MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

Reviewed by Razan AlRabah & Ibrahim AlDakhil

Anti-Anginal Drugs

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Green : Dr's notes
- Grey: Extra information, explanation

OBJECTIVES:

✓ Recognize variables contributing to a balanced myocardial supply versus demand.

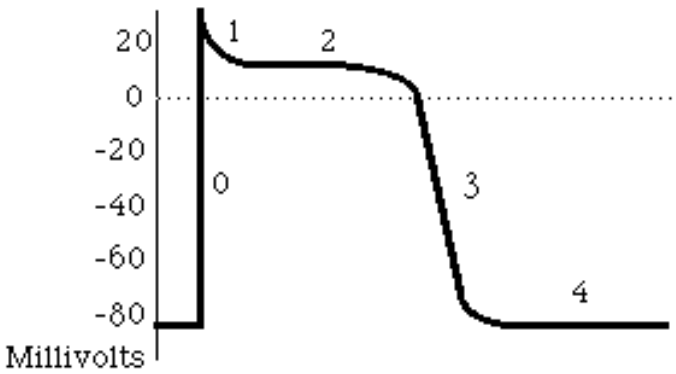
✓ Differentiate between drugs used to alleviate acute anginal attacks and those meant for prophylaxis & improvement of survival.

✓ Detail the pharmacology of nitrates and other drugs used as antianginal therapy.

Editing File

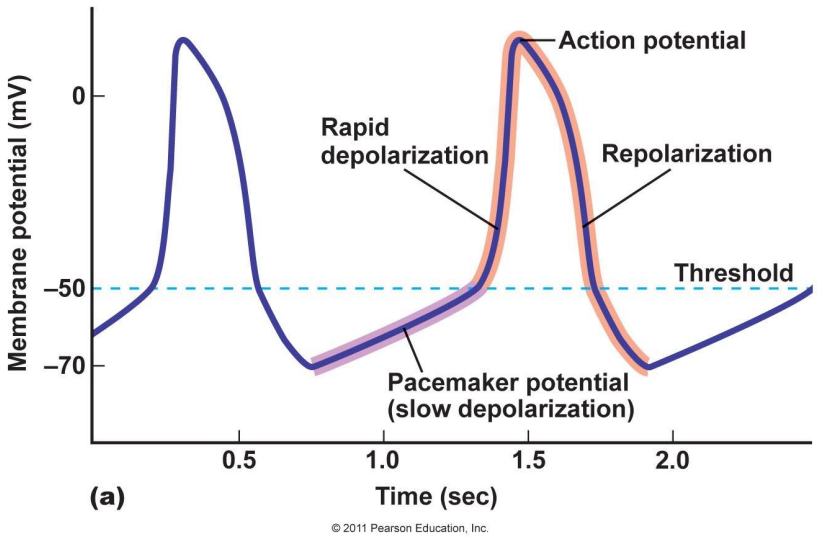
Extra information(recommended)

Ventricular Muscle Cells Action Potential



4- Resting membrane potential (polarized)
0- Rapid Depolarization Phase: Passage of cations (Sodium and Calcium) from neighboring cardiac cells causes the resting membrane potential to slightly increase, allowing voltage gated Na channels to open, and the cell is said to be depolarized.
1- Initial Repolarization: Short-term Voltage-gated K channels open and Na channels close at peak positivity of the cell and allow the membrane potential to be slightly decreased to create a potential difference for voltage gated Ca channels to open. .
2-Plateau (refractory period): Voltage gated calcium channels are open for about most of the period, but the channels are inactivated around the end of this phase and K efflux starts, if this phase is prolonged inactivated Ca channels can reopen, creating an afterdepolarization (torsades de pointes) “more on this later in the lecture”
3- Repolarization: Extra specialized K channels are opened to bring about repolarization and a return to the resting membrane potential.

Pacemaker Action Potential



SA Node is made of specialized cardiac cells, (Modified Cardiomyocytes), the cells have high permeability to Na and K, allowing constant, spontaneous action potentials to be generated and a unique way of generating an action potential.
Pacemaker potential (slow depolarization): Slow Na influx and a decreased K efflux, makes the cells more positive gradually.
Rapid Depolarization: Calcium channels open, allowing the cells to be depolarized and action potential is reached.
Repolarization: Inactivation of calcium channels and K channels are open, the cell repolarizes and Na channels begin to open allowing the cycle to restart.

