Ministry of Education and Science of Ukraine
V. N. Karazin Kharkiv National University

CLINICAL AND PHARMACOLOGICAL CHARACTERISTICS OF ANTIANGINAL AND ANTI-ISCHEMIC DRUGS

Methodical recommendations for practical classes
students of higher medical education in the 5th year of study
the discipline "Clinical Pharmacology"

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Reviewers:
Grydniev O. E. – Doctor of Medical science, Professor, leading researcher of the department study of diseases of the digestive organs and their comorbidity with non-infectious diseases of the State University "National Institute of Therapy named after L. T. Maloy, National Academy of Medical Sciences of Ukraine".
Kratenko G. S. – Ph.D., associate professor of the Department of General Practice - Family Medicine of V. N. Karazin Kharkiv National University.

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Methodical recommendations contain information on the methodology, principles and basic rules for the use of drugs in coronary heart disease. Peculiarities of use and effects of medicines, warnings, unwanted effects, interaction of medicines used for the treatment of coronary heart disease. Materials for self-control, a list of recommended literature on the discipline "Clinical pharmacology".

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CONTENT

INTRODUCTION

Since the emergence of the principles of evidence-based medicine, drug therapy has become one of the most dynamically developing branches of medicine. Currently, according to the Ministry of Health, over 12 thousand medicines are registered on the Ukrainian pharmaceutical market, which gives the doctor the opportunity to choose the most effective drug strategy in terms of an individualized approach to patients.

The large number of drugs makes it difficult to make the best choice when choosing a drug to provide both clinically and cost-effective and safe treatments.

So, among the registered drugs there are drugs with dubious efficacy and safety, due to the fact that research on them was carried out decades ago according to different requirements, and from the position of evidence-based medicine, they do not meet modern concepts. A large number of generics, a significant difference in the cost of drugs with the same international name, information materials of questionable quality, unfair advertising sometimes mislead doctors when choosing a particular drug.

Recently, due to the adopted new legislation in the field of pharmacological supervision, integration processes within the European Union, the situation is changing dramatically. The formulary system is being actively introduced into the doctor's practice, both at the state level and at local levels.

There is a strict selection of drugs based on the best world experience. Partially developed and approved in the form of orders of the Ministry of Health of Ukraine standards for the provision of medical care at different levels of accreditation. The process involves leading specialists in areas, specialized societies and associations. A list of top-priority nosologies for which it is necessary, first of all, to develop and introduce new standards has been determined. Since the modern arsenal of drugs is constantly updated, new randomized clinical trials are being conducted, approaches to treatment strategies and tactics are changing, and time intervals are being determined for revising treatment standards.

Indications and contraindications for the use of drugs can change significantly as the number of patients in whom they have been used increases, as information on adverse reactions / side effects accumulates in them, and as new information on the pharmacological properties of drugs accumulates. It is known that when conducting randomized clinical trials, depending on from the number of patients, the number of side effects is 5 % or more, and only the use of drugs in real practice makes it possible to obtain reliably complete information (up to 95 %), including depending on gender, age, and also on concomitant diseases.

Despite the existing strict recommendations for the treatment of certain diseases, it is necessary to move away from templates, and when choosing drugs, to use an individualized approach to each patient, which in turn requires deep knowledge, the use of scientifically based methods of pharmacotherapy. It is these tasks that are provided by clinical pharmacology, which in its essence is a methodology for the choice of drug therapy.

1. GENERAL CHARACTERISTICS OF ANGINA PECTORIS

Angina pectoris is a clinical syndrome characterized by episodes of chest pain. It occurs in case of decreasing in myocardial oxygen supply (myocardial ischemia). It is mostly caused by atherosclerotic plaque in the coronary arteries but may also be caused by coronary vasospasm. The development and progression of atherosclerotic plaque is called coronary artery disease (CAD). Atherosclerotic plaque narrows the coronary artery, decreases elasticity, and impairs dilation. The result is: impaired blood flow to the myocardium, especially with increasing cardiac workload during physical exercises etc. After a while CAD progress from angina to myocardial infarction.

There are three main types of angina: stable angina, variant (Prinzmetal) angina, unstable angina and microvascular angina (then affects the heart's smallest coronary artery blood vessels).

Classic anginal pain is usually described as substernal chest pain of a constricting, squeezing or suffocating nature. It may radiate to the jaw, neck, or shoulder, down the left or both arms or to the back. The pain is sometimes mistaken for arthritis, or for indigestion. Pain may be associated with nausea, vomiting, dizziness, diaphoresis, shortness of breath, or fear of death. The pain is typically lasting 5 minutes or less until the balance of oxygen supply and demand is restored.

At any stage of CAD (coronary artery disease) optimal actions is:

1. Lifestyle changes.
2. Medications, if necessary, to control or reverse risk factors for disease progression.

Risk factors are classified as nonmodifiable and modifiable.

Nonmodifiable risk factors: age, race, gender, and family history.

Modifiable risk factors: smoking, hypertension, hyperlipidemia, obesity, sedentary lifestyle, stress, and the use of drugs that increase cardiac workload (adrenergic drugs, corticosteroids).

So, patients should reduce blood pressure, weight, serum cholesterol levels and perform the physical exercise program.

Smoking is harmful to these patients because:

• Nicotine increases catecholamines which increase heart rate and blood pressure (increases myocardial oxygen demand).

