

**Ministry of Public Health of Ukraine
Higher State Educational Institution
"Ukrainian Medical Stomatological Academy"**

"Approved"

at a meeting of the Department of
Experimental and Clinical Pharmacology
with Clinical Immunology and Allergology

Head of the department

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" _____ " _____ 2017 Pr. № _____

**METHODICAL GUIDANCE FOR STUDENTS' SELF-DIRECTED
WORK WHEN PREPARING FOR PRACTICAL SESSION**

Academic discipline	Clinical Pharmacology
Topic 2/2	The clinico-pharmacological characteristic the antianginal and antiischemic medicines. The clinico-pharmacological characteristic the antihypertensive medicines.
Year of study	5
Faculty	Foreign students training (Medical)

Poltava 2017

1. Relevance of theme:

Arterial hypertension (AD - 140/90 mm Hg and above) is manifested with the mass inspections of population in 10-20% of cases. According to the data of official statistics, in the Ukraine in 2007 are registered more than 11 mln. people with AH, which composes 29,9% of adult population. The President's Decree of the Ukraine dated February 4, 1999 of № 117/99 affirmed the national program of preventive maintenance and treatment of arterial hypertension in the Ukraine. Arterial hypertension is considered as one of the factors of the risk of the development of the disease by the ischemic disease of heart. They connect arterial hypertension with the premature morbidity of cardiovascular pathology and the mortality from them.

The drug therapy of arterial hypertension usually complex and is noted by the differentiation strictly of hypertonic disease from symptomatic arterial hypertension.

2. Learning objectives:

1. To master the habits of effective and safe pharmacotherapy by antianginal means.
2. To master the skill of the individual selection of antianginal preparations in patients with the ischemic disease of heart.
3. To know how to conduct, after the need, the correction of pharmacotherapy in the case of the appearance of overdosing antianginal means.

3. Basic knowledge, skills necessary for studying the subject (interdisciplinary integration)

Discipline	To know
Anatomy	Structure and the function of cardiovascular, respiratory system, gastro intestinal tract, CNS
Pharmacology	Pharmacodynamics, pharmacokinetics, the method of application, contra-evidence, the side- actions of the antianginal preparations
Pathophysiology	Classification, pharmacokinetics, pharmacodynamics, the side- actions of the antianginal preparations
Internal diseases	Pathogenesis and treatment pressing of states in the clinical picture of the internal diseases
Nervous diseases	Pathogenesis and treatment with pressing states in the clinical picture of the nervous diseases
The infectious diseases	Pathogenesis and treatment with the pressing states in the clinical picture of the infectious diseases
Surgical diseases	Pathogenesis and treatment with the pressing states in the clinical picture of the surgical diseases

4.1. The list of key terms, parameters, characteristics which the student is to assimilate while preparing for the class:

Term	Definition
Hemorrhagic shock	severe form of hemostasis disorders, which developed as a result of significant blood loss.
Atherosclerosis	is the most common disease among residents of developed countries. With this disease (both main and concomitant) are physicians of any specialty.
Antioxidants	are substances that inhibit non-enzymatic reaction of free radical oxidation of lipids and biopolymers - proteins, nucleic acids and mucopolysaccharides.

4.2. Theoretical questions for the class:

1. What phase of blood coagulation.
2. Describe the basic properties of heparin.
3. What are the anticoagulants low.
4. Share prokoahulyantiv indications for use.
5. Share the indications for use of antiplatelet agents.
6. What are the main complication in the treatment of anticoagulant direct action.
7. Clinical and pharmacological characterization of lipid-lowering drugs.

Content topics

Drug therapy in the case of soft and moderate AH begins from mono-therapy with one of the preparations of the first row, in the case of heavy AH - from the combined designation of two or three preparations.

Preparations of the first row:

1. diuretics (hydrochlorothiazid, indapamid, chlortalidon and others)
2. β -adrenoblockers (betaksolol, acebutyl butyrateol, carvedilol, bisoprolol, metoprolol, nebivolol and

others)

3. the calcium channel-blocking agents (amlodipin, felodipin, nifedipin and others)
4. the ACE Inhibitors (captopril, enalapril, perindopril, moexipril, fosinopril, ramipril, lisinopril and others)
5. the antagonists of angiotensin II receptors (irbersartan, losartan, telmisartan, valsartan, eprosartan, candesartan).

Preparations of the second row:

1. the alkaloids of Rauwolfia (reserpine, including in the composition of the combined preparations)
2. central β_2 - agonists (clonidin, methyldopha)
3. α -adrenoblockers (doxazosin, terazosin, prazosin)
4. straight vasodilators (hidralazin, minoxidil) in the composition of the combined therapy
5. the stimulators of receptors of imidazol (moxonidin, rilmenidin)

For the change to the stepped diagram of treatment AH is alien the diagram "step by step". If anti-hypertensive effect is not achieved for a period of the 4th weeks of mono-therapy, combination from the 2 preparations adapts. In the resistance cases they come running to the combination, which includes 3 preparations, in the rare cases - 4 preparations.

Recommended combinations of the anti-hypertensive preparations:

Diuretic + ACE inhibitor

Diuretic + the blocker of angiotensin II receptors

β -adrenoblocker + the dihydropyridine antagonist of calcium

ACE inhibitor + the calcium channel-blocking agent

the blocker of angiotensin II receptors + the calcium channel-blocking agent .

On the basis of the most effective combinations of anti-hypertensive preparations are proposed the combined preparations, which make it possible to decrease the daily doses of basic components, to decrease the probability of side-line action and frequently the multiplicity of method. Such preparations are let out under the different commercial stamps, indicating components and their doses.

1. β -adrenoblocker + Diuretic (atenolol+hydrochlorothiazid; Pindolol + chlupamid; propranolol+hydrochlorothiazid;).
2. ACE Inhibitor + Diuretic (captopril+ hydrochlorothiazid; enalapril+ hydrochlorothiazid; lisinopril + hydrochlorothiazid).
3. β -adrenoblocker + the dihydropyridine antagonist of calcium (felodipin + metoprolol).
4. ACE inhibitor + the calcium channel-blocking agent (enalapril+diltiazem; trandalopril+verapamil; enalapril+felodipin).
5. Centrally acting sympatholytic agent (clophelin, or reserpin, or α -methyldopha) + Diuretic.
6. the blocker of angiotensin II receptors + Diuretic (losartan + hydrochlorothiazid).

In the case of the insufficient effectiveness of the 2nd preparations the combination in 3 of the preparations is used:

- β -adrenoblocker+ Diuretic+ vasodilator
- ACE inhibitor + the calcium channel-blocking agent+ Diuretic
- β -adrenoblocker+ the calcium channel-blocking agent+ ACE inhibitor
- β -adrenoblocker+ α -blocker+ Diuretic

The anti-adrenergic preparation of the central or mixed action (reserpin, it dopegyt) +diuretic+ vazodilator.

Reduction in the dose during the anti-hypertensive therapy

With the achievement of optimum level BP, the control of BP under the conditions of polyclinic is conducted every 4 weeks. In the case of stable anti-hypertensive effect for a period of 3 months it is possible to pass to finalizing of the supporting dose of drugs by decreasing the dose of medicines or cancellation of one of the combined preparations. In the case of increase BP of higher than the optimum level one should return to the highest dose of medicines.

