432

Pharmacology Team

Lecture : Antianginal drug

Red	**Important**
Purple	Extra Notes
Orange	To differentiate
Black	From the slides
Blue	Similar

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Antianginal drug

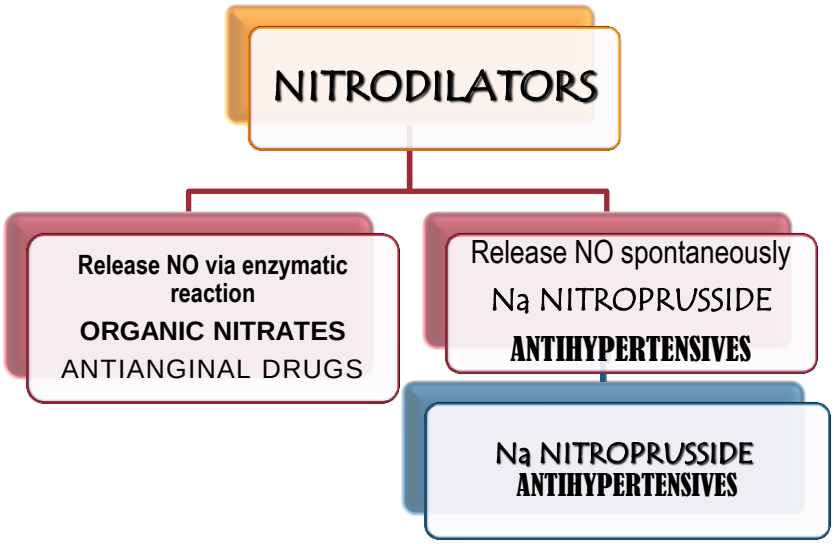
By the end of this lecture you will be able to:

- ***Recognize variables contributing to a balanced myocardial supply vs demand***
- ***Identify etiopathogenic cascades contributing to ischemic heart disease***
- ***Justify the different related clinical presentations of ischemic heart disease***
- ***Expand on the drugs used to alleviate acute anginal attacks vs those meant for prophylaxis & improvement of survival***
- ***Detail the pharmacology of nitrates, other vasodilators, and other drugs used as antianginal therapy***
- ***Sum up the varied therapeutic recommendations for treatment of different clinical presentations of ischemic heart disease***

Antianginal drug

DRUGS USED IN TREATMENT OF ANGINA :

Agents that improve symptoms & ischemia		Agents that improve prognosis
Vasodilators: "increase supply " • Organic nitrates • Calcium channel blockers • Potassium channel openers	• β-adrenoceptor blockers • Metabolically acting agents • Others	• **Aspirin / Other antiplatelets** • **Statins** • **ACE Inhibitors** • **β-AD blockers**



ANTIANGINAL DRUGS	
Short Acting	***Long Acting***
1- Nitroglycerine [GTN] **2- Amyl nitrate** • **Sublingual** • **Rapid** • **For terminating an acute attack**	1. **Isosorbide mono & dinitrate** 2. **Erythrityl tetranitrate** 3. **Pentaerythritol tetranitrate** • Oral sustained release • Transdermal patches • Slower • For long-term prophylaxis
Preparations; ***can influence a change in indications:*** ***Taking Nitroglycerine oraly will slow the reaction and taking Isosorbide mono & dinitrate sublinualy will cause a rapid reaction*** ***I.V. or infusion*** → ***Unstable angina*** ***GTN / Amyl nitrate*** → ***Heart Failure***	

Antianginal drug

ORGANIC NITRATES

Mechanism

1-In VSMC **[In SMC]**

- **Binds soluble GC**
- **Formation of cGMP**
- **Activation of PKG**
- RELAXATION

2. Cytoprotection; to endothelium

N.B. *NO is well developed in Arteriolar > Venular System*

Exogenous NO donners act on Venular > Arteriolar system

Pharmacodynamic Actions

1. Anti-Anginal Actions			2. Other Pharmacodynamic Actions
↑ Myocardial Oxygen Supply; **Dilatation of large coronary vessels. 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**	**SMC Relaxation of: 1- Bronchi →NO activates cGMP in BSMC → bronchodilatation 2-Gastrointestinal tract & biliary system 3- Genitourinary tract**

