432

Pharmacology Team

Drugs used for Treatment of Hypertension

Red	**Important**
Purple	Extra Notes
Orange	To differentiate
Black	From the slides
Blue	similar

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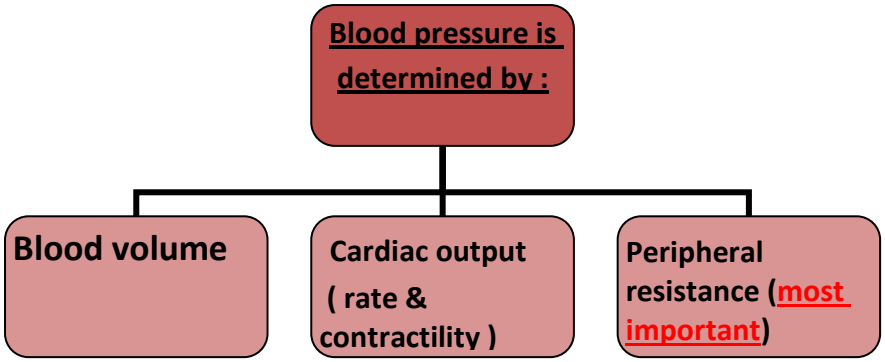
OBJECTIVES

- At the end of lectures , the students should :
- Identify factors that control blood pressure
- Identify the pharmacologic classes of drugs used in treatment of hypertension
- Know examples of each class.
- Describe the mechanism of action , therapeutic uses & common adverse effects of each class of drugs including :
- **Adrenoceptor blocking drugs** (β & α **blocking drugs)**
- **Diuretics**
- **Calcium channel blocking drugs**
- **Vasodilators**
- **Converting enzyme inhibitors**
- **Angiotensin receptor blockers.**
- **Describe the advantages of ARBs over ACEI**

Introductio

- ► 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



- **Major risk factor for** (RMCH رمش:p)

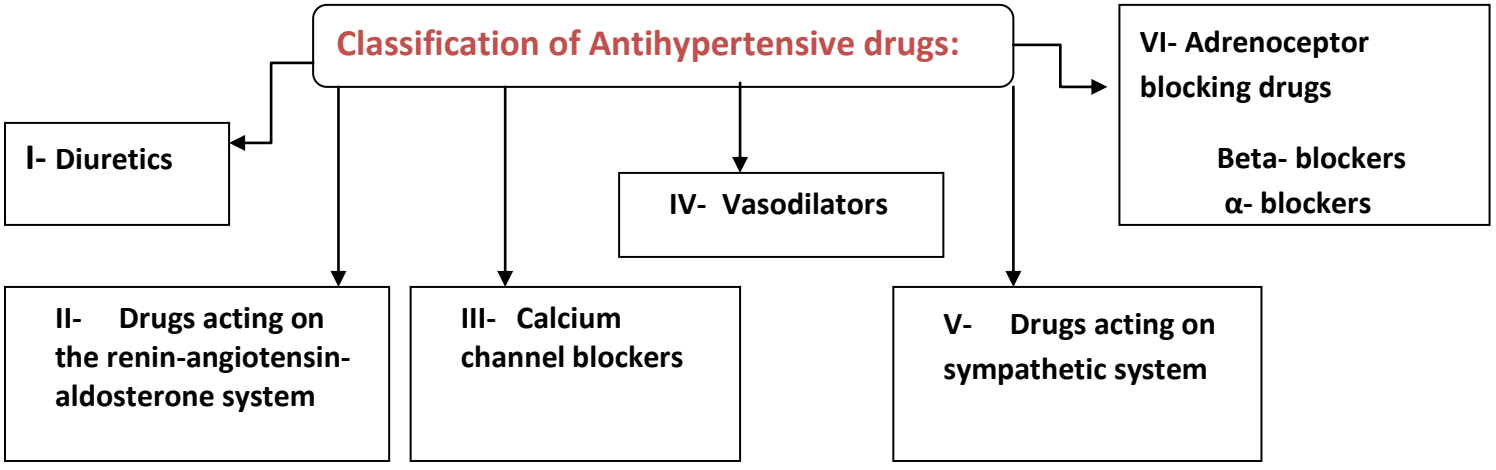
❖ **Renal insufficiency**
❖ **Myocardial Infarction**
❖ **Cerebrovascular disease**
❖ **Heart failure**

Asymptomatic until organ damages reaches a critical point.

