

CLINICAL PHARMACOLOGY OF ANTI-ARRHYTHMICS, ANTI-ANGINALS, DRUGS USED IN HEART FAILURE, HEMOSTATIC AND ANTI-THROMBOTIC DRUGS

A. Actuality

The pathology of the cardiovascular system has held stable the first place for the last decades according to the indicators of morbidity, mortality and invalidation. The evolution of cardiovascular disease is complicated in most cases with acute or chronic heart failure, cardiogenic shock and sudden death.

The clinical pharmacology of drugs with an influence on heart function, hemodynamics, as well as on other organs and systems require a thorough study of these drugs.

The possibilities of treatment and prevention of arrhythmias have recently increased due to the use of new antiarrhythmic drugs. Knowing this compartment of clinical pharmacology will allow optimizing the pharmacotherapy of rhythm disturbances and improving the vital prognosis in cardiac patients.

The balance between the coagulant, anticoagulant and fibrinolytic systems determines the state of tissue circulation and metabolic processes. In most diseases and pathological conditions, the relationship between these systems is disturbed. Moreover, platelet aggregation, hypercoagulability with the formation of microthrombi cause serious complications, including death: embolism of the pulmonary artery, cerebral vessels, etc. To ensure an adequate tissue circulation, are used drugs with the action on the coagulant, anticoagulant and fibrinolytic systems.

B. Training aim

Learning and applying the principles of clinical pharmacology (pharmacokinetic and pharmacodynamic) to the individualization and optimization of the administration of drugs with an influence on the cardiovascular system (cardiotonic glycosides, non-glycoside cardiotonics, adrenergic cardiostimulators, antiarrhythmic, antianginal drugs, preparations with an influence on blood coagulability, the anticoagulant and fibrinolytic system and appreciation of their efficiency.

C. Teaching objectives

The student must have the ability to:

- a) choose methods of clinical and laboratory examination in order to assess the effectiveness of antiarrhythmics, cardiac glycosides, antianginals, antithrombotic and hemostatic drugs;
- b) analyze and evaluate the examination results of the pharmacodynamics of antiarrhythmics, digitalis, non-glycosidic cardiotonics and adrenergic cardiostimulators, antithrombotics and hemostatics;
- c) predict the possible complications and adverse reactions of the administered drugs;
- d) predict the dependence of adverse reactions on the dosage regime and the functional state of the heart and other organs and systems;
- e) apply contemporary methods of pharmacological correction of adverse reactions, caused by antiarrhythmic, cardiotonic and cardiostimulating, antithrombotic and hemostatic drugs;
- f) select the personal form (medicines P) in the respective states;

- g) predict the interaction between the drugs used in the treatment of heart failure, heart rhythm disorders and antianginal drugs;
- h) establish the main interactions of antiarrhythmic drugs, antianginal drugs with antithrombotic drugs and hemostatic drugs with other groups of drugs and the prediction of possible adverse reactions.

D. Knowledge of the medico-biological and clinical disciplines necessary for interdisciplinary integration:

Histology, anatomy, morphopathology, physiology and physiopathology. Anatomy and physiology of the cardiovascular system. The structure of the contractile muscle fiber. Histophysiology of excito-conductive tissue. The cellular and molecular bases of muscle contraction. Anatomy of the conduction system of the heart. Histophysiology of excito-conductive tissue. The role of sodium, potassium, calcium ions in the cardiac cycle. Coupling of excitation with cardiac contraction. Notions about alpha- and beta-receptors, the adenylate cyclase mechanism. The role of sympathetic and parasympathetic systems in the regulation of heart activity and hemodynamics.

Cellular components of blood. The links of the blood coagulation cascade. Anticoagulant and fibrinolytic blood system. The role of platelets in the coagulation process. Pathology of blood coagulation and fibrinolysis.

Clinical disciplines. Pathophysiological causes of heart failure. Functional classification (NYHA) and the clinical manifestations of heart failure. Paraclinical exploration in heart failure. The etiopathogenic and clinical peculiarities of the excitability, conductivity and contractility disorders of the myocardium in different diseases. The mechanisms of the occurrence of rhythm disturbances. The clinical and electrocardiographic significance of rhythm and conduction disturbances. Clinical, laboratory and electrocardiographic criteria of hypo and hyperkalemia.

CID syndrome (disseminated intravascular coagulation), etiopathogenesis, phases, forms and clinical manifestations. Common hemostasiogram indices and their deviation in pathologies accompanied by hypo- or hypercoagulation. Physiological anticoagulants (antithrombin III, proteins C and S).

