Poltava State Medical University

Department of Pharmacology, Clinical pharmacology and Pharmacy

Lecture

Cardiotonic drugs. Pharmacology of cardiac glycosides. Antiarrhythmic drugs. Antianginal drugs

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2. Classification
3. Pharmacological effects of different classes and preparations

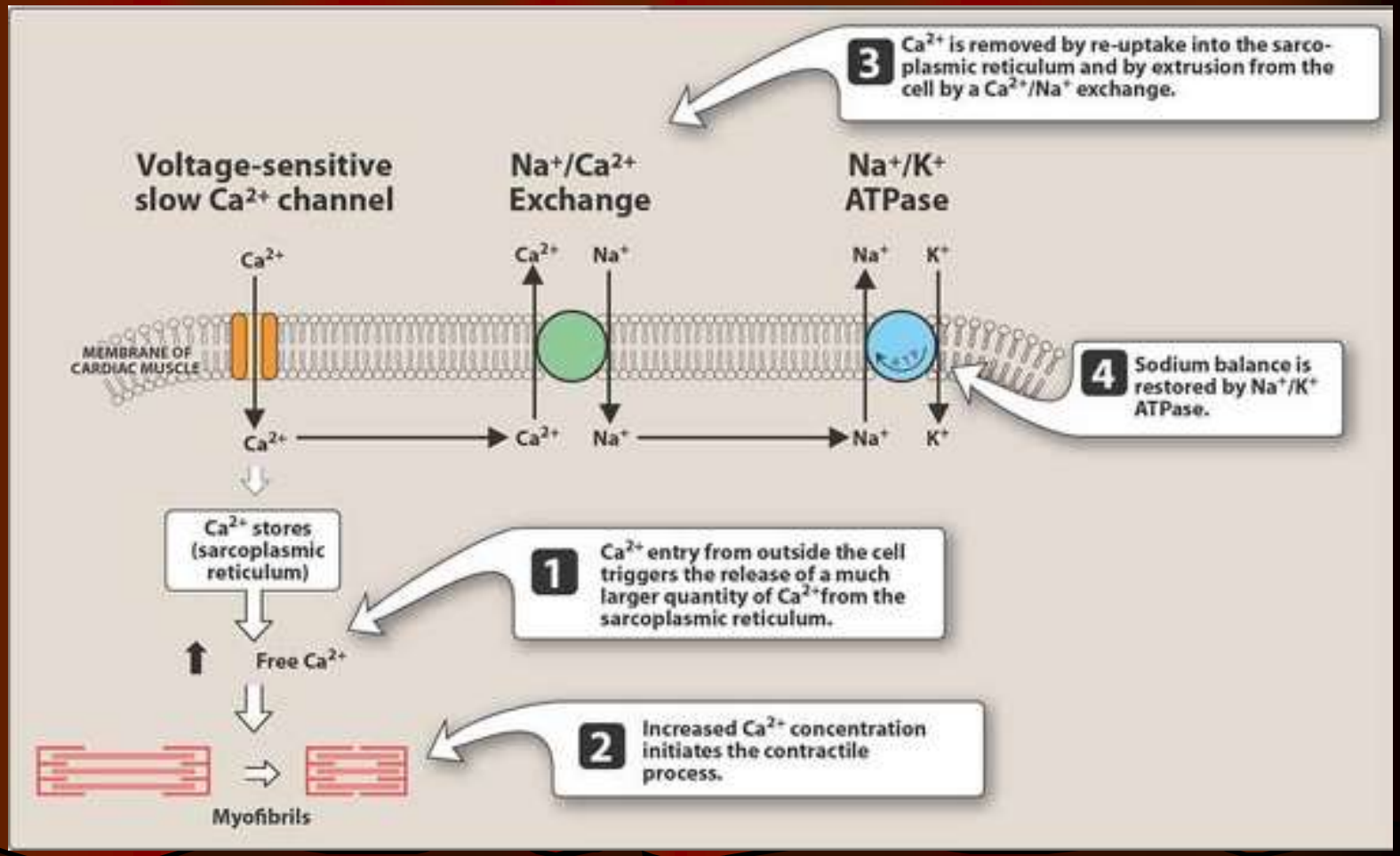
C. Antianginal drugs

1. Angina pectoris
2. Classification
3. Pharmacological effects of different classes and preparationsD

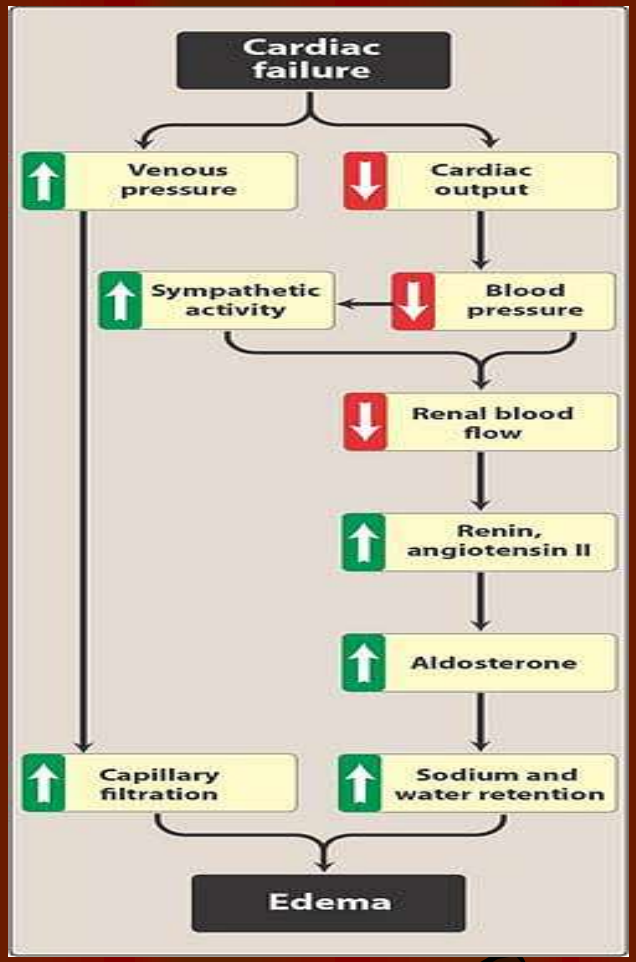
Control tasks

INOTROPIC DRUGS

CARDIAC MYOCYTE: mechanism of normal function



CONGESTIVE HEART FAILURE

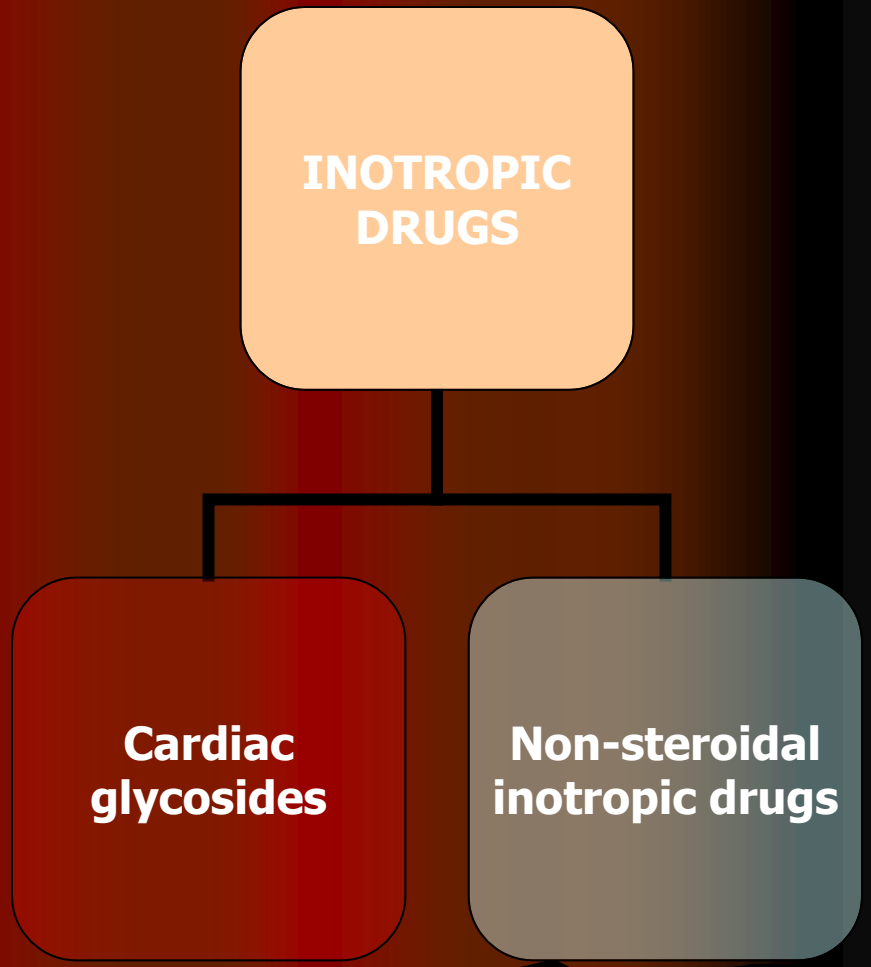


Congestive heart failure (CHF) is a decrease in pump function of myocardium resulting from different causes (myocarditis, organic lesions of the heart, hypertensive disease, etc.).

CHF may be acute and chronic.

GROUPS OF INOTROPIC AGENTS

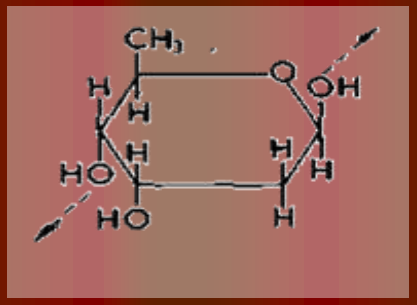
- ***Inotropic drugs*** are preparations which increase the force of myocardium contraction and cardiac output without a significant increase in oxygen consumption.
- They are divided into ***cardiac glycosides*** (steroidal inotropic drugs) and ***non-glycoside inotropic drugs*** (non-steroidal)

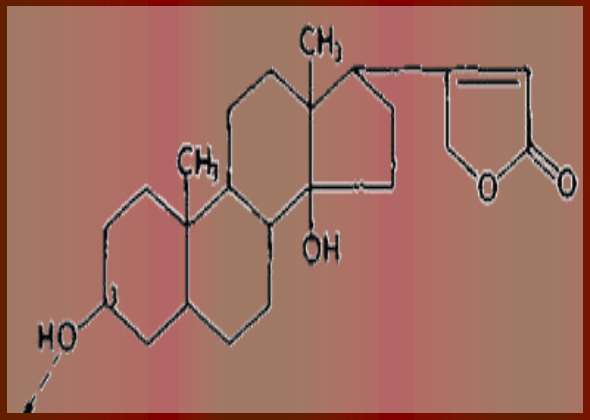


CARDIAC GLYCOSIDES: origin

Medicinal plants containing cardiac glycosides: Digitalis lanata; Adonis vernalis; Strophanthus combe; Convallaria majalis

CARDIAC GLYCOSIDES: chemical structure





Cardiac glycoside = glycone + aglycone.

Glycone contains sugar moieties and determines pharmacokinetics.

Aglycone contains steroid structure with lactone ring and determines pharmaco-dynamics

CARDIAC GLYCOSIDES: classification

On origin

1. Group of Digitalis
- Digitoxin
- Digoxin
- Celanide (Lantoside C)
- Infusion from the herb of adonis

2. Group of Strophanthus
- Strophanthin-K
- Strophanthin-G (Quabain)
- Corglycon

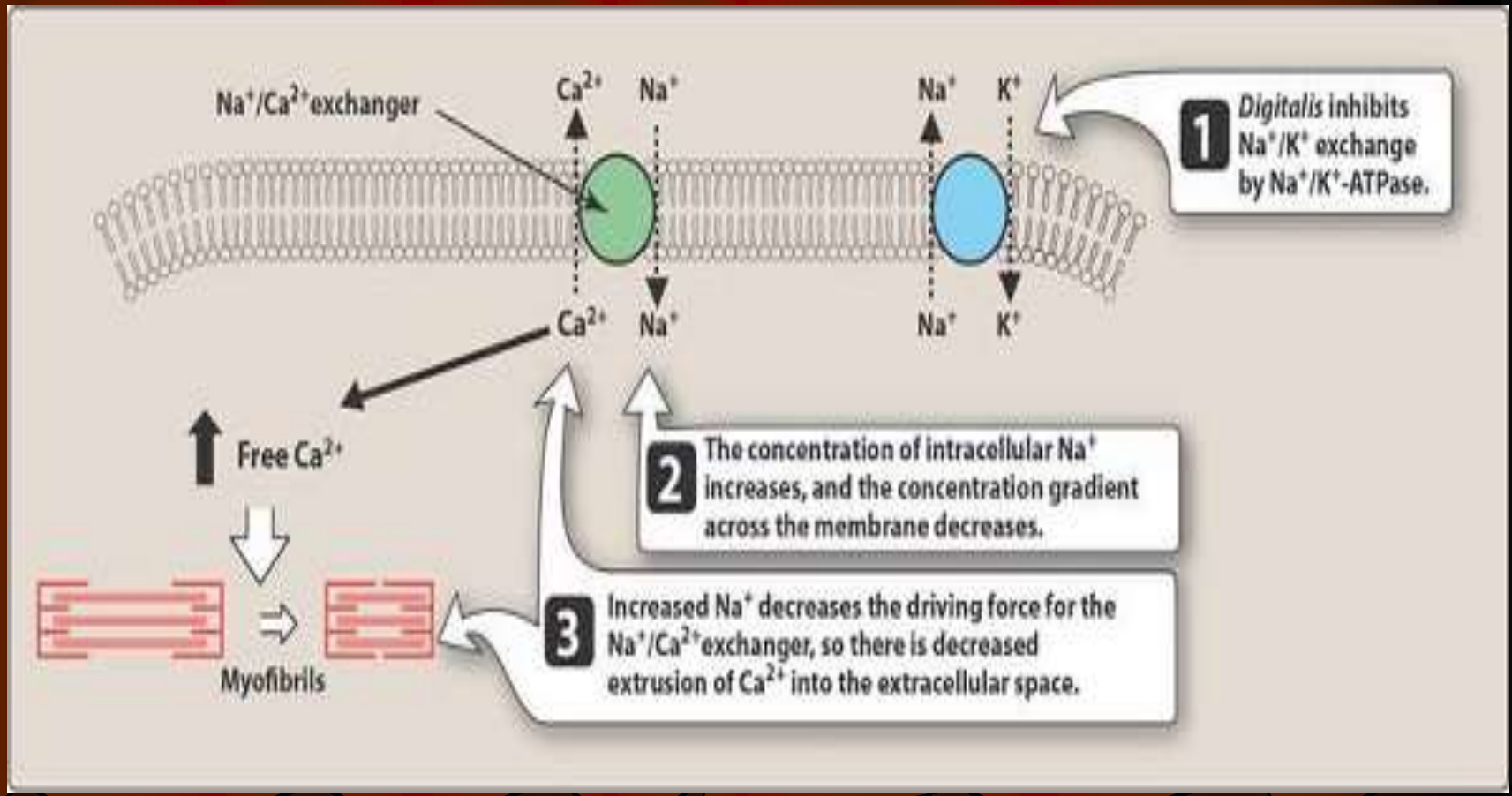
On duration of action

1. Long-acting
- Digitoxin

2. Intermediate-acting
- Digoxin
- Celanide

3. Short-acting
- Strophanthin
- Corglycon.

CARDIAC GLYCOSIDES: mechanism of inotropic action



CARDIAC GLYCOSIDES: mechanism of chronotropic action

- There are two parts in the mechanism of negative chronotropic action: ***vagal and extravagal***
- ***Vagal action*** is due to the reflexive and direct stimulation of n. vagus center.
- ***Extravagal action*** is due to the direct inhibition of SA and AV nodes and hypersensitization of SA node to acetylcholine.