Angina Pectoris:

- Angina pectoris is a consequence of Myocardial oxygen demand exceeding myocardial oxygen supply.
- Mainly caused by obstruction of blood flow Resulting in ischemia.

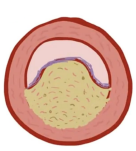
Which signs or symptoms suggest diagnosis of angina pectoris?

1. A clinical syndrome of chest pain (varying in severity) due to ischemia of heart muscle
2. Pain is caused either by obstruction (e.g. atherosclerotic plaque) or spasm (usually causes pain even at rest)
3. Pain is due to accumulation of metabolites (K + , PGs, Kinins, Adenosine....) secondary to the ischemia. These metabolites are body's response to ischemia as vasodilators.

Stable angina

known as :

Effort-induced, typical, classical, chronic



-Reduction of coronary perfusion due to a fixed obstruction of a coronary artery produced by **atherosclerosis**.
The heart becomes vulnerable when there's increased demand.
-Pain occurs upon exertion Exercise Emotion, Heavy meal.

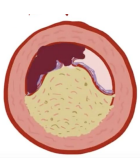
Treatment:

-Rest or nitroglycerin

Unstable angina

known as :

Accelerated (Progressive) or crescendo Angina

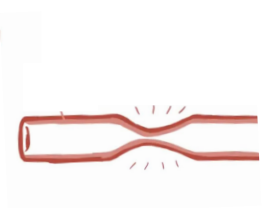


-A form of acute coronary syndrome, caused by rupture of an atherosclerotic plaque and partial or complete thrombosis of a coronary artery.
-There's increased frequency & duration of pain.

Treatment:

-Hospital admission and more aggressive therapy.

Variant angina



-Coronary artery spasm (Alpha receptor mediated vasoconstriction) With or without Atherosclerotic plaque
-Pain even at rest.

Treatment:

-coronary vasodilators, such as nitroglycerin and calcium channel blockers.

4th type: silent angina → Ischemia without pain, the most dangerous

What are the determinants of oxygen demand and supply?

1 Oxygen Demand:

O_2 demand is determined by:

1-Contractility
2-Heart rate
3-Wall tension(pressure exerted by the fibers itself)(affected by):
-LV pressure (Afterload)
Peripheral vascular resistance
-Ventricular volume (Preload)

O_2 demand is diminished by:

1-Reducing contractility
2-Reducing Heart rate
3-Reducing the Preload
4-Reducing the Afterload

2 Oxygen Supply:

O_2 supply is determined by:

1-Regional myocardial distribution
2-Arterio-Venous O_2 difference
(difference between O_2 content between atria and ventricles, it increases during exercise)
3-Coronary blood flow (affected by):
-Aortic pressure
-Coronary vascular resistance

O_2 supply is enhanced by:

1-Reducing coronary vascular resistance
2-Reducing external compression
3-Reducing LV + diastolic pressure
4-Prolong diastolic period
5-Dilating collateral vessels
6-Optimizing hemoglobin & RBCs

It is important to point out that restoration of oxygen supply to ischemic tissue should be restored **3 hours** after ischemia at most, after that period the cells will be overly **acidic** due to lactate accumulation from anaerobic metabolism, and the introduction of oxygen to the **damaged mitochondria** will result in the formation of **free radicals**, particularly H2O2, as a final product of **ETC, causing further damage to the cells and possible inflammatory reaction.** This is known pathophysiologically as Inadequate Tissue Reperfusion.

Treatment of angina pectoris

1- Agents that improve symptoms and ischemia:

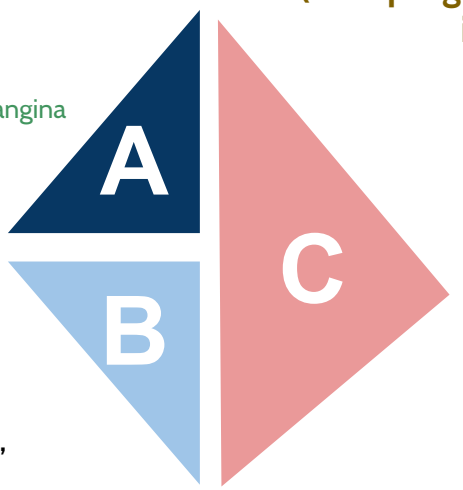
Traditional Approaches:

- **N**itrates. The main therapy of angina
- **B**eta-blockers.
- **C**alcium channel blockers (CCB).

