ANTI-ANGINAL

3

OBJECTIVES

- Vasodilators (Nitrite and Nitrates)
- Calcium Channel Blockers

Angina pectoris also known as myocardial ischaemia in which flow of blood to the heart is not able to meet the metabolic demands of the heart for oxygen. This condition occurs due to one or more of the heart's arteries are narrowed or blocked. The symptoms includes severe substernal pain, radiating to the left shoulder and along the flexor surface of the left arm. Angina is a sign that someone is at increased risk of heart attack, cardiac arrest or sudden cardiac death.

Angina is categorised on the basis of its cause and symptoms in the following manner :

1. **Classical angina :** In this type anginal attack occurs due to mental stress or physical exertion. The depression of S-T segment occurs in ECG.
2. **Unstable angina :** Blockage of coronary artery (atherosclerosis disease) is the main factor for angina and attack occurs by vasospasm.
3. **Varient angina :** It occurs due to vasospasm of coronary vessels generally in the morning and may not be associated with severe atherosclerosis. The elevation of S-T segment occurs in ECG. The drugs used in the treatment of angina pectoris are classified as follows :

ANTI ANGINAL DRUGS

Vasodilators (Nitrite and Nitrates)
- Amyl Nitrite
- Nitroglycerine
- Penta erythritol Tetranitrate
- Isosorbide dinitrate
- Dipyridamole
- Nicorandil
  - Nicardipine
  - Nimodipine

Miscellaneous
- Aspirin
- Cyclandelate

Calcium Channel Blockers
- Verapamil
- Beperidil HCl
- Diltiazem HCl
- Nifedipine
- Amlodipine
- Felodipine

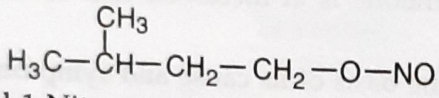
VASODILATORS (NITRITE AND NITRATES)

Nitric oxide (NO) is a potent vasodilator. It affects various physiological processes such as endothelial dependent relaxation, neuro transmission and cell mediated immune response. Nitric oxide is widely distributed in the body. It is synthesized from L-arginine by NO synthetase.

Cyclic guanosine monophosphate (cGMP) plays an important role in the regulation of smooth muscle tension. The synthesized NO diffuse to the smooth muscle cells and activates the enzyme guanylate cyclase, which leads to an increase in cGMP and then muscle relaxation.

Both nitrites and nitrates exhibits same pharmacological action. Some of the agents like papaverine, theophylline and sildenfil also relax smooth muscle by inhibiting the phosphodiestrases of cAMP and cGMP. These drugs increase the cellular level of cAMP and cGMP by preventing their hydrolysis to AMP and GMP respectively by phosphodiestrases. The official vasodilator drugs are summerized as follows :

1) AMYL NITRITE



IUPAC Name : 3-Methyl-1-Nitrosooxybutane

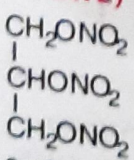
Properties : It is a mixture of isomeric amyl nitrites. It is a yellowish liquid with an etheral odor and pungent taste. It is quite volatile and inflammable in nature. Its vapours forms an explosive mixture in air and oxygen. It is almost insoluble in water but is miscible with organic solvents. It decompose in valeric acid and nitric acid. The amyl group is unreactive and the chemical and biological properties are mainly due to nitrite group.

Mechanism of Action : Amyl nitrite produces nitric oxide which results in the reduction of systemic and pulmonary arterial pressure and decreased cardiac output by peripheral vasodilation.

Uses :

1. Amyl nitrite is used to treat angina and heart diseases.
2. It is sometimes used as an antidote for cyanide poisoning by oxidation of haemoglobin to methaemoglobin. Methaemoglobin reacts with cyanide to form cyanomethaemoglobin. (Sequester)
3. In industry it is used as cleaning agent and as a solvent.
4. It is also used as inhalant drug that produces euphoric state.

