In the name of Allah the Beneficent, the most merciful

We, the PharmaPill Team have tried our best to write all the doctor slides + his explanation as well as some pictures that the doctor showed us and we were able to copy them from our books.

We hope that this booklet will be most beneficial to you and we will post the notes on Anemia and thrombolytic agents soon later…

Wishing you all the best,

Pharma Pill team

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Ischemic heart diseases

(IHD)

1-angina pectoris.

2- acute myocardial infarction.

- **Affects 3 functions of the heart :-**

  1-Arrythymia → Heart rate

  2-Heart Failure → contractility

  3- IHD → blood supply ↓es

✓ **Blockade of coronary arteries by plaque of fatty acid +cholesterol causing partial blockage (Angina) or complete blockage leading to MI.**

✓ **Electrophysiology may be changed .**

Angina Pectoris

. (Strangled breast) present as radiating chest pain due to insufficient O_2 supply .

✓ Pain occurs due to release of bradykinine or prostaglandins (pain factor) which are released due to ischemia .Ca^{++} is also released.

✓ Cell membrane integrity is maintained due to Na^+/K^+ pump that requires ATP + O_2 → but in IHD →K^+ is excessively moved to the outside dysbalancing the cellular integrity and increasing the extracellular conc. Of K+ causing pain and disrupting the electricity of the heart..

✓ Adenosine & ADP will accumulate intracellularly ,too.

✓ Can occur during exercise or stress → ischemia → release of K+ , Prostaglandines , kinines nucleotides → pain is felt in the heart , shoulder region, arm , neck –takes 15 min with activity stoppage .

Blood Flow O_2

↘ ↙

Heart muscle

↓

if deficient

↓

Pain

↓

Stop all activity

Basic mechanism is an imbalance between O_2 demand & O_2 supply .

Demanded increased

- Caused by :

✓ ↑HR

✓ ↑FOC

✓ ↑intra ventricular Pressure & volume

✓ ↑thickness of the wall of ventricle .

- How to reduce it ?

  ✓ We ↓FOC and ↓ HR

- To do this, we may need to ↓ IVP

(intra-ventricular pressure & volume)

- **O_2 supply is increased by any dilation in coronary arteries.**

  ✓ During systole, ventricular contraction presses coronaries thereby literally blood flow to the heart muscle.

  ✓ So, diastole is the period destined for blood to reach the heart muscles because the BP in Aorta (and coronaries) is more than that in the ventricle during diastole allowing blood flow.

- **Causes of angina pectoris:-**

✓ coronary atherosclerosis (atheromatous plaque)

✓ increased platelate aggregation & coronary thrombosis

✓ coronary artery spasm (even without plaque formation)

✓ vasoconstriction after adrenergic stimulation (after smoking)

✓ platelate aggretation and resulting thrombi

- Heavy meal (as tobacco) cause dilation in the GIT blood vessels to allow food digestion which causes decreased blood pressure leading to reflex sympathetic stimulation , ultimately angina.
- Tobacoo smoking stimulates ganglia increasing heart rate thereby increasing O2 demand.