New Approaches:

2nd line or add up therapy

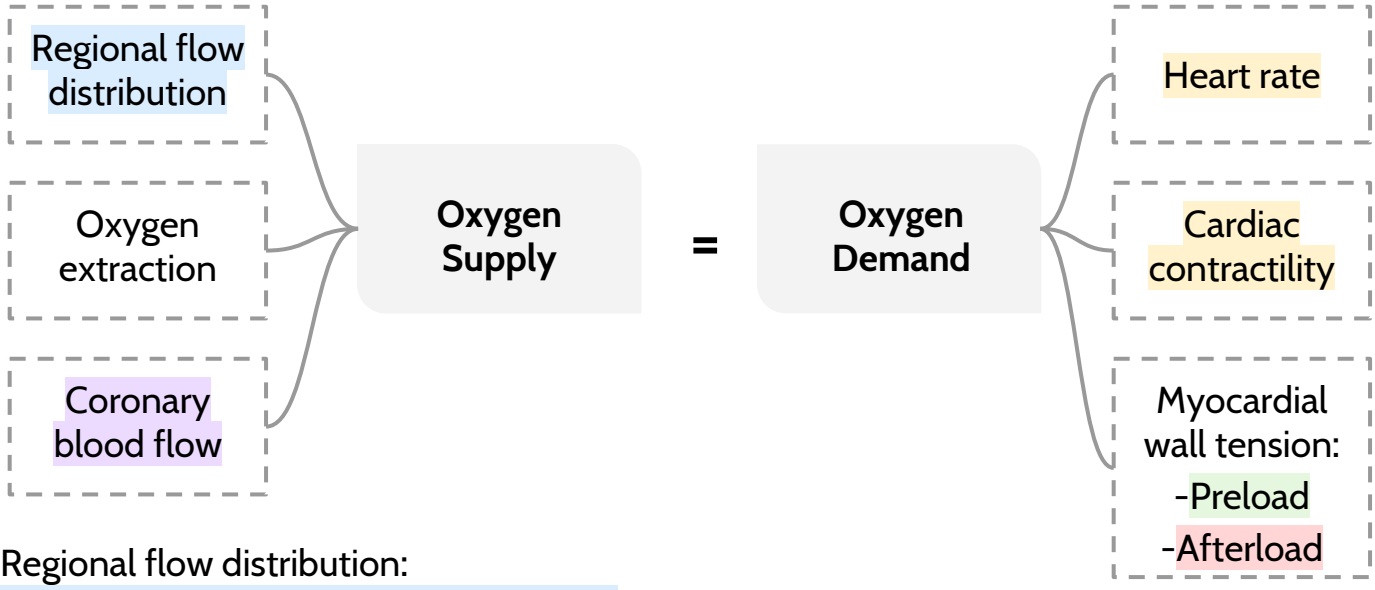
- Metabolic acting agents, e.g. Trimetazidine.
- Potassium channels openers, e.g. Nicorandil.
- Late Na+ current inhibition, e.g. Ranolazine.
- Sinus node inhibition, eg. Ivabradine. (↓ Heart rate, without effectinging force of contraction)



2- Agents that improve prognosis (Halt progression, prevent acute insult, improve survival):

- Statins (stops cholesterol synthesis)
- ACE inhibitors
- Beta-blockers
- Aspirin / other antiplatelet agents

General mechanism of antianginal drugs:



Regional flow distribution:
Flow to ischemic subendocardial tissue improved by nitrates, CCBs, B-blockers