• Carboxyhemoglobin. Formed during inhalation of carbon monoxide (CO) with smoke. It decreases delivery of blood and oxygen to the heart, decreases myocardial contractility, and increases the risks of life-threatening cardiac dysrhythmias (ventricular fibrillation) during ischemic episodes.

• Both nicotine and carbon monoxide increase platelet adhesiveness and aggregation, what causes thrombosis.

• Smoking increases the risks for myocardial infarction, sudden cardiac death, cerebrovascular disease (stroke), peripheral vascular disease (arterial insufficiency), and hypertension. It also reduces high-density lipoprotein, the "good" cholesterol.

Additional: nonpharmacologic strategy include surgical revascularization (coronary artery bypass) and interventional procedures that reduce blockages (percutaneous transluminal coronary angioplastyc [PTCA], intracoronary stents, laser therapy, and rotablation).

Drugs used for myocardial ischemia are the organic nitrates, the beta-adrenergic blocking agents, and the calcium channel blocking agents.

These drugs relieve the pain by reducing myocardial oxygen demand or increasing blood supply to the myocardium.

2. ORGANIC NITRATES

Organic nitrates (and nitrates) are simple nitric and nitrous acid esters of alcohols. These compounds cause a rapid reduction in myocardial oxygen demand with followed symptoms removal. They are effective for stable, unstable and Prinzmetal's or variant angina pectoris.

Nitrates, β-blockers, and calcium channel-blockers are equally effective for anginal symptoms relieving.

However, to fast relieve an ongoing attack of angina caused by physical exercise or emotional stress, sublingual (or spray) nitroglycerin (nitrostat) is the drug of choice.

Mechanisms of action: The organic nitrates, such as nitroglycerin, are leads to dephosphorylation of the myosin light chain, resulting vascular smooth muscles relaxation.

At therapeutic doses, nitroglycerin has two major effects.

First, it causes dilation of the large veins, resulting pooling blood in the veins. This diminishes preload (venous return to the heart), and reduces the work of the heart.

Second, nitroglycerin dilates the coronary vasculature, providing increased blood supply to the heart muscle.

Nitroglycerin causes low myocardial oxygen consumption by decreasing cardiac work.

Pharmacokinetics. The time to onset of action varies from one minute for nitroglycerin to more than one hour for isosorbide mononitrate. Significant first-pass metabolism of nitroglycerin occurs in the liver. That why, we give the drug sublingually or via a transdermal patch.

Adverse effects. The most common adverse effect of nitroglycerin, as well as the other nitrates, is headache. 30 to 60 % of patients receiving intermittent nitrate therapy with long-acting agents develop headaches. High doses of organic nitrates can also cause postural hypotension, facial flushing, and tachycardia.

Tolerance to the actions of nitrates develops rapidly. This can be overcome by providing a daily "nitrate-free interval" to restore drug sensitivity. This interval is typically 6 to 8, 10-12 hours, usually at night because of low demand in oxygen of the heart at that time. Nitroglycerin patches are worn for 12 hours and removed for 12 hours. Prinzmetal`s angina is manifested early in the morning due to increase in catecholamine levels. For these patients, the interval without nitrates should be closer to the evening.

Drug Class: antianginal, vasodilator

Mechanism of Action:

- Direct relaxation of vascular smooth muscle is the principal pharmacologic action of nitroglycerin ((Ignarro, 2002).

- Venous effects predominate at low doses, but nitroglycerin causes a dose-dependent expansion of both the arterial and venous beds.
- Venodilation promotes peripheral pooling of blood and decreases venous return to the heart, reducing left ventricular end-diastolic pressure (preload).
- Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload).
- Myocardial oxygen consumption or demand is decreased by both the arterial and venous effects of nitroglycerin, and a more favorable supply-demand ratio can be achieved.
- May cause redistribution of coronary blood flow from normal to ischemic tissue.
- Nitrates (and calcium channel blockers) may also increase myocardial oxygen delivery in variant angina by reversing coronary arterial spasm.

Indications:

1. Sublingual nitroglycerin is the drug of choice for acute treatment of angina due to its rapid onset of action & clinical efficiency
   - Classic Effort-induced Angina pectoris.
   - Vasospastic (Variant or Prinzmetal's) Angina.
   - Unstable Angina.
2. CHF (Congestive heart failure) associated with acute myocardial infarction.
3. Control of blood pressure in hypertension associated with surgical procedures.
4. Production of controlled hypotension during surgical procedures.

Contraindications:

- Type 5 PDE (phosphodiesterase) inhibitors potentiate the action of nitrates used for angina:
  - using within 24 hours of taking sildenafil is likely to produce severe hypotension,
  - the interaction with tadalafil (Cialis) lasts up to 48 hours due to tadalafil's longer half-life.
- Known hypersensitivity.
- Hypotension or uncorrected hypovolemia.
- Increased intracranial pressure (head trauma).
- Inadequate cerebral circulation.
- Constrictive pericarditis or pericardial tamponade.

Pharmacokinetics:

- The liver contains a high-capacity organic nitrate reductase that inactivates nitroglycerin, resulting in very low bioavailability (typically < 10–20 %) for the traditional organic nitrates (nitroglycerin and isosorbide dinitrate).

- Available formulations are:
- Extended-release oral tablets.
- Sublingual tablets.
- Ointments.
- Transdermal delivery system.
- Intravenous (after dilution to 5 % in dextrose).
- Very short half-life of 1–4 minutes.
- Tolerance can develop if doses are given within 10–12 hours.

