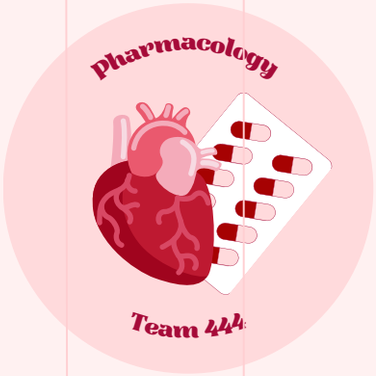
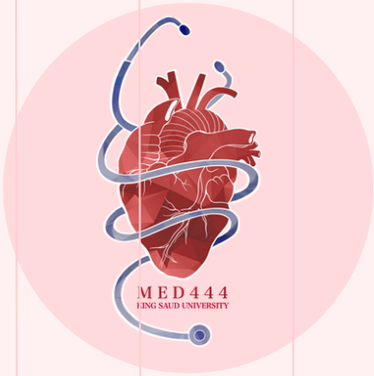




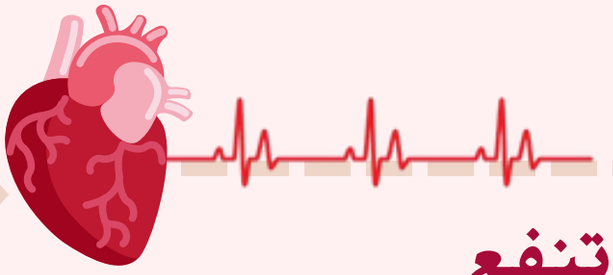
L5.

Treatment of hypertension [1]&[2]

EDITING FILE

COLOR INDEX :

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



مريض الضغط له ولعلاجه تنفع
كالسيوم قبلها ذي تقيدك
تدر بوله وبعدها الراس تقطع
واخيراً قل له بنوسّع وريدك

علي العبدالعظيم

الراس = RAAS

Objectives:

- Outline the pharmacologic classes of drugs used in treatment of .hypertension
- Describe the mechanism of action , therapeutic uses & common ADRs of each class of drugs.
- Select an antihypertensive drug to treat a specific patient according to efficacy, safety & suitability.

First video
1- Intro first 15 minutes
2- hypertension min 15:30
3- hypertension types min 19:00
4- treatment min 30:40
5- non pharmacological therapy min 33:00
6- first and second line therapy min 42:00
7- beta blockers min 46:00
8- Diuretics min 52:00

Second video (diuretics)
1- Intro first 5 mins
2- PDE inhibitors min 6:00
3- ACEI & Diuretics min 17:00
4- Spironolactone min 21:00
5- lasilactone min 24:00
6- Venodilators min 26:00
7- Beta blockers min 30:00
8- Cardiogenic pulmonary edema & Loop diuretics min 37:00
9- Nitroglycerine min 49:00

Third video part1(ACEI)
1- RAAS first 27 minutes
2- Aliskiren min 28:00#
3- ACEI min 33:00
4- MOA min 40:00

part 2
1- uses of ACEI min 10:00
2- ADRs min 16:00
3- contraindications min 30:00
4- ARBS min 37:00

fourth video (ca blockers)
1- introduction first 10 minutes
2- treatment (Verapamil, Nifedipine, Diltiazem)
min 11:00
3- effect on other organs min 21:00
4- clinical uses min 30:30
5- Verapamil uses min 31:00
6- Nifedipine min 35:00
7- Verapamil uses summary min 51:00
8- uses of Nifedipine min 51:30
9- ADRs min 58:00

Fifth video (2nd line)
1- introduction first 10 minutes
2- Drugs min 10:30
3- Hydralazine min 11:00
4- Minoxidil & Diazoxide min 18:30
5- Sodium nitroprusside min 24:00

Hypertension

GIRLS'S SLIDES

Epidemiology

Prevalence 25-30%
In majority of cases, its symptomless **'Silent Killer** 'Number one cause of death worldwide.

