Antianginal Drugs

Chapter 21

Angina Pectoris sudden, severe chest pain. It caused because of insufficient blood flow via coronary artery→ ischemia

Causes: exertion, spasm of vascular smooth muscle of coronary artery, obstruction of blood vessel with atherosclerotic lesion.

Episodes: occur within 15 sec.-15 min. in angina there is no occurrence of cellular death in myocardial infarction.

Types of Angina

A. Stable angina, effort-induced angina, classic or typical angina

It is caused by fixed obstruction of coronary artery with atheroma (atherosclerotic coronary artery)→ Ischemia. Physical activity or emotional excitement potentiate the incidence of ishemia.

Treatment: by rest or Nitroglycerin

B. Unstable Angina

Unstable angina is classified between stable angina and MI. In unstable angina, chest pain occurs with increased frequency, duration, and intensity and can be precipitated by progressively less effort.

The symptoms are not relieved by rest or nitroglycerin. Unstable angina is a form of acute coronary syndrome and requires hospital admission and more aggressive therapy to prevent progression to MI and death.

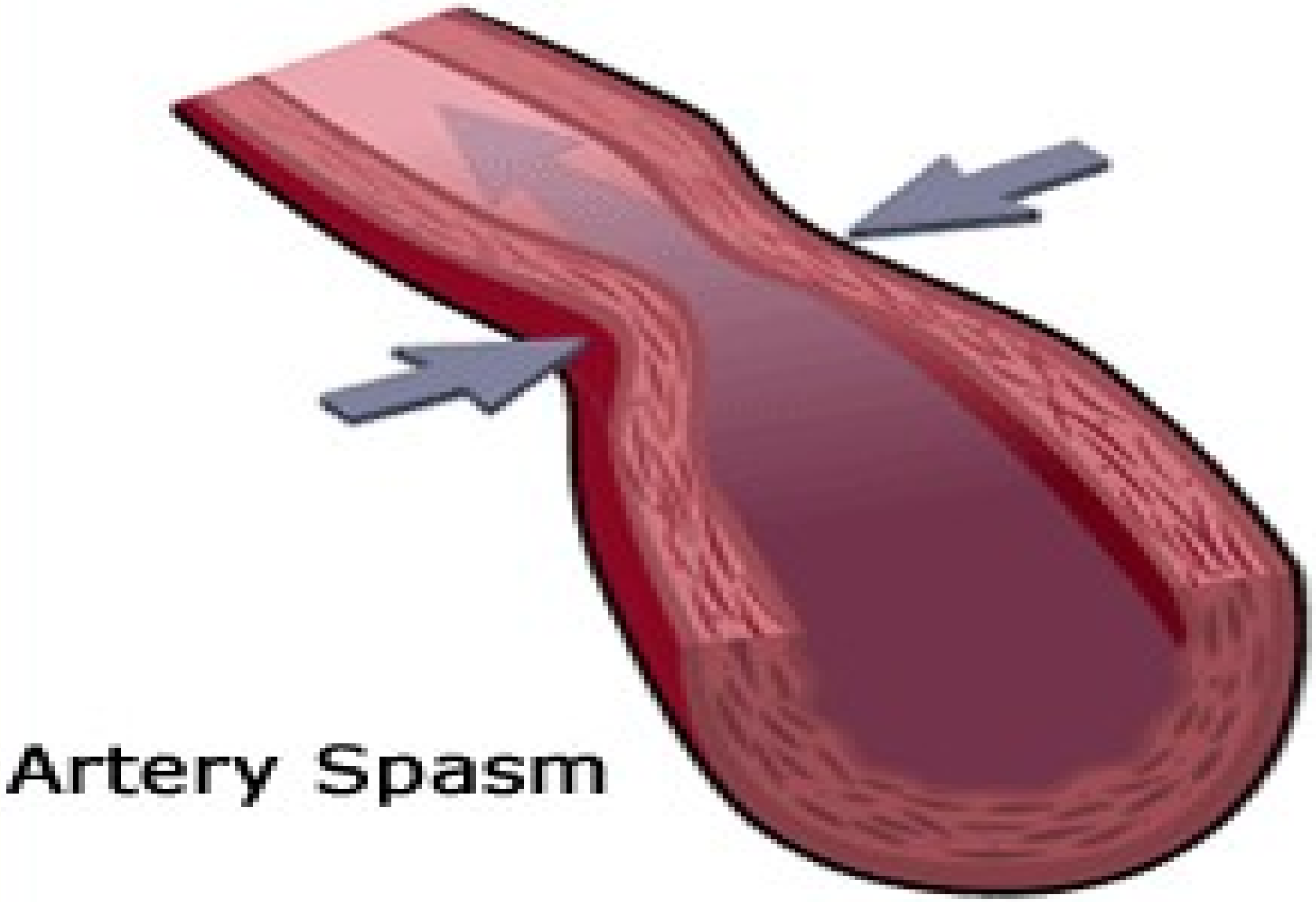
3. Prinzmetal, variant, vasospastic or rest angina

