Treatment of Hypertension

Pharmacology Team 430

Done By:

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Overview & Physiology

Hypertension:

- Hypertension is the most common cardiovascular disease (24% in USA)
- Cause damage to blood vessels in kidney, heart & brain
- Increase incidence of renal failure, coronary disease, stroke and heart failure.

MECHANISMS FOR CONTROLLING BLOOD PRESSURE

Cardiac output and peripheral resistance are controlled mainly by two overlapping control mechanisms: the baroreflexes, which are mediated by the sympathetic nervous system, and the renin-angiotensin-aldosterone system. The 2 mechanisms in detail:

I

A. Baroreceptors and the sympathetic nervous system

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Fall in blood pressure

↓

pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) send fewer impulses to cardiovascular centers in the spinal cord.

↓

This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature,

↓

vasoconstriction and increased cardiac output.

↓

Increased blood pressure

B. Renin-angiotensin-aldosterone system

↓

Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β-adrenoceptors) by releasing renin

↓

converts angiotensinogen to angiotensin I, which is then converted to angiotensin II (Potent Vasoconstrictor)

↓

some of angiotensin II vasconstricts the vessels and the rest travels to the adrenal cortex to increase thesecretion of aldestrone

↓

This increased secretion leads to salt & water retention

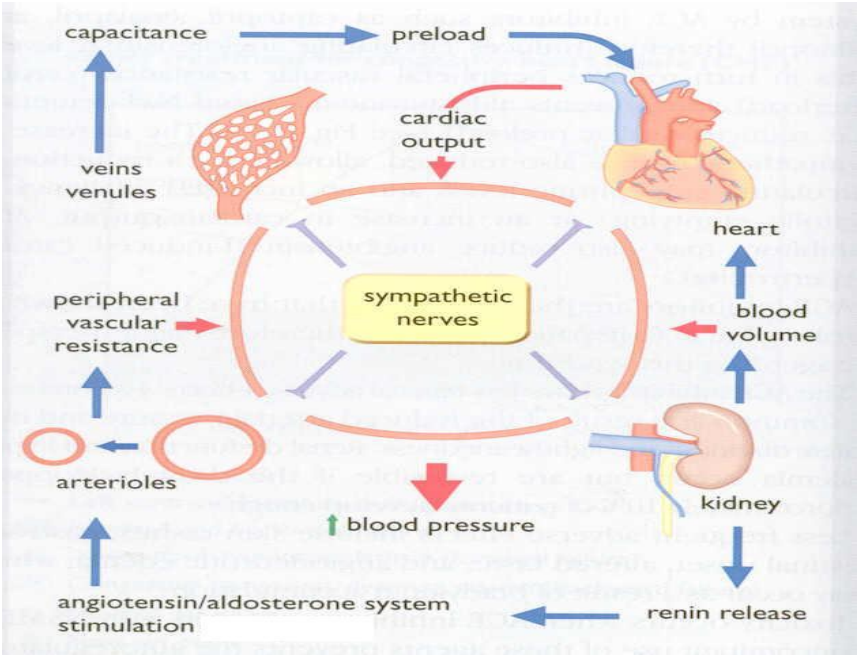
↓

Increase of blood volume

↓

Increase of blood pressure

Summary of the physiology:



Blood pressure is determined by:

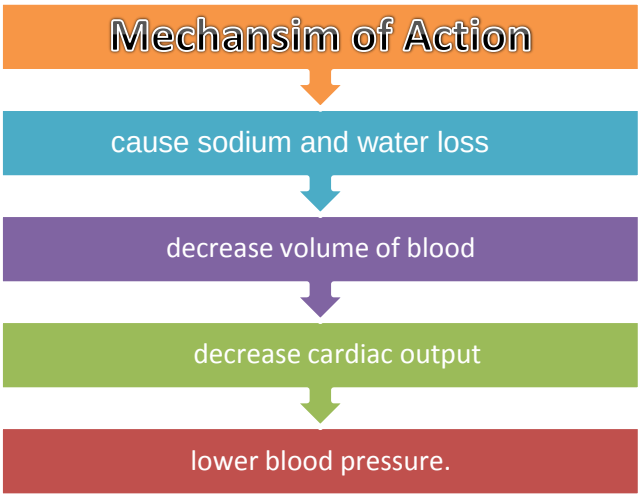
1- **Blood volume**
2- **Cardiac output (rate & contractility)**
3- **Peripheral resistance**

Classification of antihypertensive

1-Diuretics

- **hydrochlorothiazide**
- **furosemide**

Uses: diuretics may be adequate in mild to moderate hypertension.