Side Effects:

- Headache (2 % incidence).
- Tachycardia.
- Hypotension (dizziness, syncope).
- Nausea.

Nitroglycerin Extended-Release Buccal Tablets (contain 1, 2, 2.5, 3, 5 mg of nitroglycerin). When a buccal tablet is placed under the lip or in the buccal pouch, it is stick to the mucosa. Then the tablets gradually release nitroglycerin to the systemic circulation. Buccal nitroglycerin can be tried for an acute anginal attack.

Nitroglycerin tablets (NITROSTAT) – is a stabilized sublingual form, which contains 0,15, 0,3, 0,4, 0,6 mg of nitroglycerin. Nitroglycerin is rapidly absorbed by sublingual way. Its onset is approximately one to three minutes. Significant pharmacologic effects are present for 30 to 60 minutes. Nitroglycerin is indicated for the prophylaxis, treatment and management of patients with angina pectoris. One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every five minutes until symptoms relieving. If the pain persists after a 3-tablets in a 15-minute period, should be recommended drug combination.

Nitroglycerin (NITRO-BID) 2,5, 6,5, 9 mg capsules. Capsules must be swallowed. Taking two or three times a day with 8 to 12 hours' intervals. Contraindications: acute or recent myocardial infarction, severe anemia, closed-angled glaucoma, postural hypotension, increased intracranial pressure, and idiosyncrasy to the drug.

Nitroglycerin injection – for intravenous use only. Must be diluted in dextrose 5 %, or sodium chloride 0,9 %. Should not be mixed with other drugs. The concentration of the solution should not exceed 400 mg/ml of nitroglycerin.

Indication and usage:

1. Control of blood pressure in perioperative hypertension: hypertension associated with surgical procedures (especially cardiovascular procedures), such as hypertension during intratracheal intubation, anesthesia, skin incision, sternotomy, cardiac bypass.

2. Congestive heart failure associated with acute myocardial infarction.

3. Treatment of angina pectoris.

4. To achieve controlled hypotension during surgical procedures.

Isosorbide dinitrate (Isordil, Sorbitrate) Used to reduce the frequency and severity of acute anginal episodes. When given sublingually it`s onset is about 2 minutes, and its effects last 2 to 3 hours. When higher doses are given orally, more drug escapes metabolism in the liver and produces systemic effects in approximately 30 minutes. Therapeutic effects last about 4 hours after intake orally. The effective oral dose is usually determined by increasing the dose until headache occurs (it is the maximum tolerable dose). Sustained release capsules also are available.

Drug Class: antianginal, vasodilator (similar to nitroglycerin)

Pharmacokinetics:

- Absorption of isosorbide dinitrate after oral administration is almost maximal, but bioavailability varies greatly (from 10 % to 90 %), with extensive first-pass metabolism in the liver.
- Half-life is about 1 hour.
- Tolerance can develop if doses are given more frequently than every ~14 hours.

Side Effects:

- Headache.
- Methemoglobinemia (rare).

Isosorbide mononitrate (Ismo, Imdur) is the metabolite and active component of isosorbide dinitrate. It is well absorbed after oral intake/administration and almost 100 % bioavailable. Unlike other oral nitrates, this drug is not subject to first-pass hepatic metabolism. Onset of action occurs within 1 hour, peak effects occur between 1 and 4 hours, and the elimination half-life is approximately 5 hours. It is used only for prophylaxis of angina. It does not act rapidly enough to relieve acute attacks.

3. B-BLOCKERS AS ANTIANGINAL DRUGS

Sympathetic stimulation of beta1 receptors in the heart increases heart rate and force of myocardial contraction, so it increases myocardial oxygen demand and can cause of acute anginal attacks. Beta-blocking drugs prevent or inhibit sympathetic stimulation.

Thus, the drugs reduce heart rate and myocardial contractility, during physical load. A slower heart rate may improve coronary blood flow to the ischemic area. Beta blockers also reduce blood pressure and by this decreasing myocardial workload and oxygen demand.

In angina pectoris, beta-adrenergic blocking drugs are used in long-term treatment/management to decrease the frequency and severity of anginal attacks, decrease the need for sublingual nitroglycerin, and increase physical load tolerance. When we stop using beta-blockers after prolonged use, the dosage decreases gradually. Because it may occur angina of rebound.

These drugs should not be given to persons with known or suspected coronary artery spasms because they may intensify the frequency and severity of vasospasm (connected with stimulation of alpha-adrenergic receptors, which causes vasoconstriction, when beta-adrenergic receptors are blocked by the drugs).

Smokers may have reduced efficiency of beta blockers.

Persons with asthma should be observed for bronchospasm because of beta2 receptors blockage in the lung.

Beta-blockers are used with caution in diabetes, because they can hide the signs of hypoglycemia (except sweating).

The β-adrenergic blockers agents suppress the activation of the heart by blocking β_1 receptors. They also reduce the work of the heart by decreasing cardiac output and causing a slight decrease in blood pressure.

Propranolol is the first drug of this class, but other β-blockers, such as *metoprolol* and *atenolol* are equally effective. Propranolol decreases the oxygen requirement of heart muscle and effective in reducing the chest pain on physical activity. Propranolol is useful in the long treatment of stable angina (not for acute treatment). Tolerance to moderate loads is increasing, and we can see this on the electrocardiogram. Agents with sympathomymetic activity (for example, *pindolol* and *acebutolol*) are less effective and should be avoided.