Prinzmetal angina is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm. Symptoms are caused by decreased blood flow to the heart muscle from the spasm of the coronary artery.

Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure. Prinzmetal angina generally responds promptly to coronary vasodilators, such as nitroglycerin and calcium channel blockers.

D. Acute coronary syndrome

Acute coronary syndrome is an emergency that commonly results from rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery. Most cases occur from disruption of an atherosclerotic lesion, followed by platelet activation of the coagulation cascade and vasoconstriction.


Artery Spasm

Treatment strategies

Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina: β-blockers, calcium channel blockers, organic nitrates, and the sodium channel–blocking drug, ranolazine.

These agents help to balance the cardiac oxygen supply and demand equation by affecting blood pressure, venous return, heart rate, and contractility.

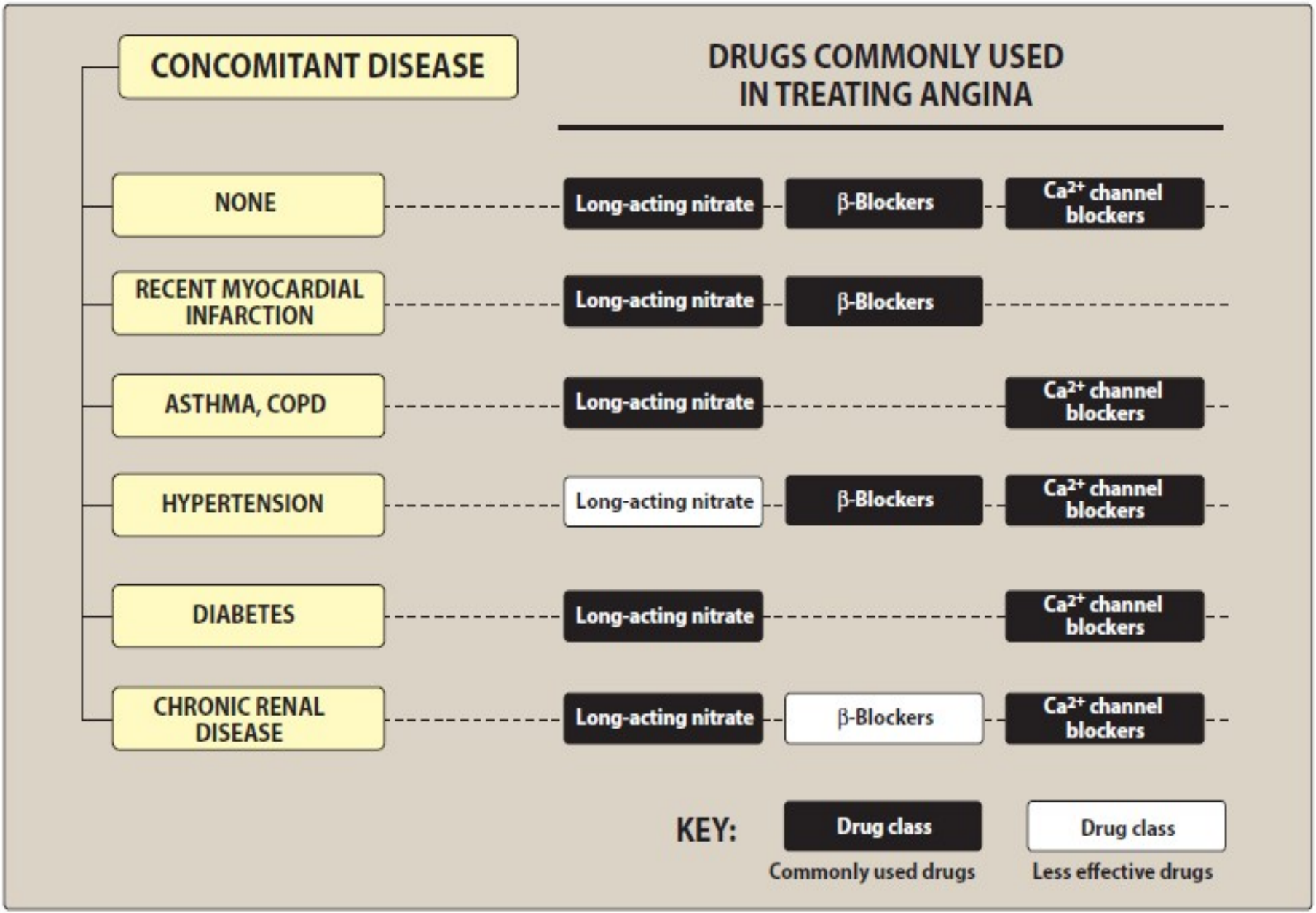


Figure 21.3
Treatment of angina in patients with concomitant diseases.

