Anti-Hypertensive 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:

By the end of this lecture, students should be able to :

✓ Identify factors that control blood pressure.

✓ Outline the pharmacologic classes of drugs used in treatment of hypertension.

✓ Describe mechanism of action, therapeutic uses & common adverse effects and contraindications of each class of drugs.

✓ Select the suitable antihypertensive drug used to treat a specific patient according to efficacy, safety and cost.

Editing File

What is Hypertension?

Is a common condition in which the long-term force of the blood against artery walls is high enough that it may eventually cause health problems.

General Information

Prevalence

25-30% of adult population have Hypertension.

tends to develop gradually over years.

cause

Goal BP

Only 6% of diagnosed hypertensive patients have goal BP even after correct treatment.

In majority of cases, hypertension persists for years without any symptoms, thus called "silent killer"

Symptoms

Complication

it may lead to many complications including end-organ failure and death.

Classification of Hypertension

1 Primary "essentials"

mostly no identifiable cause; tends to develop gradually over years.

2 Secondary

A-Drug-induced hypertension:

- Steroids
- Estrogens
- NSAIDS
- Clonidine
- Methylphenidate

B-Rebound hypertension:
occurs when blood pressure rises after you stop taking or lower the dose of a drug
(typically a hypertension medication).

C-Secondary to another disease.

Management of hypertension:

1

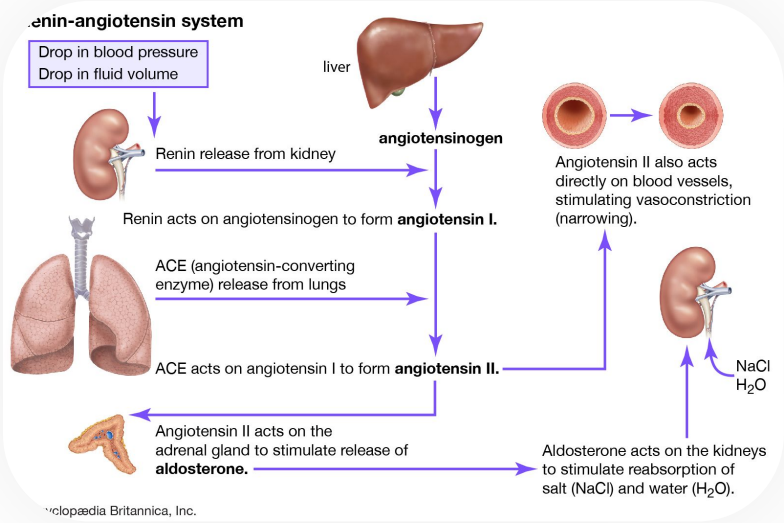
Lifestyle modification:
Thus patients with hypertension should follow some lifestyle modification, as weight loss, physical activity, sodium reduction and smoking cessation.

2

Drug Therapy:
Antihypertensive is indicated to achieve target BP
= < 140/ 90 mm Hg.
target BP for diabetics
= < 130/80 mm Hg

Physiological Mechanisms for Control of Blood Pressure

1- Renin-Angiotensin-Aldosterone System (RAAS):



1- Juxtaglomerular cells in the kidney sense a decrease in blood perfusion "due to either decrease pressure or volume" and release **renin** (enzyme) into the circulation.
2- At the same time, the liver secretes **angiotensinogen** (hepatic hormone) into the circulation.
3- **Renin** cleaves angiotensinogen into **angiotensin I**, a precursor for **angiotensin II.**

4- **Angiotensin I** then reaches the lung through pulmonary circulation "through the pulmonary artery", where it is converted into **angiotensin II** by the action of **Angiotensin-Converting Enzyme "ACE"** (note that more than one enzyme can accomplish this conversion, but **ACE** is the most prominent).

Effects:
1- Angiotensin II acts on posterior pituitary gland to secrete ADH, increasing water retention.
2- Angiotensin II acts on the adrenal cortex and stimulates secretion of aldosterone, increasing sodium and water retention.
3- Angiotensin II causes constriction of the blood vessels, increasing preload and afterload.