The β-blockers reduce the frequency and severity oh angina attacks. These agents are useful in the treatment of patients with myocardial infarction.

The β-blockers can be used with nitrates to increase physical activity duration and tolerance.

Contraindications: diabetes, peripheral vascular disease, chronic pulmonary disease.

Propranolol is well absorbed after oral intake. Then metabolized in the liver; an approximately 30% of oral dose reaches the systemic circulation. For this reason, oral doses of propranolol are much higher than doses of intravenous injection. Onset of action is about 30 minutes after oral intake/administration and 1 to 2 minutes after intravenous injection.

Atenolol, metoprolol, and nadolol have the same actions, uses, and adverse effects as propranolol, but they have long half-lives and can be given once a day. They are excreted by the kidneys, and dosage must be reduced for patients with renal impairment.

Mechanisms of Action (block of cardiac β1 receptors):

1. Decreased heart rate.
2. Reduced contractility.
3. Reduced blood pressure.
4. The combination of these effects decreases myocardial oxygen requirements at rest and during exercise.
5. Beta blockers may also be valuable in reducing "silent" ischemia.

Indications: Angina of effort (classic angina) but NOT vasospastic angina.

Contraindications:

- Asthma & other bronchospastic conditions.
- Severe bradycardia.
- AV block (Atrioventricular block).
- Severe unstable LV failure (Left Ventricular Failure).
- Vasospastic Angina.

Side Effects:

- Increase in end-diastolic volume and ejection time (reduce oxygen requirements). This can be balanced by the concomitant use of nitrates.
- Fatigue, impaired physical activity tolerance, insomnia, unpleasant dreams, erectile dysfunction.

Better outcomes & symptomatic improvement we get with beta-blockers compared to calcium channel blockers.

4. CALCIUM CHANNEL BLOCKERS

Calcium channel blockers act on contractile and conductive tissues of the heart and on vascular smooth muscles.

For optimal functionality of these cells the concentration of intracellular calcium must be high. It`s achieved by movement of extracellular calcium ions into the cell (through calcium channels in the cell membrane) and release of bound calcium from the sarcoplasmic reticulum in the cell.

So, calcium plays an important role in maintaining vasomotor tone, myocardial contractility, and conduction.

Calcium channel blocking agents prevent the movement of extracellular calcium into the cell. As a result, coronary and peripheral arteries are dilated, myocardial contractility is decreased, and the conduction system is depressed (decreasing of impulse formation (automaticity) and conduction velocity).

In angina pectoris, the drugs improve the blood supply of the myocardium by dilating coronary arteries and decrease the workload of the heart by dilating peripheral arteries (decreasing blood pressure).

In variant angina, calcium channel blockers reduce coronary artery vasospasm.

Calcium channel blockers are well absorbed after oral intake but undergo extensive first-pass metabolism in the liver. Most of the drugs (more than 90%) bound with proteins and reach plasma peak levels within 1 to 2 hours (6 hours or longer for sustained-release forms). Most have short elimination half-lives (<5 hours), so doses must be given three or four times a day (unless sustained-release forms).

Amlodipine (30 to 50 hours), bepridil (24 hours), and felodipine (11 to 16 hours) have long elimination half-lives and therefore can be given once a day.

The dosage should be reduced for patients with severe liver disease and not required with renal disease.

Seven of calcium channel blockers these are chemically dihydropyridines, of which (nifedipine is the prototype). Bepridil, diltiazem, and verapamil differ chemically from the 1ie one and each other. Nifedipine and related drugs act mainly on vascular smooth muscle to produce vasodilation, verapamil and diltiazem have greater effects on the cardiac conduction system.

The drugs also vary in clinical indications for use; most are used for angina or hypertension, and only diltiazem and verapamil are used to manage supraventricular tachydysrhythmias.

For patients with coronary artery disease (CAD), the drugs are effective as monotherapy but are commonly prescribed in combination with beta blockers.

In addition, nimodipine is approved for use only in subarachnoid hemorrhage. Contraindications: second- or third-degree heart block, cardiogenic shock, and severe bradycardia, heart failure, or hypotension. The drugs should be used carefully with milder bradycardia, heart failure, hypotension and with renal or hepatic impairment.

The calcium channel blockers inhibit the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arteries. So, all of them decrease in smooth muscle tone and vascular resistance. At clinical doses, these agents affect primarily the resistance of vascular smooth muscle and the myocardium. [Note: *Verapamil* mainly affects the myocardium, *nifedipine* exertrs a greater effect on smooth muscle of the peripheral vasculature. *Diltiazem* has intermediate in its actions].

Nifedipine (adalat) (10, 20 mg capsules) acts mainly as an arteriolar vasodilator.

Drug Class: antianginal, vasodilator, antihypertensive, dihydropyridine L-type Ca channel blocker.

Indications: for prophylactic treatment of:

- Angina of effort.
- Vasospastic angina.
- Hypertension.
- For treating patients with AV node conduction disturbances needing a calcium channel blocker (e.g. for angina or hypertension) nifedipine may be a safer choice compared to verapamil or diltiazem because it does not significantly decrease AV node conduction in situ.
- Note: Calcium channel blockers can be “tried” in refractory cases of unstable angina, but otherwise are not drugs of first or second choice in this condition.

Has a more vascular selective effect compared to diltiazem & verapamil.