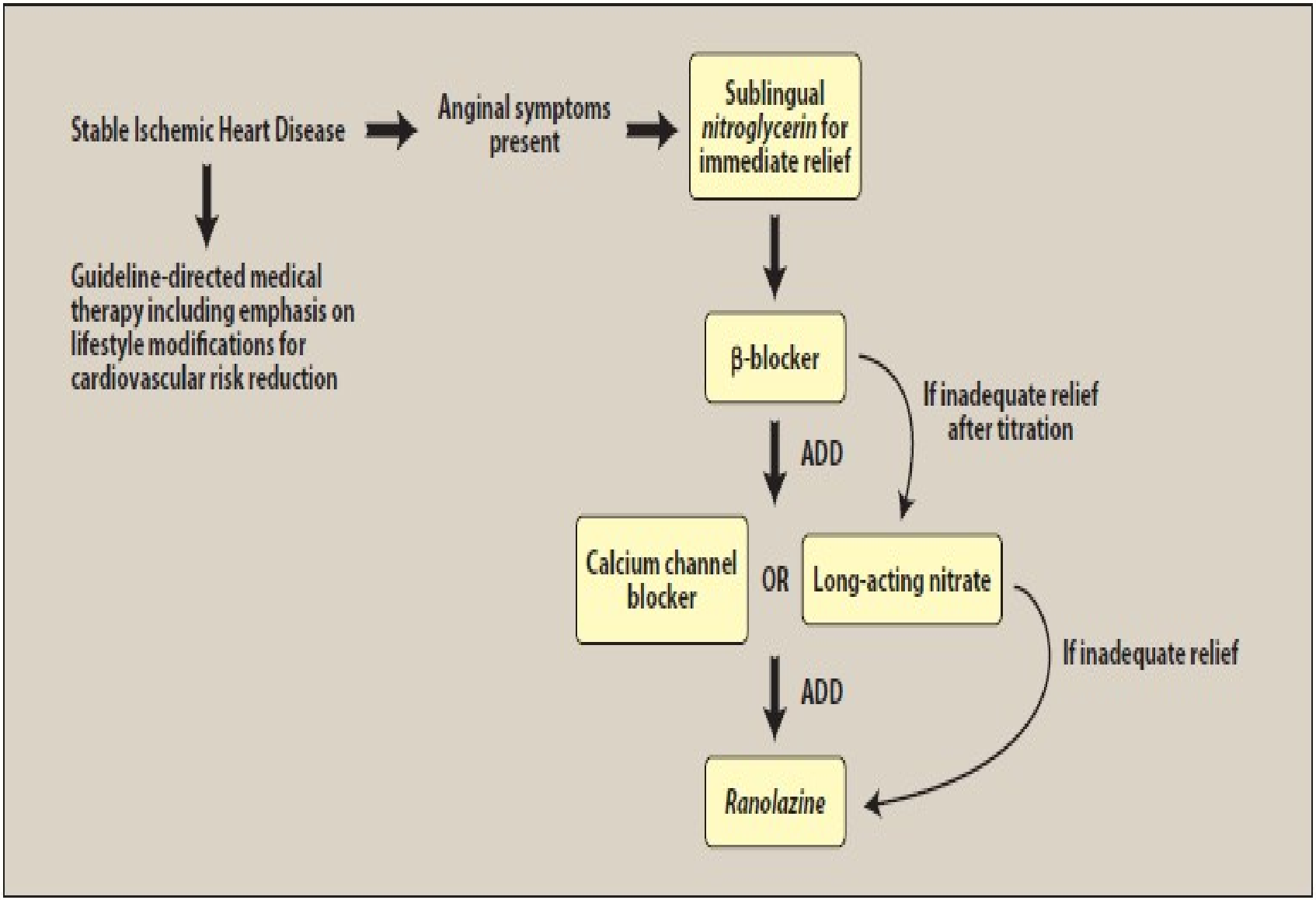


Figure 21.4

Treatment algorithm for improving symptoms in patients with stable angina.

A. β-ADRENERGIC BLOCKERS

The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β1 receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure. These agents reduce myocardial oxygen demand during exertion and at rest.

β-Blockers are recommended as initial antianginal therapy in all patients unless contraindicated. [Note: The exception to this rule is vasospastic angina, in which β-blockers are ineffective and may actually worsen symptoms.]

Agents with intrinsic sympathomimetic activity (ISA) such as pindolol should be avoided in patients with angina and those who have had a MI. Propranolol is the prototype for this class of compounds, but it is not cardioselective. Thus, other β-blockers, such as metoprolol and atenolol, are preferred.

B. Calcium channel blockers

Calcium is essential for muscular contraction. Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. In turn, this promotes the activity of several ATP-consuming enzymes, thereby depleting energy stores and worsening the ischemia.

The calcium channel blockers protect the tissue by inhibiting the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium channel blockers are, therefore, arteriolar vasodilators that cause a decrease in smooth muscle tone and vascular resistance.

1. Dihydropyridine calcium channel blockers

Amlodipine [am-LOE-di-peen], an oral dihydropyridine, functions mainly as an arteriolar vasodilator. This drug has minimal effect on cardiac conduction. The vasodilatory effect of amlodipine is useful in the treatment of variant angina caused by spontaneous coronary spasm.

Nifedipine [ni-FED-i-pine] is another agent in this class; it is usually administered as an extended-release oral formulation. Also felodipine is indicated.

[Note: Short-acting dihydropyridines should be avoided in CAD because of evidence of increased mortality after an MI and an increase in acute MI in hypertensive patients.]

B. Nondihydropyridine calcium channel blockers

Verapamil [ver-AP-a-mil] slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand. Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator. Verapamil is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities.

Diltiazem [dil-TYE-a-zem] also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator. Diltiazem can relieve coronary artery spasm and is particularly useful in patients with variant angina.

