are used subject to mandatory adherence to a dietary regimen with a restriction of the energy value of food (from 1700 to 3000 kcal).

When determining the dose of insulin, the level of fasting blood glucose and during the day, as well as the level of glucosuria during the day, are guided. The final dose selection is carried out under the control of reducing hyperglycemia, glucosuria, and the general condition of the patient.

In addition to short- and fast-acting insulin preparations, prolonged-acting insulins are produced. The presence of the main proteins in these preparations - protamine and globin, zinc, as well as a salt buffer changes the speed of onset of the sugar-lowering effect, the time of maximum action, i.e. the peak of action and the total duration of action. As a result of such a mixture, a suspension is obtained that is slowly absorbed, maintaining a low dose of the drug in the blood for a long time. Now there are a lot of long-acting insulin preparations (see classification). All these preparations are administered only subcutaneously.

Advantages of prolonged insulin preparations:

1) the preparations are administered only twice or once a day;

2) the preparations have a high pH, which makes their injections less painful and the insulin acts faster.

Disadvantages:

1) the absence of a physiological peak, which means that these preparations cannot be administered to patients with severe diabetes mellitus and should be used for relatively mild and moderate forms;

2) the preparations cannot be administered intravenously (to prevent embolism).

Contraindications.

Insulin is contraindicated in diseases and conditions that occur with hypoglycemia (for example, insulinoma), in acute diseases of the liver, pancreas, kidneys, gastric ulcer and duodenal ulcer, decompensated heart defects, in acute coronary insufficiency and some other

diseases.

Use during pregnancy.

The main drug treatment for diabetes during pregnancy is insulin therapy, which is carried out under careful supervision. In type 1 diabetes, insulin treatment is continued. In type 2 diabetes, oral hypoglycemic agents are canceled and diet therapy is carried out.

Gestational diabetes mellitus (diabetes of pregnant women) is a disorder of carbohydrate metabolism that first appeared during pregnancy. Gestational diabetes mellitus is accompanied by an increased risk of perinatal mortality, the incidence of congenital malformations, as well as the risk of progression of diabetes 5-10 years after delivery. Treatment of gestational diabetes mellitus begins with diet therapy. If diet therapy is ineffective, insulin is used.

For patients with previously achieved or gestational diabetes, it is important to maintain adequate regulation of metabolic processes throughout pregnancy. The need for insulin may decrease in the I trimester of pregnancy and increase in the II–III trimesters. During and immediately after delivery, the need for insulin may decrease dramatically (the risk of hypoglycemia increases). In these conditions, careful control of blood glucose levels is essential.

Insulin does not cross the placental barrier. However, maternal IgG antibodies to insulin cross the placenta and may probably cause fetal hyperglycemia by neutralizing its insulin secretion. On the other hand, unwanted dissociation of insulin–antibody complexes may lead to hyperinsulinemia and hypoglycemia in the fetus or newborn. It has been shown that the transition from bovine/porcine insulin preparations to monocomponent preparations is accompanied by a decrease in antibody titer. In this regard, it is recommended to use only human insulin preparations during pregnancy.

Insulin analogues (as well as other recently developed agents) are prescribed with caution during pregnancy, although there is no reliable data on adverse effects. According to the generally accepted recommendations of the FDA (Food and Drug Administration), which determine the possibility of using drugs during pregnancy, insulin preparations are classified as category B (animal reproduction studies have not shown an adverse effect on the fetus, and adequate and strictly controlled studies in pregnant women have not been conducted) or category C (animal reproduction studies have shown an adverse effect on the fetus, and adequate and strictly controlled studies in pregnant women have not been conducted, but the potential benefit associated with the use of the drug in pregnant women may justify its use despite the possible risk). Thus, insulin lispro is classified as class B, and insulin aspart and insulin glargine are classified as class C.

Complications of insulin therapy. Hypoglycemia. The introduction of too high doses, as well as insufficient intake of carbohydrates with food, can cause an undesirable hypoglycemic state, hypoglycemic coma with loss of consciousness, convulsions and depression of cardiac activity may develop. Hypoglycemia can develop due to the action of additional factors that increase sensitivity to insulin (for example, adrenal insufficiency, hypopituitarism) or increase glucose uptake by tissues (physical activity). Early symptoms of hypoglycemia, which are largely associated with the activation of the sympathetic nervous system (adrenergic symptoms), include tachycardia, cold sweat, tremor, with activation of the parasympathetic system - severe hunger, nausea, as well as a tingling sensation in the lips and tongue. At the first signs of hypoglycemia, urgent measures must be taken: the patient should

drink sweet tea or eat a few pieces of sugar. In hypoglycemic coma, a 40% glucose solution is injected intravenously in an amount of 20-40 ml or more until the patient comes out of the comatose state (usually no more than 100 ml). Hypoglycemia can also be relieved by intramuscular or subcutaneous administration of glucagon.

Weight gain during insulin therapy is associated with the elimination of glucosuria, an increase in the real calorie content of food, increased appetite and stimulation of lipogenesis under the influence of insulin. This side effect can be avoided if the principles of rational nutrition are observed.

The use of modern highly purified hormone preparations (especially genetically engineered human insulin preparations) relatively rarely leads to the development of insulin resistance and allergic phenomena, but such cases are not excluded. The development of an acute allergic reaction requires immediate desensitization therapy and replacement of the drug. If a reaction develops to bovine/porcine insulin preparations, they should be replaced with human insulin preparations. Local and systemic reactions (itching, local or systemic rash, formation of subcutaneous nodules at the injection site) are associated with insufficient purification of insulin from impurities or with the use of bovine or porcine insulin, which differ in amino acid sequence from human.

The most frequent allergic reactions are cutaneous, mediated by IgE antibodies. Systemic allergic reactions, as well as insulin resistance, mediated by IgG antibodies, are rarely observed.

Visual impairment. Transient refractive errors of the eye occur at the very beginning of insulin therapy and resolve on their own after 2-3 weeks.

Edema. In the first weeks of therapy, transient swelling of the legs due to fluid retention in the body, the so-called insulin edema, also occurs.

Local reactions include lipodystrophy at the site of repeated injections (a rare complication). Lipoatrophy (disappearance of subcutaneous fat deposits) and lipohypertrophy (increase in subcutaneous fat deposits) are distinguished. These two conditions have a different nature. Lipoatrophy is an immunological reaction caused mainly by the administration of poorly purified insulin preparations of animal origin, which is currently practically not found. Lipohypertrophy also develops when using highly purified human insulin preparations and can occur when the injection technique is violated (cold preparation, alcohol getting under the skin), as well as due to the anabolic local action of the preparation itself. Lipohypertrophy creates a cosmetic defect that is a problem for patients. In addition, due to this defect, the absorption of the drug is impaired. To prevent the development of lipohypertrophy, it is recommended to constantly change injection sites within the same area, leaving a distance between two punctures of at least 1 cm.

Local reactions such as pain at the injection site may occur.

Interaction.

Insulin preparations can be combined with each other.

Many drugs can cause hypo - or hyperglycemia, or change the response of a diabetic patient to treatment. It is necessary to take into account the interaction possible with the simultaneous use of insulin with other drugs. Alpha-blockers and beta-adrenomimetics increase the secretion of endogenous insulin and enhance the effect of the drug. The hypoglycemic effect of insulin is enhanced by oral hypoglycemic agents, salicylates, MONOAMINE OXIDASE inhibitors (including furazolidone, procarbazine, selegiline), ACE

inhibitors, bromocriptine, octreotide, sulfonamides, anabolic steroids (especially oxandrolone, methandienone) and androgens (increase tissue sensitivity to insulin and increase tissue resistance to glucagon, which leads to hypoglycemia, especially in the case of insulin resistance; a reduction in the insulin dose may be required), somatostatin analogues, guanethidine, disopyramide, clofibrate, ketoconazole, lithium preparations, mebendazole, pentamidine, pyridoxine, propoxyphene, phenylbutazone, fluoxetine, theophylline, fenfluramine, lithium preparations, calcium preparations, tetracyclines. Chloroquine, quinidine, quinine reduce insulin degradation and may increase blood insulin concentrations and increase the risk of hypoglycemia.

Carbonic anhydrase inhibitors (especially acetazolamide), by stimulating pancreatic β-cells, promote insulin release and increase the sensitivity of receptors and tissues to insulin; although the simultaneous use of these drugs with insulin may enhance the hypoglycemic effect, the effect may be unpredictable.

A number of drugs that cause hyperglycemia in healthy people and worsen the course of the disease in patients with diabetes. The hypoglycemic effect of insulin is weakened by: antiretroviral drugs, asparaginase, oral hormonal contraceptives, glucocorticoids, diuretics (thiazide, ethacrynic acid), heparin, H2-receptor antagonists, sulfinpyrazone, tricyclic antidepressants, dobutamine, isoniazid, calcitonin, niacin, sympathomimetics, danazol, clonidine, BCC, diazoxide, morphine, phenytoin, somatotropin, thyroid hormones, phenothiazine derivatives, nicotine, ethanol.

Glucocorticoids and epinephrine have an effect on peripheral tissues opposite to that of insulin. Thus, prolonged use of systemic glucocorticoids can cause hyperglycemia, up to diabetes mellitus (steroid diabetes), which can occur in approximately 14% of patients taking systemic corticosteroids for several weeks or with prolonged use of topical corticosteroids. Some drugs inhibit insulin secretion directly (phenytoin, clonidine, diltiazem) or by reducing potassium stores (diuretics). Thyroid hormones accelerate insulin metabolism.

The most significant and frequent effects on insulin action are beta-blockers, oral hypoglycemic agents, glucocorticoids, ethanol, salicylates.

Ethanol inhibits gluconeogenesis in the liver. This effect is observed in all people. In this regard, it should be borne in mind that the abuse of alcoholic beverages during insulin therapy can lead to the development of a severe hypoglycemic state. Small amounts of alcohol taken with food usually do not cause problems.

Beta-blockers can inhibit insulin secretion, change carbohydrate metabolism and increase peripheral resistance to the action of insulin, which leads to hyperglycemia. However, they can also inhibit the action of catecholamines on gluconeogenesis and glycogenolysis, which is associated with the risk of severe hypoglycemic reactions in patients with diabetes. Moreover, any of the beta-blockers can mask the adrenergic symptoms caused by a decrease in blood glucose levels (including tremor, palpitations), thereby impairing the patient's timely recognition of hypoglycemia. Selective beta1-adrenergic blockers (including acebutolol, atenolol, betaxolol, bisoprolol, metoprolol) exhibit these effects to a lesser extent.

NSAIDs and salicylates in high doses inhibit the synthesis of prostaglandin E (which inhibits the secretion of endogenous insulin) and thus enhance basal insulin secretion, increase the sensitivity of pancreatic β-cells to glucose; the hypoglycemic effect with simultaneous use may require dose adjustment of NSAIDs or salicylates and/or insulin, especially with prolonged joint use.

Currently, a significant number of insulin preparations are available, including those obtained from animal pancreases and synthesized by genetic engineering methods. The drugs of choice for insulin therapy are genetically engineered highly purified human insulins with minimal antigenicity (immunogenic activity), as well as human insulin analogues.

Insulin preparations are available in glass vials hermetically sealed with rubber stoppers with aluminum liners, in special so-called insulin syringes or syringe pens. When using syringe pens, the drugs are in special cartridge vials (penfills).

Intranasal forms of insulin and insulin preparations for oral administration are being developed. When insulin is combined with a detergent and administered as an aerosol to the nasal mucosa, an effective plasma level is achieved as quickly as with intravenous bolus administration. Insulin preparations for intranasal and oral use are under development or undergoing clinical trials.

GENERAL METHODS OF SELECTING INSULIN DOSE FOR PATIENTS WITH DIABETES

The dose of the drug is calculated on the basis that 1 U of subcutaneously injected insulin promotes the absorption of 4 g of glucose in compensated diabetes mellitus and 3 g of glucose in decompensated diabetes mellitus. Given that the purpose of insulin therapy is not only to maintain a normal blood sugar level, but also to normalize carbohydrate and fat metabolism, normalize body weight, and prevent diabetic complications, there are several ways to select the daily dose of insulin. They are calculated depending on the course and duration of the disease, as well as on the initial indicators of sugar in the blood and urine. Let's consider some schemes.

Choosing an insulin dose depending on the nature and course of diabetes mellitus

• Newly diagnosed diabetes: the daily dose of insulin is 0.5 U per 1 kg of body weight.

• The first year of diabetes mellitus without clinical manifestations of the disease: 0.3–0.4 U per 1 kg of body weight.

• Long-term current diabetes mellitus: 0.6–0.7 U per 1 kg of body weight.

In any case, the daily dose of insulin should not exceed 1 U per 1 kg of body weight, otherwise as a result of an insulin overdose, the patient may experience hypoglycemic attacks and develop a coma. In these cases, it is necessary to choose a special way to reduce the insulin dose. It is better to do this in a hospital setting, where there is the possibility of providing immediate medical assistance to remove the patient from a coma and relieve other acute complications.

Choosing an insulin dose depending on the blood sugar level (glycemia)

If the blood sugar level is above 8.3 mmol/l, then for every 0.22 mmol/l of blood glucose, 1 U of simple insulin is required, which is administered every 6-8 hours.

Choosing an insulin dose depending on several indicators for patients with complicated diabetes

This technique is used only in a hospital setting, when diabetes is complicated or cannot be compensated by conventional methods. To determine the dose of injected insulin, it is carefully monitored how insulin acts throughout the day. Therefore, the study is carried out very often. The blood sugar level is determined on an empty stomach, then the daily loss of sugar in the urine is examined, as well as the level of hemoglobin bound to glucose. In addition to these indicators, it is necessary to determine the blood sugar level 6 times a day every 4 hours. Usually, sugar samples are taken at 8 am, then at 12 pm, 4 pm, 8 pm, 12 am

and 4 am the next morning. Even more often – 5 times a day – sugar in the urine is checked. The first portion of urine is taken from 9 to 12 am, the second – from 12 to 6 pm, the third portion of urine is taken and examined for sugar from 6 pm to 10 pm, the fourth – from 10 pm to 6 am, and the fifth – from 6 am to 9 am. All this allows you to determine whether the injected insulin is enough or not enough, that is, it helps to adjust the insulin dose so that the sugar level remains stable throughout the day. Even a three-time determination of the sugar level in the urine allows you to understand the effect of the injected insulin and choose the correct dose. With a three-time determination of the sugar level in the urine, the first portion is taken from 8 am to 2 pm. The amount of sugar in this portion reflects the effect of the morning dose of insulin. The second portion of urine is taken from 2 to 7 p.m., and the amount of sugar in it indicates the effectiveness of the dose of insulin administered before lunch. Finally, the third portion of urine is taken from 7 p.m. to 8 a.m.

