FEDERAL STATE BUDGET EDUCATIONAL INSTITUTION OF HIGHER EDUCATION "NORTH-OSSETIAN STATE MEDICAL ACADEMY OF THE MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION

Department of pharmacology with clinical pharmacology

MEDICINES, AFFECTING THE CARDIOVASCULAR SYSTEM

Educational and methodical manual for students

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COMPOSITIONS L.Z. Bolieva, M.D. Daurova. DRUGS THAT AFFECT THE CARDIOVASCULAR SYSTEM. Educational and methodical manual.

This manual is intended for independent classroom and extracurricular work of students of the 3rd year of medical, pediatric, medical and preventive faculties. The manual contains theoretical material, training and monitoring tasks under " Drugs that affect the cardiovascular system."

REVIEWS:

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PRACTICAL CLASS № 1

The theme of the lesson. MEDICINE USED IN CASE OF INSUFFICIENCY OF CORONARY CIRCULATION.

The General purpose of the lesson. Get acquainted with the basic principles of therapy of pathological conditions associated with coronary circulation. To study the pharmacokinetics and pharmacodynamics of drugs used in coronary heart disease (angina and myocardial infarction), side effects, contraindications to the appointment.

Specific objectives of the lesson

The student should know:

- the main pathogenetic approaches to the treatment of Coronary heart disease (CHD);

- factors that determine the functional state of the myocardium, and ways of correction with a decrease in the delivery of O2;

- classification of antianginal agents;

- mechanisms of action of antianginal agents of different groups;

- side effects of the main groups of drugs used in angina (nitrates, calcium antagonists, beta-blockers).

The student must be able to:

- justify the choice of the drug taking into account the absolute and relative contraindications;

- - prescribe drugs for systematic treatment of coronary heart disease, relief of ischemic heart attack, treatment of myocardial infarction;

- choose the drug in the appropriate dosage form and dosage regimen based on age, comorbidity and other features;

- prescriptions for drugs studied groups.

Control question

1. Main causes and risk factors for coronary heart disease (CHD). Different types of angina: rest angina, stress (stable, first appeared, unstable), spontaneous.

2. Factors that determine myocardial oxygen demand and delivery; possible ways to eliminate inconsistencies between them.

3. Classification of antianginal agents.

4. Organic nitrates: mechanism of action, pharmacological effects, side effects, application.

5. Calcium antagonists: mechanism of action, pharmacological effects, side effects, application.

6. Beta-blockers: the mechanism of antianginal action, side effects, use.

Coronary heart disease (CHD) is one of the most common diseases of the cardiovascular system. At the heart of the development of coronary heart disease is a mismatch between the need for myocardium in oxygen and its delivery, leading to a violation of the functions of the heart.

The main pathogenetic mechanisms of the conflict situation are:

- atherosclerosis of the coronary arteries;

- spasm of the coronary arteries;

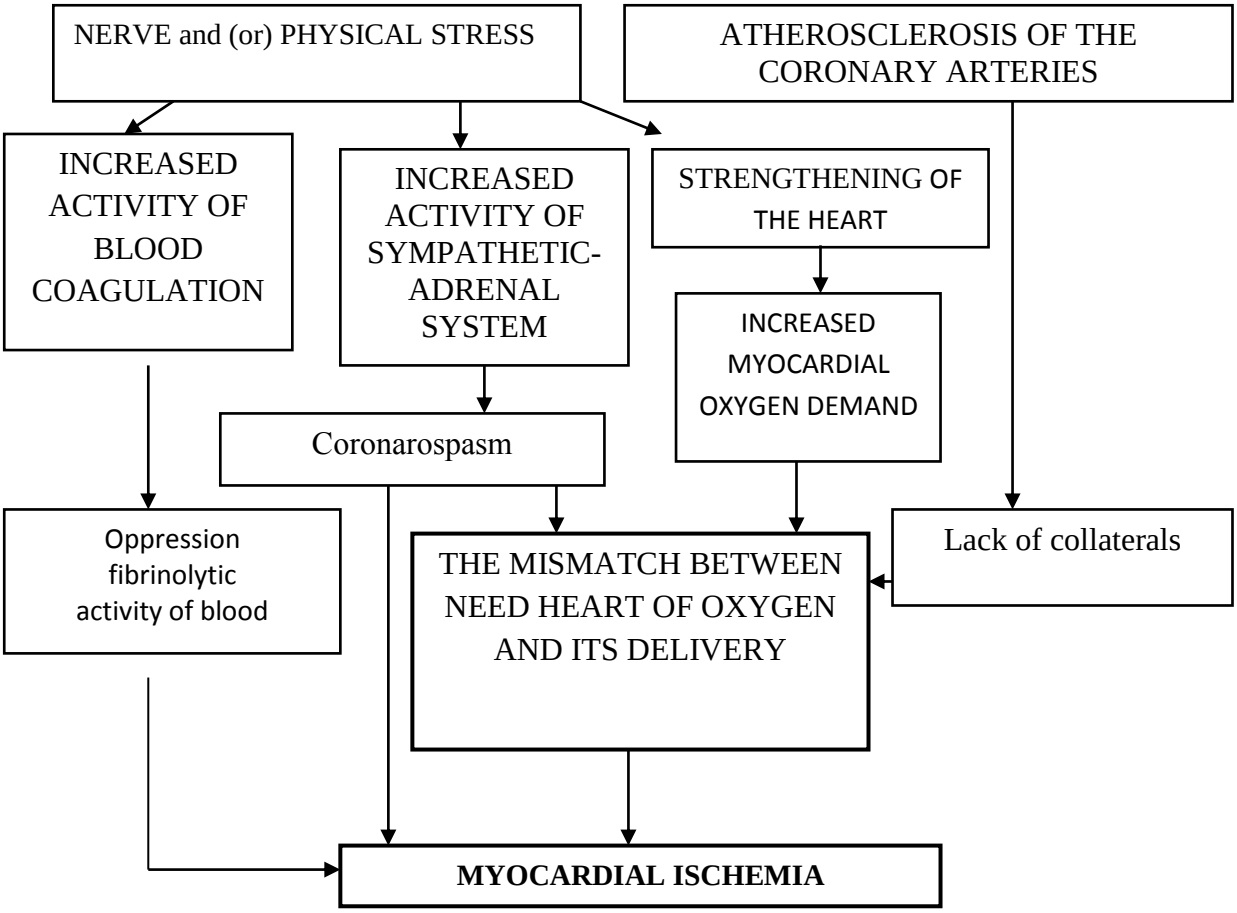
- violation of the mechanisms of expansion of coronary vessels;

- intensive physical activity, emotional stress, leading to the release of catecholamines, have a cardiotoxic effect.

Among the risk factors, the most important are excessive consumption of high-calorie food; increased blood lipid levels; hypertension; diabetes; Smoking, alcoholism; hypodynamia; hypothyroidism.

The combination of several risk factors significantly increases the risk of coronary heart disease.

Figure 1-1. Pathogenesis of angina


NERVE and (or) PHYSICAL STRESS
ATHEROSCLEROSIS OF THE CORONARY ARTERIES
INCREASED ACTIVITY OF BLOOD COAGULATION
INCREASED ACTIVITY OF SYMPATHETIC-ADRENAL SYSTEM
STRENGTHENING OF THE HEART
INCREASED MYOCARDIAL OXYGEN DEMAND
Coronarospasm
Oppression fibrinolytic activity of blood
THE MISMATCH BETWEEN NEED HEART OF OXYGEN AND ITS DELIVERY
Lack of collaterals
MYOCARDIAL ISCHEMIA

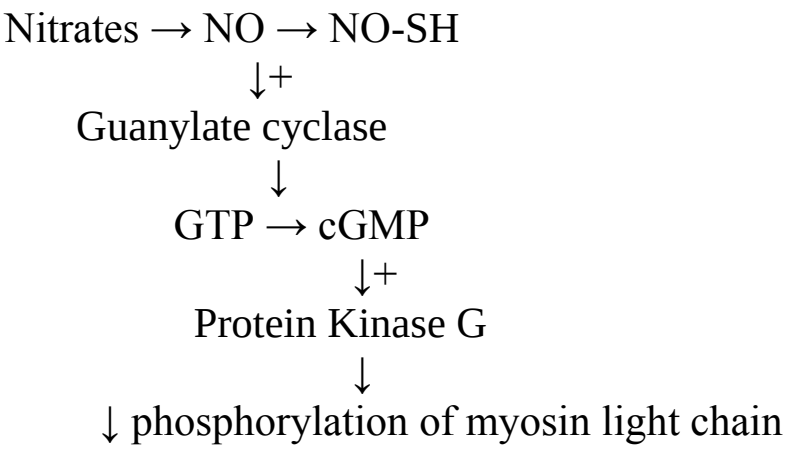
Basic principles of medical treatment of coronary heart disease:
1. reducing myocardial oxygen demand
2. increased oxygen delivery to the myocardium.

As the main means of pathogenetic therapy of angina pectoris, three main groups of drugs are used: nitrates, β-adrenoblockers, blockers of slow calcium channels. In addition, for combination therapy IBS apply funds myotropic coronary dilator action, tools to improve myocardial metabolism, antiplatelet agents, lipid-lowering means.

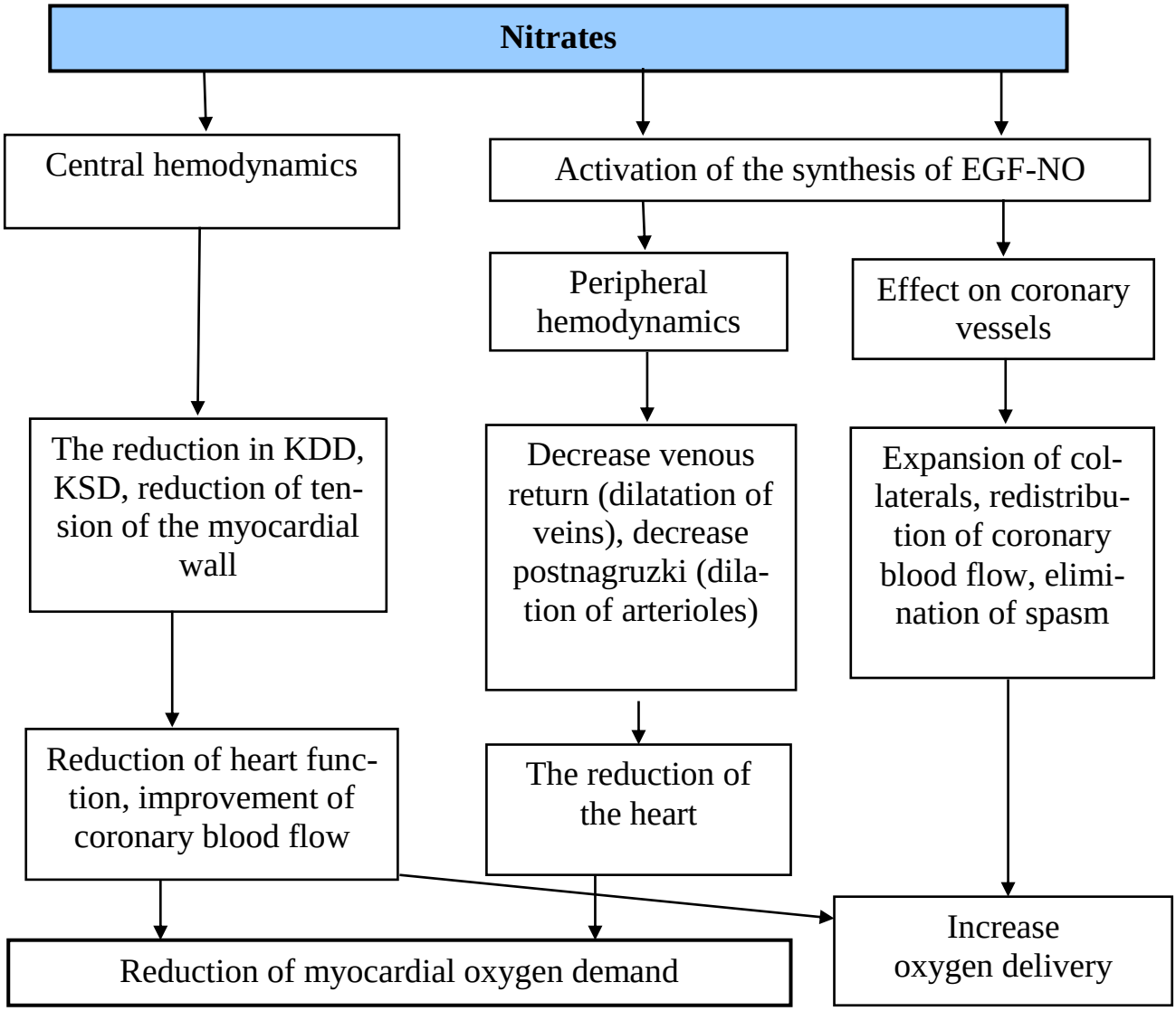
Таблица 1-1. Классификация антиангинальных средств

<table>
<tr><th>Means lowering
the need of myocardium in oxygen</th><th>Means increasing
delivery of oxygen to the myocardium</th></tr>
<tr><td colspan="2">Organic nitrates:
• short-acting-nitroglycerin (tablets, capsules, solution)
• prolonged action-sustac, nitrong, trinitrolong, erinite, nitrosorbide, isosorbide Mononitrate and dinitrate, nitro-Mac
• narutopedia funds – nicorandil, molsidomine
Agents that block calcium channels:
nifedipine, verapamil, diltiazem, amlodipine, nifedipine, mibefradil
Different means:
• channel blocker K+ - amiodarone</td></tr>
<tr><td>β blockers
Propranolol Atenolol
Oksprenolol Acebuchal
Atenolol Bisoprolol
Metoprolol Nebivolol</td><td>Koronarorasshiryayuschego funds myotropic action:
Dipyridamole
Means of reflex action:
Validol</td></tr>
</table>

Figure 1-1. The mechanism of action of nitrates.



Scheme 1-2. Pharmacological effects of nitrates on the cardiovascular system



NITRATES:

- reduce myocardial oxygen demand by reducing preload and postload.
- expand the epicardial parts of the coronary arteries and increase the delivery of oxygen to the ischemic area of the deep layers of the myocardium, improve collateral blood flow.
- inhibit platelet aggregation and thrombosis in coronary vessels.

Dosage forms of nitroglycerin:

- capsules with 1% oil solution of nitroglycerin at a dose of 0.0005 and 0.001 g;
- tablets of nitroglycerin 0.0005 g;
- aerosol for sublingual application-nitrospray;
- 1% alcohol solution of nitroglycerin;

- 2% ointment;
- copolymer of the plate – trinitrolong;
- tablets-sustak, nitrong;
- patches – Deposit, nitroderm, nitrodisc.

Organic long-acting nitrates:

• Isosorbide dinitrate (nitrosorbid, isoket) is a metered – dose sublingual spray 125 mcg/dose; table. 5 mg, 10 mg; retard1 capsules 20 mg, 40 mg, 120 mg and table. retard 20 mg, 40 mg, 60 mg; concentrate for the preparation of solution for infusions 1 mg / ml; gum film 20 mg, 40 mg.

• Isosorbide Mononitrate (monocinque) – table. 20 mg, 40 mg; table. retard 60 mg

• Pentaerythrityl TETRANITRATE (rinit) – table. 20 mg

[1] Retard-prolonged forms of drugs.

Features of the application of nitrates.

Relief of angina attacks – short-acting nitrates:

1. nitroglycerin (tablets under the tongue, aerosol on the mucous membrane, films on the gums);

2. isosorbide dinitrate (aerosol, film, W/ V)

Prevention of angina attacks-long-acting nitrates:

1. isosorbide 5-Mononitrate (tablets, capsules);

2. isosorbide dinitrate (tablets, capsules, ointment, plaster);

3. nitro, nitro Mac, erinite.

