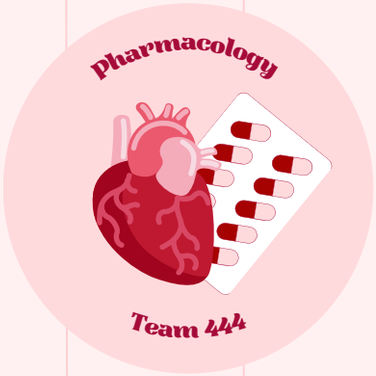

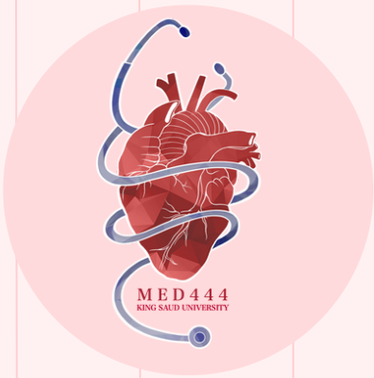

L6.
Antianginal drugs [1]&[2]

EDITING FILE

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- MAIN TEXT
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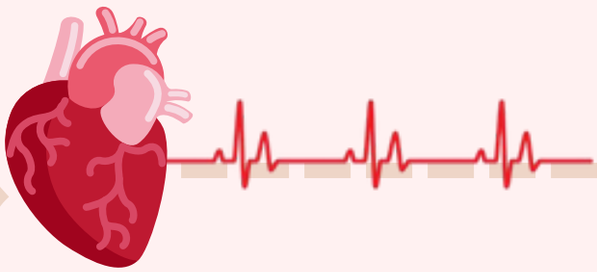
- GIRL'S SLIDES
- BOY'S SLIDES
- NOTES
- EXTRA



ترى الذبحة الصدر تذبح وتوجع
ولها النترات وكالسيوم عضيدك
وبعد بيتا مثل عادتها تلمع
وافتحها البوتاسيوم تأيدك

علي العبدالعظيم

Objectives:

- Recognize variables contributing to a balanced myocardial supply versus demand.
- Expand on the drugs used to alleviate acute anginal attacks versus those meant for prophylaxis improvement of survival.
- Detail the pharmacology of nitrates, other vasodilators, & other drugs used as antianginal therapy.

Angina Pectoris

Defintion

Angina pectoris refers to a strangling or pressure-like pain caused by cardiac ischemia. The pain is usually located substernally but is sometimes perceived in the neck, shoulder and arm, or epigastrium.

Women develop angina at a later age than men and are less likely to have classic substernal pain.

Types Of Angina

Atherosclerotic(Classic) angina [Common Type]	Attacks are predictably provoked (stable angina) by exercise, emotion, eating or coitus and subside when the increased energy demand is withdrawn. Rest, by reducing cardiac work, usually leads to complete relief of the pain within 15 min. Atherosclerotic angina constitutes about 90% of angina cases.
Vasospastic (rest/variant/Prinzmetal's) angina	Attacks occur at rest or during sleep and are unpredictable. Vasospastic angina responsible for less than 10% of angina cases.
Unstable (crescendo) angina	It is characterized by increased frequency and severity of attacks that result from a combination of atherosclerotic plaques, platelet aggregation at fractured plaques, and vasospasm.

Classification of Antianginal Drug

Nitrates	**Short acting**: Glyceryl trinitrate (GTN, Nitroglycerine) **Long acting:** Isosorbide dinitrate (short acting by sublingual route), Isosorbide, mononitrate, Erythrityl tetranitrate, Pentaerythritol tetranitrate	
β Blockers:	Propranolol, Metoprolol, Atenolol and others.	
Calcium channel blockers	**Phenyl alkylamine:** Verapamil **Benzothiazepine**: Diltiazem **Dihydropyridines**: Nifedipine, Felodipine, Amlodipine, Nitrendipine, Nimodipine, Lacidipine, Lercanidipine, Benidipine	
Potassium channel opener	**Nicorandil**	
Others	Dipyridamole, Trimetazidine, Ranolazine, Ivabradine, Oxyphedrine	
Clinical Classifaction	**Used to abort or terminate attack:** GTN, Isosorbide dinitrate (sublingually)	**Used for chronic prophylaxis:** All other drugs

