

PHARMACOLOGY

Drugs acting on Cardiovascular System: **Antianginal Drugs**

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Keywords

Hypertension, Diuretics, thiazide diuretics, Vasodilators, angiotensin converting enzyme inhibitor, ACE inhibitor, angiotensin receptor blocker, ARB, calcium-channel blocker, beta-blocker, angina, Glyceryl trinitrate, Isosorbide dinitrate, Isosorbide-5-mononitrate, Myocardial infarction, MI

Angina pectoris

Angina pectoris is the main symptom of ischemic heart disease. The condition is characterized by sudden, severe substernal pain. The primary cause of angina is an imbalance between myocardial oxygen demand and oxygen supplied by coronary vessels.

Types of Angina: There are three types of angina: stable, vasospastic and unstable angina.

Stable Angina (exertional angina, classical angina): The underlying pathology is usually atherosclerosis. Anginal episodes can be precipitated by exercise, cold, stress, emotion, or eating. Therapeutic Aim: Decrease cardiac load (preload and afterload) and increase myocardial blood flow.

Vasospastic Angina (variant angina, Prinzmetal's angina) : It is caused by transient vasospasm of the coronary vessels. Chest pain may develop at rest. Therapeutic Aim: Decrease vasospasm of coronary vessels.

Unstable Angina (angina at rest): This is associated with a change in the character, frequency, and duration of angina in patients with stable angina and when there are prolonged episodes of angina at rest. Unstable angina requires vigorous therapy as it signals the imminent occurrence of a myocardial infarction. Therapeutic Aim: Inhibit platelet aggregation and thrombus formation, decrease cardiac load, and vasodilate coronary arteries

Pharmacology

Three categories of pharmacological agents are used in the treatment of angina:

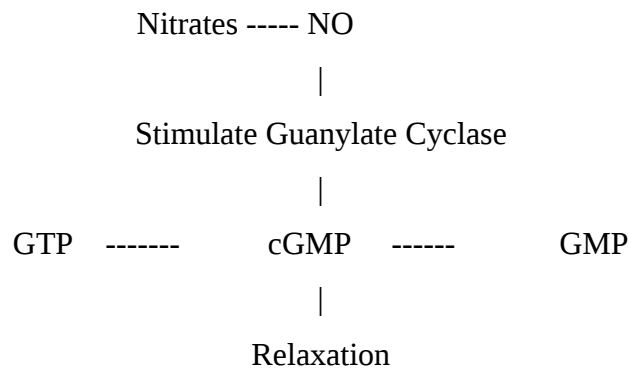
1. Organic nitrates (reduce preload and afterload, vasodilate coronary arteries, inhibit platelet aggregation)
2. Calcium channel blockers (reduce afterload, vasodilate coronary arteries, some also decrease heart rate, decrease contractility)
3. Beta-adrenergic antagonists (decrease heart rate, decrease contractility, decrease afterload by decreasing cardiac output)

Organic Nitrates

Organic nitrates have been used for more than 100 years, and are still an important class used in the treatment of angina pectoris. All these agents lead to the formation of the reactive free radical, nitric oxide (NO). Most of these agents are simple nitric and nitrous acid esters of polyalcohols: Glyceryl trinitrate (GTN, nitroglycerin), Isosorbide dinitrate (ISDN), Isosorbide-5-mononitrate (5-ISMN), Amyl nitrate (highly volatile liquid which is administered by inhalation, dose adjustment is difficult).

