Drugs used to treat Angina

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AntiAnginal Drugs

1. Agents that treat symptoms & ischemia;

Nitrodilators

A) Nanitroprusside:
- Release NO spontaneously.
- they are antihypertensive.

In case of angina we use **organic nitrates**. They release NO (nitric oxide) via enzymatic reactions.
- divided in to 2 groups of drugs;

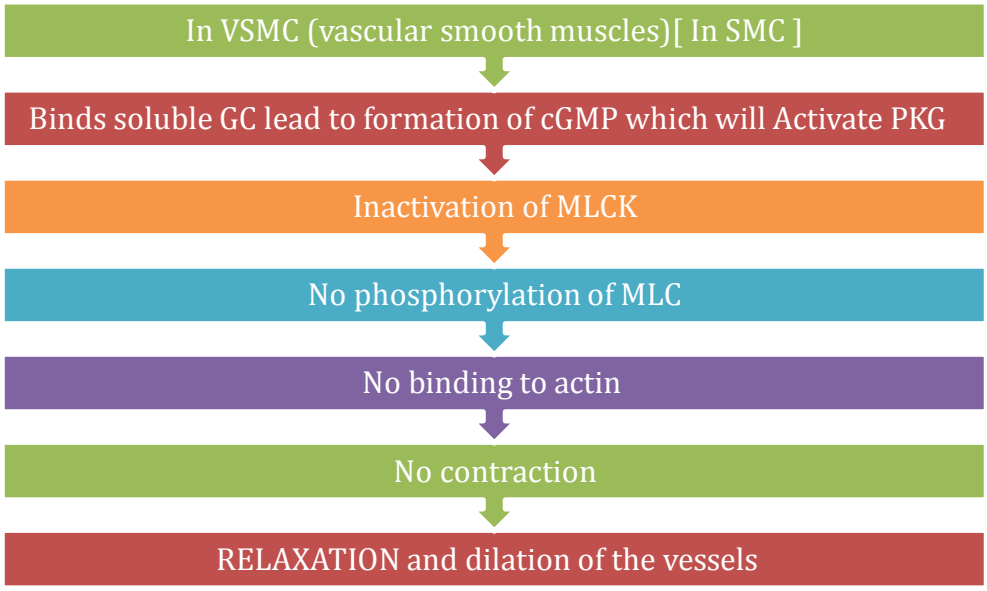
1. Short Acting :

Nitroglycerine [GTN]
Amyl Nitrite
Rabidly in the acute cases **(sublingual)**

2. Long Acting :

-Isosorbide mono & dinitrate
slowly as long term prophylaxis **(oral sustained release transdermal patches).**

MOA



Note: In normal blood vessels NO(nitric oxide) is well more developed in arteries than Venular system ,however; Exogenous NO doners (organic nitrates) act more on Venular than Arteriolar system

Pharmacodynamic Actions

1. Anti-Anginal Actions

- ↑ Myocardial Oxygen Supply : due to

Dilatation of large coronary vessels this will lead to Redistribution of coronary flow from normal to ischemic region.

-Dilatation of collaterals

- ↓Myocardial Oxygen Demand→ by ↓cardiac work indirectly :

Venodilatations : of capacitance vessels →↓preload →↓ central venous P →↓ CO
Arteriolar vasodilatation : ↓ peripheral resistance & ↓ afterload (reflex tachycardia) → ↓BP at high dose

-↓Platelet Aggregation :

(Endothelial protective action)→ ↓leukocyte-endothelial interactions (anti-inflammatory); antiatherogenic potentials.

2. Other Pharmacodynamic Actions

- SMC Relaxation of :

1. Bronchi→NO activates cGMP in BSMC →bronchodilatation. .
2. Gastrointestinal tract & biliary system

3. Pharmacokinetics :

Nitroglycrine [GTN] :

- Significant first pass metabolism occurs in the liver (10-20%) bioavailability (so sublingual or via transdermal patch)
- Oral isosorbidedinitrate & mononitrate;.
- Very well absorbed & 100% bioavailability
- The dinitrate undergoes denitration to two mononitrates → both possess antianginal activity → ($t_{1/2}$ 1-3 hours) → Furtherdenitrated metabolites conjugate to glucuronic acid in liver. Excreted in urine.

