

ANTIANGINAL DRUGS

ANGINA PECTORIS:

- chest pain, radiating to arms, neck, jaw, shoulder or back
- Main symptom of ischemic heart disease
- Most common cause - Atherosclerosis:

TYPES:

↓
Classical Angina [Stable Angina]: Predictable attacks.
Precipitated by exercise, exhaustion, cold.
cause: Severe Atherosclerosis, occlusion of large C.A.

→ Unstable Angina: Occur at Rest.
Cause: Due to Rupture of Atherosclerotic plaque
- Platelet deposition
- occlusion.

→ Variant Angina / Prinzmetal Angina: Unpredictable Attacks.
Cause: Due to localized coronary vasospasm.

ANGINA - PATHOGENESIS:

An imbalance b/w myocardial O₂ supply & demand
↑ O₂ demand ↓ supply.

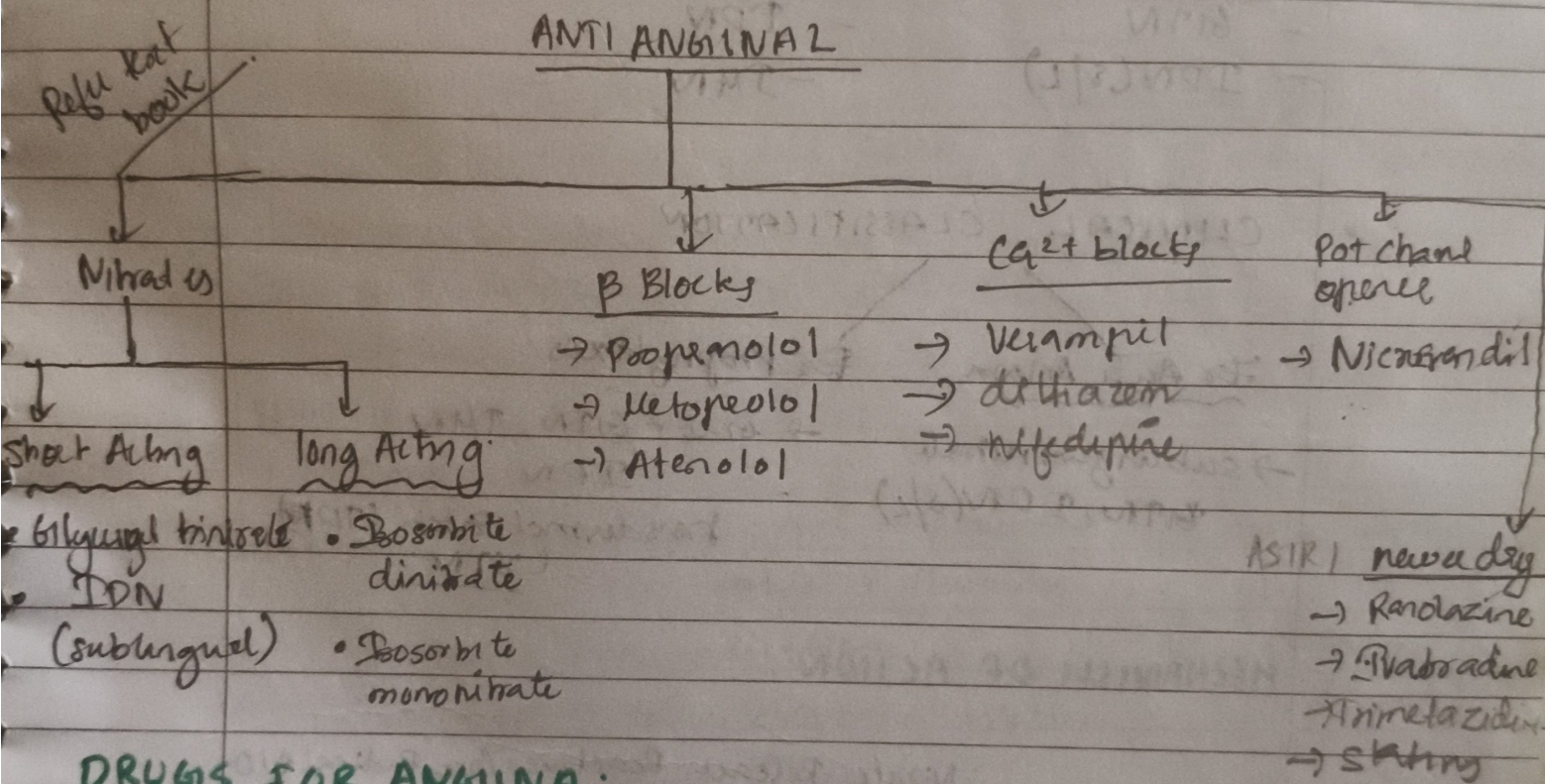
HR
Contractility
Preload
Afterload
→ O₂ Demand.