Coronary blood flow

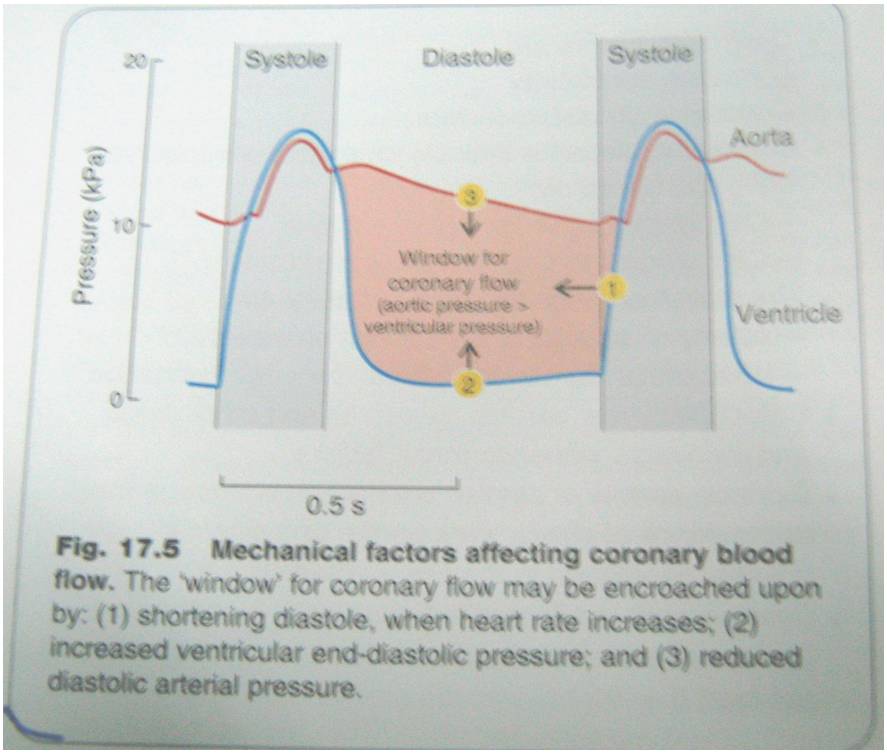


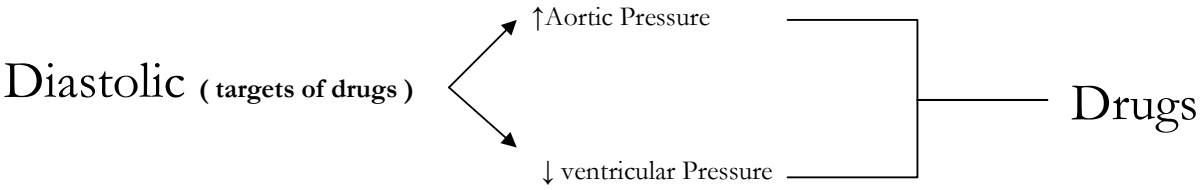
Fig. 17.5 Mechanical factors affecting coronary blood flow. The 'window' for coronary flow may be encroached upon by: (1) shortening diastole, when heart rate increases; (2) increased ventricular end-diastolic pressure; and (3) reduced diastolic arterial pressure.

- **Controlled by:-**

1- Transmural Pressure during systole:-

diastolic coronary perfusion pressure **= Diastolic aortic pressure – Diastolic ventricular pressure .**

✓ Prolongation of diastolic period will ↑ flow through coronaries.



- During systole Ventricular P > Aortic P so no flow in coronaries.
- During Diastole VP < AP so there is flow of coronary Diastole .

✓ Flow can be reduced by reduction of aortic pressure or ↑ing VP or reduction of diastolic period time.

2- vasodilators :-

- Metabolites, $\downarrow Po_2$ → ↑adenosine + K^+ Leakage of potent dilator.

✓ At rest, IHD patient don't feel pain because O_2 demand = O_2 supply, but during exercise, the Demand > Supply , Sometimes it is felt at rest → Rest Angina

Exercise Angina

Summary

- A pain result from [ischemia] →[resulting most commonly from atherosclerosis]
- If complete & sudden (like that caused by thrombi) → acute MI → overload of intracellular Ca^{++} and ultimately cell Death .
- overload of Ca^{++} inside cells due to escape of Ca^{++} from cytosol to the organelles activating many hydrolytic enzymes Causing cell death and Cardiac arrhythmia.

Types of angina

1-chronic staple :

- caused by fixed stenosis → By plaque blockade of coronary arteries .
- It is also called Classic angina = angina of effort → pain is precipitated by increased activites.

✓ During exercise, O_2 demand may ↑ 100 times (which is normally met by coronary dilation) but in those with plaque , no dilation is possible so no enough Blood supply.

2-unstaple : take place during rest .

- Pathologic change in athermomatous polaque caused by mobile thrombus

Requires immediate hospitalization and O_2 application and is considered as a warning sign for MI

- Not only partial blockage But actually submaximal blockage in the coronaries artery.

✓ Use **nitroglycine** + β-Blockers

3- variant angina :

- Vasospastic angina (also called pinzmetal angina)
- Caused by spasm & occurs at rest

✓ Drugs dilate coronaries are used to treat this angina

4. Silent, ambulatory Angina:

- Angina without pain.
- Sudden death because of heart ischemia.