4. Indications :

1-In stable angina;
-Acute symptom relief →sublingual **Nitroglycrine** (GTN)

Prevention :

- Regular prophylaxis ➔Isosorbide mono or dinitrate.
- Situational prophylaxis ➔↑exercise tolerance just before exertion.
- In variant angina ➔sublingual GTN to give a faster effect.
- In unstable angina; IV GTN.
- Refractory AHF ➔ IV GTN.
- CHF ➔Isosorbidemononitrate + hydralazine [if contraindication to ACE Is].
- Acute myocardial infarctions ➔IV GTN.
- Severe bronchial asthma ➔ sublingual GTN or inhalational.
- Genitourinary & intestinal spasm (seldom).

Preparations :

Nitroglycerine

1. Sublingual tablets or spray.-
2. Transdermal patch.-
3. Oral or bucal sustained release.-
4. I.V. Preparations.-

Isosorbidedinitrate & mononitrate

1. Dinitrate Sublingual tablets ,Oral sustained release.
2. Mononitrate Oral sustained release
3. Infusion Preparations.

Adverse effects :

- Postural **hypotension** with **reflex tachycardia** --> especially if the patient is standing stationary.
- Nitrite **syncope** with fainting & collapse due to ↑ dilatation of venous capacitance vessels + severe ↓ of venous return leading to ↓CO & BP.
- Nitrite syncope is treated by **putting the patient in a low head position.**
- **Flushing** of blush area (face, neck and upper trunk) is unpleasant
- Throbbing headache (>common) & tendency to ↑ intra-cranial pressure ➔ used cautiously in cerebral bleeding & head trauma.-
- Drug rash.-
- Visual disturbance.-
- Carcinogenesis **(rarely happens)**
- Met-hemoglobinemia***(in overdose & accidental poisoning)***

Amyle nitrite is used in cyanide poisoning by converting HB to MetHb➔ allows cyanide binding ➔ to form non-toxic cyanomethemoglobin➔ combine with toludine blue ➔ excreted in urine .

Nirate Tolerance :

- Loss of vasodilator response of nitrates on use of long-acting preparations (oral, transdermal) or continuous intravenous infusions, for more than a few hours without interruption.
- Magnitude of tolerance is a function of dosage & frequency of use.

Causes :

1.After 1st day of continuous nitrates, compensatory neurohormonal counter-regulation occur (RAAS, NE, Vasopressin ….etc activation)➔↓therapeutic efficacy (PSEUDOTOLERANCE).

2.After 3 day --> dysfunction of ECs & VSMC occur by many different molecular mechanisms, aside the partial depletion of free-SH groups that permits formation of nitrosothiols from the organic nitrate to give NO (TOLERANCE)..

-Tolerance to these effects develops quite quickly but wears off after a brief nitrate-free interval..

Nitrate tolerance can be overcomed by :

- Smaller doses at increasing intervals (Nitrate free periods twice a day).
- Giving drugs that maintain tissue SH (sulphahydrine) group e.g. Captopril.

Precautions during nitrate therapy :

- -10 hours nitrate free period.
- -Never stop nitrate therapy suddenly.
- -Do not take double dose.
- -Do not use after expiry date; GTN is volatile; shelf-life ~6w after opening.
- Must be stored in cool, tightly capped dark container, no cotton wool or others.

Contraindication :

- -Known sensitivity to organic nitrates.
- Glaucoma; nitrates will ↑ aqueous formation .
- -Head trauma or cerebral haemorrhage Increase ➔intracranial pressure
- Uncorrected hypovolemia Concomitant administration of PDE_5 Inhibitors for the treatment of erectile dysfunction ➔↓BP ➔↑Myocardial Ischemia.

2-Calcium Channel Blockers:

-Classification:

- Dihydropyridines:- **Nifedipine , nicardipine, Amlodepine**
- Phenylalkylamines:- **Verapamil**
- Benzthiazepines:-**Diltiazem**

There are four types of Calcium channels distributed at various tissues and cells throughout our bodies. We have: **L**, T, N, P/Q, and R channel types. * Only the first 4 were mentioned in the lecture.
Only L type channel receptors are used as targets for calcium channel blockers of drugs treating the cardiovascular system.