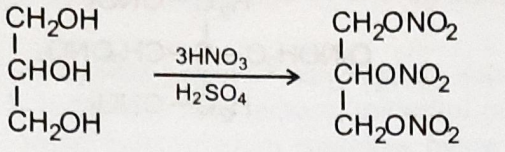
2) NITROGLYCERIN (GLYCERYL TRINITRATE)



Iupac Name : 1,3-dinitrooxypropan-2-yl nitrate

Synthesis : It is prepared by treating dehydrated. Glycerin with a mixture of fuming

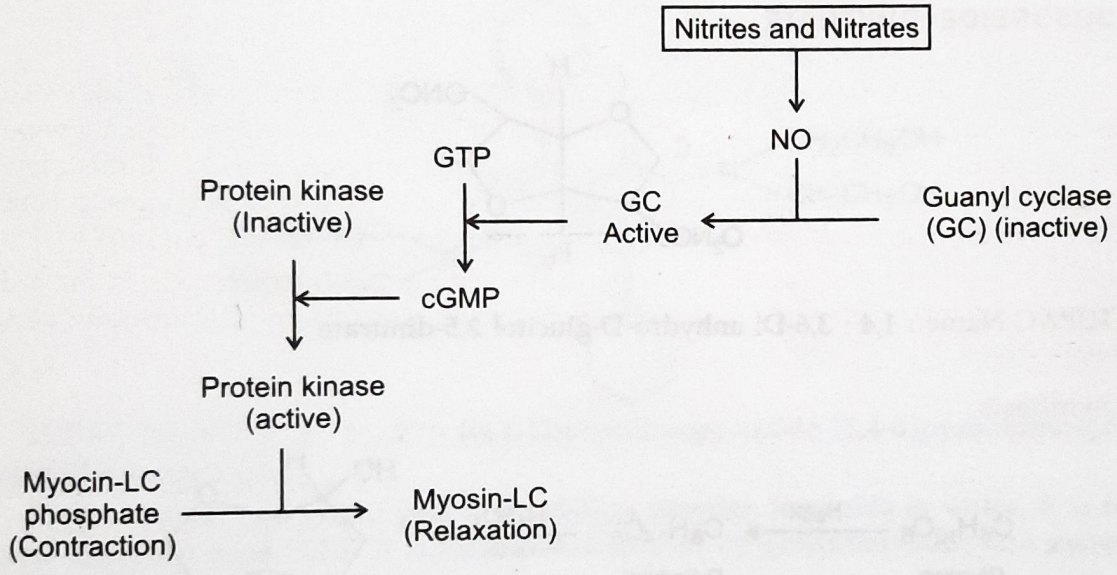
nitric acid and sulphuric acid.



Glycerin Nitroglycerin

Properties : Nitroglycerine is a colourless oil with a sweet burning taste. It is thick flammable explosive liquid which is slightly soluble in water but soluble in organic solvents. It is rapidly absorbed from oral mucosa as well as by G.I.T. Nitroglycerin is metabolised by reductase enzyme into its mono and dinitrate derivatives. These derivatives have less vasodilating property than trinitrate.

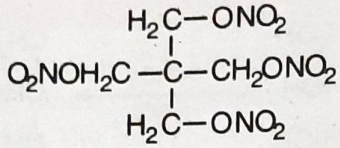
Mechanism of Action : Nitroglycerin is converted to Nitric Oxide (NO) which activate guanylate cyclase and stimulate the synthesis of cGMP which then activates a series of protein kinase dependent dephosphorylations of the myosin light chain of smooth muscles. The subsequent release of calcium ions results in the relaxation of smooth muscle cells and vasodilation.



Uses :

1. It is used in the treamtent of angina pectoris, heart failure and myocardial infaraction in the form of sublingual tablet, intravenously and transdermal patches as it rapidly absorbed by the skin.
2. It has been used as a gelatinizer for nitro cellulose and as a propellant like cardite and ballistite.

3) PENTAERYTHRITOL TETRANITRATE



IUPAC Name : 2,2-bishydroxymethyl-1,3-propanediol tetranitrate.

