CALCIUM CHANNEL BLOCKERS

Calcium plays important role in the contractile activity of the skeletal muscle, the contractility of the cardiac and vascular muscle. Voltage dependent channel which is controlled by a gate that opens and closes in response to a voltage gradient. There are 2 types of calcium channels in heart: the L and T.

CCBs are the drugs that block L-type of voltage gated calcium channels present in blood vessels and heart.

Three chemically distinct classes of CCBs are:

I Phenylalkylamines e.g., Verapamil, norverapamil

II Benzothiazepines e.g., Diltiazem.

III Dihydropyridines (DHP) e.g., Nifedipine, nicardipine, nimodipine, nisoldipine, nitrendipine, isradipine, lacidipine, felodipine, amlodipine.

Mechanism of action: CCB bind to alpha-1 subunit of L-channel, and inhibits the entry of calcium into the myocardial and vascular smooth muscles, thus decreasing availability of the intra-cellular calcium. By inhibiting the calcium channels, these agents decrease the frequency of opening of calcium channels leading to relaxation of smooth muscles in blood vessels (they are potent vasodilators) and also decreased activity of the heart (decrease heart rate, AV conduction and contractility). Verapamil and diltiazem have strong direct cardiodepressant (verapamil > diltiazem) activity.

• Antianginal action of these drugs is due to: (1) Improvement in the coronary blood flow; and (2) Decrease in the oxygen demand of the heart due to reduction in systemic vascular resistance (vasodilatation) and BP (afterload). Verapamil, in addition, reduces the heart rate. As a group, these drugs can be used in anginal patients with COPD in whom beta-blockers are contraindicated.

• Coronary artery dilatation: These drugs are more potent than NTG as coronary artery dilators. Nitroglycerine dilates the large epicardial branches of coronary arteries but not the smaller intramyocardial coronary arterioles; CCB dilate both, even in the presence of coronary artery spasm. Further, they can prevent the spasm even in diseased, atherosclerotic coronary arteries. This effect accounts for their efficacy in Prinzmetal angina.

• Effect on peripheral blood vessels: CCB relax the vascular smooth muscle in systemic as well as pulmonary arterial circulations. They thus decrease the vascular resistance and the BP in both territories, and are useful in the treatment of systemic and pulmonary hypertension. Further, reduction in the afterload contributes to their efficacy in angina of effort. The reduction in BP is accompanied by reflex tachycardia in the case of nifedipine but not in the case of verapamil which depresses the SA node. They have little effect on the venous capacitance (cardiac preload).

• Negative inotropic effect: CCB depress myocardial contractility, and decrease the cardiac workload and oxygen consumption. This effect is beneficial in the treatment of angina of effort. Verapamil and diltiazem have negative inotropic actions and hence should not be combined generally with beta-blockers in the treatment of angina of effort; however, nifedipine can be used together with beta blockers (but see later).

• Antiarrhythmic effect: CCB: (a) Decrease the rate of discharge of the SA node. (b) Suppress ectopic pacemaker activity. (c) Increase the refractoriness of the AV node and; (d) Slow the conduction

The slowing of the conduction prevents re-entrant excitation. This effect plus the improvement of cardiac ischemia accounts for the potent (though selective) antiarrhythmic action. Verapamil and diltiazem are

particularly potent in this respect. Verapamil and diltiazem (but not nifedipine), however, can aggravate A-V block.

VERAPAMIL: This drug is a synthetic papaverine derivative. It causes: • Suppression of SA and AV nodes which are Ca^{++} dependent. • Coronary and peripheral vasodilatation. • Potent antiarrhythmic effect; and • Potent negative inotropic effect and may cause A-V block.

It does not cause reflex sympathetic overactivity and tachycardia.

Verapamil is absorbed completely on oral administration but is substantially metabolised by first pass hepatic metabolism. It is highly protein bound. Adverse effects include constipation, vertigo, bradycardia, heart block, CHF, hypotension and rarely cardiac asystole. It is used in the treatment of angina and in paroxysmal supraventricular tachycardia also.

NIFEDIPINE: Compared to verapamil, it: • Has negligible negative inotropic effect • Is a more potent coronary and peripheral vasodilator, • Causes tachycardia. • Is a potent inhibitor of platelet aggregation.

Nifedipine also relaxes bronchial, ureteric and uterine smooth muscle. It is used either orally or (for a rapid effect) sublingually.

ADRs: It include headache, tachycardia, dizziness, fatigue, orthostatic hypotension, leg cramps, skin rashes and gingival hyperplasia. Occasionally, CHF may be precipitated.

It is contraindicated in Unstable Angina because of decrease in coronary perfusion pressure resulting from rapid fall in BP, increase in oxygen demand due to reflex sympathetic activation, (tachycardia) and coronary steal phenomenon. This stealing of coronary blood away from ischaemic zone may precipitate angina. The slower-onset, longer acting calcium blockers such as Amlodipine are less likely to cause this phenomenon.

Therapeutic uses: Its main use is in the treatment of: (i) Variant angina refractory to nitrate therapy. (ii) Hypertension and (iii) Raynaud's syndrome

- Nicardipine is longest acting parenteral calcium channel blocker and is drug of choice for hypertensive emergencies. It is combined with beta blockers to avoid tachycardia.

Reflex tachycardia is more marked in case of drugs with short half-life (like nifedipine)

- Nisoldipine: This dihydropyridine is available as SR tablets for prophylactic therapy for chronic stable angina and hypertension.
- Nimodipine is related to nifedipine but is claimed to have a preferential vasodilating action on the cerebral arteries in animal studies. Its use is confined to the prevention of vascular spasm and subsequent ischaemic neurological damage following subarachnoid hemorrhage; its usefulness for this purpose is, however, uncertain. It is given in the dose of 60 mg every four hours for the first few days.
- Clevidipine is a novel ultrashort acting DHP (dihydropyridine) compound available for IV administration. It has rapid action with t½ of 2 min. It is metabolised by esterases in the blood. It is preferentially an arteriolar dilator and is used to control BP in hypertensive emergencies.

Abrupt withdrawal of CCBs during long term therapy can precipitate angina/myocardial infarction.

Both, Verapamil and Diltiazem should be avoided in conditions involving decreased conductivity of the heart like CHF and along with β blockers (both cause myocardial depression)