Has minimal effect on cardiac conduction or heart rate. If intake orally has a short life (about 4 hours). The vasodilation effect of nifedipine is useful in the treatment of variant angina caused by spontaneous coronary spasm.

Therapy should be initiated with 19 mg capsule. The starting dose is 10 mg capsule 3 times/day. The usual effective dose range is 10 – 20 mg three times a day. More than 180 mg per day is not recommended. Nifedipine titration should proceed over a 7–14 day period. A single dose should not exceed 30 mg.

Pharmacokinetics:

- Oral administration, available in immediate release & extended-release formulations.

- Nifedipine is extensively converted to inactive metabolites and approximately 80 % of nifedipine and metabolites are eliminated via the kidneys.
- The half-life of nifedipine in plasma is approximately 2 hours.
- Since hepatic biotransformation is the predominant route for the disposition of nifedipine, the pharmacokinetics may be altered in patients with chronic liver disease.

Side Effects:

- Dizziness.
- Flushing.
- Headache.
- Transient hypotension.
- Peripheral edema.
- The drug may cause reflex tachycardia (if peripheral vasodilation is marked resulting in a substantial decrease in blood pressure).

Major drug interactions:

- Cimetidine (80 % increase in nifedipine plasma levels).

Verapamil directly slows down cardiac conduction and thus decreases heart rate and oxygen demand. Causes greater negative inotropic effects than does nifedipine, but it is a weaker vasodilator.

Drug Class: Calcium channel blocker (Class 4 antiarrhythmic, antihypertensive, antianginal).

Mechanism of Action:

- Phenylalkylamine class L-type Ca channel blocker (more cardiac selective).
- Blocks L-type calcium channels (at a different site on the Ca channel than diltiazem or dihydropyridines).
- Verapamil has slightly greater depressant effects on cardiac tissue vs diltiazem, and much more than dihydropyridines (which are vascular selective).

Indications:

1. Vasospastic & Effort-Associated angina (prophylactic treatment).

(Calcium channel blockers can be “tried” in refractory cases of unstable angina, but otherwise are not drugs of first or second choice in this condition).

2. Hypertension.
3. Paroxysmal Supraventricular Tachycardia (PSVT) (a drug of choice for prophylaxis; a drug of 2nd choice after adenosine for acute treatment (adenosine has been shown to produce better outcomes when used for acute conversion of PSVT to sinus rhythm)).

4. Control of ventricular rate in patients with chronic atrial fibrillation/flutter.

Contraindications:

- Severe hypotension.
- 2nd or 3rd degree AV block.
- Cardiogenic shock.
- Severe CHF (Congestive heart failure is a chronic progressive condition that affects the pumping power of heart muscles.).
- Sick sinus syndrome (unless patient has artificial pacemaker).
- Severe LV (Left Ventricular) dysfunction.

Pharmacokinetics:

- Oral administration.
- A nonlinear correlation between the verapamil dose administered and verapamil plasma levels does exist.
- Estimated average elimination half-life from 2.8 to 7.4 hours with a single dose.
- After repeating dosing, the half-life increasing to 4.5 to 12.0 hours (after less than 10 consecutive doses with an interval of 6 hours).
- Bioavailability of verapamil is higher and half-life longer if patients older than 65 years.
- Low body weight also has the opposite effect on its pharmacokinetics.

Side Effects:

- Constipation.
- Bradycardia.
- AV conduction block.
- Asystole.

Major drug interactions:

- Verapamil undergoes biotransformation by predominantly CYP3A4, however CYP1A2 and members of the CYP2C subfamily are involved in its metabolism.
- Verapamil can produce additive effects with other antihypertensive drugs & with cardiac effects of beta blockers.

Verapamil should be used carefully in digitalized patients, because it increases digoxin levels.

Diltiazem has cardiovascular effects that are similar to those of verapamil. It reduces the heart rate lesser extent than verapamil and also decreases blood pressure. In addition, can relieve coronary artery spasm (useful in patients with variant angina).

Drug Class: Calcium channel blocker (Class 4 antiarrhythmic, antihypertensive, antianginal).

Mechanism of Action:

- blocks L-type calcium channels (cardiac & vascular);
- benzothiazepine class (has a different site of action on the Ca channel compared to verapamil or dihydropyridines).

Indications:

- Vasospastic & Classic Angina (prophylactic treatment).
- Hypertension.
- Control of ventricular rate/frequency during atrial fibrillation, flutter (trepetanie).

Contraindications:

- Hypotension.
- AV block (2nd- or 3rd-degree) or sick sinus syndrome, except in the presence of a functioning ventricular pacemaker.
- Acute MI.
- Pulmonary congestion.
- Lactation.

Pharmacokinetics:

- Oral administration.
- Plasma elimination half-life is approximately 3.0 to 4.5 hours.

Side Effects (the frequency of side effects is low):

- Hypotension
- AV conduction block
- Bradycardia
- Constipation

Major drug interactions:

- Diltiazem can produce additive effects with other antihypertensive drugs & with cardiac effects of beta blockers.

5. RELATED TO ANTIANGINAL DRUGS

In addition to antianginal drugs, several other drugs may be used to control risk factors and prevent progression of myocardial ischemia to myocardial infarction and sudden cardiac death. These may include:

• Aspirin. This drug has become the standard of care because of its antiplatelet (ie, antithrombotic) effects. Recommended doses vary from 81 mg daily to 325 mg daily or every other day; apparently all doses are beneficial in reducing the possibility of myocardial reinfarction, stroke, and death.