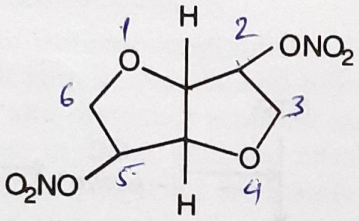
Properties : It is a white crystalline powder having m.pt. 140°C. It is insoluble in water, slightly soluble in acetone. It is highly explosive so it is diluted with lactose, mannitol or other suitable diluents for safe handling. It is extensively metabolised in liver into its mono, di and trinitrate derivatives. It is excreted mainly in urine.

Mechanism of action : Its action is similar to nitro-glycerine but duration of action is more.

Uses :

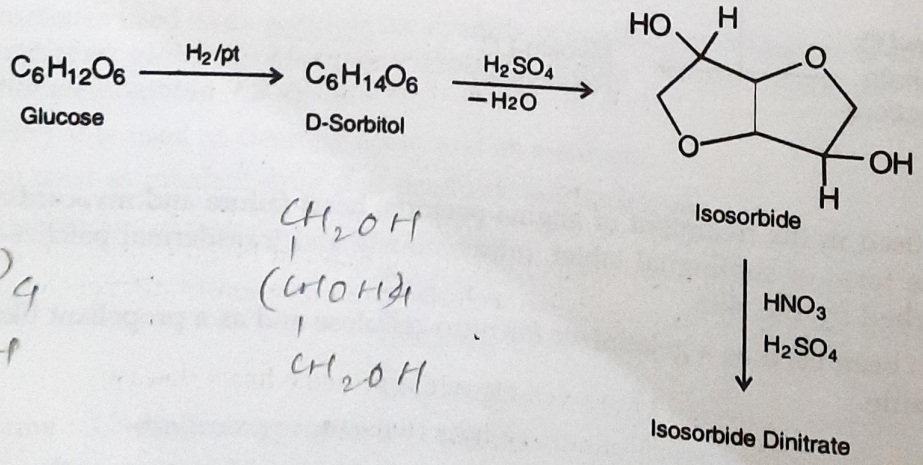
1. It is used in the treatment of angina pectoris.
2. It is also used as an explosive by military.

4. ISOSORBIDE DINITRATE



IUPAC Name : 1,4 : 3,6-Di anhydro-D-glucitol 2,5-dinitrate

Synthesis



Isosorbide dinitrate is synthesized by intermolecular dehydration of D-sorbitol into isosorbide by sulfuric acid and further interaction of two hydroxyl groups by mixture of nitric acid and sulfuric acid.

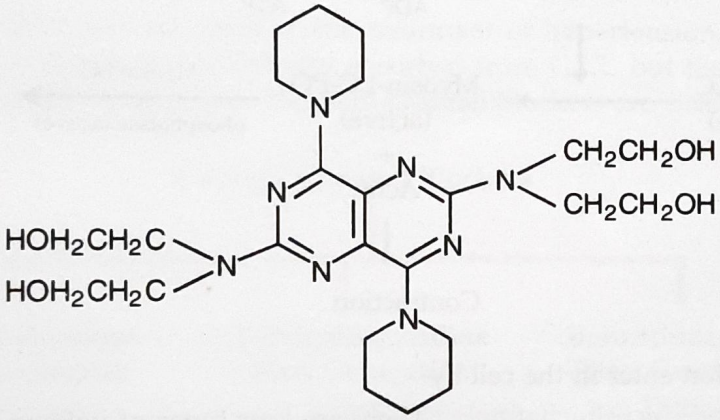
Properties : It is a white crystalline powder, very slightly soluble in water. It is explosive and sensitive to heat so it is diluted with lactose, mannitol or any other suitable inert diluent. It is stored in tightly-closed light resistant container below 15°C. It may contain 1% ammonium phosphate as a stabilizer.

Isosorbide dinitrate is readily absorbed from oral mucosa, skin and G.I.T. It is metabolised by denitration into Isosorbide 2-mononitrate and isosorbide 5-mononitrate. Both metabolites are having vasodilating activity and less first pass metabolism than isosorbide dinitrate.

Mechanism of Action : Isosorbide dinitrate acts similar to nitroglycerine by producing NO.