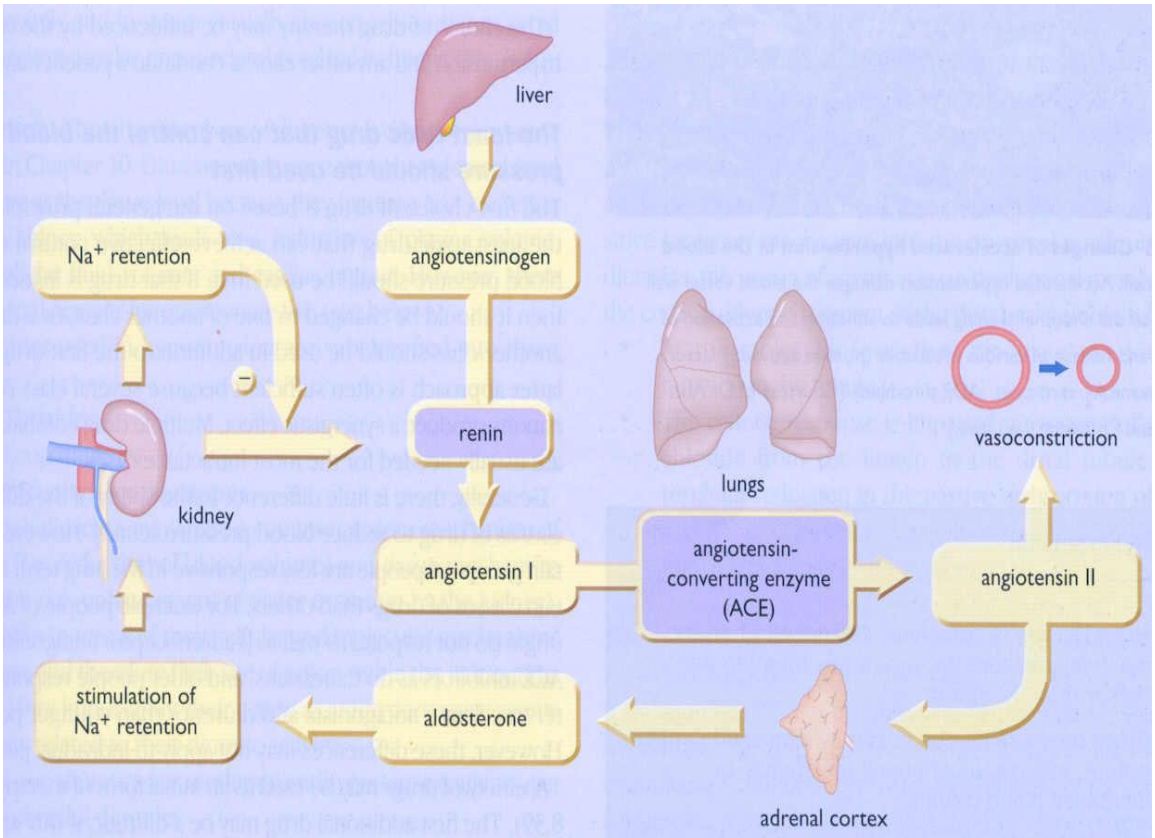


2-Drugs acting on the renin -angiotensin - aldosterone system

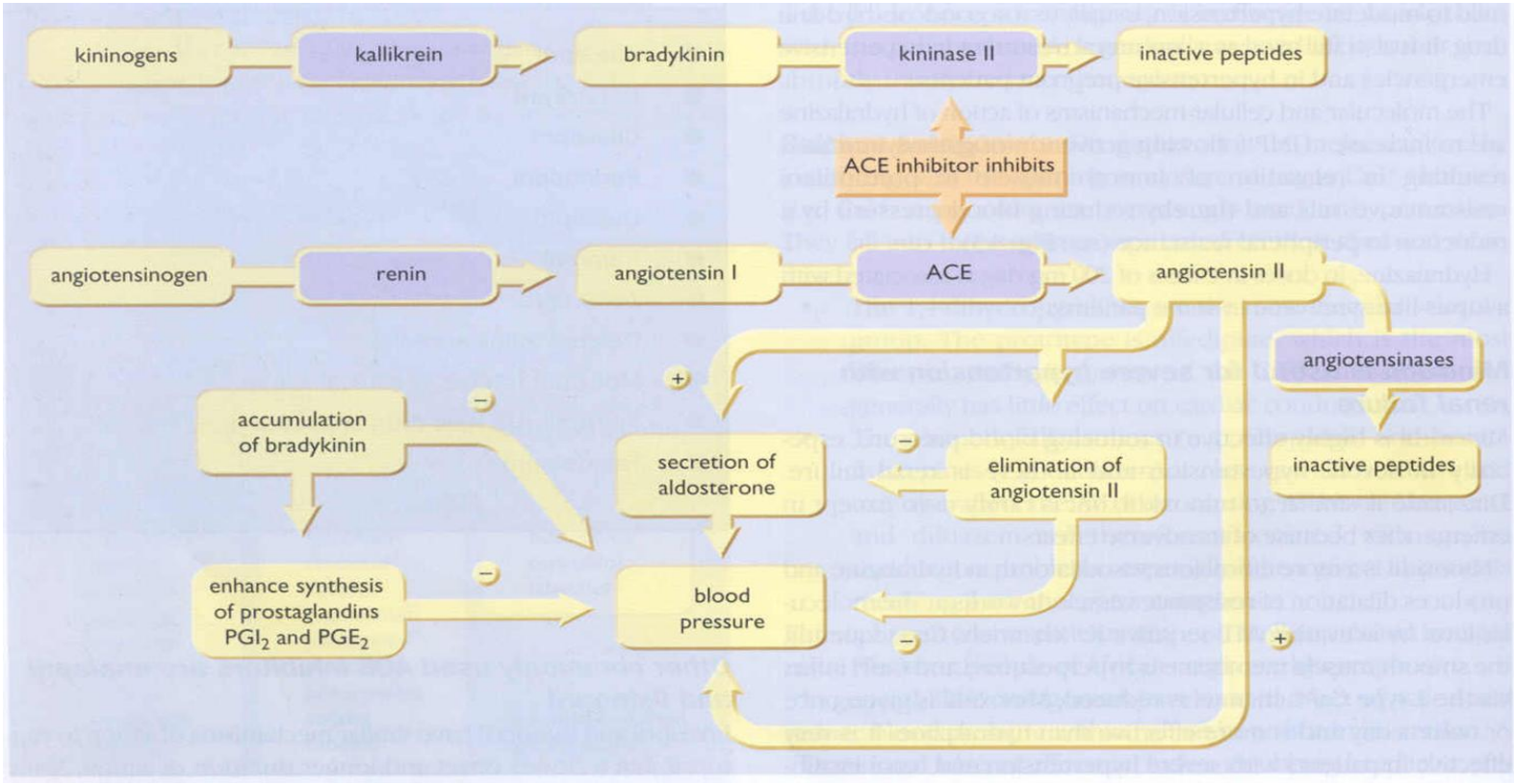
A) Angiotensin-converting enzyme inhibitors (ACEI)

- enalapril
- captopril (prototype)
- ramipril

RENIN-ANGIOTENSIN ALDOSTERONNE SYSTEM



MOA



ACE inhibitors Block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II &Stop the rate of bradykinin inactivation. (Decrease Sympatehtic activity)

ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention (decrease Blood pressure)

reduce the rate of bradykinin inactivation. (leads to Vasodilation)

Important points about ACEI:

- The antihypertensive effect of ACE inhibitors Results primarily from vasodilatation (reduction of peripheral resistance) with little change in cardiac output; a fall in aldosterone production may also contribute to decrease

-ACE inhibitors are particularly effective when hypertension results from excess renin production (renovascular hypertension)

Pharmacokinetics:

- Captopril, enalapril and ramipril .
- All are rapidly absorbed from GIT after oral administration.
- Food reduce their bioavailability.
- Enalapril , ramipril are prodrugs, converted to the active
- metabolite in the liver
- Have a long half-life & given once daily
- Enalaprilat is the active metabolite of enalapril given by i.v. route in hypertensive emergency.

Therapeutic uses

- Treatment of heart failure.

