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PREPARATIONS FOR TREATMENT OF ISCHEMIC HEART DISEASE. COMPLEX THERAPY OF MYOCARDIAL INFARCTION

General definitions

Angina pectoris is the principal symptom of **ischemic heart disease**. The primary cause of angina pectoris is an imbalance between the oxygen requirement of the heart and the oxygen supplied to it via the coronary vessels.

In classic angina, the imbalance occurs when the myocardial oxygen requirement increases, as during exercise, emotion, and coronary blood flow does not increase proportionately.

The resulting ischemia usually leads to sudden, severe, pressing substernal pain that often radiates to the left shoulder and arm and is often associated with depression of the S-T segment of the ECG.

Classic angina is therefore **"angina of effort."** In **variant angina**, oxygen delivery decreases as a result of reversible coronary vasospasm (usually superimposed on chronic obstruction). The underlying pathological process is usually advanced atherosclerosis of the coronary vasculature. In contrast, variant angina is caused by vasospasm of the coronary vessels and may not by associated with severe atherosclerosis.

In theory, the imbalance between oxygen delivery and myocardial oxygen demand can be corrected by

- **increasing delivery** (by increasing coronary flow);
- **decreasing oxygen demand** (by decreasing cardiac work).

Both measures are used in clinical practice.

ANTIANGINAL AGENTS

Agents, that diminish oxygen demand of myocardium

β-adrenergic antagonists

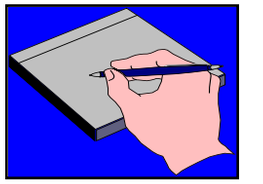
Agents, that decrease myocardial oxygen consumption and increase oxygen income to myocardium

- Organic nitrates
- Calcium channels blockers
- Agents, prolonging repolarization

Agents, that increase oxygen income to myocardium

Coronaro-dilators

ORGANIC NITRATES



Organic nitrates (and nitrites) are simple nitric and nitrous acid esters of alcohols. They differ in their volatility; for example, isosorbide dinitrate is solid at room temperature, nitroglycerin (glyceryl trinitrate) is moderately volatile, whereas amyl nitrate is extremely volatile.

Mechanism of action:

Effects on cardiovascular system:

i. At therapeutic doses, *nitroglycerin* causes dilation of the large veins, resulting in pooling of blood in the veins. This **diminishes preload** (venous return to the heart).

ii. Dilation of large arteries decreases arterial pressure. This result in **diminished afterload.** Decreased pre- and afterload causes **decreased myocardial oxygen requirement.**

iii. Nitrates **dilate the epicardial coronary arteries.** Nitrates benefit patients with variant angina by relieving coronary artery spasm.

Pharmacokinetics: Significant first pass metabolism of organic nitrates occurs in the liver. Their bioavailability is very low (typically < 10-20%). The sublingual route, which avoids the first-pass effect, is therefore preferred for achieving a therapeutic blood level rapidly (in a few minutes). Therefore, it is common to give the drug either sublingually or via a patch.

The major **adverse effects** of organic nitrates is a direct extension of therapeutic vasodilation: orthostatic hypotension, tachycardia, throbbing headache, and elevation of intracranial pressure.

Tolerance: Tolerance to the action of nitrates develops rapidly. It can be overcome by provision of a daily " nitrate-free interval " to restore sensitivity to the drug. This interval is typically 6 to 8 hours, usually at night because there is decreased demand on the heart at that time.

Organic nitrates

Agents	Route of administration	Onset (min)	Duration	Uses	
				attack	course
Nitroglycerin (tab., caps., sol.)	Sublingual	1-2	10-30 min	+	-
Nitroderm (patch)	Trans Dermal	15-30	upto 24 hrs	-	+
Isosorbide dinitrate	Sublingual, Oral	3-10 20-60	1-12 hrs	+-	+
Isosorbide mononitrate	Oral	30 min - 2 hrs	4-14 hrs	-	+

CALCIUM CHANNELS BLOCKERS

Mechanism of action and effects on cardiovascular system. The calcium channels blockers inhibit the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. The result is a marked decrease in transmembrane calcium current associated

- in smooth muscle with a long-lasting relaxation (decreased arteriolar tone and systemic vascular resistance, resulting in decreased arterial and intraventricular pressure);
- in cardiac muscle
  - with a reduction in contractility throughout the heart which in turn reduces myocardial oxygen requirements;
  - decreases in sinus node pacemaker rate and in atrioventricular node conduction velocity.