CARDIAC GLYCOSIDES: pharmacodynamics

- ***positive inotropic effect*** (an increase in force of systole, an increase in the myocardial tone)
- ***negative chronotropic effect*** (prolongation of diastole, slowing of the heart rate)
- ***negative dromotropic effect*** (deceleration of conductivity)
- ***positive bathmotropic effect*** (an increase in the myocardium excitation, manifests as extrasystoles in overdose of cardiac glycosides)
- **i**mprovement of blood circulation
- a decrease in venous pressure, a normalization of arterial blood pressure
- an increase in renal blood flow which leads to an increase in diuresis and a decrease in edema.

CARDIAC GLYCOSIDES: phases of Digitalis therapy

Phase of digitalization is a saturation of the organism by cardiac glycosides (1-7 days). The preparation is administered in a full therapeutic dose. At the end of this phase, compensation of heart failure should be obtained.

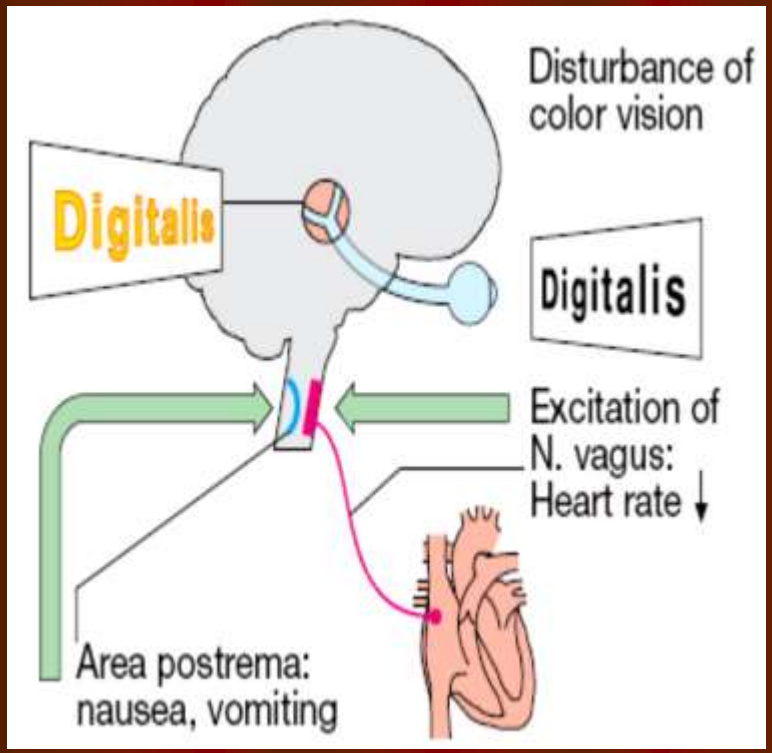
Phase of supporting therapy is a long durative treatment by the individual small dose of cardiac glycoside which is sufficient for heart compensation. Heart rate should not be less than 60 per 1 minute.

Pre-toxic phase is a beginning of overdose. Heart rate is less than 60 beats per 1 minute. The drug should be abolished.

Toxic phase (acute intoxication).

* Potassium preparations must be administered for prophylaxis of digitalis toxicity.

DIGITALIS TOXICITY



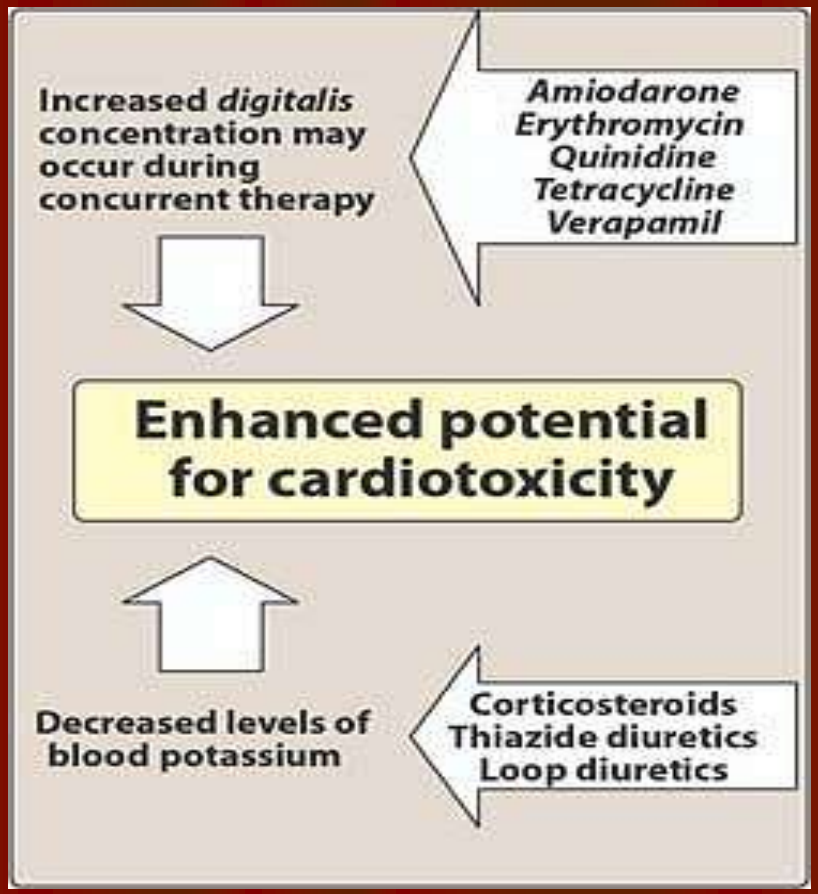
Signs:

bradycardia, then tachycardia and arrhythmia (premature ventricular beats, fibrillation)
increase in signs of heart failure
hypokalemia
anorexia, vomiting, nausea
headache, fatigue, hallucination
vision disturbances (xantopsia, micropsia, macropsia).

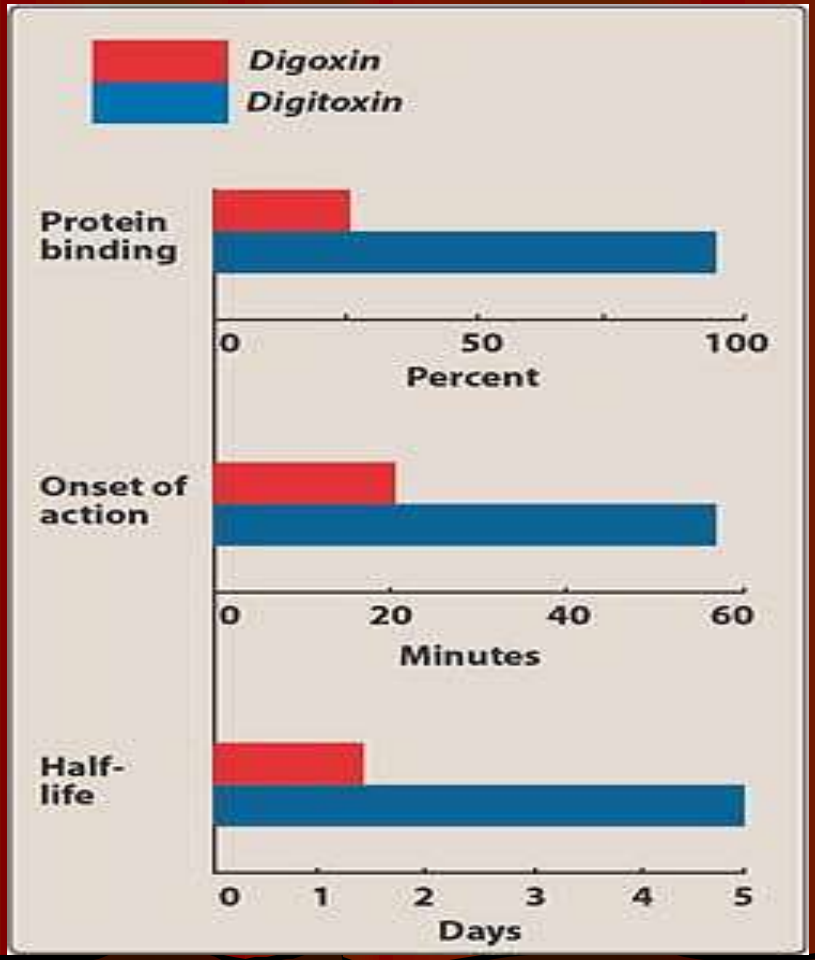
Treatment of Digitalis intoxication:

abolishing of cardiac glycoside
drugs containing potassium (potassium chloride; panangin)
SH-group donator (Unithiol)
anti-arrhythmic agents (phenytoin, lidocaine, propranolol, atropine for AV block)
digoxin antibodies (digibind)
glucose, vitamin preparations, oxygen inhalation.

DIGITALIS TOXICITY:
factors increased potential for cardiotoxicity



DIGOXIN AND DIGITOXIN:
a comparison of pharmacokinetics



CARDIAC GLYCOSIDES: peculiarities of preparations

DIGITOXIN

- is a typical representative of Digitalis group
- is lipid-soluble, non-polar
- is administered orally or rectally, is well absorbed in the GI tract (90-100%), binds to plasma proteins (95%), is metabolized in the liver; forms hepatic-intestinal cycle of re-circulation, is excreted with urine and bile; begins to act slowly in 2-4 hrs after administration; has long durative action with a half-life of 4-7 days, stays in the organism during 21 days, accumulates
- has negative chronotropic effect which exceeds inotropic and other effects on its significance
- is used in *chronic heart failure of I-II B stages, supraventricular tachyarrhythmia*
- may cause hypokalemia, bradycardia, AV block, intoxication
- is contraindicated in poisoning with cardiac glycosides, bradycardia, AV block, acute myocardial infarction, severe aortal and mitral stenosis, potassium deficiency, childhood.

CARDIAC GLYCOSIDES: peculiarities of preparations

DIGOXIN

- is water- and lipid-soluble
- is an intermediate-acting glycoside from Digitalis lanata
- may be administered orally and IV, is well absorbed in the GI tract (60-85%), binds to plasma proteins less than digitoxin (20-25%), may re-circulate, begins to act soon after IV administration, has a half-life of 36-48 hrs, accumulates less than digitoxin
- has less influence on AV conductivity than digitoxin
- is used *in chronic CHF, supraventicular tachyarrhythmia, acute CHF, attack of arrhythmia (IV)*
- is less toxic, may be used in children and in patients with non-severe AV block.

CARDIAC GLYCOSIDES: peculiarities of preparations

STROPHANTHIN

- Is a typical preparation from Strophanthus group
- is water-soluble, polar
- is administered IV (as exclusive case, may be administered IM together with procaine or sublingually); is not absorbed in the GI tract (only 5% of a dose), does not binds to plasma proteins, has not re-cycling, is not metabolized in the body, is excreted with urine, starts to act in 10-15 min after administration, develops maximal effect in 1,5-2 hrs after administration; has a half-life of 8 hrs; stays in the organism to 24 hrs; does not accumulate
- has strong positive inotropic action which is the most significant among other effects
- is used *to treat acute heart failure, attack of supraventricular arrhythmia as well as for rapid digitalization*
- as a rule, does not cause intoxication.

CARDIAC GLYCOSIDES: peculiarities of preparations

INFUSION FROM THE HERB OF ADONIS

- Is a galenic preparation which contains glycosides from Adonis vernalis
- is taken orally, does not accumulate
- is weaker than all other preparations
- has sedative and direct diuretic action
- is used for the treatment of light forms of CHF, cardioneurosis, neurosis (is combined with valerian and bromides)
- has low toxicity.

NON-GLYCOSIDE INOTROPIC DRUGS

These inotrops improve cardiac pump function by adrenergic mechanisms in the heart or by reducing of peripheral vascular resistance.