Uses : It is given as sublingual or chewable tablet in the treatment of acute anginal attack. It is not effective orally because onset of action ranges from 15 to 30 minutes. It has also been applied topically and can be given by intravenous infusion.

5) DIPYRIDAMOLE



IUPAC Name : 2, 2′, 2″, 2‴- [(4,8-Dipepridinopyrimido [5,4-d]pyrimidine-2,6-diyl) dinitriol] tetraethanol.

Properties : It is a bright yellow crystalline powder, insoluble in water. It is incompletely absorbed from G.I.T. It is metabolised in liver by glucuronidation and excreted in the bile.

Mechanism of action : Dipyridamole act by two mechanisms-

a) It inhibits the phosphodiesterase enzyme that normally break down cAMP and cGMP.
b) It inhibits the cellular reuptake of adenosine into red blood cells, endothelial cells and platelets leading to increased extracellular concentration of adenosine.

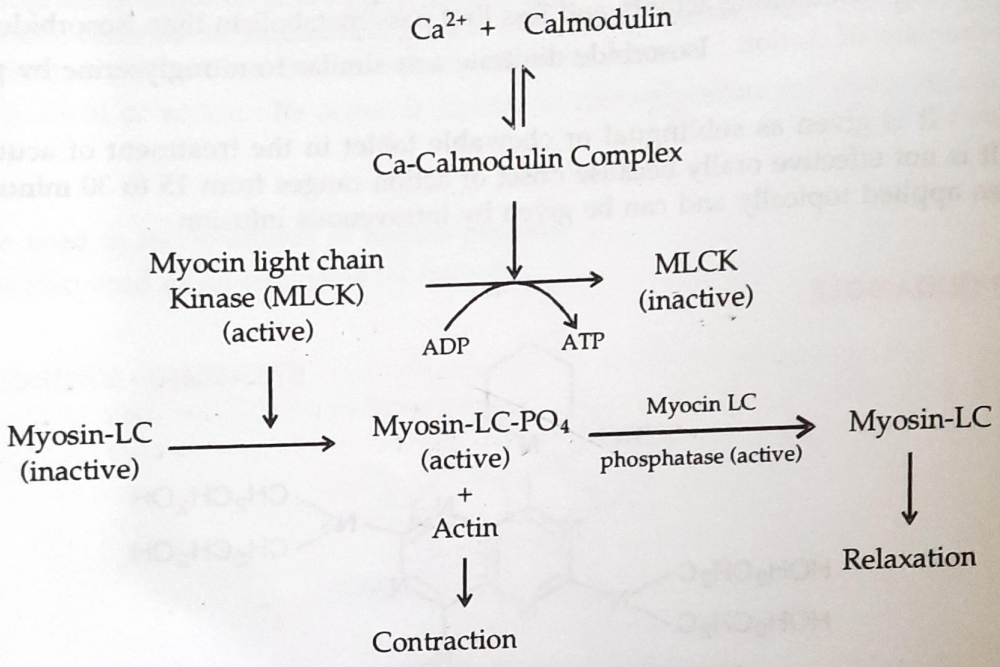
Uses :

1. It is used to dilate the blood vessels with coronary heart disease.
2. It is also used to lower pulmonary hypertension.

3. It inhibits the replication of mengovirus RNA.
4. It is mainly used as antiplatelet drug.
5. With other anticoagulant drug it is used for the prevention of thromboembolism.

CALCIUM CHANNEL BLOCKERS

Calcium ion is responsible for regulation of many cellular processes like excitation, contraction and secretion. The mechanism of contraction by calcium ion is as follows :