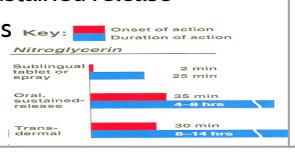
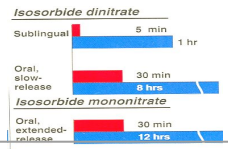
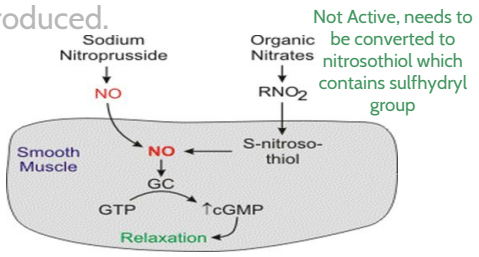
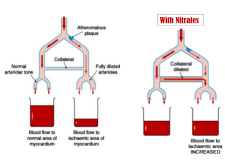
Coronary blood flow:
Increased by nitrates and CCBs

Heart rate + Cardiac contractility:
Decreased by B-blockers and some CCBs

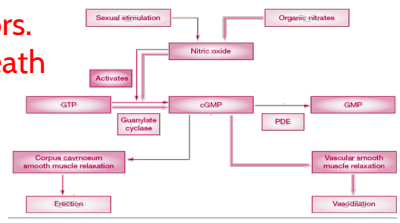
Preload:
Decrease by nitrates

Afterload:
Decreased by CCBs

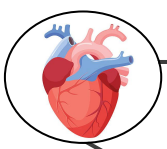
Antianginal drugs: 1.Organic Nitrates

Classification	Short acting	Long Acting
Drugs	**Nitroglycerine (GTN)** -Prototype of organic nitrates -active ingredient of dynamite (explosive material)	**Isosorbide mononitrate & dinitrate**
Pharmaco-kinetics	**•Given sublingual or transdermal patch or parenteral.** • Can't be given orally, because it goes through Significant first pass metabolism in the liver. • Only (10-20%) bioavailability (if given orally)	**• Very well absorbed . Mononitrate, 100% bioavailability** • The dinitrate undergoes denitration in liver to two mononitrates ➜ both possess antianginal activity which then conjugate to glucuronic acid in liver. • T1/2= 1-3 hours. • Excreted in urine.
Main use	• Rapid for terminating an acute attack of stable angina.	• For long-term persistent prophylaxis of stable angina.
Indications	IN STABLE ANGINA: • Acute symptom relief ➜sublingual GTN • Prevention; Situational prophylaxis➜sublingual GTN (if the patient will do effort) IN VARIANT ANGINA➜ sublingual GTN IN UNSTABLE ANGINA IV GTN • Heart failure • Refractory AHF ➜IV GTN • AMI➜IV GTN	IN STABLE ANGINA: • Prevention; Persistant prophylaxis ➜Isosorbide mono or dinitrate. IN UNSTABLE ANGINA: • CHF➜ Isosorbide mononitrate + hydralazine *[if contraindication to ACE Is used]*
Preparations	• Sublingual tablets or spray Have rapid onset of action and short duration (30min), • Transdermal patch**(8-14h)** • Oral or bucal sustained release • I.V. Preparations 	• Dinitrate Sublingual tablets • Dinitrate Oral sustained release • Infusion Preparations • Mononitrate Oral sustained release 
Mechanism The damaged endothelium in angina patients can't produce NO, this group of drugs donate it	1. Release NO through interactions with intracellular SH groups and with further enzymatic degradation, NO is produced. **Nitric oxide** then binds to guanylate cyclase in vascular smooth muscle cell to form cGMP. 2. cGMP activates PKG *(Protein Kinase G)* to produce relaxation *For the action of Nitrates we need SH groups. 	
Hemodynamic effects of nitrates	• **Nitrates can treat angina pectoris by one of 4 mechanism:** 1- Decrease the preload (in low concentrations, it causes venodilation) 2-Increase the myocardial perfusion (O2 supply) by dilating the coronary vessels. 3- Arterial vasodilation ➞ ⬇ **Afterload.** (in higher concentrations) 4- Shunting of flow from normal area to ischemic area by dilating collateral vessels **(blood in ischemic area increases).**  Collateral blood vessels are normally microvessels between arteries, when an infarct happens adenosine from infarcted cells will be released causing a dilation in these vessels, but takes years for them to dilate sufficiently, therefore pharmacological intervention is preferrable.	

Antianginal drugs: Organic Nitrates (cont.)

