

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

Academic discipline	Clinical Pharmacology
Topic 1/2	<b>Object and the task to clinical pharmacology. The basic condition of pharmacokinetics and pharmacodynamics. Interaction of medicines, the forms of the side-action of medicines, complication of the drug therapy. The clinico-pharmacological characteristic of the medicines, which influence homeostasis and lipid exchange.</b>
Year of study	5
Faculty	Foreign students training (Medical)

**Poltava 2017**

### 1. Relevance of theme:

The means, which influence hemostasis, are used by doctors of all professions. The mechanism of the action of data of means is various. The wide application to [poluchilipreparati], which are used for normalizing microcirculatory hemostasis and anti-AGREGaunt. The knowledge of this theme will allow doctors professionally to approach the treatment of thromboembolic syndrome, to learn to correct the disturbance of the system of hemostasis. The development of the ways of treatment and preventive maintenance of atherosclerosis is important. In this case large role belongs to preventive pharmaco maintenance. Against to atherosclerotic means relate the preparations, which are capable of removing, or of preventing the deposit of lipids, complex carbohydrates, salts of calcium and fibrin in the arteries.

### 2. Learning objectives:

a) to master the habits of effective and safe pharmacotherapy of the means, which influence hemostasis, by angioprotectors and by hypolipid; b) to master the skills of the individual selection of medicines; c) to know how to conduct if necessary the correction of pharmacotherapy. g) to know how to conduct the estimation of the clinical, laboratory, instrument methods of study.

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

The name of the previous disciplines	The skills
Latin	The "pharmacological terminology and medicine." To possess the ability to correct spelling of a drug Latin, according to the grammar. Have knowledge about the end of the genitive case of nouns and adjectives, different cancellations for writing out the drug: in recipes
Normal physiology	The "Physiology of the cardiovascular system" - to apply the knowledge from this section
Biological chemistry	To determine the role of certain enzymes (adenosine deaminase, phosphodiesterase, guanylate cyclase, etc.) in the cardiovascular system. Apply knowledge of this section, when considering the mechanisms of action of individual drugs
Pharmacology	Section "Pharmacology of drugs that affect the function of the cardiovascular system." Apply knowledge of this section, when considering the pharmacodynamics and pharmacokinetics of individual drugs

### 4. Organization of the content of educational material

#### DRUGS AFFECTING ON HEMOSTASIS

#### DRUGS DECREASING COAGULATION

##### 1. Anticoagulants drugs.

###### 1.1. Drugs of direct action:

a) unfractionated heparinum (*heparinum natrium*, *heparinum calcium*);  
b) low-molecular-weight heparines: *nandoparinum* (*fraxiparinum*), *dalteparinum* (*fragminum*), *enoxiparinum* (*claxanum*), *certopari-num-natrium* (*troparinum*), and similar synthetic drug - *fondapu- rinucs* (*aricstra*).

###### 1.2. Drugs of indirect action:

a) coumarine derivatives (*neodicoumarinum*, *warfarinum*, *syncumar*);  
b) indandione derivatives (*phenylinum*).

**Fibrinolytic drugs** - *streptokinatum*, *urokinatum*, and tissue type plas- minogen activator (t-PA): *alteplatum* (*actilise*), *tenecteplatum* (*metalise*).

##### Antiplatelets.

###### 3.1. Inhibitors of thromboxane A<sub>2</sub> synthesis:

a) cyclooxygenase inhibitors - *acidum acetylcysteinum*;  
b) cyclooxygenase and thromboxanesynthetase inhibitors - *indobu- phenum*.

###### 3.2. Stimulators of prostacycline receptors - *epoprostenolum*.

###### 3.3. Drugs protecting ADP action on thrombocytes - *ticlopidinum* (*ticli- durri*), *clopidogrel* (*plavix*).

3.4. Drugs inhibiting phosphodiesterase - *Dipyridamolum* (*Curantilum*, *Persantinum*), *Pentoxiphyllinum* (*Agapurin*, *Trental*)

###### 3.5. Drugs blocking thrombocytes membranes glycoproteins II b/III a:

a) monoclonal antibodies - *Absiximabum*;  
b) synthetic blocker glycoproteins II b/III a - *Eptifibatidum* (*Ag- grastatum*), *Tirqfibanum* (*Integrilinum*).

##### Anticoagulants

**Heparinum** binds to antithrombin III and induces a conformational change that accelerates the interaction of antithrombin III with coagulative factors. *Heparinum* also catalyzes the inhibition of conversion prothrombin in thrombin, fibrinogen in fibrin. It gives negative charge to vessel and brakes aggregation to adhesion. *Heparinum* improves coronary vessels circulation. It exerts an antilipemic effect by releasing lipoprotein lipase from endothelial

cells. *Heparinum* decreases platelet and inflammatory cells adhesiveness to endothelial cells, reduces of platelet - derived growth factor, inhibits tumor cell metastasis, exerts an antiproliferative effect on several types of smooth muscle. Low molecular-weight heparins depress activated Stuart-Prauers factor more than protrombinum and act longer.

**Therapeutic use:** *Heparinum* is used for prophylactic and treatment of vein thrombosis, lung artery thromboemboli, unstable angina pectoris, and myocardial infarction.

**Adverse effects** are: Hemorrhage, subdural hematoma, acute hemorrhagic pancreatitis, hemarthrosis, wound ecchymosis, thrombocytopenia, hyper-sensitivity reactions (rash, urticaria, pruritis, fever, alopecia, hypoadosteron-ism, osteoporosis, ostealgia. *Protamini sulfas* is heparinum antagonist.

**Drugs of indirect action.** These drugs are vitamin K antagonists. Oral anticoagulants block epoxide reductase and creation of active form of vitamin K. They have anticoagulant effect and are used for prophylactic of thrombosis.

**Adverse effects:** hemorrhage, diarrhea, small intestine necrosis, urticaria, alopecia, skin necrosis, purple toes, dermatitis.

### **Fibrinolytic Drugs**

**Mechanism of action:** *Streptokinase*, *urokinase*, and t-PA all facilitate the conversion of plasminogen to plasmin. Plasmin is fibrinolytic. *Streptokinase* acts indirectly, because it must interact with plasminogen to transform it into plasmin.