CLASSIFICATION

1. Adrenomimetics

– Dobutamine (β1-adrenergic agonist)
– Dopamine (β1-adrenergic agonist)
– Isoprenaline (β1-, β2- adrenergic agonist)
– Ephedrine (α-, β- adrenergic agonist)

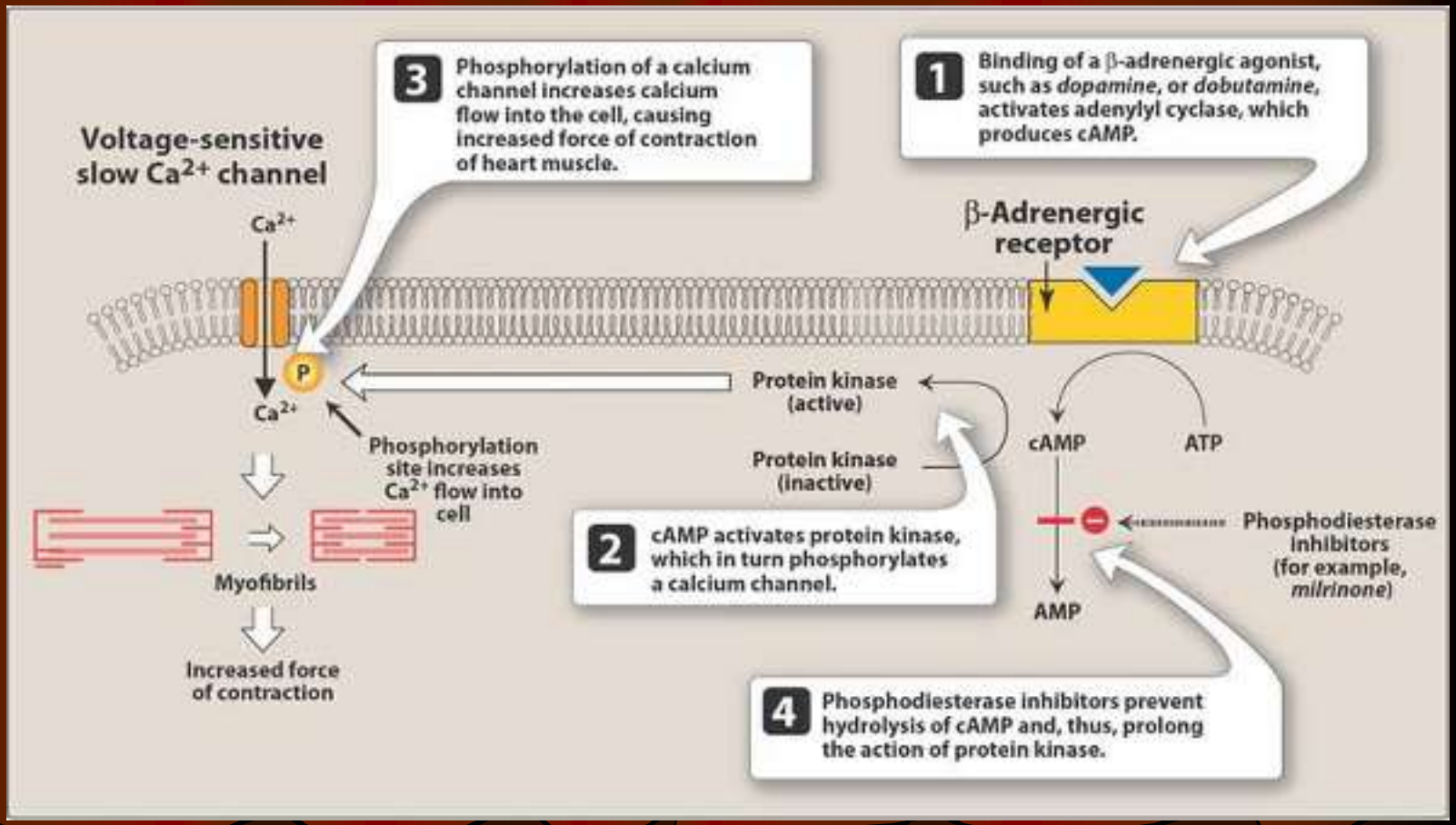
2. ACE (angiotensin converting enzyme) inhibitors

- Captopril
- Enalapril

3. Selective PDE III (phosphodiesterase III) inhibitors

– Amrinone
– Milrinone.

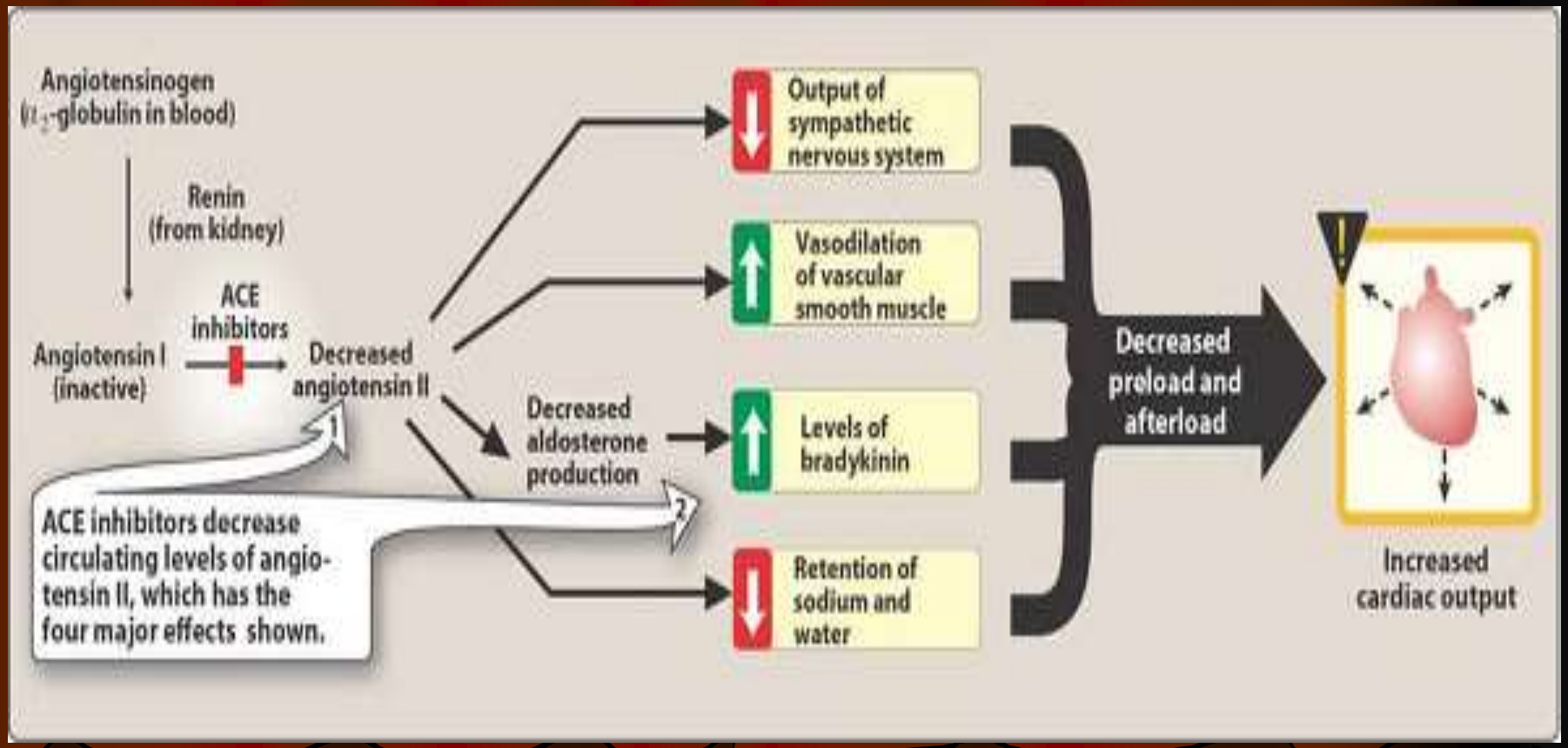
NON-GLYCOSIDE INOTROPICS:
Dobutamine's mechanism of action



NON-GLYCOSIDE INOTROPICS:
Dobutamine

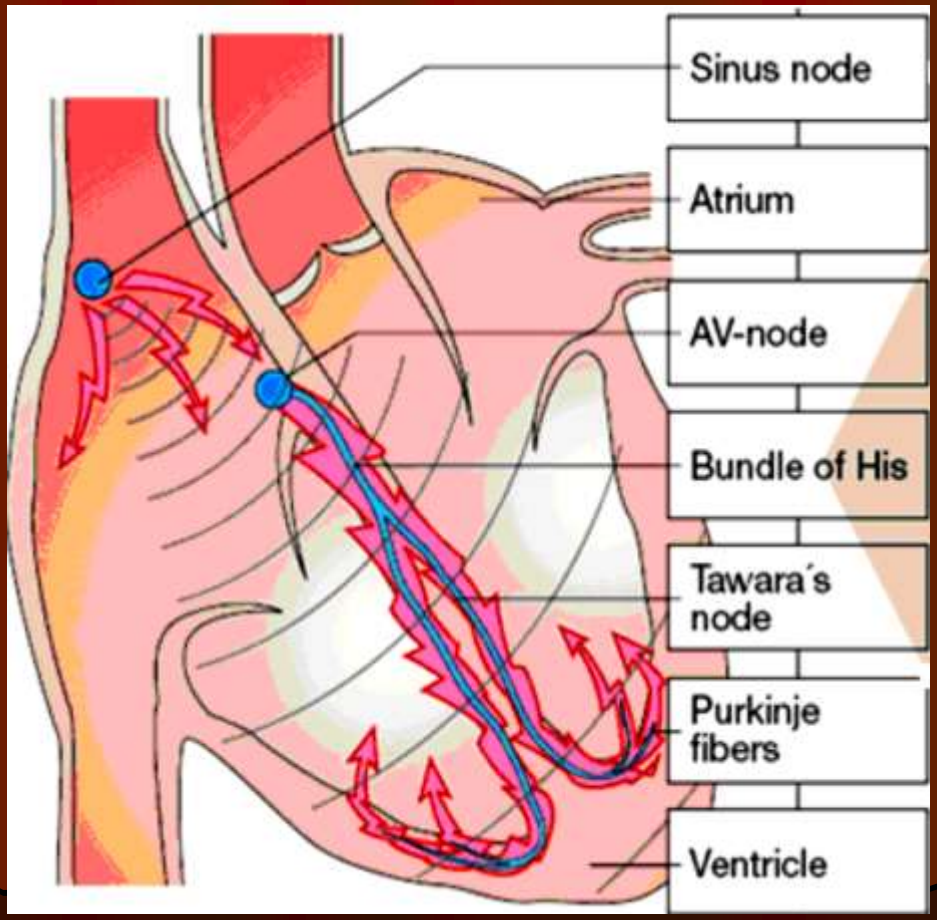
- Is a non-glycoside inotropic agent
- is similar to dopamine on chemical structure
- is administered by IV infusion
- is a selective agonist of β1-adrenoceptors in the heart, has positive inotropic action, improves coronary circulation, reduces peripheral resistance, redistributes blood flow in favor of the heart and lungs, increases renal blood flow, does not act on the heart rate; does not cause hypertension
- is used in acute heart failure, cardiogenic shock
- may cause tachycardia, arrhythmia.

NON-GLYCOSIDE INOTROPICS: ACE inhibitors in CHF

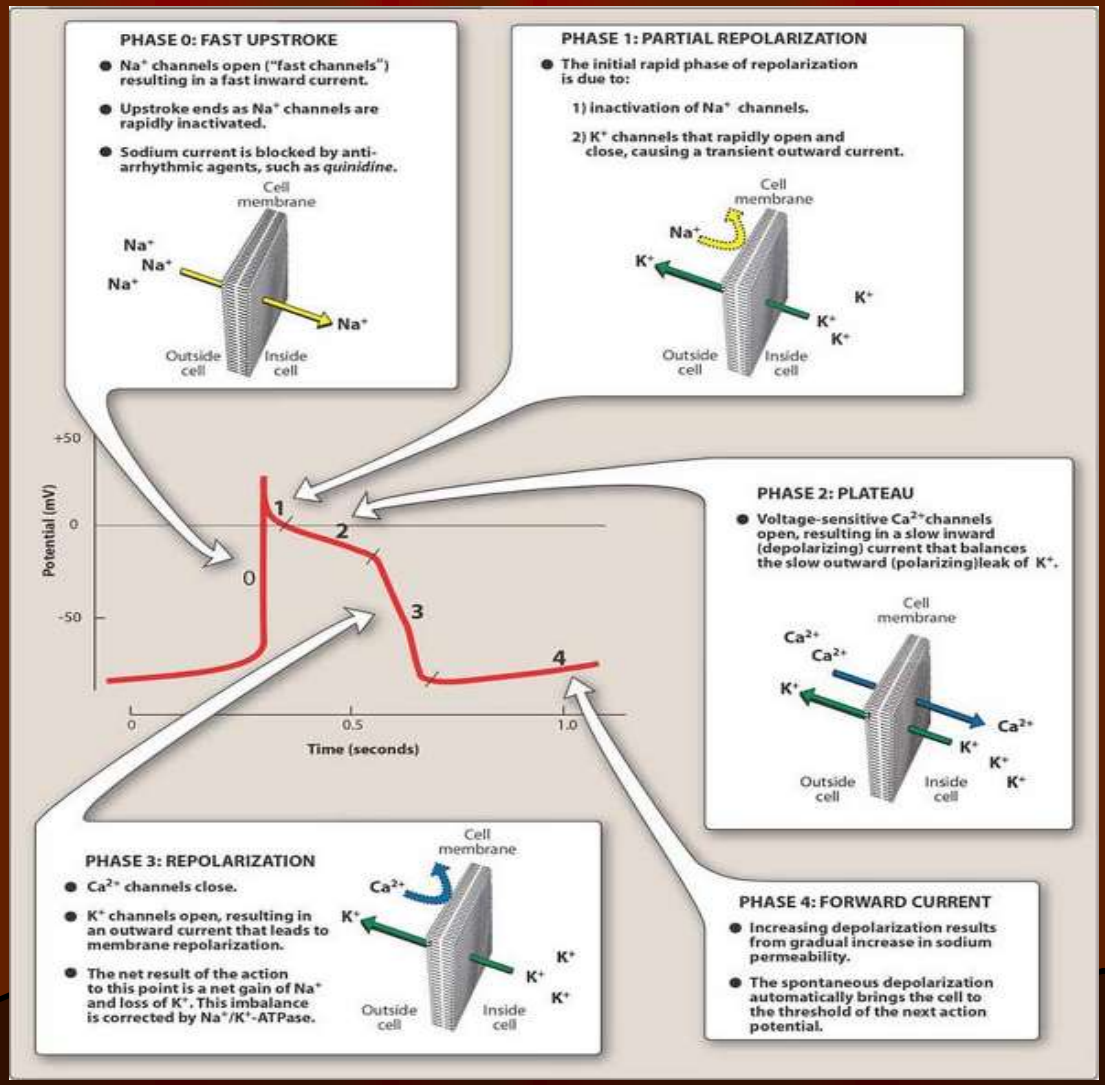


ANTI-ARRHYTHGMICS

ELECTRICAL CONDUCTION SYSTEM OF THE HEART



CARDIAC ACTION POTENTIAL (PHASES 0-4)



CARDIAC RHYTHM DISORDERS

Cardiac arrhythmia *(also* ***dysrhythmia****)* is a term for any from large and heterogeneous group of conditions in which there is abnormal electric activity in the heart They may occur due to disturbances of impulse formation, disturbances of impulse conduction, or both.