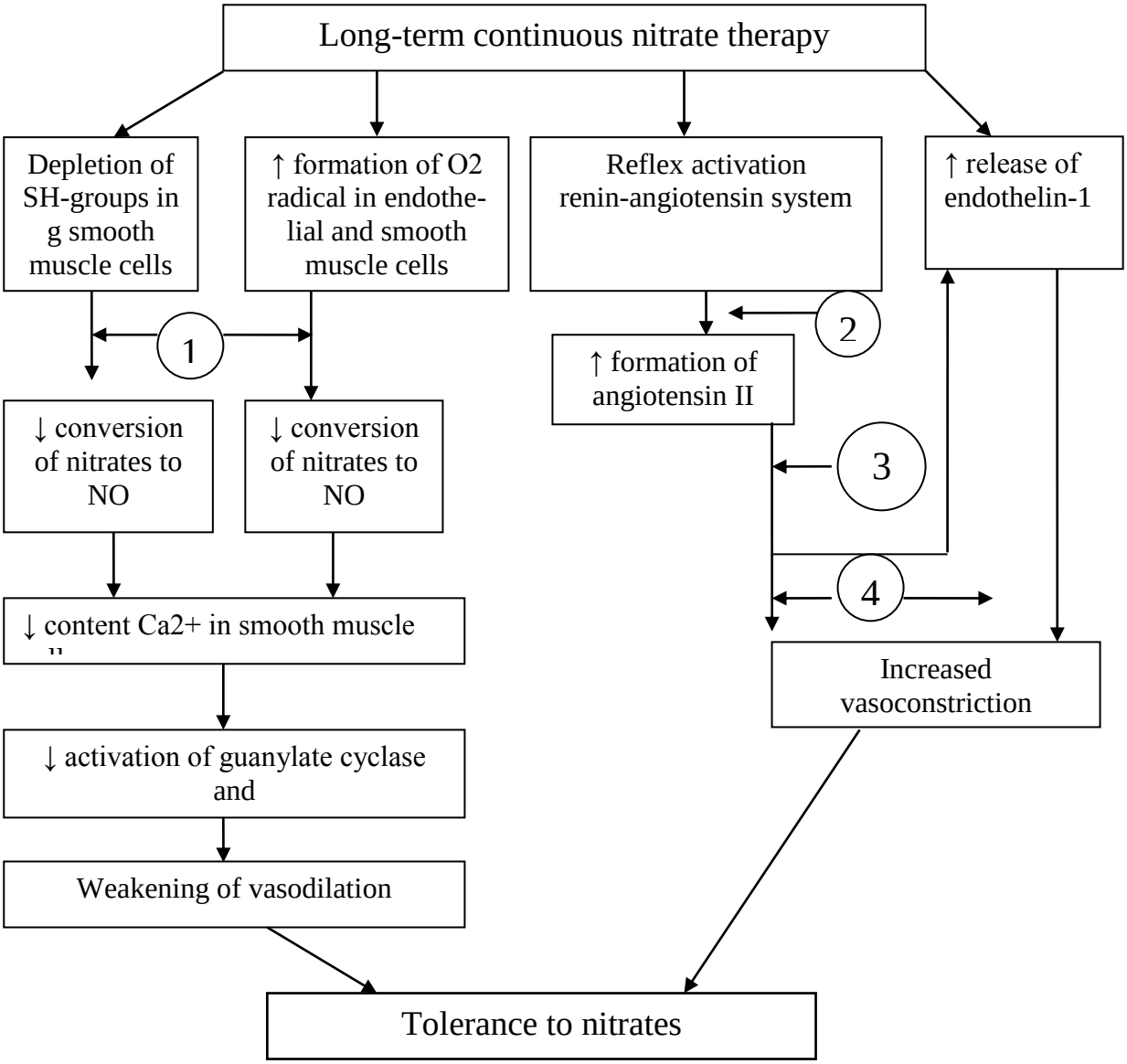
Side effects of nitrates

- headache,
- hypotension, orthostatic hypotension
- reflex tachycardia
- dizziness
- face reddening
- sensation of heat
- hypersensitivity reaction
- tinnitus
- nausea, vomiting
- withdrawal

Contraindications

arterial hypotension
- hypovolemia
- shock
- right ventricular myocardial infarction
- tamponade
- increased intracranial pressure
- • hypertrophic cardiomyopathy
- pronounced stenosis of the mouth of the aorta
- pronounced stenosis of the mitral opening
- closed-angle glaucoma

Scheme 1-2. Causes of nitrate tolerance



1-donators of sulfhydryl groups; 2-ACE inhibitors; 3 – blockers of AT1-angiotensin receptors; 4 – apressin.

To prevent the development of nitrate tolerance:

- *a rational dosage*
- *intermittent reception and alternation with other antianginal agents, non-nitrate days*
- *correction of aid donors SH-groups, ACE inhibitors*

The role of calcium ions in the regulation of the cardiovascular system

- Causes depolarization in the sinus and AV nodes.
- In cardiomyocytes, binding troponin in troponin-tropomyosin complex, create the possibility of interaction of actin and myosin, activate ATP-azu myofibrils.
- in the smooth muscle of the arteries in combination with calmodulin activate the kinase of light chains of myosin, which increases the phosphorylation of light chains of myosin.

↓

Pharmacological effect:

- tachycardia
- facilitation of AV conduction
- increased myocardial contractile activity
- increased myocardial oxygen demand
- narrowing of the arteries

Classification of calcium channel blockers

- Blockers mainly calcium channels of the heart (effect on the heart >, than the effect on the vessels) – derivatives of phenylalkylamine (verapamil, verapamil retard).
- Blocker of calcium channels mainly HL / m vessels (effect on the heart<, than the effect on blood vessels) – derivatives of 1,4 – dihydropyridine (nifedipine – I generation, nifedipine retard, nicardipine, nimodipine, felodipine – II generation, amlodipine-III generation).
- Calcium channel blockers both locations (the effect on the heart = the effect on the vessels) are derived benzothiazepine (diltiazem, diltiazem retard).

Figure 1-4. The mechanism of action of calcium channel blockers

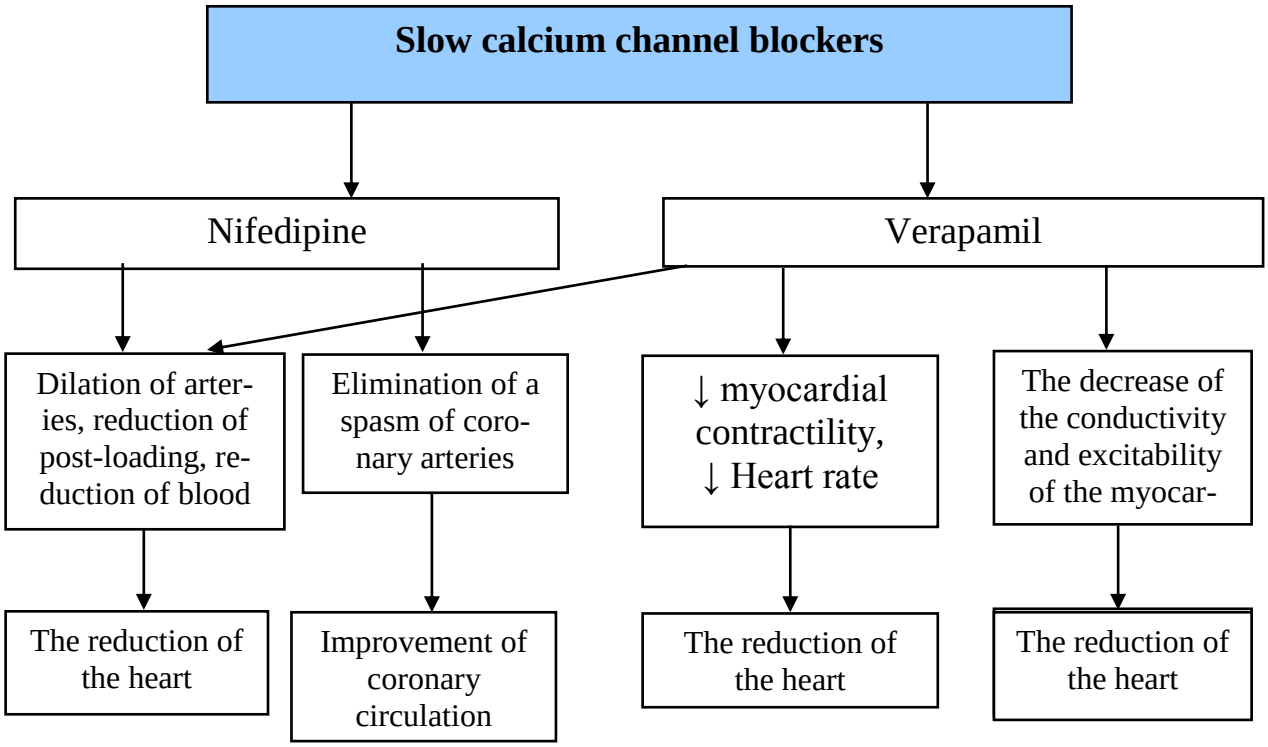


Table 1-2. Features of action of calcium channel blockers

Effects	Nifedipine	Verapamil	Diltiazem
Cardiac contractions rate	↑	↓↓	↓
Automatism of sinus node	0	↓↓	↓
AB-conductivity	0	↓↓	↓
Myocardial contractility	↓0	↓↓	↓
Peripheral vascular tone	↓↓	↓	↓
Coronary vessel tone	↓↓	↓	↓
Platelet aggregation [1]	↓	↓	↓
Antiarrhythmic effect	0	+	+

[1] the effect is described by the use of high doses of drugs

Classification of β-blockers

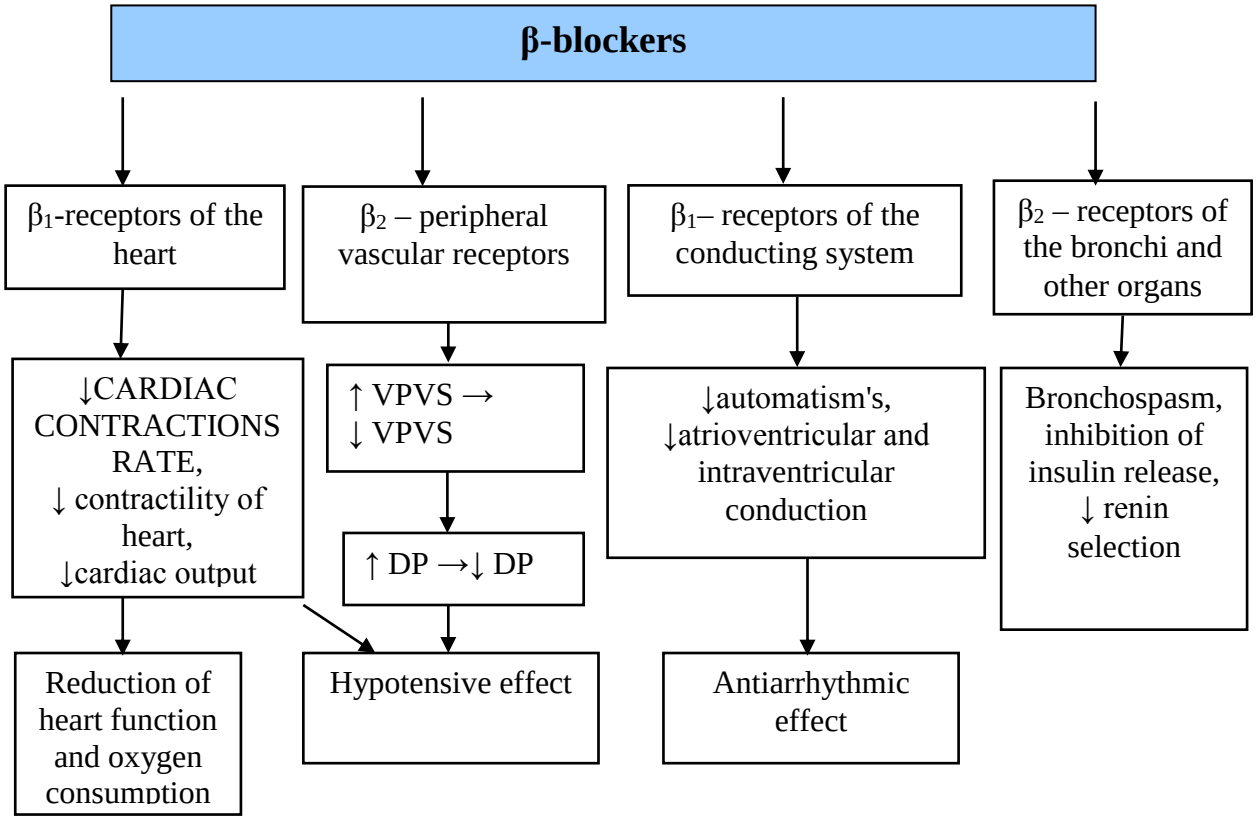
1. Nonselective β-blockers:

a) without internal adrenomimetic activity – propranolol (anaprilin, obsidan).

b) with internal adrenomimetic activity – oxprenolol (trazikor), pindolol (visken).

2. Cardioselective β-blockers: atenolol, Acebuchal, betaxolol, bisoprolol, metoprolol, esmolol.

Scheme 1-5. Mechanism of action of nonselective β-blockers



! Cardioselective β-adrenoblockers in therapeutic doses have a selective effect on β1-adrenoceptors of the heart → to a lesser extent cause spasm of smooth muscles of the arteries and bronchi, hypoglycemia and insulin resistance in patients with diabetes mellitus.

Clinical and pharmacological approach to the treatment of angina.

Basic preparations – CA++ channel blockers (dihydropyridines short (nifedipine) and long (amlodipine); long-acting nitrates, beta-blockers.

Additional preparations – means improving metabolic processes in the myocardium, means affecting the blood coagulation system.

Clinical and pharmacological approach to treatment of unstable angina.

Basic preparations fast-acting medicinal forms of nitrates, narcotic analgesics, β-blockers.

Additional preparations – antiplatelet agents and anticoagulants; CA++ antagonists (if refractoriness to beta-blockers).

Tasks for self-training

Task 1. Note the indications for the use of antianginal agents.

Indications for application / Preparations	Cupping attacks' anginas	Caution attacks' anginas
Nitroglycerin		
Sustac		
Isosorbide dinitrate		
Isosorbide dinitrate		
Nifedipine		
Diltiazem		
Propranolol		
Dipyridamole		
Validol		

Task 2. Note the side effects of antianginal agents.

Preparations / Side reactions	Nitroglycerin	Verapamil	Nifedipine	Propranolol	Dipyridamole
Tachycardia					
Bradycardia					
Inhibition of myocardial contractility					
Hypotension					
Headache, dizziness					
Dyspeptic phenomena					
Bronchial spasm					
Increased intracranial pressure					
Allergic reaction					
"Stealing" syndrome»					

Task 3. Specify the drugs used for myocardial infarction

Effect	Group	Names Preparations
1. Elimination of pain syndrome		
2. Treatment of heart rhythm disorders		
3. Correction of hemodynamic disorders		
4. Elimination of tissue hypoxia and spasm of arterioles		
5. Prevention of thrombosis		

Task 4. To determine the anti-anginal agents

Preparations	Effect on vascular tone			The mechanism of the vasoconstrictor action		
	Peripheral vessels (tone)		Coronary heart vessels	Release group NO	Activation of potassi-um chan-nels of cell membranes	Blockade of calcium channels of cell mem-branes
	veins and venules	arteries and arterioles				
	↓	↓	↓ [1]	+		
	↓	↓	↓	+	+	
		↓	↓			+

[1] Large vessel

Tasks for self-control

I. Anti-anginal agents:

1. Fenigidin. 2. Nitroglycerin. 3. Clonidine. 4. Propranolol. 5. Lidocaine.
6. Strophanthin. 7. Dipyridamole. 8. Validol _____

II. Drugs used to stop an attack of angina:

1. Propranolol. 2. Nitrong. 3. Nitroglycerin. 4. Sustac. 5. Validol. 6.
Dipyridamole. 7. Sodium nitroprusside _____

III. Preparations of nitroglycerine of prolonged action:

1. Nitrosorbidum. 2. Sustac. 3. Erinite. 4. Nitrong. 5. Nitroglycerin. 6. Trinitrolong.

_____

IV. Groups of drugs that simultaneously reduce the need for
myocardium in oxygen and increase oxygen delivery to the myocardium:

1. Organic nitrates. 2. Beta-blockers. 3. Calcium channel blockers. 4. Koronarorasshiryayuschego funds myotropic actions. 5. Potassium channel activators. 6. Bradycardic agents. _____

V. Nitroglycerin:
1. Used internally. 2. Applied sublingual. 3. The effect develops in 2-3 minutes. 4. The effect develops after 10-15 minutes. 5. The effect lasts up to 30 minutes. 6. The effect lasts up to 2 hours. 7. It is used for relief of angina attack. 8. It is used to prevent angina attacks.

_____

VI. Drugs used to prevent angina attacks:
1. Erinite. 2. Nitroglycerin. 3. Days'. 4. Trinitrolong. 5. Verapamil. 6. Validol. 7. Propranolol. 8. Nitrosorbidum.