Because t-PA is more selective than the kinases, it has a high affinity for fibrin and induces the degradation of plasminogen to plasmin only in the presence of fibrin. *Alteplase* (actilise), *tenecteplase* (metalise) have direct mechanism of action.

**Pharmacokinetics:** The plasma half-life of t-PA is 5 minutes, compared to 16 minutes for *urokinase* and 23 minutes for *Streptokinase*.

**Therapeutic uses:** t-PA, *Streptokinase*, *urokinase* have comparable efficacy in the reduction of mortality and improvement of left ventricular function. Drugs appear most effective when given less than 3 hours after the onset of symptoms. Thrombolytic therapy begins as soon as possible after the onset of symptoms of myocardial infarction. *Streptokinase* is given by intravenous or intracoronary infusion. *Urokinase* is infused into the occluded coronary artery. Drugs of t-PA are given by intravenous administration only.

**Adverse effects and contraindications.** Serious bleeding can occur; most important gastrointestinal and intracranial hemorrhages are possible. *Streptokinase* can cause anaphylaxis. With any thrombolytic agent, cardiac arrhythmias can occur upon reperfusion of the occluded vessels. Contraindications to the use of thrombolytic agents include internal bleeding, cerebral vascular accident, recent intracranial or intraspinal trauma, or surgery, known bleeding diathesis, or severe uncontrolled hypertension. Any

condition in which bleeding would be a significant hazard is a relative contraindication and calls for a careful risk-benefit analysis before using thrombolytic therapy.

### **Anticoagulants of direct action.**

#### **Heparin**

**The mechanism of the action.** Heparin presents itself mixture acid mucopolysaccharides, which are worked out in organism by mast-cells. The biological activity of heparin depends from inhibitor plasmatc proteases antithrombin III. Antithrombin III is cofactor of heparin. Antithrombin III induce inhibition of coagulate factor of proteases. Herewith heparin forms along with coagulate factor euvimolar stable complexes. Heparin intensifies this reaction in thousand once. Molecules of heparin link with antithrombin III and cause structured changes of this inhibitor. These structured changes promote the best interaction its active centre with proteases. Heparin causes acceleration of antithrombin-protease reaction. Herewith heparin is not spent. After forming antithrombin-protease complex, heparin is chipped off from it. Hereinafter heparin is used for new reaction.

Anticoagulate action of heparin reveals itself due to braking I, II and III phases of the coagulation of blood. The main effect of heparin is denominated antithrombin effect. In normal condition it provides before 70% of antithrombin function of blood. Heparin promotes also absorptions of thrombin on fibrin and conversion thrombin in inactive metathrombin. Antithromboplastin action of heparine is connected with braking of the activities of II, V, IX, X, XI, XII factori of coagulation of blood. Formation of active thromboplastin is broken. Due to this heparin prevents transition of fibrinogen in fibrin. Besides of, heparin prevents the aggregations of thrombocytes.

Ester-sulfate groups of heparin will add the molecule of strong negative charge. This negative charge creates the electric negative charge in vascular wall and prevents intracellular creation of thrombi.

Heparin has also antisclerotic effect. The preparation reduces the activity of lipoprotein lipase. This ferment reduces the level of chylomicron in plasma of blood. Besides of, heparin reduces the level of cingival holesterin and beta-lipoproteins in plasma of blood, especially in V type of hyperlipidemia.

The preparation also dissolves the холестериновые stone in bilious bubble. Heparin has an antagonism to serotonin and histamine. The preparation reduces the activity hyaluronidase and holds up the reaction of the interaction antigen-antibody. Heparin reduces the activity of proteins of system of complement and suppresses interaction between T- and B-lymphocytes. Due to this heparin possesses the anti-inflammatory, anti-allergic and immunosuppressive action. Heparin renders also antidystrophic and antihypoxia action too. It raises the intensity of the processes oxide phosphorylation. Due to this metabolism improves in vascular wall, the marrows and other tissues. Heparin causes increase of action of the insulin and other antidiabetic agents. Thereby, preparation promotes

the development of hypoglycemia.

Besides of, heparin renders diuretic action. The person of attention deserves the ability of heparin reduce the vascular tone and increase dilatation of resistive vessels. This brings about to reduction of the arterial pressure, particularly in sick with sclerotic hypertension.

#### **Pharmacokinetics.**

Heparin is used intravenously, subcutaneously, endolumbal (intratecal). Heparin may be useful for realization of electrophoresis. In case of intravenous administration the coagulation of blood is slowed immediately after injection. In case of subcutaneous administration delay of coagulation is observed after 40-60 minutes after injection. After inhalation maximum effect is reached after 18-20 hours. Anticoagulant effect lasts 4-5 hours after intravenous administration of preparation, 12 hours - after subcutaneous administration and up to 2 weeks after inhalation administration.

The preparation is used intravenously 4-6 times a day, subcutaneously administration – 2-3 times (sometimes 6 once per day). It is necessary to emphasize that subcutaneous administration of heparin is used in area of the higher part of the belly, in subcutaneous pleat, strictly perpendicular. Herewith the condition for ensuring the maximum absorbtion of heparin is created. In case of wrong administration heparin can be decay by sulfatases of tissues. It is important to note that heparin with little molecular mass has greater bioavailability after subcutaneous administration, than standard heparin. Its bioavailability is nearly 100%. Standard heparin has bioavailability 30%. Alveolar macrophages seized heparin in the case of aerosol way of administration of heparin. In these cells is created depot for long-lasting arrival of the preparation in blood. Numbers of times of administration of preparation in case of aerosol way of administration are 2-3 times a week.