GIRLS'S SLIDES

Determinants of myocardial O2 demand

The major determinants of myocardial O2 requirement/ demand:

- Ventricular wall stress (Intraventricular pressure, Ventricular volume, Wall thickness)
- Heart rate (HR) & Contractility.
- Increased HR, the myocardium must work harder to complete the cardiac cycle more efficiently.
- An increase in any of these variables requires the body to adapt to sustain adequate O2 supply to the heart.
- Drugs that reduce cardiac size, rate, or force reduce cardiac O2 demand.
  Like vasodilators, β blockers, & calcium channel blockers.

Determinants of coronary blood flow & myocardial O2 supply

- Coronary blood flow is directly related to the aortic diastolic pressure & the duration of diastole
- Coronary blood flow is inversely proportional to coronary vascular resistance
- Damage to the endothelium of coronary vessels has been shown to alter their ability to dilate and to increase coronary vascular resistance.

Treatment of Angina Pectoris

Antianginal drugs are those that prevent, abort or terminate attacks of angina pectoris.

Drugs used in angina exploit <u>two main strategies</u>:

- **reduction of oxygen demand**
- **increase of oxygen delivery to the myocardium**

Drug Used in angina pectoris

- **Vasodilators**
  - **Nitrates**
    - Short duration (Sublingual nitroglycerin)
    - Intermediate (oral nitroglycerin)
    - Long duration (transdermal nitroglycerin)
- **Cardiac depressors**
  - **Calcium blockers** (verapamil)
  - **Beta blockers** (propranolol)
- **Others**
  - **Metabolism modifiers; rate inhibitors**

GIRLS'S SLIDES

The effects of nitrates on the cardiovascular system

Preload reduction: peripheral pooling of blood-> decreased Venus return
main effect

After load reduction: nitrates also produce some arteriolar dilatation -> slight decrease in total peripheral resistance or afterload on the heart

Redistribution of coronary flow:
in the arterial tree , nitrates preferentially relax bigger conducting (angiographically visible) coronary arteries than arterioles or resistance vessels

Tolerance:

Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily "nitrate-free interval" to restore sensitivity to the drug.

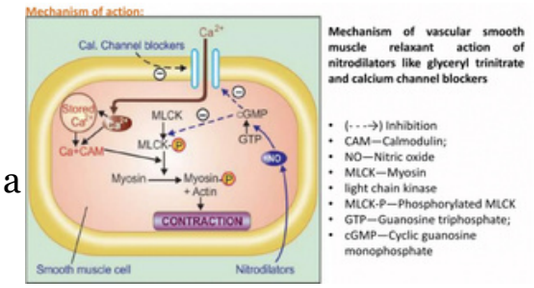
Dependence:

Sudden withdrawal after prolonged exposure has resulted in spasm of coronary and peripheral blood vessels. ***Withdrawal of nitrates should be gradual.***

Nitrates/organic nitrates

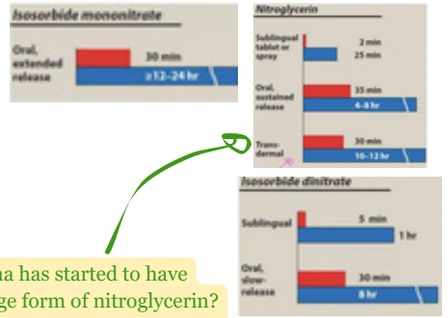
M.O.A

- Organic nitrate agents are prodrugs that are sources of NO.
- NO activates the soluble isoform of guanylyl cyclase, increasing intracellular levels of cGMP.
- cGMP promotes the dephosphorylation of the myosin light chain and the reduction of cytosolic Ca2+ → relaxation of smooth muscle cells in a broad range of tissues. (Nitrates increase oxygen supply via vasodilation.)