_____

VII. What are the mechanisms to reduce myocardial oxygen demand under the effect of nitroglycerin?
1. Reduces preload on the heart. 2. Reduces afterload on the heart. 3. Reduces heart rate. 4. Reduces the power of heart contractions.

_____

VIII. What is typical for the effect of nitroglycerin on blood supply of the myocardium?
1. Dilates mainly large coronary vessels and collaterals. 2. Dilates mainly small coronary vessels. 3. Equally improves blood supply to ischemic and healthy myocardial areas. 4. Promotes redistribution of coronary blood flow in favor of ischemic areas of the myocardium. 5. Improves blood supply to the subendocardial layers of the myocardium.

_____

IX. Specify the features of application and action of nitroglycerin:
1. It is mainly used for relief of angina attacks.2. The main route of administration when cupping angina attack-underlanguage. 3. Action with sublingual administration begins in 2-3minutes and lasts up to 30 minutes. 4. Action in sublingual introduction begins after 30minutes and lasts up to 5 hours

_____

X. Side effects of nitroglycerin and organic nitrates.
1. Collaptoid reactions. 2. Headache. 3. Bradycardia. 4. Tachycardia. 5. Dizziness.

_____

XI. What is typical for verapamil?
1. Refers to calcium channel blockers L-type. 2. Reduces myocardial oxygen demand by reducing the strength and heart rate. 3. Increases oxygen delivery to the myocardium due to the expansion of coronary vessels. 4. It has antiarrhythmic activity.

_____

XII. What is typical for beta-blockers?
1. Have koronarorasshiryayuschee effect. 2. Reduce myocardial oxygen demand by reducing the strength and heart rate. 3. Reduce myocardial oxygen demand by reducing preload on the heart.

_____

XIII. Possible side effects of anaprilin?

1. Excessive weakening of the heart rate. 2. Violation of atrioventricular conduction. 3. Increased blood pressure. 4. Increased bronchial tone. _____

XIV. What is the advantage of atenolol over anaprilin?
1. Does not reduce HELL. 2. Much less likely to cause bronchospasm. 3. Does not violate atrioventricular conduction. 4. Does not reduce the strength of cardiac contractions.

_____

XV. What is characteristic of dipyridamole?
1. Dilates mainly small coronary vessels. 2. Dilates mainly large coronary vessels and collaterals. 3. Can cause the phenomenon of"stealing". 4. Promotes redistribution of coronary blood flow in the ischemic focus. 5. It has an antiplatelet effect.

_____

Situational concerns

1. Patient R., 48 years, with coronary artery disease, new-onset angina, was appointed as nitrosorbid. After taking a tablet of nitrosorbide, the patient noted dizziness, headache. Explain the mechanism of side effects. To determine further tactics of the doctor._____
_____
_____
_____

Prescribe:

1. Means for relief of angina attack.
2. Coronary widening drug to prevent angina attacks.
3. A drug that lowers myocardial oxygen demand.
4. Calcium antagonist in coronary insufficiency.
7. Antianginal means of reflex action.
8. Antianginal agent from the group of β-blockers.
9. Cardioprotective agent that increases myocardial resistance to hypoxia.

PRACTICAL CLASS №2.

The theme of the lesson. DIURETICS. LIPID-LOWERING MEANS.

The General purpose of the lesson. To have a clear idea of the mechanisms of action of diuretics of different groups, to study the basic pharmacological properties of diuretics, indications for use, side effects and contraindications to the appointment. To have an idea about the different classes of lipoproteins and types of hyperlipoproteinemia, to know the mechanism and features of the action of hypolipidemic drugs. Конкретные цели занятия.

The student should know:

- physiological and biochemical basis of urination;
- clinical signs of diuretics;
- principles of combined use of diuretics;
- indications and contraindications for the appointment of diuretics;
- classification and mechanism of action of anti-atherosclerotic drugs;
- features of the use of lipid-lowering drugs of different groups.

The student must be able to:

- обосновать выбор препаратов при различных патологических состояниях;
- выбрать дозу и путь введения препарата с учетом степени тяжести и наличия сопутствующей патологии, возможного взаимодействия лекарств;
- выписывать рецепты на препараты изучаемых групп.

Control question.

1. . Classification of diuretics by chemical structure and mechanism of action.
2. The mechanism of action, indications and contraindications to the use of thiazide and thiazide-like diuretics.
3. The mechanism of action, indications and contraindications to the use of loop diuretics.
4. The mechanism of action, indications and contraindications to the use of potassium-sparing diuretics.
5. The mechanism of action, indications and contraindications to the use of osmotically active diuretics.
6. Comparative characteristics of diuretic activity of drugs of different groups.
7. Possible complications, prevention measures and treatment of side effects.
8. Classification of antiatherosclerotic agents.
9. The mechanism and features of the action of drugs from the group of statins, bile acid sequestrants, derivatives of fibroic acid, nicotine acid, probucol.

Diuretics- a group of drugs that are used to regulate the volume or composition of body fluids, correction of violations of water-salt metabolism. Providing a direct impact on the functional state of the nephrons, increase natriuresis and diuresis. Widely used in the treatment of edema of different etiology, hypertension, intoxication.

Traditionally, diuretics klassificeret mechanism, localization, and potency.

Table 2-1. Characteristics of the main groups of diuretics

Group	Drugs	Mechanism of action	Localization action	Force of action
Thiazide and thiazidelike diuretics	Gidrokhlorisiazit (dihlotiazid), chlorthalidone (oksodolin), clopamide (rinaldis), indapamide (Arifon)	Transport inhibitorsNa^+ и Cl^-	The initial part of the distal tubule	Moderate
Loopback Diuretics	Furosemide, K-TA ethacrynic	Transport inhibitors Na^+, K^+ и Cl^-	Ascending part of the nephron loop	Powerful
Potassium-sparing diuretics	a) triamterene, amiloride, b) spironolactone	a) the Blocker Na^+- of the epithelium of the kidneys b) blocker of aldosterone receptors	The end part of the proximal tubule and collecting tubules	Weak
Osmotically active Diuretics	Mannitol, urea	↑Osmotic pressure of blood plasma → dehydration of tissues→↓ Intracranial pressure, Intraocular pressure	It acts throughout all renal tubules	Weak
Inhibitors of carbonic anhydrase	Acetazolamide, dorzolamide (eye drops)	Inhibition of carbonic anhydrase → ↑excretion of bicarbonate and Na^+	The proximal tubule	Weak

Reabsorption of ions in different parts of the nephron occurs either due to transport with the participation of specific proteins-carriers, or due to the movement of ions through the ion channels of the apical membranes of the epithelium of the renal tubules.

In the final part of the distal convoluted tubules and collecting tubules, Na+ ion reabsorption and K+ ion secretion is regulated by aldosterone.

In collecting tubes water reabsorption occurs through water channels under the influence of vasopressin.

! Saluretics-diuretics, primarily violating the reabsorption of Na+ and Cl ions.

Table 2-2. The main properties of different groups of diuretics

Group of preparations	Ion excretion					Excretion Na^+	Diuretic effect	Effect on acid-base balance
	Na^+	K^+	Cl^-	HCO_3^-	Ca^{2+}			
Thiazide diuretic	↑	↑	↑	↓	↓	++	++	alkalosis
Loop diuretics	↑	↑	↑	↑	↓ или -	+++	+++	does not change
Potassium-sparing diuretics	↑	↓	-	↑	-	+	+	Acidosis
Aldosterone antagonists	↑	↓	-	↑	-	+	+	does not change
Osmotically active diuretics	↑	-	↑	↑	-	+	+++	does not change
Inhibitors of carbonic anhydrase	↑	↑	-	↑	-	+	+	Acidosis

Table 2-3. Indications and contraindications to the use of diuretics

Group	Indications
Thiazide and thiazide-like diuretics	Congestive heart failure, hypertension, liver cirrhosis with portal hypertension and ascites
Loop diuretics	Acute and chronic heart failure, pulmonary edema, cerebral edema, ARF and chronic renal failure, hypertensive crisis
Potassium-sparing diuretics	Primary or secondary hyperaldosteronism, heart failure, AG, hypokalemia
Osmotically active diuretics	Glaucoma, brain edema without damage to BBB, acute necrosis of the renal tubules in shock, infections, intoxication

Inhibitors of carbonic anhydrase currently, they have limited use as diuretics due to the weak diuretic effect, which is mainly implemented in the proximal part of the renal tubules. The main indications for the use of acetazolamide are: glaucoma (↓ the production of Intraocular Fluid); epilepsy (as an aid); altitude sickness; metabolic alkalosis with excessive diuretics in patients with severe Heart failure (↓reabsorptions Na^+ and ↑ excretion of hydrocarbonates).

Table 2-4. Side effects of diuretics

Side effect	Drugs	Measures to eliminate and prevent side effects
Hypokalemia	Hydrochlorthiazide, furosemide, ethacrynic acid	Combination of potassium-sparing diuretics; diet rich in potassium
Hyperkalemia	Triampur compositum,	Potassium restriction in diet;

	spironolactone	use of glucose with insulin; calcium gluconate
Hyponatremia	Hydrochlorthiazide, furosemide	Sodium chloride
Acidosis	Acetazolamide	↓dose or drug withdrawal
Alkalosis	Hydrochlorthiazide, furosemide, etakrynic acid	Triampur composite; ammonium chloride; calcium chloride
Hyperglycemia	Hydrochlorthiazide, furosemide, etakrynic acid	Triampur compositum; hypoglycemic drugs
↑ uric acid level	Hydrochlorthiazide, furosemide, etakrynic acid	Cancel diuretics; triampur compositum
Ototoxic effect	Furosemide, etakrynic acid	Withdrawal of the drug
Teratogenic effect	Diacarbum	Do not administer in the first trimester of pregnancy

! Potassium-magnesium-sparing diuretics are often used in combination with more effective diuretics to correct hypokalemia caused by them.
Combination medications: **triampur** (triamterene+gidrokhlorisiazit), **diuretic** (amiloride+hydrochlorothiazide)

Atherosclerosis – pathological process leading to changes in the arterial wall as a result of lipid accumulation, formation of fibrous tissue and the formation of plaques, narrowing the vessel lumen. This leads to an acute or chronic decrease in blood flow in vital organs. Atherosclerosis is not an independent disease, it is clinically manifested by General and/or local circulatory disorders, some of which are isolated in separate nosological forms. The most common atherosclerotic process develops in the aorta, femoral, popliteal, tibial, coronary, carotid arteries and arteries of the brain.
One of the most important risk factors is dyslipoproteidemia - a violation of the lipid profile of the plasma. The most common giperlipoproteinemii with higher levels of total cholesterol, LDL cholesterol and TG.

Table 2-5. The classification of primary dislipoproteidemia (Fredrickson)

The phenotype	of LPlevels which are in-creased,	Risk atherosclerosis'	Total cholesterol	TG	HDL CHOLESTEROL	Freque ncy, %
			Plasma level, mg %			
I	Chylomicrons (HM)	Absents	The normal or ↑ (160-400)	↑↑↑ (1500-5000)	5-20	> 1
IIa	LDL	High (+++)	↑↑ (240-1200)	Норма (менее 200)	30-50	10
IIb	LDL, VLDL	High (+++)	↑↑ (300-400)	↑↑ (250-500)	30-50	40
III	LPP	High (+++)	↑↑ (300-600)	↑↑↑ (300-800)	30-50	> 1
IV	VLDL	Moderate (+)	The normal (less than 250)	↑↑ (300-700)	30-50	45
V	VLDL, HMM	Moderate (+)	↑ (600-800)	↑↑↑ (1500-5000)	5-20	5

Less than
Dyslipoproteidemia is divided into primary (family hypercholesterolemia, etc.) and secondary, arising from:

- a number of diseases - diabetes, hypothyroidism, biliary obstruction, cirrhosis, etc.
- application of anabolic steroids, estrogens, corticosteroids, etc.
- obesity, diet with high content of saturated fat, excessive alcohol consumption.

Table 2-6. Mechanism of action of hypolipidemic agents

Class	Drugs	Mechanism of action
Statins	Lovastatin, simvas-tatin, pravastatin, fluvastatin, atorvastatin	↓ = the enzyme 3-hydroxy-3-methylglutaryl-coenzyme a(HMG-COA) reductase → ↓ cholesterol synthesis in liver → ↑receptor-dependent endocyto-sis of LDL→ ↓ LDL levels in the blood plasma
Bile acid sequestration	Cholestyramine, colestipol	Bile resin binding of K-t in the intestine →absorption of the latter → ↓
Nicotinic acid	Nicotinic acid	↓ triglicerideos in the fat cells→↓ formation of fatty to-t and TG→↓ income bold K-t in the liver →↓ of education TG and VLDL→↓ plasma levels of VLDL, LDL and LPP
Fibroevoy acid de-	Fibroevoy acid deriva-	a)↑ lipoprotein lipase activity and accelerating con-

rivatives, Gemfib-rozil, fenofibrate, bezafibrat	tives, Gemfibrozil, fenofibrate, bezafibrat	version of VLDL to LDL; b)accelerated catabolism of LDL→↓plasma levels of LDL and HDL
Antioxidants Probucol	Antioxidants Probucol	a)↑ catabolism and↓ LDL level (and HDL) b)↓ LDL oxidation and formation of foam cells in vascular intima

Table 2-7. The effect of drugs of different classes on serum lipid levels

Group of preparations	LDL CHOLESTEROL %	HDL CHOLESTEROL %	TG %
Statins	↓ on 18-55	↑ on 5-15	↓ on 7-30
Fibrates	↓ on 5-20	↑ on 10-20	↓ on 20-50
Nicotinic acid	↓ on 5-25	↑ on 15-35	↓ на 20-50
Resins	↓ on 15-30	↑ on 3-5	Varies greatly from ↑ to↓

Table 2-8. Indications and contraindications to the use of hypolipidemic drugs

Class	Indications	Contraindications
	Heavy HC and secondary prevention of coronary heart disease. With caution to appoint women of childbearing age and young men (safety of long-term use is not studied).	Absolute: acute and chronic liver dis-ease.
HMG-COA reductase inhibitors	Drugs of choice for moderate HCH, for primary prevention of IHD, for women of childbearing age and young men.	Relative: receiving cyclosporine, gem-fibrozil, nicotinic acid.
Bile acid sequestration.	Most of dislipoproteidemia	Absolute: family HC, the level of TG
Nicotinic acid	Severe hypertriglyceridemia, familial HX, mixed HX, diabetes. Do not use to reduce LDL as a secondary prevention of CHD.	>500 mg%
Fibrates	Sometimes prescribed with the ineffec-tiveness of other drugs. The effective-ness of probucol for the prevention of coronary heart disease is not confirmed by clinical trials.	Relative: TG level>200 mg%.

Tasks for self-training

Task 1. Determine diuretics A-B

Means	Increased urinary excretion of ions	Activity at acidosis	Activity in alkalosis	Route of administration	Начало эффекта	Duration of action	Content of potassium ions in the blood
A	Na^+Cl^- (K^+, $HCO3^-$)	+	+	inside	Through 1-2h	10-12ч	↓
B	Na^+, Cl^-	+	+	inside	Through 2-5 Days	Days	↑
C	Na^+, Cl^- (K^+)	+	+	inside (i/v и i/m)	Through 20-30 m	3-4ч	↓

Task 2. Fill in the table

Mechanism of action	Group of preparations
Means inhibiting the biosynthesis of cholesterol	
Means preventing the absorption of cholesterol in the gastrointestinal tract	
Means that enhance the breakdown and excretion of lipoproteins from the body	

Task 3. Determine the substance a-G (cholesterol, nicotine acid, lovastatin, gemfibrozil)

	Indications for use in dyslipoproteidemia					Side effects
	IIa	IIb	III	IV	V	
A	+	+	+	+	+	Dyspepsia, skin hyperemia, itching, arrhythmia, liver dysfunction, hyperglycemia, hyperuricemia
B	+					Dyspepsia, headache, myalgia
C		+	+	+	+	Dyspepsia, cholelithiasis, myalgia, skin rashes
D	+					Constipation, malabsorption of drugs

Task 4. Mark the major side effects of lipid-lowering drugs

Effect	Group of preparations			
	Statins	Fibrates	Nicotinic acid	Bile acid sequestration
Myopathy				
Vasculitises				
Thrombocytopenia				

Steatorrhea				
The formation of stones in the biliary tract cholecysti-tis				
Hyperemia and itching				
Cardiac arrhythmia				
Rhabdomyolysis				
Hepatotoxicity and nephrotoxicity				

Task 5. Define lipid-lowering means (A-D) according to the severity of impact on the level of lipo-proteins (lovastatin, cholestyramine, cipro-fibrate, probucol, nicotinic to-that)

Preparation	Chylomicrons	VLDL	LDL	HDL	LPP
A	-	↓	↓	↓↓↓	↑
B	-	+ -	-	↓↓↓	-
C	+ -	↓↓↓	↓	↓	↑↑
D	-	-	-	↓	↓
I	+ -	↓↓↓	↓	↓↓	+ -

Task 6.
Explain the mechanism of diuretic action of loop diuretics by placing the following statements in a logical follower-news:
a) inhibit co-transport of Na+, K+, Cl in the thick ascending segment of Henle Castilla ;
b) inhibit the reabsorption of Na+, K+, Cl, Ca2+, MD2+ions;
C) increase the excretion of Na+, K+, Cl ,Ca2+,Mg22+ and water**.**

Tasks for self-control

I. List diuretics that violate the transport of sodium ions in the renal tubules:
1)mannitol; 2) dihlotiazid; 3) furosemide; 4) spironolactone; 5) diakarb;
6) urea.