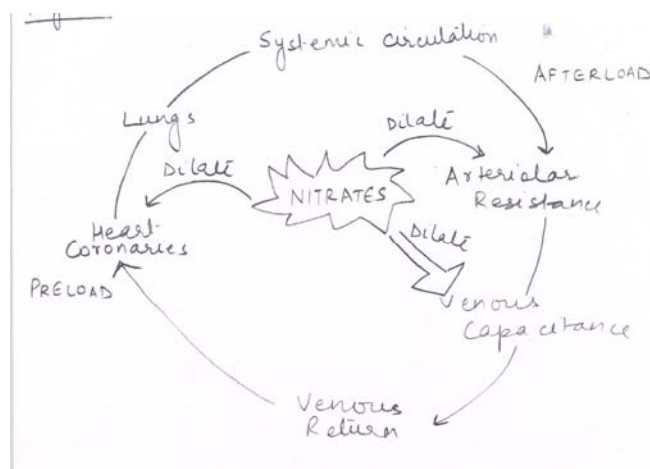
Mechanism of Action:

1. Nitrates are enzymatically converted to NO in the target tissues: Veins and large arteries appear to have greater enzymatic capacity than resistance vessels, resulting in greater effects of organic nitrates on these vessels.
2. NO is an important endogenous diffusible mediator of smooth muscle contraction and neuronal transmission: NO is very short-lived (half-life of a few seconds). Endogenous NO produced by vascular endothelium in response to acetylcholine is known as EDRF (endothelium-derived relaxing factor)
3. NO activates a cytosolic form of guanylate cyclase by binding to iron in the heme prosthetic group of the enzyme: Activated guanylate cyclase catalyzes the formation of cyclic GMP (cGMP), which subsequently activates cGMP-dependent protein kinase. Activation of cGMP-dependent protein kinase in smooth muscle results in relaxation through several possible mechanisms, all of which involve protein phosphorylation: Activation of Ca^{2+} -ATPases which increases Ca^{2+} efflux, Inhibition of Ca^{2+} channels which decreases Ca^{2+} influx, and Hyperpolarization of the sarcolemmal membrane by stimulation of Ca^{2+} -activated K^{+} channels.



Pharmacological Effects:

1. **Peripheral vasodilation:** Dilation of veins predominates over that of arterioles, resulting in a large reduction in preload and a lesser reduction in after load. Reduction in preload and after load decreases myocardial workload and results in decreased myocardial oxygen demand.
2. **Effects on coronary blood flow:** Large epicardial coronary arteries are dilated without impairing auto regulation in small coronary vessels. Collateral flow may be increased, improving perfusion of ischemic myocardium. Decreased preload improves subendocardial perfusion. Although organic nitrates can relax vasospastic coronary arteries, they have little or no effect on total coronary blood flow in patients with typical angina due to atherosclerosis



3. Inhibition of platelet function: Platelet aggregation is reduced by nitrovasodilators which may contribute to their effectiveness in the treatment of unstable angina. The mechanism involves stimulation of platelet guanylate cyclase.

Pharmacokinetics: Hepatic first-pass metabolism is high and oral bioavailability is very low for the traditional organic nitrates, GTN and ISDN (Table). Sublingual administration, which avoids the first-pass effect, is therefore preferred for administration of GTN and ISDN. The plasma clearance value of GTN (50 L/min) greatly exceeds that of cardiac output, indicating extra-hepatic metabolism also plays an important role in its inactivation. Oral ISDN is completely absorbed, but only about 20% of the dose enters into the systemic circulation as intact drug, the rest being converted (at least initially) to its active mononitrate metabolites (primarily 5-ISMN). Oral 5-ISMN is not subjected to first-pass metabolism, and is therefore 100% available following oral administration. A high-capacity hepatic glutathione-organic nitrate reductase, which sequentially removes nitrate groups from the parent drug, is a major mechanism for inactivation of the organic nitrates. The enzyme converts the lipid soluble organic nitrate esters into more water-soluble denitrated metabolites and inorganic nitrite. The denitrated metabolites are considerably less potent vasodilators than are the parent compounds. Excretion of the metabolites is predominantly via the kidney. The kinetics of hepatic denitration of the organic nitrates is influenced by hepatic blood flow and the presence or absence of hepatic disease.

