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Pharmacology

Subject name: **Antihypertensive**

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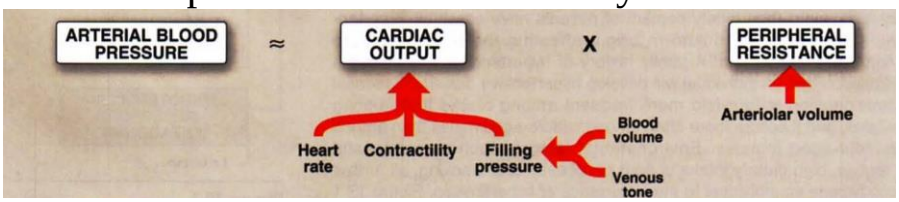
Lecture's link

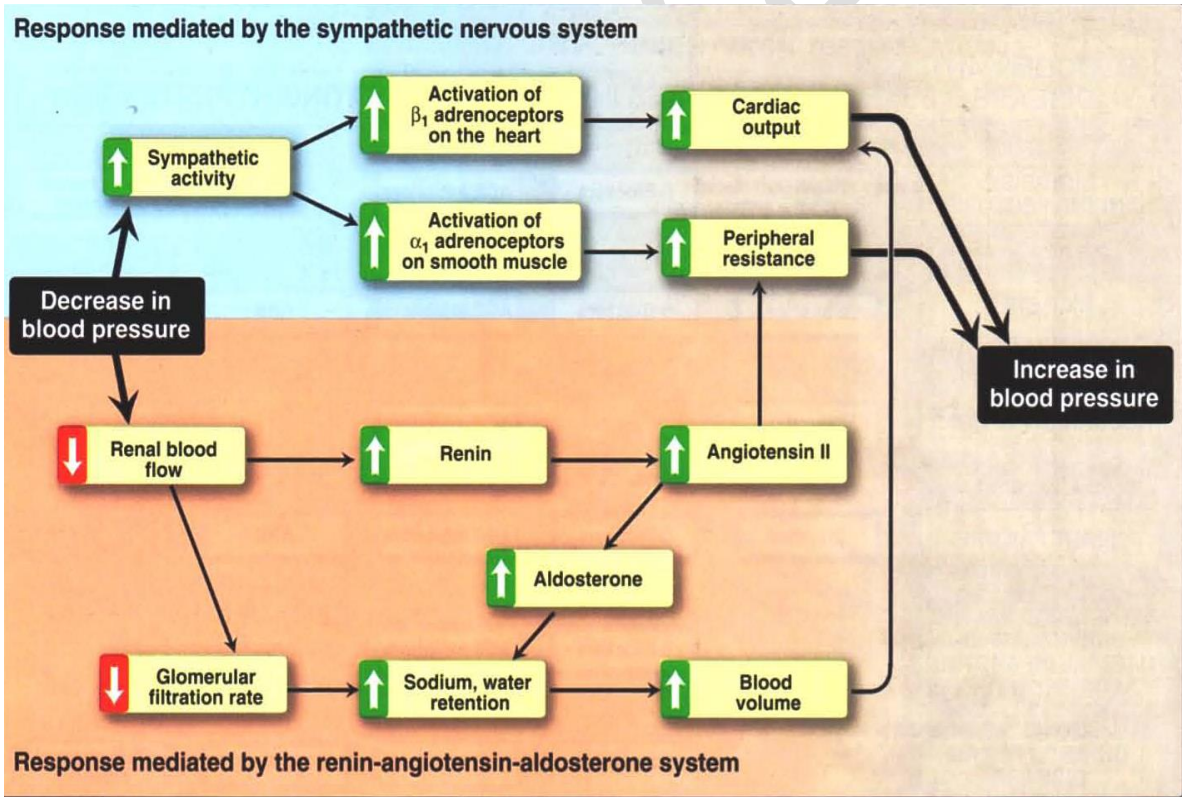
Antihypertensive treatment

Hypertension is defined as a sustained diastolic blood pressure greater than 90mm\hg accompanied by an elevated systolic blood pressure.