Any part of the heart that initiates an impulse without waiting for the SA node is called an ***ectopic focus.*** Premature beat caused by empulse from ectopic focus is named ***extrasystole***.

Re-entry arrhythmias occur when an electrical impulse recurrently travels in a tight circle within the heart, rather than moving from one end of the heart to the other and then stopping. Re-entry circuits are responsible for atrial flutter, most paroxysma slupraventricular tachycardia, and dangerous ventricular tachycardia.

When an entire chamber of the heart is involved in a multiple micro-reentry circuits, and therefore quivering with chaotic electrical impulses, it is said to be in ***fibrillation***.

There are many kinds of heart arrhythmias. According to the site of initiation ***arrhythmias may by atrial and ventricular***.

They are divided into ***tachyarrhythmias*** (more than 80 beats per min) and ***bradyarrhythmias*** (less than 60 beats per min). Paroxismal atrial tachyarrhythmia, atrial flutter, ventricular flutter, atrial fibrillation, extrasystolia, ventricular fibrillation belong to tachyarrhythmias. Bradycardia often is associated with AV block.

ANTI-ARRHYTHMIC DRUGS

Anti-arrhythmics are a group of preparations that are used to suppress fast rhythms of the heart.

VAUGHAN WILLIAMS ANTIARRHYTHMIC CLASSIFICATION

Antiarrhythmics designed for treatment of tachyarrythmias are classified on the base of their electrophysiological effects.

A. Class I. Membrane stabilizing agents (Na+ channel blockers)

1. Subclass IA
- Quinidine
- Procainamide
- Disopyramide

2. Subclass IB
- Lidocaine
- Phenytoin
- Mexiletine

3. Subclass IC
- Propafenone
- Flecainide

B. Class II. β-adrenoblockers
- Propranolol

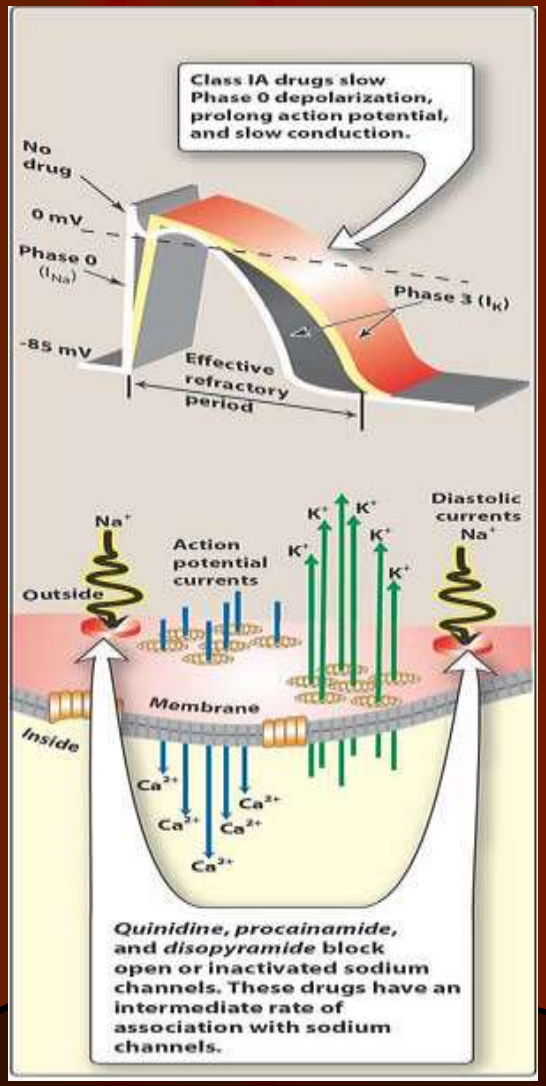
C. Class III. K+ channel blockers
- Amiodarone
- Bretylium
- Sotalol

D. Class IV. Ca+ +channel blockers (agents affect the AV node)
- Verapamil
- Diltiazem

E. Class V. Agents of other or unknown mechanisms
1. Cardiac glycosides (Digitoxin, Digoxin)
2. Potassium preparations (Pananginum.)
3. Adenosine.

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

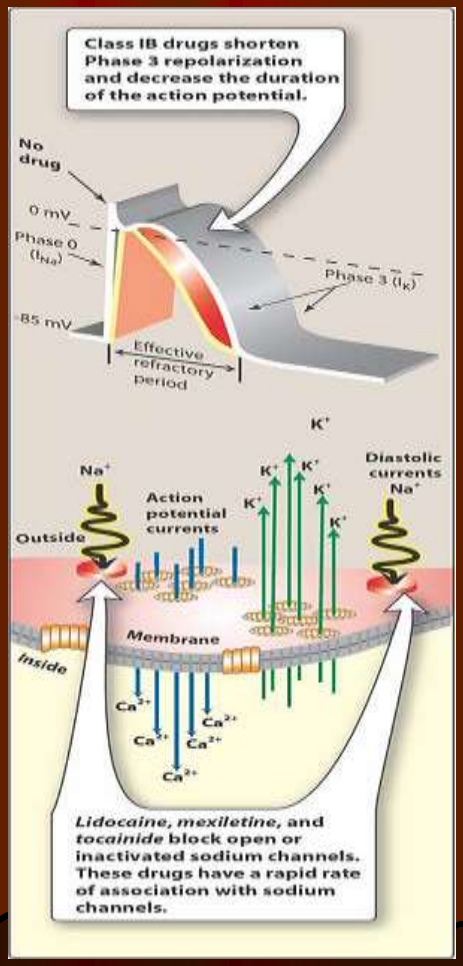
CLASS I. MEMBRANE STABILIZING AGENTS: Subclass IA



CLASS I. MEMBRANE STABILIZING AGENTS: Subclass IA preparations

- ***Qiunidine*** is an alkaloid, isomeric form of quinine; is taken orally, has duration of action of 6-8 hrs; inhibits excitability, automaticity, and conductivity in atria, AV node, bundle of His and Purkinje fibers, inhibits ectopic arrhythmias, ventricular arrhythmias caused by increased normal automaticity, prevents re-entry arrhythmias, decreases contractility of myocardium, is used in the treatment of atrial, AV junctional, and ventricular arrhythmias, is applied to maintain sinus rhythm after direct current cardioversion; may cause deformation of QRS complex, some kinds of ventricular tachyarrhythmia, heart block, asystole, heart failure, hypotension, weakness, headache, vision disturbances, spastic pain in the abdomen, nausea, vomiting, diarrhea, hemolytic anemia (as manifestation of idiosyncrasy), thrombocytopenia, skin rash.
- ***Procainamide*** is procaine derivative; is administered orally, IM, IV, has a half-life of 2-3 hrs, is acetylated in the liver to N-acetylprocainamide which has properties of class III drug; is not toxic, does not inhibit contractility; may cause side-effects, such as AV block, reversible lupus erythematosus-like syndrome, nausea, vomiting, seizures, asystole, and induction of ventricular arrhythmias (in overdose). Procainamide can be used in the treatment of atrial fibrillation in the setting of WRW syndrome, and in the treatment of hemodynamically stable tachycardias.
- ***Disopyramide*** is like to quinidine; is administered orally and parenterally (IV); increases refractory period in atria, inhibits conduction in bundle of His, produces negative inotropic effect (which is greater than the effect of quinidine and procainamide), has M-cholinoblocking properties; is used in atrial and ventricular premature beats, supraventricular tachyarrhythmia, is more effective in the treatment of ventricular arrhythmia; may cause worsening of arrhythmia, heart failure, hypotension, dry mouth, blurred vision, retention of urination, headache, allergic reactions; is contraindicated in AV block, denominated bradycardia, heart failure, cardiogenic shock.

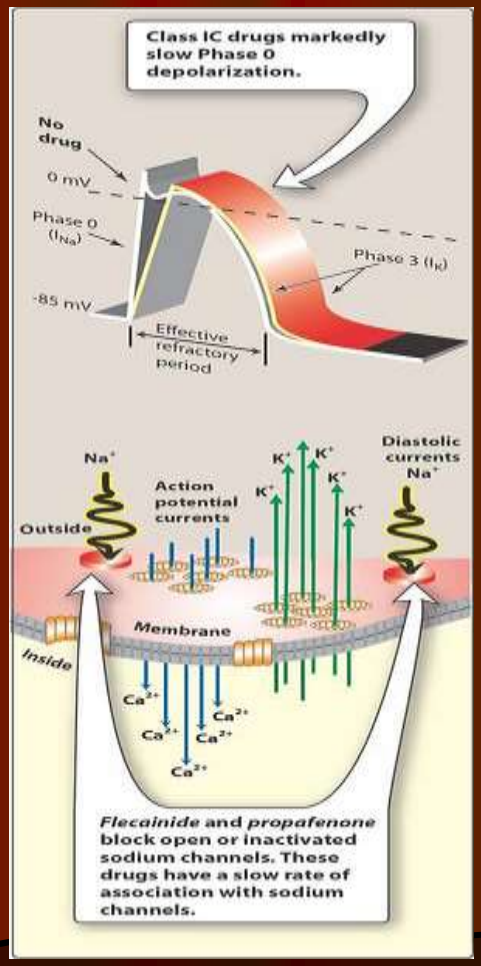
CLASS I. MEMBRANE STABILIZING AGENTS: Subclass IB



CLASS I. MEMBRANE STABILIZING AGENTS: Subclass IB preparations

- ***Lidocaine*** is a local anesthetic; is administered IV, IM, by IV infusion, is widely distributed in the body tissues, is metabolized in the liver, is excreted with urine, acts during 6-8 hrs; blocks Na+ channels, increases K+ efflux, accelerates repolarization, inhibits Phase 2, inhibits Phase 4 in Purkinje fibers, that's why decreases their automaticity, decreases re-entry, unlike to quinine, lidocaine suppresses arrhythmias caused by abnormal automaticity, does not influence on the atria; is more effective in ventricular tachyarrhythmia; is the drug of choice for emergency treatment of cardiac arrhythmias may cause vertigo, disturbances of consciousness, seizures, oppression of respiration, nausea, vomiting, hypotension, collapse, bradycardia, arrhythmia, asystole, shock, allergy; is contraindicated in hypersensitivity, epilepsy, AV block, bradycardia, weakness of SA node.
- ***Mexiletine*** is a stable preparation; is taken orally; is used for chronic treatment of ventricular arrhythmias associated with previous myocardial infarction; may cause nausea, vomiting, nistagmus, blurred vision.
- ***Phenytoin*** is an anti-epileptic drug; is administered orally and IV; in myocardium it decreases K+ loss caused by cardiac glycosides, inhibits premature beats in acute poisoning by cardiac glycosides, improves blood circulation in the heart, lowers BP; is used in acute poisoning with cardiac glycosides, heart surgeries, arrhythmias of central origin.

CLASS I. MEMBRANE STABILIZING AGENTS: Subclass IC



CLASS I. MEMBRANE STABILIZING AGENTS: Subclass IC preparations

- ***Propafenone*** is administered orally, IV; has membrane-stabilizing properties, is β-adrenoblocker and calcium antagonist, decreases automaticity, inhibits conduction of excitement in AV node, bundle of His and Purkinje fibers; is used in ventricular tachyarrhythmia if other remedies are ineffective; may cause postural hypotension.
- ***Flecainide*** is taken orally, undergoes minimal biotransformation, and has a half-life of 16-20 hrs; suppresses Phase 0 upstroke in Purkinje and myocardial fibers, causes the slowing of conduction in all cardiac tissue with a minor effect of on the duration of the AP and refractoriness, reduces automaticity; is used in treating refractory ventricular arrhythmias, is particularly useful in suppressing of premature ventricular contractions; may cause dizziness, blurred vision, headache, nausea, aggravation of CHF, induction of some kinds of dangerous ventricular arrhythmias.

CLASS II. β-ADRENOBLOCKERS

Mechanism of anti-arrhythmic action

- β-adrenoblockers block β1-adrenoceptors, prevent the action of catecholamines on myocardium.
- These drugs diminish Phase 4 depolarization.
- As a result, they prolong refractory period and decrease conductivity.
- They act by slowing conduction through the AV node
- They depress automaticity.
- Thus β-adrenoblockers decrease heart rate and contractility.

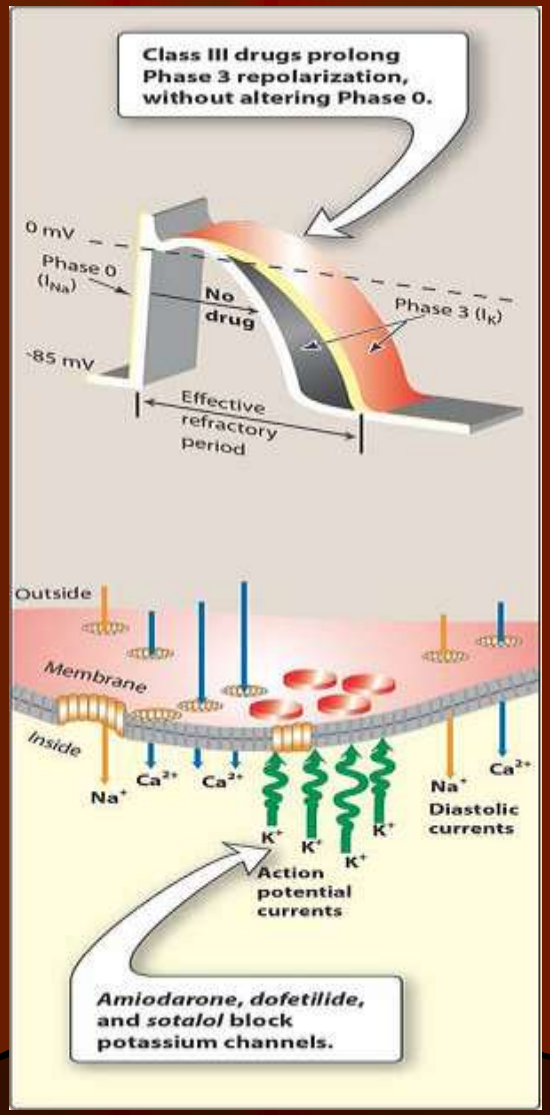
Indications

- Tachyarrhythmia caused by increased sympathetic activity
- Atrial flutter and fibrillation
- AV nodal re-entrant tachycardia.