Distribution	Type
Cardiac & VSMCs / neurons, Skelteal, endocrine, and bone.	L
Heart / neurons	T
Neurons	N
Cerebellar Purkinje neurons	P

Mechanism of Action:

Calcium channel blockers generally work by two ways to achieve their desired effects. They can be briefly described here:

1-Effects on the heart: (verapamil &dilitiazam)
Calcium channel blockers block the transmission of action potential, thus leading to less cardiac function on the heart. They block the calcium dependent cellular mechanisms that lead to the progression of cardiac contraction and transmission. This blockage reduces the frequency of opening of Ca2+ channels in response to depolarization, reducing cardiac contractility. These channel blockers also block Ca2+ influenced generation in the sinoatrial node and the conduction of impulse in the AV node.

2-Effect on the Vascular Smooth muscle cells (Nifedipine ,nicardipine, Amlodepine):block receptor –operated calcium channel blocker, leading to relaxation of Smooth muscle cell and decreasing peripheral vascular resistance. N.B: other SMC are effected but the main ones are the vascular smooth muscle cells.

Pharmacodynamic Actions :

1. Anti-Anginal Actions :

Decrease the VSMC(vascular smooth muscle) Contraction.

this will cause :

- Decrease in the After load leading to decreasing the cardiac work which will decrease the myocardial oxygen demand.

- Coronary dilatation (nifedipine&nicardipine*(short acting)* / amlodipine *(long acting)* >diltiazem& verapamil will decrease the myocardial oxygen supply.

Decrease the Cardiomyocyte Contraction ;

This will lead to:

- Decrease the cardiac work through their –ve inotropic & chronotropic action (verapamil & diltiazem) which will cause decreasing in the myocardial oxygen demand.

important :

- **Nifedipine ,amlodipine,and nicardipine ➔ VSMCs.**
- **Verapamil➔Cardiomyocytes more than VSMCs.**
- **Diltaizem➔ Intermediate action on both.**

Indications as antianginal;.

-In stable angina;

Regular prophylaxis ➔ Long acting dihydropyridines ; amlodipine & SR(sustained release) Formulation nifedipine, diltiazem> verapamil.

-Short acting dihydropyridine avoided ➔↓ BP ➔↑symathetic activation➔refelx tachycardia +syncope ➔impair coronary filling➔ischemia.

-Can short acting dihydropyridens be combined to b-AR blockers??? Which group is much safer???
- Can they be combined with nitrates??? Which group is much safer???

The answer is **B blockers** , because they oppose the adverse effect of dihydrpyridines (reflex tachycardia)

-Dihydropyridenes➔ no ↓ contractility ➔ useful antianginal if with CHF
-Verapamil &diltiazem➔<vasoactivity➔ as antianginal if hypotension.
In variant angina➔ attacks prevented (> 60%) / sometimes variably aborted..

In unstable angina; seldom added in refractory cases..

Other Indications;.

-Hypertension➔> amlodipine
- Migraine ➔ verapamil
-Cerebral dilators ➔nicardipine
-Arrhythmias ➔> verapamil -

3-K channel openers;.

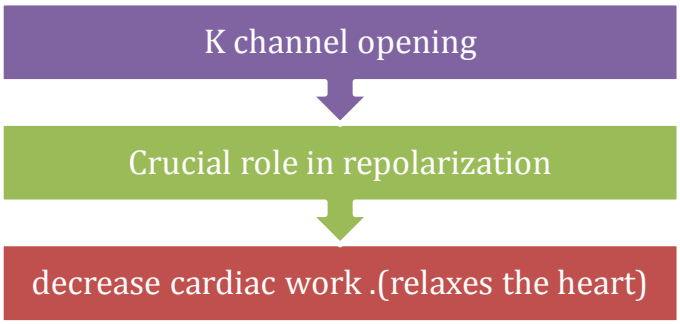
Nicorandil.

MOA

It has dual mechanism of action;
1. Opens K_{ATP} channels (arteriolar dilator)
2. NO donner as it has a nitrate moiety (venular dilator).

Pharmacodynamic;.

On cardiomyocytes:



B) On VSMC

It's a NO(nitric oxide) donner this will lead to an increase in cGMP/ PKG that the leads to VASODILATATION.

Pharmacokintics;.

- Given orally, 80% bioavailability
- Protein bound 25%, t1/2 1 hr
- Hepatiac metabolism, renal excretion.

Indications:

Prophylactic 2nd line therapy in stable angina & refractory variant angina.