Dr. Omia told us that she might ask how to increase the supply or how to decrease the demand

Pharmacokinetics

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

Antianginal drug

Cont. ORGANIC NITRATES

Emergency-> sublingually

Indications	• **IN STABLE ANGINA;** **Acute symptom relief ➔ sublingual GTN** **Prevention; Persistent prophylaxis ➔ Isosorbide mono or dinitrate "orally "** **Situational prophylaxis ➔ as before exercising, climbing…etc** **➔ sublingual GTN** • **IN VARIANT ANGINA ➔sublingual GTN** • **IN UNSTABLE ANGINA ➔ IV GTN** • **Refractory AHF ➔ IV GTN** • **CHF ➔ Isosorbide mononitrate + hydralazine *[if contraindication to ACE Is]*** • **AMI ➔IV GTN**
Preparations	**Nitroglycerine** ▪ **Sublingual tablets or spray** ▪ **Transdermal patch** ▪ **Oral or bucal sustained release** ▪ **I.V. Preparations** **Isosorbide dinitrate & mononitrate** ▪ **Dinitrate Sublingual tablets** ▪ **Dinitrate Oral sustained release** ▪ **Mononitrate Oral sustained release** ▪ **Infusion Preparations**
ADRs	1-**Postural hypotension with reflex tachycardia especially if the patient is standing stationary."imp"** 2-**Nitrite syncope with fainting** & collapse➔ due to ↑ dilatation of venous capacitance vessels ➔ severe ↓ of venous return ➔↓ **CO** & BP. **Nitrite syncope is treated by putting the patient in a low head position.** 3-**Flushing of blush area** (face, neck and upper trunk) 4-**Throbbing headache** (>common) ➔ tendency to ↑ **intra-cranial pressure** ➔ used cautiously in cerebral bleeding & head trauma 5-Drug rash. 6-Visual disturbance. 7- Carcinogenesis 8- Met-hemoglobinemia *(in overdose & accidental poisoning*
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

She told us here to know that Sublingual Nitroglycerine is the most rapid then sublingual Isosorbide dinitrate & mononitrate Then the oral drugs

Antianginal drug

Contraindication	Known sensitivity to organic nitrates. Glaucoma; nitrates➜ ↑ aqueous formation **Head trauma or cerebral haemorrhage** Increase ➜intracranial pressure . Uncorrected hypovolemia Concomitant administration of PDE_5 Inhibitors that are used for the treatment of erectile dysfunction ➜ ↓BP ➜↑Myocardial Ischemia ➜ so we must space doses i.e. Nitrates [morning], PDE_5 Inhibitors [Evening]

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

- **After 1st day , compensatory neurohormonal counter-regulation ➜ ↓therapeutic efficacy (PSEUDOTOLERANCE).**
- **After 3 days, dysfunction of ECs & VSMC occur mainly due to partial depletion of free-SH gps ➜ little formation of nitrosothiols from organic nitrate ➜↓NO➜** (TOLERANCE)

Nitrate tolerance can be overcomed by:

Nitrate free periods once or twice a day.