P.K

- Organic nitrates are lipid soluble, well absorbed from buccal mucosa, intestines and skin.
- Ingested orally, all except isosorbide mononitrate undergo extensive and variable first pass metabolism in liver. They are rapidly denitrated by a glutathione reductase and a mitochondrial aldehyde dehydrogenase.



male Dr. : let's say that an athletic person with a history of angina has started to have attacks at night (nocturnally) then, what would be the best dosage form of nitroglycerin?

transdermal patch because it has the least side effects and is long acting (it is not an urgent case that would necessitate sublingual dosage.)

ADRs

- Headache is the most common adverse effect of nitrates.
- High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia.
- **Phosphodiesterase type 5 inhibitors** such as **Sildenafil (Viagra)**, Tadalafil (Cialis) potentiate (increase signifcantly) the action of the nitrates. To preclude the dangerous hypotension that may occur, this combination is **contraindicated.**

Uses

angina pectoris

GTN (Nitroglycerin) produces relief within 3 min in 75% patients, the rest may require another dose or take longer (up to 9 min). (Nitrates are mainly used for angina pectoris)

Acute coronary syndromes

Nitrates are useful by decreasing preload as well as by increasing coronary flow.

Myocardial infarction (MI)

GTN is frequently used during evolving MI with the aim of relieving chest pain, pulmonary congestion and limiting the area of necrosis by favourably altering O2 balance in the marginal partially ischaemic zone.

Uses	**CHF and acute LVF: Nitrates afford relief by venous pooling of blood → reduced venous return (preload) → decreased end diastolic volume → improvement in left ventricular function.**
	Biliary colic
	Esophageal spasm
	Cyanide posioning: Nitrates generate methaemoglobin which has high affinity for cyanide radical and forms cyanomethaemoglobin.

β-blockers

M.O.A	• The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β1 receptors, resulting in decreased heart rate, contractility, cardiac output and blood pressure.
Cardioselective VS Non-selective	• All β-blockers are nearly equally effective in decreasing frequency and severity of attacks and in increasing exercise tolerance in classical angina, But cardioselective agents (atenolol - metoprolol) are preferred over non-selective β1+β2 blockers (e.g. propranolol).
Avoiding ISA Instead of being antagonist it acts as agonist	• Agents with intrinsic sympathomimetic activity (ISA) such as **pindolol** should be avoided in patients with angina and those who have had a MI.

Calcium Channel Blockers

GIRLS'S SLIDES

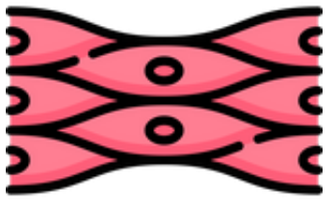
Numbers are not important.
mainly focus on the location and function.

Voltage sensitive calcium channels

	L- type (Long lasting current)	**T- type** (transient current)	**N- type** (neuronal)
1. Conductance	25 pS	8 pS	12-20 pS
2. Activation threshold	High	Low	Medium
3. Inactivation rate	Slow	Fast	Medium
4. Location and function	• Excitation- contraction coupling in cardiac and smooth muscle • SA- AV node conductivity • Endocrine cells (hormone release) • Neurons- transmitter release	• SA node pacemaker activity • 'T' Current and repetitive spikes in thalamic and other neurons • Endocrine cells (hormone release) • Certain arteries - constriction	• only on neurons in CNS, sympathatic and myenteric plexuses- transmitter release
5. Blocker verapamil	Nifedipine, Diltiazem, Verapamil	Mibefradil, Flunarizine, Ethosuximide	ω- Conotoxin

Ca2+ channel blockers (CCB)