Durg therapy for angina pectoris (in general):

1-β-Blockers

2-Ca^{++} Blockers

3-K^{+} Blockers

4-Partial FA oxidation inhibitors (PFox)

5- aspirin

6- Organic nitrate.

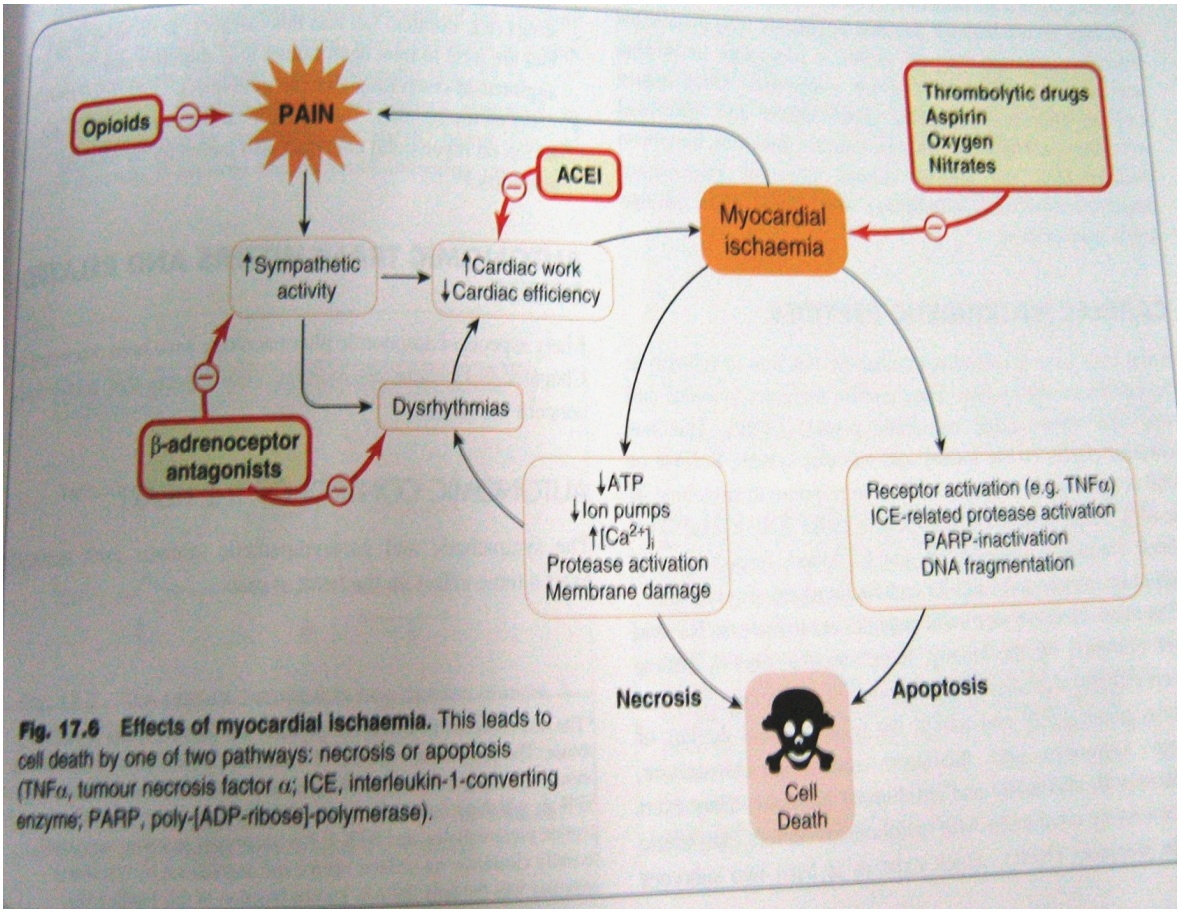
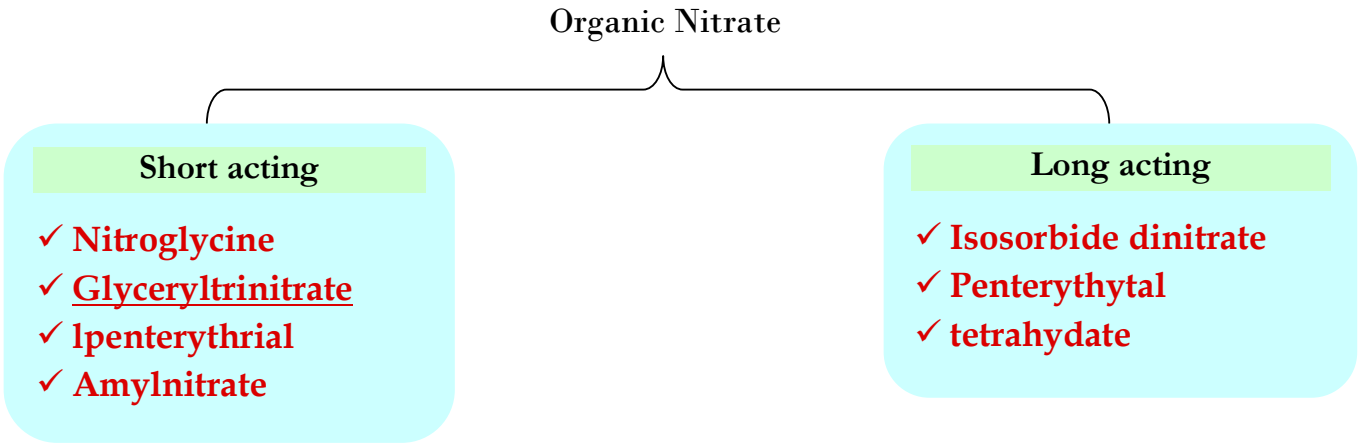