1/2 → O_2 supply → CABG, CCB, Pervent, theombus, Shaplokin
 → O_2 demand → LHR by B Blocker, 1 period

t/c of ANGINA PECTORIS:

lifestyle changes → Diet
 → exercise
 → no Alcohol no smoking

- DRUGS
- Surgery
- CABG (Coronary Artery Bypass Graft)
- PTCA (percutaneous transluminal coronary Angioplasty)



DRUGS FOR ANGINA:

- For Acute Attack — Nitrate — short Acting:
 - Nitroglycerine
 - Isosorbide dinitrate (sublingual)
- For Prophylaxis — Vaso dilator
 - Nitrate long - Acting
 - CCBs
 - K channel openers.
 - B blockers
 - Other

AKR
 AKR →

NITRATES:

- Vasodilators:
- Prodrug of nitric oxide.
- Release NO which cause smooth muscle Relaxation
↳ Nitrovasodilator.

NITRATE CLASSIFICATION

Short Acting

- GTN

- IDN (s/l)

Long Acting

- IDN

- TMN

CLINICAL CLASSIFICATION

For Anti Angina

→ sublingual nitrate
GTN, IDN (s/l)

For Prophylaxis

→ oral - GTN, TMN
IDN

Transdermal Patch (TDP)

↳ GTN

MECHANISM OF ACTION:

Nitrate Release Reactive free Radical NO



NO Activate guanylyl cyclase enzyme



↑ cGMP → Dephosphorylation of MLC (Myosin light chain)
↓ action ↓

Inhibition of Actin-Myosin Interaction & contraction



Smooth Muscle Relaxation → vasodilation

Inhibit platelet Aggregation.

PHARMACO ACTION:

1) VASODILATION:

- Mainly dilate vein.
- most important MOA.
- Reduce PRELOAD.

↓ O₂ Requirement
↑ O₂ delivery

- Dilate Arterioles (only at higher concentration)
- Reduce AFTERLOAD.

* - Dilate coronary vessel

- ↑ B.S to ischemic Area

vasodilation
↓
peripheral pooling of blood
↓
↓ venous Return to heart
↓
↓ Preload
↓

2) INHIBIT PLATELET AGGREGATION:

3) SMOOTH MUSCLE RELAXATION:

- Blood vessels

- Meningeal vessel → headache

- Facial vessels → flushing

Bronchus - bronchodilation

Esophagus - Relieve esophageal spasm.

Biliary - Relieve Biliary colic

↓ ↓ end diastolic volume

↓ ↓ cardiac work

↓ ↓ O₂ Requirement

(↓ O₂ demand)

↓
Relieve pain

PHARMACOKINETICS:

→ High PBM

→ Oral bioavailability - very low.

→ Disorbide mononitrate - BA 100%.

→ Lipid soluble → well Absorbed from skin & mucosa.

→ Rapid onset of Action

→ IV infusion of nitroglycerin can be given in Hypertensive emergency

ADRs:

vasodilation →

- Postural Hypotension
- Throbbing headache
- Flushing
- Methemoglobinemia.

DRUG INTERACTIONS:

• PDE5 inhibitor if nitrate given simultaneously can produce severe hypotension, HT.

• Dependence:

sudden withdrawal after prolonged therapy →
spasm of coronary & peripheral vessel
&
sudden death.

• Tolerance (Monday disease)

↳ - Repeated or continuous exposure to high doses.

- To prevent, intermittent therapy - provide nitrate free intervals.

C/I → Systolic BP < 90 mmHg
HR < 50 or > 100 beats per minute.

USES:

1) Stable Angina

- Fast Acting, sublingual.

2) Variant Angina / Prinzmetal Angina.

3) Unstable Angina.

RATIONALE FOR NITRATE IN STABLE ANGINA

1) Stable Angina

preload $\rightarrow$ $\downarrow$ O₂ demand $\rightarrow$ Useful in SA.
Afterload $\rightarrow$

2) Unstable Angina Variant Angina

Afterload $\rightarrow$

Coronary vasodilation $\rightarrow$ O₂ supply $\uparrow$ $\rightarrow$ useful in variant Angina

3) Unstable Angina.

platelet inhibition $\rightarrow$ useful in unstable Angina.

Uses

$\Rightarrow$ Acute MI

$\Rightarrow$ Acute coronary syndrome - STEMI
- NSTEMI

$\Rightarrow$ CHF

$\Rightarrow$ Biliary colic

$\Rightarrow$ Oesophageal spasm

$\Rightarrow$ Cyanide poisoning.