Giving drugs that maintain tissue SH group e.g. Captopril

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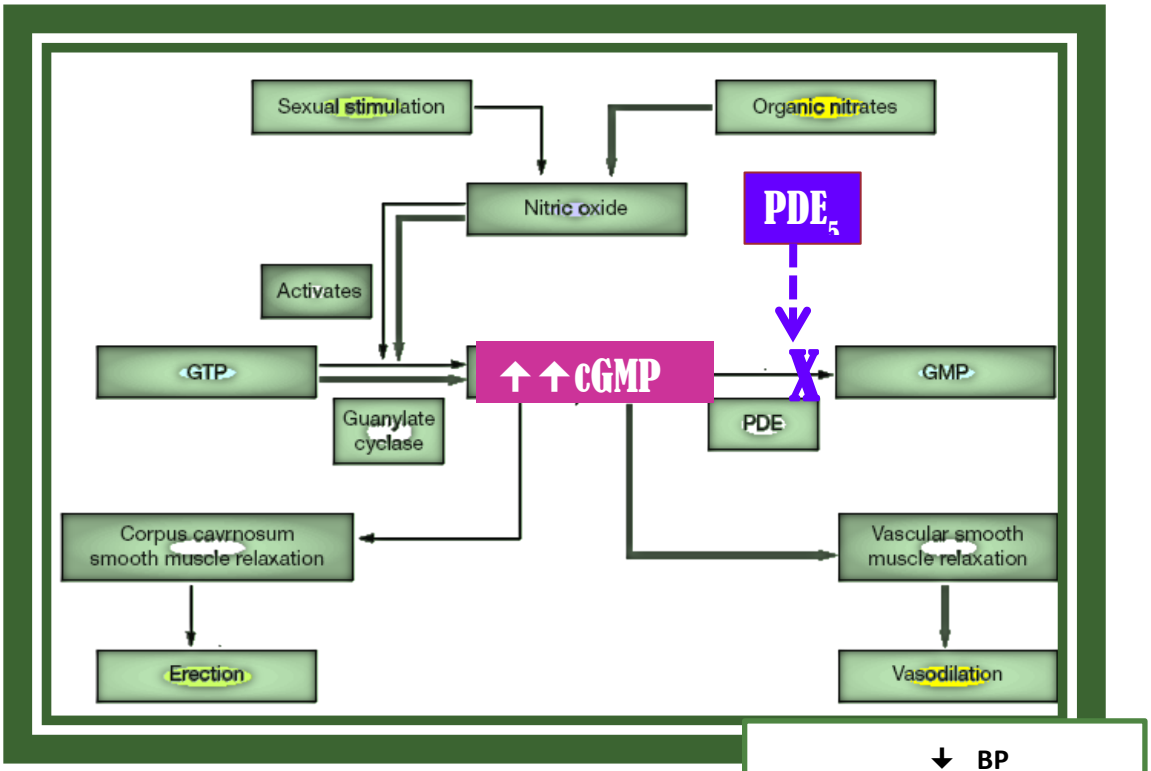

↓ BP

↓ ↓coronary perfusion

MYOCARDIAL ISCHEMIA

Antianginal drug

Ca Channel Blocker

CLASSIFICATION

Heterogeneous

Dihydropyridines:-	Phenylalkylamines:-	Benzthiazepines:-
Nifedipine , Nicardipine, Amlodepine	Verapamil	Diltiazem

N.B. Selectivity of Ca channel blockers

* Nifedipine ➔ **VSMCs**
* Verapamil ➔ **Cardiomyocytes > VSMCs**
* Diltaizem ➔ **Intermediate action of both**

Mechanisim

Binding to **L Type** calcium channel blockers [CCBs] to the L-type Ca channels

↓ their frequency of opening in response to depolarization

↓entry of Ca
➔ ↓ Ca from internal stores
➔ No Stimulus-Contraction Coupling

• **RELAXATION**

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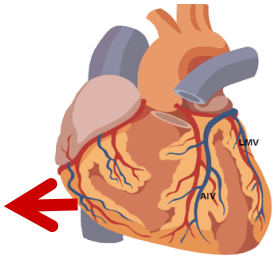
Pharmacodynamic Action

↓ Cardiomyocyte Contraction

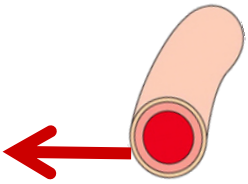
* ↓cardiac work through their –ve inotropic & chronotropic action (verapamil & diltiazem)
→ ↓myocardial oxygen demand



↓VSMC Contraction

*↓ After load → ↓cardiac work →↓myocardial oxygen demand

* Coronary dilatation (nifedipine & nicardipine *(short acting)* / amlodipine *(long acting)* > diltiazem & verapamil → ↑myocardial oxygen supply