As a result of all of these effects, left ventricular wall stress declines, which reduces myocardial oxygen requirements. Calcium channel-blocking agents also relieve and prevent focal coronary artery spasms - the primary mechanism of variant angina.

Pharmacokinetics: The calcium channel blockers are orally active agents. **Verapamil** and **diltiazem** are used by the intravenous route as well. They are characterized by high first-pass effect, high plasma protein binding, and extensive metabolism.

CALCIUM CHANNEL BLOCKERS

- **Type I (cardiotropic) –*phenylalkylamines derivatives :* verapamil and others.**

- **Type II (vasotropic) – *dihydropyridines derivatives :***
  - ✓ ***I-st generation* – nifedipine**
  - ✓ ***II-nd generation* – amlodopine, nimodipine, isradipine and others.**

- **Type III (mixed) – *benzothiazine бензотиазина:* diltiazem**

COMPARATIVE CHARACTERISTICS OF CALCIUM CHANNELS BLOCKERS

Function	Verapamil	Nifedipine
Coronary blood flow	↑	↑↑
Arterial BP	↓	↓↓
Heart rate	↓	↑
AV-conductivity	↓	-

Uses of calcium blockers.

Well-documented efficacy
- angina,
- hypertension
- supraventricular tachyarrhythmias

Probable efficiacy
- hypertrophic cardiomyopathy
- migraine
- Raynaud's phenomenon
- atherosclerosis

The most important **adverse effects** reported for the calcium channel blockers are direct extensions of their therapeutic action - serious cardiac depression, including cardiac arrest, bradycardia, atrioventricular block, and congestive heart failure. These effects have been rare in clinical use.

Recent reports suggest that prompt-acting nifedipine may increase the incidence of myocardial infarction.

Patients receiving beta-adrenoceptor-blocking drugs are more sensitive to the cardiodepressant effects of calcium channel blockers.

Minor toxicity (not usually requiring discontinuance of therapy) includes flushing, edema, dizziness, nausea, and constipation.

β-ADRENERGIC BLOCKERS

These agent by blocking β1 receptors **decrease heart rate and contractility, blood pressure,** which **decrease myocardial oxygen requirements** at rest and during exercise.

Propranolol is the prototype of this class of compounds, but other β-blockers, such as **metoprolol** and **atenolol** are equally effective. However, agents with intrinsic sympathomimetic activity (for example, **pindolol**, and **acebutolol**) are less effective in angina and should be avoided.

The β-blockers reduce the frequency and severity of angina attacks. These agents are particularly useful in the treatment of patients with myocardial infarction, because they **reduce reinfarction and mortality in patients.** The β-blockers can be used with nitrates to increase exercise duration and tolerance.

β-ADRENERGIC BLOCKERS

They are, however, **contraindicated** in patients with diabetes, peripheral vascular disease, or chronic obstructive pulmonary disease.

K^+ -channel blockers (amiodaron)

- ✓ block of K^+-channels
- ✓ block of Na^+- and Ca^{2+}-channels
- ✓ β- and α-adrenolytic action

⇒

- ➢ «-» chrono-, dromo-, batmotropic effects
- ➢ preservation of myocardial energetic resources (↑ creatinin sulfate, adenosin and glycogen)
- ➢ ↓ O_2 demand of myocardium
- ➢ ↓ peripheral vascular resistance and BP (moderate)
- ➢ dilation of the coronary vessels

K^+ -channel blockers (amiodaron)

Therapeutic uses

- stenocardia
- tachyarrhythmia

Adverse effects

- cardiac arrhythmia (disturbances of AV-conductivity, bradicardia etc.)
- tremor, ataxia, paresthesia
- thyroid gland disfunction
- pulmonary fibrosis
- liver disturbances
- drug's accumulation in cornea, skin
- photosensibilization etc.

Miscellaneous

- agents, that improve myocardial O_2 supply миокарду: miotropic (papavarin, dipyridamol etc.) and reflective action (validol)
- agents, that increase myocardial resistance to hypoxia: antihypoxants, antioxidants, anabolics etc.