Clopidogrel, 75 mg/day, is an alternative for individuals with aspirin allergy.

Side effects:

- Thrombotic thrombocytopenic purpura (incidence: four per million patients treated).
- Hemorrhage – the annual incidence of hemorrhage may be increased by the coadministration of aspirin.
- Rashes and itching were uncommon in studies (between 0.1 and 1 % of people).
- Serious hypersensitivity reactions are rare/ infrequent.

• Antilipemics. These drugs may be needed for patients which need to lower serum cholesterol levels. Lovastatin or a related "statin" is often used. The goal is usually to reduce the serum cholesterol level below 200 mg/dL and low density lipoprotein cholesterol to below 130 mg/dL.

• Antihypertensives. These drugs may be needed for patients with hypertension. Because beta blockers and calcium channel blockers are used to manage hypertension as well as angina, one of these drugs may be effective for both disorders.

6. PRINCIPLES OF ANTIISCHEMIC THERAPY.

Goals of Therapy

- To relieve acute anginal pain.
- Reduce the number and severity of acute anginal attacks.
- Improve exercise tolerance and quality of life.
- Delay progression of CAD.
- Prevent myocardial infarction.
- Prevent sudden cardiac death.

Choice of Drug and Dosage Form

1. For acute angina and prophylaxis before events that cause acute angina - nitroglycerin (sublingual tablets or translingual spray) (usually the primary drug of choice).

Sublingual or chewable tablets of isosorbide dinitrate also may be used.

2. For long-term prevention or management of recurrent angina, oral or topical nitrates, beta-blockers, or calcium channel blockers.

3. Combined drug therapy with a nitrate and one of the other drugs is common and effective. 4. Patients taking one or more long-acting antianginal drugs should carry a short-acting drug (for acute attacks).

Titration of Dosage

Dosage of all antianginal drugs should be individualized to achieve optimal effect and minimal side effects. Usually starting with relatively small doses and increasing them as necessary. Doses may vary widely among individuals.

Tolerance to Long-Acting Nitrates

Patients who take long-acting dosage forms of nitrates get tolerance to the vasodilating (antianginal) effects of the drug (usually during high-dose, uninterrupted therapy).

As a result, episodes of chest pain may occur more often or be more severe than expected. In addition, shortacting nitrates may be less effective in relieving acute pain.

Best way to prevent or manage nitrate tolerance:

1. Using short-acting nitrates when needed and avoiding the long-acting

2. Using the long-acting forms for 12 to 16 hours daily during active periods and skip them during inactive periods or sleep.

So, doses should be given every 6 hours 3 times a day with 6 hours rest period (without dose). Transdermal discs should be removed at bedtime.

If anginal symptoms occur during sleeping hours we are using short-acting nitrates to relive the symptoms.

All nitrates should be administered at the lowest effective dosage.

Use for Children

Safety and efficacy of antianginal drugs for children is unknown.

Nitroglycerin was administered intravenously for heart failure and for intraoperative control of blood pressure, with an initial dose, adjusted for weight, and subsequent doses, titrated to response.

Use for Older Adults

Usually occur side effects, such as hypotension and syncope and they may be more severe than in younger adults.

Blood pressure and the ability to move safely should be carefully monitored, especially at the start of drug therapy and then increasing dose.

Ambulatory patients should be tested for their ability to take their drugs correctly.

With calcium channel blockers, older adults may have higher plasma concentrations of verapamil, diltiazem, nifedipine, and amlodipine (because of decreased hepatic metabolism of the drugs and decreased hepatic blood flow).

In addition, older people may develop hypotension with verapamil, nifedipine and felodipine, stronger than younger patients (blood pressure should be controlled with these drugs).

Use in Renal Impairment

With nifedipine, protein binding is decreased and the elimination half-life is prolonged with renal impairment.

With nicardipine, plasma concentrations are higher in clients with renal impairment, and dosage should be reduced.

Bepridil should be used carefully because its metabolites are excreted mainly with urine.

Use in Hepatic Impairment

Nitrates, beta blockers, and calcium channel blockers are metabolized in the liver, and all should be used carefully for patients with significant impairment of hepatic function.

With oral nitrates, it is difficult to predict effects:

1. First-pass metabolism is reduced, which increases bioavailability (amount of active drug) of a given dose.

2. The nitrate reductase enzymes that normally deactivate the drug may increase their activity if large doses are given (the drug is metabolized more rapidly, possibly reducing therapeutic effects). Relatively large doses of oral

nitrates are sometimes given to counteract the drug tolerance (reduced hemodynamic effects) associated with chronic use.

In addition, drug effects of nitroglycerin and isosorbide dinitrate may be decreased.

Calcium channel blockers, should be used with reduced doses, and clients should be closely monitored for drug effects (including periodic measurements of liver enzymes).

Because:

• Bigger part of a given dose is unbound and active.

• For patients with cirrhosis, bioavailability of oral drugs is greatly increased and metabolism (of both oral and parenteral drugs) is greatly decreased.

Hepatotoxicity is uncommon for these drugs, clinical symptoms of hepatitis, cholestasis or elevation of liver enzymes (eg, alkaline phosphatase, creatine kinase [CK], lactate dehydrogenase [LDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT]) may occurred, mainly with diltiazem, nifedipine, and verapamil. These changes resolve if administration of drug is stopped.