In blood it is observed linkage of heparin basically with lipoproteins and also with fibrinogen, microglobulines and albumin. Standard heparin has a more low degree of the collecting with proteins of the plasma of blood in contrast with nonfactious heparin. The volume of distribution of heparin varies from 40 to 100 ml/kgs. Standard heparin does not get through placenta and in milk of nursing mothers. So if it is need heparin can be administrated in pregnant and nursing mothers

Heparin intensive is seized by endothelium cells, as well as cells of reticuloendothelium system. Heparin concentrates in liver and spleen. Than more accumulation of heparin in these cell, that is more so expressed and long-lasting its antithrombotic effect. Heparines with little molecular mass are better accumulated in cells of liver and spleens. So these heparines are more efficient, than standard heparin. Duration of the action of heparins with little molecular mass is more, than standard heparin. In this connection heparins with little molecular mass are used 1-2 times a day.

Heparin is subjected by disulfatations in result of influence nitrosulfamidase, which comes in all tissues easier, as well as under influence heparitinase of thrombocytes. Molecules with high molecular mass, which were formed, under influence endoglycosidase in liver is changed in fragments with little molecular mass, which are extracted with urine. Standard heparin can be eliminated by kidneys and in unchanged type only in case of intravenous administration of high doses of preparation. The half-life period of standard heparin forms nearly 90 minutes (in newborns its forms 35 minutes). In heparin little molecular mass this period is in 2-4 times more.

#### **Dosage**

The concentrations of heparin, exceeding level 0,2 ED/ml, usually prevent the development of pulmonary embolism in sick with installed diagnosis of the venous thrombosis. Such concentrations of heparin cause increase of the velocity of coagulation of blood in 2-2,5 times in contrast with checking value. This level (or degree) anticoagulant effect will be saved unchangeable during of the wgingival hole process of intravenous infusion of heparin. Herewith saving of corresponding of concentrations of heparin in plasma blood is observed. In case of fractional administration of preparation it is need to measure the velocity of coagulation of blood after each 3-3,5 hours after the next administration of heparin. This is realized in connection with necessary of need of correction of following dose heparin, providing lengthening of velocity of coagulation of blood in 2-2,5 times in contrast with checking value.

Heparin is absorbed badly in case of orally administration or sublingual administration and so it has a little efficacy after using such ways of administration. However, heparin is adsorbed well after subcutaneous administration.

Administration of heparin in the manner of aerosol in dose 10000-20000 units of action are used seldom, since in such way of the administration does not manage to reach "medical" level hypocoagulation. In case reaching in the general blood-stream heparin practically does not link with proteins of plasma, however it possesses the big relationship with lipoproteins of low density, globulins and fibrinogen.

#### **Schemes of the administration**

Intravenous infusion of heparin is realized in the following order: in the beginning of administration of heparin intravenously must be administered 5000 before 10 000 units of action of heparin, but then it is need to continue infusion at the speed of 900 units of action/hour or 10-15 units of action/kgs during hour. Usually, such dosages provide the lengthening of velocity of coagulation of bllood in 2-2,5 times in contrast with checking value. Patient with sharp pulmonary embolism are usually required else more high doses for the first days of the treatment, because of raised clearance of heparin during this period. In case of fractional administration of heparin it is necessary to administer 75-100 units of action/kgs each 4 hours usually. In case of subcutaneous administration of heparin heparin must be administered usually in dose 5000 units of action each 8-12 hours. Heparin does not

administer intramuscularly never, because of danger of the development hematomas in place of the administration of heparin(!).

#### **The undesirable effects.**

1. Hemorrhage's can be result of overdosing of heparin or in case of raised sensitivity to heparin. For eliminating the overweening effect use its antagonist - protamine sulfate. This preparation is used as infusion slowly (5000 IU of protamine sulfate is neutralized by 50 mg of protamine sulfate – 5 ml 1% solution) during 10 minutes. Thanks to administration of protamine sulfate the non-specific allergic reactions (redness of facial area, hives, pains in region veins, pain in area of breastbone, in the area of belly (abdomen), fever) can develop. However, more dangerous are complications, which are caused by liberation of thromboxane A2. Increase the liberation occurs in consequence of influence of the complex using of heparine together with protamine sulfate. The liberation of thromboxane A2 occurs in the first minute after intravenous administration protamine. As a result of liberations thromboxane A2 occurs increasing of the arterial pressure in vessels of right ventricular circle. Beside of, it is observed progression of right ventricular insufficiency, increases system hypotension.

As antagonist heparin are used also synthetic preparations: toluidin blue or ubicvin. First agent is not enough efficient. The second preparation is toxic. Ubikvin causes the defeat of renal tubes.

It is need to emphasize that administration of heparin is factor risk of the bleeding and requires the determinations of time of coagulation of blood before each injection. Besides of, is a necessary observation for early sign hemorrhagic syndrome (the study of the urine on erythrocytes, excrement - on latent blood – Gregersen reaction). It is necessary to remember that heparin has small width of the therapeutic action.

2. Thrombocytopenia. 2 types thrombocytopenia are distinguished. These are thrombocytopenia are caused by heparin. So, for 2-4 days of the treatment by preparation, transitory moderate thrombocytopenia (more than  $100 \times 10^9/l$ ) can appeared. Hereinafter such transitory thrombocytopenia is disappeared, in spite of continuation of the administration of preparation.

After 6-12 days of the treatment by preparation transitory moderate thrombocytopenia of second type can be appeared. This thrombocytopenia has grate hazardous for life. Its mechanism is connected with formation antibodies (G and M). These antibodies cause the aggregation of thrombocytes with liberation of them factor of the aggregations (adenosine triphosphat, thromboxane A2, serotonin and other). It is possible development thrombosis (the syndrome of the white clot) caused by heparin. This thrombosis can bring about appearance embolism, including in coronary vessels, kidney and pulmonary vessels. During 1-2 days before arising of the second type thrombocytopenia in patient with is hemorrhagic affection can be observed. This is connected with thrombosis of small vessels. The pains in the area of belly and in lower part of back can be appeared also.

As from 5-6 days of the administration of heparin it is necessary to check constantly the amount of thrombocytes, as well as duration of the bleeding, which must not increase in contrast with initial level in 2-3 times more then.

Should be taken in account that heparins with low molecular mass cause in rare cases appearance of hemorrhagic affection and thrombocytopenia of second type, since on them nearly are not worked out antibodies.