Pharmacology. Classification of cardiotonic drugs: cardiac glycosides, non-glycoside cardiotonics and adrenergic cardiostimulators; mechanism of action, side effects, contraindications. Classification of antiarrhythmics. Action mechanisms of antiarrhythmics, beta-adrenomimetics and sympatholytics. Adverse reactions of antiarrhythmics.

Classification of hemostatic and antithrombotic drugs. Pharmacodynamics of coagulants, antifibrinolytics, anticoagulants, fibrinolytics, antiaggregants.

E. Questions for self-training:

1. Clinical pharmacology of drugs used in heart failure: drugs with influence on myocardial tone and with influence on pre- and post-load. Cardiotonic glycosides: classification according to latency and duration of action, peculiarities of the mechanism of action and pharmacological effects, indications, contraindications, adverse reactions, pharmacokinetic peculiarities of drugs.
2. Principles of administration of cardiotonic glycosides (digitalisation): rapid, moderate, slow. Maintenance treatment with tonic-cardiac glycosides. Clinical and paraclinical methods and criteria for assessing the effectiveness of cardiotonic glycosides. Symptoms and the mechanisms of the occurrence of cardiotonic glycosides poisoning. Typical changes on the ECG, their prophylaxis and treatment.

The particularities of the action of cardiotoxic glycosides in the association with various groups of drugs (antiarrhythmic, antianginal, diuretic, anticoagulant, antihypertensive).

3. Non-glycosidic cardiotonics (phosphodiesterase inhibitors): the particularities of the mechanism of action and pharmacological effects, indications and principles of use, adverse reactions and their prophylaxis, pharmacokinetics, drug interactions.

4. Converting enzyme inhibitors and angiotensin receptor blockers in heart failure: particularities of action, pharmacological effects, efficacy, principles of use.

5. Beta-adrenoblockers in heart failure: particularities of action, pharmacological effects, effectiveness, principles of use.

6. Diuretics in heart failure: particularities of action, pharmacological effects, effectiveness, principles of use. Competitive antagonists of aldosterone in heart failure: peculiarities of action, pharmacological effects, efficacy, principles of use.

7. The drugs that increase the sensitivity of the myocardium to calcium ions in heart failure: particularities of mechanism of action and pharmacological effect. Indications and principles of use, adverse reactions and prophylaxis. Pharmacokinetics.

8. The adrenergic and dopaminergic cardiostimulators: the particularities of the mechanism of action and the cardiostimulatory effect, the indications and principles of use, the adverse reactions and their prevention. Pharmacokinetics of drugs and drug interactions.

9. Clinical pharmacology of antiarrhythmic drugs (Williams classification):

- class I (IA, IB, IC) antiarrhythmics – sodium channel blockers; mechanism of action, indications, contraindications, adverse reactions, pharmacokinetics, interactions with other drug groups.

- class II antiarrhythmics – β -adrenoblockers; mechanism of action, indications, contraindications, adverse reactions, pharmacokinetics, interactions with other drug groups.

- class III antiarrhythmics – potassium channel blockers; mechanism of action, indications, contraindications, adverse reactions, pharmacokinetics, interactions with other drug groups.

- class IV antiarrhythmics – calcium channel blockers; mechanism of action, indications, contraindications, adverse reactions, pharmacokinetics, interactions with other drug groups.

- other groups:

a) drugs containing potassium - potassium chloride, parkam, panangin;

b) drugs containing magnesium - magnesium sulfate, etc.;

c) cardiac glycosides – digoxin, strophanthin;

d) M-cholinoblockers - atropine;

e) nucleoside analogs - adenosine.

Mechanisms of action, indications, contraindications, adverse reactions, pharmacokinetics, interactions with other drug groups.

10. Classification of antianginal drugs according to the mechanism of action.

a) Clinical pharmacology of nitrates and molsidomine: the particularities of the mechanism of action and of the antianginal effect, indications and principles of use, adverse reactions and log prophylaxis, pharmacokinetics.

b) Beta-adrenoblockers used as antianginals: the particularities of the mechanism of action and of the antianginal effect, indications and principles of use, adverse reactions and prophylaxis, pharmacokinetics.