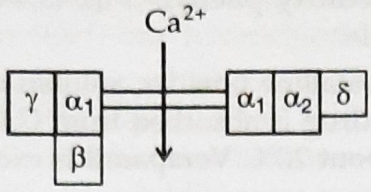
The calcium ion enter in the cell by-

1) **Voltage gated calcium channels :** There are four types of voltage gated Ca^{2+} channels-
   a) L-Type- Present in cardiac and smooth muscles and responsible for contraction of these muscles.
   b) N-Type- Found in neurons and responsible for transmitter release.
   c) T-Type- Found in pacemaker cells, causing Ca^{2+} entry, inactivated at more negative potentials.
   d) P-Type- Located in Purkinje cells but their function is unknown yet.
2) **Ligand gated calcium channels :** These are activated by excitator neuro transmitters. They are non selective and allow other ions including Ca^{2+}.
3) **Na^+/Ca^{2+} exchange :** It transport three Na^+ ions in return for one Ca^{2+} ion. Accumulation of Ca^{2+} causes activation of Na^+/Ca^{2+} exchanger which results in influx of three Na^+ and one Ca^{2+} out of the membrane and produces abnormal cellular depolarization. This abnormal cellular depolarisation leads to cardiac arrythmia.

4) **Store operated Ca^{2+} channels :** These occurs in plasma membrane and activate when endoplasmic reticulum Ca^{2+} stores are decreased.

The mechanism of cardiac muscle excitation- contraction involves the opening of L-type channel and entry of Ca^{2+}. These Ca^{2+} act on ryanodine receptors and release Ca^{2+} from sarcoplasmic reticulum. The released Ca^{2+} then combine with troponin to give troponin Ca^{2+} complex which produce contraction of heart muscles.

The calcium antagonist act only on L-type channel to produce their pharmacological effect. The L-type channel is made up of 5 different subunits α_1, α_2, β, γ and δ. The α, subunit is the central pore of the calcium ion channel. The calcium channel blockers binds to this unit and inactivate the channel and do not allow the channel to open.



L-Type Channel

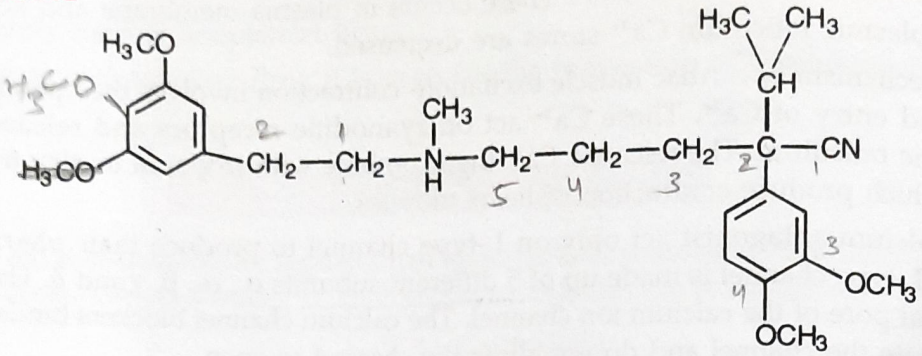
Calcium channel blockers are used in the treatment of hypertension, angina pectoris and arrhythmias. These drugs are completely absorbed from G.I.T. but their bioavailability is reduced due to first pass metabolism. Calcium channel blockers are classified as follows :

Calcium Channel Blockers

Phenylalkylamines	**1,4-Dihydropyridine**	**Benzothiazepine**
– First Generation	**– First Generation**	**– First Generation**
e.g. Verapamil	e.g. Nifedipine	e.g. Diltiazem
– Second Generation	**– Second Generation**	
e.g. Anipamil	e.g. Amlodipine	
Bepridil	Felodipine	
	Isradipine	
	Nicardipine	
	Nimodipine	

The drugs belonging to calcium channel blockers are described as follows :

1) VERAPAMIL



IUPAC Name : 2-(3,4-Dimethoxy phenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl]-(methyl) amino]-2-prop-2-yl pentanenitrile.

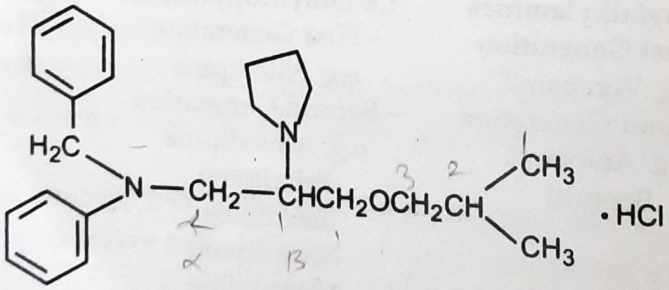
Properties : It is a white crystalline powder, soluble in water and stored in well closed light resistant container. 90% of drug is absorbed from G.I.T., first pass metabolism occur in liver so bioavailability is only about 20%. Verapamil is excreted by kidney in the form of its metabolites.