Side-effects (cardiac)

- AV block
- Bradycardia
- Worsening in CHF.

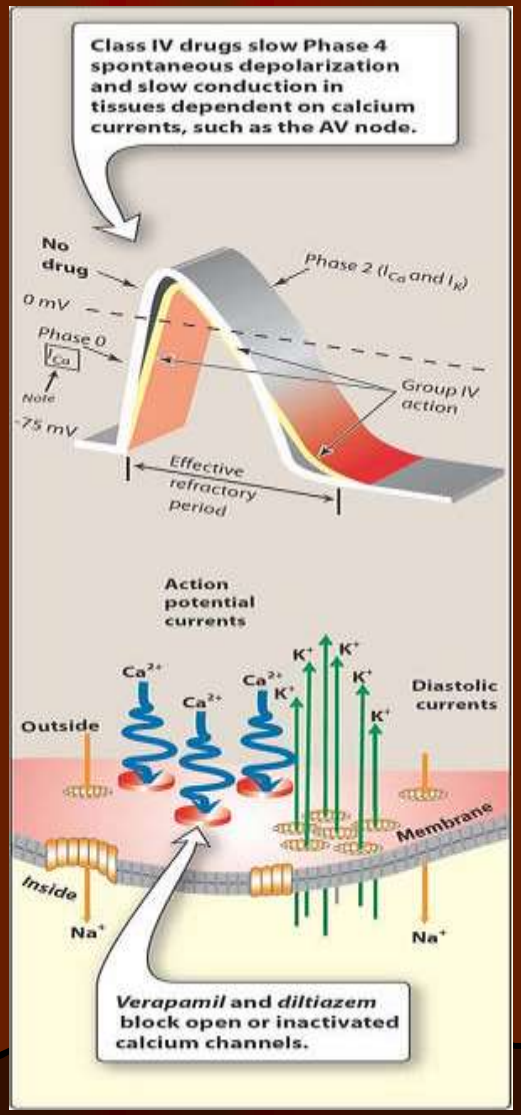
CLASS III. K+ CHANNEL BLOCKERS



CLASS III. K+ CHANNEL BLOCKERS: preparations

- ***Amiodarone*** is a benzofuran derivative, contains iodine and is related structurally to thyroxine; is administered orally or IV; binds to plasma proteins (95% of the drug), is metabolized in the liver (main metabolite is desethylamiodarone which strengthens the anti-arrhythmic action of the drug), is excreted with bile, has a half-life of 20-100 days; displays complex effects showing class I, II, III, and IV actions, blocks K+ channels, blocks Ca++ and Na+ channels; modifies the condition of α- and β-adrenoceptors, as well as glucagons receptors (non-competitive antagonism); increases the duration of AP and the refractory period in ventricular and atrial muscle; has anti-arrhythmic action; produces systemic and coronary vasodilation resulting in antianginal action; is used for treatment of ventricular arrhythmia, ventricular fibrillation in patients of risk group, supraventricular tachyarrhythmias, angina pectoris; myocardial infarction, for prevention of sudden coronary death; may cause side-effects, such as pulmonary fibrosis (reversible), bradycardia, AV block, phototoxicity, corneal microdeposits and blurred vision, hyper- and hypothyroidism, ataxia, tremor, myopathy and neuropathy, anorexia, nausea, vomiting; is contraindicated in patients with sinus bradycardia, AV block, syndrome of sinus node weakness, diseases of thyroid gland, pulmonary fibrosis, hypersensitivity to iodine, pregnancy, lactation. Course of treatment must have a provision of two days "drug-free interval" every week.
- ***Bretylium tosilate*** is administered IV, IM, is excreted unchanged with urine; has potent anti-arrhythmic effect in ventricular arrhythmias; increases the duration of refractory period in Purkinje fibers, has sympatholytic action, decreases BP; is used for ventricular fibrillation, mainly in acute period of myocardial infarction or in resistance to electrical defibrillation; may cause severe postural hypotension, transitory tachycardia and ectopic beats, nausea, vomiting; is contraindicated in pheochromacytoma, acute disorders of brain blood circulation, hypotension, collapse, severe renal failure, aortal stenosis, pulmonary hypertension, pregnancy, lactation.
- ***Sotalol*** is β-adrenoblocker and anti-arhythmic of class III; is administered orally and IV; is effective in many cases of supraventricular tachyarrhythmia, especially in atrial fibrillation, supraventricular tachycardia, WPW syndrome, ventricular tachycardia; is more effective than class I drugs in preventing of arrhythmia recurrence and in decreasing of mortality in patients with sustained ventricular tachycardia has side-effects connected with β-adrenoblocking properties (bradycardia, worsening in CHF).

CLASS III. Ca++ CHANNEL BLOCKERS



CLASS III. Ca++ CHANNEL BLOCKERS:

Mechanism of anti-arrhythmic action

- Ca++channel blockers block calcium channels of L-type.
- They inhibit Ca++entry into the cells of conductive system in the heart.
- Result is inhibition of automaticity and re-entry.
- They do not act on conductivity.

Indications

- Supraventricular tachyarrhythmia
- Fibrillation of atria, atrial flutter
- Paroxismal tachycardia.

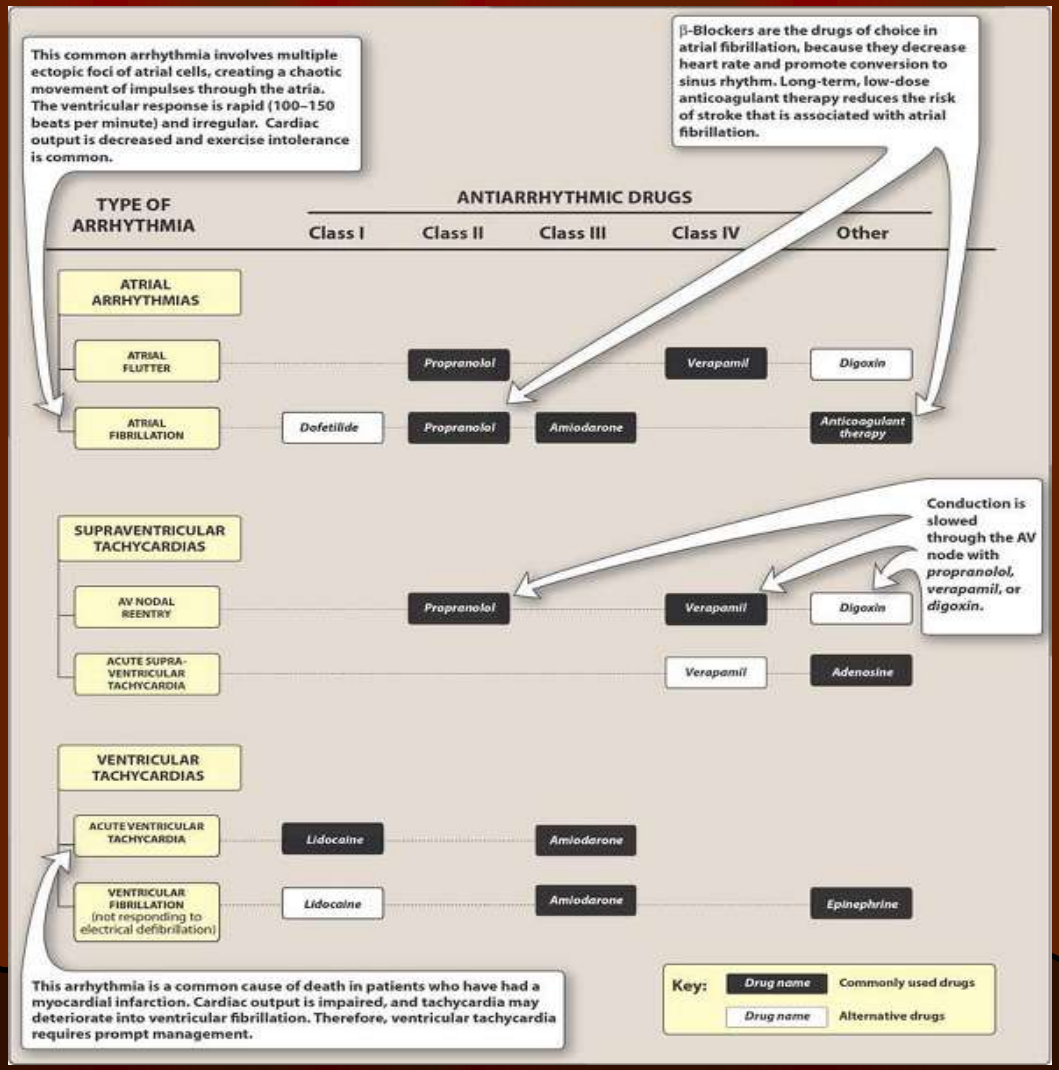
Peculiarities of preparations

- **Verapamil** is a calcium channel blocker from the first generation; is administered orally and IV; is well absorbed in GI tract; peak concentration occurs in 1-2 hrs; half-life is 3-6 hrs; it is undergoes first-pass biotransformation in the liver; is excreted with urine; has strong action on conductivity, excitability and automaticity, but weak vasodilation; is used for treatment of tachyarrhythmia and for termination of paroxysm of arrhythmia, angina pectoris, hypertension; may cause A-V block, heart failure, increase in digitalis toxicity when it is given together with digitalis preparations

CLASS V. AGENTS OF OTHER OR UNKNOWN MECHANISMS

- ***Cardiac glycosides*** (e.g., digoxin) shorten the refractory period in atrial and ventricular myocardial cells while prolonging the effective refractory period and diminishing conduction velocity in Purkinje fibers. They are used to control the ventricular response rate in atrial fibrillation and flutter.
- ***Potassium preparations*** (e.g., Pananginum) increase the speed of spontaneous depolarization in SA and AV nodes, as well as in all conduction system, thus inhibits the automaticity. They also normalize Phase 0. These drugs are used to treat tachyarrhythmias, especially caused by hypokalemia.
- ***Adenosine*** is a nucleoside which is administered IV and have very rapid and short action, is uptaken by red blood cells. It blocks A1-adenosine receptors in SA node. In high doses, adenosine decreases conduction velocity, prolongs the refractory period, and decreases automaticity in AV node. It is the drug of choice for abolishing of acute supraventricular tachycardia. Adenosine is not toxic, but may cause flushing, chest pain, hypotension.

DIFFERENCIAL USE OF ANTI-ARRHYTHMICS



DRUGS FOR THE TREATMENT OF BRADYCARDIA AND AV BLOCK

CLASSIFICATION

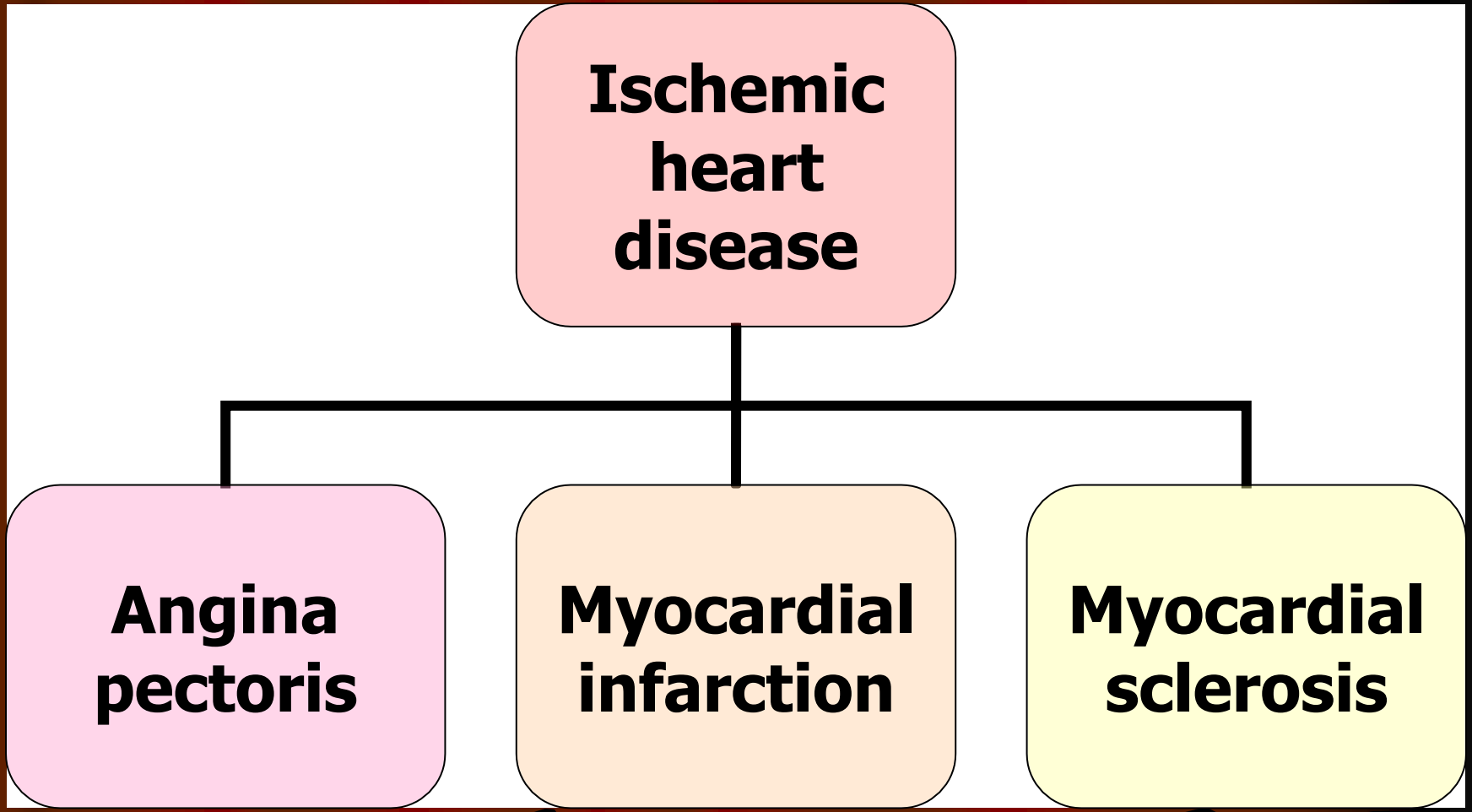
1. ***M-cholinoblockers***
   – Atropine
2. ***Adrenomimetics***
   – Isoprenaline
   – Ephedrine.