Other important notes: **ACE** is responsible for the metabolism of **Bradykinin** (Causes vasodilation and potentially angioneurotic edema when increased, and has a cardioprotective effect by limiting the rate of myocardial remodeling, it is the reason why **ACE inhibitors** have this effect in treating heart failure)

2- Baroreceptor Reflex:

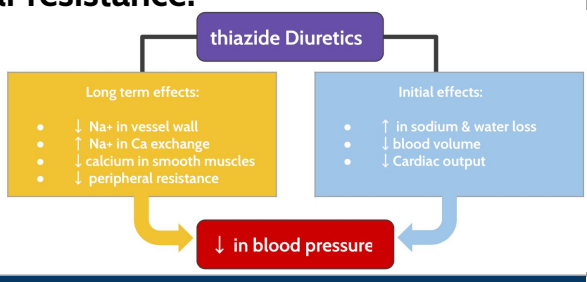
Mediated by:
1- Carotid and Aortic Baroreceptors (fire signals in response to stretch of vessels)
2- Sympathetic Neurons stretching from CNS

Increased blood pressure: When there is a stretching of the blood vessels (such as in an increased blood pressure), there is an increased firing rate through parasympathetic nerves from the baroreceptors to a regulatory region in the brain (NTS), NTS then responds to the baroreceptor signal by secretion of ACh to the heart, causing decreased heart rate **(potential bradykardia)**, and a decreased cardiac output, blood pressure then returns to normal.

Decreased blood pressure: there is less stretch of vessels due to decreased blood pressure, therefore there will be less firing from baroreceptors, this will activate the NTS in the brain to send sympathetic signals to the heart to increase heart rate **(potential tachycardia)** and an increase cardiac output, this can happen when a person is in an upright posture, there will be pooling of the blood in the veins of the lower regions due to gravitational pull, and less venous return and vessels of the heart will be less stretched as a result. Orthostatic hypotension occurs when this reflex fails.

Diuretic Drugs

Potassium Losing

Drugs	Thiazides	Loop diuretics	Potassium-sparing diuretics
Example	**Hydrochlorothiazide** **Chlorothiazide** **chlorthalidone**	**Furosemide** more potent diuresis but a smaller decrease in (Pulse volume Recording) Because they don't have any effect on smooth muscles.	**spironolactone** Act as Amiloride Aldosterone antagonist
Uses	initial drug therapy for Mild to Moderate hypertension	-hypertension with renal impairment -manage symptoms of heart failure and edema.	minimal effect on lowering BP, but used in combination with loop diuretics and thiazides to reduce potassium loss induced by these diuretics
Mechanism you should know the initial and the long term action	**The initial diuresis lasts 4-6 weeks and then replaced by a decrease in Peripheral vascular resistance.** Example: (thiazide Diuretics): Long term action has more potent effect in BP,because it decrease Ca++ this will lead to vasodilation, so blood pressure will decrease. 		

ACE Inhibitors

Example: Captopril , Lisinopril , Enalapril , Ramipril

Mechanism of action

- ACE inhibitors decrease angiotensin II (vasoconstrictor) and increase bradykinin levels (vasodilator) by preventing its degradation by ACE , so the antihypertensive effect results primarily from vasodilatation with little change in CO.
- A fall in aldosterone production may also contribute.

Pharmacokinetics

- **Polar**, excreted in urine; do not cross BBB .
- Rapidly absorbed from GIT after oral administration ,Food reduce their bioavailability.
- Have a long half-life and thus given only once daily.
- Enalapril & Ramipril are prodrugs, converted to the active metabolite in the liver , **Enalaprilat is the active metabolite of Enalapril, can be given by I.V. route in hypertensive emergency.**
- **It takes 2-4 weeks to see the full antihypertensive effect of ACEI.**

Clinical use (indications)

Essential Hypertension

- Particularly effective when hypertension results from excess renin production.
- Hypertension in patient with chronic renal disease, ischemic heart disease , diabetes.

Heart failure

By reducing both cardiac preload and afterload, thereby decreasing cardiac work, as well as inhibit remodelling

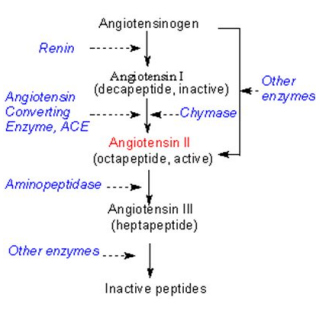
ACE Inhibitors cont...