The rule of halves of Hypertension

For every 800 adults in the community:
1- 400(half) are hypertensive (either ↑ SBP or ↑ DBP or both).
2. Of them only 200 are diagnosed HT
3. Of them only 100 are started on treatment.
4. Of them only 50 are on correct drug.
5. Of them in only 25 the goal B.P. is attained.
6. Means 25 ÷ 400 = 6% only have goal BP

MALES'S SLIDES

Hypertension Equation

Blood pressure (BP) is determined by cardiac output (**CO**) and total peripheral resistance (**TPR**), as represented by the formula **BP = CO x TPR**

Cardiac output (CO) **is affected by two factors**, *the heart rate (HR) and the stroke volume (SV),* the volume of blood pumped from one ventricle of the heart with each beat (CO = HR x SV, therefore BP = HR x SV x TPR. In reflex bradycardia, blood pressure is reduced by decreasing cardiac output (CO) via a decrease in heart rate (HR)

Classification of Antihypertensive drugs

DIURETICS
(↓ BV→ ↓ CO)

- Thiazides.
- loop Diuretics.
- Potassium-sparing diuretics.

VASODILATORS
(↓ PVR)

- Hydralazine.
- Minoxidil.
- Diazoxide.
- Sodium nitroprusside.

RAAS
(↓ PVR & Blood Volume)
renin-anaiotensin-aldosterne system

- Direct renin inhibitors.
- Angiotensin-converting enzyme inhibitors (ACEI).
- Angiotensin receptors blockers.

CALCIUM CHANNEL BLOCKERS
(↓ PVR/ ↓ CO)

- Phenylalkylamine (verapamil)
- Dihydropyridine (Nifedipine)
- Benzothiazepine (Diltiazem)

DRUGS ACTING OF THE SYMPATHETIC NS
(↓ sympathetic system)

- B- adrenoceptor blockers (propranolol, atenolol, metoprolol).
- a-adrenoceptor blockers (prazosin, doxazosin).
- Centrally acting sympatholytic drug (clonidine, a-methyldopa).

GIRLS'S SLIDES

Fouda: First line *(not ordered)* are: **ABCD**
A: Ace inhibitors and ARBs
B: Beta Blockers
C: Calcium Channel Blockers
D: Diuretics

- ***note:*** *this is according to Dr. Fouda videos. guidelines change (e.g. Beta blockers are not first line anymore)*

