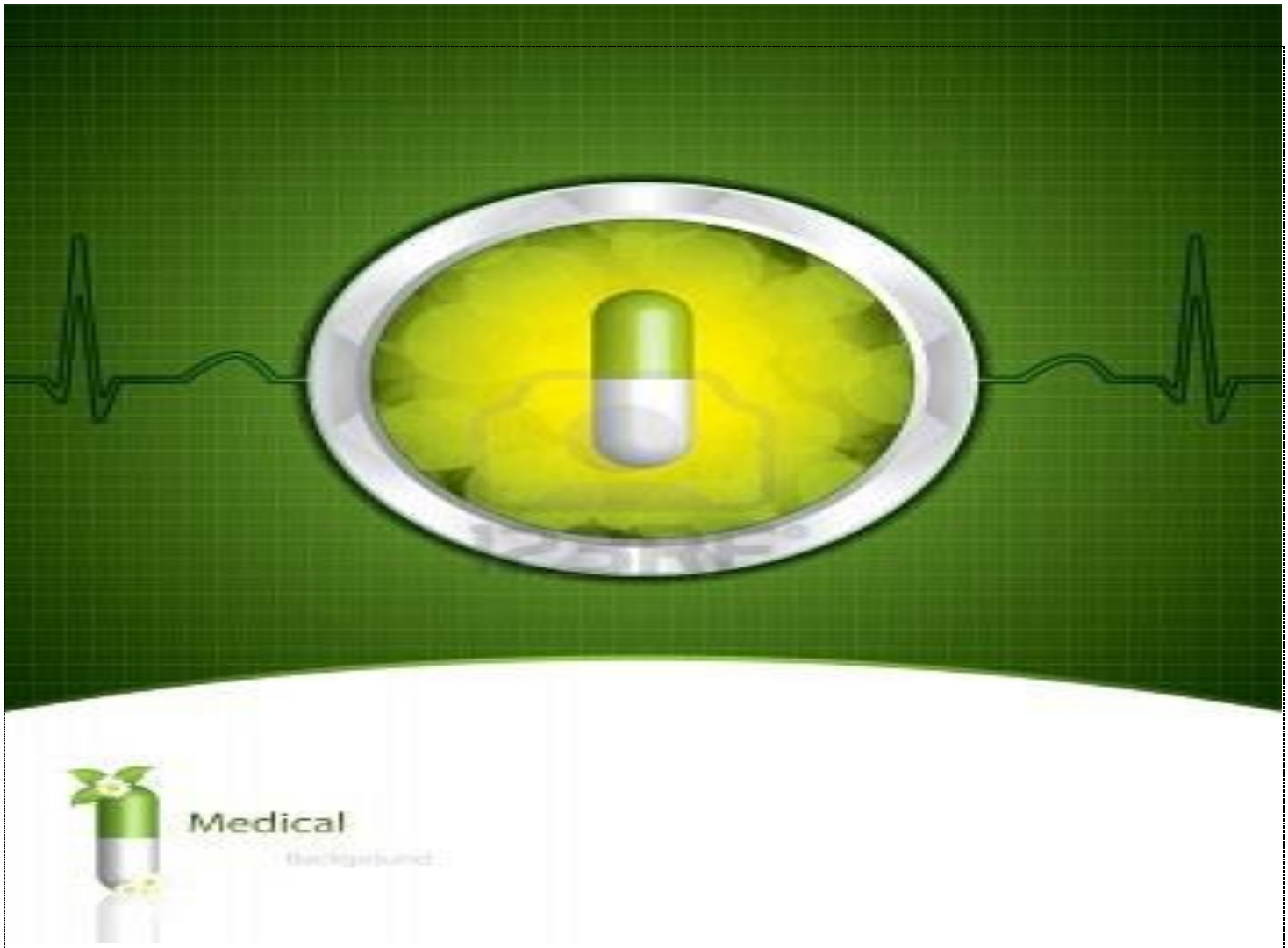

Pharmacology team

Treatment of hypertension

Contents:

*Explanation

*Questions

دعوة بظهر الغيب تكفي عن جزيل كلمات الشكر

► Hypertension is the most common cardiovascular disease (any age or gender)

► Cause damage to blood vessels in kidney, heart & brain

► increase incidence of renal failure, coronary disease, stroke and heart failure

Blood pressure is determined by :

- **Blood volume**
- **Cardiac output (rate & contractility)**
- **Peripheral resistance**

Patients with primary (essential) hypertension (unknown cause) are generally treated with drugs that :

- **Reduce blood volume**
- **Reduce systemic vascular resistance**
- **Reduce cardiac output**

Patients with secondary hypertension (known cause) so we treat the causes and underlying diseases + what we treat primary hypertension

Classification of Antihypertensive drugs:

I- Diuretics

II- Drugs acting on the renin-angiotensin- aldosterone system

III- Calcium channel blockers

IV- Vasodilators

V- Drugs acting on sympathetic system

Diuretics	Mechanism	When?
Furosemide Hydrochlorothiazide	Na & H2O ↓ Blood volume↓ CO ↓ BP ↓	Monotherapy used in Mild → moderate hypertension

Angiotensin ll work on AT_1 receptors causing vasoconstriction, and work on adrenal cortex causing Aldosterone release that will cause Na and water retention.

Bradykinin: causes vasodilatation

ACEIs (non-selective)	Mechanism	Pharmacokinetics
Captoprill Enalaprill Ramiprill (Rami's cap enalap- انقلب) Cap = قبعة	1.Blocks AgII synthesis by blocking ACE enzyme that converts AgI to AgII Causing: a.vasodilatation. b.Inhibition of aldosterone release from adrenal cortex (so Na, H2O retention↓) 2.Inactivation of bradykinin degredation ↑ vasodialation Both mechanisms cause: ↓TPR → ↓BP	*Taken orally *Food ↓ bioavailability *Enalapril & Ramipril are prodrugs, converted to active metabolite in liver **have long $t_{½}$** *given once daily *Enalaprilat (active metabolite of Enalapril) for Emergency [I.V] .

(Renovascular hypertension) : ACE inhibitors are particularly effective when hypertension results from excessive renin production. Which means if the kidney produces excess renin it will convert Angiotesinogen to AgI more. And the ACE will be active to convert it to AgII. Then ACEI can block ACE better

Therapeutic uses:

essential (primary) hypertension in patients with:

- Chronic Renal Disease, Ischemic Heart disease, Diabetese

Heart failure.

S/E of (ACEIs):

1. Acute renal failure, especially in patients with renal artery stenosis (it depends on AgII for renal perfusion)
2. **Hyperkalemia** in Renal insufficiency & diabetic patients. (important S/E for drug interaction)
3. If the patient is already hypovolumetric and ACEIs will cause Na & water excretion "Aldosterone contributed" so this will lead to sever hypotension!.

Special Adverse effect:

ACEIs will inhibit kininase ll which is responsible for converting bradykinins into **inactive peptides**, so **bradykinins accumulation** will occur, so that will lead to:

1-**Angioneurotic Edema** (nose, throat, tongue and larynx swelling).

2-**Dry cough with Wheezing** (accumulation in bronchial mucosa).

Captoprill Adverse Effect: (very imp)

Captoprill contains **sulfhydryl group** (SH group) and this will cause:
Skin rash, fever, dysgeusia (reversible loss or altered taste), protienuria (excess of serum proteins in the urine) and neutropenia (low serum neutrophils.)