Mechanism of Action : It inhibits L-type calcium channels in the heart thus reducing heart rate and blood pressure.

Uses :

1. Verapamil is used to control supraventricular tachycardia and migraine headache prevention.
2. It is used in the management of classical and variant angina pectoris and in hypertension.
3. Verapamil is also used to treat cerebral vasospasm and in cluster headache.

2) BEPRIDIL HYDROCHLORIDE



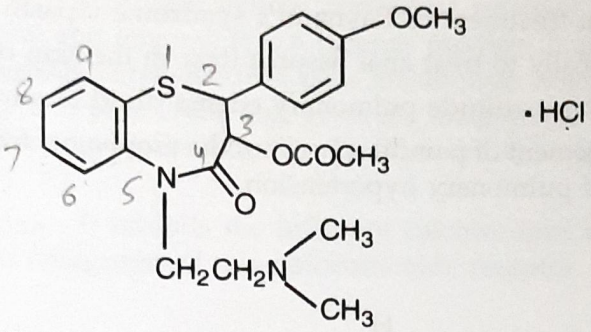
IUPAC Name : β-[(2-methyl propoxy)methyl]-N-phenyl-N-(phenylmethyl)-1-pyrrolidine ethylamine hydrochloride.

Properties : It is white crystalline powder which is slightly soluble in water. It is rapidly and completely absorbed after oral administration and metabolised in liver.

Mechanism of action : Bepridil acts by inhibiting both slow calcium and fast sodium inward current in heart and interfere with calcium binding to calmodulin, blocks both voltage and receptor operated calcium channel.

Use : It is used to treat angina pectoris.

3) DILTIAZEM HYDROCHLORIDE



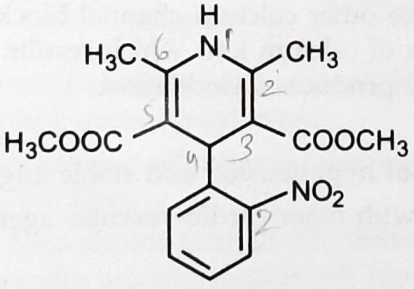
IUPAC Name : (2S, 3S)-3-acetyloxy-5-[2-(dimethylamino)ethyl]-2-(4-methoxy phenyl)-2, 3-dihydro-1, 5- benzothiazepin-4(5H)-one hydrochloride.

Properties : It is a white crystalline powder, freely soluble in water and stored in well closed light resistant container. It is rapidly absorbed and metabolised by first pass metabolism by deacetylation, oxidative O- and N-demethylations and conjugation of phenolic metabolites of the various metabolites, deacetyldiltiazem is pharmacologically active.

Mechanism of Action : It inhibits the influx of extracellular Ca^{2+} across myocardial and vascular smooth muscle by inhibiting ion-control gated channel or interfering with the release of calcium from sarcoplasmic reticulum which results in dilation of coronary and systemic artries.

Use : It is used to treat hypertension and angnia pectoris.

4) NIFEDIPINE



IUPAC Name : Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-di-carboxylate.

Properties : Nifedipine is a yellow, crystalline powder, practically insoluble in water and protected from light. It is not a nitrate but its nitro group is essential for its antianginal effect. It is absorbed efficiently after oral administration and metabolised by liver into its inactive metabolite. Nifedipine is excreted as a traces of unchanged drug in urine.

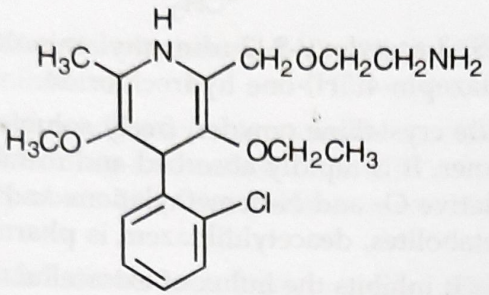
Mechanism of Action : Its action is similar to other calcium channel blockers i.e. it inhibits the influx of calcium ions through L-type calcium channels.