_____

II. Specify the effects dihlotiazida:
1) hypokalemia; 2) hyperkalemia; 3) promotes the excretion of uric acid; 4) delays the excretion of uric acid; 5) increases the excretion of calcium; 6) decreases the excretion of calcium; 7) increases the secretion of insulin; 8) reduces the secretion of insulina.

_____

III. Specify the most effective diuretic for the treatment of congestive heart failure with the development of secondary hyperaldosteronism:
1)ethacrynic acid; 2) chlorthalidone; 3) acetazolamide; 4) spironolactone; 5) triampur.

_____

IV. To determine the substance on the following grounds: used for the treatment of glaucoma, epilepsy, edema of cardiac origin, increases diuresis by reducing the reabsorption of bicarbonate, increasing the excretion of urine Na+, K+, HCO3. Long-term use may develop acidosis.

_____

V. Means that reduce the blood cholesterol content mainly.
1) Atorvastatin. 2) Cholesterol. 3) Simvastatin. 4) Bezafibrat.
5) Gemfibrozil.

_____

VI. Means, reducing the content of triglycerides in the blood mainly.
1) Nicotine acid. 2) Gemfibrozil. 3) Bezafibrat. 4) Fenofibrate.
5) Fluvastatin.

_____

VII. To identify the substance. It violates the early stages of synthesis of liver cholesterol (at the stage of mevalonic acid), reduces the content of inflammation markers (C - reactive protein in the vascular wall), platelet aggregation ability, have an antioxidant effect.

_____

VIII. Identify the drug group:
Reduce the synthesis of XC due to reversible temporary inhibition of the key enzyme of this process. Applied with severe HHS and for secondary prevention of coronary heart disease. Carefully appointed women of childbearing age and young men.

_____

IX. In the intestine form nonabsorbable complexes with bile acids, which leads to increased excretion of the latter from the body. They are the drugs of choice for moderate GCS, for primary prevention of ischemic heart disease, for women of childbearing age. The absolute contraindication is family HX and high levels of TG (above 500 mg%).
X. Which of the drugs can enhance the phenomenon of pulmonary edema?
1) Digoxin. 2) Mannitol. 3) Hydrochlorothiazide. 4) Indapamide.

_____

XI. The power of diuretic is estimated by:

1) Localization of the mechanism of action in the nephron. 2) the ability of the drug to change blood PRESSURE. 3) Natriuretic effect. 4) Hourly diuresis.

_____

XII. Combine:

	Effect
1. Hydrochlorothiazide……..	Inhibits aldosterone receptors in the final section of the distal tubules and collecting tubes
2. Furosemide	Inhibits the transport of Na+ and Cl ions in the initial section of the distal tubules
3. Spironolactone…….	Inhibits the transport of Na+, K+ and ions Cl in the ascending part of the loop of Henle
4.Manit……..	Violates the reabsorption of water throughout all the canals

Situational concerns

1.A patient with edema due to liver cirrhosis with a frequency of 1 time per week was administered a diuretic. Swelling reduced, the condition has improved. However, after a few injections, the diuretic effect of the drug disappeared. The patient was prescribed ammonium chloride and the diuretic activity of the drug was restored. What diuretic was administered to the patient? Explain the mechanism of strengthening the action of the main diuretic drug ammonium chloride._____
_____
_____

2. A patient with GB was prescribed a diuretic that reduces blood PRESSURE. HELL decreased, but the patient had pain in the heart, weakness. In order to reduce the complications, potassium chloride was prescribed. What diuretic was applied? Why was potassium chloride prescribed?_____
_____
_____

Prescribe:

1. Diuretic for the treatment of acute pulmonary edema.
2. Diuretic for the treatment of hypertension.
3. Diuretic for forced diuresis.
4. Diuretic for edema of the brain.
5. Potassium, magnesium-sparing diuretic.
6. Hypolipidemic agent, reducing the plasma content of mainly LDL.
7. Hypolipidemic agent, which reduces the plasma content of mainly LDL.
8. Hypolipidemic agent, reducing the plasma content of LDL and VLDL.
9. Hypolipidemic agent that delays the absorption of bile and cholesterol in the intestine.

PRACTICAL CLASS №3

The theme of the lesson. HYPO - AND HYPERTENSIVE MEANS

The General purpose of the lesson. To study the classification, mechanisms of action of antihypertensive agents of different groups, especially pharmacokinetics and pharmacodynamics of individual drugs. Make a clear idea of the pathogenetic principles of treatment of hypertension and symptomatic hypertension, relief of hypertensive crises, treatment of regional vascular spasms. Have an idea of the drugs used in hypotension due to a decrease in peripheral vascular resistance and / or a decrease in cardiac output.

Specific objectives of the lesson

The student should know:
- classification of antihypertensive agents by localization and mechanism of action;
- mechanisms of the antihypertensive action of neurotropic, myotropic drugs, drugs affecting the renin-angiotensin system, diuretics of antihypertensive action;
- pharmacological effects and features of the action of drugs of certain groups; side effects and contraindications to the appointment;
- drugs with maximum effective action in the treatment of hypertension of various degrees of severity;
- classification of hypertensive drugs;
- mechanisms of action of certain groups of drugs used in acute and chronic hypotension.

The student must be able to:
- write prescriptions for drugs studied groups;
- to justify the choice of drugs for various pathological conditions;
- choose the dose and route of administration of the drug, taking into account the severity and the presence of comorbidities, possible drug interactions.

Control question:
1. Regulation of vascular tone and blood pressure level.
2. The drugs of the Central action. Features of the mechanism of action and pharmacological effects of clonidine and moxonidine.
3. Drugs peripheral neurotropic hypotensive action: ganglioplegic, α-blockers, β-blockers, α, β-adrenoblockers, simpatolitiki.
4. Preparations of myotropic hypotensive action. Mechanisms sosudoras-Shiryaev actions of blockers of Ca2+channels (features of action of drugs digidropiridinovmi row); activators of K+-channels; the donators of nitrogen oxides.
5. Pharmacological effects and use of myotropic drugs.
6. Mechanism of action and pharmacological effects of ACEI. Indications for use, side effects.

7. Mechanism of action and pharmacological effects of angiotensin II receptor blockers and vasopeptidase inhibitors.
8. Comparative characteristics of ACE inhibitors and angiotensin II receptor blockers and vasopeptidase inhibitors.
9. Mechanism of hypotensive action and pharmacological effects of agents affecting water-salt metabolism (thiazide and thiazide-like diuretics, loop diuretics, aldosterone antagonists).
10. Drugs for relief of hypertensive crises.
11. Integrated drug treatment of hypertension. Principles of combined use of drugs for the systematic treatment of hypertension.
12. Classification of hypertensive agents on the localization of the action.
13. The mechanism of action and effects of funds used in acute hypotension: adrenomimetics, angiotensin receptor agonists.
14. The mechanism of action and effects of funds used in chronic hypotension: General-dose and analeptics.

ARTERIAL HYPERTENSION (AH) is a condition in which systolic BP is 140 mm Hg.V. and above and / or diastolic blood PRESSURE 90 mm Hg.V. and above. If it is possible to identify the causes of hypertension, it is considered secondary (symptomatic). In the absence of an obvious cause of hypertension, it is primary, essential, idiopathic, and in Russia – hypertension (GB). Secondary hypertension accounts for 5-10% of all cases of hypertension, the remaining cases – GB. AH is considered malignant at a level of diastolic blood PRESSURE above 120 mm Hg.V.
The main determinants of blood pressure – cardiac output and peripheral vascular resistance. There are a number of factors involved in the development of GB. Endogenous neuro-humoral factors that regulate blood PRESSURE include the sympathetic nervous system, renin-angiotensin system, Baro - and chemoreceptors, vasopressors (vasopressin, neuropeptide Y, prostaglandin F2A, thromboxane, etc.) and vasodilating substances (acetylcholine, bradykinin, histamine, nitric oxide, prostacyclin, adenosine, etc.).
Currently, six main groups of drugs are used in the treatment of hypertension: slow calcium channel blockers, diuretics, β-blockers, ACE inhibitors, atii receptor blockers, α-blockers. In addition, in practice, drugs of Central action, combined means are widely used**.**

Table 3-1. Classification of antihypertensive agents by localization and mechanism of action

Localization and mechanism of action	**Pharmacological group**	Preparations
Means reducing the stimulating effect of adrenergic innervation on the cardiovascular system (neurotropic agents)	Imidazole agonists- whether the new I1-receptors	Moxonidine
	Central α2-agonists	Clonidine (clonidine), guanfacine (estulic), methyldopa (dopegit)
	Ganglioplegics	Gexametoni benzolsulfonat (benzogeksony), azametonia bromide (pentamine)
	Sympatholytics	Reserpine, guanetidin (oktadin)
	α-blockers	Phentolamine, prazosin, doxazosin
	β-blockers	Propranolol (inderal), nadolol (corgard), atenolol (tenormin), metoprolol (betalok), betaxolol(lokren), bisoprolol (Concor), nebivolol (nebilet), tenorik (atenolol+oxodoline)
	α, β-blockers	Labetalol (trandat), carvedilol (dilatrend)
Vasodilators	Calcium channel blockers	Nifedipine (fenigidin), amlodipine (norvasc), amlodipine, lacidipine, verapamil, diltiazem,
	Potassium channel activators	Diazoxide, Minoxidil
	Arteriolar vasodilators	Hydralazine (apressin)
	Arterial and venous vasodilators	Sodium nitroprusside
Means affecting the renin-angiotensin system	ACE inhibitors	Captopril(capotene), enalapril (renitek, Enap), perindopril(Prestarium), fosinopril(monopril)
	Angiotensin II AT1 receptor blockers	Losartan, valsartan
	Vasopeptidase inhibitors	Omapatrilat
Means affecting the water-salt metabolism	Diuretics	Indapamid(Arifon), hydrochlorthiazide, furosemide (lasix), spironolactone adelfan (reserpine+dihydralazine), kristain (reserpine + dihydroergocristine + clopamide)

Table 3-2. Mechanisms of action of antihypertensive agents

Class of drugs	Mechanism of action
Agonists of imidazoline I1-receptors	Stimulation of I1 receptors in the nuclei of the solitary tract → inhibition of the vasomotor center → reduction of cardiac output and vascular tone
Central α2-agonists	• Stimulation of α2-AR and I1-receptors in the nuclei of the solitary tract→ stimulation of vagus centers→ inhibition of the vasomotor center→ inhibition of the stimulating action of the sympathetic nervous system on the heart and blood vessels • Stimulation of presynaptic α2-adrenergic receptors→decrease the release of norepinephrine
Ganglioplegics	Blockade of Nn-XP ganglion neurons, Nn-XP chromaffin cells of adrenal medulla→ reduction of adrenaline and norepinephrine→ vasodilation
Sympatholytics	• Inhibition of synthesis and reuptake of noradrenaline vesicles→depletion of mediator stocks in the end of adrenergic fibers, inhibition of adrenaline release in the synaptic cleft→inhibition of transmission in the adrenergic synapses • The penetration of the vesicles and the displacement of norepinephrine with the consequent loss of MAO→inhibition of transmission at adrenergic synapses
α-blockers	Blockade of α1-adrenergic receptors→the resistance and capacitance vessels→↓SVR→↓AD
β-blockers	• Blockade of presynaptic β2 receptors and inhibition of noradrenaline secretion • Restore baroretseptorov depressornogo jerk • Inhibition of the Central parts of the sympathetic regulation of the heart and blood vessels • Blockade of β1 receptors IN the South of the kidneys and inhibition of renin secretion
A, β-blockers	• Blockade of α1-receptors→ expansion of peripheral vessels, reduction of total peripheral resistance • Blockade of β-receptors→ decrease in the frequency and strength of cardiac contractions, cardiac output
Calcium channel blockers	Blockade of potential-dependent Ca2+ - channels of L-type→ obstacle to the entry of Ca2 + ions into the cell→ inhibition of cell membrane depolarization→ vasodilation
Potassium channel activators	Activation of K+-channels→output of K+ from cells→ hyperpolarization of cell membrane→ blockade of SA2+ - channels→ vasodilation
Arterial and venous vasodilators	The release of NO→stimulation called guanylate cyclase→↑ cGMP formation→activation of protein kinase G → ↓ activity phospholamban → ↑levels of Ca2+ ATPase→ ↓ concentration of Ca2+ in the cytoplasm→ vasodilation
Diuretics	↑ excretion of Na+ → → metabolism of extracellular Na+ to intracellular Ca2 + ions → ↓ Ca2+ in the cytoplasm of smooth muscle fibers→ muscle relaxation and vasodilation
ACE inhibitors	Blockade of conversion of angiotensin I to angiotensin II, resulting in: • ↓ vasoconstrictive effect • ↓ release of noradrenaline from sympathetic nerve end-

	ings • ↓ aldosterone secretion by adrenal cortex • ↓ inactivation of bradykinin
Angiotensin II AT1 receptor blockers	Blockade of AT1-receptors, accompanied by the activation of AT2-receptors →↓spasm of arterioles; ↑ renal blood flow and release of Na+ and water; ↓release of noradrenaline into the synaptic gap (effect on presynaptic receptors) → ↓tone SAS→vasodilation and ↓ AD

The basic principles of drug treatment can be formulated from three theses:

- Start treatment of mild hypertension is necessary with low doses of drugs.
- Combinations of drugs should be used to improve the effectiveness and safety of therapy.
- You need to use long-acting drugs.

Rational combinations for the treatment of severe hypertension should be considered:

- Diuretic+β-blocker + Ca2 + antagonist or
- Diuretic+ β - blocker + ACE-I or
- Diuretic+ β - blocker + alpha-blocker

When prescribing drugs as part of combination therapy should take into account the possible effect of interaction with other drugs, which may be different.

Table 3-3. The interaction of hypotensive drugs with different groups of means, which may be different.

Hypotensive preparation	**Combination**	
	Rational	Unwanted
Diuretics	Clonidine, dopegit, reserpine, β-blockers, hydralazine, Isobaric, captopril and other ACE inhibitors	Nifedipine
Clonidine	Diuretics, β-blockers, nifedipine, veroshpiron, hydralazine, ACE inhibitors	Dopegit, reserpine, and cardiac glycosides, antiarrhythmic drugs, antipsychotics, chlorpromazine, tisercinum; MAO inhibitors
β-blockers	Diuretics, clonidine, dopegit, hydralazine, nifedipine, veroshpiron, ACE inhibitors	Reserpine, Isobaric, antidepressants, sympathomimetics
Hydralazine	Diuretics, dopegit, clonidine, reserpine, β-adreno-	Nifedipine
Reserpine	blockers, veroshpiron, ACE inhibitors	Clonidine, dopegit, β - blockers, antiarrhythmic drugs, antipsychotics - Amazin, tisercinum, MAO inhibitors

Due to the fact that one patient often has two or more diseases of the cardiovascular system (hypertension + angina, hypertension + arrhythmia, etc.), hypotensive therapy is carried out taking into account the concomitant disease.