NITRATE IN CYANIDE POISONING:

inactivates cyanide in
cells.

Haemoglobin
 $\downarrow$ SODIUM NITRITE
Methemoglobin
 $\downarrow$ CYANIDE

Cyanomet Hb

(cyanide can dismutate)

$\downarrow$ IN SODIUM THIOSULPHATE

Met Hb + sodium thiosulphate
 $\rightarrow$ excrete in urine

→ Alternate Drug: Hydroxocobalamin,
Dicobalt edetate

why Na nitrite

→ very weak vasodilator;
no hypotension Rine.

B-BLOCKERS:

- currently first line drug in all stable Angina patients.
- cardioselective Agent Required.

Mechanism

As a consequence of ↓ heart rate, ↓ coronary mean B.P
↓ cardiac work, ↓ O₂ consumption.

- won't dilate coronaries.
- Total coronary flow is ↓ due to β₂ blockade.

↓ HR → prolonged diastole → improve coronary perfusion

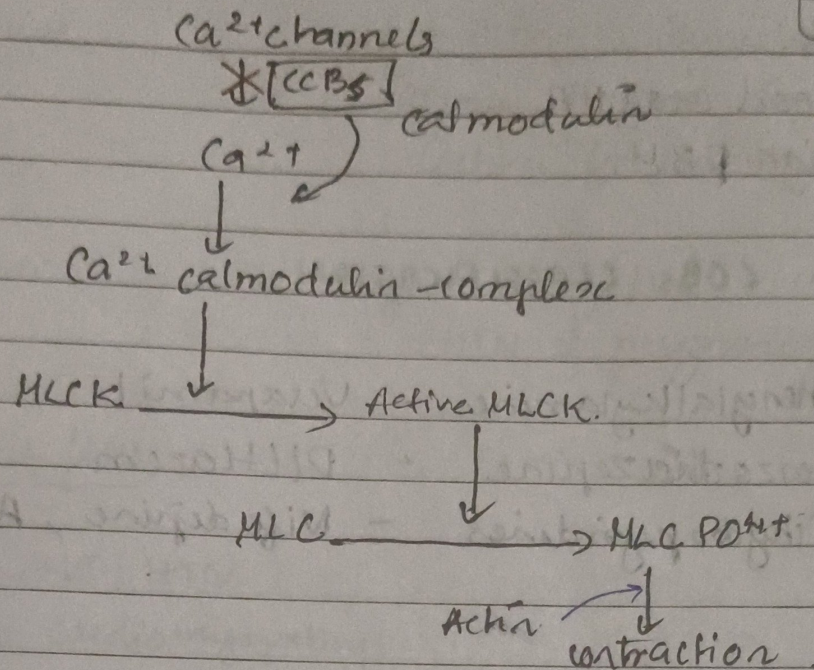
↓
subendocardial perfusion

- Flow to ischemic subendocardial Region decrease due to favorable disturbance and decreased ventricular wall tension

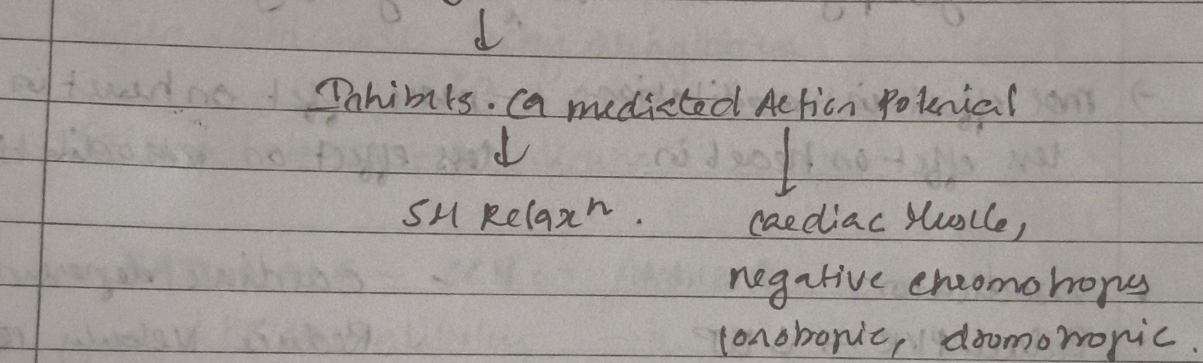
Sudden withdrawal → Precipitate severe attacks, MI

VA/N stenosis → Routinely used / start after (nitrates)
to counteract coronary vasospasm.

CALCIUM CHANNEL BLOCKERS:



CCBs Block L type Ca^{2+} channels.