Uses :

1. It is used in management of hypertension. It has no antiarrhythmic activity.
2. It is used in prophylaxis of angina pectoris.

3. It is also used as a tocolytic (that delays premature labor).
4. Nifedine is used in treatment of Raynand's syndrome (Spasm of arteries).
5. It is also used topically to treat anal fissures (tear in the skin of anal canal).
6. It is used to treat high attitude pulmonary edema (fluid accumulation in lungs).
7. It is used in management of painful spasms of the esophagus from cancer and also used in the treatment of pulmonary hypertension.

5) AMLODIPINE



IUPAC Name : 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridine dicarboxylic acid 3-ethyl 5-methyl ester.

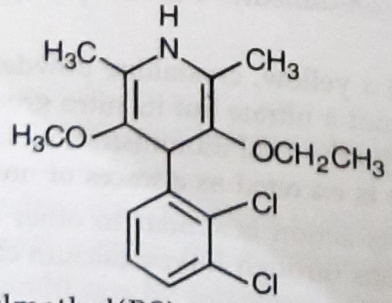
Properties : It is white crystalline solid powder, slightly soluble in water, having melting point 178-179°C. It is slowly and completely absorbed from G.I.T. and metabolise by liver into its inactive metabolites via the cytochrome P450 enzyme. Its 60% of the metabolites excreted in urine.

Mechanism of Action : Like other calcium channel blockers it blocks L-type calcium channels by inhibiting the influx of calcium ions which results in decrease in contraction of arterial smooth muscle cells and produces vasodilation.

Uses :

1. It is used in management of hypertension and stable angina pectoris.
2. It is used in combination with other cardio-vascular agents to lower blood pressure.

6) FELODIPINE



IUPAC Name : Ethylmethyl(RS)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1, 4-dihydropyridine 3,5-dicarboxylate.

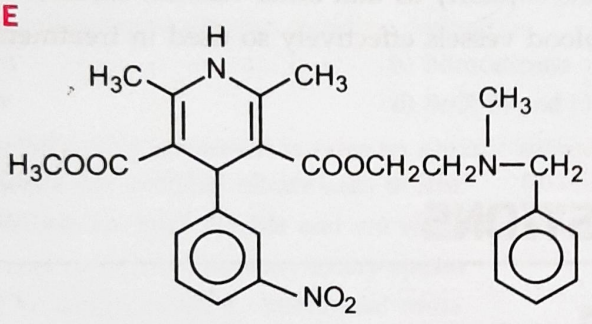
Properties : It is a white or light yellow crystalline powder, insoluble in water but soluble in dichloromethane and ethanol. It is a racemic mixture. It exhibits higher degree of protein binding. It undergoes extensive first pass metabolism after oral administration. It metabolise in liver by cytochrome P-450 and gives six metabolites having no activity. It is more selective for vascular smooth muscle than for myocardial tissue and act as a vasodilator.

Mechanism of Action : It inhibits the influx of calcium ions through L-type calcium channel. It also act as an antagonist of mineralocorticoide receptor.

Uses :

1. It is used in the treatment of high blood pressure.
2. It is also used to stablize angina.
3. By blocking calcium channel it relaxes and widens the blood vessels hence blood can flow easily.

7) NICARDIPINE



IUPAC Name : 1,4-dihydro-2,6-dimethyl-4-(3-nitro phenyl)-3,5-pyridinedicarboxylic acid methyl 2 [methyl (phenyl methyl)amino] ethyl ester.