Doctor, assigning anti-hypertensive means, must consider:

- force, the duration of action, transference and the side effects of anti-hypertensive means;
- the ability of preparation to achieve influence on the hypertrophy of left ventricle;
- the ability the preparation to achieve the influence on the level of atherogenic lipoproteins;
- the age of patients;
- the presence of the complications of hypertension.

Individual characteristic of the anti-hypertensive preparations

Diuretics

Diuretics are drugs which promote a net loss of sodium ions (Na^+) and water from the body, leading to an increase in urine output. Some drugs can increase urine flow by non renal mechanisms (e.g. by increasing cardiac output in a patient with congestive heart failure), but these drugs are not generally regarded as diuretics.

Diuretics can be classified by structure and mechanism of action into eight groups listed below.

1. Diuretics directly influence on the epithelium of renal tubules:

- 1.1. On apical membrane - Potassium (K^+)-sparing diuretics;

- 1.1.1. Antagonists of aldosteronum — *Spironolactonum*, *Eplerenomin*;

- 1.1.2. Concurents for transport of Na^+ - *Triamterenum*, *Amiloridum*;
- 1.2. On distal membrane;
 - 1.2.1. Inhibitor carbonic anhydrase - *Diacarbum*;
 - 1.2.2. Thiazide diuretics - *Hydrochlorthiazidum* (*Dichlothiazidum*), *Cyclomethiazidum*;
 - 1.2.3. Thiazide - like diuretics - *Clopamidum*, *Chlortalidomim*, *In-dapamidum*;
 - 1.2.4. High ceiling (loop) diuretics - *Furosemidum*, *Torasemidum*, *Acidum etacrynicum*, *Bumetanidum*;
2. Osmotic diuretics - *Mannitum*, *Urea purer*.
3. Drugs that increase circulation - *Euphyllumim*, *Teophyllinum*;
4. Herbs - *Folium Ortosiphoni*, *Herba Equiseti arvensi*, *Folium Uvae Ursi*;

Although an individual diuretic can action several areas of the nephron, the major sites of action for the diuretics may be summarized as follows:

1. Those acting on the proximal tubules mainly:
 - a. Osmotic diuretics;
 - b. Xanthine diuretics (hydrouretics);
 - c. Carbonic anhydrase inhibitors;
 - d. Acidifying salts.
2. Those acting on the ascending limb of the loop of Henle:

High-ceiling (loop) diuretics.
3. Those acting on the distal tubule:

Thiazide diuretics and thiazide like diuretics.
4. Those acting on the collecting tubules (K^+ sparing diuretics).

High ceiling (loop) diuretics, osmotic diuretics have quick action. Antagonists of aldosterone have slow action. Other diuretics have moderately quick action. Diuretics are frequently employed for the clinical management of disorders involving abnormal fluid distribution, such as edema, or for hypertension. They are also used to reduce the toxicity of ingested or administered substances. For example, *mannitolum*, an osmotic diuretic, reduces the renal toxicity of the antitumor agent *cisplatinum*, and *acetazolamidum*, a carbonic anhydrase inhibitor, is used to alkalinize the urine and increase salicylate elimination. The efficacy of the different classes of diuretics varies significantly with the xanthine diuretics being the least effective and the "high-ceiling," or "loop," diuretics being the most effective. The establishment of a net negative Na^+ balance, particularly with the less efficacious diuretics, can also depend upon limiting the Na^+ intake.

Diuretics Directly Influence Renal Tubules

Carbonic anhydrase inhibitors

Mechanism of action: *Diacarbum* inhibits the carbonic anhydrase enzyme predominantly at the proximal convoluted tubules, causing a reduction in hydrogen ions for $\text{Na}^+ - \text{H}^+$ exchange. Carbon dioxide (CO_2) reabsorption from the glomerular filtrate is suppressed, and HCO_3^- -excretion is increased. Due to decreased Na^+ reabsorption, the $\text{Na}^+ - \text{K}^+$ exchange in the distal convoluted tubule increases, causing a loss of K^+ in the urine. To maintain ionic balance, Cl^- is retained by the kidneys, resulting in a hyperchloremic acidosis. Increased urinary amounts of Na^+ , K^+ , and HCO_3^- - result in an alkaline urine. *Diacarbum* may decrease intraocular pressure.

Therapeutic uses: *Diacarbum* is used in glaucoma for reducing the rate of aqueous humor formation, as helping agent in petit mal epilepsy, to decrease the rate of spinal fluid formation,

Adverse effects are: blood dyscrasias and allergic skin reactions, drowsiness and paresthesias, inhibition iodide uptake.

Thiazide Diuretics (Benzothiadiazides) and Thiazide Like Diuretics

Mechanism of action: The thiazide diuretics - *dichlothiazidum* (*Hydrochlorthiazidum*) vary widely in their potency of carbonic anhydrase inhibition. Structurally these drugs have a sulfonamyl group, which accounts for their inhibition of carbonic anhydrase activity. They inhibit energetic metabolism — Na-K-ATPase activities, adenylatcyclase, they inhibit Cl^- reabsorption, particularly in the distal portion of the ascending limb of Henle's loop and the very early portion of the distal tubule. There is an increased renal excretion of Na^+ , Cl^- , HCO_3^- , and K^+ , keep Ca^{2+} .

Hypotensive effect of the thiazide diuretics is a result of a reduction in blood volume, direct relaxation of arteriolar smooth muscle, decrease of its sensitivity to noradrenaline influence. *Dichlothiazidum* decreases intraocular pressure. Certain other thiazidelike sulfonamide diuretics - *indapamidum*, *clopamidum*, *chlortalidonum*, *quinethazonum*, and *metolazonum* are pharmacologically similar to the thiazides, but act longer because they also influence proximal tubules, they are used in lower doses than thiasides.

Hydrochlorthiazidum is given orally 1-2 times a day. *Cyclomethiazidum* than given orally 1 time a day. *Indapamidum* stimulates prostaglandine synthesis and blocks calcium channels.

Therapeutic uses: Thiazides and thiasidlike diuretics are used to treat chronic edema, usually associated with cardiac decompensation. A diuretic response occurs in 2-3 hours and lasts for about a day. Thiazides and thiasidlike are used in the treatment of essential hypertension. *Indapamidum* is used only in hypertension. They sometimes are effective in the treatment of nephrosis. They are occasionally used for the palliation of nephrogenic and pituitary - antidiuretic hormone (ADH)-sensitive - diabetes insipidus. By decreasing the urinary volume through their natriuretic action, these drugs may enhance the action of the ADH. They are used in the management of hypercalciuria.

Adverse effects: Electrolyte abnormalities such as hypokalemia may occur. Thus, K^+ supplementation is recommended. Particular caution is needed when a thiazide is administered in combination with a digitalis preparation for the treatment of congestive heart failure. If digitalis is administered in the presence of hypokalemia, digitalis intoxication and serious cardiac arrhythmias may result. Hyperuricemia may result from an inhibition of renal tubular secretion of uric acid. Since thiazides are excreted by glomerular filtration and tubular secretion, the thiazides compete with uric acid for tubular secretion. Hyperglycemia can occur, aggravating preexisting diabetes mellitus. Thiazides may interfere with the conversion of proinsulin to insulin. Thiazide diuretics may reduce urinary calcium excretion. Hypercalcemia and hypophosphatemia may be occurred. Suppression of parathyroid hormone and reduction in intestinal calcium absorption may also occur. Thiazide diuretics occasionally may aggravate renal or hepatic insufficiency. Lassitude, weakness, and vertigo may occur with large doses. Rarely thiazide-induced pancreatitis, elevating lipid and lipoprotein changes may occur.