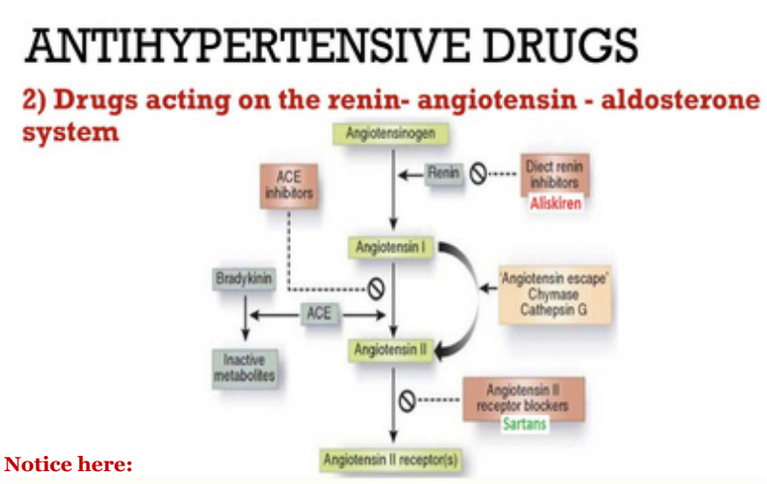
RAAS SYSTEM

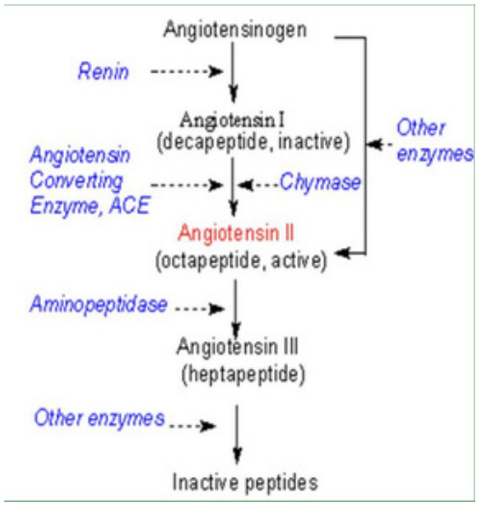
renin-angiotensin-aldosterone system

- *Drops in blood pressure reduce renal perfusion.*
- ↓pressure in the renal artery → **renin** is released from the juxtaglomerular apparatus → renin *(from kidney)* converts **angiotensinogen**(*inactive -"gen"- from liver)* to **angiotensin I** → **ACE** *(from lung)* converts angiotensin I to **angiotensin II**.

2 main effects of angiotensin ll:

1) **vasoconstriction** → ↑BP
2) stimulates the release of **aldosterone** → promotes reabsorption of sodium and water (excretes potassium) → ↑ blood volume → ↑ BP





Notice here:

ACE enzyme has two roles:
1) converting ATI → ATII *(which we want to block)*
2) converting Bradykinin → Inactive Metabolites *(which we don't want to block)*

Therefore if you inhibit ACE this causes →↓ Breakdown of bradykinin → High bradykinin will cause dry cough and angioedema *(side effects most prominently seen with ACEi)*

Other RAAS Inhibitors *(Direct Renin Inhibitors - ARBs)* do not affect Bradykinin and → won't have the same ADRS as ACEi.

- note that side effects that depend on inhibiting ATII are seen in ALL RAAS inhibitors *(i.e. Hyperkalemia / ↓GFR)*

By: Khalid Ibraheem 44

1:-Drugs acting on the renin- angiotensin - aldosterone system

A- Direct renin inhibitors

علي سكيرين
Aliskiren
(Tekturna)
"only renin inhibitor on the market"

- Inhibits (renin) the first and rate limiting step of the RAAS
- Approved as monotherapy or in combination therapy for hypertension. However, because it represents a new drug class and has not been shown to prevent CV events, it is not preferred as first-line therapy.

B- Angiotensin-receptors blockers (ARBs)

Losartan - Valsartan

M.O.A

- **Cause selective block of AT1 receptors** (Angiotensin II receptor type 1 → bad receptor)
- **No effect on bradykinin, no cough, no angioedema**
- Produce more complete inhibition of angiotensin.

Pharmacokinetics:

Losartan :-

- Has a potent active metabolite, Orally effective.
- Long half-life, taken once daily, Does not cross BBB.

Valsartan:-

- No active metabolites

ADRs

- Same contraindications as ACEI.
- Same ADRs, except for dry cough & angioneurotic edema. (see bottom of slide 6)

Drugs acting on the renin- angiotensin - aldosterone system

C- Angiotensin-converting enzyme inhibitors (ACEI)

Captopril - Lisinopril - Enalapril - Ramipril - Perindopril.

M.O.A	Inhibiting ACE.
Pharmacokinetics:	• Polar, excreted in urine. • Do not cross BBB. • Have a long half-life & given once daily. • Rapidly absorbed from GIT after oral administration. • Food reduces their bioavailability. • It takes 2-4 weeks to see the full antihypertensive effect of ACEIs. • Enalapril & ramipril are prodrugs. • Enalaprilat is the active metabolite of enalapril given by i.v. route in hypertensive emergency.
Clinical Uses:	• Treatment of essential hypertension • Hypertension in patients with chronic renal disease, ischemic heart disease, Heart Failure, diabetes (because they have been shown to be nephroprotective + reduce cardiac remodeling) • Treatment of heart failure. • Particularly effective when hypertension results from excess renin production (renovascular hypertension).