3. Dyspeptic frustration (the sickness, retching, anorexia, diarrhea).

4. The Allergic reactions (the hives, skin itch, myalgia, arthralgia (arthrodynamia, joint pain).

5. Osteoporosis and calcification of soft tissues. The clinical signs of osteoporosis can appear under long using of heparin in 6 months and later from begin treatments and they be expressed in reduction of the mass of the body, backache and loin, aptitudes to fracture. Osteoporosis is in result of bounding of calcium by heparin and fat acids, which are formed under influence lipoprotein lipase and activations of parathormone.

6. Local (less generalized) alopecia and/or blanching hair.

7. Rethrombosis is appeared in result of wrong administration of heparin (too quick or premature). In this case it is reasonable cancellation of heparin on background administration of indirect anticogulants. Hereinafter, it is need reduce gradually the dose of heparin. It is need gradually enlarge the intervals between administration of heparin.

#### **The indication for using.**

1. Thrombocytopenic purpura, violation of brain circulation. Should be taken in account that using of heparin in the first hours and days after appearance of ischemic insult is limited by two main mechanism: progressing current stroke (as a rule, in consequence of growth of atherosclerotic process) and cardio-cerebral embolism. The indications for administration of heparin is steadfast high pressure (above 180 mm Hg or, on the contrary, significant its reduction, comatose condition, epileptic attack, severe liver diseases, kidneys diseases, peptic ulcer of the stomach and duodenum, and different hemorrhagic manifestations).

2. Syndrome of disseminative intravascular coagulation of I stage.

3. The preventive maintenance venous thrombosis and embolism in patients with prosthesis of valves of heart, angina pectoris, myocardium infarction, atrial fibrillation.

4. Realization of extracorporeal hemodialis and hemosorbition.

5. The festering meningitis (under this pathology contents of heparin decreases in spinal fluid and increases the level of proteins (в том count;calculate;list фибриногена), серотонина, different ferment that leads to некротическим changes to shell and to formation blood clod in container of the brain. In case of endolumbal (intratecal) administration of heparin it links and cause inactivation of the ferments, and it reduces the frequency of the neurological complications.

Heparin may be administered for treatment of the rheumatism, hyperaldosteronism, bronchial asthma, for improvement kidney blood flow and for increasing of diuresis under sharp nephritis, as well as for parenteral nutrition of the power supply born prematurely newborn (for improvement of the assimilation of fat).

Cancellation of heparin must be realized gradually. In period of the cancellation the preparation it is need to administered indirect anticoagulants, for instance varfarin.

It is produced in flacons, contains 5 ml of solution of the sodium salt heparin, containing 5000, 10 000 and 20 000 international units in 1 ml.

#### **Fibrinolytics. Fibrinolysin**

Fibrinolysin is produced from III fraction of placenta serum of blood. After extraction from it of gammaglobulin from this serum it is processed by the small doses of trypsin. Fibrinolysin has the structure of globulin, its molecular weight hesitates from 75000 to 12000 Dalton. The molecule of fibrinolysin consists of two amino acid chainlets. Composition and distributing of amino acid is similar to trypsin and chymotrypsin, for this reason these preparations are also attributed to one group.

**Pharmacodynamics.** In the generally accepted doses (40000-200000 IU) fibrinolysin renders the outward lysis of blood clot in the first clock after his creation. It is conditioned to those that administered from outside fibrinolysin is neutralized by antipain (alpha-2- antipain, alpha-1- antipain, alpha-3-macroglobulin by antithrombin III). Calculations are shown, that for creation of surplus of fibrinolysin doses are needed, in 1,5 times the exceeding generally accepted daily doses. Administration of fibrinolysin in such doses is not used, because it results in the sharp increase of frequency of hemorrhagic side effects.

**Medicinal forms.** It is produced small bottles containing for 10 000, 20 000, 30 000 and 40 000 units of action of fibrinolysin.

**Therapeutic using.** In patient with acute myocardium infarction this preparation is used in dose from 20 000 to 60 000 IU. In thromboembolism of branches of pulmonary artery it is used in dose from 80 000 to 100 000 IU. .

**Side effects.** The hemorrhagic side effects of fibrinolysin are related with combine treatment together with heparin. This side effect is removed after administration of protamine-sulfate. Now and then it is necessary to add 100-200 ml 5 % solution of aminocaproic acid, and in especially heavy cases may be used 100-200 ml fresh conservator blood.

Side effects can show up also as pains in breastbone and in stomach, by hyperemia of person, palpitation, nausea, vomiting, falling of arterial pressure, chill, increase of temperature to 40°C both during infusion and after 1-2 hours after ending of infusion. The pyrogenic reaction, as a rule, arises up after infusion and well terminate by narcotic analgetics, antihistaminic agents. Quite often it is observed phlebitis of veins. Development of allergic reactions of 1-th type is possible: hives, Quincke edema, spasm of bronchi, anaphylaxis.

#### **Streptolysa**

**Pharmacodynamics.** It is indirect by the activator of fibrinolysis. At first in a blood, streptolysa operates as proactivator of plasminogen. In result of activation of plasminogen is observed, whereupon plasminogen (profibrinolysin) transforms in plasmin (fibrinolysin). Streptolysa accelerates the lysis of blood clots, influencing not only on their surface but also penetrating inward.

**Pharmacokinetics.** After intravenous administration of streptolysa it has undergone inactivation quickly in result of interaction with antibodies present in human organism. These antibodies are accumulated in result of staphylococcus infections. It is distributed from a vascular bed in interstitial liquid, lymph, tissues of liver. Preparation does not penetrate over the placenta hurdle. It is observed excretion with urine during one day (up to 40%).

**Medicinal using.** Streptolysa is administered for treatment thrombosis of vessels of low extremities, myocardial infarction, ischemic stroke. For treatment of thrombosis of vessels of low extremities it is used in dose 500 000 IU. For treatment myocardial infarction streptolysa is used in dose 750 000 IU as infusion. It is possible repeat administration of this agent in the same dose.

**Side effects.** Allergic reactions, fibrinolytic bleeding, the danger of which sharply increases in case of combine administration together with heparin.