PECULIARITIES OF PREPARATIONS

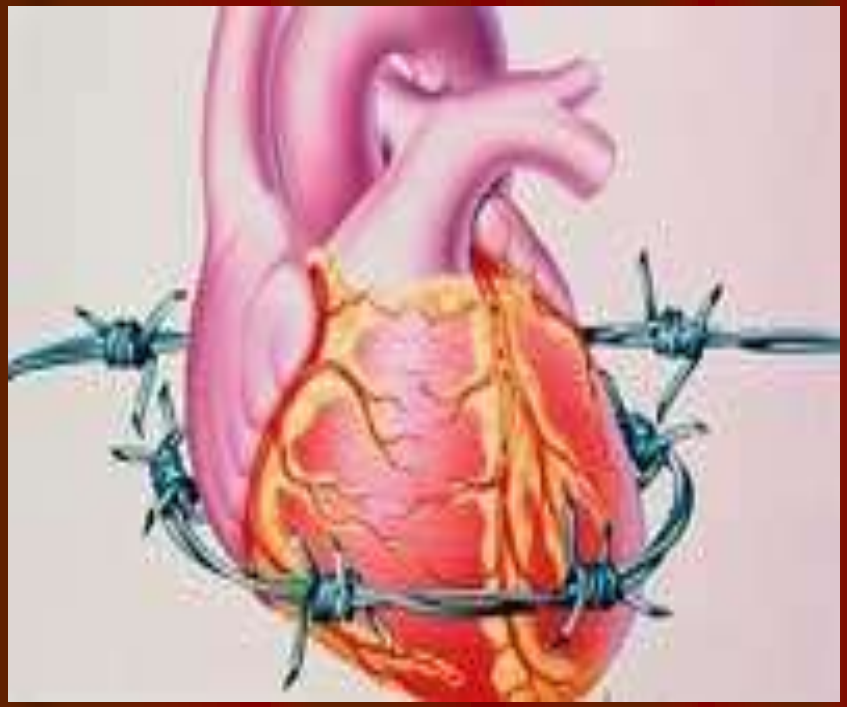
- ***Atropine*** is non-selected M-cholinoblocker, has dose-dependent action on the heart rate. At low doses, the predominant effect is a decreased heart rate (bradycardia) due to blockade of M1-receptors on the inhibitory pre-junctional neurons. With higher doses of atropine, the cardiac receptors on the SA node are blocked, and the cardiac rate increases (tachycardia).
- ***Isoprenaline*** is non-selective β-adrenergic agonist, stimulates β1-adrenoceptors in the heart and increases heart rate.
- ***Ephedrine*** is indirect-acting adrenomimetic, has presynaptic action, stimulates norepinephrine release and its action on adrenergic receptors in the heart, in such way increases cardiac rate and causes tachycardia.

ANTIANGINAL DRUGS

ISCHEMIC HEART DISEASE



ANGINA PECTORIS



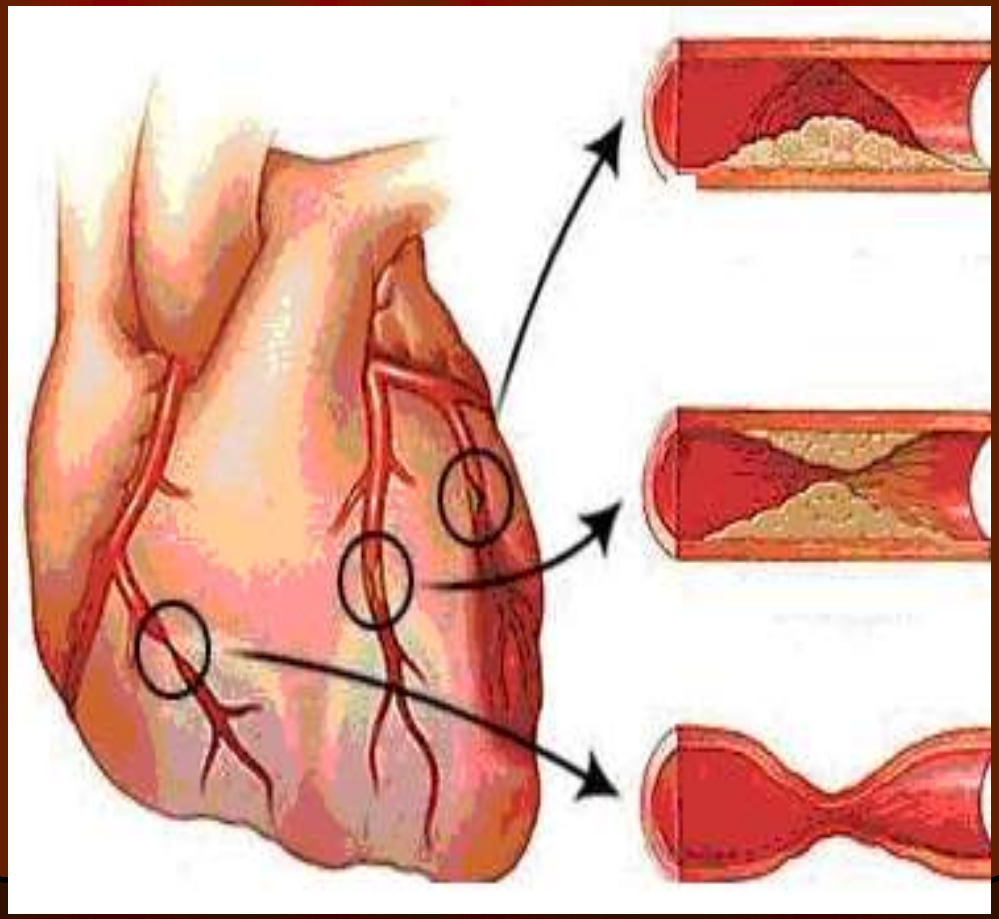
Angina pectoris is characterized by a sudden, severe pressing or acute chest pain radiating to the left arm and neck.

Anginal pain occurs when the oxygen supply to myocardium is insufficient for its needs.

The imbalance between oxygen delivery and utilization may result from a spasm or from obstruction of heart blood vessels.

The coronary blood flow is insufficient to meet the heart's metabolic requirements. It causes the onset of anginal pain.

MAIN CAUSES OF ANGINA ATTACK: thrombosis, atherosclerosis and spasm of coronary blood vessels



PHARMACOLOGICAL MANAGEMENT OF ANGINA PECTORIS

Pharmacological management in angina pectoris includes:

- ***Decrease in oxygen demand of myocardium***
- ***Increase in oxygen supply***
- ***Changes of myocardium metabolism in favor of stability to oxygen insufficiency.***

ANTIANGINAL DRUGS: classification

***A**. Drugs that decrease oxygen demand of myocardium and increase oxygen supply*

1. Organic nitrates

– Nitroglycerine (glyceril trinitrate, GTN)
– Isosorbide dinitrate
– Isosorbide mononitrate
– Sustac

2. Calcium channel blockers

– Verapamil
– Nifedipine
– Amlodipine

***B**. Drugs that decrease oxygen demand of myocardium*

1. β-adrenoblockers

– Propranolol
– Metoprolol
– Talinolol
– Atenolol

***C**. Drugs that increase oxygen supply:*

1. Substances of myotopic action

– Dipyridamole
– Papaverine
– Drotaverine (No-spa)

2. Substances of reflexive mechanism of action

– Validolum

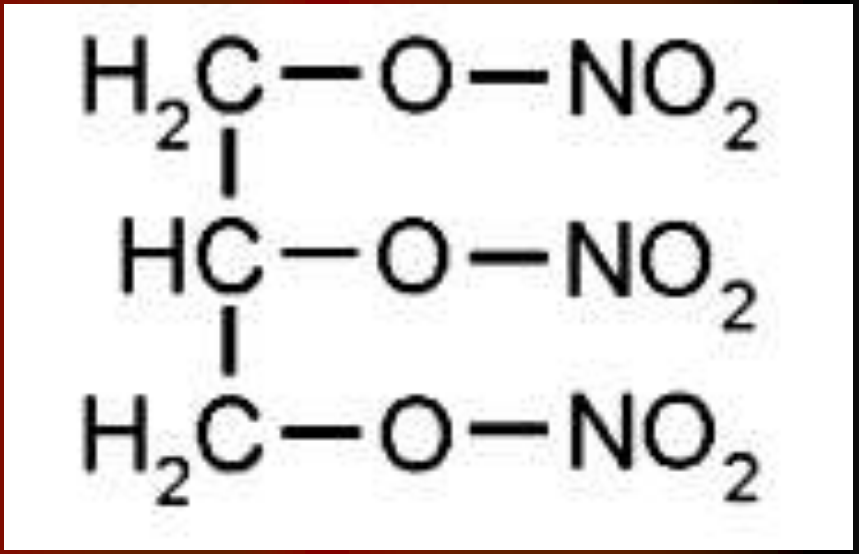
***D**. Drugs acting on myocardial metabolism*

– Sodium adenosine triphosphate
– Trimethazide
– Tocopherol acetate.

DRUGS THAT DECREASE OXYGEN DEMAND AND INCREASE OXYGEN SUPPLY

ORGANIC NITRATES. NITROGLYCERINE

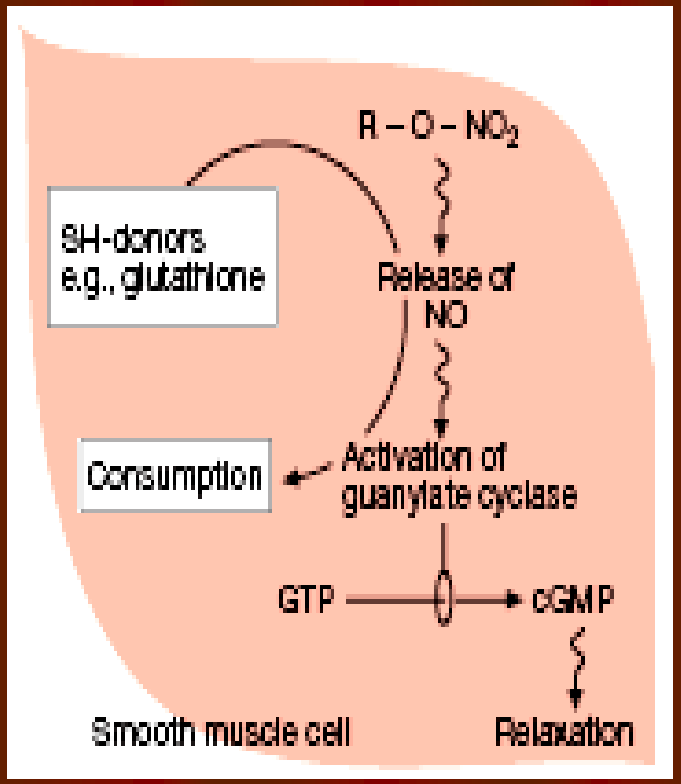
The drug has chemical structure of ***glyceril trinitrate***; is lipid- and alcohol-soluble.



NITROGLYCERINE: pharmacokinetics

- is taken sublingually
- is well absorbed from the oral cavity
- does not undergo hepatic first-pass metabolism after sublingual administration
- starts to act in 15-30 sec, develops peak concentration in 3-5 min after administration
- is metabolized in erythrocytes and in the liver with formation of active metabolites (mono- and dinitrates)
- finally is inactivated in the liver by conjugation
- is excreted with urine and air
- stays in the organism during 30-45 min.

NITROGLYCERINE: mechanism of action



Nitrate (NO2) transforms into nitrous oxide - **NO, endogenous endothelial-derived relaxation factor, EDRF**

It binds to SH-groups of nitrate receptors.

That is resulting in activation of guanyl cyclase and leads to increase in cGMP content in cells and decrease in Ca++ entry.

Such processes are resulting in dephosphorilation of the myosin light chain and relaxation of vascular smooth muscles.

NITROGLYCERINE: pharmacodynamics

- dilation of venous vessels, pooling of blood in the veins, as a result redistribution of blood in the body and decrease in preload on myocardium
- dilation of arterial vessels, decrease in total peripheral vascular resistance, as a result decrease in afterload on myocardium
- decrease in load on myocardium resulting in ***decrease of oxygen demand***
- dilation of coronary vessels, redistribution of coronary blood flow in favor of area of ischemia and ***increase in oxygen supply***
- inhibition of impulses from vasomotor center
- relaxation of smooth muscles of bronchi and biliary system.

NITROGLYCERINE: indications

- Angina pectoris attack
- Thrombosis of central vein of retina
- Combined therapy of hypertensive crisis
- Myocardial infarction and edema of lungs (special medicinal form of nitroglycerine for IV injections is used).