Table 3-4. Selection of drugs for the treatment of hypertension, depending on comorbidities

Indications	**Drugs of choice**
Heart failure	Diuretics ACE inhibitors
Angina	β-blockers Calcium antagonist
Old age	Diuretics Calcium antagonist
After myocardial infarction	β-blockers ACE inhibitors
Diabetic nephropathy	ACE inhibitors
Metabolic syndrome	Imidazoline receptor agonists
Dry cough in the treatment of ACE inhibitors	At receptor antagonists II
Hypertrophy of the prostate	α-blockers

Table 3-5. Side effects and contraindications to the use of antihypertensive agents

Class of drugs	Side effect	Contraindications
Diuretics	Hypokalemia, hyponatremia, headache, paresthesia, dyspepsia, thrombocytopenia, ↑ cholesterol and triglyceride levels	Gout
Nonselective β-blockers	↓Heart rate and myocardial contractility; bronchospasm; increased fatigue; cold limbs; hypoglycemia in patients with diabetes	Bronchial asthma and COPD; AB-blockade of II-III degree;
ACE inhibitors	Paroxysmal dry cough; cholestasis; hyperkalemia; proteinuria; renal dysfunction	Bilateral renal artery stenosis. Hyperkalemia. Pregnancy
Calcium antagonist	Headache; palpitations; swelling of legs; bradycardia; AV-blockade	Congestive heart failure.
A-blockers	"The phenomenon of the first dose" (arterial hypotension and orthostatic collapse after the first dose)	Orthostatic hypotension (relative contraindication)
Angiotensin II receptor antagonists	The same as the iapf, but develop less. The frequency of development is about the same as when using a placebo	Bilateral renal artery stenosis. Hyperkalemia. Pregnancy.
Imidazoline receptor agonists	Dry mouth; fatigue; headaches; sleep disorders;	Severe heart failure. Blockade of the cardiac conduction pathways (relative contraindications).

In the treatment of elderly patients with isolated systolic hypertension and edema syndrome as monotherapy or as part of combination therapy, thiazide-like and thiazide-like diuretics are recommended (who Recommendations 2003; VOK 2004). Along with prolonged antagonists Ca2+ thiazide diuretics are the most effective antihypertensive agents according to these indications.

One of the drugs of choice of this group is indapamide, which in addition to diuretic and even vasodilator effect. The mechanism of vasodilating action of the drug is associated with:

- the blockade of Ca2+channels and to lower SVR;
- the stimulation of the synthesis of prostaglandins I2 and E2, vasodilating properties;
- agony in relation to+ - channels.

! Indapamide increases the speed of glomerular filtration and has a hypotensive effect in patients with both normal and impaired renal function. The appointment of high doses of the drug despite the increase in diuresis does not affect the degree of reduction of blood PRESSURE.

The hypotensive effect of antagonists of Ca2+ is associated with peripheral vasodilatation. This not only reduces blood pressure, but also increases blood flow to the heart, brain, kidneys. Hypotensive effect is combined with moderate natriuretic and diuretic effect, which leads to additional ↓OPSS and BCC.

- **!** Ингибиторы АПФ и ингибиторы вазопептидаз - гипотензивные препараты, которые одновременно подавляют прессорные системы регуляции АД (↓уровня ангиотензина-II ,альдостерона, норадреналина) и активирует вазодепрессорные процессы (↑уровня брадикинина, простагландинов E_2 и I_2, NO).

The main pharmacological effects of ACE inhibitors:

- Neurohumoral: ↓formation of angiotensin II, aldosterone; ↓ activity of the sympathoadrenal system; ↑activity of the parasympathetic system; ↑release of NO.
- Hemodynamic: ↓ CBP, ↓ systemic blood PRESSURE; ↓ post-and preload; improvement of blood circulation in the heart, kidneys, Central nervous system.
- Vscular: improving endothelial function; prevention of atherosclerotic plaque damage.
- Cardinal: reverse development of left ventricular hypertrophy; ↓heart chamber volume; antiarrhythmic effect.
- Kidney: enlargement of renal arterioles and glomeruli ↓severity of vnutrikletochnogo; ↑natriuresis and diuresis delay K.
- Metabolic: ↓insulin resistance; ↑synthesis of HDL and disintegration of VLDL.

Side effects of iACE

- headache
- dizziness
- nausea, decreased appetite
- fatigability
- neurological disorder
- hyperkalemia
- worsening of renal failure
- dry cough (cause of drug withdrawal in 2% of patients)
- ngioneurotic edema
- allergic reaction
- neutropenia
- proteinuria

At II receptor blockers-losartan, irbesartan, eprosartan, valsartan,
are the drugs of choice in the appearance of dry cough during treatment iapf.

One of the most severe and common complications of hypertension is a **hypertensive crisis** - a condition that requires urgent and urgent reduction of blood PRESSURE.

For immediate reduction of blood PRESSURE, drugs are used, the beginning of which varies from 1 to 10-20 minutes after the on / in: sodium nitroprusside, enalapril, hydralazine hydrochloride, diazoxide, fentolamine, furosemide, clonidine.

! Rapid decrease in blood PRESSURE can provoke the development of cerebral circulation failure or other dangerous complications

In uncomplicated course of hypertensive crisis (requires ↓AD for several hours), drugs are used, the beginning of which varies from 5 to 60 minutes after ingestion or sublingual*: clonidine, nifedipine, captopril.*

α,β -blockers: ↓ cardiac output (block β-adrenergic receptors) and peripheral vascular tone (block α -adrenergic receptors) → ↓ AD, it does not increase peripheral vascular resistance and does not change renal blood flow.

Table 3-6. Comparative characteristics of hemodynamic effects of α and β-blockers

Indicators	α -blockers	β-blockers	α, β-blockers
hemodynamics	↑	↓↓	↓-
CARDIAC CONTRACTIONS RATE	↓	↓	↓↓
HELL	-	↓↓	↓
AV-carrying out	-↑	↓↓	↓-
Contractility	↓↓	↓[1]	↓
Myocardium's	↑	↓	

[1] with systematic therapy

HYPERTENSIVE MEANS

There are physiological hypotonia (in trained athletes, prandialno hypotension) and pathological hypotension. Pathological hypotension includes primary or essential hypotension (hypotonic disease), idiopathic orthostatic hypotension and symptomatic forms of the disease.

Most of the authors diagnose chronic arterial hypotension by reducing SD below 100-110 mm of mercury. art. , and DD below 50-60 mm Hg. art alone.

Orthostatic hypotension - a form of transient hypotension occurs when the patient moves from horizontal to vertical position and causes discomfort

Primary arterial hypotension (neurocirculatory dystonia) - a disease in which the decrease in blood PRESSURE is caused by a violation of the function of the apparatus that regulates blood circulation, and occurs primarily. It is characterized by symptoms of insufficient perfusion of organs (dizziness, nausea, tachycardia).

Hypotension is severe resistant form of neurocirculatory hypotension.

T able 3-7. Classification of symptomatic hypertension

Forms of arterial Hypotensions	Diseases	The main factor of hemodynamic disorders			
		↓MVB	↑VPR	↑VCB	↑Venous return To heart
Chronic arterial hypotension Orthostatic	Primary hypotension		+		
	Ulcer		+		
	Hypothyroidism	±			
	Primary hypoallergenic		+	+	
Hypotension	Cerebral atherosclerosis	±	+		
	Idiopathic orthostatic hypotension				+
	Long-term bed rest	±	±		+

Таблица 3-8. Classification of agents that increase vascular tone

Drugs of Central Action	Psychostimulants	Caffeine
	Analeptic	Cordiaminum
	Psychologizers Preparations	Preparations of ginseng, lemongrass
Drugs that stimulate the peripheral nervous system	α, β-adrenomimetics	Noradrenaline hydrotartrate, adrenaline hydrochloride
	α-adrenomimetics	Mesaton, midodrin
	Dopaminomimetics	Dopamine
Drugs of Central Action		The angiotensinamide

Table 3-9. Indications and side effects of antihypertensive agents

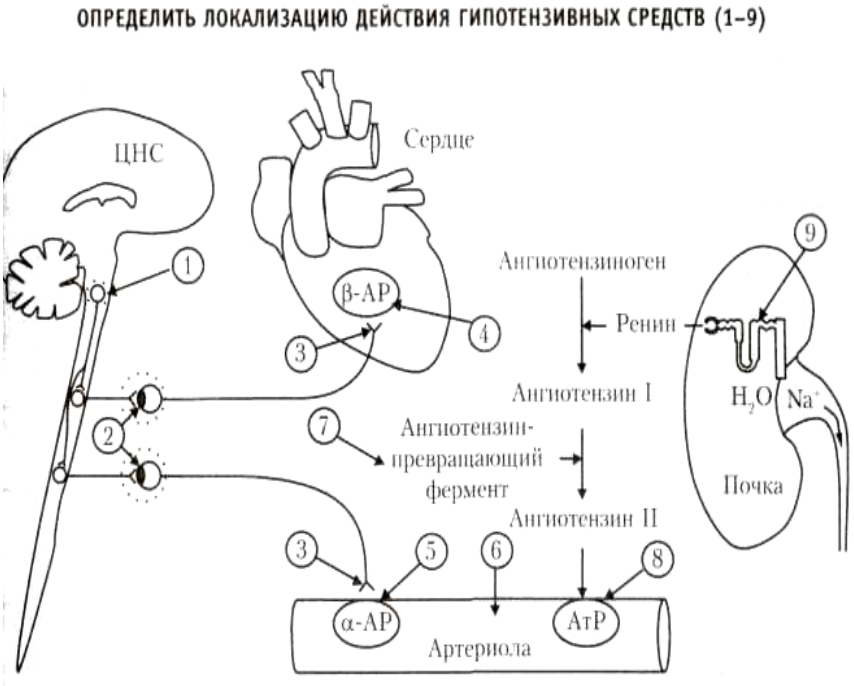
Preparation	Indications for use	Contraindications
Noradrenaline	A state of shock and the associated vasomotor collapse Indications for use	Full AB-blockade, halotane anesthesia
Dopamine		Thyrotoxicosis, pheochromocytoma
The angiotensinamide		Hypovolemic shock
Midodrin	Long treatment	Full AB-blockade, halotane anesthesia
Etilefrine		

Tasks for self-training

Task 1. Determine the pharmacological effect of calcium antagonists

Preparation	Cardiac contractions rate	Myocardial contractility	Conductivity	Peripheral vascular tone
Nifedipine				
Verapamil				
Diltiazem				

Task 2. Determine the drug in accordance with the localization of action.



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Task 3. Specify rational combinations of antihypertensives:

	Dihlotia-zid	Proprano-lol	Prazosin	Reserpine	Clonidine	Nifedipine	Captopril
Hydrochlorthiazide							
Propranolol							
Prazosin							
Reserpine							
Clonidine							
Nifedipine							
Captopril							

Task 4. Specify the group of funds that cause these pharmacological effects:

Pharmacological effect	Funds group
Weakening of psycho-emotional tension	
The decrease in cardiac output	
Inhibition of angiotensin II synthesis	
Excretion of Na+, chlorine+ and water ions from the body	
Reduction of sympathetic impulses in the vas-omotor center	
Direct inhibition of vascular smooth muscle contractions	
Inhibition of vasoconstrictor receptors in vas-cular	

Task 5. Explain the causes of therapeutic nonequivalence of drugs in the treatment of hypertension of varying severity

Preparation	Severity of hypertension		
	light	medium weight	Heavy
Methyldopa	++	+++	+
Octadine	-	+	+++
Apressin	+	+++	-
Ganglioplegics	-	-	+++
Diuretics	+++	+++	+++
Reserpine	+++	+	-

_____

_____

_____

Task 6. Specify drugs of choice for indications:

Initial forms of Hypertension	Systematic	Hypertensive crisis

Task 7. Identify hypertensive agents

Preparations	Properties				
	VPRV	Heart Rate	Duration of action	Effect on renal blood flow	Route of administration
A	↑	↓	Minutes	↓	intravenous drip
B	↑	↑	Minutes	↑	intravenous drip
C	↑	↓	2-3 ч	↑	Inside, intramuscular-ly, intravenous

Tasks for self-control

I. Identify the substance:
Alkaloid, chemical structure close to caffeine, dilates blood vessels, lowers blood PRESSURE, has a direct effect on smooth muscles, has a urine-racing effect. It is used in the treatment of GB, IHD in the intercept period.

_____

II. Inorganic compound, lowers blood PRESSURE due to myotropic action, inhibits the Central nervous system, with/in the introduction can cause anesthesia. Reduces swelling of the brain. It is used in hypertensive crises.

_____

III. Synthetic compound. Reduces cardiac output and peripheral vascular resistance. It has α-adrenomimetic effect. It has a sedative effect. Used for the treatment of hypertension and edema hypertensive crisis.

_____

IV. How do inhibit the activity of the renin-angiotensive system □ - adrenoblokatory?
1.Inhibit the secretion of renin. 2.Inhibit renin. 3.Inhibit angiotensin converting enzyme. 4.Block angiotensin receptors..

_____

V. What is characteristic of omapatrilat?
1. It inhibits angiotensin converting enzyme and reduces the formation of angiotensin II. 2. Inhibits neutral endopeptidase and reduces degradation of endogenous vasodilating peptides. 3. It is a donator of nitric oxide and acts like an endothelial relaxing factor.

_____

VI. Mark the answers corresponding to the questions:
1. Means, increasing blood PRESSURE. 2. The drug, the hypotensive effect of which is associated with a decrease in BCC and OPSS due to a decrease in Na ions in the body
3.Means, lowering the tone of vasomotor centers

4. A remedy that violates the conversion of angiotensin 1 to angiotensin 2
5.The product has a direct myotropic effect on the smooth muscles of blood vessels

A. Clonidine
B. Perindopril
C. Omapatrilat
D. Angiotensinamide.
E.Spironolactone
F.Nifedipine
G.Magnesium sulphate

VII. Combine:

Effects:	Preparations:
1. The drug, increasing Hypo-tensiunii effect clonidine	Spironolactone
2. Drug, weakening Hypo-hypotensive effect simpatolitikov	Digitoxin
3. Drug, preventing development of hypokalemia under influence of diuretics	Atropine
4. The drug, reinforcing effect of β-blockers on contractility and conductivity of the myocardium	Hydrocortisone
5. Drug, weakening effect of β-blockers on contractility and the conductivity of myocardium	Quinidine

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VIII. Note the features of reserpine compared with octadine:
1.For the efficiency of hypertension exceeds oktadin. 2.For the efficiency of hypertension oktadin inferior. 3.Less likely to cause orthostatic hypotension. 4.More often causes orthostatic hypotension. 5.It has a sedative effect. 6.It does not act on the Central nervous system.

IX. In the treatment of α-blockers occurs:
1) Decrease in total peripheral vascular resistance.
2) increasing the volume of circulating blood.
3) Reduction of renin formation.
4) Increasing the formation of renin.

X. When using any antihypertensive agents may develop orthostatic hypotension.
1.Ganglioplegics. 2.Sympatholytics. 3.Means of myotropic action. 4.Drugs affecting the fluid and electrolyte balance. 5.β-blockers. 6. α-blockers.

XI. In patients with arterial hypertension and heart failure to reduce blood PRESSURE, it is advisable to use:

1) Clonidine, 2)Propranolol, 3)Captopril, 4) Dopegit.

_____

XII. Note the side effects that can be observed when using anaprilin.
1.Heart failure. 2.Pronounced bradycardia. 3.Inhibition of atrioventricular conduction. 4.Orthostatic hypotension. 5.Increased bronchial tone. 6.Increased tone of peripheral vessels.

_____

Situational challenges

1. In a patient with elevated BP numbers, suffering from GB for several years, a drug was used to stimulate labor activity, increasing the contractility of the myometrium. However, after the use of the drug, blood PRESSURE increased even more. What medication was used? What drug should be prescribed in this situation?

_____

2. In a patient with GB, after taking the drug, blood PRESSURE significantly decreased. However, he developed muscle weakness, lethargy. These symptoms gradually over the course of the day passed. What kind of drug could cause such side effects? What drug should have been taken simultaneously with this drug in order to prevent complications?

_____

3. The patient, who has a history of gastric ulcer, went to the doctor with complaints of weakness in the morning, dizziness when standing up, blurred outlines of objects, frequent fainting. These symptoms gradually passed after the systematic use of the drug for two weeks, but the patient began to complain of frequent urination, skin itching and sweating. What medication was prescribed and what were the side effects?

_____

Prescribe:
1. Means of neurotropic action for relief of hypertensive crisis.
2. Means of myotropic action for relief of hypertensive crisis.
3. Blocker for the systematic treatment of hypertension.
4. ACE inhibitor for the treatment of hypertension.
5. A remedy for controlled hypotension.
6. Drug of choice in anaphylactic shock.
7. A remedy for acute hypotension.
8. General-toning agent for chronic hypotension.

PRACTICAL LESSON № 4

The theme of the lesson. MEDICINES USED TO TREAT HEART FAILURE. ANTIARRHYTHMIC FUNDS.