High-Ceiling (Loop) Diuretics

Furosemidum, Torasemidum, Acidum etacrynicum

Mechanism of action: These diuretics inhibit electrolyte reabsorption in the thick ascending limb of the loop of Henle (Na^+ , K^+ , Cl^- , Mg^{2+} , Ca^{2+} , PO_4^{3-} , HCO_3^-) and also *acidum etacrynicum bromidum*. They inhibit energetic metabolism and may interact with Na^+ and Cl^- channels. Cl^- -excretion is greater than Na^+ excretion. These diuretics increase renal blood flow without increasing the glomerular filtration rate. Large doses promote uric acid excretion. Hypochloremic alkalosis may occur, but it does not produce a refractory state. *Furosemidum*, a structural derivative of the thiazides, and *bumetanidum* are weak inhibitors of carbonic anhydrase, probably as a result of the diuretics substituted sulfonamide side chain. *Torasemidum* excretes K^+ less. *Acidum etacrynicum* lacks of a sulfonamyl group and does not inhibit carbonic anhydrase, but inhibit antidiuretic hormone. The drugs decrease arterial pressure, pre- and postload on heart.

Furosemidum, *torasemidum*, and *bumetanidum*, *acidum etacrynicum* are administered orally, intramuscularly or (more frequently) intravenously. One of the main differences between *furosemidum* and *acidum etacrynicum* is that the former has a broader dose-response curve.

Therapeutic uses: The high-ceiling diuretics are the most effective diuretic agents available. They are useful for the treatment of acute episodes of pulmonary edema. Edema associated with congestive heart failure, cirrhosis, and renal disease. Because of its potent edema-reducing ability, *furosemidum* has been used to treat elevated intracranial pressure.

Adverse effects: Fluid and electrolyte imbalances are the most commonly seen adverse effects. The high-ceiling diuretics frequently are administered to patients on digitalis so hypokalemia may be a particular problem. Hyperuricemia results because these diuretics are actively secreted by the renal and biliary secretory systems, and thus, they block (by competition) renal uric acid secretion. While hyperuricemia is relatively common, it is benign. The drugs make worse lymph circulation in ears. Transient deafness is a risk if a potentially ototoxic drug (e.g. an aminoglycoside antibiotic) is administered concomitantly in such circumstances, another class of diuretic should be employed. Transient granulocytopenia and thrombocytopenia occur. Severe muscle pain and tenderness seldom occur.

Potassium (K^+)-sparing Diuretics

Triamterenum and Amiloridum

Mechanism of action: *Triamterenum* and *amiloridum* inhibit active Na^+ reabsorption, because their physical and chemical characteristics are similar to hydrotating sodium in cortical collecting duct. They influence distal Na^+ and Cl^- transport. This reduces the net driving force for K^+ secretion. *Triamterenum* and *amiloridum* cause a moderate increase in Na^+ , Cl^- and HCO_3^- -excretion. Their action is independent of aldosterone. *Triamterenum* is administered orally twice a day. *Amiloridum* is administered orally once a day.

Therapeutic uses: *Triamterenum* or *amiloridum* are used in combination with other diuretic agents for the treatment of hypertension; this combined therapy augments the natriuretic effect while diminishing kaliuresis.

Adverse effects: Hyperkalemia may occur; thus, K^+ -sparing diuretics are not given in combination with one another and are contraindicated in hyperkalemic patients. Hyperkalemia is especially likely in diabetics or in those with impaired renal function. Reversible azotemia is relatively common. Gastrointestinal disturbances, including nausea and vomiting, occur on occasion. Leg cramps may occur. Dizziness has been reported.

Spironolactonum (aldactonum), eplerenonum (inspra) - competitive antagonist of the mineralocorticoid, aldosteronum.

Mechanism of action: They interfere with the aldosterone-mediated Na^+ - K^+ exchange, increasing Na^+ loss at the distal tubular site while decreasing K^+ loss.

Therapeutic uses: *Spironolactonum*, *eplerenonum* are often used as an adjunct to other diuretics to reduce the loss of K^+ in the management of refractory edema, such as that associated with Laennec's cirrhosis. They are also used when adrenal gland tumors result in increased aldosterone levels. They can be used for edema due to congestive heart failure, although other diuretic agents are more effective. *Eplerenonum* is more active than *spironolactonum*.

Adverse effects: Hyperkalemia may occur or be exacerbated, especially in patients with impaired renal function. *Spironolactonum*, *eplerenonum* are contraindicated in patients with acute renal insufficiency or hyperkalemia and are not given in combination with another K^+ -sparing diuretic. Gastrointestinal disturbances include diarrhea. Androgenic side effects include menstrual irregularities and hirsutism. The CNS disturbances include

lethargy.

Osmotic Diuretics

Mannitolum and **urea pura** owe their effects to the physical retention of fluid within the nephron rather than to direct action on cellular sodium transport.

Mechanism of action: Osmotic diuretics are filtered at the glomerulus but are poorly reabsorbed due to their molecular size. The presence of these unresorbed solutes in the proximal tubule causes decreased reabsorption of Na⁺ and water, resulting in a large volume of urine. **Mannitolum** causes an increase in renal medullary blood flow via a prostaglandin-mediated mechanism. Osmotic diuretics do not markedly influence Na⁺ and Cl⁻ excretion.

Mannitolum and **urea** are administered intravenously.

Therapeutic uses: The osmotic diuretics are used to reduce cerebrospinal fluid pressure. They will transiently reduce intraocular fluid pressure in glaucoma. They have also served as an adjunct in the prevention or treatment of oliguria and anuria. The osmotic diuretics, especially **mannitolum**, are employed for prophylaxis for acute renal failure in situations such as cardiovascular operations, treatment with nephrotoxic anticancer agents, severe traumatic injury, and management of hemolytic transfusion reactions. **Mannitolum** is used to promote the elimination of injected toxic substances.

Adverse effects are the following: headache, nausea, vomiting, chest pain. Because they do not penetrate cells and their mode of excretion is by glomerular filtration, osmotic diuretics increase blood volume, which can cause decompensation in patients with congestive heart failure. When osmotic diuretics are used for the treatment of renal failure or cirrhotic disease, hyperosmolality and hyponatremia can occur.

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|---------------------------|---|
| 1. Dichlothiazidum | Tab. 0,1; 0,025 |
| 2. Klopamidum (Brinaldix) | Tab. 0,02 |
| 3. Furosemidum | Tab. 0,04; Amp. 1% 2ml |
| 4. Acidum etacrynicum | Tab. 0,05, 0,1; Amp. 0,05 |
| 5. Spironolactonum | Tab. 0,025 |
| 6. Triamterenum | Pulv., caps. 0,05 |
| 7. Mannitum | Flac. 15% - 200, 400, 500ml; Flac. 30,0 |

β-adrenoblockers

β-Adrenergic blocking agents (β blockers) are divided into selective and nonselective drugs, the drugs with and without sympathomimetic activity. Some of them act as α-β-adrenoblockers

Drug P-Blocking Selectivity

Labetalolum Nonselective β- and selective α₁-blocking activity

Carvedilolum Nonselective β- and selective α₁-blocking activity

Nadololum Nonselective

Pindololum Nonselective intrinsic sympathomimetic

Propranololum Nonselective

Timololum Nonselective

Betaxololum β₁selective, intrinsic sympathomimetic

Esmololum β₁selective, intrinsic sympathomimetic

Celiprololum β₁selective, intrinsic sympathomimetic, β₂-agonist

Talinololum β₁selective, intrinsic sympathomimetic

Atenololum β₁selective

Metoprololum β₁selective

Bisoprololum β₁selective

Nebivololum β₁selective

Propranololum (anaprilinum) is a nonselective β-antagonist: It competes for both β₁- and β₂receptors.