Devices for administering insulin. Syringe pens and other devices

Each device is used for a specific purpose, but in home insulin therapy, only insulin syringes and syringe pens are used, with the help of which diabetics successfully adjust their blood sugar levels.

They are used in uncomplicated diabetes.

In very serious cases, and only in a hospital, a special device is used - a biostator. It allows not only to quickly determine the blood sugar level, calculate and adjust the rate of insulin administration, but also injects glucose and insulin itself. In essence, it is a pancreas simulator.

Biostator is used in the following cases:

• in newly diagnosed diabetes;
• in labile diabetes;
• to remove the patient from ketoacidosis and diabetic coma;
• during childbirth and surgical operations.

If diabetes is complicated, then insulin is administered in a hospital using microdosers. These devices can be used to administer short- and long-acting insulin subcutaneously and intravenously at a set rate. Microdosers are equipped with a device for blood sugar control. They are used to stabilize the course of diabetes and select an insulin dose in the following cases:

• in newly diagnosed diabetes;
• in severe diabetes;
• in labile diabetes;
• in frequent hypoglycemia;
• in the presence of acetone in the urine;
• in chronic insulin overdose;
• in the presence of insulin addiction.

Microdosers allow you to gradually increase the dose of insulin under the control of blood sugar levels and urine, until a stable effect of lowering blood sugar to normal levels is obtained. After that, the patient can switch to using syringe pens or insulin syringes.

The needle is built into the syringe, so insulin dosing can be done quite accurately. However, it should be borne in mind that the syringe must be sterilized after each injection and stored in a protective case. If you follow these simple hygiene rules, a plastic syringe can

be used repeatedly until the needle becomes blunt.

Most diabetics prefer to use syringe pens, which are equipped with an insulin cartridge (penfill) and a sterile needle. They work like ink fountain pens. In a syringe pen, the needles are disposable, and the penfills are changed as insulin is used. To enter a certain dose of insulin, a button is used, under the action of which the required amount of the drug enters the needle. The advantage of the syringe pen is also that the injections are absolutely painless. Among the most popular devices are the Novopen-1, Plivapen-1, Optipen-1 syringe pens, which are used for short-acting insulins, as well as the Novopen-2, Plivapen-2, Optipen-2 syringe pens, designed for long-acting insulins.

Insulin injection rules

Diabetics and parents of sick children have to master the insulin injection technique themselves. There are no particular difficulties in this, but you need to know the injection rules well, as well as the places where insulin can be injected.

So, the areas for subcutaneous insulin injection: the front wall of the abdomen, under the shoulder blades, the outer side of the thigh, buttocks, shoulder. Since even during the day you have to make several injections, the places for insulin injection must be alternated, and according to a certain scheme. If the previous injection was made in the anterior abdominal wall, then the next injection should be made in the same area, but 2-3 cm higher, then move the insulin injection site 23 cm lower, then to the left and, finally, to the right of the previous injection site. After that, insulin can be injected into the thigh, where the injection sites should also be changed. Then to another area, etc. Then, by the time the insulin injection is made again in the anterior abdominal wall, the traces of the injections will have time to heal.

Different areas react slightly differently to insulin. So, insulin is absorbed from the anterior abdominal wall the fastest, and the slowest from the anterior surface of the thigh. Therefore, it is recommended to inject into certain places at the same time. For example, if you injected insulin into the thigh in the morning and under the shoulder blades in the evening, then the next day follow the same scheme: in the thigh in the morning, in the evening - under the shoulder blades. Then the effectiveness of insulin action during the day will be approximately the same.

Different types of insulin are better absorbed in certain areas. Thus, short-acting insulin is most often recommended to be injected into the anterior abdominal wall. Long-acting insulin is usually injected into the buttock, anterior thigh, under the shoulder blades or into the shoulder.

Insulin injection into the shoulder should be done very carefully and in the most extreme cases, when other places are too open and there is a risk of complications. The fact is that the muscles are very close to the skin in the shoulder, and insulin can accidentally get there. In the muscle, it is absorbed into the blood much faster than subcutaneously, as a result, the effect of insulin will be faster.

How to inject insulin

Insulin is injected subcutaneously to a depth of 0.5 cm. In this case, it is necessary to get the needle into the subcutaneous layer between the muscles and the skin. In order not to get into the muscle, you need to know the technique and sequence of the injection.

1. With the thumb and index finger of one hand, slightly pull the skin at the injection site so that a fold forms on the skin. But do not squeeze the skin with your fingers too much.

2. With the other hand, take the syringe as you normally hold a pencil.

3. Holding the syringe vertically, with one movement of the hand, insert the needle to its entire length into the base of the fold.

4. Press the plunger or press the button, injecting insulin into the subcutaneous tissue, and count to ten.

5. Remove the needle from the skin.

Needles come in lengths of 12 and 8 mm. Depending on the patient's build, the needle size is chosen. Thin people are recommended to use a shorter needle (8 mm), others - a standard needle (12 mm). After the injection, a small bruise may appear at the injection site, which will quickly pass.

Insulin storage rules

To preserve the activity of insulin, it must be kept in the refrigerator at a temperature of 2-8 ° C, and before use, it must be heated to body temperature. Be sure to pay attention to the shelf life of the insulin preparation, which is written on the ampoule, as it has a limited time. If the insulin preparation is a suspension, that is, a mixture, then it looks cloudy, so it must be mixed thoroughly by rolling the ampoule between your palms. Thus, the insulin solution will become homogeneous, and it can be injected under the skin. If flakes appear in the insulin, it has changed color or thickened, it means that it has already spoiled and should not be used under any circumstances. Insulin can spoil both at very high and very low temperatures, as well as under the influence of direct sunlight.

Possible complications of insulin therapy

If certain safety measures and rules are not followed, then insulin treatment, like any other type of treatment, can cause various complications. The complexity of insulin therapy lies in the correct selection of insulin dosage and treatment regimen, so a diabetic needs to monitor the entire treatment process especially carefully. It seems difficult only at first, and then people usually get used to it and cope with all the difficulties perfectly. Since diabetes is a lifelong diagnosis, they learn to handle a syringe in the same way as all other people - with a knife and fork. However, unlike other people, diabetics cannot afford even a little relaxation and "rest" from treatment. Otherwise, this threatens with complications, although such can arise not only through the fault of the patients themselves, but also due to circumstances beyond their control. All the more so, you need to know about them in order to be able to prevent complications in time, which will be discussed later.

Lipodystrophy

This complication develops at injection sites as a result of impaired formation and breakdown of adipose tissue, i.e. at the injection site, induration (when adipose tissue increases) or depression (when adipose tissue decreases and subcutaneous fat disappears) appears. Accordingly, this is called the hypertrophic iatrophic type of lipodystrophy.

Lipodystrophy develops gradually as a result of prolonged and constant traumatization of small peripheral nerves by a syringe needle. This is its most common cause.

Another cause of the complication is the use of insufficiently pure insulin. Usually this complication of insulin therapy occurs after several months or even years of insulin administration. The complication is not dangerous for the patient, although it leads to impaired insulin absorption, and also brings a person some discomfort. Firstly, these are cosmetic skin defects, and secondly, soreness in the areas of complications, which increases with a change in weather.

Treatment of atrophic type lipodystrophy consists in the use of porcine insulin together

with novocaine, which helps restore the trophic function of the nerves. Hypertrophic type of lipodystrophy is treated with physiotherapy: phonophoresis with hydrocortisone ointment.

Using preventive measures, you can protect yourself from this complication.

Prevention of lipodystrophy

• Alternating injection sites.

• Administering only insulin heated to body temperature.

• After treatment with alcohol, the injection site should be thoroughly wiped with a sterile napkin or wait for the alcohol to dry completely.

• Slowly and deeply inject insulin under the skin.

• Use only sharp needles.

Allergic reactions

This complication is explained by the presence of foreign proteins in the composition of insulin. There are local allergic reactions that occur in and around the injection sites in the form of redness of the skin, seals, swelling, burning and itching. Much more dangerous are general allergic reactions that manifest themselves in the form of urticaria, Quincke's edema, bronchospasm, gastrointestinal disorders, joint pain, enlarged lymph nodes and even anaphylactic shock.

Life-threatening allergic reactions are treated in a hospital with the introduction of the hormone prednisolone, other allergic reactions are treated with antihistamines, as well as the introduction of the hormone hydrocortisone along with insulin. However, in most cases, allergy can be ruled out by switching the patient from pig insulin to human insulin.

Chronic insulin overdose

Chronic insulin overdose occurs when the need for insulin becomes too high, that is, exceeds 1-1.5 U per 1 kg of body weight per day. At the same time, the patient's condition worsens significantly. If such a patient's insulin dose is reduced, he will feel much better. This is the most characteristic sign of insulin overdose.

Other manifestations of the complication:

• severe diabetes;

• high fasting blood sugar;

• sharp fluctuations in blood sugar levels during the day;

• large losses of sugar in the urine;

• frequent fluctuations in hypo- and hyperglycemia;

• tendency to ketoacidosis;

• increased appetite and weight gain.

Complications are treated by adjusting insulin doses and selecting the correct drug administration regimen.

Hypoglycemic states and coma

The causes of this complication lie in the incorrect selection of the insulin dose, which turned out to be too high, as well as in insufficient carbohydrate intake. Hypoglycemia develops 2-3 hours after the administration of short-acting insulin and during the period of maximum activity of long-acting insulin. This is a very dangerous complication, because the concentration of glucose in the blood can drop very sharply, and the patient may develop a hypoglycemic coma.

The development of hypoglycemic complications is quite often caused by prolonged intensive insulin therapy combined with increased physical activity.

If the blood sugar level is allowed to fall below 4 mmol/l, then in response to this a sharp rise in sugar may occur, that is, a state of hyperglycemia.

Prevention of this complication is to reduce the dose of insulin, the effect of which occurs when blood sugar drops below 4 mmol/l.

Insulin resistance

This complication is caused by getting used to certain doses of insulin: over time, they no longer have the proper effect and their increase is required. Insulin resistance can be both temporary and long-term. If the need for insulin reaches 100-200 units per day, but the patient does not have attacks of ketoacidosis and does not have other endocrine diseases, then we can talk about the development of insulin resistance.

The causes of the development of temporary insulin resistance include: obesity, high blood sugar levels, dehydration, stress, acute and chronic infectious diseases, lack of physical activity. Therefore, you can get rid of this type of complication by eliminating the listed causes.

Long-term, or immunological, insulin resistance develops due to the production of antibodies to the administered insulin, a decrease in the number and sensitivity of insulin receptors, as well as impaired liver function. Treatment consists of replacing pig insulin with human insulin, as well as using the hormones hydrocortisone or prednisolone and normalizing liver function, including through diet.

SELF-CONTROL OF DIABETES

To avoid complications and maintain good health, every diabetic should learn self-control methods. This is the only way to live with diabetes, feeling like a normal person.

It is impossible to choose a scheme for insulin administration and its dosage for life. The amount of insulin and the time of its administration have to be constantly adjusted, because blood sugar levels depend on many factors that cannot be predicted and excluded. These are unplanned physical exertion, emotions, errors in the diet, infections, stress. These circumstances make up the life of any person, but for a diabetic they can be dangerous, as they change his physiological indicators too much, on which his health depends. Therefore, a diabetic should be constantly aware of these changes, monitoring his condition and monitoring laboratory indicators. Self-control is necessary for all diabetics, both insulin-dependent and insulin-independent. The only difference is that with INSD, blood sugar control is carried out much less often than with ISD, but constantly, and with worsening health, monitoring of blood sugar levels becomes more frequent.

Self-monitoring of an ISD patient

• Before and after eating, it is necessary to determine blood sugar levels.

• Compare these indicators with physical activity and other unusual (emotional, stressful, painful) situations.

• Conduct a thorough analysis of your subjective feelings.

• Evaluate the data obtained.

• Adjust the dosage of insulin and other medications, as well as your diet, in a timely manner.

To quickly and accurately control your blood sugar levels and urine, there are special devices - test strips and glucometers. They allow you to quickly and painlessly do a sugar test for yourself and immediately see its result.

Measuring blood sugar levels and urine using test strips and a glucometer

A test strip is a strip with a reagent applied to it - a substance that reacts to the blood depending on the sugar level in it. Using a special device in the form of a pen (lancet), you need to pierce the skin on the pad of your finger and place a drop of blood on the test strip where the reagent is applied (the colored part). This sensitive substance immediately changes its color depending on the sugar level in the drop of blood.

There are two ways to determine the blood sugar level.

• Compare the color on the test strip with the color scale, which indicates which color corresponds to which blood sugar level.

• Using a glucometer - a device into which a test strip is inserted and in which an automatic assessment of the blood sugar level occurs. The patient only has to read the result of the study on the digital display of the device.

Although the device is used for faster and more convenient testing, with some skill, the visual method of determining blood sugar is just as accurate. There is a minimal error in the calculations in both cases, but it does not play a role in determining the treatment regimen and insulin dosage.

Measuring the level of sugar in the urine is carried out with special test strips according to the same scheme. The test strip is immersed in urine, and the test field changes its color depending on the concentration of sugar in the urine. The most accurate are test strips with a double test field. They are recommended for use, although the analysis of sugar in the urine provides less information about the course of diabetes than the study of blood sugar levels.

Urine test for ketonuria

A patient with diabetes needs to check for the presence of ketone bodies (acetone) in the urine if he has a persistent increase in blood sugar levels and its high concentration in the urine, that is, when several test results in a row show high numbers: above 14 mmol/l in the blood and 3% in the urine. Indications for such a test are also deterioration in well-being (nausea and vomiting) and concomitant diseases with elevated body temperature.