The General purpose of the lesson. To study the basic principles of treatment of heart failure, to justify the choice of the main groups of drugs for acute and chronic heart failure. To study pharmacokinetics and pharmacodynamics of cardiotonic and anti-arrhythmic drugs.

Конкретные цели занятия

The student should know:

-the main causes and manifestations of acute and chronic heart failure (OSN and CHF);

- classification of basic, additional and auxiliary means of treatment of CHF;

- - mechanisms of action of cardiotonic glycoside and non-glycoside structures;

- pharmacological effects, hemodynamic parameters, side effects, overdose symptoms and methods of their prevention and elimination;

- causes and types of SS rhythm disturbances;

- classification and mechanisms of action of antiarrhythmic agents;

- comparative characteristics of drugs, their influence on electrophysiological parameters (automatism, conductivity, excitability);

- side effects of antiarrhythmic drugs, complications, measures of assistance at the same time.

The student must be able to:

- to justify the choice of drugs for the treatment of acute and chronic heart failure;

- write prescriptions for drugs in appropriate dosage forms, taking into account the severity of the disease and comorbidity;

- prescribe drugs for various arrhythmias, prescribe, choose the dose and route of administration.

excitability);

- side effects of antiarrhythmic drugs, complications, measures of assistance at the same time.

Control question

1. Classification and General characterization of the cardiotonic funds.
2. Sources of cardiac glycosides, galenic, novogalenovye drugs and individual glycosides.
3. The mechanism of action of cardiac glycosides.
4. Intra-and extracardial effects of cardiac glycosides.
5. Comparative characteristics of cardiac glycosides.
6. Indications for use of cardiac glycosides. The choice of funds depending on the type and manifestations of heart failure.
7. Symptoms of an overdose of cardiac glycosides and relief measures.
8. "Non-glycoside" cardiotonic agents: classification, mechanism of action, indications for use, side effects, comparative characteristics of drugs.

9. Rationale for the use of iapf, β-blockers, α, β-blockers, diuretics in the treatment of CHF.
9. Classification of antiarrhythmic drugs.
10. Mechanisms of action of antiarrhythmic drugs.
11. Comparative characteristics of antiarrhythmic agents.
12. The choice of antiarrhythmic drugs depending on the type of cardiac arrhythmias.
Heart failure is a pathological condition in which the heart does not provide normal oxygenation of organs and tissues, which leads them to hypoxia. As a result, there is shortness of breath, cyanosis of the skin, fatigue, swelling, ↑ VD, ↓ SV and other symptoms of CHF.

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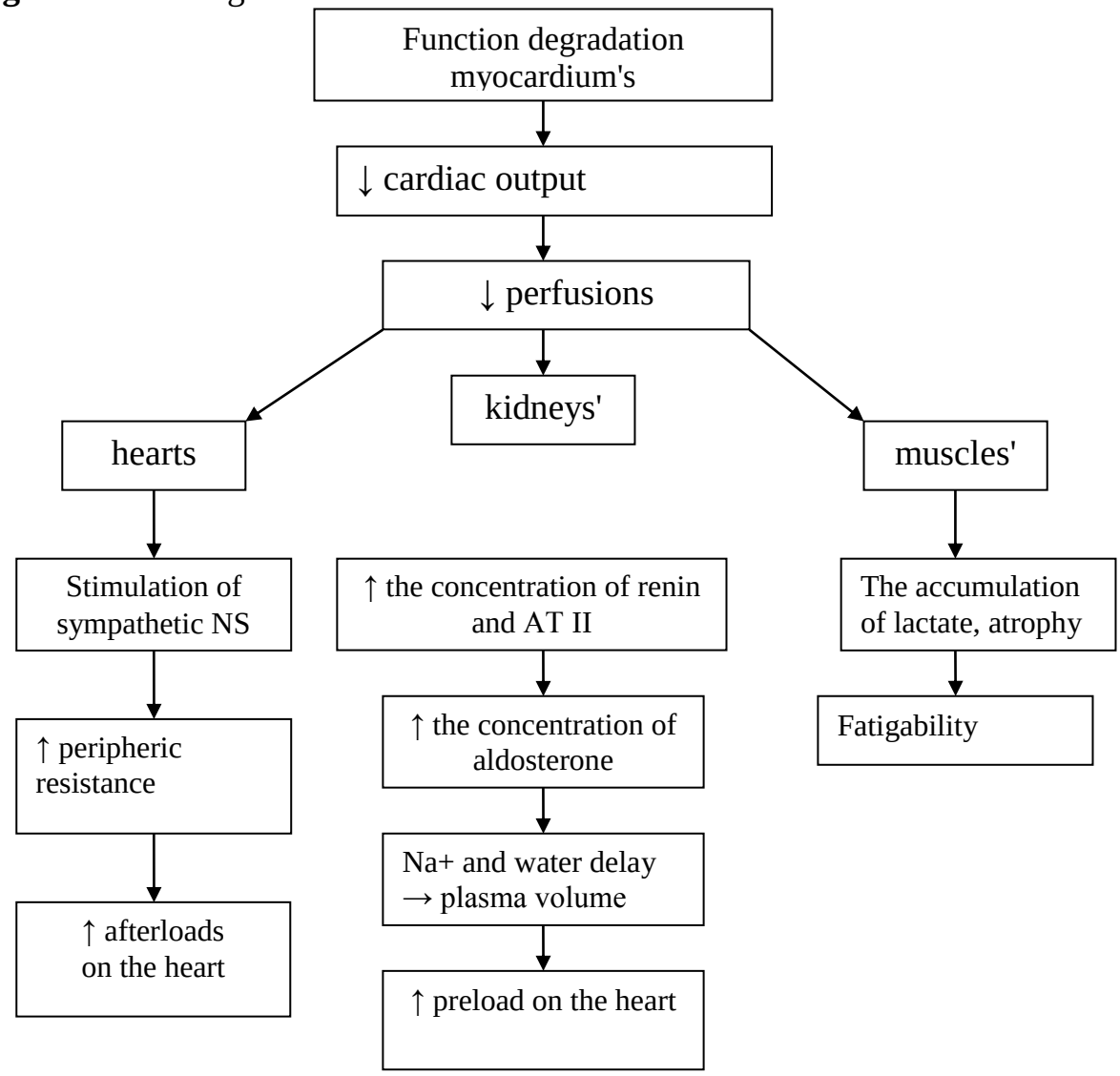
Figure 4-1. Pathogenesis of heart faure



Treatment of heart failure includes a set of therapeutic measures aimed at restoring the functions of the myocardium, providing hemostasis in the body:

- diuretics, ACE inhibitors (reducing the load on the heart, improving the condition of patients and > life expectancy: a) by ↓ b) preload on the heart and eliminate swing;
- cardiotonic and antiarrhythmic means leading to the restoration of the ion composition of cardiomyocytes and electrophysiological indicators of heart activity.

Table 4-1. Means reducing the load on the myocardium

Groups	Preparations	**Механизм действия**
ACE inhibitors	• Captopril • Enalapril	* Reduction of OPSS, blood PRESSURE, post - and preload on the myocardium, reducing pressure filling the left ventricle * Cardioprotective effect (prevention and reverse development of left ventricular hypertrophy) * Angioprotective effect (prevention of hyperplasia of the arterial vascular wall MMC)
Diuretics	•Hydrochlorothiazide • Furosemide	* Reduction of BCC, venous return, load on the heart, stagnation in the lungs and other organs * Reducing swelling of the vascular wall and reducing its reactivity to vasoconstrictive substances (catecholamines, etc.)
β-blockers - selective (β1); - α1-adrenoblocker-rousey activity	• Bisoprol • Metoprolol • Carvedilol	* Elimination of the negative effects caused by the activation of the sympathoadrenal system: reduction of tachycardia and myocardial ischemia, improvement of left ventricular diastolic filling; reduction of OPSS and CB, reduction of myocardial hypertrophy (with long-term use) * Reduction of stagnation as a result of RAAS activity decrease * Carvedilol also has α-adreno-blocking, vasodilating and antioxidant effects

Table 4-2. Means stimulating myocardial contractility (cardiotonic agents

	Cardiotonic means of glycoside structure			**Neglikozidnye cardiotonic structure**	
Preparations of cardiac glycosides	short actions	average duration of action	long actions		
	• Strophanthin • Corglicon	• Digoxin	• Digitoxin	Dopamine, dobutamine	Amrinone, milrinone
Mechanism of action	Blockade of the Na+, K+-dependent ATPase → ↓ concentration of K+ and ↑ TA+ in the cytoplasm of cardiomyocytes → ↑ content of calcium ions in cardiomyocytes → CA++ binds-lated to troponin, removing its braking effect on AK-tin and myosin → stimulation of interaction of threads active-and myosin → contraction			β-agonists to the interaction point with the receptor, associative-Rovaniemi with GS-proteins. Activate adenylate cyclase, increase the flow of CA++ into the cell and ↑ camp.	Inhibit phosphodiesterase → > camp → > CA++ in the cell.
Pharmacological effect	• Positive inotropic (strengthening and shortening of systole) • Negative chronotropic (slowing heart rate) • Negative Chrono dromotroponoe (reduction in conductivity of the myocardium) • Positive batmotropic (increase of excitability of myocardium)			Positive inotropic effect, do not affect heart rate, dilate renal and Mezen-thermal vessels.	Positive inotropic effect, and vasodilation.
Hemodynamic parameters	• Increased cardiac output, decreased venous pressure • Increased blood flow rate, elimination of tissue hypoxia • Decrease in circulating blood volume			Stimulate dopamine receptors → dilate kidney vessels → improve renal blood flow.	
Indications	Acute and chronic heart failure, cardiac arrhythmias (paroxysmal tachycardia, atrial tachyarrhythmia)			Acute heart failure (cardiogenic shock).	Acute heart failure.

Table 4-3. Comparative characteristics of pharmacokinetic parameters of some cardiac glycosides

Preparations / Indicators	Strofantin, korglikon	Digoxin	Digitoxin
The absorption in the digestive tract (in % of the administered dose)	2%	50-80%	до 100%
Plasma protein binding (%)	5%	25-30%	90-97%
The latent period at: (a) oral administration; b) intravenous administration	- 5-10 мin.	2 5-30 мin.	> 2 h 80-90 мin.
Duration of action	1-3 d.	2-7 d.	2-3 w.
The severity of cumulation	+	+++	+++++

! Cardiac glycosides can cause material accumulation-the accumulation of the substance in the body. This effect is most pronounced in digitoxin, which explains its toxicity to myocardial function (functional cumulation): the appearance of extrasystole in the block, ventricular flicker.

Table 4-4. Symptoms of intoxication with cardiac glycosides

Violations heart activity	**Noncardiac disorders**		
	neurological	gastrointestinal tract	Kidneys
• Extrasystoles ($K^+ \downarrow$, $Ca^{++} \uparrow$) • Atrioventricular block • Ventricular fibrillation	• Mental disorder • hallucinations headache • blurred vision – xanthopsia	• diarrhea • nausea • vomiting	↑ diuresis'

Basic principles of treatment of poisoning by cardiac glycosides

1. Elimination of potassium and magnesium deficiency-potassium chloride, Panangin, etc.
2. Antiarrhythmic action (block of Na+ channels) - lidocaine
3. The binding of CA++ - EDTA
4. Solving activity n. vagus (in severe bradycardia) atropine sulfate
5. The donor of SH-groups – unitiol
6. The preparation of antibodies to digoxin – digibind

! Cardiac glycosides act only when the heart is decompensated.

Tabl 4-6. Comparative characteristics of the action of cardiac glycosides and adrenaline on heart activity

The Index	Action	
	Cardiac glycosides	**of Adrenaline**
Type of action	- cardiotonic	- cardiac pacemaker
Stroke volume	- increases	- increases less
Heart rate	- decreases	- increase dramatically
Minute volume	- increases	- greatly increases
Oxygen use per unit of work	- decreases	- increases
The content of creatine phosphate, glycogen in myocardium	- increases	- decreases
General orientation in action on metabolic processes in the myocardium	- prevails	- catabolism prevails

Therapy of pulmonary edema:

- Adequate oxygenation by 100% oxygen supply
- Morphine hydrochloride 2-5 mg I / V.
- Furosemide 40-100 mg V / V
- Dobutamine, dopamine/V
- Sodium nitroprusside at a dose of 20-30 μg / min
- Aminophylline at a dose of 240-480 mg/V

Therapy of cardiogenic shock:

The main purpose of therapy is to increase blood PRESSURE.
Dobutamine is a selective β1-adrenomimetic with positive inotropic action and minimal positive chronotropic action-in the dose of 2.5-10 μg / kg / min .
Dopamine has a more pronounced chronotropic effect, i.e. it can increase the heart rate and myocardial oxygen demand, slightly aggravating myocardial ischemia-2-10 μg / kg / min with a gradual increase in the dose every 2-5 min to 20-50 μg/kg/min.
Norepinephrine is a hydrotartrate at a dose of 2-4 μg / min, but it should be borne in mind that the drug significantly increases the OPS, which can worsen myocardial ischemia.

ANTIARRHYTHMIC FUNDS

The rhythm of cardiac activity depends on the activity of pacemaker cells (pacemakers) sinoatrial node (SS). The violation of their functions, the Kli, but manifests itself in different symptoms, from discomfort to core Noi failure.

Arrhythmias can occur even in healthy people, but they are without me-dokumentacneho intervention. Serious arrhythmias are caused by various diseases: myocarditis, congenital heart disease, myocardial infarction and others.
Foci of arrhythmogenic activity can be in the junction of the Atria, Atri-ventricular node and in the ventricles.
Arrhythmias can occur through the mechanism of "re-entry" (re-entry). In this case, in some areas of the heart muscle, having a short refractory period, there is a re-entry of excitation, which causes a new wave of depolarization.
The main types of arrhythmias heart rate: tachycardia, sconces-Giardia and arrhythmia. They are due to changes in the functional state of the conductive system, cardiomyocytes and the tone of adrenergic and cholinergic innervation of the heart.

THE PHYSIOLOGICAL MECHANISMS OF RHYTHMIC ACTIVITY OF THE HEART AND PATHOPHYSIOLOGICAL ARRHYTHMIAS

There are 2 depolarization flows in myocardial cells: fast Na+ current and slow CA++ current. In sinoatrial node (SU) and atriventricular uz-Le (AVA) is carried out only CA++ current, which is slow, leading to the emergence of an interval between contractions of the Atria and ventricles. Normally, this refractory period of myofibrils protects them from re-excitation.
The action potential in different parts of the heart is formed by different ion flows and consists of the following phases:
"0" is the phase of rapid depolarization (> Na+ current to the cell through fast sodium channels). V0 phase determines the conductivity of cardiomyocytes - the more co-Roche, the > V pulse propagation through Purkinje fibers.
"1" is the phase of early repolarization (K+ exit from the cell along the concentration gradient through potassium channels).
"2" - the middle phase of repolarization (slow CA++ entrance into the cell that over-medley process of repolarization).
"3" – late repolarization phase (K+ exit from the cell-resting potential, 90 mV).
Phases 0-2-(3) – Absolute refractory period (refractive effect and ERP). Basically, the ETA value is determined by the phase " 3 " -its duration.
"4" is a phase of slow diastolic depolarization (slow Na+ input, insignificant CA++ input and < K+output).
The automatism depends on V4: the ↑ V4 , the ↑ automatism.

! In the SA-node in phase 0 and 4 membrane depolarization associated with the entrance of CA++ in cardiomyocytes.

! In the AV node in phase 0 and 4, membrane depolarization is associated with the input of CA++ and Na+ into cardiomyocytes.

Conduction disturbance affects the rate of increase of the amplitude of the action potential (PD) – phase 0. With a decrease in conductivity, the rate of systolic depolarization – phase 0 – decreases (Pdma is achieved slowly, heart rate - <). On the ECG, an increase in the p-R interval (in case of violation in the atriventricular node) and

lengthening of the QRST (in case of violation of intraventricular conduction) are recorded.
An increase in the rate of systolic depolarization and a rapid achievement of the PD threshold leads to > SS frequency (positive chronotropic effect). When this occurs, the increased current of CA++ into the cell during repolarization (phase 2), leading to increased strength of cardiac contractions.
The activity of the pacemaker is adjusted by changing the permeability of cellular membranes for accurate To+ and trigger the neurotransmitters acetylcholine and norepinephrine.
Thus, activation of M2-cholinergic receptors of the myocardium leads to ↑ permeability for K+ and to a slowdown in the processes of depolarization (↓steepness of the pacemaker potential) – phase "0".
Activation of β-adrenergic receptors of the pacemaker leads to ↓ permeability to K+ and to accelerate the processes of depolarization – phase "4".
Violation of automatism is accompanied by the appearance of ectopic foci of excitation (rhythm drivers). This may be due to the increase in the speed of diastolic depolarization, ↓ resting potential, ↓ threshold of PD.