Fig. 17.6 Effects of myocardial ischaemia. This leads to cell death by one of two pathways: necrosis or apoptosis (TNFα, tumour necrosis factor α; ICE, interleukin-1-converting enzyme; PARP, poly-[ADP-ribose]-polymerase).

Organic Nitrate

- Explosive substance which were invented by Nobel whose uncle dead of nitrate explosive.

  ✓ ***N.B.:*** Nitrites (IN THIS FORM) are **NOT** used in Angina treatment.



Organic nitrate :

- MOA → Relax smooth muscles (Especially those in bloood vessels).

Organic Nitrates → Organic Nitrites → NO → activation of guanylate Cyclase → production of excess cGMP → phosphorylation – thereby inactivation – of protein kinase → No phosphorylation – thereby no activation – of Myosine light chain kinase -→ reduced phosphorylation of Myosine light chain therefore actine – myosine binding is reduced→ smooth muscles are relaxed…

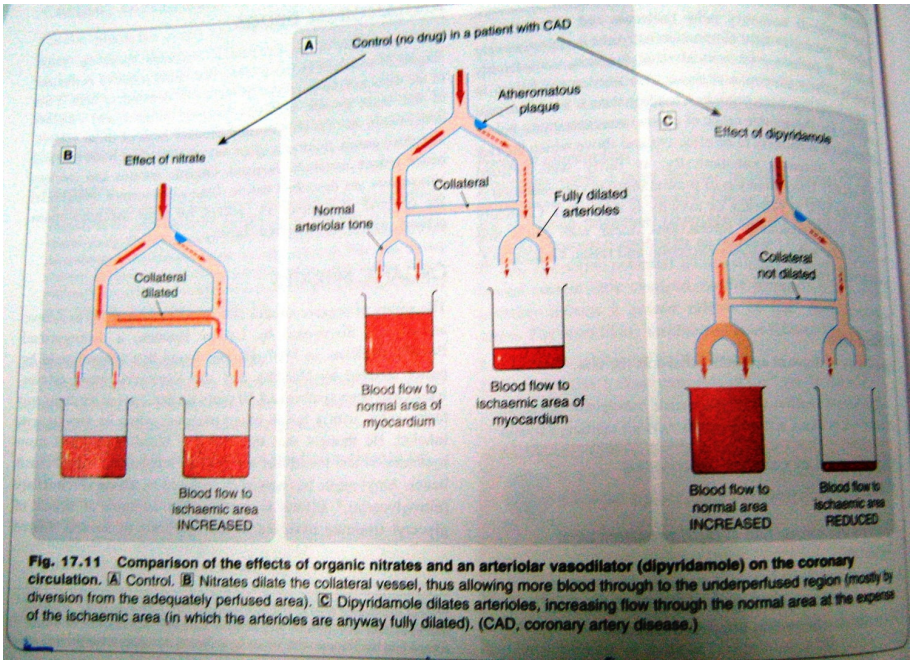


Fig. 17.11 Comparison of the effects of organic nitrates and an arteriolar vasodilator (dipyridamole) on the coronary circulation. A Control. B Nitrates dilate the collateral vessel, thus allowing more blood through to the underperfused region (mostly by diversion from the adequately perfused area). C Dipyridamole dilates arterioles, increasing flow through the normal area at the expense of the ischaemic area (in which the arterioles are anyway fully dilated). (CAD, coronary artery disease.)

Pharmacodynamics :

nitrates are converted to nitrites , this requires SH group which could be blocked by ethacrynic acid (bind to SH of cysteine in ascending thick loop of Henly).

- Dilate large veins " more sensetive than arteries " ⇨↓ central venous pressure ⇨ ↓ C.O
- reduce stroke output is compensated for by tachycardia .