Drugs acting on the renin- angiotensin - aldosterone system

C- Angiotensin-converting enzyme inhibitors (ACEI) 

Captopril - Lisinopril - Enalapril - Ramipril.

ADRs

- Dry cough
- Acute renal failure, especially in patients with renal artery stenosis. *(due to ↓ GFR - which may help patients with chronic kidney disease that's why its 1st line. but if kidney disease is acute especially renal artery stenosis ACEi are contraindicated)*
- Severe hypotension in hypovolemic patients. *(RAAS dependent)*
- Cause renal agenesis/failure in the fetus, resulting in oligohydramnios's (too little amniotic fluid) . (Teratogenic)
- Angioneurotic edema, swelling in the nose, throat, tongue, larynx. *(explained in slide 6)*
- First dose effect.

ADRs Specific to Captopril:

- Skin rash, fever
- Dysgeusia
- Proteinuria and neutropenia

Dysgeusia = a condition in which a foul, salty, rancid, or metallic taste sensation persists in the mouth.

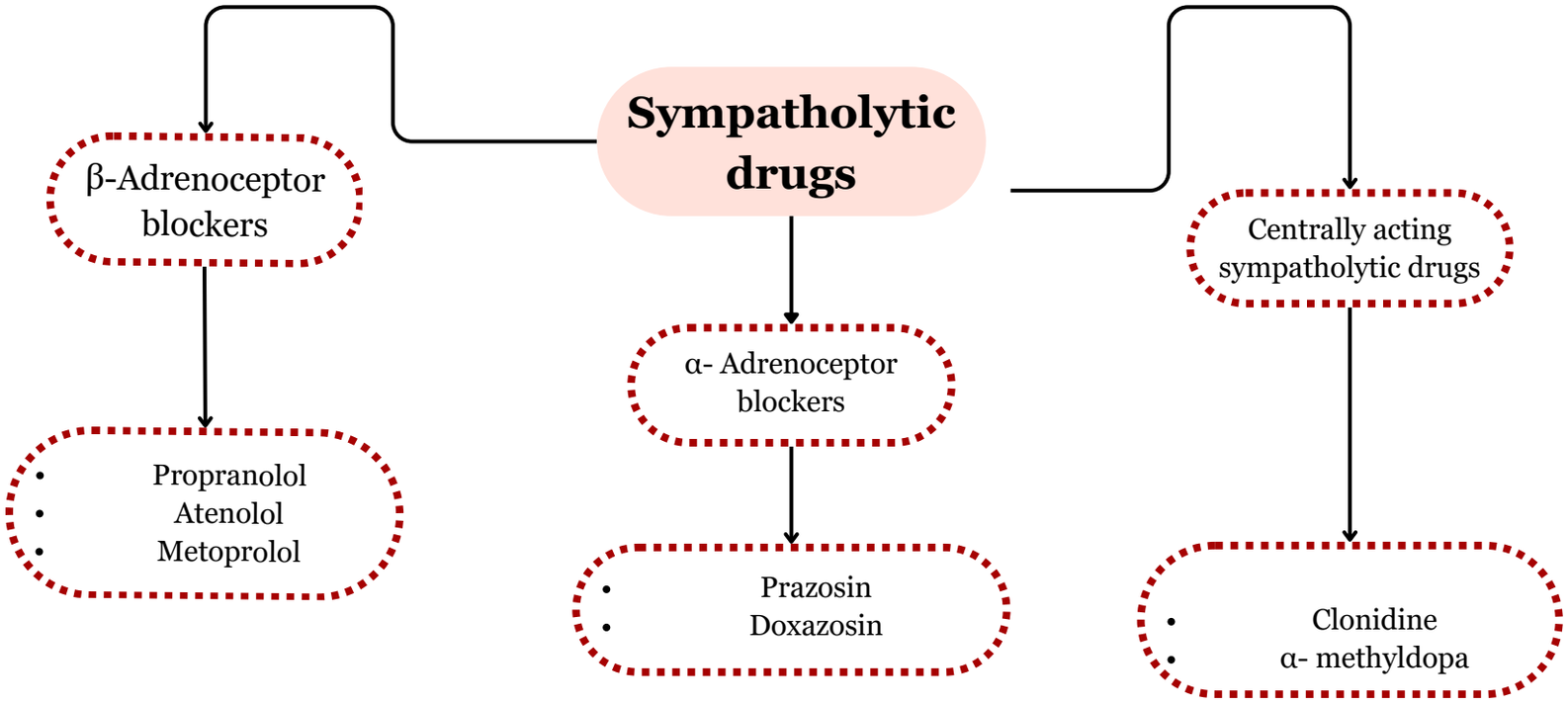
Proteinuria = the presence of abnormally large amounts of protein in the urine.

