Calcium – Channel Blockers :-

Calcium-channel blockers are recommended when the preferred first-line agents are contraindicated or ineffective. They are effective in treating hypertension in patients with angina or diabetes. High doses of short-acting calcium hannel blockers should be avoided because of increased risk of myocardial infarction due to excessive vasodilation and marked reflex cardiac stimulation.

A. Classes of calcium-channel blockers:

The calcium-channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications .

Diphenylalkylamines:-Verapail is the least selective of any calcium-channel blocker and has significant effects on both cardiac and vascular smooth muscle cells. It is used to treat angina, supraventricular tachyarrhythmias, and migraine headache.

Benzothiazepines: Like *verapamil*, *diltiazem* affects both cardiac and vascular smooth muscle cells; however, it has a less pronounced negative inotropic effect on the heart compared to that of *verapamil*. *Diltiazem* has a favorable side-effect profile.

Dihydropyridines: This rapidly expanding class of calcium-channel blockers includes the first-generation *nifedipine* and five second-generation agents for treating cardiovascular disease: *amlodipine*, *felodipine*, *isradipine*, *nicardipine*, and *nisoldipine* .

These second-generation calcium-channel blockers differ in pharmacokinetics, approved uses, and drug interactions. All dihydropyridines have a much greater affinity for vascular calcium channels than for calcium channels in the heart. They are therefore particularly attractive in treating hypertension.

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B. Actions:-

The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in he contraction of the myocardium. Calcium enters muscle cells

through special voltage-sensitive calcium channels. his triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium. Calcium-channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral vasculature. This causes vascular mooth muscle to relax, dilating mainly arterioles.

C. Therapeutic uses:-

Calcium-channel blockers have an intrinsic natriuretic effect and, therefore, do not usually require the addition of diuretic. These agents are useful in the treatment of hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease.

D. Pharmacokinetics:-

Most of these agents have short half-lives (8 hours) following an oral dose. Treatment is required three times a day to maintain good control of hypertension. Sustained-release preparations are available and permit less frequent dosing. *Amlodipine* has a very long half-life and does not required a sustained-release formulation.

E. Adverse effects:-

Constipation occurs in 10 percent of patients treated with *verapamil*. Dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure are more frequent with dihydropyridines. *Verapamil* should e avoided in patients with congestive heart failure or with atrioventricular block due to its negative inotropic force of cardiac muscle contraction and dromotropic (velocity of conduction) effects.

Vasodilators :

The direct-acting smooth muscle relaxants, such as *hydralazine* and *minoxidil*, have traditionally not been used as primary drugs to treat hypertension. Vasodilators act by producing relaxation of vascular smooth muscle, which decreases resistance and,

therefore, blood pressure. These agents produce reflex stimulation of the heart, resulting in the competing reflexes of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals. Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be blocked by concomitant use of a diuretic and a ß1-blocker.

A. Hydralazine

This drug causes direct vasodilation, acting primarily on arteries and arterioles. This results in a decreased peripheral resistance, which in turn prompts a reflex elevation in heart rate and cardiac output. *Hydralazine* is used to treat moderately severe hypertension. It is almost always administered in combination with a ß -blocker, such as *propranolol* (to balance the reflex tachycardia), and a diuretic (to decrease sodium retention). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance. *Hydralazine* monotherapy is an accepted method of controlling blood pressure in pregnancy-induced hypertension. Adverse effects of *hydralazine* therapy include headache, tachycardia, nausea, sweating, arrhythmia, and precipitation of angina. A lupus-like syndrome can occur with high dosage, but it is reversible on discontinuation of the drug.

B. Minoxidil

This drug causes dilation of resistance vessels (arterioles) but not of capacitance vessels (venules). *Minoxidil* is administered orally for treatment of severe to malignant hypertension that is refractory to other drugs. Reflex tachycardia and fluid retention may be severe and require the concomitant use of a loop diuretic and a - ß - blocker.*Minoxidil* causes serious sodium and water retention, leading to volume overload, edema, and congestive heart failure. *Minoxidil* treatment also causes hypertrichosis (the growth of body hair). This drug is now used topically to treat male pattern baldness.]