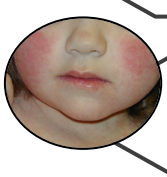
Nitrate tolerance	• **WHEN ?** **Loss of vasodilator response of nitrates** on use of long-acting preparations (oral, transdermal) or continuous intravenous infusions, for more than a few hours **without interruption.** • **How?, mechanism:** 1. Compensatory neurohormonal counter-regulation (Like baroreceptors and RAAS due to continuous vasodilatation) 2. Depletion of free-SH groups. (Nitrates are converted to NO through various intermediate reactions that require SH groups from tissues for the enzymes to function). • **How to overcome tolerance? by:** free periods (Smaller doses at increasing intervals) & Giving drugs that maintain tissue SH group **e.g. Captopril,** N-acetyl cysteine.
Contra-indications	1. Known sensitivity to organic nitrates. 2. Glaucoma. nitrates increase synthesis of aqueous humor thus increase IOP 3. Head trauma or cerebral haemorrhage → Increased intracranial pressure . 4. Uncorrected hypovolemia, because reduction of volume in the body will result in vasoconstriction. Hypovolemia must be corrected before administration of nitrates. 5. Concomitant administration of PDE5 Inhibitors. Sildenafil + nitrates → Severe hypotension & death Sildenafil (viagra), inhibit PDE which responsible for inactivation of cGMP , thus increase the effect of NO> severe vasodilation lead to severe hypotension could cause death. 

ADRs



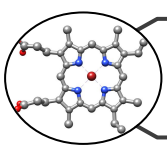
Reflex tachycardia and palpitation
Leading to increasing oxygen demand.

Throbbing headache
(most common), due to dilation of cranial blood vessels.



Flushing of blush area
(due to dilation of cutaneous blood vessels).

Postural hypotension , dizziness and syncope.



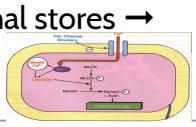
Rarely Methemoglobinemia

Nitrite bind to HB, converts ferrous "Fe^{+2}" to ferric "fe^{+3}" which's not able to carry O_2

Effects of nitrates in treatment of angina and their results

Effects	Results
↓ arterial pressure	↓ O2 demand
Reflex ↑ in contractility	↑ O2 demand
↑ Collateral flow	Improved perfusion to ischemic myocardium
↓ Ventricular volume	↓ O2 demand
Reflex tachycardia	↑ O2 demand
↓ Left ventricular diastolic pressure	Improve subendocardial perfusion
↓ Diastolic perfusion time due to tachycardia	↓ Myocardial perfusion
Vasodilatation of epicardial coronary arteries	Relief of coronary artery spasm

2.Calcium Channel Blockers

Class	Dihydropyridine	Phenylalkylamine	Benzothiazepine
Drugs	•Nifedipine •Amlodepine •Nicardipine	Verapamil	Diltiazem
Selectivity	Dihydropyridine group act mainly on smooth muscle. (thus, more selective as vasodilators than cardiac depressants).	act more on myocardium as cardiac depressant.	has intermediate effect. Do both actions but with less effectiveness
MOA	Calcium channel blockers → Bind to L Type Ca channels (the most important type, involved in anginal pain) → decrease their frequency of opening in response to depolarization → ↓ entry of Ca → ↓ Ca release from internal stores → No Stimulus-Contraction Coupling → **RELAXATION** 		
Pharmaco-dynamic Antianginal actions	**1-verapamil & diltiazem** ↓ Cardiomyocyte Contraction → ↓ cardiac work through their –ve inotropic & chronotropic action → ↓ myocardial oxygen demand **2-Dihydropyridines** ↓ VSMC Contraction → arteriolar vasodilation ↓ Afterload → ↓ cardiac work → ↓ myocardial oxygen demand 3-coronary dilatation ↑ myocardial oxygen supply		
Indications in Angina	Stable	Regular prophylaxis.	
	Unstable	Seldom (rarely) added in refractory cases.	
	Variant	Attacks are prevented	

Should the short acting dihydropyridines (Nifedipine , Nicardipine) be AVOIDED?

Yes, because it is a short acting calcium channel blocker that works on blood vessels, which means that it will lead to vasodilation, hypotension, and syncope. Thus, the sympathetic response will be activated leading to reflex tachycardia, less diastolic duration, impaired coronary filling, ischemia or MI.