Both vasodilators & decreasing the CO

Classification	Phenylalkylamines	Benzothiazepines	Dihydropyridines
Drug	**Verapamil**	**Diltiazem**	**Nifedipine, Felodipine, Amlodipine, Nitrendipine, Nimodipine, Lacidipine, Lercanidipine, Benidipine**
Pharmacological actions	**On smooth muscles** 	Keep in mind these actions include all CCBs mentioned above • The CCBs cause relaxation by decreasing intracellular availability of Ca2+. The **DHPs** have the most marked smooth muscle relaxant and vasodilator action, **Verapamil** is somewhat weaker followed by **diltiazem**. -DHPs > Verapamil > diltiazem	
	On the heart 	• Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. The CCBs protect the tissue by **inhibiting the entrance of calcium** into cardiac and smooth muscle cells of the coronary and systemic arterial beds and **decrease smooth muscle tone and vascular resistance, afterload.**	

Ca2+ channel blockers (CCB)

Drug	Phenylalkylamines **Verapamil**	Benzothiazepines **Diltiazem**	Dihydropyridine (DHP) **Nifedipine**
Overview	• Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator.	• It is somewhat less potent vasodilator than **Nifedipine** and **verapamil**, and has modest direct negative inotropic action, but direct depression of SA and AV conduction are equivalent to verapamil.	• prototype DHP. • Rapid onset. • Short duration of action. • Administered as an extended-release oral formation.
M.O.A	• Cause arteriolar dilatation and decrease total peripheral resistance. • It slows AV conduction directly and decreases heart rate, contractility, blood pressure and O2 demand. • It also has some α adrenergic blocking activity.	• Slows AV conduction. • decreases the rate of firing of the sinus node pacemaker. • Coronary artery vasodilator.	• Cause arteriolar dilatation and decrease total peripheral resistance. • Cause direct depressant action on the heart in higher dose.
Clinical use	**• Calcium channel blockers can be safely given to patients with obstructive lung disease and peripheral vascular disease in whom B-blockers are contraindicated.** CCBs are used for the treatment of : - Angina pectoris - Hypertension - Cardiac arrhythmias - Hypertrophic cardiomyopathy **Diltiazem** can relieve coronary artery spasm and particularly useful in patients with **variant angina.**		
ADRs	• Verapamil **should not** be given with, **β-blockers**, **Digoxin**, **cardiac depressants** like: quinidine and disopyramide.	-	- Palpitations -flushing -Ankle edema - hypotension -headache -drowsiness - nausea -Nifedipine has paradoxically increased the frequency of angina in some patients.

Other DHP calcium channel blockers

Drug	Amlodipine	Nitrendipine	Lacidipine	Nimodipine	Lercanidipine, Benidipine
Duration	**-**			**Short acting DHP**	**DHP with Long duration of action**
M.O.A	**Functions mainly as an arteriolar vasodilator.**	**Ca2+ channel blocker With additional action of Vasodilation (due to release NO from the endothelium and inhibit cAMP phosphodiesterase**	-		
P.K	**An oral DHP**	**-**		High lipid soluble. Cross BBB.	-
orher characteristecs	**-**		Highly vasoselective newer DHP.	-	

Potassium channel agonists (opener)

Nicorandil

Overview	• **Antianginal action of nicorandil is mediated through ATP sensitive K+ channel (KATP) therapy hyperpolarizing vascular smooth muscle.**
MECHANISM OF ACTION	it is Potassium channel agonists (opener), Regulates the process of cardiac outbot also helps in the relaxation of smooth Muscles so it works as a vasodilationtion.
P.K	• Well absorbed orally, nearly completely metabolized in liver and is excreted in urine. • Administered IV during angioplasty for acute MI, it is believed to improve outcome.
ADRs	• Flushing, palpitation, weakness, headache, dizziness, nausea and vomiting.

