Lecture -3 - Anti anginal drugs **د.رياض الموسوي**

Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms. It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia. The imbalance between oxygen delivery and utilization may result during exertion, from a spasm of the vascular smooth muscle, or from obstruction of blood vessels caused by atherosclerotic lesions.

Types of Angina

A. Stable angina

Stable angina is the most common form of angina and, therefore, is called typical angina pectoris. It is characterized by a burning, heavy, or squeezing feeling in the chest. It is caused by the reduction of coronary perfusion due to a fixed obstruction produced by coronary atherosclerosis. The heart becomes vulnerable to ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload. Typical angina pectoris is promptly relieved by rest or *nitroglycerin* (a vasodilator).

B. Unstable angina

Unstable angina lies between stable angina on the one hand and myocardial infarction on the other. In unstable angina, chest pains occur with increased frequency and are precipitated by progressively less effort. The symptoms are not relieved by rest or *nitroglycerin.* Unstable angina requires hospital admission and more aggressive therapy to prevent death and progression to myocardial infarction.

C. Prinzmetal's or variant or vasospastic angina

Prinzmetal's 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 due to 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's angina generally responds promptly to coronary vasodilators, such as *nitroglycerin* and calcium-channel blockers.

D. Mixed forms of angina

Patients with advanced coronary artery disease may present with angina episodes during effort as well as at rest, suggesting the presence of a fixed obstruction associated with endothelial dysfunction.

Anti anginal drugs:-

1- Organic Nitrates

Organic nitrates (or nitrites) used in the treatment of angina pectoris are simple nitric and nitrous acid esters of glycerol. They differ in their volatility. For example, *isosorbide dinitrate* and *isosorbide mononitrate* are solids at room temperature, *nitroglycerin* is only moderately volatile, and *amyl nitrite* is extremely volatile. These compounds cause a rapid reduction in myocardial oxygen demand, followed by rapid relief of symptoms. They are effective in stable and unstable angina as well as in variant angina pectoris.

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Nitrates decrease coronary vasoconstriction or spasm and increase perfusion of the myocardium by relaxing coronary arteries. In addition, they relax veins, decreasing preload and myocardial oxygen consumption. Organic nitrates, such as *nitroglycerin*, which is also known as *glyceryl trinitrate*, are thought to relax vascular smooth muscle by their intracellular conversion to nitrite ions, and then to nitric oxide, which in turn activates guanylate cyclase and increases the cells' cyclic guanosine monophosphate (GMP).1 Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation

Effects on the cardiovascular system

All these agents are effective, but they differ in their onset of action and rate of elimination. For prompt relief of an ongoing attack of angina precipitated by exercise or emotional stress, sublingual (or spray form) *nitroglycerin* is the drug of choice. At therapeutic doses, *nitroglycerin* has two major effects. First, it causes dilation of the large veins, resulting in pooling of 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 an increased blood supply to the heart muscle. *Nitroglycerin* decreases myocardial oxygen consumption because of decreased cardiac work.

Pharmacokinetics

The time to onset of action varies from 1 minute for *nitroglycerin* to more than 1 hour for *isosorbide mononitrate* .Significant first-pass metabolism of *nitroglycerin* occurs in the liver. Therefore, it is common to take the drug either sublingually or via a transdermal patch, thereby avoiding this route of elimination. *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.

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The most common adverse effect of *nitroglycerin*, as well as of the other nitrates, is headache. From 30 to 60 percent 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. *Sildenafil* potentiates the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is contraindicated.

Tolerance

Tolerance to the actions of nitrates develops rapidly. The blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily â€oenitrate-free intervalâ€ to restore sensitivity to the drug. This interval is typically 10 to 12 hours, usually at night, because demand on the heart is decreased at that time. *Nitroglycerin* patches are worn for 12 hours then removed for 12 hours. 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. Patients who continue to have angina despite nitrate therapy may benefit by addition of another class of agent.