Use for Critical Illness

Antianginal drugs may be used alone or in combination with other cardiovascular drugs for patients with critical illness.

They are used most often to manage severe angina, severe hypertension, or serious cardiac dysrhythmias.

For example:

- nitroglycerin may be used for angina and hypertension;

- beta blockers or calcium channel blockers may be used to improve cardiovascular function with angina, hypertension or supraventricular tachyarrhythmia's.

With any of these drugs, dosage must be carefully titrated and patients must be closely monitored for hypotension and other drug effects.

In addition, may be decreasing the absorption of oral medications or local forms of nitroglycerin for patients with extensive oedema, heart failure, hypotension, or other conditions with the impaired blood flow in the gastrointestinal tract or skin.

CONTROL QUESTIONS

One correct answer:

1. In a patient 54 years old, who is ill for about 4 years with cirrhosis of the liver, during the examination in the inpatient room there was vomiting, dizziness, inadequate reaction, and then lost consciousness. Objectively: the skin is jaundiced, "liver" odor from the mouth. Pulse 54/min, poor filling. Tones of the heart are weakened. Abdomen slightly increased in size. The liver is not palpable. Spleen + 3cm pastosity of the legs. Which of the following diuretics should be used in this case?

A. Manitol.
B. Hydrochlorothiazide (Hypothiazide).
C. Furosemide.
D. Spironolactone.
E. Acetazolamide (Diacarb).

2. A patient with myocardial infarction complains of severe breathlessness, pink, flashing spasms. The general condition is heavy, AT 100/75 mmHg, pulse 120 / min, rhythmic. Heart tones are weakened, the second tone is accentuated above the pulmonary artery. Breathing vesicular, weakened, in the lower parts of the lungs of many numerous moist rales. What drug is appropriate to appoint a patient?

A. Diltiazem.
B. Strofanthin.
C. Anaprilin
D. Pentamine.
E. Furosemid.

3. The doctor of emergency medical care at the patient's house found an acute myocardial infarction, which anamnestically arose around the clock. Condition is heavy: pale, cyanosis of the lips, acrocyanosis. orthopnoe, BH 40 with a min. In the lungs hears small-bubbling wheezing. Heart rate 110 beats / min, AT 160/110 mmHg in the lungs a lot of moist rales are heard, edema of the legs. Which drug should first be administered to the patient?

A. Eufilin.
B. Furosemide.
C. Strophantine.
D. Labetalol.
E. Heparin.

4. In a patient 58 years old, who is ill for about 6 years with cirrhosis of the liver, during the examination in the receiving department there was vomiting, dizziness, inadequate reaction, and then lost consciousness. Objectively: the skin is jaundiced, "liver" odor from the mouth. Pulse 49/min, weak filling. Tones of the heart are weakened. Abdomen slightly increased in

size. The liver is not palpable. Spleen + 4cm pastosity of the legs. Which of the following diuretics should be used in this case?

A. Manitol.

B. Hydrochlorothiazide.

C. Furosemide.

D. Spironolactone.

E. Acetazolamide.

5. A patient with myocardial infarction complains of severe breathlessness, pink, flashing spasms. The general condition is heavy, AT 100/75 mm Hg, pulse 120/min, rhythmic. Heart tones are weakened, the second tone is accentuated above the pulmonary artery. Breathing vesicular, weakened e, in the lower parts of the lungs are numerous in loose wheezing. What drug is appropriate to appoint a patient?

A. Diltiazem.

B. Strofanthin.

C. Anaprilin.

D. Pentamine.

E. Furosemid.

6. The doctor of emergency medical care at the patient's house found an acute myocardial infarction, which anamnestically occurred around the clock. Condition is heavy: pale, cyanosis of the lips, acrocyanosis. ortopnoe, BH 30/min. In the lungs hears small-bubbling wheezing. Heart rate 120 beats/min, AT 150/100 mm Hg In the lungs a lot of moist rales are heard, edema of the legs. What drug with ice is first to introduce the patient?

A. Eufilin.

B. Furosemide.

C. Strophantine.

D. Labetalol.

E. Heparin.

7. A man 45 years old suffers from an acute myocardial infarction. Objectively: MD – 16 beats/min, heart rate 72 beats/min, blood pressure – 130/80 mmHg. The liver is not palpated, no edema. In the complex of medical treatment bisoprolol was prescribed. Most likely, this is done in order to:

A. Reduction of the general peripheral vascular resistance.

B. Antishesis and antiarrhythmic action.

C. Decrease of cardiac output.

D. Inhibition of renin activity.

E. Increased blood glucose levels.

8. A 48-year-old patient complains of shortness of breath, attacks of rebound pain during physical activity, headache. HR 92 beats/min. AT – 180/95 mm Hg. Art. Systolic noise at the top of the heart. Echocardiography – an asymmetric non-thickening of the walls of the left

ventricle, reduction of the left ventricular cavity. Choose the most optimal hypnotic remedy?

A. Triampur.
B. Hypothiazide.
C. Klofelin.
D. Metoprolol.
E. Prazosin.

9. Patient '50 n donkey examination diagnosed IXC: cardiosclerosis. Stable stress angina III FC. Drug therapy has been prescribed, which has improved the quality of life significantly. Which of the listed prescription drugs has been shown to reduce mortality?