Adverse Effects and contraindications

Acute renal failure	**Dry cough**
➔ Contraindicated in Patients with renal artery stenosis.	(due to increased bradykinin levels).
Severe hypotension in hypovolemic patients	**Renal failure and agenesis in the fetus**
➔ Contraindicated in hypovolemic patients .	**Can lead to oligohydramnios[1].** ➔ Contraindicated in pregnancy
Hyperkalemia	**First dose effect (severe hypotension)**
➔ Contraindicated in patients using Potassium-sparing diuretics	(should be given gradually)
Angioneurotic edema	**Adverse effects Specific to captopril**
(swelling in nose, tongue, throat & larynx) -caused by inhibition of bradykinin metabolism which accumulate in bronchial mucosa. (first dose effect)	➔ **skin rash, fever, dysgeusia** (loss of taste)**,Proteinuria and neutropenia.** These effects are due to a **sulfhydryl group** in the molecule of captopril.

- ACE inhibitors should be contraindicated in patients using **NSAIDs** .
(because NSAIDs reduce their hypotensive effects by blocking bradykinin-mediated vasodilatation)

Angiotensin receptors blockers (ARB)

Drugs	Losartan	Valsartan	others: Candesartan, Telmisartan
Pharmaco -kinetics	• Has a Potent active metabolite. • Effective Orally once daily. • long half life. • Do not cross BBB.	No active metabolite	-
Mechanism of action	- selective block of AT1 receptors. (thus, decreasing the activation of AT1 receptors by angiotensin II. Blocking the receptor itself, not the ACE enzyme). - No effect on bradykinin, no cough, no angioedema. - Produce more complete inhibition of angiotensin than ACE inhibitors because there are other enzymes (not only ACE) that can generate angiotensin thus they are more potent than ACEI		
Clinical uses	They may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease.		
A.D.R & Contra -indications	• As ACEI except dry cough & angioneurotic edema. • Same contraindications as ACEI .		

Calcium channel blockers

Class	Dihydropyridine	Phenylalkylamine	Benzothiazepine
Drugs	Nifedipine	Verapamil	Diltiazem
Features	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
Pharmaco -kinetics	• given orally (onset= 0.5-2h) and I.V. injection (for emergency) (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. (it is preparation that allows slow release of drug).		
Mechanism of action	Block the influx of calcium through calcium channels resulting in: 1- Peripheral vasodilatation. 2- Decrease cardiac contractility.		
Clinical uses	• Treatment of chronic hypertension. especially for Nifedipine • Nicardipine 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. CCBs are used along with diuretics (1st line) in black patients		
A.D.R	Tachycardia	- peripheral edema (ankle edema) - constipation	- peripheral edema We can use combination of Thiazides & Diltiazem for ankle edema
	Headache , Flushing , Hypotension (due to vasodilation)		

Vasodilator

Classified into arterial, venous or mixed vasodilators

Drugs	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Site of action	Arteriodilator			Arterio & venodilator
Mechanism of action	Direct Opening of potassium channels.	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate (Active form)	Opening of potassium channels.	Release of nitric oxide (NO)
Administration	Oral		Rapid I.V	I.V infusion
Uses	Moderate-severe hypertension.		Hypertensive emergency.	
Uses In combination with a diuretic & first-line. β-blockers:	Hypertensive pregnant woman But not the first-line.	Correction of baldness, since it causes Hypertrichosis (the growth of body hair).	Treat hypoglycemia due to Insulinoma Tumor of the pancreas that increase the secretion of insulin	Severe heart failure.
Adverse effects	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema).			Severe hypotension
Specific adverse effects	Lupus erythematosus like syndrome	Hypertrichosis excess hair growth thus contraindicated in females	Inhibit insulin release from β cells of the pancreas causing hyperglycemia. contraindicated in diabetics	-Methemoglobin during Infusion - Cyanide toxicity - Thiocyanate toxicity - Headache, palpitations which disappear when infusion is stopped. - Cyanide accumulation cause cyanide poisoning (metabolic acidosis, arrhythmias, severe hypotension and death)

- The ADRs are due to activation of the sympathetic system & the RAAS after vasodilators-induced fall in BP.
- Sodium nitroprusside ADR mechanism: enters RBCs and steals an electron from Hb, resulting in Methemoglobin (Fe +3), the reduced drug then becomes unstable and disintegrates into cyanide, which is metabolized into thiocyanate.