Pharmacokinetics: Although **propranololum** is completely absorbed from the gastrointestinal tract, a large portion of the drug is extracted by the liver before it enters the systemic circulation. Wide variation in the hepatic metabolism of the drug among individuals causes significant differences in the plasma concentrations attained. **Propranololum** is approximately 90% bound to plasma proteins. The elimination half time is approximately 3 hours for a small dose, but it is prolonged with larger doses and is significantly prolonged in the presence of cirrhosis. A metabolic product, 4-hydroxypropranolol is active but has a short half-life.

Pharmacologic effects: **Propranololum** decreases the heart rate and cardiac output and prolongs systole, has membranostabilising action. It decreases total coronary blood flow and oxygen consumption. It reduces blood flow to most tissues except the brain.

The antihypertensive effect of **propranololum** is slow to develop. **Propranololum** inhibits the renal secretion of rennin. It depresses sodium (Na⁺) excretion because it alters renal hemodynamics, an effect that is secondary to the decrease in cardiac output. **Propranololum** increases airway resistance by β₂blockade. Since most of the effects of catecholamines on carbohydrate and fat metabolism are mediated by β-receptors, **propranololum** will interfere with these events. **Propranololum** has sedative effect. **Propranololum** increases the contractility of bronchial, intestinal, uterine smooth muscles.

Propranololum decreases intraocular pressure in increases the contractility open-angle glaucoma.

Therapeutic uses: Treatment of hypertension, often in combination with a diuretic. Prophylaxis of angina pectoris. Prophylaxis of supraventricular and ventricular arrhythmias. Long-term prophylaxis in patients who have

had a myocardial infarction and are at high risk for infarction or sudden death. Management of hypertrophic obstructive cardiomyopathies to reduce the force of myocardial contractions. Management of hyperthyroidism and anxiety states to decrease the heart rate. Prophylaxis of migraine headaches.

Adverse effects and precautions: *Propranolol* can induce heart failure, especially in patients with compromised myocardial function. Rapid withdrawal can lead to "super sensitivity" of β -adrenergic receptors, which can provoke anginal attacks, arrhythmias, or myocardial infarction. Because *propranolol* increases airway resistance, it must be used with caution in asthmatics. Because of its effects on carbohydrate metabolism, the hypoglycemic action of insulin may be augmented. Therefore, diabetics being treated with insulin and persons prone to hypoglycemia must use *propranolol* with caution. Rash, fever, and purpura are characteristic of an allergic response and require discontinuation of the drug. Prolonged use may cause fatigue, depression, nightmares, sexual dysfunction, and peripheral arterial insufficiency. Because of its effects on peripheral blood flow, *propranolol* is contraindicated in patients with Raynaud's phenomenon and other peripheral vessels disorders.

Timolol is a nonselective β -adrenergic antagonist that is 5-10 times more potent than propranolol. *Timolol* lowers intraocular pressure by reducing the production of aqueous humor; the mechanism is not clear. It does not change the size of the pupil, and vision is not affected. *Timolol*, in the form of eye drops, is, therefore, useful in the treatment of glaucoma.

Nadolol is a nonselective β -adrenergic blocking agent that is not metabolized and is excreted unchanged in the urine. Its effect and adverse reactions are similar to those of *propranolol*, but it influences longer. The introductions are the same as *propranolol*.

Labetolol is a nonselective β -blocker, which also has a 1-blocking activity. It is used in the treatment of mild to severe hypertension. *Labetolol* reduces peripheral vascular resistance while preventing reflex tachycardia. It can be given intravenously in hypertensive emergencies. *Labetolol* may cause postural hypotension and jaundice in addition to the adverse effects which are seen with other β -blockers.

In contrast to labetolol, a β -adrenoblocking agent carvedilol has similar pharmacological properties and also antioxidant action, may be used also in congestive heart failure.

Pindolol is a nonselective β -blocker, which also has some degree of intrinsic sympathomimetic (α -adrenergic) activity. Unlike the case with *propranolol*, no rebound tachycardia occurs upon abrupt withdrawal of *pindolol*. It is used in arterial hypertension.

Acebutolol is a β -blocker with mild intrinsic sympathomimetic activity (ISA). Its β_1 blocking effects exceed its β_2 blocking effects. Because of its ISA, it may not cause as slow a bradycardia as *propranolol* does. It is used for hypertension treatment. *Talinolol* has the same effects and indications.

Esmolol has short duration of action and intrinsic sympathomimetic activity. It is mainly used during operations.

Celiprolol blocks β_1 -adrenoreceptors and stimulates β_2 -adrenoreceptors. It may be used in patients with bronchial asthma and arterial hypertension.

Metoprolol is a selective β_1 adrenergic antagonist. It is absorbed well when given orally.

Pharmacologic effects: *Metoprolol* inhibits the inotropic and chronotropic cardiac responses and penetrates through haemato-encephalic barrier. It is 1/50 as potent as *propranolol* in inhibiting the vasodilator response to *isadrinum*; however, it is long acting, has membranostabilising action. It is used for treatment arterial hypertension, supraventricular, ventricular arrhythmias, ischemic heart disease.

Therapeutic uses: *Metoprolol* is used chiefly in the treatment of hypertension, angina pectoris, subventricular and ventricular arrhythmias.

Adverse effects: *Metoprolol* produces fewer deleterious effects in asthmatic patients because of its selective β_1 -adrenergic antagonism, but its use in asthmatics still requires caution. Other adverse effects are similar to those of *propranolol*.

Atenolol is a selective β_1 -adrenergic antagonist, hydrophilic, which is administered two times a day and doesn't influence CNS.

Betaxolol is a selective β_1 adrenergic antagonist, which is administered once a day. It is more lipophilic than *atenolol*. It is also available as a topical formulation for the treatment of glaucoma.

Bisoprolol is a selective β_1 -adrenoblocking agent with long duration of action. It may be used in arterial hypertension and congestive heart failure.

Nebivolol has own vasodilative properties by means of ability to influence the synthesis of NO.

Calcium Channel-Blocking Agents

Calcium channel blockers (e.g. *nifedipinum*, *verapamilum*, *foridonum*, *nicardipinum*, *amlodipinum*, *felodipinum*, *lacidipinum*, *lercanidipinum*, *mani-dipinum*, and *diltiazemum*) are effective vasodilators, because they are orally active. These drugs are suitable for chronic use in hypertension of any severity. *Nifedipinum* is used in combination connecting with tachycardia. *Nifedipinum* sustained release and retard are available for treatment. *Diltiazemum*, *verapamilum*, and *nicardipinum* increase vasodilation and decrease peripheral resistance. *Verapamilum* and *diltiazemum* cause little change in heart rate, while *nicardipinum* produces an initial increase, which is reflex-mediated. *Diltiazemum* and *verapamilum* depress A-V conduction and should not be used with β -blockers. Diuretics may enhance the efficacy of Ca^{2+} -channel blockers.