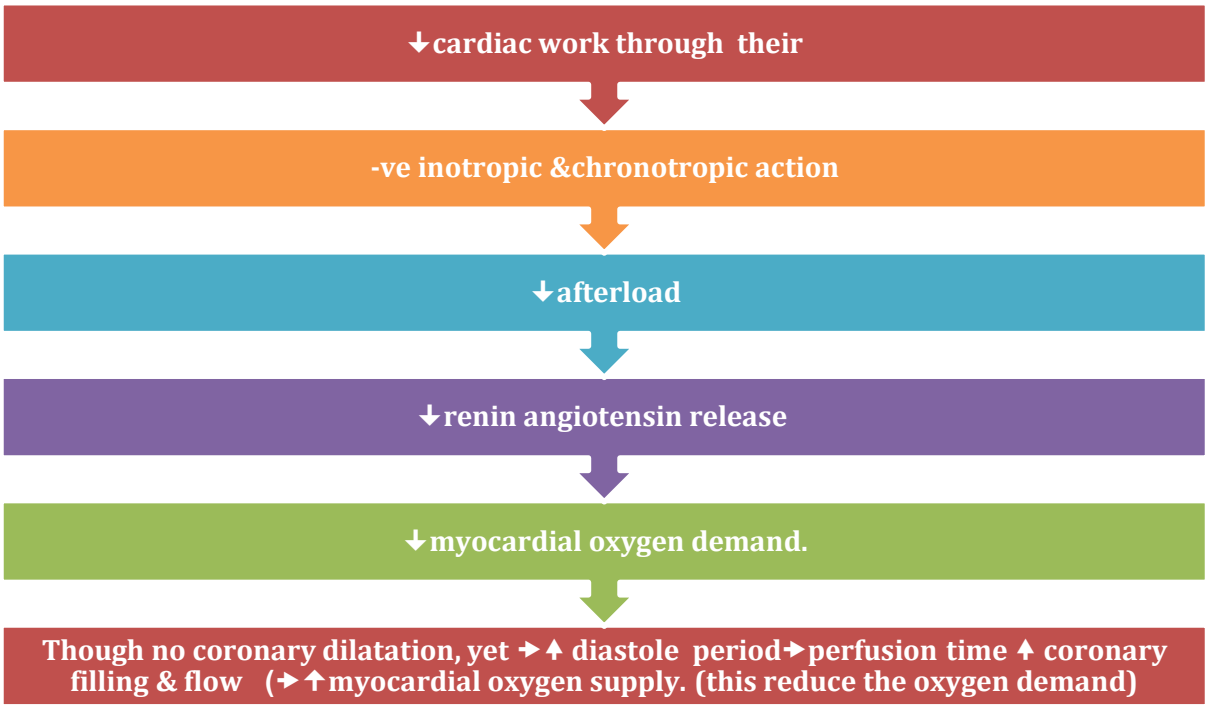
adverse effect;.

- Flushing, headache, -
- Hypotension, palpitation, weakness-
- -Mouth &peri-anal ulcers, nausea and vomiting.

4 – B Adrenergic BLOCKERS:

Pharmacodynamic Actions;.

1. Anti-Anginal Actions



Indications as antianginal;.

In stable angina;

- Regular prophylaxis ➔ Cardio-selective are better. Why??? ➔to spare b_2-AR
- They are 1st choice on prolonged use ➔↓ incidence of sudden death if acute insult & ventricular tachycardia sets in ➔ by their antiarrhythmic action.
- Can be combined with nitrates ➔ abolish its induced reflex tachycardia.
- Can be combined with dihydropyridene CCBs but not verapamil nor diltiazem➔ for fear of conduction defect (bradycardia, heart block).

In variant angina➔ contraindicated ➔ as it has no vasodilator action & may allow unopposed α-adrenergic coronary vasoconstriction to occur.

In unstable angina ➔ halts progression to AMI (Acute myocardial infarction) ➔ improve survival.
In Myocardial Infarction; given early ➔↓infarct size,morbidity& mortality➔CARDIOPROTECTIVE.

They improve the AMI by the following mechanisms:

1. 1.decrease the myocardial O_2 demand.
2. 2.increase the Redistribution of blood flow in the myocardium.
3. 3.decrease the free fatty acid.
4. 4.decrease the Anti-arrhythmic action which will lead to decrease the incidence of sudden death.

Precautions:

-β- blockers should be withdrawn gradually as sudden stoppage ➔ give rise to a withdrawal manifestations:
Rebound angina, arrhythmia, myocardial infarction &hypertension WHY? ➔Up-regulation of β-receptors. So they should not be stopped suddenly.