Hypertensive result from increased peripheral vascular smooth muscle tone ,which leads to increased arteriolar resistance and reduced capacitance of the venous system.



There are fourth control sites to maintain blood pressure:- Kidney, baroreflexes, and rennin –angiotensin –aldosterone system.



The classes of drugs most commonly used to treat primary hypertension include :-**1)diuretic agents ,2) B-adrenergic blocking agents, other sympathetic agents ,4) calcium channel blockers, other vasodilators, and 5) rennin-angiotensin blockers.**

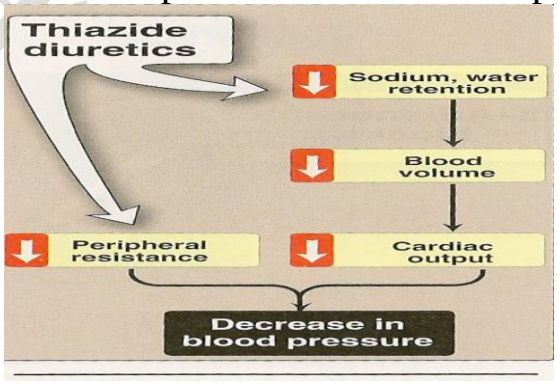
Clinical usage.:-1- mild hypertension : can often be controlled with single drug.
2-moderate to sever hypertension is similarly to mild hypertensive except that single –agent therapy is rarely used my require treatment with several drugs and arterial vasodilators often are added to the combination therapy.
3-hypertensive emergencies: parenteral therapy. Nitropussider or diaoxide .intravenous labetalol or sublingual nifedipine.

Diuretics:-

Diuretics or B-blocker recommended as the first –line drugs therapy for hypertension. low dose diuretics therapy is safe and effective in preventing stroke ,myocardial infraction ,congestive heart

a- thiazid diuretics : all oral diuretics drugs are effective in the treatment of hypertension .

Action: such as (hydrochlorothiazide) lower (Bp) initially by increasing sodium and water excretion ,this causes a decrease in extracellular volume, resulting in a decrease 1)in a cardiac output,2) renal blood flow, and 3) decrease PVR .often used with thiazide ----spironolactone lead to potassium sparing diuretic.



Pharmacokinetics:-

Thiazide diuretics can be administrated orally they induce considerable disturbances in electrolyte balance. blood levels of K &Mg reduced and Ca is retained by the body.

Adverse effect:-hypokalemia,hyperuricemia, hyperglycemia.

b-Ioop diuretics:-

Act promptly, even in patients who have poor renal function or who have not responded to thiazid .

Action : decrease renal vascular resistance and increase renal blood flow ------increase Ca content of urine. Such as (bumetanide, furosemide)

c-Osmotic diuretics:-a emergency use only:- mannitol(osmitrol), urea(ureaphil).

B-Sympathoplegics:

1-adrenoceptor blocking agents:-

Action:

The β-blockers reduce blood pressure primarily by

a- decreasing cardiac output lead to decrease the work load of the heart.

b- decrease sympathetic out floe from the CNS .

C-inhibit release of rennin from the kidney lead to decrease formation of angiotensin II and secretion of aldosterone.

Type of B-blocker is proponaolol(inderal), which act at both B1+B2 receptors.

Selective B1erceptors(atenolol, meoprolol)these agent are commonly used in disease state (asthma).