! For the development of arrhythmia, the value of ERP (effective refractory period) is important.

The decrease in ETA is accompanied by a shortening of the repolarization phase (2, 3) and, accordingly, the duration of PD.
Against this background, increases the risk of extrasystoles, as well as re-input excitation, causing the circulation of pulses.
Long Qt syndrome IS a syndrome that manifests itself by increasing the QT interval, accompanied by syncopal States and / or cardiac arrest and sudden cardiac death.

! Lengthen the Qt interval can phenothiazines, some antimicrobial agents (ketoconazole, macrolides, co-trimoxazole), cocaine, terfenadine, tricyclic antidepressants.

Tabl 4-7. Classification of antiarrhythmic drugs used in tachyarrhythmias

Class I	Blockers of sodium channels (mem-branostabiliziruyuschee funds)	IA	Quinidine Procainamide (procainamide) Disopyramide
		IB	Lidocaine Mexiletin
		IC	Propafenone Etatsizin
Class II	Beta-blockers		Propranolol (inderal) Atenolol Metoprolol
Class III	A means of slowing the repolarization (potassium channel blockers)		Amiodaronum Bretilia tosilat (ornid) Sotalol
Class IV	Slow calcium channel blockers		Verapamil Diltiazem
Other			Potassium and magnesium preparations Cardiac glycoside Adenosine

Tabl 4-8. Classification of antiarrhythmic agents used in bradyarrythmia and atrioventricular block

№ п/п	**Group of preparations**	**Preparations**
1.	M-holinoblokatory	Atropine
2.	Beta-agonists	Isoprenaline (izadrin)
3.	Alpha, beta-adrenomimetics	Epinephrine (adrenaline)
4.	The hormone of the pancreas	Glucagon

Tabl 4-9. Effect of antiarrhythmic agents on electrophysiological parameters

Antiarrhythmic drugs						
Classes of antiarrhythmic drugs	Class I			Class II	Class III	Class IV
	Class IA	Class IB	Class IC			
Influence on electrophysiological parameters	- reduction of automatism, - deceleration of conductivity, - slow repolarization, - increase ERP, - elongation of PD	- decrease automaticity, - minor effect on conductivity, - acceleration of repolarization, - shortening of ERP, - shortening of the PD	- reduction of o-Semitism, - deceleration of Pro-ducibility, - increase ETA (in-node), - no influence on the duration of PD	- decrease automaticity, - deceleration of conductivity, - increase ETA (in-node), - elongation of PD	- decrease automaticity, - slow repolarization, - increase ERP, - elongation of PD	- decrease automaticity, - significant slowing of conduction, - increase ETA (in-node), - elongation of PD
Effect	Heart rate recovery					

Table 4-10. The choice of drugs in tahiaritmiah

Nature of arrhythmia	Influence on the electrophysiological mechanism	Drugs of choice
Sinus tachycardia	Reduction of spontaneous diastolic depolarization in phase 4	β-blockers, Na-channel blockers
Atrial tachycardia, ventricular extrasystole	The hyperpolarization activated, a decrease in spontaneous diastolic depolarization during phase 4	Na - or Sa-channel blockers
Ventricular tachycardia	Shortening of the action potential, the suppression of early postdepositional	Cholinolytics, CA-channel blockers, β-blockers, magnesium sulfate
Arrhythmias in glycosides intoxication	Reducing the overload of Sa. Suppression of the delayed postdeposition	Sa channel blockers.
Atrial flutter (micro-re entry)	Suppression of conductivity and excitability	Na channel blockers

Table 4-10. Choice of drugs for tachyarrhythmias

Nature of arrhythmia	Influence on the electrophysiological mechanism	Drugs of choice
Sinus tachycardia	Reduction of spontaneous diastolic depolarization in phase 4	β-blockers, Na-channel blockers
Atrial tachycardia, ventricular extrasystole	The hyperpolarization activated, a decrease in spontaneous diastolic depolarization during phase 4	Na - or Sa-channel blockers
Ventricular tachycardia	Shortening of the action potential, the suppression of early postdepositional	Cholinolytics, CA-channel blockers, β-blockers, magnesium sulfate
Arrhythmias in glycosides intoxication	Reducing the overload of Sa. Suppression of the delayed postdeposition	Sa channel blockers.
Atrial flutter (microreentry)	Suppression of conductivity and excitability	Na channel blockers

Table 4-11. The effect of some antiarrhythmic agents on ECG.

Preparations	Interval P-Q	Duration QPS	Interval Q-T
Quinidine	↑	↑↑	↑↑
Procainamide	0	0	0
Lidocaine	↑	↑↑↑	0
Propafenone	↑↑	0	0
Propranolol	↑↑	↑	↑↑↑↑
Amiodaronum	↑↑	0	0

Table 4-12. Побочные эффекты антиаритмических средств

Preparation	Side effect
Procainamide	Anaphylactic shock, intraventricular blockades, decrease in blood PRESSURE, nausea and vomiting, syndrome by type of systemic lupus erythematosus.
Quinidine	Conduction disorders, thrombocytopenia, leukopenia, idiosyncrasy, decreased hearing and vision.
Lidocaine	Dizziness, hypotension, conduction disturbances, stiff neck, seizures.
Propranolol	Bronchospasm, bradycardia, conduction disturbances, hypotension.
Verapamil	Conduction, transient hypotension, polyneuritis.
Amiodaronum	Nausea, dizziness, bradycardia, visual impairment, cataract, hypothyroidism, violation of skin color.
Ornid.	Hypotension.
Aymalin.	Conduction disturbance.

Drugs that increase the duration of the action potential include amiodarone and ornid. Amiodarone is moderately inhibits the sympathetic innervation. Its antiarrhythmic effect is associated with a decrease in automatism, conductivity and excitability of the sinus and atrioventricular nodes. It increases the duration of the action potential and the effective refractive period of the Atria, atrioventricular node and ventricles. The action of amiodarone is slow. Ornid has an antiarrhythmic effect, the mechanism of which is considered unclear. It is believed that it is due to the sympatholytic properties i.e. the depressing effect of this drug on the release of norepinephrine from the endings of the sympathomic nerves. It increases the duration of the action potential and the effective refractor period. The speed of impulses in the ventricles and Purkinje fibers does not change. Along with the antiarrhythmic effect, ornid causes a hypotensive effect, the development of which may be preceded by a short-term phase of blood PRESSURE increase.Among the calcium channel blockers, verapamil has the most pronounced antiarrhythmic activity. It reduces the activity of the sinus node, inhibits conduction in the atrioventricular node.

! The most resistant to drug therapy atrial flicker and flutter, which is used for cupping quinidine, novocaine-Mead, disopyramide.

Tasks for self-preparation

Task 1. What are the main parts of the molecule of cardiac glycoside and specify what role they perform.

_____

_____

Task 2. Determine the drug that has the following properties:
Activates adenylate cyclase of cardiomyocytes, increases heart rate, lowers OPS. Apply mainly in acute heart failure, can cause cardiac arrhythmias.

_____

Task 3. Determine the drug that has the following properties:

Poorly soluble in water, well – in lipids. Almost completely (90-95%) is absorbed from the gastrointestinal tract. The severity of the negative chronotropic effect ranks first among cardiac glycosides. Applied for the treatment of chronic heart failure and cardiac tachyarrhythmias. _____

Task 4. Effect of cardiac glycosides in therapeutic doses on heart activity

Systole		Diastole		Heart rate	Conductivity (direct action)	Refractoriness (direct action)	
Reducing	the dura-tion	of relax-ation	the dura-tion			A-B node's	Atriums'

Task 5. Changes in ECG parameters with the introduction of cardiac glycosides in therapeutic doses

R-R	P-Q	QRS		ST
		voltage	Duration	

Task 6. Comparative characteristics of antiarrhythmic agents

Characteristic		Groups of antiarrhythmic drugs				
		IA	IB	IC	III	IV
Channel blockade	Sodium					
	Potassic					
	Calcic					
Effect on PD of Purkinje fibers	Phase 0					
	Phase 3					
	Phase 4					
	The duration of PD					
Influence on the parame-ters of the myocardium	Conductivity					
	The duration of ERP					
Use in arrhythmias	Supraventricular					
	Ventricular					

+ - the existence of the effect; ↓ - the weakening effect; ↑ - the weakening effect.

Task 7. The use of antiarrhythmic drugs.

The nature of heart rhythm disorders / Preparations	Atrial fi-brillation	Ventricular extrasys-toles	Paroxysmal tachycardia	intoxica-tion SG	AB-blockade
Quinidine					
Procainamide					
Lidocaine					
Phenytoin					
Propranolol					
Verapamil					
Amiodaronum					
Ornid.					
Panangin					
Cardiac glycoside					
Izadrin					

Tasks for self-control

I. When using cardiac glycosides in patients with heart failure are observed:
a) increased venous pressure; b) slowing blood flow;
C) reduction of edema; d) slowing the heart rate;
e) elimination of tissue hypoxia _____

II. Contraindications to the appointment of digoxin are:
a) hyperkalemia; b) a-blockade I-II degree; C) hypotension; d) tachycardia;
d) hypocalcemia _____

III. With the introduction of cardiac glycosides in therapeutic doses are possible:
a) lowering the tone of the bronchi and smooth muscles of the gastrointestinal tract
b) increased bronchial tone and smooth muscles of the gastrointestinal tract
C) decrease of excitability of respiratory center
d) increased kidney function
d) lower blood clotting _____

IV. The mechanism of cardiotonic action of cardiac glycosides is related:
1. With increased activity of Na+, K+-ATPase of cardiomyocyte membrane.
2. With the decrease of activity of Na+, K+-ATPase membrane of cardiomyocytes.
3. With the blockade of the enzyme succinate dehydrogenase.
4. With increased potassium content inside the cell.
5. With an increase in the concentration of CA++ inside the cell.
6. With stimulation of β2-adrenergic receptors of the heart.

_____

V. How does the content of free ions in myocardial cells under the influence of cardiac glycosides?
1. The content of potassium ions increases. 2. The content of potassium ions decreases. 3. The content of calcium ions increases. 4. The content of calcium ions decreases.

_____

VI. What is characteristic of digoxin?
1. Well absorbed from the gastrointestinal tract. 2. Poorly absorbed from the gastrointestinal tract. 3. It can be administered orally and intravenously. 4. The beginning of actions through 5-30 minutes after the introduction of. 5. It is used only in acute heart failure. 6. It is used in acute and chronic heart failure. 7. Has a moderate ability to cumulation.

_____

VII. What is characteristic of strophantine K?
1. Completely absorbed from the gastrointestinal tract. 2. Almost not absorbed from the gastrointestinal tract. 3. Enter only intravenously. 4. The onset of action after intravenous injection of 5-10 minutes. 5. Practically does not cumulate. 6. Has a moderate ability to cumulation. 7. The maximum effect develops in 30-90 minutes. _____

VIII. The main effects of cardiac glycosides in heart failure:
1. An increase in stroke and minute volume. 2. Reduction of venous pressure. 3. Increased venous pressure. 4. Tachycardia. 5. Bradycardia. 6. The reduction of swelling. 7. Reducing shortness of breath. 8. Increase urine output. 9. Reduction of diuresis.

_____

IX. Indications for use of cardiac glycosides:
1. Tachyarrhythmic form of atrial fibrillation. 2. Edema of renal origin. 3. Acute heart failure. 4. Chronic heart failure. 5. Complete atrioventricular block. 6. Hypertensive crisis.

_____

X. The main manifestations of the toxic effect of cardiac glycosides:
1. Severe bradycardia. 2. Deceleration of atrioventricular conduction. 3. Relief of atrioventricular conduction. 4. Extrasystole. 5. Nausea. 6. Vomiting. 7. Violation of color vision.

_____

XI. What means are used for intoxication with cardiac glycosides?
1. Potassium chloride. 2. Calcium chloride. 3. Atropine. 4. Phenytoin. 5. Tablets "Asparkam".

_____

XII. The principles of operation of funds neglikozidnye cardiotonic structure:

1. Increase of camp content in cardiomyocytes due to inhibition of phosphodiesterase.
2. Increase of camp content in cardiomyocytes due to stimulation of β1-adrenergic receptors.
3. Direct inhibition of the activity of the troponin complex in cardiac myocytes.

_____

Situational challenges

1. Patient S., 63 years old, chronic heart failure stage III. Appointment Zelanda when you reach a saturation dose has not led to an improvement in the patient's condition. To determine the further tactics of the doctor at the choice of the drug.

_____

2. The patient P., 52 years old, in the treatment of chronic heart failure with digoxin, there were changes in color perception, extrasystole. On ECG" trough-shaped " segment ST. Prescribe the necessary medication.

_____

Prescribe drugs according to indications:

1. Cardiac glycoside in acute heart failure.
2. Cardiac glycoside in patients with chronic heart failure.
3. The preparation of potassium by intoxication cardiac glycosides.
4. The drug for conduction disorders caused by cardiac glycosides.
5. The preparation of potassium by intoxication cardiac glycosides.
6. Cardiotonic agent for cardiogenic shock.
7. Preparation for relief of ventricular arrhythmias in myocardial infarction.
8. A tool used only in supraventricular tachyarrhythmias and extrasystole.
9. Remedy for atrioventricular block.

PRACTICAL CLASS № 5

The theme of the lesson. DRUGS THAT AFFECT THE HEMOSTATIC SYSTEM.

The General purpose of the lesson. To study the pharmacological properties, mechanisms and features of the action of the main drugs that affect blood clotting and fibrinolysis.

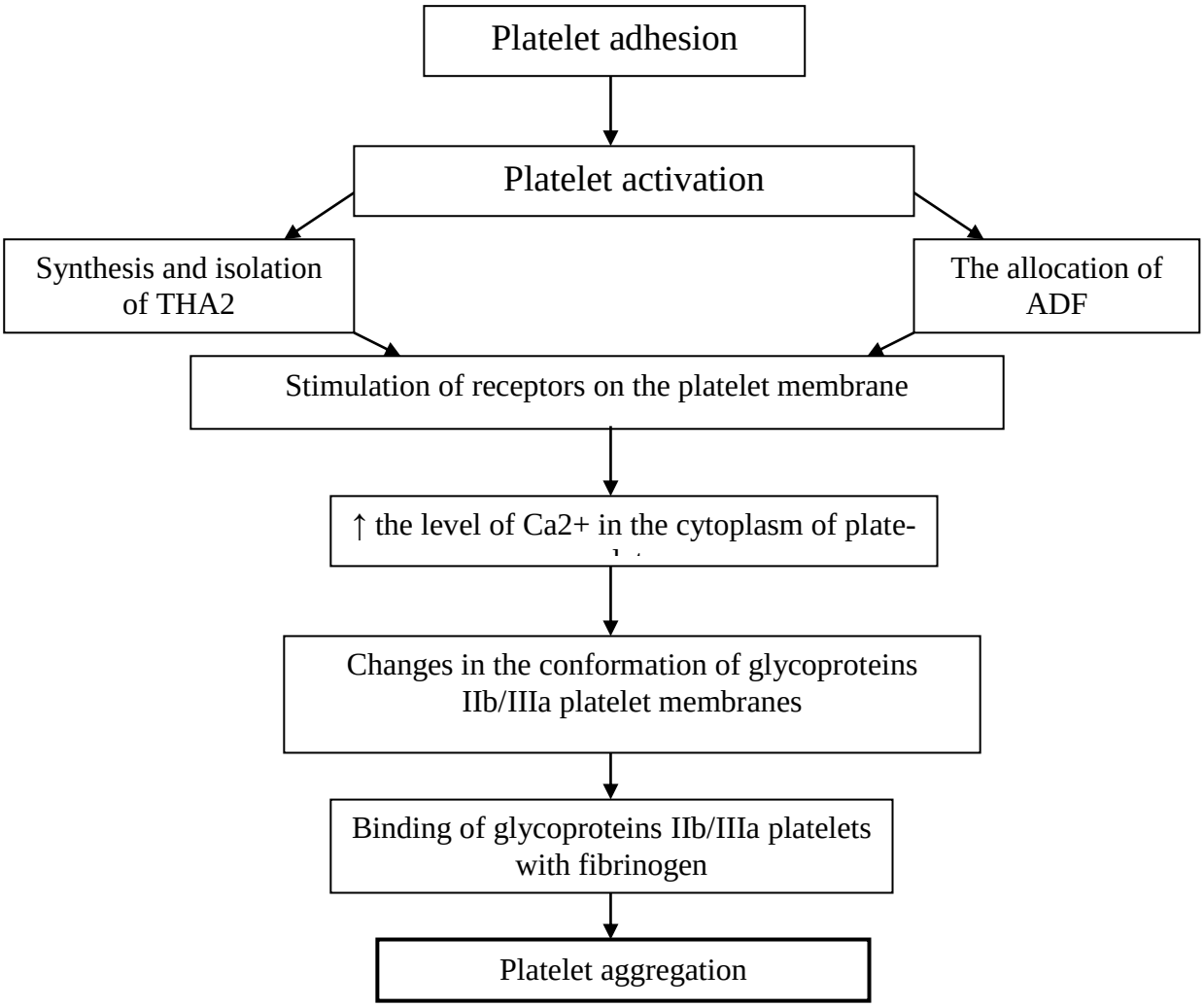
Specific objectives of the lesson

The student should know:
- physiological mechanisms of hemostasis regulation;
- possible ways of action and mechanisms of action of drugs affecting the blood system;
- pharmacological properties and comparative characteristics of drugs affecting hemostasis;

The student must be able to:
- to justify the choice of means that affect the blood system, taking into account the absolute and relative contraindications;
- choose the right dose and route of administration of the drug, taking into account the nature of the pathological process and the presence of concomitant diseases;
- prescribe in the appropriate dosage form.