Contraindications:

- During the second and third trimesters of pregnancy due to the risk of: fetal hypotension, anuria, renal failure & malformations.
- Renal artery stenosis.
- Potassium-sparing diuretics both cause increase in potassium level cause hyperkalemia
- NSAIDs. cause it reduce the effect of ACEI

GIRLS'S SLIDES

2: Sympatholytic drugs



β-Adrenoceptor blockers

Drugs	Propranolol	Atenolol	Metoprolol
Type	short- Non selective "Contradicted with asthma patients"	Selective beta 1 blocker	
Clinical use	• They should not be the primary agent for primary prevention but are effective as add-on therapy. • May take two weeks for optimal therapeutic response. • Evidence support the use of ß-blockers in patients with concomitant coronary artery disease • When discontinued, ß- blockers should be withdrawn gradually. "receptors are upregulated"		
M.O.A	1. Decrease cardiac output 2. Inhibit renin release 3. Centrally mechanism		
ADRS	Aggravate peripheral arterial disease Hypoglycemia - Fatigue Increase triglycerides Erectile dysfunction Mask hypoglycemia symptoms in diabetics (GIVEN CAUTIOUSLY to diabetes)		

GIRLS'S SLIDES

α- Adrenoceptor blockers

Drugs	Prazosin	Doxazosin
P.k	short- acting	preferred for its long half life
M.O.A	• Block α- receptors in arterioles and venules • Reduce blood pressure by decreasing both afterload & preload	
Clinical use	treatment of hypertension in patients with benign prostatic hypertrophy (BPH) thanks 443🙏	
ADRS	causes first dose hypotension (given in gradual dose),and postural hypotension **"Especially if it is the first time to use the drug" Thanks 443**	-

Centrally acting sympatholytic drugs

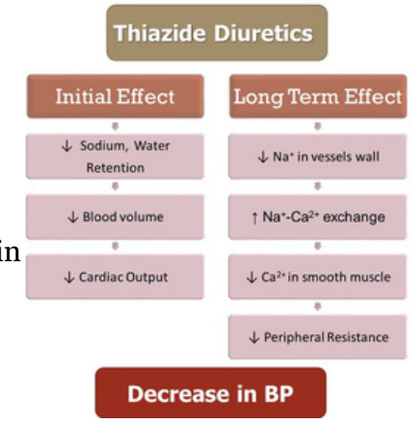
Drugs	Clonidine	α- methyldopa
M.O.A	**α2-agonist, diminishes central adrenergic outflow & ↑ parasympathetic outflow**	**An indirect α- 2 agonist, is converted to methyl noradrenaline centrally to diminish the adrenergic outflow from the C.N.S. Lead to reduced total peripheral resistance, and a decreased in blood pressure**
clinical use	**• Hypertension complicated by renal disease (it does not decrease renal outflow or glomerular filtration** **• Resistance hypertension**	**α -Methyldopa is the first line treatment of hypertension pregnancy**
ADRs	**Abrupt sudden withdrawal of clonidine can lead to rebound hypertension.** **"down regulation of receptor and increase BP"** **Thanks** 443	-