2- **B**-Adrenergic Blockers

The ß-adrenergicâ€“blocking agents decrease the oxygen demands of the myocardium by lowering both the rate and the force of contraction of the heart. They suppress the activation of the heart by blocking ß1 receptors, and they reduce the work of the heart by decreasing heart rate, contractility, cardiac output, and blood pressure. With ß-blockers, the demand for oxygen by the myocardium is reduced both during exertion and at rest. *Propranolol* is the prototype for this class of compounds, but it is not cardioselective. Thus, other ß-blockers, such as *metoprolol* or *atenolol*, are preferred. [All ß-blockers are nonselective at high doses and can inhibit ß2 receptors. This is particularly important to remember in the case of asthmatics.]

Agents with intrinsic sympathomimetic activity (for example, *pindolol*) are less effective and should be avoided in angina. The ß-blockers reduce the frequency and severity of angina attacks. These agents are particularly useful in the treatment of patients with myocardial infarction and have been shown to prolong survival. The ß-blockers can be used with nitrates to increase exercise duration and tolerance. They are, however, contraindicated in patients with asthma, diabetes, severe bradycardia, peripheral vascular disease, or chronic obstructive pulmonary disease.

3- 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 adenosine triphosphate consuming enzymes, thereby depleting energy stores and worsening the ischemia. The calciumchannel 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. At clinical doses, these agents affect primarily the resistance of vascular smooth muscle and the myocardium. [*Verapamil* mainly affects the myocardium, whereas *nifedipine* exerts a greater effect on smooth muscle in the peripheral vasculature. *Diltiazem* is intermediate in its actions.] All calcium-channel blockers lower blood pressure. They may worsen heart failure due to their negative inotropic effect. [Note: Variant angina caused by spontaneous coronary spasm (either at work or at rest) rather than by increased myocardial oxygen requirement is controlled by organic nitrates or calcium-channel blockers; ß-blockers are contraindicated.]

A. Nifedipine

Nifedipine, a dihydropyridine derivative, functions mainly as an arteriolar vasodilator. This drug has minimal effect on cardiac conduction or heart rate. Other members of this class, *amlodipine, nicardipine*, and *felodipine*, have similar cardiovascular characteristics except for *amlodipine*, which does not affect heart rate or cardiac output. *Nifedipine* is administered orally, usually as extended-release tablets. It undergoes hepatic metabolism to products that are eliminated in both urine and the feces. The vasodilation effect of *nifedipine* is useful in the treatment of variant angina caused by spontaneous coronary spasm. *Nifedipine* can cause flushing, headache, hypotension, and peripheral edema as side effects of its vasodilation

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activity. As with all calcium-channel blockers, constipation is a problem. Because it has little to no sympathetic antagonistic action, *nifedipine* may cause reflex tachycardia if peripheral vasodilation is marked.

B. Verapamil

The diphenylalkylamine *verapamil* slows cardiac atrioventricular (AV) conduction directly, and decreases heart rate, contractility, blood pressure, and oxygen demand. *Verapamil* causes greater negative inotropic effects than *nifedipine*, but it is a weaker vasodilator. The drug is extensively metabolized by the liver; therefore, care must be taken to adjust the dose in patients with liver dysfunction. *Verapamil* is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities. It also causes constipation. *Verapamil* should be used with caution in patients taking *digoxin,* because *verapamil* increases *digoxin* levels.

C. Diltiazem

Diltiazem has cardiovascular effects that are similar to those of *verapamil*. Both drugs slow AV conduction and decrease the rate of firing of the sinus node pacemaker. *Diltiazem* reduces the heart rate, although to a lesser extent than *verapamil*, and also decreases blood pressure. In addition, *diltiazem* can relieve coronary artery spasm and, therefore, is particularly useful in patients with variant angina. It is extensively mmetabolized by the liver. The incidence of adverse side effects is low (the same as those for other calcium-channel blockers). Interactions with other drugs are the same as those indicated for *verapamil*.