- at high dose arterioles are dilated ⇨ ↓ arterial blood pressure .
- Organic nitrates increase coronary blood flow although the mean arterial blood pressure is reduced ⇨ ↓ vascular resistance :

↓ CO + ↓ ABP ⇨ ↓ O2 demand

1- ↓ O2 demand + ↑blood flow ⇨ ↑O2 supply .

2- in variant angina organic nitrates relieve coronary spasm . " directly "

3- organic nitrates divert blood flow from normal to ischemic areas of myocardium ⇨ dilation of large collateral arterioles enabling partially blocked venules to be by-passed . " in the ischemic area arterioles are fully dilated "

Dipyridamole :

Dilates the arterioles of normal tissue but cannot dilates the collateral of ischemic area ⇨ the blood will shift drug solution to the normal area .

Administration :

- Glycerytrinitrate formulated as :-

1- sublingual tablets . " because it has low bioavailability in the oral route "

2- preparation for transdermal absorbtion .

- 2% in lanolin prophylaxis, 4-8 hours , occluded into dressing on the chest , well absorbed through the skin , more sustained effect .

3- oral sustained-release preparation .

4- buccal sustained-release .

5- I.V preparation .

- The sublingual tablet of nitroglycerine may lose potency when stored , as a result of volatization and adsorption to plastic surfaces .

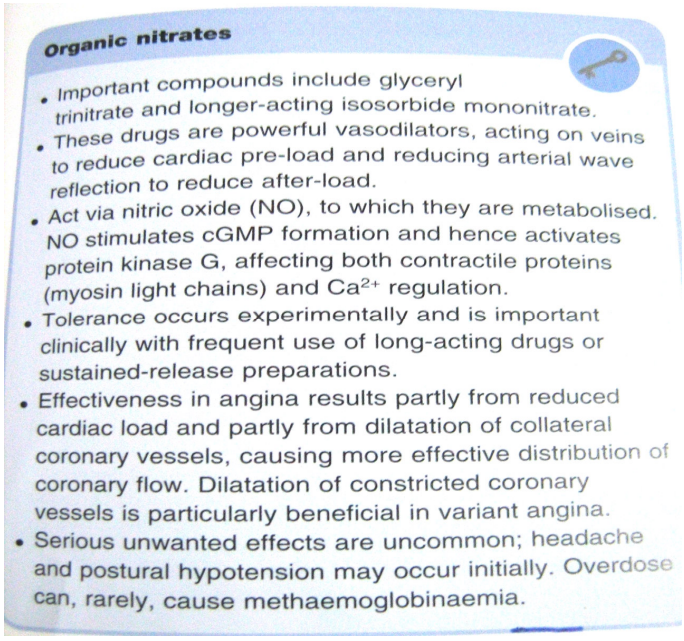
- GTN metabolized by liver by removal of nitrate groups in stepwise fashion from parent molecule ⇨ little dilator effect , duration of effect 15-30 min , if sollowed the drug is ineffective because of first-pass inactivation (10-20 % bioavailabiltity) .

amylnitrate : is available in fragile glass ampoules packaged in a protective cloth covering .