#### **Streptokinase**

Other patent names are: Streptase, Avelysin, Tselyase

Streptokinase is the protein. Material for synthesis of streptokinase is  $\beta$ -hemolytic streptococcus of group C. It interact with proactivator of plasminogen. This enzyme complex accelerate the process of transformation of plasminogen in active plasmin. Thus streptokinase does not possess own ferment activity.

Depending on the dose of streptokinase plasminogen can transform in a blood mainly in activator of plasminogen (large doses) or in plasmin (small doses). The active complex (streptokinase + plasmin) operates not only on plasminogen, located on a blood clot, but also on plasminogen, which circulate in a blood stream. In result of this development of high level of plasmin in plasma of blood is observed and can cause breaking up of fibrinogen and fibrin, that can result in the end in rapid diminishment of concentration of fibrinogen on 40% and more from initial level (up to afibrinogenemia). The fibrinolytic effect of streptokinase is observed during 36 hours after administration of this agent. In result it promotes the decline of viscosity of blood, stipulates positive action of preparation yet to beginning of destruction of blood clot.

**Medicinal using.** Streptolysa is administered for treatment thrombosis of vessels of low extremities, myocardial infarction, ischemic stroke. For treatment of thrombosis of vessels of low extremities it is used in dose

500 000 IU. For treatment myocardial infarction streptolydase is used in dose 750 000 IU as infusion. It is possible repeat administration of this agent in the same dose.

**Side action.** The protracted administration of streptokinase causes destruction of blood microthrombs and development of stasis of blood because of decrease of level of fibrinogen. Thank to this it is observed accumulation in the blood of products of degradation of fibrinogen. That is why it is observed development of the states reminding a syndrome of disseminative intravascular coagulation.

#### **Antiplatelets**

Platelet aggregation is the most defense mechanism against leakage of blood from circulation. The antiplatelets must remove thromboxane A<sub>2</sub> ADP action, increase level of cAMP in thrombocytes, decrease Ca<sup>2+</sup> concentration, block thrombocytes membranes glycoproteins II b/III a. These drugs are used for prophylactics of myocardial infarction, instable angina, for prophylactics of insults thrombosis, in case of angioplastics etc.

*Acidum acetylsalicylicum* inhibits platelet aggregation and prolongs bleeding time. It acetylates and irreversibly inhibit cyclooxygenase (primarily cyclooxygenase I) both in platelets, preventing the formation of thromboxane A<sub>2</sub> and endothelial cells, inhibiting the synthesis of prostaglandin I<sub>2</sub>. *Ticlopidinum* and *dopidogrel* are structurally related drugs that irreversibly inhibit platelet activation by blocking purinergic receptors for ADP in the platelet membranes. This action inhibits ADP-induced excretion in platelet membrane GPII b/III a and fibrinogen binding to activated platelets. Abciximab, eptifibatide, tirofiban interrupt the interaction of fibrinogen and Von Willebrand factor with the platelet GP II b/III a complex.

#### **DRUGS INCREASING COAGULATION**

##### **1. Coagulants (hemostatics).**

1.1. For local applications - Spongia Haemostatica with ambenium; talc (collagenum, fibrinogenum, thrombinum, aprotininum, riboflavinum).

1.2. For systemic application - vitamin K, calcium chloride, calcium gluconate; drugs of coagulation blood factors - factor IX (Amafrix, imminum); factor VII (Novosevenum), factor VIII (Immunatum, Ergopraecipitatum siccum), protamini sulfas.

##### **2. Aggregants.**

##### **3. Fibrinolysis inhibitors.**

3.1. *Aprotininum* (Contrycalum, Trasylolum, Gordox).

3.2. *Acidum aminocaproicum* (Pamba, Ambenium), *Acidum tranexamicum* (Cyclocapronum).

**Etamsylatum (Dicenonum)** has platelet and angioprotective properties, decreases hemorrhage time, capillaries permeability, increases quantity and physiological activity of thrombocytes.

**Therapeutic use** - hemorrhage after surgical operations, hemorrhage diathesis, other hemorrhages in urology, gynecology etc.

**Contrycalum (Aprotininum)** inhibits plasmin and other proteolytic enzymes (trypsinogenum, trypsinum).

**Therapeutic uses:** fibrinolytic hemorrhage.

**Adverse effects:** hypotension, tachycardia, nausea, vomiting, allergic reactions.

*Acidum aminocaproicum* is conjugated with plasminogenum, inhibits its transformation into plasminum.

**Therapeutic uses:** fibrinolytic hemorrhage.

**Adverse effects:** hypotension, bradycardia, arrhythmias, dizziness.

#### **Procoagulants**

1. **Adroxon** (ampoules for 1 ml 0,025% solution). It is the product of oxidation of adrenalin. Promotes contractility and resistivity of walls of capillaries, reduces their permeability. In the arterial bleeding this preparation is non-effective. Adroxon does not have influence upon arterial pressure and coagulation of blood. Adroxon is used in parenchymatous and capillary bleeding, which is conditioned by traumas of operations on nose, in the cavity of mouth, after extraction of teeth, at the gastric and intestinal bleeding. Preparation is applied in dose 1 ml 0,025% solution i/m or i/v in the evening on the eve of operation, in time or after an operation, in case of the gastric and intestinal bleeding. Preparation is used intravenously or intramuscularly in dose 1-3 ml in daily dose in combination with other hemostatic agents locally by imposition on gauzes, serviettes or tampons, moistened by 1-2 ml 0,025% solution of adroxon. It is possible this simultaneously using pre to apply locally and perenteral administration.

**Side action:** absent. It is possible to use in combination with other hemostatic preparations of common and local action.

2. **Protamin sulfate.** (small bottles, containing 5 ml 1% solution, ampoules at 2 and 5 ml 1% solution). Preparation of protein origin is produced from sperm of different types of fishes (mainly salmon). Preparation is contained from arginin, prolin, serin, alanin and other amino acid. Protamin sulfate has specific anti-hemorrhagic action in the case of overdose of heparin. For neutralization 1 000 IU of heparin it is necessary to enter 1 ml of protamin sulfate.