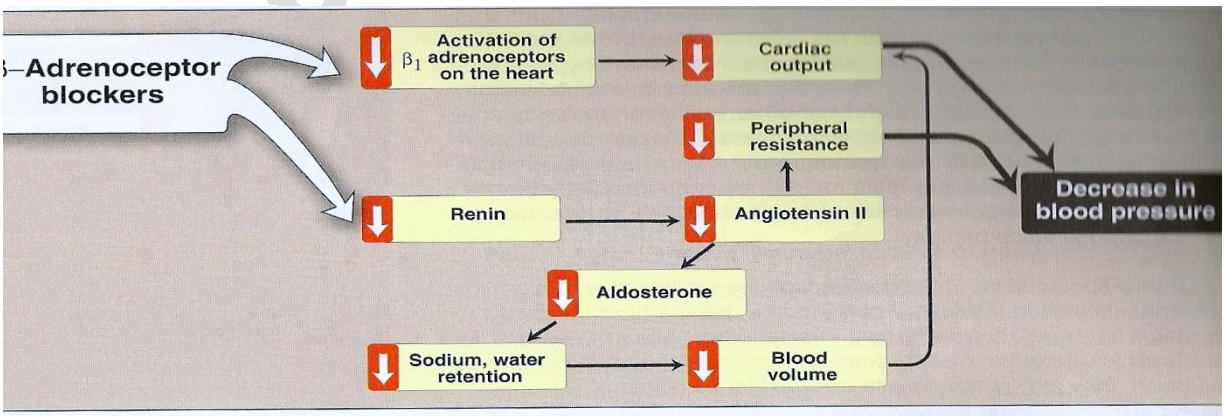


Figure 19.7
Actions of β-adrenoceptor blocking agents.

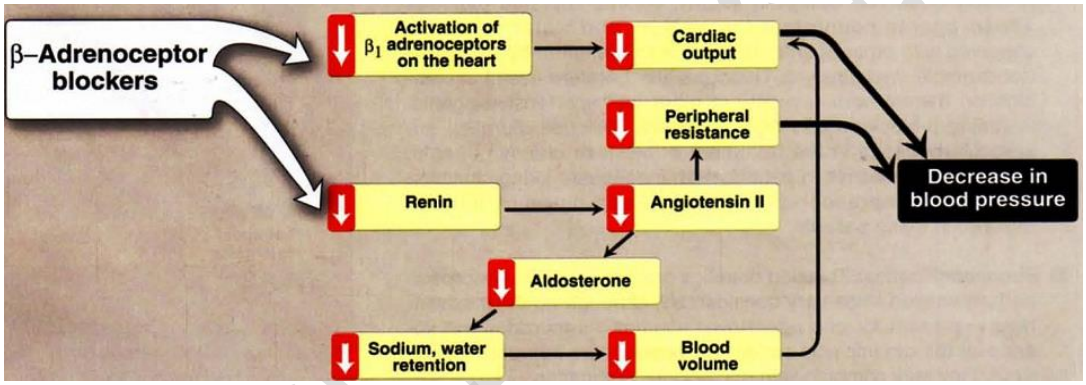
Adverse effects:-

1-fatigue, insomnia, hallucination.
2- alteration in serum lipid patterns---decrease HDL and TG.
3-abrupt withdrawal may cause rebound hypertension.

Propranolol (inderal)

Very useful for lowering blood pressure in mild to moderate hypertension. In sever hypertension useful in preventing the reflex tachycardia that often result treatment that often result from treatment with direct vasodilatation .

Atenalol : selective B1 – Block these agent are commonly used in disease state (asthma)



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2-Prazosin:- alpha 1 selective blocker agents **(block α1 receptors)** , its decrease PVR and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle . prescribed in combination with proponalol or a diuretic . prazosin is used to treat mild to moderate hypertention

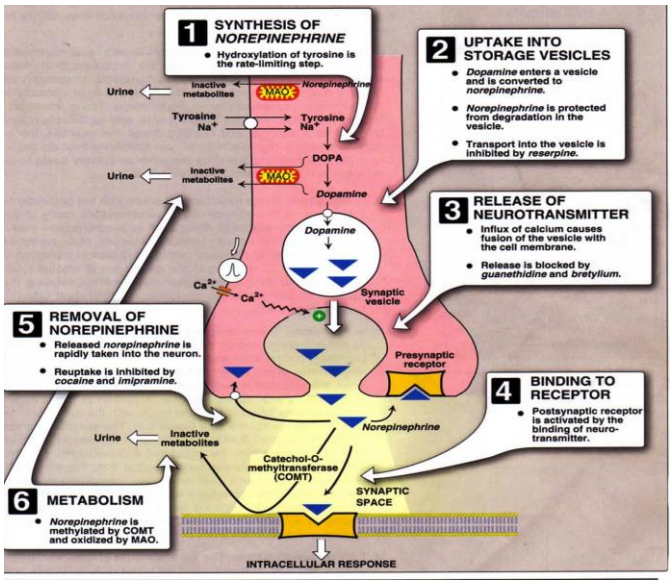
-3-central acting sympathetic agonist: (clonidine,methyldopa)