Urine testing for the presence of ketone bodies is necessary in order to prevent an attack of ketonuria and prevent diabetic coma. For this study, there are special test strips that are immersed in urine and change their color depending on the concentration of ketone bodies in the urine. The very presence of ketone bodies in the urine indicates a serious metabolic disorder and requires immediate treatment.

Body weight control

It is necessary to control body weight in order not to miss the first signs of obesity and the associated development of diabetic complications and other concomitant diseases. To control body weight, a special test has been developed that detects excess body weight. It is called the body mass index (BMI) or the Quetelet index and is measured in kg/m2. Therefore, people suffering from diabetes should regularly measure their body weight and height. Based on these data, the Quetelet index is calculated.

Calculation of the Quetelet index: BMI = weight (kg) / (height (m2)).

The normal Quetelet index for men is 20-25, for women - 19-24.

TREATMENT OF DIABETES COMPLICATIONS

The fight against diabetes complications primarily consists in their prevention, that is, constant compensation of diabetes. Even if complications have already begun, normalization of blood sugar levels allows you to reverse the process, that is, not only stop their

development, but also minimize the disease.

Treatment of angiopathy

The main treatment is stable and long-term compensation of diabetes. Therefore, the patient is recommended to strictly monitor the diet, eat several times a day and little by little, and exclude carbohydrates from his diet. In addition to the diet, the patient should have moderate physical activity, which helps the absorption of sugar and improves the functioning of the cardiovascular system.

Drug treatment is prescribed by a doctor. Usually these are angioprotectors, anticoagulants and antiplatelet agents, which help normalize blood circulation and strengthen blood vessels. In addition, physiotherapy methods are used - hyperbaric oxygenation, acupuncture, laser irradiation, magnetotherapy.

Treatment of retinopathy (pathology of retinal vessels)

In this case, the main effort of the patient himself should be directed to compensating for diabetes mellitus. For therapeutic purposes, the patient is prescribed angioprotectors and anticoagulants to stabilize the vascular wall and improve blood circulation, and also use resorption therapy, introducing drugs such as trypsin and lidase.

If there is a risk of retinal detachment, then physiotherapy procedures are performed, primarily photocoagulation.

Treatment of nephropathy

The patient is recommended to follow a low-protein diet and take vitamins. It is necessary to monitor blood pressure and use drugs that lower blood pressure, as well as anti-hypoxia agents.

If nephropathy occurs with the development of renal failure, the patient is recommended to include alkaline mineral waters, natural berry and fruit juices in the diet.

In the hospital, special therapy is carried out to detoxify the body, that is, to remove toxic substances. In case of severe nephropathy, blood purification using hemodialysis is used.

Treatment of polyneuropathy

First of all, the patient is faced with the task of complete compensation of diabetes mellitus. Only in this case, treatment of the complication with medications and other means will give a positive result. For the treatment of polyneuropathy, drugs are used that improve the functions of blood vessels and nerve fibers (i.e., angioprotectors, anticoagulants, antiplatelet agents, vitamins, lipoic acid). To improve the conductivity of nerve impulses along nerve fibers, the drug Prozerin is used.

Physiotherapy methods for treating complications include the following procedures: electrophoresis, balneotherapy, paraffin treatment, ozokerite, massage and acupuncture. They help improve the condition of nerve fibers, as well as relieve pain and restore sensitivity in tissues.

ORAL DRUGS FOR THE TREATMENT OF DIABETES.

A person with type 2 diabetes has two problems that can increase the level of sugar:

1. Production of a small amount of insulin, so glucose does not enter the cells. This problem is the most common today.

2. Resistance of cells to insulin. They do not perceive glucose. This problem occurs, but is not as common as the first.

If this process is not controlled, then cellular failure may develop, which is dangerous. A person has to make constant injections of insulin. If this does not help, then treatment is necessary by combining insulin and blood sugar-lowering pills or taking them as separate therapy.

Glucose-lowering L C - sulfonylurea derivatives

SULPHONYLUREA DERIVATIVES OF THE 1ST GENERATION:

Carbutamide (INN) - tab. Sp. B Bukarban (Hungary);

Chlorpronamide (INN) - tab. Sp. B (Poland).

SULFONYLUREA DERIVATIVES OF THE 2ND GENERATION:

Glibenclamide (INN) - the first drug of the 2nd generation, on the market since 1969; tab. Sp. B. On the pharmaceutical market there are offers of Glibenclamide in the amount of 21 trade names, including Gylemal (Hungary), Glibenclamide (Germany and others), Daonil (Germany, India), Maninil (Germany) and others

Gliclazide (INN) - tab. Sp. B (Switzerland, India),

Glidiab (Russia),

Diabeton (France) and others

Glipizide (INN) — tab. Sp. B.

Minidiab (Italy),

Glibenez (France).

Glikvidon (INN) — tab. Sp. B.

Glyurenorm (Austria).

Glidifen (still does not have an INN) — tab. Sp. B (Russia).

Since 1995, the world pharmaceutical market has released a 3rd generation SULFONYLUREA DERIVATIVE PREPARATION:

Glimeniride (INN) — tab Amaril (Germany). In terms of the strength of the sugar-lowering effect, it is stronger than 2nd generation sulfonylurea derivatives, it is taken once a day.

BIGUANIDES. These include 2 active ingredients, including:

Buformin (INN) - dragee, Silubin-retard (Germany),

Metformin (INN) - inhibits the process of glucose formation from non-carbohydrate products in the liver, slows down the absorption of carbohydrates in the intestines (appeared on the US pharmaceutical market in 1994), tab. Sp. B (Poland, Croatia, Denmark),

Glucophage (France),

Siofor (Germany) and others

The class of ALPHA-GLUCOSIDASE INHIBITORS includes

Acarbose (INN), produced in Germany under the trade name Glucobay,

Miglitol (INN) -

Diastabol (Germany).

The mechanism of their action is to slow down the breakdown of carbohydrates entering the body into simple sugars (glucose, fructose, lactose). Taking these drugs does not replace insulin therapy, but is an additional treatment for type 2 diabetes. It is prescribed to patients when the use of a diet does not lead to normalization of blood glucose levels.

PRANDIAL GLYCEMIC REGULATORS, which belong to the class of chemical substances CARBAMOYLBENZOIC ACID DERIVATIVES, have a similar effect to sulfonylureas of the 2nd generation:

Repaglinide (MNN) - tab. NovoNorm (Denmark);

Nateglinide (MNN) - tab., Starlix (Switzerland).

These drugs protect the beta cells of the pancreatic islets from excessive depletion, they are characterized by a rapid corrective effect on reducing the level of postprandial glycemia.

Among the new drugs - insulin sensitizers - GLITAZONES OR THIAZOLIDINEONES. This new group of substances gives a good effect of increasing the supply of glucose to peripheral tissues, improves metabolism, without increasing the need for insulin. However, the drugs have some adverse side effects. These drugs include:

Rosiglitazone (INN) - tab., Avandia (France);

Pioglitazone (INN) - tab., Actos (USA).

COMBINED ORAL SUGAR-LOWERING drugs allow us to offer the patient drugs with an optimal effect due to different mechanisms of action. In addition, as a rule, in combinations it is possible to reduce the dose of individual components, thus reducing side effects.:

Glibomet - contains glibenclamide and metformin, tab. (Italy).

SUGAR-LOWERING MEDICINES OF PLANT ORIGIN

Arfazetii — contains blueberry shoots, common bean fruit flaps, Manchurian aralia root or rhizome with zamanikha root, rosehip fruits, horsetail grass, St. John's wort, chamomile flowers (Russia, Ukraine).

The following plant raw materials can be used for diabetes: Manchurian aralia root, Aralia tincture, Psoralea drupe fruit, etc.

In recent years, a new drug has appeared on the pharmaceutical market — Glucagon, an insulin antagonist, which is a protein-peptide hormone that participates in the regulation of carbohydrate metabolism. It is used for severe hypoglycemic states that occur in patients with diabetes after insulin injections or taking oral medications.

Glucagon (MNN) - lyophilized powder in a vial with a solvent for injection.

Classification of oral antidiabetic drugs.

Oral hypoglycemic drugs can be divided into several types. Each of the presented types has its own principle of action on human organs:

1. Sulfinyl urea drug. These hypoglycemic tablets stimulate the pancreas to produce more insulin. First-generation drugs are now practically not used, since they did not have the strength and their duration of action was short. Now they use maninil, minidiab, amaril. These pills can reduce the sugar content by several percent, which is quite significant in the patient's situation.

2. Biguanides. These tablets, used in diabetes, were given the ability to improve the work of insulin to move glucose into cells. They block the release of sugar by the liver. There are contraindications for the use of biguanides. They cannot be prescribed to people who have heart or kidney disease.

3. Thiazolidinediones. The oral hypoglycemic drugs in question are able to increase the efficiency of insulin in muscle tissue. The action of the drugs begins 7 days after the first dose. It is necessary to monitor liver function when using these drugs.

4. Alpha-glucosidase inhibitors. Block those particles that allow starch to be absorbed, which is a good way to slow down the increase in sugar. Side effects include diarrhea and bloating. It should be emphasized that there may be no side effects. Everything is individual.

5. Starlix and Novonorm tablets. Stimulate the pancreas, as a result of which a large amount of insulin is released. It all depends on how much glucose is in the blood.

6. There are drugs that can signal the liver about a large amount of sugar, increase insulin secretion. They control the increase in sugar levels, but do not affect the patient's weight. They can be taken alone or in combination with other medications.

7. Combination treatment. There are drugs that contain several medications in one shell. However, this type of therapy is always allowed strictly after the patient passes a number of tests, which, in turn, are prescribed exclusively by the attending physician. Along with existing drugs, a new type of drugs has appeared that act on the hormones of the digestive tract (incretins). They react to the food consumed and are able to increase the insulin content, that is, contribute to the following processes:

 Significantly increase the insulin content and inhibit the production of glucagon by the pancreas.

 Significantly increase the insulin level, thereby helping to utilize glucose in peripheral tissues.

 Control the release of glucose by the liver when combined with high insulin and low glucagon content.

Use of oral hypoglycemic agents

1. Sulfonylurea derivatives

Despite the presence of hyperinsulinemia in patients with type 2 diabetes (at least at the beginning of the disease), to overcome the existing insulin resistance, the body's own insulin is not enough, and it is necessary to increase the concentration of this hormone in the blood. An increase in the level of insulin in the blood under the influence of sulfonylurea derivatives ensures the utilization of glucose by insulin-dependent tissues and the suppression of glucose production by the liver. Sulfonylurea drugs are prescribed starting with minimal doses, gradually (with an interval of 1-2 weeks) assessing the effect and increasing the dose as necessary. In each specific case, the dose of the drug should be selected individually, remembering the high risk of hypoglycemic states in elderly people.

2. Biguanides

The effect of biguanides on glycemia can be assessed as antihyperglycemic, not hypoglycemic. Drugs that reduce elevated blood glucose levels (especially on an empty stomach) to normal values, but not to low ones.

Metformin is practically the only oral hypoglycemic agent, the treatment of which may lead not to an increase, but to a decrease in the body weight of patients, therefore the indication for the use of metformin is the inability to achieve compensation for the disease in people with type 2 diabetes (primarily with obesity) against the background of diet therapy alone.

Metformin is prescribed, starting with a small dose (usually 500 mg), during or immediately after the evening meal (despite the fact that the absorption rate slows down, this allows you to reduce side effects), then the dose is gradually increased to 850 mg 2-3 times a day.

3. Meglitinides (prandial glycemic regulators) Meglitinides stimulate insulin secretion by binding to their own specific sites on the β-cells of the pancreas. They are rapidly absorbed. The onset of action occurs after 5-10 minutes, which allows the patient to take these drugs immediately before a meal. The peak concentration in the blood plasma is reached after

40-60 minutes, which regulates the level of postprandial glycemia. The drugs are inactivated just as quickly, so the insulin level returns to the initial level 3 hours after administration, which mimics normal insulin secretion during a meal and reduces the likelihood of hypoglycemia in the intervals between meals. Thus, these drugs allow the patient to be more flexible in terms of adherence to the diet. In case of skipping carbohydrates (for example, at lunch), the drug is also skipped. If postprandial glycemia improves with meglitinides, but fasting glycemia remains elevated, they can be successfully combined with metformin or long-acting insulin before bedtime.

4. Thiazolidinediones

The action of thiazolidinediones (pioglitazone, rosiglitazone) is to increase the sensitivity of tissues to insulin. However, unlike biguanides, thiazolidinediones affect the transcription of genes responsible for the transmission of insulin effects in cells, and, therefore, it takes several months for their effects to be realized. Drugs of this group do not cause hypoglycemia, so they can be safely combined with insulin and PSSP.

Pioglitazone is prescribed once a day, regardless of meals, during treatment it is necessary to monitor the activity of liver enzymes.

Dipeptidyl peptidase-4 inhibitors

Vildagliptin is a new dipeptidyl peptidase-4 inhibitor that improves glycemic control by correcting impaired function of pancreatic β-cells, thus enhancing insulin secretion and reducing glucagon secretion. The drug is not biotransformed with the participation of cytochrome P-450, and no drug interactions with the most commonly prescribed drugs have been identified.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is an emergency condition that develops due to absolute (usually) or relative (rarely) insulin deficiency, characterized by hyperglycemia, metabolic acidosis and electrolyte disturbances. The extreme manifestation of diabetic ketoacidosis is ketoacidotic coma. Statistical data: 46 cases per 10,000 patients with diabetes mellitus. Predominant age - up to 30 years.

Risk factors

- Late diagnosis of diabetes mellitus.
- Inadequate insulin therapy.
- Concomitant acute diseases and injuries.
- Previous dehydration.
- Pregnancy complicated by early toxicosis.

Basic provisions

- It is necessary to remember about the mandatory control of glycemia in patients receiving insulin and having any complaints or in the presence of objective symptoms.
- It is necessary to identify concomitant acute diseases (for example, infectious), which contribute to an increase in the concentration of glucose in the blood.

Ketoacidosis should be treated in a hospital setting. In outpatient treatment of a patient with glycemia (but without ketoacidosis), it is necessary to make sure that:

- the patient receives insulin, and the blood glucose content begins to decrease;
- the patient can take care of himself and is able to seek help in case of deterioration of well-being.