- **Non- pharmacological treatment : lifestyle changes , such as**
  Weight reduction, Smoking cessation,
  Reduction of :
  salt, saturated fat and alcohol intake
  and Increased exercise

Indications for Drug Therapy

❖ **Sustained blood pressure elevations > 140/ 90 mmHg.**
❖ **Elevated blood pressure is associated with other cardiovascular risk factors (smoking, diabetes, obesity, hyperlipidemia, genetic predisposition).**
❖ **End organs are affected by hypertension (heart, kidney , brain).**



I- Diuretics

Diuretics	Mechanism	When?
A- Thiazide group (hydrochlorothiazide)	Na & H2O ↓ Blood volume↓ CO ↓ BP ↓ SVR ↓	Monotherapy used in Mild → moderate hypertensio n
B- Indapamide		
C- *Potassium-sparing diuretics* (*Amiloride*, *spironolactone*) **(aldosterone antagonist)**	reduce potassium loss in the urine. ***Spironolactone*** has the additional benefit of diminishing the remodeling that occurs in blood vessels & in heart failure.	

Best drug for HTN is the drug that eliminate more sodium than water from the body

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

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

Angiotensin-converting enzyme inhibitors (ACEI)

Captopril

Enalapril

Lisonopril

BLOCKERS OF AT_1 RECEPTOR

Losartan

Valsartan

irbesartan

ACEIs (non-selective)	Mechanism	Pharmacokinetics	Uses	S/E	Contraindication
Captopril ***Enalapril*** ***Ramipril***	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 ↑ vasodialatin Both mechanisms cause: ↓TPR → ↓BP	*Taken orally *Food ↓ bioavailability (better to be taken on empty stomach) *Enalapril & Ramipril are prodrugs, converted to active metabolite in liver **have long t½** *given once daily *Enalaprilat (active metabolite of Enalapril) for Emergency [I.V] . **Captopril is not a prodrug** **Has a short half-life & given twice /day** (السيد كابتو من عائلة بريل يرفض انه يكون prodrug وبسبب عنادة فترة حياته قصيره) **All ACEI are distributed to all tissues except CNS.**	**hypertension** **HF** **Diabetic nephropathy** **(next page)	1. Acute renal failure, especially in patients with renal artery stenosis (it depends on AgII for renal perfusion) 2. **Hyperkalemia**. (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!.	**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** **Contraindications to ACE inhibitor are, 'PARK' - Pregnancy, ~~h/o Allergy (angioedema),~~ Renal artery stenosis -- hyperKalemia.** **Drugs Interaction** **-Potassium-Sparing diuretics** **- NSAIDs**
effects of ACEIs:	***Dilatation of arteriol ⍰ reduction of peripheral vascular resistance(afterload) *Increase of Na+ and decrease of K+ excretion in kidney * reduction of sympathetic activity *Inhibition of aldosterone secretion *Reduce the arteriolar and left ventricular remodelling that are believed to be important in the pathogenesis of human essential hypertension and post-infarction state**				

-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**

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.)

:D(السيد كابتو العنيد له مشاكل زيادة عن اصحابة لدرجة انه ممكن يسبب فقد لحاسة التذوق وغيرها)

Taste loss due to SH group

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)

**due to the effect of vasodilatation, these drugs improve renal outflow ==< improve renal function ==<So, proteinuria will be reduced (which is one of the manifestation of Diabetic nephropathy)

Angiotensin Receptors Blockers (ARBs selective)

ARBs	Mechanism	S/E
Losartan Valsartan Irbesartan	*Selective, block AT_1 receptors *No effect on bradykinins (no dry cough and angioneurotic edema => we can use it in ASTHMA most of the effects of angiotensin II including vasoconstriction and aldosterone release - are mediated by the AT1 receptor *Competitively 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.