- c) Clinical pharmacology of calcium channel blockers, used as antianginal: the particularities of the mechanism of action and of the antianginal effect, indications and principles of use, adverse reactions and their prophylaxis, pharmacokinetics.
- d) Drugs with other mechanisms of action, used are antianginal: potassium channel activators, bradycardia drugs. Peculiarities of the mechanism of action, pharmacological effects, indications and principles of use.
- e) Coronarodilators. The mechanism of action. Pharmacodynamic and pharmacokinetic peculiarities. Management tactics.
- f) Drugs with cardioprotective action (anabolic substances, antihypoxants, vitamins, antioxidants), used in the treatment of ischemic heart disease. Pharmacological and administration peculiarities.
11. The particularities of antianginal medication in patients with associated pathology (hypertension, cardiac arrhythmias, heart failure, bronchial asthma).
12. Drugs that reduce pre-load and post-load: classification, peculiarities of the mechanism of action and pharmacological effect, indications and principles of use, adverse reactions and their prophylaxis, pharmacokinetics of drugs and drug interactions.
13. Drugs with influence on hemostasis and fibrinolysis. Classification according to the mechanism of action, pharmacological effects and clinical use.
14. Anticoagulants with direct action: classification, pharmacodynamic and pharmacokinetic peculiarities of standard heparin and low molecular weight heparins, comparative characteristics, indications, dosing regimen and principles of use, contraindications, adverse reactions and their prophylaxis. The methods to verify the effectiveness and harmlessness of the direct anticoagulants administration.
15. Anticoagulants with indirect action: classification, pharmacodynamic and pharmacokinetic peculiarities, dosing regimen and principles of use, indications, contraindications, adverse reactions and their prophylaxis. The methods of verifying the effectiveness and security of the administration indirect anticoagulants. Antagonists of indirect anticoagulants. The principles of selection and rational use in stationary and ambulatory. Comparative characterization of direct and indirect (oral) anticoagulants.
16. Clinical pharmacology of antiplatelet (antiaggregant) agents: classification, particularities of the mechanism of action, indications, contraindications and adverse reactions, principles of selection and rational use.
17. Fibrinolytics: classification, pharmacodynamic and pharmacokinetic peculiarities, indications, dosing regimen and principles of use, contraindications, adverse reactions, prophylaxis and their treatment.
18. Classification of hemostatic drugs. Coagulants: the particularities of the mechanism of action, indications, contraindications and adverse reactions. The principles of rational selection and use.
19. Antifibrinolytics: classification, particularities of mechanism of action, indications, contraindications and adverse reactions, principles of selection and rational use.
20. Aggregants: the particularities of the mechanism of action, the indications, contraindications and adverse reactions, the principles of selection and rational use.
21. Hemostatics with local action: characteristics of vasoconstrictors, astringent and thromboplastinic drugs, indications, contraindications and adverse reactions. The principles of selection and rational use.
22. Drugs that improve blood rheology: classification, pharmacodynamic and pharmacokinetic peculiarities, indications and principles of use, contraindications, adverse reactions.

23. Angioprotectors: classification, pharmacodynamic and pharmacokinetic features, indications, contraindications and adverse reactions, principles of selection and rational use.

24. The particularities of the use of drugs with an influence on hemostasis, fibrinolysis during pregnancy, in pediatric and geriatric patients.

F. Individual work (the 1.1 and 1.2 sequences are to be done in writing form):

1.1. Indicate the pharmacological groups and drugs used in (for): acute heart failure; heart failure with pulmonary edema; chronic heart failure, NYHA class I and II; chronic heart failure, NYHA class III and IV; heart failure with hyperaldosteronism; chronic atrial fibrillation, tachysystolic form; paroxysmal atrial or junctional tachycardia; cardiogenic shock, heart failure in acute myocardial infarction; cardiotonic glycoside intoxication; arrhythmias due to cardiac glycoside intoxication; atrial extrasystoles; paroxysms of ventricular tachycardia; paroxysmal supraventricular tachycardias; ventricular extrasystoles; arrhythmias of sympathoadrenal origin; ventricular arrhythmias in patients with acute myocardial infarction; atrioventricular block; angina pectoris attacks; prophylaxis of angina pectoris attacks; stable angina pectoris; vasospastic angina pectoris; unstable angina pectoris; acute myocardial infarction; acute myocardial infarction with hypercoagulability, thromboembolic myocardial infarction, ischemic heart disease with arrhythmias; ischemic heart disease with hypertension; ischemic heart disease in patients with obstructive pulmonary diseases; acute coronary syndrome; epistaxis; hemorrhages during otorhinolaryngological surgeries; hypofibrinogenemia; hemophilia; hemorrhages due to overdose of direct-acting anticoagulants; hemorrhages due to overdose of indirect-acting anticoagulants; hemorrhagic disease of the newborn; hemorrhages due to capillary fragility; hemorrhages with hyperfibrinolysis; menorrhagia; hemorrhages due to fibrinolytic overdose; pulmonary artery thromboembolism; deep vein thrombosis; prophylaxis of thrombosis in surgical and obstetric interventions; diagnostic procedures on the heart and vessels; disseminated intravascular coagulation syndrome; atrial fibrillation in mitral valve disease and prosthetic valves; primary and secondary prevention of cerebrovascular and coronary events; obliterative endarteritis; transient cerebral ischemic attacks; heparin-induced thrombocytopenia.