Is a calcium channel blocker a useful antianginal in patients with CHF (Congestive heart failure)?

Yes, dihydropyrdine.To reduce the afterload (vasodilator) and thus decrease the cardiac workload.

Can we combine Calcium Channel Blocker with a beta blocker?

Except verapamil

Yes, dihydropyrdine: because beta blockers work on the heart so we can not combine it with CCB that also works on the heart (cardiomyocyte). but we can give something that works on the blood vessel like the long acting dihydropyrdnes: amlodepine

Can we combine Calcium Channel blocker with Nitrate ?

Yes, Verapamil: Because Nitrate is a vasodilator, that causes hypotension which leads to reflex tachycardia (increasing in the heart rate) and increasing in the force of contraction, so we can combine it with a CCB that works on the heart (cardiomyocyte) like verapamil to reduce the heart rate and the contraction.

β Adrenergic blockers

3. β1 Selective blockers

Drugs		•Atenolol •Bisoprolol •Metoprolol
Pharmaco-dynamic		**Acts on cardiomyocyte:** 1. Negative inotropic effect (force of contraction) 2. Negative chronotropic effect (Heart rate = bradycardia) 3. ↓cardiac work 4. Increase diastolic duration Due to the bradycardia 5.Increase coronary blood flow 6.↓ myocardial oxygen demand 7.↑ myocardial oxygen supply.
Indication as antianginal	Stable	1.Cardioselective (beta 1 blockers) are preferred 2.prolonged use reduces incidence of sudden death by preventing ventricular tachycardia due to their antiarrhythmic action.
	Variant	Contraindicated, because they are ineffective and may actually worsen symptoms.
	Unstable	halts (stops) progression to AMI improve survival
Indication as acute Myocardial infarction		Given early to ↓ Infarct size, morbidity & mortality (↓ incidence of sudden death)

Are Cardioselective beta blockers preferred in angina?

Yes, beta 1 blockers are preferred, and non-selective beta blockers are better avoided as they block vasodilatory effects of sympathetic stimulation that tend to increase afterload & O2 consumption.
Especially if the patient has tachycardia

Prolong use of beta blocker reduces incidence of sudden death?

Yes, they are 1st choice on prolonged use to reduce incidence of sudden death especially due to preventing ventricular tachycardia by their antiarrhythmic action (the Negative chronotropic effect)

should Beta blocker be withdrawn gradually?

Yes, because sudden stoppage will give rise to a withdrawal syndrome: Increase pain, Rebound angina, arrhythmia, myocardial infarction & Hypertension (due to stimulation or Up-regulation of beta-receptors).

Can we give a beta blocker to a diabetic patient with ischemic heart disease?

We can give it CAUTIOUSLY, بحذر if benefits are more than risks
They cause masking of hypoglycemia in diabetics (increase insulin and reduce glycogenolysis) and mask its symptoms, they also inhibit the counter-regulatory mechanism and thus prevent recovery of hypoglycemia. They inhibit insulin release

بالتالي نقيس فائدتها على المريض، إذا ضررها أكثر من نفعها فالأفضل طبعًا عدم إعطاءه.

New Approaches
Antianginal drugs: K+ Channel Openers

4. K+ channel openers		
Drug	**Nicorandil**	
Pharmaco-dynamic (dual mechanism)	**1.Opening of KATP channels.**	2. Acting as NO donner
	On VSMCs :K+ channel opening → Hyperpolarization with shutting off the calcium channel leading to relaxation → VASODILATATION (improve coronary flow & ↓ afterload)	On VSMCs: NO donner → cGMP/ PKG → VASODILATATION
	On Cardiomyocyte : K channel opening Repolarization → relaxation of myocardial cells → ↓ Cardiac work	
Indications	1. Prophylactic 2nd line therapy in stable angina. 2. Refractory (not responding) variant angina if not responding to nitrate and CCB.	
ADRs	Flushing, headache, Hypotension, palpitation (due to nitrate effect) Weakness, Mouth & peri-anal ulcers, nausea and vomiting	

