[Drugs in Angina Pectoris]

Angina: is a syndrome characterized by squeezing chest pain, due to myocardial ischaemia that resulted from imbalance between myocardial oxygen demand (consumption) and oxygen supply. The cause is narrowing of coronary arteries due to spontaneous spasm or atheromatous plaque that impaired endothelial function and reduced release of nitric oxide (NO) which is the main physiological vasodilator normally produced by endothelial cells.

Drugs aim to: decrease the myocardial O_2 consumption (demand) and / or improve the myocardial O_2 supply.

Organic Nitrates

Examples: glyceryl trinitrate (GTN)(nitroglycerin), Isosorbide dinitrate, isosorbide mononitrte.

Mechanism of action and effects:

They relax vascular smooth muscle by their intracellular conversion to nitrite ions and then to nitric oxide (NO). This process requires a presence of free SH groups. Nitric oxide activates the soluble guanylate cyclase and increases the cells' cyclic guanosine monophosphate (cGMP) .This is the second messenger which alters Ca^{+2} fluxes in the cells and decreases intracellular Ca^{+2} levels resulting in vascular smooth muscle relaxation and vasodilatation.

They mainly **dilate large veins**, which results in pooling of blood in the veins. This reduces venous return and left ventricular filling pressure. The resultant decrease in the ventricular wall tension (preload) reduces the cardiac work and decreases the myocardial oxygen consumption.

They dilate coronary arteries and relax coronary spasm or vasoconstriction and improve myocardial perfusion.

- The relief of chest pain by nitrates does not prove the diagnosis of angina pectoris because they can relax smooth muscle in the bronchi, esophagus, gall bladder and biliary tract and can relieve chest pain due to spasm of smooth muscle of these organs.

Side Effects: are direct results of their vasodilating actions.

1-Postural hypotension, dizziness, fainting and syncope. The patient should remain supine and if symptoms are severe he should also spit out or swallow the remainder of the tablet.

2- Reflex tachycardia 3 –facial flushing 4- Throbbing headache: Tolerance to headache develops quickly but re-occurs after a brief nitrate- free period.

5-Over doses can cause methaemoglobinaemia, due to oxidation of iron in haemoglobin to ferric ions.

TOLERANCE (tachyphylaxis):

Continuous administration of nitrates, results in **diminished vasodilatation and antianginal effect,** possibly **because of depletion of free SH groups** in vascular smooth muscle cell.

It **does not occur with short-acting** preparations as sublingual glyceryl trinitrate, but mostly **occurs with long- acting** preparations as isosorbide mononitrate, or when glycery trinitrate is administered by prolonged I.V infusion or as sustained-release skin patches.

Tolerance **develops very quickly** (within 24 hours), and **wears off quickly** after a brief nitrate-free period and can be prevented by providing a daily nitrate- free interval to restore sensitivity to the drug. This interval is typically **8-10- hours** at night. I.e. skin patches are removed at night and worn at morning or isosorbide mononitrate is administered in the morning and at lunch, to allow nitrate-free period during the night.

Interactions: ***Sildenafil*** (a vasodilator drug for erectile dysfunction) potentiates nitrates effect and cause dangerous hypotension that may lead to death.

Glyceryl trinitrate :

- is the prototype of the group
- is well absorbed from the oral mucosa and when administered sublingually, it produces effect within few minutes, so the sublingual route is preferred to terminate acute angina attack .By this route the effective duration of action is short (about 30 minutes).
- If the tablet (formulated for sublingual route) or saliva that contains the dissolved tablet, is swallowed, the drug will be ineffective (systemic bioavailability is very low) because of extensive ^{1st} pass metabolism in the liver.
- is well absorbed through the skin, and intestinal mucosa, more sustained (prolonged) effect can be achieved by applying it as a transdermal patch or sustained –release oral tablet.
- Because of FPM, the oral dose is much higher than this required by sublingual route.
- The active substance in the tablet is volatile, and once a bottle of the tablets has been opened its shelf life (effectiveness) is quite short, because of evaporation. The patient must be aware of this if their tablet is no longer gives them the usual headache.