**

Nowaday, most ARBs are combined with Diuretics like Valsartan (DiovanR + hydrochrothiazide. (80/12.5 or 160/12.5)

to Increase activity and compliance

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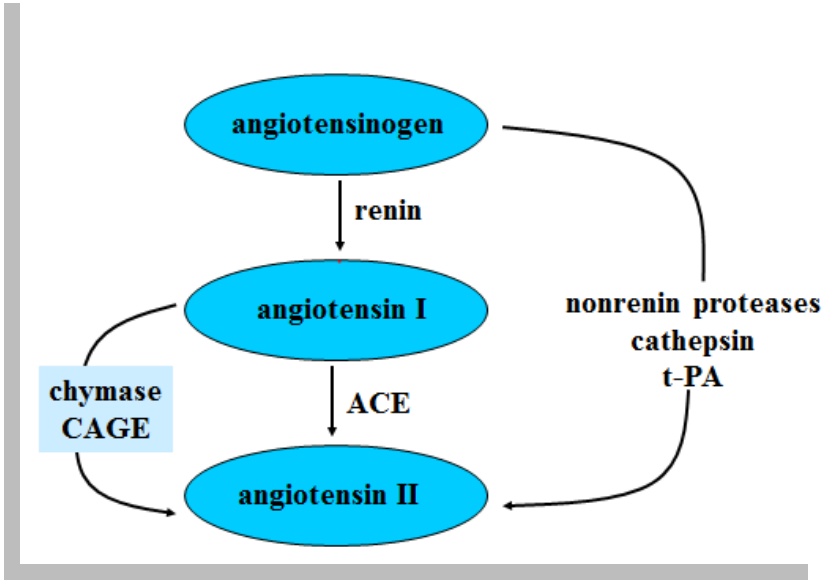

III - CALCIUM CHANNEL BLOCKERS

<table>
<tr><th>Drugs</th><th>Verapamil</th><th>Dihydropyridine group (Nifedipine, amlodipine, nicardipine)</th><th>Diltiazem</th></tr>
<tr><td>Features</td><td>more effective as cardiac depressant

used in arrhythmia (eg. supraventricular tachycardia)</td><td>more selective as vasodilator(mainly arteriolar) than a cardiac depressant
Used for treatment of hypertension</td><td>Used mainly for angina and Peripheral vascular disease</td></tr>
<tr><td>Actions</td><td colspan="3">Block the influx of calcium through L-type calcium channels resulting in:
Peripheral vasodilatation
Decrease cardiac contractility & heart rate
Both effects lower blood pressure</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">❑ given orally(90%) 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></td><td colspan="2">are highly bound to plasma proteins (more than 90%)</td><td>less (70-80%)</td></tr>
<tr><td></td><td>has active metabolites.</td><td>Doesn't have active metabolites.</td><td>has active metabolites.</td></tr>
<tr><td>Therapeutic uses</td><td colspan="3">-Treatment of chronic hypertension with oral preparation (Nifedipine and Amlodipine)
Nicardipine can be given by I.V. route & used in hypertensive emergency</td></tr>
<tr><td>ADVERSE EFFECTS</td><td colspan="3">- Headache , Flushing , Hypotension
- Peripheral edema (ankle edema) (due to ↑ aldosterone which is due to ↑ renin)</td></tr>
<tr><td></td><td>Cardiac depression, A-Vblock , bradycardia</td><td>Tachycardia (due to vasodilatation>↓CO>activate baroreceptor >release NE >↑HR , ↑contractility , ↑ renin</td><td>Cardiac depression, A-Vblock , bradycardia</td></tr>
<tr><td></td><td>Constipation!!</td><td></td><td></td></tr>
</table>