ACEIs Contraindicated in:

- **Pregnancy** ⟶ will hurt the fetus causing hypotension, renal failure, anuria and malformation. (most dangerous in 2nd and 3rd trimester)
- Patients with **Renal Artery Stenosis** ⟶ lead to Acute Renal Failure

ACEIs Drugs Interaction with:

- **Potassium-Sparing diuretics** because they're drugs that prevent K^+ exertion, so with Hyperkalemia that ACEIs are causing ⟶ these two drugs will lead to Sever Hyperkalemia!.
- **NSAIDs block bradykinins vasodilatation**, so this will impair ACEIs hypotensive effect. (in other words lower ACEIs efficacy)

Angiotensin Receptors Blockers (ARBs selective)

	Mechanism	S/E
Losartan **Valsartan** **Irbesartan** **Value your skin!** **Loser tan بسرطان قد يتسبب** **So use sun block!** **(Ag receptor blockers)**	***Selective, block AT_1 receptors** ***No effect on bradykinins** **(no accumulation, no dry cough and angioneurotic edema)** ***Complete inhibition of Angiotensin. (blocking all AgII selective receptors). ACEI inhibit ACE enzyme -> blocks most (not all) of AgII synthesis because there're other enzymes that synthesize AgII, too.**	**As ACEIs except cough and angioedema.** **Same contraindications as ACEIs.**

Pharmacokinetics:

Losartan	Valsartan
Taken orally **Has a potent active metabolite** **Long $t_{½}$ so once daily** **No BBB crossing**	**No active metabolites → shorter $t_{½}$**

Finally both of them have same clinical uses as ACEIs.

3- CALCIUM CHANNEL BLOCKERS

Drugs	Verapamil	Dihydropyridine group (Nifedipine, amlodipine, nicardipine)	Diltiazem
Features	Act more on the **myocardium** and used as **antiarrhythmic drug**	Act mainly on **smooth muscle** and used as **vasodilators**	It has intermediate effect

<table>
<tr><th>Drugs</th><th>Verapamil</th><th>Nifedipine</th><th>Diltiazem</th></tr>
<tr><td>Actions</td><td colspan="3">❑ Block the influx of calcium through calcium channels resulting in:
1- Peripheral vasodilatation
2- Decrease cardiac contractility
Both effects lower blood pressure</td></tr>
<tr><td rowspan="4">Pharmacokinetics</td><td colspan="3">❑ given orally and intravenous injection
❑ well absorbed from G.I.T
❑ onset of action → within 1-3 min --- after i.v.
(30 min – 2 h) → after oral dose
❑ sustained-release preparations can permit once-daily dosing</td></tr>
<tr><td colspan="2">are highly bound to plasma proteins (more than 90%)</td><td>less (70-80%)</td></tr>
<tr><td>has active metabolites.</td><td>Doesn’t have active metabolites.</td><td>has active metabolites.</td></tr>
<tr><td></td></tr>
<tr><td>Therapeutic uses</td><td colspan="3">Treatment of chronic hypertension with oral preparation •
Nicardipine can be given by I.V. route & used in hypertensive emergency •</td></tr>
<tr><td rowspan="5">ADVERSE EFFECTS</td><td>Headache , Flushing , Hypotension</td><td>Headache, Flushing, Hypotension</td><td>Headache , Flushing, Hypotension</td></tr>
<tr><td colspan="3">Peripheral edema (ankle edema)</td></tr>
<tr><td>Cardiac depression, A-V block , bradycardia</td><td>Tachycardia</td><td>Cardiac depression , A-V block , bradycardia</td></tr>
<tr><td>Constipation</td><td>----------</td><td>----------</td></tr>
<tr><td></td></tr>
</table>

4- VASODILITORS

Drugs	Hdralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Site of action	Arteriodilator	Arteriodilator	Arteriodilator	Arterio & venodilator
Mechanism of action	Direct	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate (active metabolite)	Opening of potassium channels	Release of nitric oxide (NO)
Route of admin.	Oral		Rapid intravenous	Intravenous infusion
Therapeutic uses	1.Moderate - severe hypertension	1.Moderate - severe hypertension.	1.Hypertensive emergency	1.Hypertensive emergency
	In combination with diuretic & β-blockers			
	2.Hypertensive pregnant woman	2. baldness	2.Treatment of hypoglycemia due to insulinoma	2.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 Contraindicated in females	-Inhibit insulin release from β cells of the pancreas causing hyperglycemia. Contraindicated in diabetics	1.Methemoglobin during infusion 2. Cyanide toxicity 3. Thiocyanate toxicity 4- Nausea, vomiting, headache, palpitations which disappear when infusion is stopped