-Treatment of essential hypertension and hypertension in patients with:

- chronic renal disease
- Ischemic heart disease.
- diabetes

ADVERSE EFFECTS:

1- Acute renal failure, especially in patients with renal artery stenosis.
2- Hyperkalemia, especially in patients with renal insufficiency or diabetes.
3- severe hypotension in hypovolemic patients (due to diuretics, salt restriction or gastrointestinal fluid loss)
4- Dry cough sometimes with wheezing
5- Angioneurotic edema (swelling in the nose , throat, tongue, larynx)
6- Dysgeusia (reversible loss or altered taste)
7- Skin rash and fever.
8- Proteinuria (excess of serum proteins in the urine) and neutropenia (low number of neutrophils).

- Effects 4 & 5 may be caused by inhibition of bradykinin metabolism which accumulates in bronchial mucosa. (use and NSAID to treat these effects)
- Effects 6, 7, & 8 occur only in the use of Captopril because it contains sulfhydryl group in its molecule.

Contraindications

- During the second and third trimesters of pregnancy due to the risk of: fetal hypotension, anuria (means non passage of urine), renal failure, and malformations. (ACE inhibitors are teratogenic).
- Renal artery stenosis. (Because ACE inhibitors cause renal failure)

Drug interactions

- With potassium-sparing diuretics. (they are weak antihypertensive when used alone, but provide an additive hypotension effect when combined with diuretics).
- With NSAIDs (they impair ACE inhibitors hypotensive effects by blocking bradykinin mediated vasodilation)

B) Angiotensin receptor blockers

- losartan
- valsartan
- irbesartan

losartan	Valsartan
• Orally effective • Has a potent active metabolite. • Long half-life, taken once daily. • Can not cross BBB	Has no active metabolites. - As losartan in side effects and contraindications.

Both have the same Clinical uses as ACEI.

MOA:

Extremely potent competitive blockers of the AT 1 receptor.

Leads to a block of action of angiotensin II

Advantages compared with ACE inhibitors:

- No effect on bradykinin (more selective)، so they have the advantage of not causing the adverse effects of ACE inhibitors such as cough & angioedema.
- Produce more complete inhibition of angiotensin, because there are other enzymes (not only ACE) that can generate angiotensin.

Adverse Effects:

Same as ACE inhibitors except for cough, wheezing, and angioedema.

Contraindications:

Same as ACE inhibitors.

Note: Both ACE inhibitors & angiotensin receptor blockers are teratogenic (fetotoxic) meaning that they are harmful to the fetus. That is why they contraindicated in the last 2 trimesters pregnancy

3-Calcium Channel blockers:

They are divided into three classes.

Dihydropyridine group (nifedipine, nicardipine , amlodipine)	Verapamil	Diltiazem
act mainly on smooth muscle and used as vasodilators	act more on the myocardium and used as antiarrhythmic drug	has intermediate effect.(act on both smooth muscles & myocardium)

MOA:

Block the influx of calcium through calcium channels resulting in:

1-Peripheral vasodilatation

2- Decrease cardiac contractility

Both effects 1 & 2 lower blood pressure

Pharmacokinetics:

- given orally and intravenous injection
- well absorbed from G.I.T
- Verapamil and nifedipine are highly bound to plasma protiens (more than 90%(while diltiazem is less (70-80%)

Therapeutic uses

- Treatment of chronic hypertension with oral preparation
- Nicardipine can be given by I.V. route & used in hypertensive emergency

ADVERSE EFFECTS

Verapamil	Diltiazem	Nifedipine
Headache , Flushing , Hypotension	Headache, Flushing, Hypotension	Headache , Flushing, Hypotension
Peripheral edema (ankle edema)	Peripheral edema (ankle edema)	Peripheral edema (ankle edema)
Cardiac depression, A-V block , bradycardia	Cardiac depression , A-V block , bradycardia	Tachycardia
Constipation		

4- VASODILATORS

Vasodilators				
Drug	**Hdralazine**	**Minoxidil**	**Diazoxide**	**Sodium nitropruside**
Site of action	Arteriodilator	Arteriodilator	Arteriodilator	Arteriodilator & venodilator
MOA	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	Oral	Rapid IV	IV infusion
Therapeutic Uses	Moderate -severe hypertension.	Moderate -severe hypertension.	Hypertensive emergency	Hypertensive emergency
Uses in combination with In combination with diuretic & β-blockers	Hypertensive pregnant woman	Baldness	Treatment of hypoglycemia due to insulinoma	Severe heart failure
Adverse effects	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema)			Severe hypotension
Specific adverse effects	• lupus erythematous like syndrome	• Hypertrichosis (abnormal hair growth) . • Contraindicated in females	• Inhibit insulin release from β cells of the pancreas causing hyperglycemia • Contraindicated in diabetics	1.Methemoglobinduring infusion 2. Cyanide toxicity 3. Thiocyanate toxicity 4.Nausea, vomiting, headache, palpitations which disappear when infusion is stopped 5.Cyanide accumulation cause (cyanide poisoning metabolic acidosis, arrhythmias, severe hypotension and death)