- ✓ The ampoule is crushed of the drug is inhaled through cloth covering .
- ✓ Due to unpleasant odor and short duration of action , now little used " sex enhanced " .

Long-acting organic nitrates : pentaerythritol tetranitrate and isosorbide dinitrate :

- Isosorbide dinitrate is rapidly metabolized in the liver to mononitrate which is biologically active T½ = 4h .
- Isosorbide mononitrate is available for clinical use and has 100% bioavailability .
- Isosorbide dinitrate is administered orally for prophylaxis , chewed for more rapid effect .
- they have slow onset of action .
- **Isosorbide dinitrate :-**
  - ✓ sublingual : 1-5 h
  - ✓ oral slow release : 8-30 h



Organic nitrates

- Important compounds include glyceryl trinitrate and longer-acting isosorbide mononitrate.
- These drugs are powerful vasodilators, acting on veins to reduce cardiac pre-load and reducing arterial wave reflection to reduce after-load.
- Act via nitric oxide (NO), to which they are metabolised. NO stimulates cGMP formation and hence activates protein kinase G, affecting both contractile proteins (myosin light chains) and Ca^{2+} regulation.
- Tolerance occurs experimentally and is important clinically with frequent use of long-acting drugs or sustained-release preparations.
- Effectiveness in angina results partly from reduced cardiac load and partly from dilatation of collateral coronary vessels, causing more effective distribution of coronary flow. Dilatation of constricted coronary vessels is particularly beneficial in variant angina.
- Serious unwanted effects are uncommon; headache and postural hypotension may occur initially. Overdose can, rarely, cause methaemoglobinaemia.

Adverse drug reaction (ADP) :

- Unpleasant sensation of flushing and headache
- orthostatic hypotension .
- tachycardia .
- formation if methaemoglobin ⇨ treated by tolonium chloride " anti oxidant "
- CN poisoning : result in bind of CN to cytochrome oxidase " bind to ferric ion " so administration of sodim nitrate detoxify this poisoning .
- tolerance ⇨ is more when long-acting preparation (oral , trandermal) or continuous I.V infusion are used for more than a few hours without interruption .

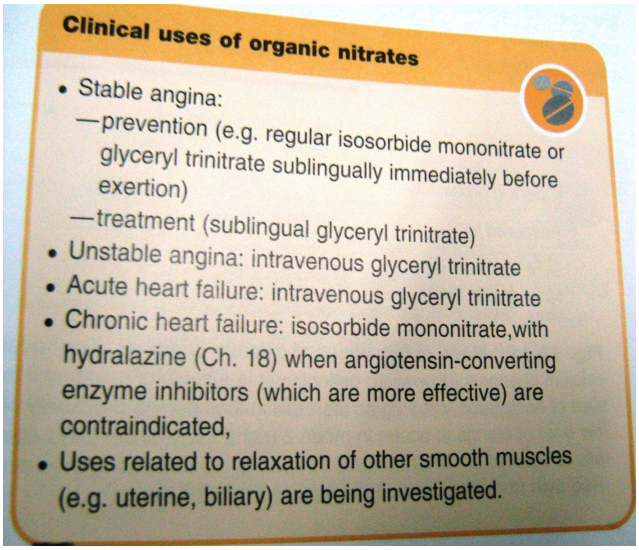
1- may be partly due to diminished release of nitric oxide or systemic compensation (initial sympathetic discharge & salt and water retention after one or two days) .

2- endothelin ⇨↑ sensitivity to vasoconstrictors ⇨ nitrate tolerance .