β- ADRENOCEPTOR BLOCKERS

Type	non selective	selective beta 1 blocker
Drugs	propranolol	atenolol , metoprolol
Mechanism of action	• decrease cardiac output • inhibit renin release (inhibit vasoconstriction) • Centrally acting by inhibition of NE release from adrenergic nerves	
Clinical uses	• used in mild to moderate hypertension In severe cases used in combination with other drugs • therapeutic response may take up to two weeks • evidence support their use in patient with coronary heart disease • should be withdrawn gradually	
Adverse effects	• Aggravate peripheral arterial disease • hypoglycemia • increase triglycerides • erectile dysfunction (could be due to vasoconstriction)	bradycardia,hypotension
	• mask hypoglycemia symptoms in diabetics • Fatigue	

** clinically, evidence shows that both selective and non selective beta blockers cause the same adverse effects (theoretically they have different adverse effects)

α- ADRENOCEPTOR BLOCKERS

Drugs	prazosin	doxazosin
P.K	short acting.	prefered for its long half life
Mechanism of action	-blocks alpha 1 receptors in arterioles and venules - reducing blood pressure by decreasing preload and afterload (this happens due to dilation of venules which decreases pressure of the veins, hence decreasing venous return (decrease preload). Afterload decreases due to dilation of arterioles which decreases their resistance)	
Clinical use	treatment of hypertension in patients with benign prostatic hypertrophy	
ADRs	causes first dose hypotension (given in gradual dose),and postural hypotension	-

centrally acting sympatholytic drugs

drugs	Clonidine (Direct α2-agonist)	α-methyldopa (Indirect α2 agonist, converted to methyl norepinephrine)
Mechanism of action	Diminish central adrenergic outflow from the CNS & increase parasympathetic outflow to the heart. This leads to reduced total peripheral resistance and decrease BP.	
Uses	• hypertension with renal disease (it does not decrease renal outflow or glomerular filtration) • Resistance hypertension.	• **α -Methyldopa is the first line treatment of hypertension in pregnancy**
Adverse effects	**Sudden withdrawal of clonidine can lead to rebound hypertension.**	-

The using of combination to treat hypertension

Roles to use combination

- Decrease the dose of each drug to reduce the ADRs
- Select a drug that ↓ the ADR of another, e.g. thiazides versus ACEI
- Select a drugs that act by different mechanisms

Examples:

★ **Once vasodilators are administered, fall in BP produced will activate the sympathetic system & the RAAS ,So we give B blockers and Diuretics or ACEI**

★ **thiazides and diltiazem can be used for ankle edema.**

Compelling Indications of Antihypertensive Drugs

	HF	Pregnancy	Diabetes	CKD	IHD	Black patient	Resistant HT
Diuretics	+	–	–	furosemide	–	+	–
ACEI/ARB	+	–	+	+	+	–	–
CCB	–	–	–	–	–	+	–
B-blockers	selective	–	cautiously	–	+	–	–
Hydralazine	acute +	+	–	–	–	–	–
Clonidine	–	–	–	–	–	–	+

HF: Heart failure.

CKD: Chronic kidney disease.

IHD: Ischemic heart disease.

HT: Hypertension.

ACEI: angiotensin converting enzyme inhibitor.

ARB: angiotensin receptor blockers.

CCP: Cyclic citrullinated peptide.

Clinical Case

- Osman a 51-year-old man (95Kg weight, 176cm tall) is referred for further evaluation of his BP. He is a computer engineer and has a past history of type 2 diabetes for 5 years and high BP for 12 years. His somatic complaints include fatigue and dry mouth. He has no known history of hypertension target-organ damage, and his medications are listed in the accompanying table . He has no remarkable family history other than hypertension in both parents.

His examination was otherwise unremarkable (including normal heart sounds and no peripheral edema), aside from mild arteriolar narrowing in the fundus. His seated BP was 156/90 mmHg and 158/90 mmHg in the right arm (similar to the left arm), with a regular heart rate of 70 beats/min. His BP did not change on standing. His urinalysis showed an unremarkable dipstick evaluation. The patient was suspected as having drug- resistant hypertension.