DIABETIC COMA. Pharmacological correction.

Diabetic coma is a condition that develops as a result of a lack of insulin in the body in patients with diabetes. Insulin deficiency leads to an increase in the concentration of glucose in the blood and "starvation" of peripheral insulin-dependent tissues, which are unable to utilize glucose without the participation of insulin.

In response to the "hunger" of the body, the liver begins the synthesis of glucose (gluconeogenesis) and ketone bodies from acetyl-CoA - ketosis develops, and with insufficient utilization of ketone bodies and increased acidosis - ketoacidosis. The accumulation of underoxidized metabolic products, in particular lactate, leads to the development of lactic acidosis. In some cases, gross metabolic disorders against the background of decompensation of diabetes mellitus lead to the development of hyperosmolar coma.

Diabetic coma can last a very long time - the longest case in history of a patient being in this state is more than four decades.

Diabetic ketoacidotic coma is a consequence of absolute or relative insulin deficiency and a sharp decrease in glucose utilization by body tissues. Most often it develops in patients with VID, which is characterized, as a rule, by a severe labile course.

The serum glucagon content in diabetic ketoacidosis is increased and there is a close relationship between the increase in the blood glucagon level and the increase in the concentration of glucose and ketoacids. Counterinsular hormones, especially glucagon, increase gluconeogenesis, glycogenolysis, lipolysis and the production of ketone bodies in the liver.

Lipolysis is enhanced to such an extent that the concentration of triglycerides, phospholipids, cholesterol and NEFA often increases by 50%. The massive influx of lipids into the liver is accompanied by its fatty infiltration and an increase in size. Fatty acids are a source of energy mainly for muscles, and ketone bodies for the brain. Lipolysis and proteolysis are stimulated by glucocorticoids, catecholamines, GH and glucagon.

Fatty acids are metabolized in the liver to acetyl-CoA, which is completely oxidized to CO2 and H2O in the Krebs cycle or used for the synthesis of fatty acids in the processes of lipogenesis. Under normal conditions, only a small part of it is converted into acetoacetyl-CoA, acetoacetic acid and b-hydroxybutyric acid. Acetoacetic acid, in turn, is converted into acetone. In diabetes and especially in ketoacidotic coma, increased breakdown of fats and an increase in their supply to the liver lead to the formation of excess acetyl-CoA and enhanced ketogenesis. Amino acid imbalance also develops, since the concentration of ketogenic amino acids (leucine, isoleucine, valine) increases in the blood plasma with a relative decrease in the level of glucogenic amino acids (glycine, serine, alanine, glutamine), which are spent on gluconeogenesis.

Diabetic ketoacidosis begins with insulin deficiency. The resulting increase in glucose concentration, together with increased protein catabolism and lipolysis, leads to dehydrating diuresis, electrolyte depletion, severe hyperglycemia, and severe acidosis. To correct this condition, insulin, electrolyte, and fluid replacement therapy is necessary.

A massive influx of ketogenic substrates (lipids and amino acids) into the liver contributes to the increase in ketogenesis during diabetes decompensation. The progressive accumulation of ketone acids in the blood causes the depletion of its alkaline reserves, resulting in a decrease in blood pH and the development of metabolic acidosis, i.e.,

ketoacidosis.

The pathogenesis of disorders of consciousness and other psychoneurological symptoms of diabetic coma is not fully understood. These disorders are usually associated with the following factors:

1) the toxic effect on the brain of excess ketone bodies;

2) cerebrospinal fluid acidosis (possibly intracellular acidosis in the CNS);

3) dehydration of brain cells;

4) hyperosmolarity of the intracellular space in the CNS;

5) CNS hypoxia due to a decrease in 2,3-diphosphoglycerophosphate;

6) a decrease in the content of GABA in the CNS.

Hyperosmolar (non-ketonemic) diabetic coma occurs more often in people suffering from mild or moderate INZD, receiving only diet therapy or oral hypoglycemic drugs. Various infections (pneumonia, pyelitis, cystitis, etc.), acute pancreatitis, burns, myocardial infarction, cooling, inability to quench thirst (in lonely elderly patients confined to bed) contribute to the development of hyperosmolar coma.

The absence of ketoacidosis in hyperosmolar coma is due to the fact that, on the one hand, this pathology reveals residual insulin secretion, which is insufficient to eliminate hyperglycemia, but quite sufficient to inhibit lipolysis, and on the other hand, the sensitivity of peripheral tissues to insulin differs from that in ketoacidosis.

The trigger for water and electrolyte disturbances in this type of coma is hyperglycemia, which is accompanied by an increase in osmotic pressure in the vascular bed. To maintain isoosmolarity of the media, compensatory movement of fluid from cells and the extracellular space into the vascular bed begins. At the same time, glycosuria develops and, as a consequence, polyuria, since the high osmotic pressure of primary urine prevents the reabsorption of water in the renal tubules. This so-called osmotic diuresis leads to a massive loss of not only water, but also electrolytes, primarily Na+, K+, CI+, HCO3 ions.

Restoration of isoosmolarity between the three spaces occurs not by reducing hyperosmolarity in the vascular bed, but by cellular dehydration and increasing intracellular osmotic pressure.

Compared with ketoacidosis, hyperosmolar coma is characterized by an increased susceptibility to various hemocoagulation disorders, especially such as disseminated intravascular coagulation (DIC), arterial and venous thrombosis.

Lactic acidotic coma occurs in diabetes much less frequently than ketoacidosis and hyperosmolar coma. Lactic acidosis can be combined with ketoacidosis or hyperosmolar coma. Sometimes it develops against the background of taking biguanides (phenformin and adebit) in patients with heart and kidney failure, liver and lung diseases, as well as in shock, blood loss, sepsis.

It is known that the liver is able to metabolize about 3400 mmol of lactic acid per day. But in the above conditions, accompanied by significant tissue hypoxia, the formation of lactic acid prevails over the processes of its utilization. The development of lactic acidosis is also facilitated by parenteral administration of fluids containing fructose, sorbitol or xylitol.

The general treatment regimen for diabetic coma includes:

• elimination of insulin deficiency and normalization of carbohydrate metabolism;

• optimally rapid rehydration of the body;

• restoration of normal extracellular and intracellular electrolyte composition;

• restoration of glucose (glycogen) reserves in the body;

• restoration of normal acid-base balance (KOR);

• diagnosis and treatment of diseases or pathological conditions that caused diabetic coma;

• carrying out a complex of therapeutic measures aimed at restoring and maintaining the functions of internal organs (heart, kidneys, lungs, etc.).

Hypoglycemic (insulin) coma develops in patients with diabetes mellitus when an excessive dose of insulin or sulfonamides is administered (especially in combination with salicylates, alcohol) against the background of insufficient carbohydrate intake with food or in the presence of insulinoma.

Hypoglycemic coma is certainly determined by neuroglycopenia (decreased glucose levels in the brain). The pathogenesis of hypoglycemic hypoxia is based on energy starvation of neurons, disorganization of redox processes in neurons, i.e. acute substrate hypoxia of the brain

It is the brain cells that are most sensitive to hypoglycemia, since they receive energy from aerobic oxidation of glucose and are unable to:

1) accumulate glucose in significant quantities;

2) synthesize glucose;

3) metabolize other substrates, except glucose and ketone bodies. Moreover, the latter satisfy the energy needs of the brain to a small extent;

4) extract insufficient amounts of glucose from the extracellular fluid; insulin does not promote the entry of glucose from the extracellular fluid into neurons.

Hypoglycemic comas associated with an overdose of insulin require correction with glucose, and to prevent them, detailed instructions to the patient regarding the time of administration of the drug in relation to food intake.

Pharmacotherapy of carbohydrate metabolism pathologies.

Pharmacotherapy of hypoglycemic states usually includes enteral or parenteral (intravenous) administration of glucose. In the latter case, it should be remembered that an isotonic plasma solution of glucose is its 5% solution, this must be taken into account in order to avoid damage to cells by insufficient or excessive osmolarity during prolonged intravenous infusions, although slow infusion of more concentrated preparations is also permissible for a short time.

Another approach to hypoglycemia (unless it is a consequence of prolonged fasting) is the appointment of drugs that enhance glycogenolysis (adenylate cyclase stimulators of the type of beta-adrenoreceptor stimulators or phosphodiesterase blockers that destroy cAMP, such as caffeine and other representatives of this group).

REGULATION OF KETOGENESIS

For the synthesis of large amounts of β-hydroxybutyric and acetoacetic acids, it is necessary to enter the liver with an appropriate amount of free fatty acids and start their oxidation. The stimulus for lipolysis is insulin deficiency, the oxidation of fatty acids is started by glucagon. A direct signal to the start of oxidation is a decrease in the concentration of malonyl-CoA.

When collecting the patient's history, it is necessary to ask:

- about the presence of diabetes mellitus;

- previous episodes of diabetic ketoacidosis;

- currently taking medications and any changes or errors in their administration;
- recent illnesses;
- presence of polyuria, polydipsia and weakness.

Diabetic ketoacidosis

• Hyperglycemia (>14 mmol/L).
• Metabolic acidosis (pH <7.35 or bicarbonate concentration <15 mmol/L).
• Increased anion gap.
• Ketonemia.
• Presence of ketone bodies in the urine.

Hyperosmolar state non-ketoacidotic

• Blood glucose concentration is higher (often >33 mmol/L).
• Absence of acidosis.
• Maximum ketonuria (+) in urine analysis using indicator strips.
• Higher sodium concentration (often >150 mmol/L). It should be remembered:

- up to 25% of cases of DKA are noted in patients with newly diagnosed diabetes mellitus.

HYPEROSMOLAR HYPERGLYCEMIC NON-KETOACIDOTIC COMA

Diabetic hyperosmolar coma is a special type of diabetic coma that occurs with extremely high hyperglycemia in the absence of ketoacidosis.

Table Hyperosmolar coma: laboratory data at the time of hospitalization

Clinical picture

• Blood glucose concentration is usually more than 50 mmol/l.
• Absence of ketoacidosis or slight ketoaciduria.
• Increased body temperature (occurs frequently in this condition).

Risk factors

1. Taking medications that increase blood glucose concentration.
2. Surgical interventions and comparable stressful situations.
3. Acute diseases.
- Infections.
- Diabetic gangrene.
- Urethritis.
- Sepsis.
- Burns.
- Gastrointestinal bleeding.
- Acute brain injury (paralysis).
- Myocardial infarction.
- Pancreatitis.
4. Chronic diseases.
- Kidney disease.
- Heart disease.
- Arterial hypertension.
- Cerebral infarction.
- Alcoholism.
- Dehydration due to insufficient fluid intake on the background of mental illnesses.

Pathogenesis

• Insulin deficiency, which causes hyperglycemia with subsequent glucosuria, osmotic diuresis and polyuria, intensifies the preceding dehydration.

• Hypovolemia develops with increased aldosterone secretion, which contributes to sodium retention, hypokalemia and increased blood osmolarity.

• Blood hyperosmolarity leads to impaired hemodynamics (arterial hypotension), oliguria and anuria.

• Increased tendency to thrombosis with possible development of DIC.

• Dehydration of the brain leads to the appearance of neurological symptoms (convulsions, nystagmus, hemiparesis).

• The absence of ketoacidosis is explained by the partially preserved production of endogenous insulin, sufficient to block lipolysis and ketogenesis, but insufficient to reduce hyperglycemia.

The clinical picture is determined by dehydration.

Diagnosis

• Hyperglycemia (44-55 mmol/l and more) and glycosuria.

• Hypernatremia.

• Hypokalemia.

• Hyperchloremia.

• Hyperazotemia.

• Increased plasma osmolarity above 360 mOsm/kg

• The reaction to acetone and urine is negative.

Treatment

Extremely important:

- early diagnosis of hyperosmolar hyperglycemic non-ketoacidotic coma;
- adequate rehydration;
- correction of hyperglycemia with short-acting insulin preparations;
- restoration of electrolyte balance;
- treatment of underlying diseases (e.g. infections). During the first 2 hours

• 0.45% sodium chloride solution 2 l intravenously with the addition (if serum potassium levels decrease) 8-5 ml of 10% potassium chloride solution.

• Soluble insulin (human genetically engineered) 20 U intravenously, then 5-8 U every hour intravenously or intramuscularly. When the blood glucose concentration drops to 200-300 mg% (11-12 mmol/l), an infusion of 5% glucose solution is administered to prevent hypoglycemia□.

Further treatment

• Continue the administration of 0.45% sodium chloride solution at a rate of 1 l/h until the CVT or blood osmolarity normalizes.

• Continue potassium chloride infusion in severe hypokalemia.

• Continue insulin administration at a dose of 5-8 U/h intramuscularly or intravenously until blood glucose levels are normalized.

For successful treatment, a good laboratory base, experience in insulin therapy and correction of water and electrolyte disorders are required.

After emergency therapy, diet and oral medications are required.

Complications

Swelling of the brain with excessive administration of 0.45% sodium chloride solution.

The thyroid gland (thyroid) is the largest endocrine gland in the human body, has only an endocrine function. Its mass in an adult is about 15-20 g. The thyroid gland consists of two lobes and an isthmus, located on the anterior surface of the trachea and on its sides.

The thyroid gland consists of cells of two different types: follicular and parafollicular (C-cells). Follicular cells that produce thyroxine (T4) and triiodothyronine (T3) form numerous follicles in the gland, each of which consists of a central cavity filled with colloid, the main component of which is the protein thyroglobulin, surrounded by a single layer of cuboidal epithelial cells. Parafollicular cells (C cells) produce the protein hormone calcitonin.

T4 and T3 are synthesized from the amino acid tyrosine. In addition, there is a biologically inactive reversible triiodothyronine (pT3), which is formed during the deiodination of the inner ring of T4.