Contraindications :-

1. known sensitivity to organic nitrates .
2. acute circulatory failure (shock , circulatory collapse) .
3. uncorrected hypovolemia .
4. increased intracranial pressure " e.g. head trauma or cerebral hemorrhage "

Clinical uses :-



- Stable angina ⇨ sublingual .
- unstable angina ⇨ I.V .
- acute heart failure ⇨ I.V .
- chronic heart failure ⇨ ACE inhibitors are more effective .
- Spasm of uterus or biliary or bladder .
- β-adrenoceptor blockers antagonizes the effect of NA (noradrenaline) from sympathetic nerve ending of AD (adrenaline) from adrenal medulla prevent ↑ in cardiac activity , ↑ O2 demand .
- Catecholamines ⇨ ↑ cAMP ⇨ contraction of heart muscle .
- Antihypertensive effect decrease the load against which the heart should work in order to pump blood into arteries .
- prolongation of diastolic period resulting from decrease heart rate ⇨ ↑ coronary blood flow contraindicated in variant angina , may allow unopposed α-adrenergic coronary vasoconstrictor to occur .
- β -blockers should not be rapidly withdrawn from patients ⇨ rebound & increase in the frequency & severity of pain .

Clinical uses :

- prophylactic treatment of classic & unstable angina .
- not used in variant angina .
- silent or ambulatory angina " no pain " .
- ↓ mortality of patients with recent myocardial infarction .

Ca++ blockers :-

- Bending of calcium channel blockers with channels reduces the frequency of opening in response to depolarization .
- this result in a marked relaxation in smooth muscle & in cardiac muscle in reduction of contractility .

Types of calcium channel :

1- L-type calcium channel , distributed in muscle & neurons .

2- T- type calcium channel , distributed in hearts & neurons .

3- N-type calcium channel , distributed in neurons .

4- P-type calcium channel distributed cerebellar purkinji neurons .

Types of L-type blockers :

- Dihydropyridine series : nifedipine , isradepine , amlodipine .
- phenylalkylamines : verapamile .
- benzathiazepines : diltiazem .
- Mainly effect heart & smooth muscle of vessels , inhibiting Ca^{++} entry caused by depolarization .

✓ selectivity between heart & smooth muscle varies :

- **verapamile ⇨ heart .**
- **nifedipine ⇨ smooth muscle .**
- **diltiazem ⇨ intermediate .**

N.B : in angina Ca^{++} antagonist reduce cardiac work and O2 consumption .

Clinical uses :

- dysrhythmias (verapamile) : atrial fibrillation , supraventricular tachyarrhythmias (SVT) by I.V .
- hypertension : amlodipine
- to prevent angina : Dihydropyridine
- Aspirin : ↓ chances of coronary thrombosis .
- acetylates α amino group of terminal serine of COX enzyme used in stable & un stable angina .

ADR :

1. GIT bleeding .
2. gastric ulceration .
3. reduce renal function .
4. -occasionally bronchospasm with high dose .

K+ channel openers :- (nicorandil)

- **Relaxes vascular smooth muscle especially veins by :**

✓ activation of K^+ channel ⇨ stabilize membrane potential near resting potential.

✓ NO release .

✓ used prophylactically .

- **may cause :**

  - ✓ flushing .
  - ✓ palpitation .
  - ✓ weakness .
  - ✓ headache .
  - ✓ mouth & perianal ulcer .
  - ✓ nausea & vomiting .

Fatty acid oxidation inhibitors:

e.g. ranolazine & trimetazidine ⇨ inhibit 3-ketoacyl CoA + thiolase .

- ranolazine also inhibit a late Na current that facilitates calcium entry .

Drug treatment of angina :-

✓ acute attack : short-acting nitrates or nitrites .

✓ prophylactic therapy : long-acting nitrates , Ca++ blockers , β- adrenergic blockers , K+ channels openers .

Combination therapy :

- nitrates + β-blockers .
- Ca^{++} blockers + nitrates .
- Ca^{++} blockers + β-blockers + nitrates

Unstable angina & acute coronary syndrome :

- Anticoagulants (heparin) & antiplatelets (aspirin) play major rule in therapy .
- nitroglycerin & β- blockers should be added .
- Ca^{++} channels blockers should be added in refractory cases .

Surgical treatments :

- ballon catheter.
- coronary bypass surgery .

Wishing you all the best,

PharmaPill Team