5.Metabolically Acting Agents	
Drug	**Trimetazidine**
Pharmaco- dynamic (dual mechanism)	During ischemia, metabolism shifts to oxidation of FFA (fatty acids), which provides more energy but requires more O2 than Glucose utilization. So, to decrease O2 consumption & demand, we can enhance utilization of glucose (less O2 requirement) by giving Partial FFA Oxidation Inhibitors (e.g. Trimetazidine)
Indications	Used as an add on therapy
ADRs	GIT disturbances
Contra-indications	•Hypersensitivity reaction •In pregnancy & lactation (excreted in milk)

6.Late Na+ current inhibition

Drug	Ranolazine
Pharmaco-logical effect	•Inhibits the late sodium current, which increases during ischemia and affects Na dependent-Ca Channels The late sodium current is active in the plateau phase, it prolongs the plateau phase (therefore QT interval), trapping more Ca in the cell, normally we'd expect that by blocking the channel the QT interval would be shortened, but this drug also blocks potassium efflux so the effect is reversed and it increases it. However, it has been shown that this mechanism decreased the risk of Torsades de pointes in susceptible patients (congenital QT syndromes, by preventing afterdepolarization by Na.)
Indication	Used in chronic angina concomitantly (in combination) with other drugs
ADRs	dizziness & constipation
Contra-indications	-
Precautions	•It prolongs the QT interval so **contraindicated** with Class Ia & III antiarrhythmic drugs . • Toxicity develops due to interaction with CYT 450 inhibitors as; diltiazem, verapamil, ketoconazole, macrolide antibiotics, grapefruit juice

7.Sinus node inhibition

Drug	Ivabradine
M.O.A	-Selectively blocks I_f (I_f current is an inward Na+/K+ current that activates pacemaker cells of the SA node)
Pharmaco dynamic effect	-Acts on the " Funny Channel" a special Na channel in SAN, reduces slope of depolarization HR myocardial work Myocardial O2 demand
Indication	-Used in treatment of chronic stable angina in patients with normal sinus rhythm who cannot take ß-blockers. -Used in combination with beta blockers in people with heart failure with LVEF lower than 35 percent inadequately controlled by beta blockers alone and whose heart rate exceeds 70/min
ADRs	luminous phenomena

Helmi's case

Helmi, a 62-year-old male smoker with type 2 diabetes mellitus and hypertension presents with a 4-month history of exertional chest pain. Physical examination shows a blood pressure of 152/90 mm Hg but is otherwise unremarkable. The ECG is normal, and laboratory tests show a fasting blood glucose value of 110 mg/dL, glycosylated hemoglobin 6.0%, creatinine 1.1 mg/dL, total cholesterol 160, LDL 120, HDL 38, and triglycerides 147 mg/dL. He exercises for 8 minutes, experiences chest pain, and is found to have a 2-mm ST-segment depression at the end of exercise.

Questions and answers

- **Q1) Which signs or symptoms of Helmi suggest diagnosis of angina pectoris?**

  -Exercise induced chest pain and depression of ST segment.
  -Pain is caused either by obstruction,or spasm.

- **Q2) What triggers the onset of symptoms in Helmi case?**

  Exercise.(increase in cardiac demand)

- **Q3)What factors worsen the symptoms in case of Helmi?**

  Smoking, hypertension, diabetes and enhanced LDL.

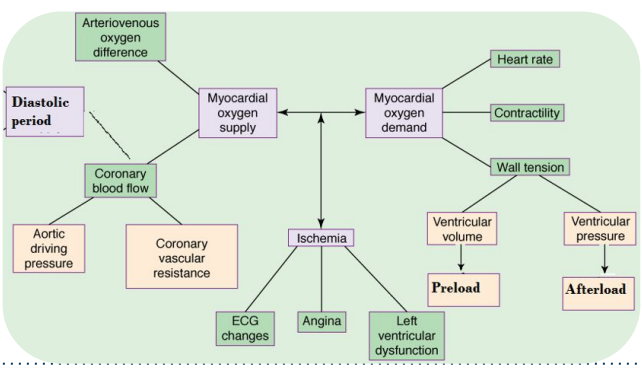
- **Q4) What lifestyle modifications should Helmi carry out?**

  Quit smoking, control of diabetes, diet control and moderate exercise.