5- Drugs acting on sympathetic system

	B-Adrenoceptor – Blocking Agents	α-ADRENOCEPTOR BLOCKERS	Centrally Acting Adrenergic Drugs	CENTRALLY ACTING SYMPATHOLYTIC DRUGS
Drugs	**Propranolol, atenolol**	**prazosin**	**METHYLDOPA**	**CLONIDINE**
Uses	-B adrenoceptrs are used in mild to moderate hypertension. - In severe cases used in combination with other drugs. -May take two weeks for optimal therapeutic response.		❑ Safely used in hypertensive pregnant women	
Effect	They lower blood pressure by : - decreasing cardiac output. - inhibiting the release of renin.	block α- receptors in arterioles and venules - reduce blood pressure by decreasing both afterload & preload	❑ reduce sympathetic outflow from vasopressor center in brain stem (stimulating central α-2 receptors presynaptically) ❑ reduce peripheral resistance with little change in heart rate or cardiac output	❑ similar to methyldopa, it acts to reduce sympathetic outflow from vasopressor centre in brain stem ❑ lowers blood pressure by reducing cardiac output (due to decreased heart rate and relaxation of capacitance vessels with a reduction in peripheral resistance)
ADVERSE EFFECTS			1- sedation, tremors 2- nightmares, mental depression (CNS effect) 3- lactation due to increase in prolactin secretion	1- dry mouth 2- sedation 3- mental depression

PRECAUTIONS of CLONIDINE

- Tricyclic antidepressants may block the antihypertensive effect of clonidine .
- Sudden withdrawal may cause hypertensive crisis due to increased sympathetic activity.
- Stop gradually with initiation of other antihypertensive therapy.
- Management of the hypertensive crisis give clonidine i.m. or α- & β- beta-blockers.

MCQ

-1-Which one of the following drugs can use to treat a hypertensive patient in the ER?

A- Minoxidil.

b- Hdralazine.

c- Sodium nitroprusside

-2- The most common side effect of **Minoxidil** is..:

A- Hypertrichosis.

B- mental depression.

C- Cyanide toxicity.

-3- a pregnant women came to the hospital, and she also has hypertension, the best drug to treat her is:

A- METHYLDOPA

B- CLONIDINE.

C- MINOXIDIL

-4- A 66-year-old man present to your office with a 5-month history of dry cough. He denies any other symptoms. His past medical history includes a recent myocardial infarction(MI), after which he was placed on several medications. He does not smoke, nor has he had a history of asthma. You decide that a medication side effect is the most likely cause of this patient's symptoms. Which medication might this be?

A- Ramipril

B-Nitroglycerin

C-Lovastatin

D-Digoxin

E-Quinidine

-5- Since the side effect of the medication you prescribed preclude the patient in the above scenario from taking it, you switch him to therapy with an agent that is said to produce similar mortality benefits, while working via slightly different mechanism of action. What agent is it?

A-Furosemide

B- Captopril

C-Losartan

D- Esmolol

E-Ezetimibe

-6- A 47-year-old women is admitted for treatment of acute . Her prior medication include digoxin for atrial fibrillation She also suffers from hypertension, for which she is currently not taking anything. Before you discharge her home, you decide to add a medication that works well for hypertension. While she is still on floor she develops a dangerous arrhythmia, which you are fortunately able to treat promptly .Which medication you added likely increased the effects of digoxin that this patient was already taking?

A-Valstran

B-Hydrochlorothiazide

C-Hydralazine

D-Tadalafil

E-Lovastatin

Answers:

1-C , 2-A, 3-A, 4-A, 5-C, 6-B