Uses: 1- acute attack of angina pectoris 2-rapid prophylaxis before exertion

3- Long term prophylaxis in chronic angina as skin patches or sustained- release oral tablets

4-congestive heart failure

Isosrbide dinitrate: has a similar properties to glycerryl trinitrate.

Uses 1-sublingually for acute angina 2- orally for chronic prophylaxis 3-congestive heart failure and left ventricular failure.

Isosorbide mononitrate : has similar pharmacological actions but longer- duration ,slower onset , much less hepatic 1st pass metabolism and higher systemic bioavailability when administered orally, than glyceryl- trinitrate .It is taken orally for chronic of angina .

Nicorandil

is an arterial and venodilator, reduces preload and after load so reduce cardiac work and O2 consumption. It liberates NO and increases the level of cGMP which causes vasodilatation.

It also activates and opens K^+ channels in vascular smooth muscle cell's membrane to allow K^+ efflux (exit) which leads to hyper polarization that reduces Ca^{+2} entry and induces vasodilatation.

It is administered orally and it is an alternative to nitrates in patients who develop tolerance, or to other classes when these are contraindicated.

Calcium Channel Blockers

A) Dihydropyridines (DHPs): a- rapid onset and short-acting ex. nifedipine b-slow onset and long-acting ex. amlodipine , felodipine
B) Non-dihydropyridines ex. Diltiazem, Verapamil

Mechanism of Action: They Block Ca^{+2} channels and inhibit calcium entrance into cardiac and smooth muscle cells of coronary and systemic blood vessels.

They decrease coronary vasoconstriction or spasm and improve myocardial perfusion; particularly useful in angina due to coronary artery spasm.

They dilate arterioles, decrease the blood pressure, peripheral resistance (after- load) and reduce the myocardial O_2 demand.

Selectivity between heart and vascular smooth muscle varies. The dihydropyridines are relatively selective to calcium channels in vascular smooth muscle and mainly dilate arterioles.

Verapamil @Diltiazem:

Show greater effect on the calcium channels in the heart and a weaker effect as an arteriolar vasodilator, than (DHPs). They decrease heart rate and myocardial contractility (negative inotropic effect) which reduces myocardial O_2 requirement.

Have anti arrhythmic effect because they decrease the rate of firing of SA node and slow cardiac AV conduction which is useful in treatment of supraventricular tachycardia (SVT) and in decreasing ventricular rate in case of atrial fibrillation and flutter.

Are contraindicated in patients with bradycardia and second or third –degree heart block, because of their negative effect on myocardial conducting and contracting system.

Their co-administration with β blockers potentiates the AV block and can lead to heart failure.

Uses:

1--Prophylaxis in chronic angina 2-Hypertension 3- Reynaud's disease 4- migraine prophylaxis 5- Verapamil and diltiazem also used in atrial fibrillation **,** flutter and SVT

Side Effects: (are extensions of their pharmacological actions)

- headache, flushing ,dizziness ,peripheral (ankle) oedema, Constipation
- Short and rapid acting DHPs as nifedipine can cause hypotension with sympathetic stimulation resulted in reflex tachycardia and palpitation. Tachycardia can increase cardiac work, so the slower and longer acting ones as felodipine and amlodipine are preffered in angina because they produce less reflex sympathetic stimulation and tachycardia.
- diltiazem and verapamil can cause bradycardia .

Beta Blockers

decrease myocardial O_2 requirement at rest and during exercise, because they decrease the heat rate ,blood pressure and myocardial contractility .

are useful in chronic prophylaxis for exercise- induced angina .

members that posses intrinsic sympathomimetic activity are less effective in angina.

should not discontinued abruptly , but the dose should be gradually tapered over 5-10 days to avoid risk of rebound angina.

are contraindicated in angina due to coronary artery spasm.

Drugs that inhibit platelet aggregation: prevent occurance of myocardial infarction or recurrence of myocardial infarction.

Low dose aspirin (75-325mg) ,clopidogril, abciximab