- **Q5)What is the possible underlying cause of Helmi's exertional pain?**

  Coronary artery occlusion due to atherosclerotic plaque.

- **Q6)What are the determinants of oxygen demand & supply?**



- **Q7)If Helmi was prescribed nitrates & tolerance developed to their effects, how to overcome tolerance to nitrates?**

  Nitrate tolerance can be overcome by: Smaller doses at increasing intervals (Nitrate free periods twice a day) & Giving drugs that maintain tissue SH group e.g. Captopril.

- **Q8) Which antianginal drug is the best choice for the case of Helmi? And Why?**

  We should avoid B-blocker because he is Diabetic , we can start with Nitrate or Ca++ channel blocker.

- **Q9)If Helmi does not respond to monotherapy, what other drug should be added to his regimen?**

  Aspirin, to improve prognosis
  and we will treat
  Hypercholesterolaemia.
  if this didn't work, we will give add up therapy
  (2nd line)

- **Q10)Which antihyperlipidemic drug should be prescribed to Helmi?**

  Statins + Fibrates

QUIZ

MCQ

1-A 72-year-old male presents to the primary care clinic complaining of chest tightness and pressure that is increasing in severity and frequency. His current medications include atenolol, lisinopril, and nitroglycerin. Which intervention is most appropriate at this time?

A. Add amlodipine. B. Initiate isosorbide mononitrate.
C. Initiate ranolazine. D. Refer the patient to the nearest emergency room for evaluation.

2- Which side effect is associated with amlodipine?

A. Bradycardia. B. Cough.
C. Tachycardia. D. QT prolongation.

3- A 68-year-old male with a history of angina had a MI last month, and an echocardiogram reveals heart failure with reduced ejection fraction. He was continued on his previous home medications (diltiazem, enalapril, and nitroglycerin), and atenolol was added at discharge. He has only had a few sporadic episodes of stable angina that are relieved with nitroglycerin or rest. What are eventual goals for optimizing this medication regimen?

A. Add isosorbide mononitrate. B. Increase atenolol.
C. Stop atenolol and increase diltiazem. D. Stop diltiazem and change atenolol to bisoprolol

4- Which of the following medications would be safe to use in a patient taking ranolazine?

A. Carbamazepine. B. Clarithromycin.
C. Enalapril. D. Quetiapine.

5- Which medication should be prescribed to all anginal patients to treat an acute attack?

A. Isosorbide dinitrate. B. Nitroglycerin patch.
C. Nitroglycerin sublingual tablet or spray. D. Ranolazine.

6- A 65-year-old male experiences uncontrolled angina attacks that limit his ability to do household chores. He is adherent to a maximized dose of β-blocker with a low heart rate and low blood pressure. He was unable to tolerate an increase in isosorbide mononitrate due to headache. Which is the most appropriate addition to his antianginal therapy?

A. Amlodipine. B. Aspirin.
C. Ranolazine. D. Verapamil.

1) D 2) C 3) D 4) C 5) C 6) C

QUIZ

SAQ

A 55 year old hypertensive woman presented to the clinic with episodes of severe crushing chest pain despite minimal to no effort exerted. Recently, her hypertension combined with her chest pain developed into CHF. Past medical history showed she had been taking NSAIDs to relieve the pain.

1) Which drug is most suitable to relieve her case? and mention Hemodynamic effects.

2) Name another drug that can be combined for better efficacy

3) What effect did NSAIDs have in making your drug choices?

Answers:

1) Nitroglycerine (GTN)
2)
   - Venous vasodilation (Decrease the preload) and decrease diastolic pressure.
   - Coronary vasodilation (Increase the myocardial perfusion).
   - Arterial vasodilation (decrease afterload).
   - Shunting of flow from normal area to ischemic area by dilating collateral vessels.

2) Hydralazine.

3) They eliminated the option to use ACEi

pharmacology

Team 438

GOOD LUCK

Team Leaders:

May Babaeer

Zyad Aldosari

Team Members:

Alwaleed Alsaleh

Bassam Alkuwaiter

Khalid Nagshabandi

Mohaned Makkawi

Mohamed ajaarm

Mohamed alotaibi

Special thanks to: Nouf Alshammari

Share with us your ideas !