PHARMACOLOGICAL ACTION:

1) Vascular SM

- Dilates Arteries > veins

↓ Afterload ↓

↑ coronary Blood Flow.

2) Other SM:

- Relaxation of GIT, gut, Bronchi.

3) Heart:

- negative inotropic, chronotropic, dromotropic.

PK:

- Good oral BA
- high FBM.

CCBs CLASSIFICATION:

- Phenylalkylamine - Verapamil
- Benzothiazepine - Diltiazem
- Dihydropyridines - Nifedipine, Amlodipine, Clevidipine

Dihydropyridines Vs ^{Non} Dihydropyridine

- more effect in vasodilation
less effect on heart is.
- more effect on heart is
less effect on vasodilation.
- vasodilator
- Reduce PVR → ↓ BP.
- Rx of HTN
- cardiac depressant
- Reduce velocity conduction
- Rx. Arrhythmia.

DRUGSREMARKS:

Amlodipine

- longest Acting, highly selective
- less Reflex tachycardia

Clevidipine

- Inhibit V_L type Ca channel
- in HTN, Angina

Nifedipine

- Release NO from endothelium
- Inhibit PDE

Nicardipine

short acting is hypotensive
emergent, Angina, Ryand's
selective for coronary B.V

Nifedipine

Rapid acting short DOA
HTN in pregnancy.

→ Therapeutic Uses

- Angina, HT, HTN
- Hypertrophic cardiomyopathy.
- Migraine prophylaxis - verapamil
- Ryand's disease - DHPs.
- Supra ventricular tachy arrhythmias.
↳ ↓ AV nodal conduction.
- Prolong labour - Nifedipine.

##

RATIONALE - CCB in ANGINA

→ ↓ HR contractility →
① cardiac workload ↓ O₂ demand → useful in stable Angina.

↓ Afterload →

→ Coronary vasodilation → ↑ O₂ supply → useful in variant Angina

DRUG INTERACTIONS:

→ verapamil / diltiazem with β blockers → Additive cardiac depression

ADR:

Vasodilation → hypotension
→ Reflex tachycardia
→ flushing

→ Headache
← Ankle

- constipation - vasopressin
- hyperglycaemia

COMBINATION OF DRUGS

→ β Blockers + long Acting nitrate:

- 1) Tachycardia due to nitrate is $\downarrow$ by β Blockers
- 2) Ventricular dilation by β Blockers is $\downarrow$ by nitrate

3) $\downarrow$ total coronary flow by β blocker is opposed by nitrate

→ concurrent use of 3 Antianginals

→ Nitrate $\downarrow$ preload

→ $\downarrow$ PVR $\downarrow$ afterload $\uparrow$ coronary flow $\uparrow$

→ β blockers $\downarrow$ cardiac work

K⁺ channel openers:

→ Nicorandil, Peracidal, Cheomakalin.

MOA:

open ATP - sensitive K⁺ channel in SM membrane $\rightarrow$ hyperpolarization $\rightarrow$ Relaxation $\rightarrow$ vasodilation.

- Donate NO $\rightarrow$ vasodilator vascular SM R₂

→ Arterial & Venous Dilation

→ Preload & Afterload $\downarrow$

Uses:

cardiovascular uses.

ADR

- Tachycardia
- Headache

- flusiology..
- large painful Aphthous ulcers in mouth - Reversible
- Ad $\rightarrow$ no tolerance

Newer AntiAnginals:

Trimetazidine
Ranolazine
Diltiazem

$\downarrow$ freq of Angina.
 $\uparrow$ exercise duration
Add on drugs with 1st line Anti-Anginal.

TRIMETAZIDINE:

MOA $\rightarrow$ PFOX inhibitor.

inhibits fatty acid oxidation path

Inhibit mitochondrial long chain β -
ketacyl CoA thiolase. (C₁₂ - KAT). ~~ketacyl CoA thiolase~~
imp for fatty acid oxidation.

$\downarrow$ fatty acid oxidation & improve glucose oxidation
in myocardium $\rightarrow$ $\downarrow$ O₂ demand.

RANOLAZINE

Inhibit late sodium channels.
cardioprotective

ADR $\rightarrow$ Prolonged QT interval.

Diltiazem

Pure heart ^{rate} lowering Antianginal, Alternative to β Blockers.

Uses:

- Chronic stable Angina with normal sinus Rhythm.
- sinus tachycardia.

CHF

RANKA

DATE

PAGE

ADP

sinus bradycardia

visual disturbance

110A:

Inhibit funny current of SAN

↓

Inhibit spontaneous depolarization of SAN node

↓

Reduce HR.