Name	Dose
Hydrochlorothiazide	25mg
Valsartan	160mg
Diltiazem, long-acting	300mg
Clonidine	0.2mg
Metoprolol, long acting	100mg
Simvastatin	40mg
Fenofibrate	145mg
Metformin	1g

Questions and answers

- **List as many reasons as you can, why Osman failed to respond to antihypertensive therapy?**

1- abnormalities in hormones e.g aldosterone
2- smoking
3-obesity
4- pheochromocytoma
5-Drug induced e.g NSAIDs

- **The seated BP of Osman was 156/90, what are the target BP values for treatment of hypertensive patients?**

= < 130/80 mm Hg

- **What stage of hypertension is Osman?**

Stage 1 hypertension

CLASSIFICATION	SYSTOLIC BLOOD PRESSURE (SBP)		DIASTOLIC BLOOD PRESSURE (DBP)
LOW**	<90	or	<60
NORMAL	<120	and	<80
PREHYPERTENSION	120 – 139	or	80 – 89
HIGH: STAGE 1 HYPERTENSION	140 – 159	or	90 – 99
HIGH: STAGE 2 HYPERTENSION	≥160	or	≥100

- **Osman has no history of hypertension- target organ damage. Which organs are usually affected adversely by persistent high BP?**

-Kidney
-Brain
-Heart

- **Osman was prescribed hydrochlorothiazide & valsartan. What is the rationale for combining hydrochlorothiazide and valsartan?**

Hydrochlorothiazide induce the loss of K , which oppose the Hyperkalemia caused by valsartan

- **Osman was prescribed hydrochlorothiazide & diltiazem. What is the benefit of combining hydrochlorothiazide and diltiazem?**

Reduce peripheral edema

- **The BP of Osman did not change on standing. What is your conclusion?**

the drugs has no postural hypertension effect.

- **The BP of Osman was almost the same in both arms. What does that imply?**

No vascular disease.

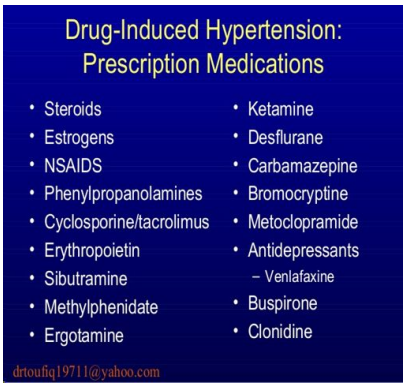
- **Is the concomitant prescribing of clonidine, diltiazem and metoprolol to Osman wise?**

No, because this will lead to severe hypotension (all of them depress myocardium)

- **Could the failure of control of Osman's BP be due to secondary drug – induced effects?**

Yes

- **Which drugs elevate blood pressure?**



- Could the "white coat phenomenon" be the cause for Osman's high blood pressure readings?

No. Pulse rate is normal.

QUIZ

MCQ

Q1 :A 45-year-old man was just started on therapy hypertension and developed a persistent dry cough. Which is most likely responsible for this side effect?

A- Enalapril. B-Losartan. C-Prazosin.

Q2:A 60-year-old white female has not reached her blood pressure goal after 1 month of treatment with a low dose of captopril. All of the following would be appropriate next steps in the treatment of her hypertension except:

A- Increase dose of captopril. B-Clonidine. C-Add on an ARB medication.

Q3 : 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-diuretic medication. C-Losartan

Q4 : A 58-year-old female reports that she recently stopped taking her blood pressure medications because of swelling in her feet that began shortly after she started treatment. Which is most likely to cause peripheral edema?

A-Atenolol. B-verapamil. C-Hydralazine

Q5 : Which is an appropriate choice for hypertension treatment during pregnancy?

A-Hydralazine. B-Valsartan. C-Fosinopril.

MCQ Answers :

- **Q1 : A ,** because of bradykinin accumulation .
- **Q2: C ,** ARBs and ACE inhibitors almost have the same Adverse effects .
- **Q3: C ,** ARB's cause hyperkalemia
- **Q4: B ,** less heart contractility ➔ Edema
- **Q5: A ,** ACE and ARB can cause agenesis and renal failure in the fetus (Oligohydramnios)

pharmacology

Team 438

GOOD LUCK

Team Leaders:

May Babaeer

Zyad Aldosari

Team Members:

Abdullah Alassaf

Bader Aldhafeeri

Abdulaziz Alghamdi

Mohsen Almutairi

Hashim Alhalaby

Editors and Theoretical Aspects:
Nayef Alsaber & Hameed M. Humaid

Share with us your ideas !