3-Calcium channel blockers Very Nice Drugs

Drugs	Nifedipine	Diltiazem M.O.A	Verapamil
Feature	**Act mainly on smooth muscle** less effect on myocardium	**Has intermediate effect** "act on both myocardium and smooth muscle "	**Act mainly on myocardium**
M.O.A	**Block the influx of calcium through calcium channels resulting in:** **1. Peripheral vasodilatation** **2. Decrease cardiac contractility**		
Pharmacokinetics:	• Given orally (onset: 0.5-2h) and I.V. injection (onset 1-3min), well absorbed • Verapamil & diltiazem have active metabolites, nifedipine has not. • Verapamil and nifedipine are highly bound to plasma proteins (more than 90%) while diltiazem is less bound (70-80%). • Sustained-release preparations can permit once-daily dosing. "longer DOA"		
Uses	• **Treatment of chronic hypertension.** • **Nicardipine**(same family as nifedipine) **can be given by I.V. route & used in hypertensive emergency.** • Sustained-release formulations are preferred for the treatment of hypertension due to the short half-life of CCBs.		
ADRs	• Headache, Flushing, Hypotension • Nifedipine: reflex tachycardia. **"Due to baroreceptors(stretch receptors in aorta & c.carotid) effect==>CNS==>Cardiac stimulation==>HR+"** • Verapamil & Diltiazem: peripheral edema (ankle edema). "they dilate arterioles not venules, blood will pool inside the arterioles so it can't pass easily to the venules (they are not dilated)the blood will accumulate in the arterioles and capillaries, this will lead to leaking of fluid in the surrounding tissue and will result in Edema" "common ADRs" • Verapamil: constipation (inhibit GI smooth muscle → low motility → Constipation)		

4- Diuretics

	i-Thiazides	ii-Loop Diuretics	iii-Potassium-sparing Diuretics
e.g. of drug	**1- Hydrochlorothiazide** **2-Chlorthalidone** M.O.A: Decrease sodium reabsorption and therefore decreased fluid reabsorption	**Foursemide** -More potent diuresis but a smaller decrease in PVR, thick ascending loop of Henle	**Spironolactone**
Uses	Routine management of Hypertension (because of their effect on PVR and long duration of action)	Hypertensive patients with - renal impairment(Thiazides do not enhance the excretion of Na and water when kidney function is impaired) or - heart failure (because they are very potent)	Minimal effect on lowering BP (Less effect on PVR)
M.O.A (of thiazides only) ***Important***	Initially: ↓ sodium and water retention → ↓ blood volume → ↓ cardiac output → ↓ blood pressure Long term: ↓ Na+ in vessel wall → ↑Na+-Ca2+ exchange *(Na+ in/ Ca2+out)* → ↓ Ca2+in smooth muscle cell*(Ca2+is essential in smooth contractility so if decreased it cause vasodilation)* → ↓ Peripheral resistance →↓ blood pressure The initial diuresis lasts 4-6 weeks and then is replaced by a decrease in PVR initially: ↓CO → ↓BP | Long term: ↓ TPR →↓ BP		
Use in Hypertension	Adequate in mild to moderate Hypertension (not very potent HT drugs) Diuretics are very useful Anti HT drugs and should be the initial treatment of HT According to ALLHAT trial, chlorthalidone (first choice diuretic) is superior to an ACE inhibitor, a calcium channel blocker and an alpha1-adrenergic antagonist in preventing one or more cardiovascular events.		