α2-selective agonists cause a decrease in sympathetic outflow by mechanism the involves activation of α2 receptor in **CNS.** **Both drugs** reduce blood pressure by reducing cardiac output, vascular resistance or both. these drugs readily enter the **CNS**

when given orally.(clonidine,methyldopa) can used to treat mild hypertension or moderate to severe hypertension.
Adverse effects:- clonidine: dry mouth, drowsiness, sedation ,rebound hypertensive after sudden discontinuation.
Methyldopa: sedation, hepatic necrosis, hemolytic anemia, +coombs test (detect initially by test tube agglutinntion red B.C.)

4-ganglion- blocking agents.(trimethphan)
Nicotinic blockers that act in the ganglia are very efficacious but because of their severe adverse effects are now considered obsolete.
Toxicities:- parasympathetics blockade (blurred vision, constipation, urinary hesitancy, sexual dysfunction).
Sympathetic blockade(sexual dysfunction, orthostatic hypotension).
5-adrenergic neuron-blocking agent. (guanethidine, reserpin)
These agents lower blood p. by preventing normal physiological of norepinphrine from postganglionic sympathetic neurons .
--Reserpine:-
Deplete catecholamine stores in the peripheral and central N.S. and causes impaired sympathetic nerve discharge.
Effects: its decrease BP. Lead to decrease heart rate and CO. and decrease PVR.
Used in low oral doses in combination with other antihypertansion agents to control moderate hypertensive. Its usually give orally ,also available for parenteral rout.
Adverse effects: sedation ,breadycaria, nasal congestion, depression because readily enters the CNS.
---Guanethidine:
-decrease release of neurotransmitter from peripheral adrenergic neurons and reducing the response of sympathetic nerve activation.
-direct inhibitory effect on skeletal M. contraction.
-used in treat of moderate and sever hypertension combination with thiazid or diuretic and vasodilators . its give orally.

Side effects: orthostatic hypotension. Salt and water retention can prevent by diuretic .



Vasodilators:-

Drugs that dilate blood vessels by acting directly on smooth muscle cells. **Three major mechanisms are utilized by vasodilators: 1-release of nitric oxide,**
2-opening of potassium channels(which leads to hyperpolarization),
3- blockade of calcium channels.

1(-calcium channel blockers_

The intracellular concentration of calcium play an important role in maintaining the tone of smooth –muscle and in the concentration of the myocardium. Calcium enters muscle cells through special voltage sensitive calcium channels.
Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channel in the heart and smooth M. of the coronary and peripheral vasculature .this causes vascular smooth M. to relax dilating mainly arterioles. Selectively between heart and smooth M.varies:
There are three structurally different classes of calcium channel blocker:
1- Dihydropyridines (nifedipin, amlodipine)
2- phenylakylamine(verapamil)

3-benzothiozopine(diltizem).

1- **verapamil-------is relatively cardio selective.**
2- nifedipin-------is relatively smooth M. selective.
3- diltizem ------is intermediate in its selective.

Pharmacokinetics
1- all are well absorbed form (git) orally.
2- undergo first –pass metabolism.
3-they readily bind to plasma proteins.
4- have short elimination half-life (4-6h.).while amoldipine has long elimination half-life.
Drug uses in hypertensive : **nifedipin, verpamil,**

-2- hydralazine (phthalazine derivative)
has greater effect on arterioles than on veins. Its may reduce diastolic more than systolic blood p.
Action:phydralazine acts through the release of nitric oxides, its rarely used at high dosage because of its toxicity(tachycardia, salt and water retention).
Therapeutic uses: - used to treat moderate to sever hypertensive
-its administered orally ,in combination with B-blocker and diuretic agent.(the former to prevent tachycardia and increase rennin secretion due to reflex sympathetic stimulation ,the latter to prevent sodium and water retention)
Rout of administration:- orally or I\M
Adverse effects**: headache ,nausea, dizziness, arrhythmia.**
3-**minoxidil:** -
directly relaxes arteriolar smooth m.
-decrease PVR more than hydralazine
- it decrease renal vascular resistance while preserving renal blood flow and glomerular filtration rate.
- Action: is a potassium channel opener.
Therapeutic uses: treat sever hypertensive, coupled with renal function impairment
-used combine with B-blocker or diuretic
-orally uses

Adverse effects: hirsutism,pericardial abnormalities, increase reflex sympathetic stimulation-----retention sodium and water.