Control question:
1. Physiological mechanisms of hemostasis.
2. Classification of antiplatelet agents and mechanisms of action of antiplatelet agents in different groups.
3. Comparative characteristics of drugs and features of the choice of antiplatelets.
4. Classification of anticoagulants and mechanisms of action of anticoagulants of direct and indirect action.
5. Comparative characteristics of drugs and features of the choice of anticoagulants.
6. Fibrinolytic agents, comparative characteristics of drugs.
7. Drugs that help stop bleeding: mechanisms of action, comparative characteristics and features of the choice of hemostats.

Scheme 5-1. Mechanisms of platelet aggregation



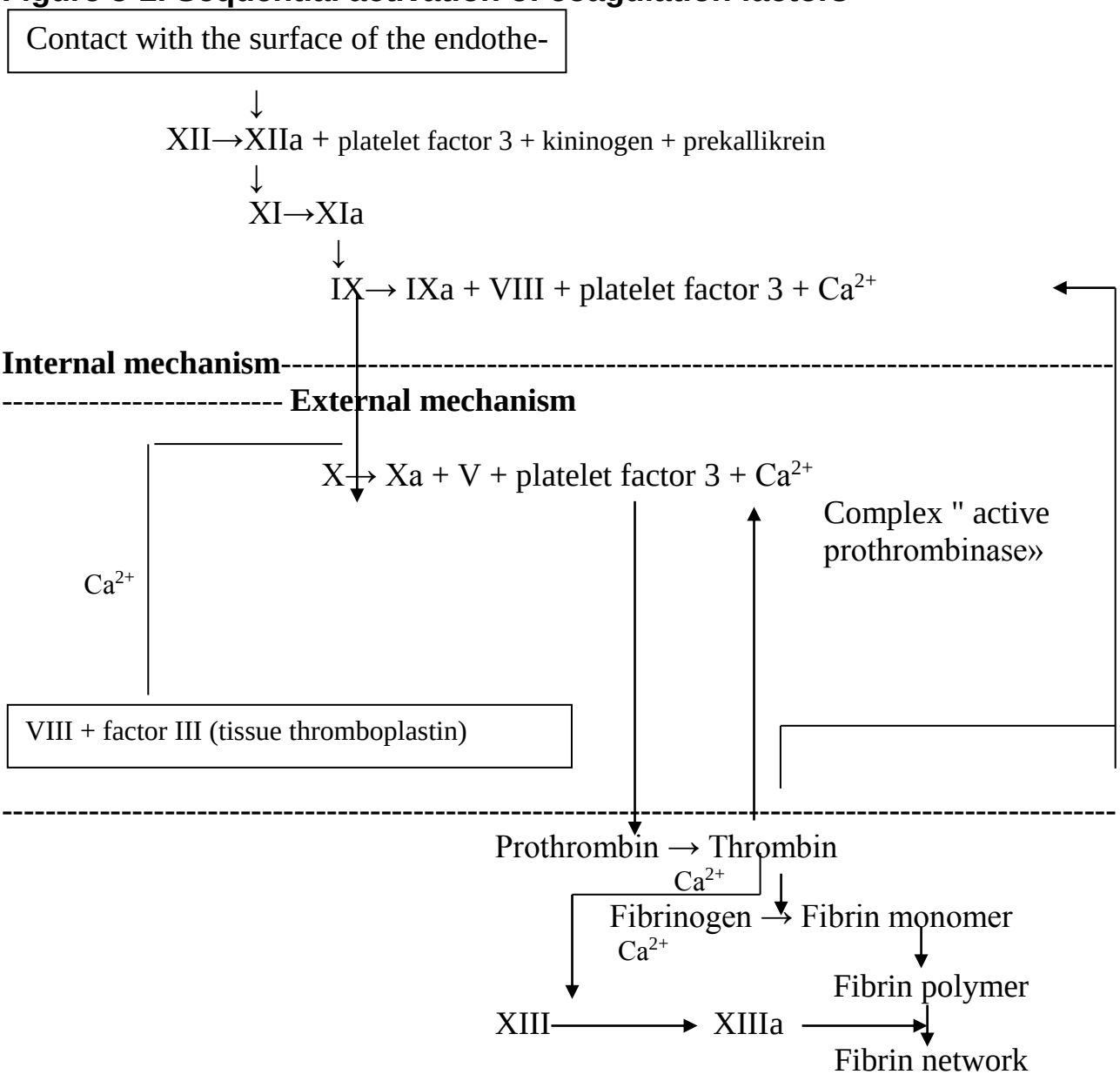
Classification of antiplatelet agents

I. Средства, ингибирующие синтез тромбоксана A_2
   1. Inhibitors of cyclooxygenase
   Acetylsalicylic acid
   2. Inhibitors of cyclooxygenase and thromboxane synthetase
   Indobufen
II. Means stimulating the receptors prostacycline
   Epoprostenol
III. Tools preventing the action of ADP on platelets
   Ticlopidine, clopidogrel
IV. Inhibitors of phosphodiesterase
   Dipyridamole
V. Agents that block the glycoprotein IIb/IIIa platelet membrane
   1. Monoclonal antibody *2.* Synthetic drug
   Abciximab *Eptifibatid, tirofiban*

Blood clotting factors

I – fibrinogen
II-prothrombin
III-thromboplastin
IV-calcium ions
V-proaccelerin
VI-accelerin
VII-proconvertin
Viii - antihemophilic globulin A
VIII – von Willebrand factor
IX-antihemophilic globulin BX-Stuart-Prower factor
XI – plasma thromboplastin precursor
XII – Hageman factor
XIII-fibrin stabilizing factor
Plasminogen
Prekallikrein
High molecular weight kininogen

Figure 5-2. Sequential activation of coagulation factors



Drugs that affect blood clotting

I. decreasing the blood clotting (anticoagulants)

A) direct-acting Anticoagulants (acting directly in the blood):

• Heparin unfractionated

• Low molecular weight heparins: enoxaparin, nadroparin, dalteparin, reviparin

Heparinoids

Antithrombin III preparation

• Preparations of hirudin: lepirudin

B) Anticoagulants of indirect action (inhibiting the synthesis of coagulation factors in the liver).

a) coumarin derivatives: acenocumarol, warfarin;

b) derivatives of indandione: fenindion.

II. Means that increase blood clotting

• Vitamin K: menadione

• Drugs coagulation factors blood: antihemophilic factor VIII (Hemofil M, Immunet), cryoprecipitate, factor IX complex (Immonen), the drug thrombin, hemostatic sponge.Drugs affecting fibrinolysis

The Promoters of fibrinolysis (thrombolytic preparations)

Drug	Origin
Fibrin specific thrombolytics	
Streptokinase	Protein obtained from the culture of C group β-hemolytic Streptococcus
Urokinase	Enzyme derived from human embryo kidney culture
Fibrin specific thrombolytics	
Alteplase	Biosynthetic preparation of human tissue plasminogen activator
Anistreplase	Complex preparation consisting of streptokinase and plasminogen
Dasmarinas	Protein obtained from the salivary glands of a bat (Desmodus rotundus)
Lanoteplase	Modified by genetic engineering preparation of human tissue plasminogen activator
Prourokinase	Biosynthetic drug of prourokinase
Reteplase	Modified by genetic engineering preparation of human tissue plasminogen activator
Staphylokinase	Protein derived from the culture of Staphylococcus aureus
Tenecteplase	Modified by genetic engineering preparation of human tissue plasminogen activator

II. Inhibitors of fibrinolysis

- E-aminocaproic acid (amicar))
- Acid n-aminometilbensana (ambien, Pamba)
- Tranexamova acid (azazil)
- Antifermental funds (contrical, gordox).

Indications for use of thrombolytic agents:

- Acute myocardial infarction no later than the first 4-6 hours after the onset of the attack.
- Massive or submassive pulmonary embolism (within 5-14 days).Peripheral arterial thrombosis.
- Central retinal vein thrombosis.
- Thrombosis of hepatic, renal and. veins in addition to veins of the lower extremities.
- Thrombosis of additional vascular grafts.
- Thrombosis of the tricuspid valve prosthesis.

! The most dangerous complications of thrombolytic therapy are bleeding. If life-threatening bleeding must be entered in/in 2-4 ED of fresh frozen plasma; 100 EDof cryoprecipitate that contains fibrinogen and factor VIIIa; inhibitors of fibrinolysis.

Tasks for self-training

Task 1. Complete the table.

Comparative characteristics of antiplatelet agents

Preparations	Ways of introduction	Mode dosing	Side effects
Acetylsalicylic acid			
Ticlopidine			
Dipyridamole			
Abciximab			

Task 2. Give a comparative description of fibrinolytics

Comparison options		Streptokinase	Urokinase	Alteplase
Action localization	In the clot and in the blood plasma			
	Predominantly in the blood clot			
Pyrogenic and allergic reactions				

Task 3. Give a comparative description of anticoagulants.

		Preparations			
		Heparin	Nadroparin	Lepirudin	Acenocumarol
Activity in vitro					
Activity in vivo					
Mechanism of action	Inhibits coagulation f-ry in plasma (in complex with antithrombin III)				
	Inhibits plasma coagulation f-ry (independent of antithrombin III)				
	Inhibits the synthesis of coagulation f-ROV in the liver				
Route of administration	Parenteral				
	Inside				
The rate of development of effect					
Antagonist in case of overdose					

Task 4.

Показания	Preparations					
	Heparin	Acetylsalicylic acid	Dalteparin	Acenocumarol	Aminocaproic Acid	Alteplase
Acute thrombosis, thromboembolism						
Prevention of thrombosis						
Prevention of THEM						
Bleedings						
Overdose of anticoagulants						
Therapy of Myocardial Infarction						

Tasks for self-control

I. What means inhibits platelet aggregation?
1. Counterbalanced. 2 Dipyridamol. 3. Ambenum. 4. Neodikumarin. 5. Amino acid-proic. 6. Phenilinum.

_____

II. Mark drugs – derivatives of coumarin:
1. Phenilinum. 2. Singular. 3. Warfarin. 4. Neodikumarin. 5. Dipyridamole.

_____

III. Note drugs that increase the activity of profibrinolysin:
1. Streptokinase. 2. Aminocaproic acid. 3. Urokinase. 4. Alteplase.

_____

IV. Which of the following drugs are only in vivo?
1. Hirudin. 2. Heparin. 3. Phenilinum. 4. Sodium citrate. 5. Neodikumarin.

_____

V. For the prevention of thrombosis used:
1. Urokinase. 2. Dipyridamole. 3. Ticlopidine. 4. Streptokinase. 5. Alteplase.

_____

VI. Specify the possible mechanisms of action of funds that reduce platelet aggregation:
1. A decrease in the synthesis of thromboxane in platelets. 2. Blockade of thromboxane receptors in platelets. 3. Prostatsikliny blockade of receptors in the thrombotic-zitah. 4. Blockade of glycoprotein receptors in platelets. 5. Blockade of the PU-ranovich receptors in platelets. 6. Blockade of serotonin receptors in platelets.

_____

VII. The mechanism of action of acetylsalicylic acid:
1. Inhibits cyclooxygenase and disrupts the formation of thromboxane. 2. Blocks-ruet thromboxane platelet receptors. 3. Stimulates prostacyclin-tions receptors of platelets. 4. Blocks glycoprotein receptors of platelets. 5. It has an antiplatelet effect in low doses.

_____

VIII. The mechanism of antiplatelet action abziksimaba:
1. Tromboksanov blocks receptors of platelets. 2. Inhibits cycloak-shinasu and disrupts the formation of thromboxane. 3. Stimulates prostacyclin-tions receptors of platelets. 4. Blocking of purine receptors of platelets and inhibits the action of ADP. 5. Blocks glycoprotein receptors of platelets and prevents the binding of fibrinogen.

_____

IX. What is characteristic of dipyridamole?
1. Blocks glycoprotein receptors of platelets. 2. Inhibits cyclo-oxygenase and disrupts the formation of thromboxane. 3. Inhibits phosphodiester-zu platelets and increases the content of camp. 4. Causes a corona-widening effect.

_____

X. the mechanism of the anticoagulant action of heparin:
1. Inhibits the synthesis of prothrombin in the liver. 2. Binds calcium ions, disrupting the transition of prothrombin to thrombin. 3. It enhances the inhibitory effect of antithrombin III on the transition of prothrombin to thrombin.

_____

XI. What is characteristic of low molecular weight heparins?

1. Enhance the inhibitory effect of antithrombin III on the transition of prothrombin to thrombin. 2. Against the background of the drugs, there is no inhibition of thrombin activity. 3. Against the background of the drugs, the activity of thrombin is inhibited to a greater extent than against the background of heparin. 4. Have a pronounced antiplatelet activity. 5. They act longer than heparin.

_____

XII. The mechanism of the anticoagulant action of indirect anticoagulants:
1. Violate the transition of prothrombin to thrombin. 2. Inhibit the synthesis of prothrombin and proconvertin in the liver. 3. Inhibit thrombin.

_____

XIII. What is typical for anticoagulants indirect action:
1. Injected inside. 2. Administered parenterally. 3. The action develops immediately and lasts 2-6 hours. 4. The action develops slowly and lasts 2-4 days. 5. Effective only in vivo. 6. Effective in vivo and in vitro. 7. Cumulate. 8. Used to prevent thrombosis. 9. The antagonist of vitamin K1.

_____

XIV. What is characteristic of streptokinase?
1. Causes a fibrinolytic effect by interacting with profibrinolysin. 2. Stimulates the transition of profibrinolysin into fibrinolysin only in the blood clot. 3. Stimulates the transition of profibrinolysin into fibrinolysin in the blood clot and plasma. 4. Could cause bleeding.

_____

XV. Mechanism of antifibrinolytic action of aminocaproic acid:
1. Inhibits the transition of profibrinolysin into fibrinolysin. 2. It has a direct inhibitory effect on fibrinolysin. 3. It acts directly on the fibrin, stabilizing it.

_____

Situational concerns

1. Patient S., 68 years old, entered the emergency room with symptoms of gastric bleeding. The condition of the patient allowed to carry out surgery. Assign the necessary hemostatic agents._____
_____

2. Patient P., 71 years old, entered the cardiology Department with a diagnosis of"acute myocardial infarction". Determine the tactics of the doctor in the appointment of anticoagulant therapy. What are the criteria for the adequacy of therapy?_____
_____

3. Patient Z., 58 years old entered the cardiology Department after 2 hours after the appearance of acute chest pain. According to the ECG, he was diagnosed with myocardial infarction. What is the drug that regulates hemostasis, is the drug of choice in this situation? What side effect is the most common when using the selected drug?
_____

Prescribe:

1. Anticoagulant in acute myocardial infarction.
2. A means for the dissolution of fresh blood clots.

3. The operation for the prevention of myocardial infarction.
4. The drug to stop bleeding associated with fibrinolysis.

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REDUCTIONS

IOP – intraocular pressure
HGH-intraocular fluid
ICP-intracranial pressure
GB-hypertension
GK-hypertensive crisis
iACE – angiotensin converting enzyme inhibitors
IHD-coronary heart disease
IM-myocardial infarction
CDD-final diastolic pressure

CONTENT