1.2. Prescribe the following medications in their respective pharmaceutical forms, indicating the dosage regimen according to the respective pathology.

No.	Drug Name	Pharmaceutical Form; Dosage
1	Strophanthin	Solution 0.025% - 1 ml ampoules
2	Digoxin	Tablets 0.00025; Solution 0.025% - 1 ml ampoules
3	Captopril	Tablets 0.05; 0.025; 0.0125
4	Nifedipine	Tablets 0.01; 0.02
5	Enalapril	Tablets 0.005; 0.01; 0.02; Solution 0.125% - 1 ml ampoules
6	Lisinopril	Tablets 0.005; 0.01; 0.02

7	Bisoprolol	Tablets 0.0025; 0.005; 0.01
8	Trimetazidine	Tablets 0.035
9	Lidocaine	Solution 2%; 10% - 2 ml; 1%, 2% - 20 ml ampoules
10	Metoprolol	Tablets 0.025; 0.05; 0.1
11	Amiodarone	Tablets 0.2; Solution 5% - 3 ml ampoules
12	Verapamil	Tablets 0.08
13	Potassium chloride	Solution 4% - 10 ml; 15% - 20 ml ampoules
14	Sotalol	Tablets 0.08
15	Heparin	Solution 5000 IU/ml – 5 ml, 10 ml ampoules; Gel 1000 IU/g – 30.0; 50.0; 100.0
16	Nadroparin	Injectable solution in prefilled syringe 2850 IU Axa/0.3 ml; 5700 IU anti-Xa/0.6 ml; 7600 IU anti-Xa /0.8 ml
17	Enoxaparin	Injectable solution in prefilled syringe 2000 IU (20 mg)/0.2 ml; 4000 IU (40 mg)/0.4 ml; 8000 IU (80 mg)/0.8 ml; 10000 IU anti-Xa/1 ml
18	Rivaroxaban	Tablets 0.0025; 0.01; 0.015; 0.02
19	Warfarin	Tablets 0.003; 0.005
20	Clopidogrel	Tablets/Capsules 0.075
21	Acenocoumarol	Tablets 0.002
22	Acetylsalicylic acid	Tablets 0.075; 0.1; 0.15; 0.324; Capsules 0.075
23	Alteplase	Powder 0.05 in vials
24	Aminocaproic acid	Solution 5% - 500 ml in vials
25	Protamine sulfate	Solution 1% - 10 ml ampoules
26	Phytomenadione	Solution 1% - 1 ml ampoules
27	Tirofiban	Solution 0.025% - 50 ml in vials
28	Etamsylate	Solution 12.5% - 2 ml ampoules; Tablets 0.25

2. Tests. Tests on clinical pharmacology (for faculty of medicine). Chisinau, 2014,

G. Interactive activity

1. The didactic instructional work and the patient's discussion.

2. Clinical-pharmacological selection and use of drugs in cardio-vascular system disorders:

- The principles of selection and use of drugs in acute and chronic heart failure.
- The principles of selection and use of drugs in different forms of tachyarrhythmias and bradyarrhythmias.

- Principles of treatment of acute coronary syndrome and acute myocardial infarction.
 - The principles of selection and use of drugs in pulmonary embolism, ischemic or hemorrhagic stroke, acute myocardial infarction.
 - The principles of selection and use of drugs in the DIC syndrome (disseminated intravascular coagulopathy).
- 3. Clinical cases. *Clinical cases in clinical pharmacology*. Chisinau, 2017, p. 66-99.**
- 4. Personal Drug (P-Drug) selection according to the criteria of efficacy, safety, acceptability and cost.**