Table: Pharmacokinetics of Prototypical Nitrovasodilators in Man

Property	GTN	ISDN	5-ISMN
Half-life (min)	3	10	280
Plasma clearance (L/min)	50	4	0.1
Apparent volume of distribution (L/kg)	3	4	0.6
Oral bioavailability (%)	< 1	20	100

Routes of Administration: Amyl nitrate, a gas at room temperatures, can be administered by inhalation and has a very rapid onset and very short duration of action (3 - 5 min). The sublingual route of administration is rapid (onset of action 1-3 min) and effective for the treatment of acute attacks of angina pectoris and avoids first-pass effects. The short duration of action (20-30 min) is not suitable for maintenance therapy. Intravenous nitroglycerin may be useful in the treatment of severe recurrent unstable angina because the onset of action is also rapid. Slowly absorbed preparations (oral, buccal, transdermal) can be used to provide prolonged prophylaxis against angina attacks (3 - 10 hrs), but can lead to the development of tolerance.

Tolerance: Continuous or frequent exposure to organic nitrates may lead to the development of complete tolerance (tachyphylaxis). Diminished release of nitric oxide resulting from depletion of tissue thiol compounds and systemic compensation – volume expansion and neurohumoral activation, play a role in development of tolerance. For instance, transdermal administration of GTN may provide therapeutic blood levels for 24 hours or more, but efficacy does not persist for more than 8-10 hours. Nitrate-free periods of at least 8 hours (e.g. overnight) are suggested to avoid or reduce the development of tolerance. Industrial exposure to organic nitrates has been associated with "Monday morning sickness" and with the development of physical dependence manifest by variant angina occurring after 1-2 days "withdrawal" from source of organic nitrates. Myocardial infarction resulting from coronary vasospasm has occurred in the most severely affected individuals. There is no evidence that physical dependence occurs with therapeutic doses of short-acting organic nitrates, even at high doses.

Adverse Effects: Due to excessive vasodilation the major acute adverse effects of organic nitrates are: Orthostatic hypotension, Tachycardia, Severe throbbing headache, Dizziness, Flushing, Syncope (fainting), Contraindications. Organic nitrates are contraindicated if intracranial pressure is elevated.

Calcium Channel Blockers

Chemistry: Four chemically distinct classes of calcium channel blockers are currently used to treat angina. These are Phenylalkylamines: Verapamil, Benzothiazepines: Diltiazem, Dihydropyridines: Nifedipine, nimodipine, nicardipine, and Diarylaminopropylamine ethers: Bepridil.

Mechanism of Action :

- The primary action of the calcium channel blockers is to block voltage-sensitive calcium channels. These drugs act from the inner side of membrane. They bind to the channels in depolarized membrane. As a consequence of drug binding, channels open rarely after depolarization. A marked decrease in transmembrane Ca^{2+} current leads to smooth muscle relaxation.

- Dihydropyridines, verapamil, and diltiazem block L-type calcium channels which are abundant in cardiac myocytes, arteriole smooth muscle cells, SA nodal tissue, and AV nodal tissue
- Bepridil blocks L-type channels, but also has significant sodium and potassium channel blocking activity in the heart

Pharmacological Effects: All of the calcium channel blockers vasodilate coronary arterioles and reduce afterload, but each class has different effects on heart rate and cardiac contractility.

Actions on cardiac cells: Verapamil, diltiazem, and bepridil have direct negative inotropic, chronotropic, and dromotropic effects. The dihydropyridines have negligible direct effects on heart rate or contractility, but reflex increases in sympathetic tone (due to decreased arterial pressure) can increase heart rate and contractility which may aggravate angina

Haemodynamic effects: The calcium channel blockers have little effect on preload. The desired therapeutic effects of calcium channel blockers in treating angina are to:

- Reduce myocardial oxygen consumption by reducing after load.
- Reduce myocardial oxygen consumption by reducing heart rate and contractility (except for the dihydropyridines which have minimal effects on contractility).
- Improve oxygen delivery to ischemic myocardium by vasodilating coronary arteries and by reducing heart rate (increased time spent in diastole).