Activity of preparation is expressed in international units. In 1 ml 1% solution contained no less than 750 international units. a 1 mg neutralizes approximately 85 IU of heparin (for neutralization 100 IU of heparin in 15 minutes after introduction 0,1-0,12 ml is required 1% solution of protamin sulfate).

Preparation is entered intravenously stream or intravenously tiny by good control of time of coagulation of blood and other indexes of coagulogram of blood.

Normal indexes of coagulogram of blood:

1. Bleeding in accordance with Li-White – 5-10 minutes.
2. Duration of time of recalcification plasma of blood – 120 seconds
3. Tolerance of plasma to heparin – 7-13 minutes.
4. Protrombin index – 80-100%
5. Fibrinogen of blood – 2-4 g/l

**6. Partial activated prothrombin time – 35 seconds**

Intravenous administration of protamine sulfate is realized slowly at the rate of 1 ml during 2 minutes. In case of necessity an injection repeat with an interval 15-30 minutes. The general dose of preparation makes 5 ì.

After administration of protamine sulfate allergic reactions are possible, in particular hives. In this case it is need to use antihistaminic preparations.

**3. Vikasol.** Sprinkles of snow and pills for 15 mgs. Ampoules for 1 мл 1% solution. Preparation is the analogue of vitamin of Ê. Vikasol is specific remedy in bleeding, related with low maintenance prothrombin in blood. The action of preparation shows up in 12-18 hours after introduction to the organism. Vikasol is used at паренхиматозных and capillary bleeding. Vikasol is used also for treatment of hepatitis and treatment of radiation illness.

Preparation is used orally in dose 15 mg 3 times per day. It is used intramuscularly in dose 1 ml 1% solution.

Daily dose for adult's makes 0,015-0,03 g orally, in case of intramuscularly administration – 0,01-0,015 g (1-1,5 мл 1% solution).

Preparation is administered during 3-4 days. And then must be break during 4 days. Before the operations of vicasol is recommended using of this preparations during 2-3 days prior to operation.

Contra-indications for using of vicasol are the promoted coagulating of blood and thrombolism.

In the case of development of bleeding in the end of тромболической therapy it is necessary to use inhibitors of fibrinolysis:

1. Epsilon aminocaproic acid (amicor) is used in dose 100 ml 5% solution is administered intravenously during 30 minutes. Then preparation is used in a dose 1 g/hour.

2. PAMA (PAMBA, gumbixs, streptosolut) possesses small toxic effect. Preparation in accordance with the pharmacological properties excels antifibrinolytic activity excels in 3 times excels Epsilon aminocaproic acid. Preparation is used intravenously in dose 1-1,5 g 3-4 times per day

3. Aprotinin (trasilol, contrical) Preparation is inhibitor of proteolytic enzymes and fibrinolysis. Preparation is used as infusion in a dose 300 000 international units.

**EMERGENCY CARE IN BLEEDING**

Serious danger for life can present the massive bleeding at traumas, pathology of respiratory tracts, stomach, intestine, and uterus. Severe form of violations of hemostasis, developing as a result of to considerable bleeding, is *hemorrhagic shock*. Severity of clinical displays in such conditions depends on velocity of bleeding, its volume, duration, and also expressed of compensate reactions of organism. In bleeding it is observed disorders of hemodynamic (diminishing of the cardiac out-put, arterial pressure, appearance of arrhythmia, violation of microcirculation in tissues and other), violations of the external breathing, hypoxia, changes of coagulation of blood and other pathological changes. In patients it is observed pallor of integuments, drop in the temperature of extremities, death damp, anxiety, stupor, is observed.

*Urgent care* includes the immediate stopping of bleeding (finger pinning of bleeding vessel, application of plait, pressing bandages). In bleeding from small vessels it is possible to fall back to upon tamponade of wounds, to imposition of pressing bandage through which most bleeding can be stopped in case of wounds of jaw-facial area.

In case of presence of the large wounds trunks of external carotid artery, the first aid is temporal stopping of bleeding (finger pinning, imposition of pressing bandage). First medical aid in case of stopping of bleeding carried out in-patient either by bandaging of vessels in a wound or with help tight tamponade wound. In severe bleeding from the "mouth cavity" the stopping with help traditional method of treatment is impossible, a doctor must make urgent tracheotomy and realize tightly tamponage of mouth cavity and pharynx.

In case of the final stopping of bleeding, which is not terminate in early period or arising again out of large vessels, when it is not succeeded to bandage vessel in a wound in its revision, make bandaging of outward carotid on the proper side in surgical, jaw-facial or trauma of departments of hospital.

For the stopping of the external bleeding hemostatic agents are used widely. Thrombin is most effective as thrombostatic agent for external using. 125 IU of thrombin is dissolved in sterile isotonic solution of sodium of chloride and moisten them the tampons of gauzes and bandages for imposition on a bleeding surface. Effect is rapid, in 3-5 minutes. After that, bandage can be avoided. In proceeding of bleeding a bandage is again laid on. Thrombin can be used for termination of bleeding from the overhead department of gastrointestinal tract. Before administration of thrombin sodium hydrocarbonate must be given preliminary. **It is impossible intravenous administration of thrombin!** Hemostatic sponges from native plasma is applied locally. Thromboplastin and fibrin tape are used also. A bleeding surface is dried out and after that hemostatic sponge (pieces of hemostatic sponges must be grinding up preliminary) upon this surface. Termination of bleeding is used also the special antiseptic sponge, containing penicillin and furacillinum, antiseptic candles, bioplastic). Bioplastic, and also hemostatic fibrin tape is recommended before application to saturate with solution of thrombin.



The dose of the using preparations is depended from massiveness of bleeding. In incessant bleeding in result of using of local preparations bleeding, preparations with common hemostatic action must be used. These preparations are most effective and safe in bleeding, related to violations in the system of physiological hemostasis.