Indications AS ANTIANGINAL

STABLE ANGINA	VARIANT ANGINA	UNSTABLE ANGINA
Regular prophylaxis → Long acting dihydropyridines ; Amlodipine & SR Formulation nifedipine, diltiazem > verapamil Short acting dihydropyridine avoided →↓ BP →↑symathetic activation →reflex tachycardia +syncope →impair coronary filling→ischemia …..	Attacks prevented (> 60%) / sometimes variably aborted	Seldom added in refractory cases

#

- Can be combined to b-AR blockers??? Which group is much safer???
- Can be combined with nitrates??? Which group is much safer???
- Dihydropyridenes → no ↓ contractility → useful antianginal if with CHF
- Verapamil & diltiazem → ↓vasoactivity → as antianginal if hypotension

Antianginal drug

	Drug	Mechanism	Used with	Prohibited in	Indications	ADS
K Channel openers	**Nicorandil**	Dec. Oxygen demand: 1) opening K channels → inc, repolarization of cardiac muscle → dec. it's work Inc. Blood supply : 1) opening K channels and → hyper polarization → vasodilatation 2) Unique : it has a NO group → releases NO → vasodilatation	**Stable and refractory variant** (prinzmetal) **angina**	–	2nd line therapy for Angina	Flushing (because of VD) , headache, Hypotension, palpitation
B- Ad blockers	**Prefer the selective ones:** **Atenolo** **Bisoprolol** **Metoprolol**	Dec. Oxygen demand: Bradycardia → dec. myocardiac work Inc. blood supply: NOT by VD! (so not used for variant Angina) But by inc. diastole time → inc. time of coronary filling	**Stable angina** (antiarrhythmic action) **Unstable angina** (cardioprotective given early to dec. incidence of MI) Could be used with diabetic in specific dose.	Variant angina	Can be combined with **nitrates** and **Ca blockers** which only work on vessels (with those work on heart might cause loss of conduction) and ACE in acute coronary syndrome.	–
Metabolically acting drugs (the only metabolic all others are hemodynamic)	**Trimetazidine (pFOX inhibitors)** **Ranolazine**	Dec. demand: Heart usually oxidizes fat to get energy and that requires so much O2. This drug prevents fat oxidation (blocking 3KAT) → forces heart to use glucose (aerobically) which requires less O2	**All Anginas**	Pregnancy	Not enough alone and could be given with all antiangina drugs. Ranolazine (affect Na dependant Ca channel → increases QT interval → not used with K channel blockers : class 1a, 3 antiarrhythmic drugs : Amiodarone Quinidine	GIT disturbance.
Funny channel blockers	Ivabradine	Dec. oxygen demand : Act on special Na channel on SAN → dec. myocardial work	-	-	-	-

Antianginal drug

MCQ's

1- Ahmad Abdullah is having angina and he lives in an apartment in the 5thfloor. the elevator is out of order so, he has to climb up the stairs.the Situational prophylaxis that he has to take it before he climbs the stairs is:

A. GTN sublingual administration
B. Oral isosorbide dinitrate
C. GTN IV administration
D. Nicorandi

2- Which one of the following drugs will prescribe for A patient has angina and hypotension as an anti angina drug:

A. GTN sublingual administration
B. Amlodepine
C. GTN IV administration
D. Verapamil

3- A patient who was taking Nitrate, he suddenly had Nitrate syncope, what is the best way to treat him?

A.Putting him in lower head position
B.Administration of small GTN dose (IV)
C.Administration of small GTN dose (sublingual)
D.Gastric lavage.

4- Nitroglycerin, either directly or through reflexes, results in which one of the following effects?

A. Decreased heart rate
B. Decreased venous capacitance
C. Increased afterload
D. Increased cardiac force (increase of heart rate)
E. Increased preload

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5 -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.

6- The patient described in question1 is also prescribed propranolol to prevent episodes of angina. The B-blocker has the added benefit of preventing which of the following side effects of sublingual nitroglycerin?

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

7- A 86-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

The last 3 questions from lippincott's

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ANSWERS

Question	Answer
1	**A**
2	**D**
3	**A**
4	**D**
5	**B**
6	**D**
7	**C**