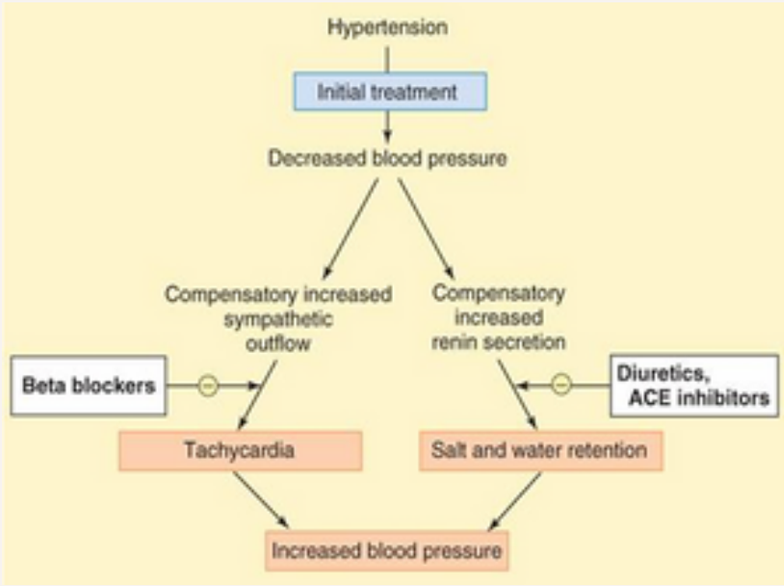


5. Vasodilators

an amazing 4 min vid for Minoxidil & Diazoxide

- Classified into arterial, venous or mixed vasodilators .
- Once vasodilators are administered, fall in BP produced will activate the sympathetic system → Reflex Tachy & the RAAS → Salt and Water Retention.

Extra note: They affect the muscles in the walls of the arteries and veins, preventing the muscles from tightening and the walls from narrowing. As a result, blood flows more easily through the vessels. The heart doesn't have to pump as hard and the blood pressure will reduced.



Harry **M**akes **N**ice **D**inners.

Drug	Hydralazine	Same as أفوجين Minoxidil M.O.A	Diazoxide	Sodium nitroprusside
Site of action	Artiodilator			Arterio & venodilator
M.O.A	Release of nitric oxide	**Opening of K+ channels in smooth muscle membranes by minoxidil sulfate (Active metabolite)**	Opening of potassium channels.	Release of nitric oxide
Administration	Oral		Rapid I.V	I.V infusion

Drug	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Therapeutic uses	Moderate -to- severe hypertension		Hypertensive emergency	
	In combination with diuretics & β-blockers "to prevent tachycardia & salt and water retention"			
	Hypertensive pregnant woman But not the first-line (α-methyldopa is more recommended)	Baldness (الصلع)used to help hairgrowth	Treat hypoglycemia due to Insulinoma (Tumor of the pancreas that increase the secretion of insulin)	Severe heart failure
ADRs	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema). "And blood pressure will increase again"			Severe hypotension
Specific ADRs	Lupus erythematosus like syndrome 5-10%	Hypertrichosis excess hair growth thus contraindicated in females.	Inhibit insulin release from β cells of the pancreas causing hyperglycemia. "When the patient doesn't have Insulinoma" Contraindicated in diabetics	-Methemoglobin during infusion -Cyanide toxicity -Thiocyanate toxicity -Headache,palpitations which disappear when infusion is stopped.Cyanide accumulation cause cyanide poisoning (metabolicacidosis, arrhythmias, severe hypotension and death)

“ study smarter , not harder “

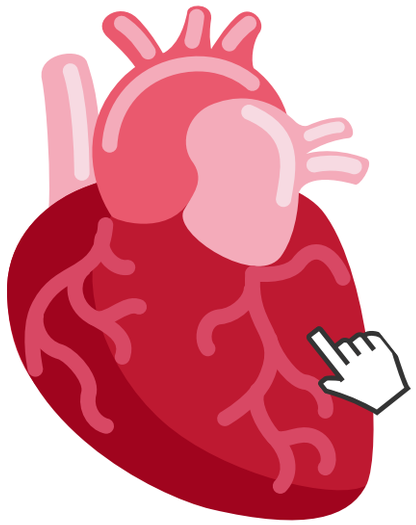
Active recall

For Anki flash cards click the icon

Take active quizzes in our team channel to test your understanding.

click the icon to get free flash cards

summary



MCQs

1 Which one of the following drugs can be used to treat hypoglycemia due to insulinoma?

A Clonodine
B Verapamil
C Diaoxide
D Thizazides

2 Which one of the following Drugs is more of a Vasodilator and can cause Reflex Tachychardia?

A Nifedipine
B Verapamil
C Diltiazem
D Chlorothiazide

3 Which medication should be avoided for a 50-year-old man who has started hypertension treatment and is experiencing a dry cough?