#### **HYPOLIPID MEANS**

Atherosclerosis - most extended disease among the inhabitants of the developed countries. The doctors of any profession are encountered with this illness (both basic and associating). Change in the means of life (emotional overvoltage, nourishment, motoring) - the most urgent actual task in the preventive maintenance of atherosclerosis. In connection with this that not refuted, together with the social measures, there is a role of medical preventive maintenance. The contemporary means of braking atherogenesis in the arteries (angioprotectors) contain the large group of the preparations, which influence the lipid exchange, the free-radical oxidation of lipids and proteins and the processes of microcirculation. Hyperlipemia (hyperlipoproteinemia) is the most investigated factor of the development of atherosclerosis, which causes one of the primary pathologic processes in the vascular wall - lipid infiltration of the intima. According to the contemporary ideas, the cholesterol, which settles on the structures of the intima, is reached in the composition of  $\beta$ - of lipoproteins (lipoproteins of low density) and pre-  $\beta$  - the lipoproteins of the plasma of the blood (lipoproteins of very low density). Alphaslipoproteins (macromolecules from the high density) capable "of carrying" cholesterol from the arterial wall, and therefore their high level in the blood prevents the postponement of lipids in the vessels. This became base for using the angioprotectors as hypolipid means. In the clinic widely used clofibrat (miskleron) and nicotinic acid. However, in their our time are used rarely because of those expressed the side effects: the formation of bilious stones, dyspeptic phenomena, rash and other. The preparations of the unsaturated fatty acids (linetol) together with the lithogenic action can also decrease the peroxide oxidation of lipids and even improve clinical state with the ischemic disease of the heart. Among the hypolipid means the side effects are expressed the smallest in inhibitors suction of cholesterol - preparations of saponin. Polisponin. It contains 17% of water-soluble steroid saponin, which connect in the bowels cholesterol and they prevent its suction. Polisponin assume on 1-2 tablets 2 times every 1 day after food. The cycle of the method of preparation is 20 days, then makes interruption to 10 days. Course of treatment - 2-4 months. Hypocholesterinemia effect is developed gradually. Side-line phenomena - sweating, disfunction of the organs of digestion, catarrhal phenomena in the upper respiratory tract - pass after the cancellation of preparation. The fact of the participation of peroxide mechanisms in atherogenesis became base for using the antioxidants as angioprotectors.

The substances, which inhibit the reactions of nonenzymatic free-radical oxidation of lipids and biopolymers - proteins, mucopolysaccharides and nuclein acids, are called antioxidants. The peroxide oxidation of lipids and proteins participates in the genesis of all basic humoral and morphological manifestations of atherosclerosis. The accumulation of lipids in the intima depends on two major factors - hyperlipemia and disturbance of the utilization of lipoproteins in the smooth-muscle cloths. Free-radical oxidation contributes to hypercholesterolemia, since peroxides of lipids in the cells of the liver disrupt the processes of transforming the sterols into the bilious acids. The autooxidation of the phospholipids of atherogenic lipoproteins decreases their ability to retain cholesterol. Peroxide oxidation disrupts the utilization of lipids in the arterial wall. Antioxidants respectively prevent the development of these processes. Free radicals, peroxides and aldehydes, being formed in the arterial wall, directly damage its structural proteins and ferments. Peroxides of lipids inhibit in the endothelium of vessels prostacyclin- synthetase - ferment, which forms the natural substance, which prevents the aggregation of thrombocytes - prostacyclin.

From the antioxidants the tocopherol widely is used in the clinic. It as lipid antioxidant is concentrated mainly in the cellular membranes. Inhibits reactions auto okislen in the microsomes of liver, it supports the physiological level of catabolism of cholesterol, prevents the peroxide decomposition of lipoproteins. Inhibiting free-radical processes in the wall of vessels, tocopherol prevents the destruction of elastic fibers, the precipitation on them of calcium ions, and also sclerous processes. Ascorbic acid, stimulating the transformation of cholesterol into the bilious acids, manifests hypolipid action. The hypolipid action of ascorbate depends on the time of the year, diet (entering into the organism of antioxidant- synergists), dose and initial state of lipid exchange. Bioflavonoids include the group of the substances, which contain in their structure several phenol hydroxyls, united by the name "vitamin R". Synergistic with ascorbate and by tocopherol bioflavonoids impede the peroxide mechanisms of atherogenesis, in particular the oxidizing depolymerization of mucopolysaccharides. Among the preparations of bioflavonoids rutin, quercetin, vitamin r. have the greatest value. Practically convenient of the combination of flavonoids with ascorbate - askorutin and the tablet of aronii of chernoplod with the ascorbic acid. Metilmetionin, is glutamic and lipoic of acid they contribute to raising the level of endogenous bioantioxidants in the blood and the cloths. Metilmetionin also increases the level of phospholipids in the blood and because of this is stabilized the level of lipoproteins, catabolism of cholesterol increases. The daily dose of glutamic acid in the tablets is 1,5-2 g. Metilmetioninsulfon chloride assigns on 2 tablets (0.2 g) 3 times every 1 day. Lipoic acid or lipamid - on 0,025 g of 3-4 times in 1 day. The duration of the course of treatment by indirect antioxidants is 1 month. To repeat course is possible through 1 mo. Side effects (dyspeptic disorders) in the case of using the doses named above are rarely. Komplamin (xantinola nicotinate) is simultaneously with the vasodilator and [antiagregantnym] effects capable to increase the antioxidant activity of cloths. It is expedient to assign by patient with the increased arterial pressure. The tablets of komplamin (0,15 g) assume 3 times in a 24 hour period for a period of 3-4 weeks. To the angioprotectors, which influence the thrombogenic mechanisms of atherogenesis, belong acetylsalicylic acid and heparin. Acetylsalicylic acid reduces the synthesis of cholesterol in the liver. The anti-aggregate properties of acetylsalicylic acid are connected with its ability to inhibit the synthesis of the