Other antianginal drugs

Drugs	Characteristics male dr: it's for your information female dr: Drugs and M.O.A are important
Dipyridamole	• **- inhibit platelets aggregation.** • **Powerful coronary dilator.**
Trimetazidine	• **Acts by non-hemodynamic mechanism** • **MOA: it is uncertain but it may improve cellular tolerance to ischemia by inhibiting mitochondrial long chain 3-ketoacyl-CoAthiolase.**
Ranolazine	• **Novel antianginal drug** • **Acts by inhibiting a late Na+ current in the myocardium.**
Ivabradine	• **pure heart rate lowering drug has been introduced recently as an alternative to B-blockers.** • **Block cardiac pacemaker (Sino-atrial) cell 'f' channels.**
Oxyfedrine	• **improve myocardial metabolism**

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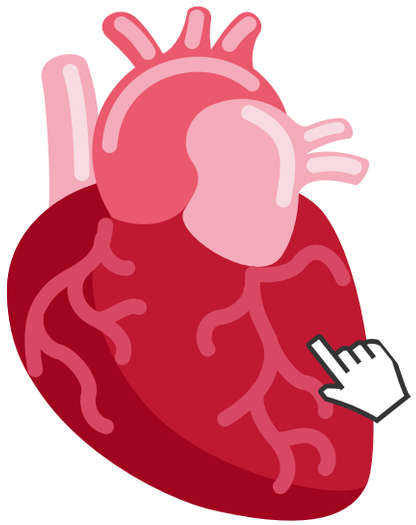
summary



Case Scenario Qs.

1 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. What drug would be useful in preventing this patient's nocturnal angina?

- A: Transdermal nitroglycerin
- B: Oral nitroglycerin
- C: nicronodil
- D: Propanolol

2 A 45 year old male patient visited his doctor with complain of erectile dysfunction (ED). The doctor diagnoses ED and prescribe phosphodiesterase type 5 inhibitor drugs, to improve the patient's sexual function. Recently, he is experiencing a chest pain. Which drug is contraindicated in this case?

- A: Calcium channel blockers
- B: Nitrates
- C: Potassium channel blockers
- D: B blockers

3 An 83 year old man has history of smoking habit, hypertension, COPD. Last day, he visited a doctor complaining from chest pain, the doctor diagnosed him with stable angina, which one is the safest drug can be prescribe from the following?

- A: Ca Channel blocker
- B: beta blockers
- C: k channel opener
- D: nitrates

4 A 58 years old male with a past history of hypertension, present to the emergency department with a severe chest pain. he was diagnosed with MI and its currently experiencing an atack of angina. what is the drug that should avoided in patients with MI?

- A: Atenolol
- B: Metoprolol
- C: Pindolol
- D: Propanolol

1-A, 2-B, 3-A, 4- C

MCQs

1 an athletic person with the history of angina has started to have attacks at night (nocturnally) then, what would be the best drug for him?

- A Transdermal nitroglycerin
- B Oral nitroglycerin
- C Nicronodil
- D Propanolol

2 A 50 year old patient on Sildenafil presents with hypertension, which are the following would be contraindicated?

- A Calcium channel blockers
- B Nitrates
- C Potassium channel blockers
- D B blockers

3 Which of the following is a potassium channel opener?

- A Dipyridamole
- B Trimetazidine
- C Oxyphedrine
- D Nicorandil

4 Which dosage form has the least side effects and the longest duration?

- A Oral
- B Sublingual
- C Transdermal
- D Spray

1-A, 2-B, 3-D, 4- C

MCQs

5 What is better used for angina patients with obstructive lung disease ?

- A Nitrates
- B Potassium channel blockers
- C Beta blockers
- D Calcium channel blockers

6 What is the best dosage form of nitratoglycrin in emergency case?

- A Oral
- B sublingual
- C Transdermal
- D IV

7 Flushing - Palpitations ankle edema, this side effects belong to :

- A Atenolol
- B Diltiazem
- C Nicorandil
- D Nifedipine

8 Diltiazem is One of:

- A Beta Blocker
- B K Channel opener
- C Ca Channel Blocker
- D None

5-D, 6-B, 7-D, 8-C

SAQs

1. **Explain why should pindolol be avoided in patients with angina and who have had MI?**

   - because it have intrinsic sympathetic activity

2. **What is the Mechanism of action of Nicorandil?**

   - potassium channel agonist (opener)

3. **Mention 2 of Nicorandil Side effect**

   - Flushing, Palpitation Weakness, headache nausea, Vomiting

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