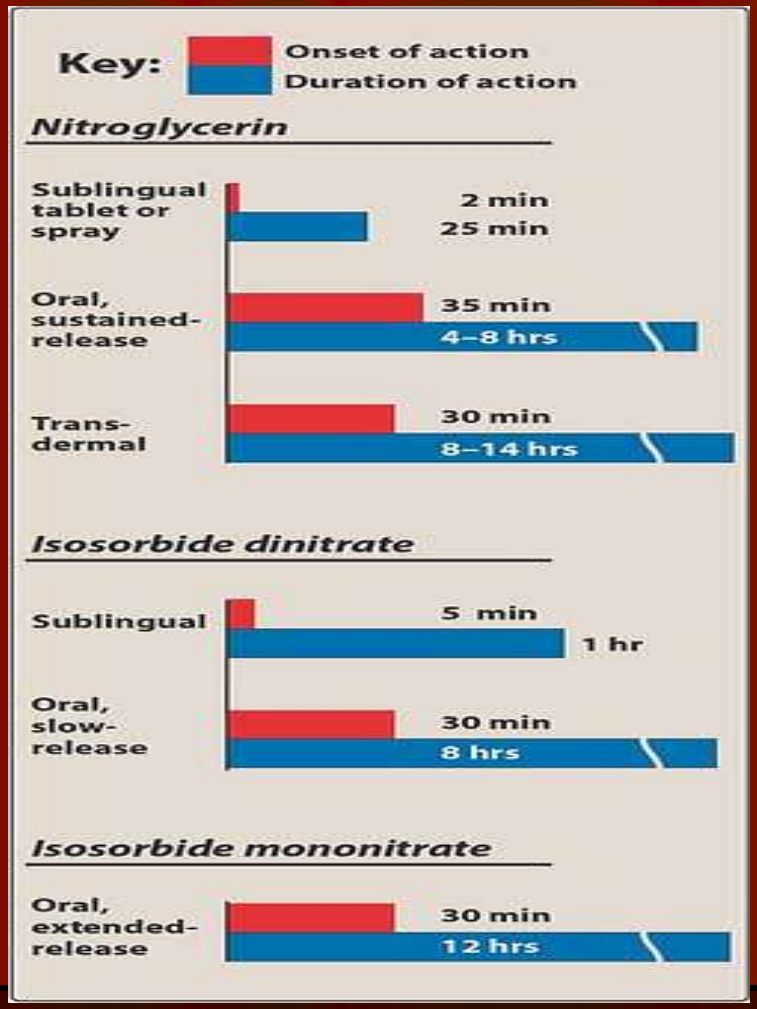
NITROGLYCERINE: side-effects

1. **Headache** (as a result of dilation of blood vessels in brain tunics and increasing of intracranial pressure; may be diminished by applying of Validolum or non-narcotic analgesics)
2. **Hypotension**, postural hypotension, collapse (may be treated by Mesatonum)
3. **Reflex tachycardia**
4. **Pain in eyes**, increase in intraocular pressure (as a result of dilation of ocular blood vessels)
5. **Flushing of the skin** (as a result of dilation of blood vessels in the skin)
6. **Tolerance** (as a result of the oxidizing of SH-groups of nitrate receptors; may be overcome by provision of a daily "nitrate-free interval" and by use of thiodrugs or antioxidants)
7. **Overdose** (forming of methemoglobin, hypoxia, collapse, respiratory failure; needs administration of Methileni coeruleum as an antidote).

NITROGLYCERINE: contraindications

1. Hypersensitivity
2. Hypotension
3. Myocardial infarction accompanied by hypotension
4. Hypertrophic obstructive cardiomyopathy
5. Aortic and mitral stenosis
6. Cardiac tamponade
7. Constrictive pericarditis
8. Increase in intracranial pressure (trauma of brain, hemorrhagical insult)
9. Glaucoma.

LONG-ACTING NITRATES



CALCIUM CHANNEL BLOCKERS: classification

On chemical structure

1. Phenylalkylamines
- Verapamil

2. Dihydropyridines
- Nifedipine (Phenigidinum)
- Amlodipine

3. Benzodiazepines
- Diltiazem

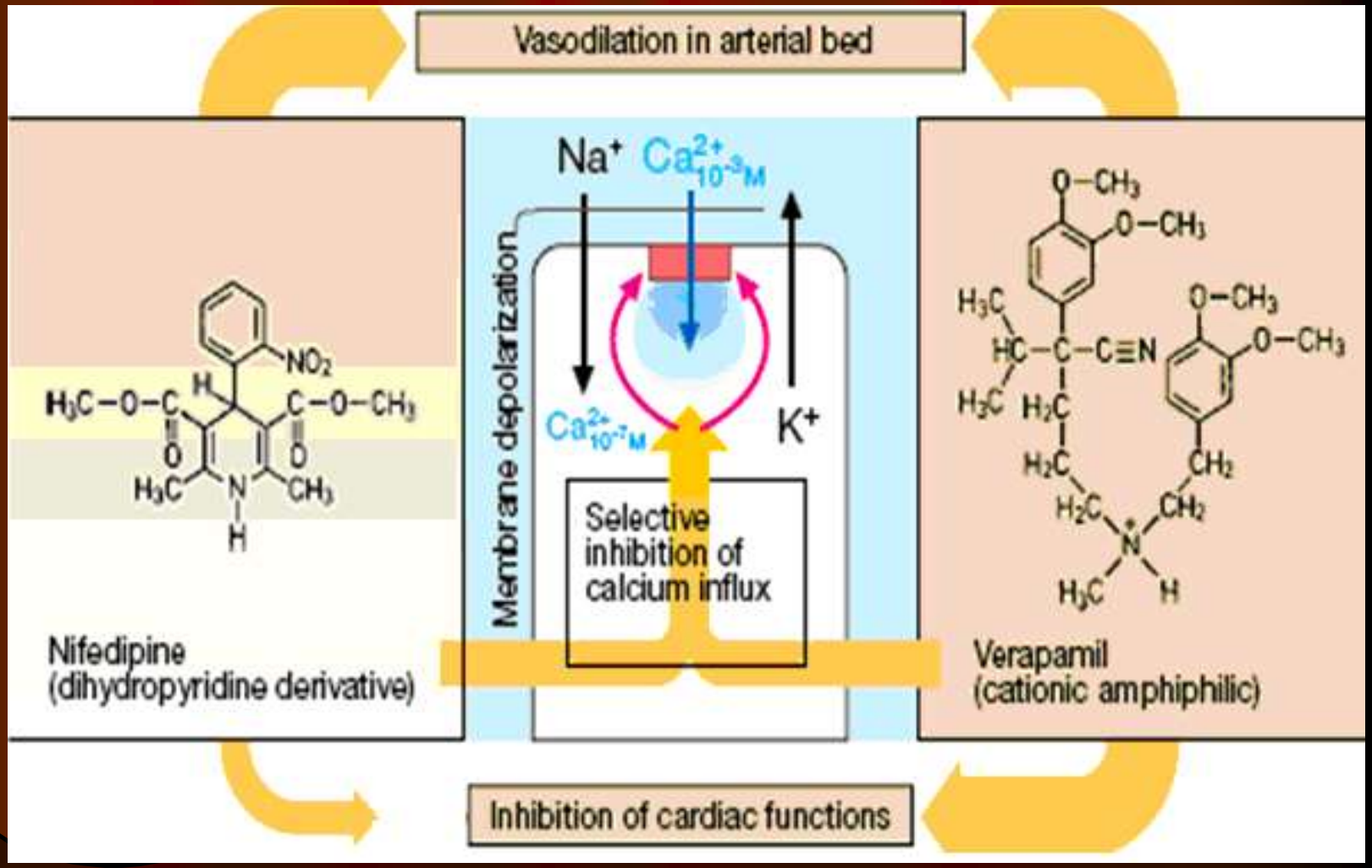
On generations

1. The first generation
- Verapamil
- Nifedipine
- Diltiazem

2. The second generation
- Nifedipine-retard

3. The third generation
- Amlodipine.

CALCIUM CHANNEL BLOCKERS: mechanism of action



CALCIUM CHANNEL BLOCKERS: pharmacodynamics and indications

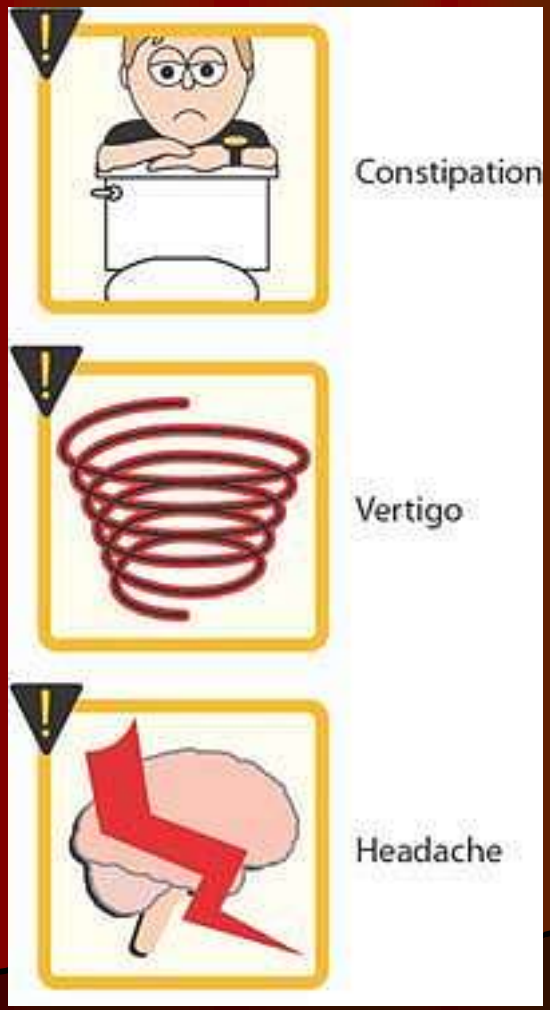
PHARMACODYNAMICS

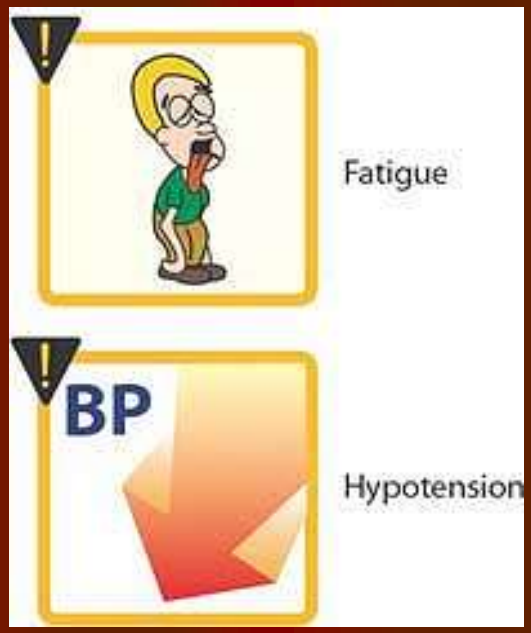
- dilation of blood vessels, reduction of total peripheral resistance and redistribution of blood in the body, decrease in the load on myocardium and ***decrease in oxygen consumption***
- dilation of coronary arteries and arterioles and ***increase in oxygen supply***
- decrease in A-V and S-A node conduction, prolongation of effective refractory period within the A-V node resulting in ***anti-arrhythmic action***
- dilation of peripheral blood vessels resulting in decrease of BP and ***antihypertensive action***
- anti-platelet action and decrease in blood viscosity
- relaxation of smooth muscles of uterus, bronchi and gut.

INDICATIONS

- Angina pectoris
- Hypertension
- Tachyarrhythmia.