The choice of calcium channel blockers especially for combination therapy, is largely influenced by the effect of the drug on cardiac pacemakers and contractility and coexisting diseases such as angina, asthma, peripheral

vascular diseases.

ACE Inhibitors

ACE Inhibitors are divided into:

1. Drugs which have SH-group - *captoprilum*, *soprenoprilum*;
2. Drugs which have carbonyl group - *enalaprilum*, *lisinoprihim*, *celaso-prilum*, *ramiprihim*, *perindoprinum*, *trandaloprilum*, *spiraprilum*, and *quadroprilum*;
3. Drugs which have phosphoryl group - *phosynoprilum* (*monoprilum*).

Captoprilum is transformed into inactive compound. *Enalaprilum*, *ramiprilum*, *spiraprilum*, *trandaloprilum*, and *cilasoprylum* are prodrugs. They are biotransformed in an active form. *Phosynoprilum* and *quadroprilum* are transformed into active compounds. *Lisinoprilum* is not biotransformed in organism. *Lisinoprihim* is one hydrophilic compound. *Monoprilum*, *quadroprylum* are transformed in liver and are excreted also by kidneys.

Mechanism of action: *Captoprilum*, *enalaprilum*, *lisinoprilum* and other drugs are specific competitive inhibitors of peptidyl dipeptidase (an ACE), the enzyme which converts angiotensin I to angiotensin II. Angiotensin II is a potent direct vasoconstrictor. Thus, *captoprilum*, *enalaprilum*, and *lisinoprilum* inhibit vasoconstriction. Angiotensin II stimulates the secretion of aldosterone, which promotes salt and water retention. Thus, *captoprilum*, *enalaprilum*, and *lisinoprilum* inhibit the secretion aldosterone salt and water retention and slightly increase serum K^+ levels. The drugs decrease level of renin, aldosterone, endotheline-1, vasopressin, noradrenaline. Because peptidyl dipeptidase is necessary to catalyze the degradation of bradykinin, the ACE inhibitors may increase the concentration of bradykinin, which is a potent vasodilator, nitric oxide, prostaglandinum E_2 , I_2 . The ACE inhibitors also exert an antihypertensive effect in low-renin hypertension.

Pharmacokinetics: *Captoprilum* is rapidly absorbed following oral administration and reaches peak blood levels within an hour. Approximately 95% of a dose is eliminated by the kidneys within 24 hours. *Enalaprilum* is more potent than *captoprilum* and its duration of action is more than 24 hours, twice as long as that of *captoprilum*. *Lisinoprilum* is absorbed more slowly than *enalaprilum* and has a slower onset of action.

Pharmacologic effects: The cardiovascular effects of *captoprilum* and *enalaprilum* include a reduction in total peripheral resistance and mean arterial blood pressure preload, postload and either no change or an increase in cardiac output. *Captoprilum* is given orally 1 hour before meals. The initial dose can be increased at 1- to 2-week intervals. *Enalaprilum* is given orally once or twice a day, *enalaprilatum* is administered parenterally. *Lisinoprilum* is given orally once a day.

Therapeutic uses: The ACE inhibitors are increasingly used for the treatment of mild to moderate hypertension. The ACE inhibitors are effective for low-renin, as well as high-renin, hypertension. They are effective when used alone but are often administered with a thiazide diuretic, in which case the antihypertensive effects appear to be additive. The ACE inhibitors also relieve chronic congestive heart failure by reducing both preload and afterload.

Adverse effects: Proteinuria can occur, especially in patients with compromised renal function. The ACE inhibitors are contraindicated in patients with bilateral renal artery stenosis because acute renal failure may ensue. Cough and bronchospasm can occur. Hypotension has followed the first dose of the ACE inhibitors in Na^+ -depleted patients. Neutropenia can occur, and in patients who have impaired renal function or serious autoimmune disease (e.g. systemic lupus erythematosus), *captoprihim* should be used with caution. Neutropenia is rare with *enalaprihim* or *lisinoprilum*. Approximately 10% of patients treated with *captoprilum* develop reversible skin rashes, alterations in taste, proteinuria, and leucopenia. Headache, dizziness, and fatigue are the most common side effects associated with *enalaprilum*. Hyperkalemia has been reported.

Antagonists of Angiotensin II Receptors

Saralasinum, an angiotensin II, antagonist, exemplifies the drugs which interfere with the renin-angiotensin system by this mechanism. The drug can be given only by intravenous infusion. It is primarily used diagnostically to detect a renal cause of hypertension.

Now these drugs are divided in three groups according chemical structures.

1. Biphenyltetrazoles (*losartanum*, *irbersartanum* and other);
2. Nonbiphenyltetrazoles (*eprosartanim*, *telmisartaniim*, *candesartanum* and others);
3. Nonheterocyclic compounds (*valsatanum*).

The compounds block effect of angiotensin II on receptors AT II (1) independently from ways of their synthesis. They decrease vessels peripheral resistance (afterload), cardiac venous return (preload), but have less adverse effects (cough, bronchospasm) than inhibitors of the ACE because do not influence synthesis of bradykininum. They also increase effect of angiotensin II on the receptors angiotensin II (2) which stimulate regeneration, vasodilatation and other curative effects. Plasma renine activity also increases.

Losartanum (*Cozaar*) active metabolite is a long acting (6-8 hour) noncompetitive antagonist at the AT_1 receptor which contributes to the pharmacological effects of losartanum. *Valsartanum* (*Diovan*) has a higher affinity for the AT_1 receptor than *losartanum*, it does not have an active metabolite and has a slightly longer duration of action than *losartanum*. *Ir-besartanum* (*Avrovel*) exhibits high bioavailability and high affinity for the AT_1 receptor, it does not have an active metabolite and has a considerably longer duration of action than *losartanum*. *Candesartanum cilexetil* (*Ata-cand*) has an active metabolite with a long duration of action, is a prodrug and exhibits an AT_1 receptor affinity 80 times that of *losartanum*. *Telmis-artanum* (*Micardis*) is a longest-acting AT_1 receptor antagonist and has no active metabolites.

Therapeutic use: Angiotensin II receptor antagonists are effective as monotherapy in the treatment of hypertension and of congestive heart failure in patients who do not tolerate the ACE inhibitors.

Centrally Acting Sympatholytic Agents

Clophelinum and *methyldopha* act centrally on the vasomotor centers of the brain and are predominantly **α_2 -receptor agonists**, cause a decrease in sympathetic outflow to the peripheral vessels by a mechanism which involves activation of α_2 -receptors in the CNS. Both *clophelinum* and *methyldopha* reduce blood pressure by reducing cardiac output, vascular resistance, or both. The major compensatory response is salt retention. Sudden discontinuation of *clophelinum* causes rebound hypertension, which may be quite severe. Both drugs (but *methyldopha* to more extent) may cause sedation.

Clophelinum is imidazoline derivative to stimulate α -adrenergic receptors (probably presynaptic α_2 -receptors) in the vasomotor centers of the brain, resulting in decreased sympathetic outflow to the peripheral vessels.

Pharmacokinetics: The antihypertensive effects of *clophelinum* develop within 30-60 minutes of oral administration, peak in 2-4 hours, and last approximately for 8 hours. The drug and its metabolites are excreted primarily in the urine.