An essential structural component of thyroid hormones is iodine. This trace element is almost completely absorbed in the intestine, from where it enters the blood plasma in ionized form. The transfer of iodine into the thyrocyte is energy-dependent and is carried out in conjunction with the reverse transport of sodium by the sodium-iodide symporter (NIS). In the cells, the iodine ion is oxidized, after which it undergoes organification, joining the residues of the amino acid tyrosine molecules, which are present in thyroglobulin, synthesized by follicular cells. After this, thyroglobulin changes its structure in such a way that the tyrosyl residues come closer to each other, facilitating the condensation reaction between them. Iodination of tyrosyl residues and the condensation reaction occur with the participation of thyroid peroxidase (TPO), localized in the microsomal fraction of follicular cells. Then, thyroglobulin containing bound iodothyronines is transported through the apical membrane and deposited in the colloid cavity of the follicle, after which it again enters the thyrocytes, moves to their basal membrane, releases iodothyronines, which are secreted into the blood. Once in the blood, T4 and T3 are distributed throughout the body mainly in the form bound to plasma proteins (thyroxine-binding globulin, prealbumin (transthyretin), albumin). The half-life in the blood of T4 is 7-9 days, for T3 - 2 days.

Free iodothyronines relatively easily penetrate the cell membrane. Intracellular effects of thyroid hormones are closely related to the processes of their metabolism (primarily with the mechanisms of deiodination). The most important of these transformations is the conversion of T4 into the more active T3. Since it is mainly T3 that directly interacts with thyroid hormone receptors, and not T4, the latter is usually considered a prohormone, and T3 - as a true hormone. T3, acting on specific nuclear receptors that are present in most cells, leads to a change in the expression of various genes, which is manifested by the physiological effects of thyroid hormones, the main of which is the regulation and maintenance of basal metabolism. Only 5 - 10% of T3 circulating in the blood is synthesized directly by the thyroid gland; most of it is formed as a result of T4 deiodination in peripheral tissues. The transformation (conversion) of T4 into T3 is catalyzed by various deiodinases that have tissue specificity.

Thyroid function is regulated by the adenohypophysis according to the principle of negative feedback. Thyroid-stimulating hormone (TSH) of the pituitary gland stimulates the production of thyroid hormones, which suppress the production of TSH (Fig. 1).

The effects of thyroid hormones are diverse. They maintain the basic metabolism in

most cells, regulating their metabolic activity, as well as the processes of proliferation and apoptosis. A normal level of thyroid hormones is necessary for the functioning of all body systems without exception, and in case of thyroid dysfunction, pathological changes are polysystemic in nature. Thyroid hormones are necessary for the formation of the nervous and other systems of the fetus and newborn. Thyroxine deficiency during this period leads to significant neurological disorders.

Hormones produced by the epithelium of the thyroid follicles are called thyroid. They include thyroxine and triiodothyronine. In addition to thyroid hormones, the gland produces the hormone calcitonin, which reduces the calcium content in the blood by depositing it in the bones. Recently, it has been shown that calcitonin inhibits the secretory activity of many digestive and endocrine glands.

The role of the hormones thyroxine and triiodothyronine:

-provide the body's basic metabolism, increase oxygen consumption by tissues;

-prevent fat deposition, reduce overall weight;

-provide physical and mental development.

With a lack of these hormones, cretinism develops in children, and myxedema in adults. Hyperfunction of the thyroid gland is called Graves' disease.

In general, the effect of thyroid hormones is traditionally described as calorogenic: under their action, there is an increase in basic metabolism due to increased oxygen consumption and increased heat production of tissues.

CLASSIFICATION OF THYROID DISEASES

Before discussing the classification, it is necessary to consider a number of terminological issues. The term thyrotoxicosis refers to a clinical syndrome caused by an excess of thyroid hormones in the body, while pathogenetically it is divided into three variants:

♦ Hyperthyroidism - hyperproduction of thyroid hormones by the thyroid gland (Graves' disease, multinodular toxic goiter)

♦ Destructive (thyroidolytic) thyrotoxicosis, which is a typical pathological reaction of the thyroid gland to a number of external and internal factors, which consists in the massive destruction of thyroid follicles with the release of their contents (thyroid hormones) into the bloodstream. In this variant, thyroid hyperfunction is absent. Diseases that occur with destructive thyrotoxicosis, such as subacute and postpartum thyroiditis, are accompanied by much less pronounced thyrotoxicosis than those caused by hyperthyroidism (Graves' disease). In addition, they usually have a good prognosis.

♦ Drug-induced thyrotoxicosis associated with an overdose of thyroid hormone drugs.

ETIOLOGY OF HYPERTHYROIDISM

• Diffuse toxic goiter (Graves' disease) is the most common cause of hyperthyroidism.

• Nodular toxic goiter (thyrotoxic adenoma, Plummer's disease) is observed less often than Graves' disease, and usually in older people.

• Subacute thyroiditis (de Quervain's thyroiditis) can cause transient thyrotoxicosis (in the absence of hyperthyroidism).

• Artificial hyperthyroidism can be a consequence of uncontrolled intake of thyroid hormones.

Rare causes of hyperthyroidism

• Pituitary tumors with excessive secretion of TSH (for example, Truell-Junet

syndrome or acromegaly hyperthyroidism with hyperostosis, a combination of diffuse hyperostosis of the cranial vault, acromegaly and signs of thyroid hyperfunction, caused by increased secretion of somatotropic hormone and TSH by the adenohypophysis).

• Ovarian teratomas that produce thyroid hormones (ovarian struma).

• Hyperproduction of hormones by the thyroid gland after excessive intake of iodine into the body ("iodine-based syndrome").

Etiological classification of thyrotoxicosis

• Caused by hyperfunction of the thyroid gland:

- excessive production of TSH (rarely);
- pathological stimulation of the thyroid gland;
- antibodies to TSH receptors in diffuse toxic goiter;
- chorionic gonadotropin in trophoblast tumors;
- functional autonomy of the thyroid gland;
- toxic adenoma;
- multinodular toxic goiter.

• Caused by other causes:

- impaired storage of T4 and T3;
- subacute granulomatous thyroiditis;
- subacute lymphocytic thyroiditis;
- ectopic source of T4 and T3;
- ectopic thyroid gland;
- T4 and T3-secreting ovarian teratoma;
- metastases of functionally active thyroid cancer;
- latent source of T4 and T3;
- overdose or abuse of thyroid hormones;
- foods containing animal thyroid tissue.

The most common cause of thyrotoxicosis is diffuse toxic goiter. This autoimmune disease is characterized by the presence of thyroid-stimulating antibodies. Graves' ophthalmopathy (the main symptom is exophthalmos) and pretibial myxedema are observed in it, which do not occur in thyrotoxicosis of other etiologies. Other causes of thyrotoxicosis: iodine-containing drugs (amiodarone, radiopaque substances), thyroid adenomas, subacute granulomatous thyroiditis, subacute lymphocytic thyroiditis, postpartum thyroiditis (a type of lymphocytic), abuse of thyroid hormone drugs. Secondary (caused by increased TSH levels) thyrotoxicosis is extremely rare.

Special notes

• In the elderly, the only manifestations of thyrotoxicosis may be cardiovascular disorders, more often arrhythmias and heart failure.

• In severe neurosis, thyrotoxicosis must be excluded.

Goiter (strimoi), as indicated, means an increase in the volume of the thyroid gland above the established standards (18 ml - in women, 25 ml - in men). According to macroscopic characteristics, it is divided into diffuse (the entire thyroid gland is enlarged), nodular, multinodular (two or more nodular formations) and mixed (a combination of a general increase in the thyroid gland with the presence of one or more nodular formations). According to the functional state of the thyroid gland, goiter can be euthyroid, toxic and

occurs with a decrease in thyroid function.

The first group includes quite a few autoimmune thyroid diseases. In terms of their general population prevalence, they occupy first place among other autoimmune pathologies of humans. Benign hyperplastic processes of the thyroid gland are even more common, which include various forms of colloid proliferating goiter.

Most often, the formation of goiter is promoted by various goitrogenic factors, the most common of which is a deficiency of iodine in the body and the thyroid gland. Here it is necessary to note a unique feature of thyroid pathology in general: the spectrum, prevalence and prognosis of most thyroid diseases will largely depend on the region with which iodine intake (insufficient, normal, excessive) the patient lives.

Infectious thyropathies, with the exception of subacute thyroiditis, the etiology of which is not fully understood, are relatively rare, as are infectious diseases of all endocrine glands in general. Separate categories of thyroid diseases include tumors, which differ significantly in morphology and prognosis, and congenital (hereditary) diseases, for some of which the direct cause of development is already known today.

GRAVES' DISEASE - Basedow's disease

Graves' disease (CG, Basedow's disease, diffuse toxic goiter) is a systemic autoimmune disease that develops due to the production of antibodies to the thyroid-stimulating hormone (TSH) receptor, clinically manifested by damage to the thyroid gland with the development of thyrotoxicosis syndrome in combination with extrathyroidal pathology: endocrine ophthalmopathy, pretibial myxedema, acropathia (Table 5). The disease was first described in 1825 by Caleb Parry, in 1835 by Robert Graves, and in 1840 by Karl von Basedow.

As a result of the violation of immunological tolerance, autoreactive lymphocytes (CD4+ and CD8+ T-lymphocytes, B-lymphocytes) with the participation of adhesive molecules (ICAM-1, ICAM-2, E-selectin, VCAM-1, LFA-1, LFA-3, CD44) infiltrate the thyroid parenchyma, where they recognize a number of antigens that are presented by dendritic cells, macrophages and lymphocytes. Subsequently, cytokines and signaling molecules initiate antigen-specific stimulation of B-lymphocytes, resulting in the production of specific immunoglobulins against various components of thyrocytes. In the pathogenesis of CG, the main importance is given to the formation of stimulating antibodies to the TSH receptor (AT-rTSH).

Etiology

BG is a multifactorial disease in which genetic features of the immune response are realized against the background of environmental factors. Along with ethnically associated genetic predisposition (carriership of haplotypes HLA-B8, -DR3 and -DQA1*0501 in Europeans), psychosocial and environmental factors play a certain role in the pathogenesis of CG. Emotional stressors and exogenous factors, such as smoking, can contribute to the realization of genetic predisposition to CG. Smoking increases the risk of developing CG by 1.9 times, and the development of endocrine ophthalmopathy with existing CG by 7.7 times. CG is sometimes combined with other autoimmune endocrine diseases (type 1 diabetes mellitus, primary hypocorticism); such a combination is usually designated as autoimmune polyglandular syndrome type II.

Unlike most other autoimmune diseases, in CG or Graves' disease, there is not destruction, but stimulation of the target organ. In this case, autoantibodies are produced to a

part of the TSH receptor, which is located on the membrane of thyrocytes. As a result of interaction with the antibody, this receptor becomes active, triggering the postreceptor cascade of thyroid hormone synthesis (thyrotoxicosis) and, in addition, stimulating thyrocyte hypertrophy (thyroid enlargement). For reasons that are not entirely clear, T-lymphocytes sensitized to thyroid antigens infiltrate and cause immune inflammation in a number of other structures, such as retrobulbar tissue (endocrine ophthalmopathy), tissue of the anterior surface of the tibia (pretibial myxedema).

Pathogenesis

The most clinically significant syndrome that develops in CG due to hyperstimulation of the thyroid gland by antibodies to the TSH receptor is thyrotoxicosis. The pathogenesis of changes in organs and systems that develop in thyrotoxicosis is a significant increase in the level of basal metabolism, which subsequently leads to dystrophic changes. The most sensitive to thyrotoxicosis structures, in which the highest density of receptors for thyroid hormones is the cardiovascular (especially the atrial myocardium) and nervous system.

• Thyroid hormones increase oxygen consumption by tissues, increase heat generation and energy metabolism.

• The sensitivity of tissues to catecholamines and sympathetic stimulation increases.

• The conversion of androgens to estrogens in tissues increases and the content of circulating sex hormone-binding globulin increases, which increases the ratio of estrogens to androgens. These hormonal changes can cause gynecomastia in men.

• The rapid destruction of cortisol under the influence of thyroid hormones causes the clinical picture of hypocorticism (reversible adrenal insufficiency).

RISK FACTORS

• A strong family history.

• Female gender.

CLINICAL PICTURE

In most cases, HCG is characterized by a relatively short history: the first symptoms usually appear 4-6 months before consulting a doctor and making a diagnosis. As a rule, the key complaints are associated with changes in the cardiovascular system, the so-called catabolic syndrome and endocrine ophthalmopathy

The main symptom from the cardiovascular system is tachycardia and a fairly pronounced feeling of palpitations. Thyrotoxicosis is accompanied by dilation of resistive arterioles and decentralization of blood circulation. On the one hand, this leads to the fact that patients can feel palpitations not only in the chest, but also in the head, arms, and abdomen. On the other hand, the hyperkinetic state of the heart (high heart rate) in combination with decentralization of blood circulation leads to an increase in pulse pressure (the difference between systolic and diastolic blood pressure). Heart rate at rest in sinus tachycardia caused by thyrotoxicosis can reach 120-130 beats per minute.

With long-term existing thyrotoxicosis, especially in elderly patients, pronounced dystrophic changes in the myocardium develop, a frequent manifestation of which are supraventricular rhythm disturbances, namely fibrillation (fibrillation) of the atriums. This complication of thyrotoxicosis rarely develops in patients under 50 years of age. Further progression of myocardial dystrophy leads to the development of changes in the ventricular myocardium and congestive heart failure.

As a rule, a pronounced catabolic syndrome is observed, which is manifested by

progressive weight loss (sometimes by 10-15 kg or more, especially in people with an initial excess of weight) against the background of increasing weakness, increased appetite. The skin of patients is hot, sometimes there is pronounced hyperhidrosis. A feeling of heat is characteristic, patients do not freeze at a sufficiently low temperature in the room. Some patients (especially in old age) may have an evening subfebrile temperature.

Changes in the nervous system are characterized by mental lability: episodes of aggressiveness, excitement, chaotic unproductive activity are replaced by tearfulness, asthenia (irritable weakness). Many patients are not critical of their condition and try to maintain an active lifestyle against the background of a rather severe somatic condition. Long-standing thyrotoxicosis is accompanied by persistent changes in the patient's psyche and personality. A frequent but non-specific symptom of thyrotoxicosis is fine tremor: fine trembling of the fingers of outstretched hands is detected in most patients. In severe thyrotoxicosis, tremor can be determined throughout the body and even complicate the patient's speech.