Important points:

Both Sodium thiosulphate &hydroxocobolamine are used to prevent cyanide poisoning

- Sodium thiosulphate increases metabolism of cyanide to thiocyanate (which is less toxic).
- hydroxocobolamine combines with cyanide to form cyanocobolamine (nontoxic)
- Thiocyanate accumulation cause thiocyanate toxicity (in renal disease) manifested as weakness, psychoses, muscle spasms and convulsions.

Note:

- Nitroprusside is poisonous if given orally because of its hydrolysis to cyanide
- Nitroprusside is metabolized rapidly (half-life of minutes) and requires continuous infusion to maintain its hypotensive action.

5- Drugs acting on sympathetic system

Adrenoreceptor blocking agents		Centrally acting adrenergic drugs	
β- adrenoceptors blockers (Propranolol,atenolol)	α-ADRENOCEPTOR BLOCKERS (prazosin)	Clonidine	α - methyldopa
• Used in mild to moderate hypertension. • In severe cases used in combination with other drugs. • May take two weeks for optimal therapeutic response • They lower blood pressure by : 1- Decreasing cardiac output. **2-** Decreasing renin release.	• block α- receptors in arterioles and venules • reduce blood pressure by decreasing both afterload & preload	This α2-agonist diminishes central adrenergic outflow. Clonidine does not decrease renal blood flow or glomerular filtration and, therefore, is useful in the treatment of hypertension complicated by renal disease.	α 2 agonist is converted to methyl norepinephrine centrally to diminish the adrenergic outflow from the C.N.S. This lead to reduced total peripheral resistance, and a decreased blood pressure.

Review questions

1- A 45-year-old man has recently been diagnosed with hypertension and started on monotherapy designed to reduce peripheral resistance and prevent NaCl and water retention. He has developed a persistent cough. Which of the following drugs would have the same benefits but would not cause cough?

A) Losartan.
B) Nifedipine.
C) Prazosin.
D) Propranolol.

Correct answer = A. The cough is an adverse effect of an ACE inhibitor. Losartan is an ARB that will have the same beneficial effects as an ACE inhibitor but will not produce a cough. The other drugs also do not cause this side effect.

2- Which one of the following drugs may cause a precipitous fall in blood pressure and fainting on initial administration?

A. Atenolol.
B. Hydrochlorothiazide.
C. Nifedipine.
D. Prazosin.
E. Verapamil.

Correct answer = D. Prazosin produces first-dose hypotension, presumably by blocking α1-receptors. This effect is minimized by initially giving the drug in small, divided doses. The other agents do not have this adverse effect.

3- Which one of the following antihypertensive drugs can precipitate a hypertensive crisis following abrupt cessation of therapy?

A. Clonidine.
B. Diltiazem.
C. Enalapril.
D. Losartan.
E. Hydrochlorothiazide.

Correct answer = A. Increased sympathetic nervous system activity occurs if clonidine therapy is abruptly stopped after prolonged administration. Uncontrolled elevation in blood pressure can occur. Patients should be slowly weaned from clonidine while other antihypertensive medications are initiated. The other drugs on the list do not produce this phenomenon.

4- A 48-year-old hypertensive patient has been successfully treated with a thiazide diuretic for the last 5 years. Over the last 3 months, his diastolic pressure has steadily increased, and he has been started on an additional antihypertensive medication. He complains of several instances of being unable to achieve an erection and that he is no longer able to complete three sets of tennis. The second antihypertensive medication is most likely which one of the following?

A. Captopril.
B. Losartan.
C. Minoxidil.
D. Metoprolol.
E. Nifedipine.

Correct answer = D. The side effect profile of β-blockers, such as metoprolol, are characterized by interference with sexual performance and decreased exercise tolerance. None of the other drugs is likely to produce this combination of side effects.