Pharmacologic effects: Intravenous injection of *clophelinum* causes an initial increase in both systolic and diastolic pressure; oral administration does not normally produce this hypertensive effect. The initial rise in blood pressure is caused by direct stimulation of peripheral α -adrenergic receptors, producing transient vasoconstriction. *Clophelinum* also causes peripheral α -adrenergic blockade, and thus, it is a partial agonist. The increase in blood pressure following intravenous injection is transient and is soon followed by a fall in blood pressure, resulting from a decrease in cardiac output and heart rate, usually not accompanied by a significant change in peripheral resistance. Vagal discharge is increased by *clophelinum* in association with increased **baroreceptor** reflex sensitivity. *Clophelinum* decreases intraocular pressure. *Clophelinum* does not block the homeostatic control mechanisms of the peripheral autonomic system. It decreases plasma renin activity, primarily through a centrally mediated decrease in sympathetic stimulation of the juxtaglomerular cells of the kidneys. Renal vascular resistance decreases, while renal blood flow remains essentially unchanged.

Clophelinum is given orally, parenterally, in eye drops. *Clophelinum* is also available as a transdermal patch, which is applied once in a week.

Therapeutic uses: Now *clophelinum* can be used to treat mild hypertension or moderate to severe hypertension very seldom. It indicates for treatment hypertensive emergencies and narcomania. It may be used as a single agent or in combination with other antihypertensive agents. In eye drops it is used in glaucoma.

Adverse effects: Dry mouth, drowsiness, and sedation are the most frequent problems and may require discontinuation of *clophelinum*. Rebound hypertensive crises can result from abrupt cessation of *clophelinum* tablets or patches when the drug is used as a single agent. Fluid retention often occurs, requiring concurrent diuretic therapy. *Clophelinum* can cause or worsen depression.

Guanabenz, *guanfacinum* are central α_2 -agonists and exhibit antihypertensive effect similar to *clophelinum* but act longer.

Moxonidine is a selective agonist of imidazoline receptors in CNS. It has hypotensive effect and increases sensitivity to *insulinum*. Sedative effect and dryness in mouth are rare.

Adrenoreceptor Blockers

α_1 -selective agents (e.g. *prazosinum*, *doxazosinum*, and *terazosinum*) and β -blockers (e.g. *propranololum*, *atenololum*, *metoprololum*, *bisoprololum*, *betaxololum*, *nebivololum*, and *celiprololum*) are effective antihypertensive drugs. α -blockers reduce vascular resistance and venous return. The nonselective α -blockers (*phentolamini sulfas* and *pyroxanum*) are of no value in chronic hypertension because of excessive compensatory responses, especially tachycardia. α_1 -selective adrenoreceptor blockers are relatively free of the severe adverse effects of the nonselective α -blockers and postganglionic nerve terminal sympathoplegic agents.

Prazosinum. This quinazoline derivative is a selective postsynaptic α_1 adrenergic receptor blocking agent which causes vasodilation both of arteries and veins.

Pharmacokinetics: *Prazosinum* is highly bound to plasma protein. Its plasma concentration peaks in about 3 hours. Plasma half-life is usually 2-3 hours but can be prolonged by congestive heart failure. *Prazosinum* is extensively metabolized, may undergo significant first-pass metabolism, has a bioavailability of about 60%, and is probably excreted in the feces and bile.

Pharmacologic effects: *Prazosinum* reduces peripheral vascular resistance and lowers arterial blood pressure in both supine and erect patients. Unlike nonselective α -adrenergic blockers it does not usually produce reflex tachycardia. *Prazosinum* seems to produce minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

Prazosinum is given orally, two or three times a day.

Therapeutic uses: *Prazosinum* is used to treat mild to moderate hypertension. It may be more effective in combination with a diuretics or β -adrenoblocking agents than when used alone. It is also sometimes used in the treatment of acute congestive heart failure.

Adverse effects: Dizziness, headache, drowsiness, and palpitations can occur but often disappear with continued therapy and rarely cause discontinuation of the drug. The initial dose of *prazosinum*, especially if larger than 1 mg can induce postural hypotension and syncope, probably due to decreased venous return to the heart. It is, therefore, best to give the initial dose at bedtime.

Doxazosinum, terazosinum has longer hypotensive effect.

Vasodilators

Drugs which dilate blood vessels by acting directly on smooth muscle cells through nonautonomic mechanisms are useful in treating many hypertensive patients. Three major mechanisms are utilized by vasodilators: release of nitric oxide, opening of potassium channels (which leads to hyperpolarization), and blockade of calcium channels. **Arteriolar vasodilators** directly relax arteriolar smooth muscle and, thus, decrease peripheral vascular resistance and arterial blood pressure. The beneficial effect of these drugs on peripheral vascular resistance can be partially negated by the increased reflex sympathetic activity they produce, which can result in increased heart rate, stroke volume, and cardiac output. These drugs also can increase plasma renin activity as a result of increased reflex sympathetic discharge, causing a pressor effect. This group of drugs often causes salt and water retention and, thus, expansion of the extracellular fluid and plasma volume. Therefore, arteriolar vasodilators should be used in conjunction with diuretic and β -adrenergic blocking therapy.

Apresininum (hydralazinum) has a greater effect on arterioles than on veins (which minimizes the incidence of postural hypotension). It may reduce diastolic more than systolic blood pressure. It may block phosphodiesterase.

Apresininum can be given orally or intramuscularly, but now it is used as component of complex drugs.

Therapeutic uses: *Apresininum* is used to treat moderate to severe hypertension, in the treatment of acute and chronic congestive heart failure, is combined with a β -adrenoblockers to prevent tachycardia and increased renin secretion due to reflex sympathetic stimulation, with a diuretic agent to prevent salt and water retention and with isosorbidi dinitras to combine influence on veins and arteries.

Adverse effects: Headache, anorexia, nausea, dizziness, and sweating occur frequently but tend to diminish as *apresininum* is administered over a period of time. *Apresininum* can worsen coronary artery disease because of the myocardial stimulation it produces. *Apresininum* can cause a reversible lupus-like syndrome, especially when more than 400 mg/day are administered to slow acetylators of the drug.

Arterial and venous vasodilators reduce both arterial resistance and venous tone and markedly decrease arterial blood pressure.

Natrii nitroprussidum is used in hypertensive emergencies. *Natrii nitroprussidum* is a short-acting agent (duration of action is a few minutes) which must be infused continuously. The drug mechanism of action involves the release of nitric oxide (from the molecule itself, not from the endothelium), which stimulates guanylyl cyclase and increases cGMP concentration in smooth muscle. The toxicity of *natrii nitroprussidum* includes excessive hypotension, tachycardia, and, if infusion is continued over several days, accumulation of cyanide or thiocyanate ions in the blood.

Pharmacokinetics: Onset of action occurs within 1 minute of intravenous administration, and effects cease within 5 minutes of stopping an infusion. The drug is rapidly inactivated by hepatic enzymes, first to cyanide and then to thiocyanate.

Pharmacologic effects: *Natrii nitroprussidum* acts directly on arterial and venous smooth muscle but has little effect on other smooth muscle. It decreases blood pressure in both the supine and upright positions. The increased venous capacitance that it produces results in decreased cardiac preload and, thus, decreases myocardial oxygen demand for a given output. *Natrii nitroprussidum* causes a slight increase in heart rate and decrease in cardiac output except when heart failure is present. In the latter case the heart rate may decrease and the cardiac output increase. Renal blood flow is maintained with *natrii nitroprussidum* and renin secretion is increased.