A. Bisoprolol.
B. Mildronate.
C. Nitrosorbide.
D. Corinfar.
E. Panangin.

10. A 30 year old patient in the therapeutic department about rheumatic endocarditis suddenly experienced a heart attack. Pulse – 170/min, rhythmic, weak. At the ECG intervals RR is equal, the ventricular complexes are not changed. In the history - acute respiratory and viral diseases, bronchitis. What drug is most appropriate to appoint a patient?

A. Propranolol.
B. Lidocaine.
C. Corinth.
D. Verapamil.
E. Digitoxin.

11. The urgent hospital received a paroxysmal tachycardia in the background of the WPW syndrome. Which drug is not appropriate for this pathology?

A. Amiodarone.
B. Lidocaine.
C. Verapamil.
D. Digoxin.
E. Propranolol L.

12. A 58 year old patient suffering from gouty arthritis, is concerned about headache, increased blood pressure. Ob-o: pulse 56 beats/min, rhythmic. AT – 190/100 mm Hg. Art. Auscultatory: heart tone sounds, the second tone accent above the aorta, noises are not listened. The level of blood uric acid is 0.52 mmol / l. Which of the antihypertensive drugs is the most appropriate to prescribe?

A. Verapamil.
B. Amlodipine.

C. Hydrochlorothiazide.

D. Propranolol.

E. Triampur.

13. A 58-year-old patient suffers from hypertension of the Ib, which is complicated by the CHI-IIA. What drug is most appropriate to appoint a patient?

A. ACE inhibitors.

B. Beta-blockers.

C. Raunatin.

D. Calcium antagonists.

E. Klofeline.

14. A 40-year-old man with a hypertension was prescribed a medicinal product that improved the patient's condition and normalized the blood pressure in 3 days. After some time, the patient turned to the doctor with complaints of an unproductive cough that did not change under the influence of cough and aroused the patient's sleep. In the history of obstructive lung disease. What drug is most likely to be taken by the patient?

A. Anaprilin.

B. Klofeline.

C. Captopril.

D. Verapamil.

E. Reserpine.

15. In the patient of 49 years on chronic glomerulonephritis, chronic nephrology and art. 3 years ago, arterial hypertension was detected. Amount: heart rate 64 beats/min, blood pressure - 200/110 mm Hg. Blood analysis: Nv – 100 g/l, ESR – 38 mm/h. Proteinuria 0.5 g/l. ECG – left ventricular hypertrophy. Both of them throw the most optimal anti-hypertensive medications for initial therapy?

A. Atenolol.

B. Hydrochlo rthiazide.

C. Klofeline.

D. Enalapril.

E. Triampur.

16. What is the renonoprotective effect of angiotensin II receptor antagonists?

A. Reduction of hydraulic pressure in renal glomeruli.

B. Increase effective renal plasma flow.

C. Decrease of the degree and rate of progression of microalbuminuria.

D. Slowdown of tubulointerstitial fibrosis.

E. All of the above.

17. Indicate contraindications for the administration of angiotensin II receptor antagonists:

A. Bilateral stenosis of the renal arteries (stenosis of the artery of a single functioning kidney).

B. AV blockade of II–III degree.

C. X Rheumatic heart failure.

D. Bronchial asthma, COPD.

E. WPW Syndrome.

18. Which of the following is not an indication for the use of angiotensin II receptor antagonists?

A. AH, including renovascular hypertension and hypertension after kidney transplantation.

B. Chronic kidney disease with type 2 diabetes.

C. Metabolic syndrome.

D. Stable angina pectoris.

E. Non-diabetic chronic kidney disease.

19. What is the renonoprotective effect of angiotensin II receptor antagonists?

A. Reduction of hydraulic pressure in renal glomeruli.

B. Increase effective renal plasma flow.

C. Decrease of the degree and rate of progression of microalbuminuria.

D. Slowdown of the tubule's interstitial fibrosis.

E. All of the above.

20. Indicate contraindications for the administration of angiotensin II receptor agonists:

A. Bilateral stenosis of the renal arteries (stenosis of the artery of a single functioning kidney).

B. AV blockade of II-III degree.

C. Rheumatic heart failure.

D. Bronchial asthma, COPD.

E. WPW Syndrome.

Correct answers:

1–A; 2–E; 3–A; 4–A; 5–E; 6–B; 7–D; 8–D; 9–A; 10–C; 11–C; 12–B; 13–D; 14–C; 15–C; 16–A; 17–C; 18–D; 19–E; 20–A.

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Information resources:

1. ***https://www.clinicalpharmacology.com/***
2. ***http://www.pharmaresearchlibrary.com/wp-content/uploads/2013/03/A-Textbook-of-Clinical-Pharmacology-and-Therapeutics-5th-edition.pdf***
3. ***https://pubmed.ncbi.nlm.nih.gov/***
4. ***http://www.cochrane.org/***
5. ***https://ascpt.onlinelibrary.wiley.com/journal/15326535?tabActivePane=***

https://www.euro.who.int/__data/assets/pdf_file/0004/156217/euro_series_39.pdf

Навчальне видання

Резніченко Олександр Георгійович
Шерстюк Людмила Леонідівна
Власенко Ольга Олександрівна
Гріднєва Світлана Вікторівна
Бєляєва Людмила Володимирівна
Вовк Кіра Віталіївна

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Видавець і виготовлювач
Харківський національний університет імені В. Н. Каразіна,
61022, м. Харків, майдан Свободи, 4.

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Тел. 705-24-32