C. Organic Nitrates

These compounds cause a reduction in myocardial oxygen demand, followed by relief of symptoms. They are effective in stable, unstable, and variant angina.

Mechanism of action

Organic nitrates relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide, which activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP).

Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation. Nitrates also dilate the coronary vasculature, providing an increased blood supply to the heart muscle.

Pharmacokinetics

Nitrates differ in their onset of action and rate of elimination. The onset of action varies from 1 minute for nitroglycerin to 30 minutes for isosorbide [eye-soe-SOR-bide] mononitrate. For prompt relief of an angina attack precipitated by exercise or emotional stress, sublingual (or spray form) nitroglycerin is the drug of choice.

All patients suffering from angina should have nitroglycerin on hand to treat acute angina attacks. Isosorbide mononitrate owes its improved bioavailability and long duration of action to its stability against hepatic breakdown. Oral isosorbide dinitrate undergoes denitration to two mononitrates, both of which possess antianginal activity.

Adverse effects

Headache is the most common adverse effect of nitrates. High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia. Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation.

Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug. This interval of 10 to 12 hours is usually taken at night because demand on the heart is decreased at that time.

However, variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. Therefore, the nitrate-free interval in these patients should occur in the late afternoon. demand on the heart is decreased at that time.

D. SODIUM CHANNEL BLOCKER

Ranolazine inhibits the late phase of the sodium current (late INa), improving the oxygen supply and demand equation. Inhibition of late INa reduces intracellular sodium and calcium overload, thereby improving diastolic function. Ranolazine has antianginal as well as antiarrhythmic properties.

It is indicated for the treatment of chronic angina and may be used alone or in combination with other traditional therapies. It is most often used in patients who have failed other antianginal therapies. Ranolazine is extensively metabolized in the liver.

Thank You