Natrii nitroprussidum is administered only as an intravenous infusion with sterile 5% dextrose in water.

Therapeutic uses: *Natrii nitroprussidum*, like *diazoxidum*, is used for a short-term, rapid reduction of blood pressure in hypertensive emergencies. It is preferable to *diazoxidum* for treating hypertensive emergencies in patients with coronary insufficiency or pulmonary edema because, in contrast to *diazoxidum*, it reduces cardiac preload (by increasing venous capacitance) and, thus, myocardial oxygen demand. *Natrii nitroprussidum* can also be used to produce controlled hypotension to minimize bleeding during surgery. *Natrii nitroprussidum* can improve left ventricular function (lower ventricular filling pressure) in patients with acute myocardial infarction and has beneficial hemodynamic effects in the treatment of acute congestive heart failure.

Adverse effects: Hypotension, nausea, diaphoresis, headache, restlessness, palpitations, and retrosternal pain can occur secondary to excessive, rapid vasodilation. The rate of conversion of *natrii nitroprussidum* from its metabolite cyanide to thiocyanate is dependent on the availability of sulfur (usually as thiosulfate). Rarely, when high doses of *natrii nitroprussidum* are administered for a prolonged period and sulfur stores are low, cyanide toxicity can occur. Because thiocyanate is cleared slowly by the kidneys, it can accumulate during prolonged *natrii nitroprussidum* therapy, especially in patients with poor renal function. A plasma thiocyanate concentration of greater than 10 mg/dl can cause weakness, nausea, muscle spasms, and psychosis, as well as hypothyroidism due to interference with iodine transport. A case of methemoglobinemia following prolonged infusion of *natrii nitroprussidum* has been reported.

TREATMENT OF THE HYPERTONIC CRISES

Complicated crises. Any delay of treatment in the case of the complicated crisis can cause irreversible consequences or death. Treatment must begin from intravenous introduction of one of the preparations, indicated in the table of survey to the fact that the market for drugs in the Ukraine is continuously supplemented by new preparations, table gives practically all contemporary means, which are recommended for treating hypertension in the special situations, even those, which are not yet registered in the Ukraine. Next to this, taking into account the

scarcity of the medicines of the mentioned group, are given also the means, which already leave from the custom and by the foreign authors they are not directed in the recommendations relative to the treatment of special states (clonidin, dibasol). In the case of the impossibility to immediately carry out an intravenous infusion to its beginning it is possible to apply the sublingual ingestion of some medicines: nitrates, nifedipin, clonidin, Captopril, β -blockers and/or the intramuscular injection of clonidin, fentolamin or Dibasol. Nifedipin in some patients can cause intensive headache, and also not control hypotension, especially in combination with magnesium sulfate, therefore its application bottom to limit by the patients, who reacted well to this preparation earlier (during the planned treatment). Advantage should be allowed to preparations with the short duration of action (nitroprussid of sodium, nitroglycerine), since they give the controlled anti-hypertensive effect. The preparations of long-term effect are dangerous by the possible development of unguided hypotension. Optimum decrease BP - to 25% of the initial level. A sharper decrease BP increases the risk of the complications: the decrease of cerebral blood circulation, coronary blood circulation (it appears stenocardia, arrhythmia, sometimes myocardial infarction). Especially large risk of complications with a sudden decrease BP in sick old years with expressed atherosclerosis of the vessels of the brain.

Uncomplicated crises. In the cases of the development of the uncomplicated crisis, as a rule, there is no need for the intravenous injection of preparations. Internal administration the preparations, which have rapid anti-hypertensive action, or intramuscular injections, uses. Effective is in such cases the application of clonidin. It does not cause tachycardia, does not increase heart emission and therefore it is possible to assign it by patient with the stenocardia. Furthermore, this preparation can be used in patients with the kidney deficiency.

Clonidin one ought not to assign by patient with the disturbance of the heart conductivity, especially those, which obtain heart glycosides. Is used also nifedipin, which must ability descend general peripheral resistance, increase heart emission and nephritic blood flow. A decrease BP is observed after only 15-30 min. after its method, anti-hypertensive effect remains for the elongation of 4-6 hours. At the same time it should be noted that the national committee of the USA on development, estimation and treatment of high arterial pressure considers inadvisable the application of nifedipin for treating the crises, since it is heavy to control speed and degree of a pressure decrease with its sublingual method, in connection with which rises the risk of cerebral or coronary ischemia. The ACE inhibitor Captopril decreases BP after only 30-40 min. after method because of the rapid absorption in the stomach. It is possible to use also the intramuscular injections of clonidin or Dibasol. In the case of vegetative disturbances are effective the sedative preparations, in particular, the benzodiazepin derivatives, which can be used per os or in the form intramuscular injections, and also pirroksan and droperidol.

For the preventive maintenance of hypertensive crises the regular therapy of chronic hypertension has decisive importance. Treatment improves the motion of disease and decreases the frequency of complications. The development of the second forms of arterial hypertension at the beginning of disease and individual approach to their treatment is also the necessary condition for their warning.

Materials for students' self-directed work.

Materials for self-control

1. To determine the classification of hypotensive preparations, their mechanisms of action, pharmacodynamics, pharmacokinetics, side effects.
2. To determine the basic principles of pharmacotherapy by hypotensive preparations the patients have with the different types of arterial hypertension.
3. To name the preparations, which are used with the hypertonic crises.
4. To compile the plan of pharmacotherapy in patients with the different stages of hypertonic disease to compile the plan of pharmacotherapy with renal of arterial hypertension.
5. To develop the plan of pharmacotherapy with the endocrinological diseases.
6. To compile the plan of pharmacotherapy in patients with the neurologic diseases, which are accompanied by arterial hypertension.

Test for students' self-directed work.

Test 1. In patient with the hyper-kinetic type of blood circulation (for the classifications of heart insufficiency) and arterial hypertension the advantage returns to the following preparations: 1. Propranolol 2. Hypothiazide 3. Nifedipin 4. Verapamil 5. Atenolol 6. Furosemide

The answers: advantage returns to propranolol, verapamil, atenolol.

Test 2. In patient with the hypo-kinetic type of blood circulation (according to the classification of heart insufficiency) and arterial hypertension advantage return to the following preparations: 1. Diltiazem 2. Metoprolol 3. Nifedipin 4. Verapamil 5. Enalapril 6. Furosemide

The answers: advantage returns nifedipin, enalapril, furosemid.

Test 3. Mechanism of action to reserpin is connected:

1. By disturbance of the synthesis of noradrenalin
2. With the acceleration of the liberation of noradrenalin from the nerve cells in the section of presynaptic nervous ends
3. By the disturbance of the reverse seizure of noradrenalin in the section of presynaptic nervous ends

The answers: by the disturbance of the synthesis of noradrenaline, by the disturbance of the reverse seizure of noradrenaline in the section of presynaptic nervous ends.

Test 4. Which of the enumerated hypotensive preparations cause remodeling of myocardium (decrease of the value of hypertrophy myocardium) in the case of the prolonged use: 1. Propranolol 2. Hypothiazid 3. Nifedipin 4. Verapamil 5. Atenolol 6. Lizinopril 7. Clophelin 8. Reserpin 9. Apresin 8. Captopril 9. Enalapril 10. Furosemid

The answers: remodeling of the hypertrophied myocardium cause atenolol, propranolol, nifedipin, verapamil, lizinopril, captopril, enalapril.