Muscle weakness and a decrease in the volume of muscles, especially the proximal muscles of the arms and legs, are characteristic of thyrotoxicosis. Sometimes quite pronounced myopathy develops. A rather rare complication (possibly a manifestation of BG) is thyrotoxic hypokalemic periodic paralysis, which is manifested by periodically occurring sharp attacks of muscle weakness. Laboratory examination reveals hypokalemia, increased CPK levels. It is more common in representatives of the Asian race.

Intensification of bone resorption leads to the development of osteopenia syndrome, and thyrotoxicosis itself is considered one of the most important risk factors for osteoporosis. Frequent complaints of patients are hair loss, brittle nails.

Changes in the gastrointestinal tract develop quite rarely. Elderly patients may have diarrhea in some cases. With long-term severe thyrotoxicosis, dystrophic changes in the liver (thyrotoxic hepatosis) may develop.

Menstrual cycle disorders are quite rare. Unlike hypothyroidism, moderate thyrotoxicosis may not be accompanied by reduced fertility and does not exclude the possibility of pregnancy. Antibodies to the TSH receptor penetrate the placenta, and therefore children born (1%) to women with BG (sometimes years after radical treatment) may develop transient neonatal thyrotoxicosis. In men, thyrotoxicosis is quite often accompanied by erectile dysfunction.

In severe thyrotoxicosis, a number of patients have pronounced symptoms of thyrogenic (relative) adrenal insufficiency, which must be differentiated from true. Hyperpigmentation of the skin, exposed parts of the body (Ellinek's symptom), and arterial hypotension are added to the symptoms already listed. In most cases, with hyperthyroidism, there is an increase in the size of the thyroid gland, which, as a rule, has a diffuse nature. Often the gland is significantly enlarged. In some cases, a systolic murmur can be heard above the thyroid gland. Nevertheless, goiter is not an obligatory symptom of hyperthyroidism, since it is absent in at least 25-30% of patients.

Of key importance in the diagnosis of hyperthyroidism are changes in the eyes, which are discussed in section 3.5 and are a kind of "calling card" of hyperthyroidism, that is, their detection in a patient with thyrotoxicosis almost unequivocally indicates hyperthyroidism, and not another disease.

Very often, due to the presence of pronounced ophthalmopathy in combination with symptoms of thyrotoxicosis, the diagnosis of BG is obvious already during the examination of

the patient.

Another rare (less than 1% of cases) disease associated with HG is pretibial myxedema. The pathogenesis of the lesion of the pretibial tissue is probably similar to that of EOP. The skin of the anterior surface of the lower leg becomes swollen, compacted, purple-red in color ("orange peel"), often accompanied by erythema and itching.

The clinical picture of thyrotoxicosis may deviate from the classical version. Thus, if BG in young patients is characterized by a developed clinical picture, in elderly patients its course is often oligosymptomatic or even monosymptomatic (heart rhythm disturbances, subfebrile temperature). In the so-called "apathetic" variant of the course of BG, which occurs in elderly patients, clinical manifestations include loss of appetite, depression, and hypodynamia.

A rather rare complication of HG (extremely rare in other diseases occurring with thyrotoxicosis) is thyrotoxic crisis, the pathogenesis of which is not entirely clear, since the crisis can develop without an excessive increase in the level of thyroid hormones in the blood. The cause of thyrotoxic crisis may be acute infectious diseases concomitant with HG, surgical intervention or radioactive iodine therapy against the background of severe thyrotoxicosis, cancellation of thyrostatic therapy, administration of an iodine-containing contrast agent to the patient. Clinical manifestations of thyrotoxic crisis include a sharp worsening of symptoms of thyrotoxicosis, hyperthermia, confusion, nausea, vomiting, and sometimes diarrhea. Sinus tachycardia of more than 120 beats / min is recorded. Atrial fibrillation, high pulse pressure followed by severe hypotension are often observed. Heart failure and respiratory distress syndrome may dominate the clinical picture. Relative adrenal insufficiency in the form of skin hyperpigmentation are often expressed. The skin may be icteric due to the development of toxic hepatosis. Laboratory studies may reveal leukocytosis (even in the absence of concomitant infection), moderate hypercalcemia, and increased alkaline phosphatase levels. Mortality in thyrotoxic crisis reaches 30-50%.

Diagnostics

Diagnostic criteria for HCG include:

1. Laboratory-confirmed thyrotoxicosis (TSH↓, T4 and/or T3 ↑).
2. Endocrine ophthalmopathy (60-80% of cases).
3. Diffuse enlargement of the thyroid gland (60-70%).
4. Diffuse enhancement of 99mTc uptake according to thyroid scintigraphy.
5. Elevated levels of antibodies to the TSH receptor.

Treatment

There are three methods of treatment for BG (conservative treatment with thyreostatic drugs, surgical treatment and 131I therapy), while none of them is etiotropic. In different countries, the proportion of use of these treatment methods traditionally differs. Thus, in European countries and in the Russian Federation, conservative therapy with thyreostatics is the most widely accepted primary treatment method, in the USA the vast majority of patients receive 131I therapy.

BASIC RULES OF TREATMENT OF HYPERTHYROIDISM

1. Initial treatment with radioactive iodine. Patients with mild hyperthyroidism and satisfactory general condition can be immediately prescribed radioactive iodine in combination with a β-blocker. Other patients should first be brought to a euthyroid state by prescribing a short course of thyreostatic drugs.

2. Long-term treatment with thyreostatics (12-18 months) is prescribed for pregnant women and children with a small thyroid gland.

3. Surgical treatment is performed for a large thyroid gland.

MEDICAL TREATMENT OF HYPERTHYROIDISM

1. Symptomatic treatment.

- β-Adrenoblockers:
- propranolol 40 mg 3 times a day;
- metoprolol 50 mg 2 times a day;
- sotalol 80 mg 2 times a day (especially in atrial fibrillation).

2. Primary preventive treatment.

Conservative therapy is carried out using thiourea drugs, which include thiamazole (mercazolil, tyrosol, metizol) and propylthiouracil (PTU, propicyl). The mechanism of action of both drugs is that they actively accumulate in the thyroid gland and block the synthesis of thyroid hormones by inhibiting thyroid peroxidase, which attaches iodine to tyrosine residues in thyroglobulin. There is quite contradictory evidence that thiamazole simultaneously has some immunomodulatory effect, which in some cases contributes to remission of the disease.

Thyrostatic therapy can be prescribed in order to prepare the patient for other methods of treatment (surgery), which are carried out against the background of euthyroidism, or as a course of thyrostatic therapy lasting 12-18 months. It should be emphasized that against the background of taking thyrostatic drugs, the gradual achievement of a euthyroid state can be achieved in almost all patients: cases of resistance to thyrostatics are casuistic.

Long-term (12-18 months) conservative therapy makes sense to plan far from all patients. First of all, we are talking about patients with a moderate increase in the volume of the thyroid gland (up to 35-40 ml); with a large goiter, thyrotoxicosis will inevitably develop after the abolition of thyrostatics. In addition, conservative therapy should not be planned in patients with severe complications of thyrotoxicosis (atrial fibrillation, severe osteoporosis, etc.). It is practically hopeless and dangerous for the patient to prescribe repeated courses of treatment in the development of relapse of thyrotoxicosis after 12-18 months of thyrostatic therapy. If a course of thyrostatic therapy is planned for the patient, thionamides are initially prescribed in relatively large doses: 30-40 mg of thiamazole (for 1-2 doses) or PTU - 300-400 mg for 3 doses). Against the background of such therapy, after 4-6 weeks, 80-90% of patients with moderate thyrotoxicosis manage to achieve a euthyroid state, the first sign of which is the normalization of the level of free T4 and T3. The TSH level may remain low for a long time. For the period before achieving euthyroidism, and often for a longer period, most patients are advised to prescribe beta-blockers (propranolol - 120-180 mg/day, atenolol - 50-100 mg/day), which quickly relieve many cardiovascular symptoms of thyrotoxicosis. After the level of free T4 is normalized, the dose of the thyrostatic agent is reduced to a maintenance dose (5-15 mg of thiamazole per day). In the future, two options for thyrostatic therapy are possible. The first option (the “block” scheme) involves the appointment of a small (5-10 mg/day of thiamazole) dose of only one thyrostatic drug. In the second option (the “block and replace” scheme), levothyroxine (L-T4) is prescribed together with a relatively higher dose of a thyreostatic (10-20 mg of thiamazole), which prevents the development of drug-induced hypothyroidism in the patient. The criterion for the adequacy of therapy is the stable maintenance of normal levels of T4 and TSH (the latter may return to normal within several months of the start of treatment). Maintenance therapy lasts from 12 to 18 months.

Throughout the entire treatment, the patient must determine the level of leukocytes and platelets. A rare but serious complication of thionamides (both thiamazole and PTU) is agranulocytosis, very rarely - isolated thrombocytopenia. After the end of the course of treatment, the drugs are canceled; most often relapse develops during the first year after discontinuation of therapy. The probability of relapse even among patients with a small initial increase in the thyroid gland is quite high and reaches 70-75%. In the event of recurrence of thyrotoxicosis, as well as if the patient initially does not meet the criteria for which long-term thyreostatic therapy is appropriate, he is shown radical treatment: surgery or 131I therapy.

Mechanism of action and pharmacological effects

Thyrostatics are a group of drugs used to inhibit the synthesis of thyroid hormones (T4 and T3) in the syndrome of endogenous thyrotoxicosis. Drugs of the thionamide group have a general ability to block thyroid peroxidase - a key enzyme in the synthesis of thyroid hormones. Propylthiouracil also inhibits the peripheral conversion of T4 to the more biologically active T3 by inhibiting selenodeiodinase type 1 in peripheral tissues.

Pharmacokinetics

Thionamides are well and rapidly absorbed from the GASTROINTESTINAL tract. Therapeutic concentration of propylthiouracil in the blood is achieved already 20-30 minutes after oral administration. Thyrostatics are mainly metabolized in the liver, where they undergo glucuronidation.

Indications for use

Thyrotoxicosis caused by hyperproduction of thyroid hormones.

Principles of choice in various clinical situations

Currently, in Graves' disease, it is recommended to use lower doses (15-20 mg of thiamazole) to avoid side effects. The effectiveness of the low-dose regimen has been confirmed by the results of the European Multicenter Study.

Two regimens of exposure are used as maintenance treatment: low doses of thyrostatics ("block" regimen) or higher doses in combination with levothyroxine sodium ("block and replace" regimen).

In patients with multinodular toxic goiter, thyrostatics are indicated only as preparation for surgery or radioiodine therapy.

Contraindications

Hypersensitivity to thionamides.

Adverse drug reactions and safety monitoring methods

The most serious complication of the use of thionamides is agranulocytosis. It is recommended to examine the number of leukocytes and the leukocyte formula of peripheral blood every 7-10 days in the first 3 months of treatment, and then every 3-4 weeks. If the leukocyte level decreases to less than 3x109/l, treatment with thyreostatics is interrupted.

The use of thionamides is associated with the possibility of developing thrombocytopenia and an increased risk of spontaneous bleeding, therefore it is necessary to monitor the prothrombin time, especially before surgical manipulations.

Skin rashes of various genesis that occur during treatment should not be automatically considered an allergic reaction to thyreostatic drugs. It can only be confirmed by skin testing.

Interaction of thionamides

Thionamides can enhance the effect of anticoagulants. They increase the risk of side effects of β-blockers, cardiac glycosides, and impair the clearance of theophylline.

Simultaneous administration of drugs that can cause agranulocytosis (NSAIDs, clozapine, sulfasalazine, etc.) should be avoided.

Use in special cases

Thionamides are classified as class D for the risk of use during pregnancy, so they can still be used under strict medical supervision in pregnant and lactating women as an alternative to surgery. Propylthiouracil is preferred. Pregnancy is an absolute contraindication for the "block and replace" regimen, since thyrostatics (but not levothyroxine sodium) easily cross the placenta and can cause severe hypothyroidism in the fetus.

- A thyrostatic drug (usually carbimazole□) should be prescribed as monotherapy or, preferably, in combination with a β-blocker.

1 week after the start of treatment, it is necessary to check the content of leukocytes in the blood, and subsequently this procedure should be repeated at each visit to the doctor. The patient should be informed about the possible development of agranulocytosis (the patient should be aware of the need to consult a doctor if fever or sore throat occurs).

Continuous preventive treatment

• It is carried out if the patient refuses surgical treatment or the use of radioactive iodine.

• A combination of the thyreostatic carbimazole (20 mg/day) and levothyroxine sodium (50-100 mcg/day) or only levothyroxine sodium should be used.

SIDE EFFECTS OF THYROSTATIC DRUGS

1. Agranulocytosis (caused by thyreostatics).

- The first signs are fever and sore throat.

- Develops within 3 months after the start of treatment.

- Most common in elderly patients.

- The highest risk of developing agranulocytosis is in patients who have used the same thyreostatic drug in the past.

- Treatment consists in the immediate withdrawal of drug treatment.

- β-Adrenoblocker (iodide) + surgical treatment or treatment with radioactive iodine - alternative treatment.

2. Leukopenia.

3. Skin rashes.

4. Joint damage.

5. Permanent remission is rarely achieved.

THYROTOXIC CRISIS

Thyrotoxic crisis is a rare but life-threatening syndrome, manifested by a sharp increase in the severity of symptoms of thyrotoxicosis in patients with diffuse or diffuse-nodular toxic goiter.

Thyrotoxic crisis develops more often in patients who have not been treated for thyrotoxicosis. Risk factors include surgery and acute infectious diseases.

Clinical manifestations - tachycardia (more than 150 min, anxiety, weakness, fever), arrhythmias, heart failure.

EMERGENCY CARE IS NECESSARY

To prevent death (its frequency, according to various sources, from 10 to 75%) in thyrotoxic crisis, early diagnosis and adequate intensive therapy are necessary. Treatment is carried out in the intensive care unit. Treatment includes the administration of antithyroid

drugs, saline solutions, glucocorticoids, antiarrhythmic and cardiotonic agents.