predecessor of thromboxane of  $\text{A}_2$ - of prostaglandin  $\text{PGE}_2$ . The anti-aggregate effect of acetylsalicylate is prolonged, it remains to 3-4 days. Its ability to simultaneously suppress formation in the vessels of prostacyclin- natural anti-atherogenic means is a drawback in the acetylsalicylate. Preparation is recommended with the increased aggregation of thrombocytes, especially if it is combined from hypercholesterolemias. Acetylsalicylate is assigned in the tablets, which assume after food, having ground well. The general course of preventive therapy lasts by 1-2 month. It is necessary to remember about the possibility of the appearance of a stomachic hemorrhage and allergic reactions. Preparation is contrasted with the stomach ulcer and duodenum. In heparin inherently many-sided antyaterosklerotiche action. Activating lipoprotein lipase, it contributes to reduction in hyperlipemia. Being connected with the atherogenic lipoproteins, it impedes their fixation by mucopolysaccharides of the intima of arteries. As straight anticoagulant it impedes the thrombogenic mechanisms of the development of atherosclerotic changes. Heparin is assigned hypodermically or it is intravenous in the isotonic solution of sodium of chloride on 5000 units of operation of 3 times on 6 weeks for period 1- of 1,5 months. Side effects it is not observed. Parmidin (prodictin), noticeably without influencing the level of lipids in the blood, prevents the reduction of the cells of the endothelium of arteries. As the antagonist of thromboxane of  $\text{A}_2$  of parmidin it inhibits the aggregation of thrombocytes and neutralizes his ability to suppress the release of lipids. Parmidin renders also antibradykinin action. Preparation is assigned on 2 tablets (0,25 g) 3 times in 1 day. In the case the appearance the side effects (skin allergic reactions, nausea, headache) daily dose descend or preparation abolish. Duration of the course of treatment - 2-3 months.

### **THE COMBINED THERAPY**

If therapeutic purpose is not reached with the aid of one preparation - the combined therapy can be used. The combined therapy has its advantages. This is - the possibility to treat mixed hyperlipemias, to avoid undesirable side-line actions due to the application of lower doses of each of the preparations, which are combined. Using the combined therapy, it is possible to avoid the undesirable changes in the lipid spectrum of the blood, by which the mono-therapy can be accompanied; with refractory hyperlipemias it is possible to reach the synergistic influence of preparations. Outstanding is also a question of the cost of the treatment: the preparation of significant cost (for example, the inhibitor of GMG-CoA- reductase) in certain cases can be successfully substituted with the combination of other preparations. There are also combined preparations etofibrat it, for example, contains in equimolar quantities of klofibrin and nicotinic acid. It is used at the dose of 500-780 mg/day and is decreased cholesterol by 25%. Cholesterol of the lipoproteins of low density does not change. The level of the triglycerides of blood serum is reduced to 50%. Skin rashes rarely are observed. The patients, who need the combined hypolipid therapy, must be directed toward the specialized departments.

### **Materials for students' self-directed work.**

#### **Tests for students' self-directed work:**

1. Expound classification of agents, acting upon hemostasis.
2. Expound the mechanism of action, anticoagulants of direct action.
3. Expound of sides effects of agents, influencing upon hemostasis.
4. Expound indications to using of agents, acting upon hemostasis.
5. Expound contra-indications and indications to using of agents, influencing upon hemostasis.
6. Expound testimonies to application and principles of choice of facilities, influencing upon hemostasis.
7. Expound classification and mechanism of action of antioxidants.
8. Expound testimonies to application and principles of choice of antioxidants.
9. Expound principles of application of facilities, влияющих on hemostasis in urgent situations.

#### **A. Tests for students' self-directed work.**

Name the pharmacological effects of heparinum.

Choose preparation, promoting coagulation of blood:

- a) thrombin;
- b) ketoprofen;
- c) promedol.

Choose preparation, lowering coagulation of blood (from the group of anti-plateletes):

- a) thrombinum;
- b) aspirin;
- c) erhythromycinum;
- d) ticlopidinum.

Name effective thrombolytic agents:

- a) actilise;
- b) fraxiparinum;
- c) fibrinilysine.

Name effective anticoagulant for treatment of peripheral thrombosis:

- a) actilise;
- b) fraxiparinum;
- c) fibrinolysinum.

Name antidote, applied at the overdose of heparin:

- a) thiosulfate of sodium
- b) protamine sulfate;
- c) atropine sulfate.

Define testis to using of agents, influencing on hemostasis.

Define contra-indication to using of agents, reducing coagulation of blood.

Choose an antioxidant for treatment of diseases of пародонта.

- a) tocopherol acetate
- b) thiamine bromide
- c) ergocalciferol

#### **B. Test for students' self-directed work.**

1. What preparation is appointed before operative interference during 3-4 days?
2. What preparation is applied for a stop by bleeding only locally?
3. What preparations for local using have hemostatic and antibacterial action?
4. What preparation is it necessary to use locally in capillary bleeding, related to the promoted permeability of vessels?

What preparation is it necessary to use in marginal wrinkle in pulpitis, parodontosis with the purpose of improvement of microcirculation and anti-inflammatory action?

What ointment preparation is necessary to use in complex treatment of ulcer-necrotic gingivitis?

What ointment preparation is necessary to administer in complex treatment of parodontitis?

Task 1. The diagnosis was placed to patient: atherosclerosis of coronary and cerebral arteries, the ischemic disease of heart, chronic coronary and cerebral deficiency. With the inspection: cholesterol - 6,5 mmol/liter (standard 5,2 mmol/liter), the peroxide hemolysis of erythrocytes 18% (standard 10%), fibrinogen into +++ (standard +). Determine the pathogenetic type of atherosclerosis, to appoint appropriate pharmacotherapy.

Task 2. To patient placed diagnosis atherosclerosis of coronary arteries, aorta, the ischemic disease of heart, cardiosclerosis atherosclerotic and postmyocardial infarction, obliterating endarteritis of lower extremities. With the inspection: cholesterol 10,2 mmol/liter (standard 5,2 mmol/liter), the peroxide hemolysis of erythrocytes 18% (standard 10%), fibrinogen into +++ (standard +). To establish the pathogenetic type of atherosclerosis, to appoint appropriate pharmacotherapy.

Task 3. To patient for neutralizing the action of heparin during the operation with the extracorporeal blood circulation was appointed protein preparation. What preparation was assigned and why?

Task 4. To patient with the stenocardia as addition to the basic therapy doctor appointed the means of anti-aggregation from the group of nonsteroid antipyretic means. What this for the means? At what dose it must assume its patient? Indicate the mechanism of the action of preparation.

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