Pharmacokinetics

The calcium channel blockers are orally active. The calcium channel blockers exhibit high first-pass metabolism and high protein binding. Most of the channel blockers used to treat angina are active within about 30 minutes after oral administration and have plasma half-lives of several hours. Bepridil and the newer dihydropyridines have longer half-lives (24-50 hours).

Adverse Effects: The major adverse effects of calcium channel blockers are typically direct extensions of their therapeutic actions and are relatively rare: Depression of contractility and heart failure, Bradycardia, AV block, Cardiac arrest. Short-acting dihydropyridines have been associated with an increased incidence of sudden death (cardiac arrhythmia), perhaps by increasing sympathetic tone. Minor toxicities include: Hypotension and first dose (hypotensive) effect, Dizziness, Edema in dependent parts (e.g. ankle region), Flushing, Increased difficulty in urine voiding in elderly males, hamper diabetes control. Because of its ability to block potassium channels, bepridil can prolong the cardiac action potential and cause *torsades de pointes* (drug-induced long QT syndrome)

Patient has to be advised about these possible adverse effects by treating physician. Care has to be taken to start therapy at low dose and titrate to achieve optimal effect.

Contraindications: Verapamil, diltiazem, and bepridil can worsen cardiac performance in patients with overt heart failure. Verapamil, diltiazem, and bepridil may depress contractility and produce AV block in patients receiving beta-blockers. Verapamil may increase serum digoxin levels in digitalized patients.

Beta-Adrenergic Blockers

Propranolol (Inderal) is the prototypic beta-adrenergic blocker; other widely used agents include metoprolol, nadolol, and timolol.

Mechanism of Action : These agents block beta-adrenergic receptors in the cardiovascular system. They have a negative chronotropic and inotropic effect and reduce afterload which decrease myocardial oxygen consumption, especially during exercise and improve myocardial perfusion due to lower heart rate.

Adverse Effects and Contraindications: They may dangerously reduce myocardial performance in patients with overt heart failure or may depress contractility and produce AV block in patients receiving calcium channel blockers. Contraindicated in patients with asthma. Caution should be used in diabetic patients since tachycardia due to hypoglycemia can be blocked.

Therapeutics

The goal of drug therapy is to reduce cardiac ischemia by: reducing oxygen demand (decrease preload, afterload, contractility, heart rate) and increasing oxygen delivery to ischemic tissue (coronary vasodilation, decrease preload, decrease heart rate, minimize intracoronary thrombi). In addition to specific drug therapies, it is important to modify risk factors associated with atherosclerosis (smoking, hypertension, hyperlipidemia). The HMG-CoA reductase inhibitors (statins) have been shown to reduce coronary atherosclerosis in some patients.

Stable Angina (Angina of effort)

Maintenance therapy of chronic stable angina includes long-acting nitrovasodilators, calcium channel blockers, or beta-adrenergic blockers. In hypertensive patients, monotherapy with calcium channel blockers or beta-blockers may be sufficient. In normotensive patients, monotherapy with long-acting nitrovasodilators may be adequate. For patients with persistent hypertension, sinus bradycardia, or AV node dysfunction, nifedipine or a longer-acting dihydropyridine is the drug of choice. Surgical revascularization (coronary bypass) and angioplasty should be considered for patient's refractory to drug therapy.

Vasospastic Angina (Variant angina, Prinzmetal's angina)

Nitrates and the calcium channel blockers are much more effective than beta-adrenergic blocker therapy in relieving and preventing ischemic episodes in patients with variant angina. Angina attacks are completely abolished in 70% of patients treated with channel blockers plus nitrates; marked reduction in frequency of attacks is seen in another 20%. The calcium channel blockers all have similar efficacy in treating variant angina. Beta-blockers may worsen angina due to increased coronary resistance secondary to the unopposed effects of catecholamines acting at alpha-adrenergic receptors. Surgical revascularization and angioplasty are not indicated for patients with variant angina.