The thyroid gland belongs to the pituitary-dependent glands, the insufficiency of which is divided into primary and secondary. Primary hypothyroidism means a deficiency of thyroid hormones in the body caused by pathology (destruction, removal) of the thyroid gland itself, and secondary hypothyroidism means a deficiency of thyroid hormones caused by a decrease (absence) of the trophic and secretory effects of TSH on the thyroid gland (hypothalamic-pituitary hypothyroidism).

The goal of surgical treatment, as well as 131I therapy, is to remove almost the entire thyroid gland, on the one hand, ensuring the development of postoperative hypothyroidism (which is quite easily compensated), and on the other hand, eliminating any possibility of recurrence of thyrotoxicosis. For this purpose, thyroidectomy or extremely subtotal thyroid resection (with a thyroid remnant of no more than 2 ml) is recommended, which is functionally identical to thyroidectomy (in both cases, the result is hypothyroidism).

The peculiarity of the treatment of HCG during pregnancy is that the thyreostatic (preferred to PTU, which penetrates the placenta worse) is prescribed in the minimum necessary dose (only according to the "block" scheme), which is necessary to maintain the level of free T4 at the upper limit of the norm or slightly above it. Usually, as the gestation period increases, the need for thyreostatic decreases and most women after 25-30 weeks do not take the drug at all. However, most of them develop a relapse of the disease after childbirth (usually after 3-6 months). Treatment of thyrotoxic crisis involves intensive measures to prescribe large doses of thyreostatics. PTU is preferred at a dose of 200-300 mg every 6 hours, if the patient cannot take it independently - through a nasogastric tube. In addition, β-blockers are prescribed (propranolol: 160-480 mg per day per os or IV at the rate of 2-5 mg/h), glucocorticoids (hydrocortisone: 50-100 mg every 4 hours or prednisolone (60 mg/day), detoxification therapy (saline solution, 10% glucose solution) under hemodynamic control. An effective method of treating thyrotoxic crisis is plasmapheresis. The prognosis in the absence of treatment is unfavorable and is determined by the gradual development of atrial fibrillation, heart failure, and exhaustion (Marantis thyrotoxicosis). In the case of normalization of thyroid function, the prognosis of thyrotoxic cardiomyopathy is favorable - in most patients, cardiomegaly regresses and sinus rhythm is restored. The probability of recurrence of thyrotoxicosis after a 12-18-month course of thyrostatic therapy is 70-75% of patients.

HYPOTHYROIDISM

Hypothyroidism is a clinical syndrome that develops due to a deficiency of thyroid hormones. By pathogenesis, hypothyroidism can be primary (due to pathology of the thyroid gland itself) and secondary (due to TSH deficiency) (table), with more than 99% of cases being primary acquired hypothyroidism. The prevalence of hypothyroidism in the general population is about 2%, and in certain age groups (elderly women) it can reach 6-8%.

It is one of the most common endocrine diseases (table). The main cause of persistent primary hypothyroidism is chronic autoimmune thyroiditis (AIT), followed by iatrogenic hypothyroidism, which develops as a result of thyroid surgery or radioactive 131I therapy.

Etiology

The greatest clinical significance is hypothyroidism, which developed as a result of

chronic autoimmune thyroiditis (AIT), as well as iatrogenic hypothyroidism (postoperative, as a result of radioactive 131I therapy). Iatrogenic hypothyroidism accounts for at least 1/3 of all cases of hypothyroidism. In these diseases, hypothyroidism in most cases is persistent and irreversible. Along with this, in many thyroid diseases (destructive thyroiditis), as well as under the influence of a number of substances (large doses of iodine, thyrostatics), transient hypothyroidism may develop, which is self-limited either in the process of the natural course of these diseases, or upon cessation of the influence of the factor that caused it (the abolition of the thyrostatic). In some cases, the genesis of primary hypothyroidism remains unclear (idiopathic hypothyroidism).

Pathogenesis

With a deficiency of thyroid hormones, changes develop in all organs and systems without exception. Since the main function of thyroid hormones is to maintain basic metabolism (cellular respiration), with their deficiency there is a decrease in oxygen consumption by tissues, as well as a decrease in energy expenditure and utilization of energy substrates. For the same reason, hypothyroidism reduces the production of a number of energy-dependent cellular enzymes that ensure their normal functioning. A universal change that is detected in severe hypothyroidism is mucinous edema (myxedema), most pronounced in connective tissue structures. Myxedema develops due to excessive accumulation in interstitial tissues of hyaluronic acid and other glycosaminoglycans, which, due to their hydrophilicity, retain excess water.

The clinical picture of hypothyroidism is generally characterized by polysystemicity, but in individual patients complaints and symptoms from one system dominate, in connection with which the patient is often diagnosed with "mask" diseases (Fig.).

With pronounced and long-term existing hypothyroidism, the patient develops a rather characteristic "myxedematous" appearance, which is characterized by general and periorbital edema. The face is puffy, pale-jaundice, aloof look, poor facial expressions (mask-like face) (Fig.).

In addition, thinning and darkening of the hair, their increased loss are noted. In general, patients are apathetic, slowed down or even inhibited. Slowing of speech is very characteristic of severe hypothyroidism; sometimes it seems that the patient has something in his mouth (the tongue is tangled). Swelling of the larynx mucosa is manifested by a low or even hoarse timbre of the voice. The patient may stumble when pronouncing individual words, after which, with some effort, pronounces them more clearly. Classically, hypothyroidism is described as swelling of the tongue, on which teeth impressions can be seen. Swelling of the Eustachian tube mucosa may manifest as some hearing loss. Dry skin is a common complaint.

Among the changes in the nervous system, it is worth noting a decrease in memory and intelligence, drowsiness, and depression. In children over 3 years of age and in adults, changes in the nervous system are not irreversible and are completely stopped against the background of replacement therapy. In contrast, congenital hypothyroidism in the absence of replacement therapy leads to irreversible neuropsychiatric and physical disorders. Changes in the peripheral nervous system rarely develop, although in some patients, the phenomena of myxedema provoke the development of tunnel syndromes (carpal tunnel syndrome).

The general decrease in the level of basal metabolism is manifested by a certain tendency of patients with hypothyroidism to gain weight, while hypothyroidism itself never

leads to the development of severe obesity. In extremely severe hypothyroidism, hypothermia may develop. Patients often complain of feeling cold (they are cold all the time). In the genesis of this symptom, along with a decrease in basal metabolism, the centralization of blood circulation characteristic of hypothyroidism is important.

The most frequent changes in the cardiovascular system are a tendency to bradycardia, mild diastolic arterial hypertension and the formation of effusion in the pericardial cavity. Most patients with hypothyroidism develop atherogenic dyslipidemia.

From the digestive system, constipation is a common symptom. In addition, biliary dyskinesia and hepatomegaly may develop; some loss of appetite is characteristic. With severe hypothyroidism, hypochromic anemia may develop. In some cases, hypothyroidism in the outcome of AIT is combined with another autoimmune disease - B12-deficiency anemia.

Very often, especially in women, changes in the reproductive system come to the fore. With hypothyroidism, various menstrual cycle disorders can occur: from amenorrhea to dysfunctional uterine bleeding. Both men and women experience a decrease in libido. Secondary hyperprolactinemia plays a certain role in the pathogenesis of changes in the reproductive system. Severe hypothyroidism is almost always accompanied by infertility, but a less pronounced deficiency of thyroid hormones in some women (about 2% of all pregnant women) cannot prevent pregnancy, which in this case is accompanied by a high risk of its interruption or the birth of a child with a developmental disorder of the nervous system.

With long-term hypothyroidism, hyperstimulation of pituitary thyrotrophs can result in the formation of a secondary adenoma. After compensation of hypothyroidism on a background of replacement therapy as a result of reduction of volume of a pituitary gland the formation of "empty" Turkish saddle can occur

The most severe, but at present extremely rare complication of hypothyroidism is hypothyroid (myxedematous) coma. Hypothyroid coma, as a rule, develops in elderly patients with long-term undiagnosed hypothyroidism, severe concomitant diseases at low social status and lack of care. The development of hypothyroid coma is provoked by intercurrent diseases (more often infectious), cooling, injuries, appointment of drugs that suppress CNS. Clinically hypothyroid coma is manifested by hypothermia, hypoventilation with hypercapnia, hypervolemia, hyponatremia, bradycardia, arterial hypotension, acute urinary retention, dynamic intestinal obstruction, hypoglycemia, heart failure, progressive inhibition of CNS. The mortality rate in myxedema coma reaches 80%.

Diagnosis

Diagnosis of hypothyroidism, that is, proving the fact of decreased thyroid function, is quite simple. It involves determining the level of TSH and T4, while the detection of an isolated increase in TSH indicates subclinical hypothyroidism, and a simultaneous increase in TSH and a decrease in T4 - about obvious or manifest hypothyroidism. A much greater problem is the determination of indications for this study, since the nonspecificity of the clinical picture of hypothyroidism determines the fact that even obvious symptoms may not be confirmed by hormonal testing, along with this, in some cases hypothyroidism, even accompanied by a significant increase in TSH and a decrease in T4, sometimes proceeds asymptomatically. If we talk about subclinical hypothyroidism, then in the vast majority of cases it does not have any manifestations at all that would allow us to suspect it. When comparing these facts, a natural question arises about the feasibility of screening determination of thyroid function for the purpose of diagnosing hypothyroidism, which is

supported by many recommendations. Risk groups for the development of hypothyroidism, that is, in fact, indications for assessing thyroid function, regardless of the presence or absence of any symptoms, are presented in Table 13.

Thyroid hormones are of exceptional importance for the establishment and formation of the CNS, both during intrauterine development and in the postnatal period.

Treatment

Manifest hypothyroidism (TSH↑, T4↓) is an absolute indication for the appointment of replacement therapy with levothyroxine (L-T4) regardless of any additional factors (age, comorbidity). Only the option for starting treatment (initial dose and rate of its increase) may differ. The question of the advisability of treating subclinical hypothyroidism (TSH↑, T4 - normal) remains controversial. An absolute indication for replacement therapy for subclinical hypothyroidism is its detection in a pregnant woman, or planning a pregnancy in the near future.

THYROID HORMONES

Currently, synthetically produced thyroid hormones are widely used.

Classification

• Levothyroxine preparations.
• Liothyronine preparations.
• Combined.

Mechanism of action and pharmacological effects

Under the influence of thyroid hormones, oxygen consumption increases in almost all tissues of the body, basal metabolism increases and heat production increases. Thyroid hormones have a positive inotropic and chronotropic effect on the myocardium, increase the expression of catecholamine receptors and increase the myocardial oxygen demand. Under the influence of thyroid hormones, the processes of gluconeogenesis and glycogenolysis are activated, erythropoiesis is stimulated, cortisol metabolism is accelerated, and the activity of the respiratory center is activated.

Pharmacokinetics

Thyroid hormones are well absorbed in the gastrointestinal tract. Absorption decreases when mixed with food, therefore it is recommended to take the entire dose of the drug in the morning on an empty stomach, at least 30 minutes before the first meal.

In tissues, peripheral conversion of T4 to T3 occurs by splitting off an iodine atom from the outer tyrosyl ring of T4, therefore, when prescribing monotherapy with levothyroxine sodium in an adequate dose, the body's need for thyroid hormones is fully met. When prescribing levothyroxine sodium, the concentration of T3 in the blood plasma increases gradually, over several weeks. Some pharmacokinetic parameters of thyroid hormones are presented in Table. Thyroid hormones are excreted mainly by the kidneys.

Indications for use

• Replacement therapy for hypothyroidism.
• Suppressive therapy.

Principles of choice in various clinical situations

With manifest hypothyroidism in adults, the estimated dose of levothyroxine sodium is 1.6-1.8 mcg/kg. With subclinical hypothyroidism, the dose of levothyroxine sodium is approximately 1 mcg per kilogram of body weight. The TSH level against the background of treatment should be within normal values (0.5-3.5 mIU/l).

Suppressive therapy, i.e. a supraphysiological dose of levothyroxine sodium (2.2-2.8 mcg/kg), preferably a TSH level of at least 0.5-0.1 mIU/l, is prescribed to patients operated on for highly differentiated thyroid cancer.

Contraindications

• Uncompensated thyrotoxicosis.

• Untreated adrenal insufficiency.

• Acute myocardial infarction.

Relative contraindications

• Cardiac arrhythmias.

• Unstable angina.

• Myocarditis.

Adverse drug reactions and safety monitoring methods

In case of overdose or too rapid dose increase, symptoms of thyrotoxicosis are observed. In patients with coronary artery disease, the administration of thyroid hormones, especially liothyronine, can cause a decrease in tolerance to physical exertion and an increase in angina attacks. Long-term suppressive therapy with thyroid hormones can lead to a decrease in bone mineral density, especially in menopausal women.

In primary hypothyroidism and endemic goiter, treatment is carried out under the control of TSH concentration, and in secondary hypothyroidism - under the control of free T4 level.

Use in special cases

Thyroid hormones are classified as class A in terms of risk of use during pregnancy, so their use in pregnant women if indicated is absolutely safe. Minimal amounts of thyroid hormones are excreted in breast milk, which is not an obstacle to their use in nursing women.

The need for levothyroxine sodium in children is much higher than in adults. The initial dose of levothyroxine sodium in congenital hypothyroidism is 10-15 mcg/kg per day.

In young patients without concomitant pathology, L-T4 can be immediately prescribed a full replacement dose, which is initially calculated based on the patient's weight (1.6 mcg/kg body weight). For women, the dose of L-T4 is on average 100 mcg, for men - 150 mcg per day. The drug is taken once a day, in the morning 30 minutes before breakfast. The control parameter by which the quality of hypothyroidism compensation is assessed is the TSH level. If it was initially significantly elevated, then its normalization can continue for up to 4-6 months (the first control study is usually done after 2-3 months). After compensation of hypothyroidism (normal TSH level) is achieved, this parameter is assessed at intervals of one year.

Compensated hypothyroidism is not a contraindication for planning pregnancy (with its onset, the dose of L-T4 should be increased by approximately 2.3 mcg/kg of weight).

The principles of replacement therapy for secondary hypothyroidism are similar, except that the assessment of its quality of compensation is based on the T4 level. Treatment of hypothyroid coma involves intensive measures, including the appointment of thyroid hormone preparations, glucocorticoids, correction of hemodynamic and electrolyte disorders.