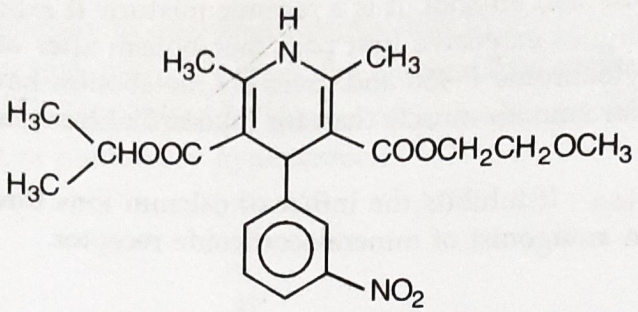
Properties : It is a white crystalline solid having melting point 136–138°C. It is insoluble in water. It is metabolised by the liver.

Mechanism of Action : Nicardipine inhibits the influx of extra cellular calcium ions across the myocardial and vascular smooth muscle cell membrane. It probably acts by deforming the calcium channels or interfere with the release of calcium from sarcoplasmic reticulum.

Uses :

1. It is a potent vasodilator of systemic coronary, cerebral and renal vasculature so, used in the treatment of high blood pressure.
2. It is used to stabilise the angina and effective in the treatment of coronary spasm.

8) NIMODIPINE



IUPAC Name : 2-Methoxyethyl 1-methyl ethyl (4RS)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Properties : It is a light yellow crystalline powder, practically insoluble in water and shows polymorphism. It is metabolised by liver after oral administration and bioavailability is about 13%.

Mechanism of Action : It acts similarly as that other calcium channel blockers.

Use : It dilate the cerebral blood vessels effectively so used in treatment of cerebrovascular disorder.

REVIEW QUESTIONS

SHORT ANSWER QUESTIONS

Q.1. Write a short note on vasodilators.

Q.2. Classify antianginal drugs. Explain any two drugs belongs to organic nitrates.

Q.3. Give mechanism of action of

a) Vasodilators b) Calcium channel blockers

Q.4. Write the structure and uses of-

a) Amilodipine b) Isosorbide dinitrate c) Ditiazem

Q.5. Give the synthesis of Nitroglycerine and Isosorbide dinitrate.

LONG ANSWER QUESTIONS

Q.1. What is angina pectoris. Classify antianginal agents. Explain structure, properties, mechanism of action and uses of Nitroglycerine, Dipyridamole.

Q.2. Comment on calcium channel blockers.

MULTIPLE CHOICE QUESTIONS

Q.1. Mechanism of action of nitrate is-
a) Stimualtes guanylate cyclase
b) β-blockers
c) Calcium channel blockers
d) Inhibits phosphodiestrase

Q.2. The antianginal drug that inhibits phosphodiestrase is-
a) Nifedipine
b) Isosorbide dinitrate
c) Dipyridamole
d) Aspirin

Q.3. Which of the following drug belong to vasodilator-
a) Dipyridamole
b) Isosorbide dinitrate
c) Verapamil
d) Both a) and b)

Q.4. Which of the following antianginal drug useful for emergency treatment of cyanide poisoning-
a) Aspirin
b) Amyl nitrite
c) Dipyridamole
d) Glyceryl trinitrate

Q.5. Which of the following is dihydro pyridine derivative-
a) Nicorandil
b) Nimodipine
c) Felodipine
d) Both b) and c)

Q.6. Which of the following statement is false on organic nitrate-
a) These generate the unstable nitrate salts in situ.
b) Organic nitrates are lipid soluble and are well absorbed through te skin
c) They prevents or reverse coronary artery spasm
d) These can be administered by sublingual route

Q.7. Mostly calcium channel blocker act by inhibiting influx of Ca^{2+} ion through-
a) P-type calcium channel
b) T-type calcium channel
c) L-type calcium channel
d) N-type calcium channel

Q.8. Verapamil belongs to
a) 1,4-dihydropyridine
b) Benzothiazepine
c) Phenylalkylamine
d) None of above

Q.9. The second generation dihydropyridine drugs are-
a) Amilodipine
b) Isradipine
c) Nicardipine
d) All of above

Q.10. Which of the following drug is not belong ti second generation dihydropyridine-
a) Nifedipine
b) Isradipine
c) Felodipine
d) Nimodipine

ANSWERS

1.a)	2.c)	3.d)	4.b)	5.d)	6.a)
7.c)	8.c)	9.d)	10.a)		