Test 5. Which of the enumerated hypotensive preparations does draw the stimulation of the β_2 -adrenoreceptors of the vasomotor center of the medulla oblongata? 1. Nifedipin 2. Clophelin 3. Reserpin 4. Apresin 5. Captopril 6. Enalapril

The answers: clofelin

Test 6. Which of the enumerated preparations does cause the development of such side effect as cough? 1. Clofelin 2. metoprolol 3. Verapamil 4. Furosemid 5. Nitroprussid sodium 6. Captopril 7. propranolol 8. Dibazol

The answers: Captopril

Test 8. Which of the enumerated hypotensive means can be used sublingually for the purpose of a rapid decrease AD? 1. Nifedipin 2. atenolol 3. Dopegyt (methyldopa) 4. propranolol 5. adelfan 6. clofelin 7. cristepin 8. metoprolol

The answers: Nifedipin, propranolol, clofelin

Test 9. Which of the enumerated preparations should be returned advantage in the case of the appearance of the spasms, which did arise in patient during the hypertonic crisis? 1. Propranolol 2. Diazepam (sibazon) 3. Dibazol 4. magnesia sulfate 5. reserpine 6. apresin 7. aminazin 8. Atenolol

Test 10. What preparation you will select for the assignment to special aid with arterial hypertension, which does have a threat for the life? Nifedipin, Dibazol, nitroprussid of sodium, magnesium sulfate?

The answer: advantage should be returned to nitroprussid of sodium

SITUATION TASKS:

1. To the patient of 42 years, who suffers to the hypertonic disease II st. (slowly progressive flow) is assigned propranolol (anaprilin) on 120 mg in a 24 hour period. For the elongation 2 months of a constant method BP remained at the level 130/80-140/80 mm Hg. However, 2,5 months after the beginning of the adoption of obzidan developed bradycardia (Ps - 52-54 for 1 minute), BP - 100/70/-90/60 mm Hg.

By what special features of pharmacokinetics and pharmacodynamics of propranolol it is possible to explain the state, which it developed in patient.

Standard of the answer: The decrease BP and bradycardia are caused by a phenomenon of the primary metabolism of propranolol - decrease of primary elimination in the liver and by an increase of its bioaccessibility, which is characteristic for conducting prolonged pharmacotherapy. This dictates the need for reduction in the dose of propranolol in the cases of prolonged treatment.

2. Patient G. Diagnosis: Hypertonic the disease II st. Ischemic disease of the heart: Atherosclerotic myocardiosclerosis, heart insufficiency I st. In recent 4th years it systematically assumes inside clophelin 0,075 mg 4 times a day. For a period of last year in connection with the insufficiency of effectiveness clophelin is assigned corinfar (nifedipin) on 10 mg of 3 times in the day. For a period of recent 2nd day in connection with a substantial increase in the arterial pressure (to 190/110-205/120 mm Hg.) patient began to assume clophelin on 0,15 mg of 4-5 times in a 24 hour period and corinphar on 10 mg of 3 times in a 24 hour period. In patient arose vertigo, expressed sleepiness, edemas in the section of feet and shins. A decrease in arterial pressure to 90/55 mm Hg. was recorded. You will explain the reason for this. Your tactics of therapy.

Standard of answers. The reason for hypotension became the use in the combination of clophelin in the large dose with nifedipin. Necessary for the purpose of increase BP is application of 10% of solution of sulfocamfocain on 2 ml i/m. In the case of the insufficiency of effect it is necessary to appoint i/v 3% solution of prednisolon of phosphate on 2 ml. After increase BP expedient to eat a designation of the ACE inhibitor - Captopril or enalapril.

3. To patient V. by the purpose the stopping hypertonic the crisis it adapted intravenously it is drop the β -adrenoblocker esmolol. In the first minute preparation was introduced at the dose 500 g/kg, then preparation was introduced at the dose 100 g/kg into 1 minute. 25 minutes after the beginning of the esmolol introduction with the electrocardiogram began to be recorded bradycardia of 45-50 heart contractions into 1 minute, atrioventricular blockade II degree on the type of Mobitts II. Your tactics of the subsequent therapy?

Standard of answers. To urgently abolish esmolol. To appoint intravenously atropine sulfate 0,1% solution on 1 mg or itrop on 1 ml 0,05% of solution (0,5 mg). Furthermore, it is possible to appoint β -agonists - isopropyl noradrenaline (neopinephrine) on 0,5-1 ml 0,05% solution on 200-300 ml of physiological solution is intravenously drop or orsiprenalin sulfate (alupent) on 1 ml 0,05% solution to 200 physiological solutions it is intravenously drop. It is possible to use neopinephrine under the language - on 1 tablet (5 mg) of 3-4 times in the day.

4. Patient G. Diagnosis: Hypertonic disease II st. Ischemic disease of the heart: Atherosclerotic myocardiosclerosis, heart insufficiency II- A st. For a period of recent two weeks assumes enalapril at the dose 10 mg of 3 times in the day, nitrosorbid on 20 mg of 4 times in the day, panangin on 1 tablet (0,298 g) of 3 times in the day. In patient the cough appeared. What did cause the appearance of these side-line phenomena?

Standard of answers. The appearance of a cough is caused by the application of enalapril. Under the action of enalapril increases the activity of the bradykinin, which caused the appearance of a cough.

5. To patient N. by the purpose the stopping hypertonic the crisis was assigned the intravenous drop introduction of sodium of nitroprussid at the dose of 2,5 mkg (kg per minute). During the injection of preparation arterial pressure was reduced to 70/40 mm Hg. What your tactics of the subsequent therapy?

Standard of answers. Necessary is the designation of vasopressor preparations - dopamine or suttamin with a velocity of 5-20 g/kg/min. In the case of their ineffectiveness is assigned noradrenaline hydrotartrate with a speed of the introduction of 2-8 g/min.

6. Sick k., 63 years for a period of 2 weeks obtained 0,15 mg of clofelin inside 3 times a day. In connection with the fact that BP was reduced with 190/110 mm Hg. to 110/70 mm Hg. doctor abolished preparation. After 2 days appeared expressed headaches, palpitation, BP increased to 180/100 mm Hg. You will explain the reason of worsening in the state of patient. How it is possible to avoid worsening the state of patient?

Standard of answers. In patient developed the syndrome of the cancellation as a result of the curtailment of the adoption of clophelin. The dose of preparation must be lowered for a period of several days.

7. The patient of 48 years for a period of 18 years suffers to diabetes mellitus II of the type. For treating diabetes mellitus insulin of 40 units of operation in a 24 hour period, which support the level of glycemia within the limits of 7,5-8,6 mmole/liter, is obtained. Increase BP to 170/90-180-100 mm Hg. recently is noted. In connection with this the doctor appointed propranolol at the daily dose of 80 mg (20 mg of 4 times in the day). What side effects should be expected during this combination of medicines? Your proposals relative to the treatment of patient.

Standard of answers. The combination of β - adrenoblockers with the hypoglycaemic preparations can raise to a higher power sugar reducing effects of the latter, in connection with this one should not assign propranolol in the patients with diabetes mellitus.

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