Unstable Angina

Verapamil has been found to be more effective than propranolol in controlling unstable angina. Nifedipine alone is no more effective than nitrates or beta-blockers in reducing the frequency of angina at rest. Adding nifedipine to beta-blocker and nitrate therapy can decrease the frequency of angina at rest, the incidence of myocardial infarction, and the necessity for emergency revascularization. Aspirin has been shown to reduce the incidence of cardiac events in these patients. IV heparin or thrombolytic agents may also be indicated in some patients.

Combination Therapy

Since nitrates, calcium channel blockers, and beta-adrenergic antagonists are each useful in the treatment of angina and reduce oxygen consumption by different mechanisms, concurrent therapy is considered to be more beneficial than monotherapy.

Myocardial Infarction

Myocardial infarction (MI) is the irreversible necrosis of heart muscle secondary to prolonged ischemia. This usually results from an imbalance of oxygen supply and demand. Typical symptom is chest pain, lasting longer than 30 minutes, radiating to the left arm or neck.

Medical Management: Initial therapy for acute MI is directed toward restoration of perfusion in order to salvage as much of the jeopardized myocardium as possible. This may be accomplished through medical or mechanical means, such as angioplasty or coronary artery bypass grafting. Further treatment is based on (1) restoration of the balance between the oxygen supply and demand to prevent further ischemia, (2) pain relief, and (3) prevention and treatment of any complications that may arise.

Thrombolytic therapy has been shown to improve survival rates in patients with acute MI if administered in a timely fashion in the appropriate group of patients. If surgical capability is not available or will cause a delay greater than 90 minutes, then the optimal approach is to administer thrombolytics within 12 hours of onset of symptoms. Tissue plasminogen activator (t-PA) is superior to streptokinase in achieving a higher rate of

coronary artery patency. Recent trials show a high patency rate if a IIb/IIIa receptor antagonist is combined with a half dose of a thrombolytic agent as the initial reperfusion strategy.

Aspirin and/or antiplatelet therapy: Aspirin has been shown to decrease mortality and re-infarction rates after MI. Administer aspirin immediately, which the patient should chew if possible upon presentation. Continue aspirin indefinitely unless an obvious contraindication, such as a bleeding tendency or an allergy, is present. Clopidogrel may be used as an alternative in cases of a resistance or allergy to aspirin. Administer a platelet glycoprotein (GP) IIb/IIIa-receptor antagonist, in addition to acetylsalicylic acid and unfractionated heparin (UFH), to patients with continuing ischemia or with other high-risk features and to patients in whom a percutaneous coronary intervention (PCI) is planned. Eptifibatide and tirofiban are approved for this use. Abciximab also can be used for 12-24 hours in patients with unstable angina.

Beta-blockers reduce the rates of reinfarction and recurrent ischemia and possibly reduce the mortality rate if administered within 12 hours after MI. Administer routinely to all patients with MI unless a contraindication is present.

Heparin (and other anticoagulant agents) has an established role as an adjunctive agent in patients receiving t-PA but not with streptokinase. Heparin is also indicated in patients undergoing primary angioplasty.

Nitrates have no apparent impact on mortality rate in patients with ischemic syndromes. Their utility is in symptomatic relief and preload reduction. Administer to all patients with acute MI within the first 48 hours of presentation, unless contraindicated (ie, in RV infarction).

ACE inhibitors reduce mortality rates after MI. Administer ACE inhibitors as soon as possible as long as the patient has no contraindications and remains in stable condition. ACE inhibitors have the greatest benefit in patients with ventricular dysfunction. Continue ACE inhibitors indefinitely after MI. Angiotensin-receptor blockers may be used as an alternative in patients who develop adverse effects, such as a persistent cough, although initial trials need to be confirmed.

Suggested Readings

1. Goodman & Gilman's The Pharmacological Basis of Therapeutics. Eleventh Edition Chapter 31,32
2. Katzung, Basic & Clinical Pharmacology (10th ed.) Chapter 11 (p.159-182), Chapter 12 (p.183-197)