Due to AV block → never administer it with B-blocker

IV -VASODILITORS

Drugs	Hdralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Site of action	Arteriodilator			Arterio & venodilator
Mechanism of action	Direct smooth muscle relaxant	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate (active metabolite) (best Arteriodilator)	Opening of potassium channels So, it cause relaxation	Release of nitric oxide (NO)
Route of admin.	Oral		Rapid intravenous *it's highly bound vascular tissue so we cannot give it slowly	Intravenous infusion
Therapeutic uses	1.Moderate - severe hypertension CHF	1. Resitance – severe hypertension	1.Hypertensive emergency (in the past)	1.Hypertensive emergency
	In combination with diuretic & β-blockers			
	2.Hypertensive pregnant woman	2. baldness (treatment of alopecia)	2.Treatment of hypoglycemia due to insulinoma (tumor of pancreas, release excessive amount of insulin)	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 (Lengthen and elongation of fine hair) 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

V- Drugs acting on sympathetic system

	B-Adrenoceptor – Blocking Agents	α-ADRENOCEPTOR BLOCKERS	Centrally Acting Adrenergic Drugs	CENTRALLY ACTING SYMPATHOLYTIC DRUGS
Drugs	**Propranolol, atenolol**	**Prazosin(short t1l2) , terazocin (long t1l2)**	**METHYLDOPA**	**CLONIDINE**
Uses	**-B adrenoceptrs are used in mild to moderate hypertension.** **- In severe cases used in combination with other drugs.** Nadolol (non cardio selective) with long Half live Bisoprolol, Atenolol, metoprolol (cardioselective) Labetalol , carvidalol (α – and β blockers)	**1- Hypertension of pheochromocytoma** **2- heart failure** **3- perepheral vascular disease**	**❑ Safely used in hypertensive pregnant women**	In HTN
Effect	**They lower blood pressure by :** **- decreasing cardiac output.** **- inhibiting the release of renin. (more important)** **Has some diuretic actions**	**-Their action is mainly vasodilatation** **Prazocin elevate HDL levels (very important)**	**α 2 agonist (acts as a False Neurotrasmitter)** **Centrally diminish the sympathetic outflow .** **Resulting in reduction in peripheral resistance, and ↓ blood pressure**	**α2-agonist (works as a Direct a2 agonist) Thus:** **↓sympathetic out-flow** **To the Heart→ decreasing cardiac output** **to the Blood vessels → vasodilation & reduced systemic vascular resistance.** **decreases BP**
ADVERSE EFFECTS	----------		**Depression** **Dry mouth, nasal mucosa** **Bradycardia** **Impotence** **Fluid retention & edema with chronic use**	

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 :

- **Labetalol**
- **Hydralazine** (in pregnancy)

- **Sodium nitroprusside** (2nd line)

❑ General characters

- **Fast & short acting (gradually decrease BP)**
- **Given by IV**

** hypertensive crisis => (160 over 110) or more

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

-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

7- Which of the following drug cause constipation ?

A- Verapamil
B- Valsartan
C- Losartan
D- Esmolol

8- Which of the following increase HLD levels in the body ?

A- Perazocin
B- Terazocin
C- Verapamil
D- Losartan

9- which of the following drugs cause cyanide toxicity ?

A- Diazoxide
B- Sodium nitroprusside
C- Hdralazine
D- Minoxidil

10- Which of the following drugs is treatment for hypertension and alopecia ?

A- Diazoxide
B- Sodium nitroprusside
C- Hdralazine
D- Minoxidil

11-Which of the following drugs convert to active metabolite?

A- Enalapril
B- Captoprill
c- Hdralazine

Answers:

1	***C***
2	*A*
3	*A*
4	*A*
5	*C*
6	*B*
7	*A*
8	*A*
9	*B*
10	*D*
11	*A*