A Verapamil
B Valsartan
C Captopril
D Diltiazem

4 A 45 year old woman with hypertension, she experienced cough and angioedema because of using Captopril. The doctor prescribed an alternative drug for her that block AT1 receptor?

A Diltiazem
B Verapamil
C Ramipril
D Valsartan

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

MCQs

5 A 35 year old woman diagnosed with hypertension. After giving her Chlorthalidone, the doctor prescribed another drug that reduced her blood pressure. after days she came to the hospital because of skin rash, fever, and problems in tasting. The doctor test her urine which shows proteinuria. Which drug cause her problems?

A Enalapril
B Chlorthalidone
C Valsartan
D Captopril

6 A patient returns to her health care provider for routine monitoring 3 months after her hypertension regimen was modified. Labs reveal elevated serum potassium. Which is likely responsible for this hyperkalemia?

A Chlorthalidone.
B Captopril
C Valsartan
D B AND C

7 Which is the first choice for hypertension treatment during pregnancy?

A Aliskiren.
B α -Methyldopa
C Hydralazine
D Fosinopril

B C

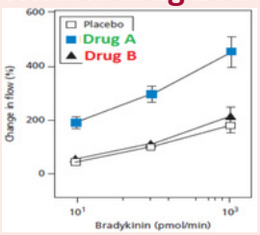
B

5-D,6-D,7-B

SAQs

1

The brachial artery was continuously infused with bradykinin and the blood flow is monitored. Placebo, drug A and drug B (both affect the RAAS) induced the effects on blood flow shown in the graph.
What is drug A? Justify.
What is drug B? Justify.



drug A is an ACE inhibitor. it inhibits degradation of bradykinin, accumulation of bradykinin -> vasodilation-> increase in blood flow

Drug B is an ARB or Renin Inhibitor. because it has no effect on bradykinin

2

What is the M.O.A of Diltiazem?

Block the influx of calcium through calcium channels resulting in:
1. Peripheral vasodilatation 2. Decrease cardiac contractility

3

What is the M.O.A of Monoxidil?

Opening of K+ channels in smooth muscle membranes by minoxidil sulfate (Active metabolite)

4

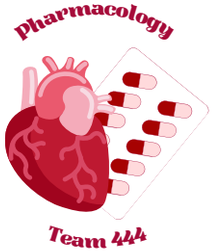
A doctor gave Hydrochlorothiazide to a patient come with essential hypertension, how can this drug reduce his blood pressur?

Important

Initially:
↓ sodium and water retention → ↓ blood volume → ↓ cardiac output → ↓ blood pressure

Long term:
↓ Na+ in vessel wall → ↑Na+-Ca2+ exchange (Na+ in/ Ca2+out) → ↓ Ca2+in smooth muscle cell(Ca2+is essential in smooth contractility so if decreased it cause vasodilation) → ↓ Peripheral resistance → ↓ blood pressure

The initial diuresis lasts 4-6 weeks and then is replaced by a decrease in PVR
initially: ↓CO → ↓BP | Long term:↓ TPR → ↓ BP



Lecture Done by :

Raseel aldajany **Abdulrahman khaldi**

Hanan alanazi **Tariq alshamrani**

Team Leaders :

Ritaj Alsubaie **Ali Al Abdulazem**

Sarah Alajmy **Waleed Alanazi**

Abdullah Balbaid

Contact us at : pharmacology.444ksu@gmail.com