-Non-selective **B blockers** are better avoided as they blocks vasodilatory effects of sympathetic stimulation ➔↑afterload &↑ oxygen consumption.

Not used in variant angina ➔ worsen symptoms
-Given to diabetics with ischemic heart disease ➔ [Benefits > hazards) & ACE inhibitor must too be added specially in ACSs

4-Metabolically acting agents;.

-Trimetazidine.

MOA:

↓OXYGEN DEMAND WITHOUT ALTERING HEMODYNAMICS by:

- -O_2 requirement for glucose utilization is less than that required for FFA "free fatty acids" utilization
- During ischemia, metabolism shifts to oxidation of FFA. However still, the ↑FFA➔blunts glucose utilization.
- Partial FFA oxidation inhibitors
- Restores energy balance in the cell (↓ fatty acid metabolism, inhibiting anaerobic glycolysis, Allowing only aerobic glycolysis)

pharmacokinetics;.

Rapidly absorbed.-
Peak concentration➔ 2 hrs.-
-$t_{1/2}$➔ 6hrs.
-Excretion, mainly unchanged in urine.

Indications:

-Used when ever needed as add on therapy to nitrates, CCBs or b-blockers.

Adverse effect:➔**GIT disturbances.**

Contraindications;.

- Hypersensitivity reaction.-
- In pregnancy & lactation.-

Ranolazine;.

Newly introduced.Considered one of the metabolically acting agents like trimetazedine.
+ Affects Na dependent-Ca Channels → prevents Ca load →↓ apoptosis →cardioprotective.
It prolongs the QT interval so not given with; Class Ia& III antiarrhthmics

Toxicity develops due to interaction with CYT 450 inhibitors as; *diltiazem, verapamil, ketoconazole, macrolide antibiotics, grapefruit juice.*

5-Other:

Ivabradine not classified drug

MOA:

Acts on the "Funny Channel" a special Na channel in SAN it decrease HR ;leading to a decrease in myocardial work ;leading to a decrease Myocardial O2 demand

Agents that improve prognosis;.

- Aspirin / Other antiplatelets.-
- Statins.-
- ACE Inhibitors.-
- β-AD blockers -

Main Stay of Prophylactic Treatment

- Halt progression

-Prevent acute insults

- Improve survival

In attack & situational prophylaxsis

Short acting nitrates.

For prophylactic therapy

-β-adrenoceptorsblockers(In Combinations)
-Calcium channel blockers
-Long - acting nitrates.
-Potassium channel openers.
-Metabolic modifiers & others.

Review questions

1-A 56-year-old patient complains of chest pain following any sustained exercise. He is diagnosed with atherosclerotic angina. He is prescribed sublingual nitroglycerin for treatment of acute chest pain. Which of the following adverse effects is likely to be experienced by this patient?

A. Hypertension.
B. Throbbing headache.
C. Bradycardia.
D. Sexual dysfunction.
E. Anemia.

Correct answer = B. Nitroglycerin causes throbbing headache in 30 to 60 percent of patients who are taking the drug. The other choices are incorrect.

2-The patient described in Question 18.1 is also pre-scribed propranolol to prevent episodes of angina. The β-blocker has the added benefit of preventing which of the following side effects of sublingual nitroglycerin?

A. Dizziness.
B. Methemoglobinemia.
C. Throbbing headache.
D. Refex tachycardia.
E. Edema.

Correct answer = D. Nitroglycerin can cause a reflex tachycardia because of its vasodilating properties. This reflex is blocked by propranolol. The other effects are either not prevented by propranolol or are not caused by nitroglycerin (edema).

3-A 68-year-old man has been successfully treated for exercise-induced angina for several years. He recently has been complaining about being awakened at night with chest pain. Which of the following drugs would be useful in preventing this patient's nocturnal angina?

A. Amyl nitrite.
B. Nitroglycerin (sublingual).
C. Nitroglycerin (transdermal).
D. Esmolol.
E. Hydralazine.

Correct answer = C. Transdermal nitroglycerin can sustain blood levels for as long as 24 hours. Because tolerance occurs, however, it is recommended that the patch be removed after 8 to 10 hours to al-low recovery of sensitivity. Amyl nitrite, sublingual nitroglycerin, and esmolol all have short durations of actions. Hydralazine may actually precipitate an angina attack.