2. Questions for self-control (list of questions):

1. Etiology, pathogenesis, clinical manifestations, complications of diabetes mellitus.

2. Methods of studying diabetes mellitus.

3. The main etiological factors and pathogenetic mechanisms that are the object of drug influence.

4. Pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics, interaction of insulin preparations, oral hypoglycemic drugs.

5. Principles of complex therapy of diabetic coma.

6. Indicate the mechanism of neurohumoral regulation of the synthesis of thyroid hormones.

7. Evaluate the molecular and biochemical mechanisms of the influence of thyroid hormones on metabolic processes in the body.

8. Explain the pathogenesis of diffuse toxic goiter and other thyroid diseases with thyrotoxic manifestations.

9. Explain the pathogenesis of hypothyroidism (myxedema).

10. Name the modern classification of drugs used in hypo- and hyperthyroidism.

3. Tasks for independent study of the material:

Practical work / individual tasks:

A. Write out prescriptions for the main drugs used in endocrinology (tablets and/or ampoules), indicate possible use, spectrum of diseases (syndromes) indicated for their appointment. Indicate and explain possible effective and undesirable drug combinations.

B. Independent practical work in class.

1. Curation of a thematic patient in the ward.

2. Study the working history of the disease (data from laboratory and instrumental studies, consultants' conclusions) and the list of medical prescriptions.

3. Write a protocol of independent work on the selection and selection of basic drugs and justification for the appointment of combined drug therapy.

4. To identify the signs during the subjective and objective examination of the patient that characterize the presence of diabetes mellitus, thyroid diseases, to write a clinical diagnosis of the disease.

5. To determine the group of drugs needed by the patient; based on theoretical data on pharmacodynamics and own observations, to select the drug for the patient.

6. To choose the optimal dosage regimen of the drug, taking into account the features of pharmacokinetics, pathogenesis of the disease, method of administration, age, body weight.

7. To identify clinical and instrumental criteria for assessing the effectiveness and safety of drugs.

8. To justify the need for combined drug therapy and to suggest possible options for a safe combination of drugs.

9. To make a forecast of the side effects of drugs prescribed to the patient and to outline a plan for their detection at the early stages.

10. To justify the duration of basic and maintenance therapy.

B. Solving situational tasks.

Task No. 1.

Patient C., 63 years old, suffers from diabetes. For the last year, he has been taking the drug Glibenclamide. Due to an acute cold, he was prescribed aspirin 0.5 g 2 times a day, biseptol-480 1 tablet 2 times a day and tetracycline 1 tablet 2 times a day. In the evening, the patient's condition deteriorated significantly, he has all the signs of hypoglycemia.

What is the reason for this phenomenon? What can you recommend in this case?

Task No. 2.

Patient K., 32 years old, suffers from diabetes. She independently injected herself with 25 units of insulin, after which she developed severe weakness. The patient went to the pharmacy and sought help. She fainted in the pharmacy, and when they tried to put her down, she had convulsions.

What is the reason for this condition? What assistance should be provided to the patient?

Task No. 3.

Patient D., 42 years old, who suffers from hyperthyroidism. For two weeks, he receives therapy: mercazolil 0.01 g 2 times a day, propranolol 60 mg per day, valerian tincture 20 drops 3-4 times a day. As a result of treatment, the following decreased: psychoemotional lability, irritability, tachycardia, sweating.

Is it possible or not to speculate on the effectiveness of antithyroid therapy with mercazolil based on these data? Justify your answer.

Task No. 4.

Patient M., 52 years old, complained of general weakness, thirst, frequent urination, and itching of the skin. During the examination, obesity (weight 100 kg with height 167 cm) is noted, blood sugar content is 7.8 mmol/l, urine is 1% sugar, and the reaction to acetone is negative.

What hypoglycemic drugs should be recommended in this case? Justify your choice.

Task No. 5.

Patient K., 63 years old, has been suffering from non-insulin-dependent diabetes mellitus of moderate severity for 8 years. She constantly uses glibenclamide. Furunculosis has been detected in the last three months. She has currently been admitted to the therapeutic department with complaints of cough with scanty mucopurulent sputum, an increase in body temperature to 37.60 C, chills, pain in the right half of the chest during deep inspiration. On examination: on the right below the angle of the scapula, weakened vesicular breathing, moist rales, dullness of percussion sound. In the same place, X-ray: focal shadows of small caliber. A decrease in renal excretory function was also detected: creatinine clearance 25 ml/min.

Formulate a preliminary diagnosis. What additional methods of further examination would you recommend? Make differentiated choice a priority antimicrobial pharmacotherapy with an indication of the dosage regimen of the selected drug. Specify the methods of monitoring the effectiveness of the treatment.

Task No. 6.

A patient, 13 years old, fell ill acutely: thirst, polyuria, general weakness appeared. In 2 weeks he lost 4 kg. Objectively: the general condition is satisfactory, there is no smell of acetone from the mouth. The level of glucose in the blood is 32 mmol/l, in the urine - 6%, acetone (+).

What diagnosis will you make? What is the treatment strategy?

Task No. 7.

The mother of a child, 6 years old, notes that for the last 2 weeks the child has been constantly going to the toilet several times, drinking a lot of water, has lost weight, and periodically complains of abdominal pain. Objectively: the skin is pale, dry, peeling on the soles, a blush on the cheeks. The lips and tongue are bright red, dry. Internal organs are unremarkable. The smell of acetone from mouth. Glycemia – 12 mmol/l.

What diagnosis will you make? What therapy is appropriate in the near future?

Task No. 8.

Patient D., 42 years old, suffering from hyperthyroidism. For two weeks, she receives therapy: mercazolil 0.01 g 2 times a day, propranolol 60 mg per day, valerian tincture 20 drops 3-4 times a day. As a result of treatment, the following decreased: psychoemotional lability, irritability, tachycardia, sweating.

Is it possible or not to speculate on the effectiveness of antithyroid therapy with mercazolil based on these data? Justify your answer.

9. Patient 36 years old. Diagnosis: diffuse toxic goiter II-III degree; thyrotoxicosis of moderate severity, decompensated.

Which thyrostatic drugs should be prescribed to the patient? Choose the dose, frequency of administration, indicate the criteria for the effectiveness of use. Requires patient prescribed thyroid hormones?

10. Patient, 32 years old. Diagnosis: diffuse toxic goiter III-IV stage; thyrotoxicosis, severe form, decompensated. The patient was hospitalized in the endocrinology department in order to prepare for surgical treatment.

Make up a combined drug therapy, determine the doses of drugs, the frequency of administration, the criteria for the effectiveness of therapy, after which surgical treatment is possible.

11. Patient, 36 years old. Diagnosis: autoimmune thyroiditis of Hashimoto type, moderate hypothyroidism, decompensated.

Choose an adequate dose of thyroid hormone, indicate the criteria for effectiveness.

12. Patient, 55 years old. Diagnosis: secondary moderate hypothyroidism, decompensated. Concomitant: coronary artery disease: stable angina pectoris of II f.kl., extrasystolic arrhythmia, NC I stage.

Choose an adequate dose of thyroid hormone, indicate the features its selection taking into account the concomitant disease. To justify the need and plan for combination therapy.

13. Patient 35 years old. A subtotal resection of the thyroid gland was performed in connection with diffuse toxic goiter. The postoperative period was without complications. 3 months after the operation, the patient complained of an increase in weight by 4 kg, facial swelling, drowsiness after lunch, palpitations, sweating in the afternoon. On the ECG, there was a decrease in the voltage of the waves.

Give a clinical assessment of the patient's condition. Outline a plan of examination and justify drug therapy.

14. Patient 36 years old. Diagnosis: diffuse toxic goiter of the II-III degree; moderate thyrotoxicosis, decompensated.

Which thyrostatic drugs should be prescribed to the patient? Choose the dose, frequency of administration, indicate the criteria for the effectiveness of use. Does the patient need to be prescribed thyroid hormones?

15. Patient. 32 years old. Diagnosis: diffuse toxic goiter of III-IV degree;

thyrotoxicosis, severe form, decompensated. The patient was hospitalized in the endocrinology department in order to prepare for surgical treatment. Make up a combination drug therapy, determine the doses of drugs, the frequency of administration, the criteria for the effectiveness of therapy, after which surgical treatment is possible.

Test tasks for self-control:

1. The patient, 13 years old, fell ill acutely: thirst, polyuria, general weakness appeared. In 2 weeks he lost 4 kg. Objectively: the general condition is satisfactory, there is no smell of acetone from the mouth. The blood glucose level is 32 mmol/l, in the urine - 6%, acetone (+). What is the treatment strategy?

A. Sulfonylurea drug.

B. Long-acting insulin.

C. Biguanides.

D. Short-acting insulin.

E. Diet.

2. The mother of a 6-year-old child notes that for the last 2 weeks the child has been going to the toilet several times, drinking a lot of water, losing weight, and periodically complaining of abdominal pain. Objectively: the skin is pale, dry, peeling on the soles, and there is a blush on the cheeks. The lips and tongue are bright red, dry. Internal organs are unremarkable. The smell of acetone from the mouth. Glycemia is 12 mmol/l. What therapy is appropriate in the near future?

A. Biguanides.

B. Diet therapy.

C. Intermediate-acting insulin.

D. Simple insulin.

E. Long-acting insulin.

3. A patient with diabetes was prescribed insulin. What is one of the mechanisms of action of this drug?

A. Inhibition of amino acid transport.

B. Activation of gluconeogenesis.

C. Inhibition of glycogenolysis.

D. Inhibition of triglyceride synthesis.

E. Inhibition of glucose utilization.

4. A patient with diabetes mellitus was prescribed insulin. What is the mode of administration of this drug?

A. 40 minutes after eating.

B. Before bedtime.

C. 30 minutes before eating.

D. During eating.

E. 1.5 hours before eating.

5. During an objective examination of a woman, 38 years old, pasty face, dry skin, hair loss on the pubic and inguinal areas were detected. The patient is malnourished. The isthmus of the thyroid gland is palpated, painless, mobile. Pulse - 56 per minute, rhythmic. Blood pressure - 100/60 mm Hg. Moderately expanded borders of relative dullness of the heart.

Heart activity is rhythmic, tones are weakened. Tendency to constipation. Daily urine output 400-500 ml Which of the following drugs should be prescribed?

A. Estrogen replacement drugs.

B. Cardiac drugs.

C. Cholesterol-lowering drugs.

D. Iron drugs.

E. Thyroid hormones.

6. A 47-year-old woman underwent thyroid resection due to nodular euthyroid goiter. Which treatment is most likely to help prevent recurrence of nodular goiter?

A. Antistrumin.

B. Mercazolil.

C. Thyrotropin.

D. Thyroid hormones.

E. Radioactive iodine.

7. A 46-year-old woman developed paresthesias in the face and extremities, difficulty breathing, and pain behind the sternum after subtotal thyroid resection. Heart rate – 89 min RR – 20 per min, BP – 150/100 mm Hg. What medications should be prescribed to prevent a sharp deterioration in the condition?

A. Nitrates.

B. Neuroleptics.

C. Tranquilizers.

D. Calcium preparations.

E. β-Blockers.

8. A 40-year-old woman takes 50 mcg of L-thyroxine daily due to primary hypothyroidism. What examination is appropriate to assess the effectiveness of the drug dose?

A. Determination of cholesterol levels.

B. Determination of triiodothyronine levels.

C. Determination of thyroxine levels.

D. Determination of thyroglobulin levels.

E. Determination of TSH levels.

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.

Aditional :

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. State Expert Center of the Ministry of Health of Ukraine http://www.dec.gov.ua/index.php/ua/
2. National Scientific Medical Library of Ukraine http://library.gov.ua/
3. National Library of Ukraine named after V.I. Vernadsky http://www.nbuv.gov.ua/
4. Resource for predicting drug interactions (based on FDA instructions, in English) URL: http://www.drugs.com
5. Interregional Society of Evidence-Based Medicine Specialists: http://www.osdm.org/index.php
6. Bulletin of Evidence-Based Medicine: http://www.evidence-update.ua
7. European Society of Clinical Pharmacologists and Pharmacotherapists: http://www.eacpt.org
8. Resource on drug interactions: http://medicine.iupui.edu/flockart/

Appendix 1

Study protocol for the efficacy and safety of drug use (according to the

supervision of patients)

Educational research work

Student _____

(Name, course, group, faculty)

Head _____

PROTOCOL

studies of the pharmacodynamics of the drug _____

Patient (name, age, body weight) _____

Clinical diagnosis: underlying disease _____

Complications of the underlying disease _____

Concomitant diseases _____

Study date: from _____ to _____

1. Treatment of the patient (provide in the form of prescriptions the 5 most significant drugs, including those selected for careful analysis)
2. The rationale for the appointment of drugs (international, commercial names, chemical structure, features of the introduction, pharmacokinetics, pharmacodynamics of drugs) _____
_____
_____
_____
3. Expected therapeutic effect _____
_____
_____
_____
4. Possible side effects _____
_____
_____
_____
5.List the signs by which the therapeutic effectiveness of the drug will be monitored

Before treatment	After treatment
Subjective	
A)_____	_____
B)_____	_____
C)_____	_____
D)_____	
_____	
E)_____	_____
Objective	
A)_____	_____
B)_____	_____
C)_____	_____
D)_____	_____
Laboratory-instrumental	
A)_____	_____

B)_____
_____
C)_____ _____
D)_____ _____

6. List the symptoms by which side effects of the drug will be controlled.

Side effects The presence of a reaction in the patient (yes, no)

Subjective

A)_____ _____
B)_____ _____
C)_____ _____
D)_____
_____
E)_____ _____

Objective

A)_____ _____
B)_____ _____
C)_____ _____
D)_____ _____

Laboratory-instrumental

A)_____ _____
B)_____
_____
C)_____ _____
D)_____ _____

7. Evaluation of combination therapy (consider the possibility of co-administration of the studied drug with other drugs from section No. 1: pharmacokinetic, pharmacodynamic, pharmaceutical compatibility)_____
_____
_____

8. Conclusions and recommendations (effectiveness of treatment, prognosis of further use, the possibility of replacing other drugs)_____
_____
_____
_____

The study conducted _____ Protocol checked _____

List of references literature