CALCIUM CHANNEL BLOCKERS: side-effects



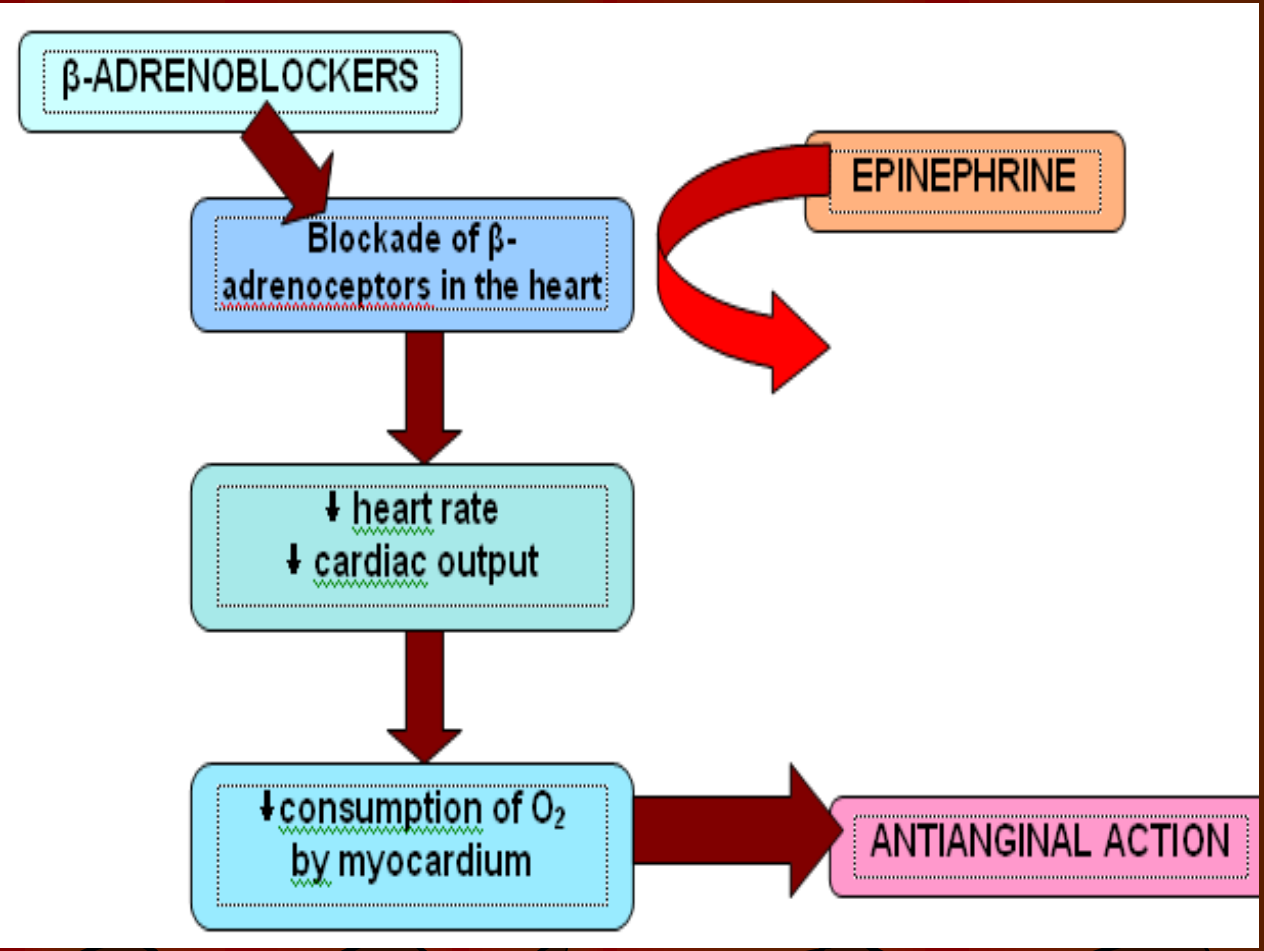


CALCIUM CHANNEL BLOCKERS: peculiarities of preparations

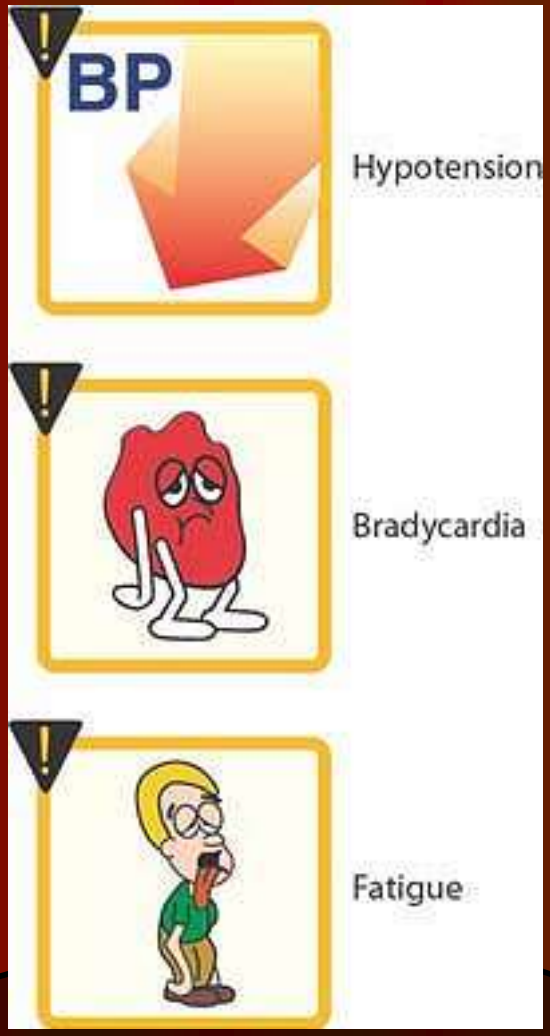
- ***Verapamil*** is calcium channel blocker from the first generation; is administered orally and IV; is well absorbed in GI tract; peak concentration occurs in 1-2 hrs; half-life is 3-6 hrs; it is undergone first-pass biotransformation in the liver; is excreted with urine; has strong action on conductivity, excitability and automaticity and denominated vasodilation; is used for treatment of tachyarrhythmia and for termination of paroxysm of arrhythmia, angina pectoris, hypertension; may cause A-V block, heart failure, increase in digitalis toxicity when it is given together with digitalis preparations.
- ***Nifedipine*** is calcium channel blocker from the first generation; is administered orally and sublingually; begins to act in 10 min after sublingual administration; peak level occurs in 30 min; half-life is 3-6 hrs; has strong vasodilation and weak action on heart rate; is used for angina pectoris, especially for Prinzmetal's angina, for hypertension; may cause reflexive tachycardia, hypotension, peripheral edema.
- ***Amlodipine*** is calcium channel blocker from the third generation; is taken orally; is absorbed in GI tract more fully and slower than nifedipine; is bound to plasma proteins stronger; is metabolized minimally; has long period of half-excretion; does not cause tachycardia.

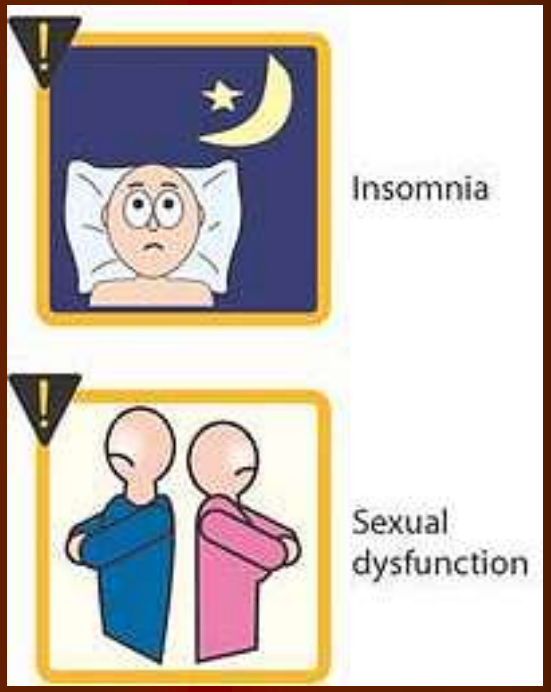
DRUGS DECREASING OXYGEN DEMAND OF MYOCARDIUM

β-ADRENOBLOCKERS: mechanism of antianginal action



β-ADRENOBLOCKERS: side-effects





β-ADRENOBLOCKERS: peculiarities of preparations

- ***Propanolol (Anaprilinum)*** is administered orally, IV; is absorbed in the GI tract; binds to proteins in blood serum; penetrates CNS; acts during 3-4hrs; *blocks both β1- and β2-adrenoceptors*; decreases the heart contractility, striking and minute volume, as a result, decreases consumption of oxygen by myocardium (***antianginal* effect**); decreases excitability and conductivity of myocardium, decreases the heart rate ***(anti-arrhythmic effect)***; decreases cardiac output and renin's secretion in the kidney, thus lowers BP ***(antihypertensive effect)***; also decreases intraocular pressure; has sedative action; is used to treat ischemic heart disease (prevention of angina pectoris attack, myocardial infarction); supraventricular tachyarrhythmia; hypertension; hyperthyroidism; migraine; glaucoma; has side-effects, such as: bradycardia, AV block, heart failure, hypotension, worsen of peripheral blood circulation, spasm of bronchi, gastric ulcer, hypoglycemia (when insulin is co-administered), weakness, drowsiness.
- ***Metoprolol*** has *cardioselective action on β1-receptors*; is taken orally for treatment of hypertension, angina pectoris, and arrhythmia, may be administered IV in acute cases, has less side-effects than propranolol, does not produce spasm of bronchi and stimulation of gastric secretion, may be used in patients with bronchial asthma, ulcerative disease, and diabetes mellitus.
- ***Talinolol*** has *cardioselective action on β1-receptors, inner sympathomimetic activity and membrane stabilizing effect* (does not inhibits heart contractility and conductivity), has less side-effects and less contraindications connected with influence on β2-adrenoceptors.
- ***Atenolol*** is preparation of *cardioselective action on β1-receptors*, is similar metopolol in action but acts longer, does not penetrate CNS.

DRUGS INCREASING OXYGEN SUPPLY IN MYOCARDIUM

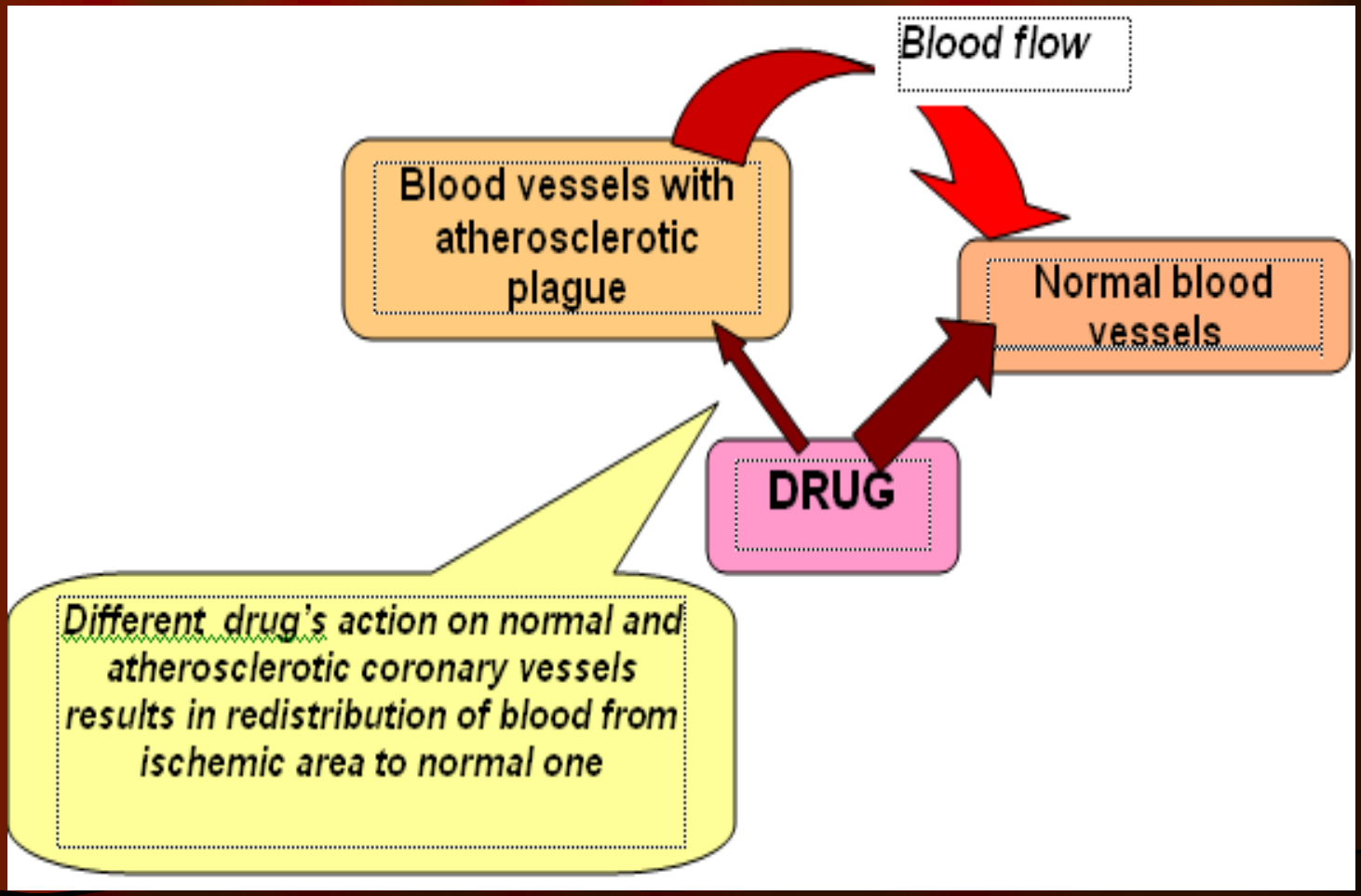
VALIDOLUM

- is menthol derivative
- is taken sublingually
- has reflexive mechanism of action: irritates sensitive nerve endings in oral mucous membrane and initiates reflex changes in vasomotor center activity, thus dilates coronary blood vessels, ***increases oxygen supply*** in myocardium and terminates angina attack
- is less active than nitroglycerine
- is used for termination of angina pectoris attack
- has not significant side-effects; may cause glossitis if it is taken very often.

DIPYRIDAMOLE

- is administered orally or IV
- inhibits adenosine desaminase, decreases the re-uptake of adenosine by myocardiocytes and erythrocytes, increases the concentration of adenosine in plasma resulting in dilation of coronary vessels and an ***increase in oxygen supply***
- produces dilation of coronary vessels, increase in amount of collateral vessels in myocardium, improving of coronary blood flow; increase in coronary sinus oxygen saturation, anti-platelet action
- is used for prevention of angina pectoris attack (is less effective than nitrates and other drugs), for prevention of thrombosis and re-thrombosis in patients with atherosclerosis or prosthetic cardiac valves; for treatment of disturbances of cerebral and peripheral blood circulation
- may cause side-effects, such as hypotension, flushing of the skin, headache, dyspepsia, syndrome of "*stealing*" in myocardium (dilation of normal coronary vessels is more intensive than the same of vessels with atherosclerotic lesions and the drug redistributes coronary blood flow in favor of normal areas of myocardium with worsening of blood supply in area of ischemia).

MECHANISM OF "STEALING" SYNDROME



DRUGS ACTING ON MYOCARDIUM METABOLISM

DRUGS ACTING ON MYOCARDIUM METABOLISM: peculiarities of preparations

- ***ATP-long*** is complex compound of ATP and metals (sodium and magnesium); is taken orally; is well absorbed in the gut; enhances ATP content in myocardium; ***limits ischemia***; improves contractility; has anti-arrhythmic action; is the additional drug in prophylaxis of angina attack.
- ***Antioxidants*** *(vitamin E, vitamin C)* inhibit non-enzymic free-radical oxidation, protect cell membranes, decrease hypoxia, ***limit area of ischemia***; are the additional drugs in treatment of angina pectoris and infarction.

PRINCIPLES OF TREATMENT OF MYOCARDIAL INFARCTION

Myocardial infarction is formation of an area of necrosis in myocardium due to local ischemia resulting from obstruction of circulation to the area, most commonly by thrombus or embolus. It is manifested persistent intense cardiac pain, diaphoresis, pallor, hypotension, faintness, nausea, vomiting, may be complicated by cardiogenic shock.

Main groups of preparations for myocardial infarction therapy:

- For analgesia: narcotic analgesics, neuroleptanalgesia, nitrous oxide
- For decrease in ischemia: nitroglycerine, β-adrenoblockers
- For decrease in arrhythmia: lidocaine, β-adrenoblockers, amiodarone, polarizing solution
- For inhibition of blood coagulation: anticoagulants, especially heparin
- For lysis of thrombus: thrombolytics: streptokinase, alteplase
- For decrease in acute heart failure: inotrtopic drugs, especially dobutamine; vasodilators.

CONTROL TASKS

During digitalization a patient had headache, fatigue, nausea, color vision impairment, and bradycardia. What drug should be prescribed to relieve these symptoms of digitalis toxicity?

Unithiolum
Atropine
Naloxone
Neostigmine
Nikethamide.

A patient with the signs of acute heart failure is delivered to a hospital. Which drug should be included into the urgent therapy first of all?

Corglyconum
Digitoxin
Nikethamide
Adrenaline
Noradrenaline.

Myocardiosclerosis is accompanied by chronic heart failure. Digoxin is administered in small individual dose for maintenance of heart compensation. Which mechanism is responsible for its positive inotropic action?

Blockage of sodium / potassium ATP-ase
Blockage of phosphodiesterase III
Blockage of calcium channels
Activation of calcium channels
Stimulation of beta1-adrenergic receptors.

CONTROL TASKS

Course of the treatment with amiodarone (Class III anti-arrhythmic) must have "drug-free" interval every week because:
It has a half-life of 20-100 days
It is related structurally to thyroxin
It forms active metabolite which strengthen the action of the drug
It may cause reversible pulmonary fibrosis as a side-effect
It may cause corneal microdeposits.

Calcium channel blockers (Class IV anti-arrhythmics) are effective in:
All listed arrhythmias
Supraventricular tachyarrhythmia
Fibrillation of atria
Flutter
Paroxismal tachycardia.

An old man has pressing retro-sternal pain. The drug of choice to terminate such angina attack is:
Nitroglycerine
Nifedipine
Drotaverine
Papaverine
Molsidomine.