4- diazoxide:- chemically similar to thiazide diuretics

Action:-opens potassium channel

- vasodilator effect on arterioles.
-fall in both systolic and diastolic pressure .
-relaxes other smooth m. and vascular m.
-decrease the release insulin.

Therapeutic uses: -intravenous diazoxide used for hypertensive emergencies .
-used orally treat hypoglycemia

Adverse effects: can cause sever hypotension
-reflex sympathetic stimulation ----cause angina
-hyperglycemia. salt and water retention.

5-Sodium nitroprusside : These drug reduce both arterial resistance and venous lead decrease arterial blood p.

mechanism of action:-- involve the release of nitric oxide .its a short acting (duration of action is a few minutes)

- rapid reduction of blood p. in hypertensive emergencies.
-only intravenous infusion with sterile5% dextrose in water.

Adverse effects: excessive hypotension, nausea , diaphoresis, headache ,tachycardia.

ACE inhibitors:-

Inhibitors are recommended when the preferred first-line agents (diuretic-B-blocker).

Action:-Its lowered pressure by reducing peripheral vascular resistance increasing cardiac output rate or contractility. These drugs block the ACE----convert AgI to form AgII (

--- vasodilatation occur as result combined effect of lower vasoconstriction caused by:-

- diminished AgII
- and potent vasodilatation effect of increase bradykinine.
-Also decrease secretion of aldosteron -----lead to decrease sodium and water retention.

Captopril: (capoten)t1\2

Is rapidly absorbed following oral administration and reaches peak blood levels within an hour,95%of dose is eliminated by kidney within 24h. captopril is finding increase use for the treatment of mild to moderate hypertension because it is without the side effects associated with adrenergic blockers. its given orally.

Enalapril :- is more potent than captopril

Angitoensin II receptor blockers:

Losartan: non peptide highly selective (AgII) receptor blocker---produce vasodilatation and block aldosterons secretion. and cause potassium retentions.

Saralasin : is partial agonist can be given only by intravenous infusion ,they are primarily used diagnostically to detect a renal cause of hypertension.

Hypertensive emergency

- sodium nitroprusside
-diazoxide
-labetalol.

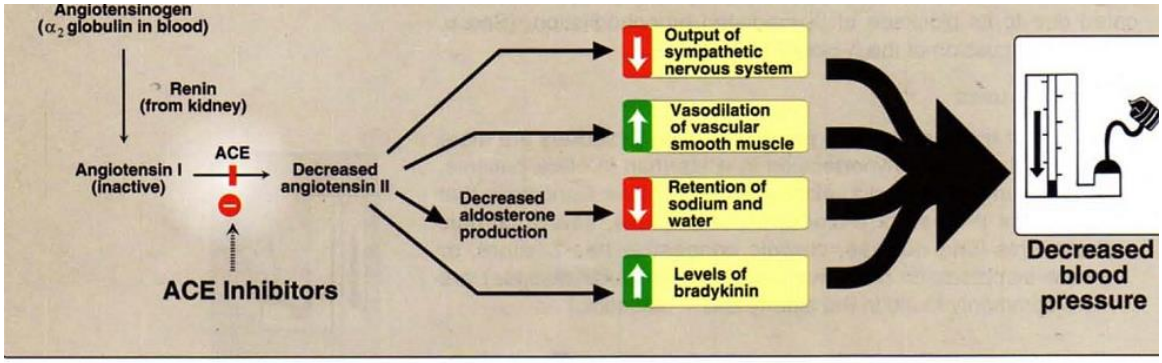


Figure 19.9
Effects of angiotensin-converting enzyme (ACE) inhibitors.