sympathetic nervous system

Additional table

Receptor Type	Primary Location in CVS	Main CVS Function	Example of Clinical Use in CVS
Alpha-1 (α1)	Blood vessels (especially arteries)	- Causes vasoconstriction, increasing blood pressure	Used in treating hypotension (e.g., midodrine)
Alpha-2 (α2)	CNS (sympathetic nerve endings)	- Reduces norepinephrine release, decreasing sympathetic tone & BP	Antihypertensive drugs (e.g., clonidine for lowering blood pressure)

Beta-1 (β1)	Heart (myocardium and SA node)	- Increases heart rate (chronotropy) and force of contraction (inotropy)	Beta-blockers (e.g., metoprolol, atenolol) to reduce blood pressure & HR
Beta-2 (β2)	Blood vessels (especially in muscles)	- Causes vasodilation in skeletal muscle, lowering peripheral resistance	Occasionally used in shock to improve blood flow (e.g., isoproterenol)
Beta-3 (β3)	Limited direct role in CVS	- Minor effects on lipolysis and blood vessel relaxation	Experimental; potential target for metabolic support in heart failure

VASOMOTOR CENTER AGENTS

Methyldopa and Clonidine

MOA
Chlonidine
Alpha-2 agonists
reduces the release of EPI &NEP

Methyldopa
actually inhibits the production of dopamine and catecholamines, which leads to a decrease in the amount of norepinephrine in neurons.

Result
beta-1 receptors are less stimulated, and alpha-1 receptors are not activated,
leading to vasodilation, a reduction in cardiac output, and decreased contractility of the heart

SIDE EFFECTS
Clonidine is sedation with no depression effect

USES
Chlonidine--> resistant hypertension.
Methyldopa --> managing gestational hypertension during pregnancy (Drug of choice)

NOTES
Don't cause orthostatic hypotension

taking these medications for a **long time**, physiological changes can occur, leading to
resistance or tolerance (**downregulation,desensitization**)

An abrupt or sudden stop of Clonidine is not recommended, whereas it is generally safe to discontinue Methyldopa because of the differences in their mechanisms of action.

The sudden stop of chlonidine could lead to rebound hypertension.

the definition of an alpha-2 agonist applies to Clonidine not Methyldopa,

HEART BETA BLOCKERS

- Beta-1 selective : atenolol
- Beta-1 non-selective: propranolol (inhibit beta-1 and beta-2),Carvedilol inhibit (beta-1, beta-2 and alpha-1)

MOA
blocking beta receptors, you decrease both contractility and heart rate

SIDE-EFFECTS
fatigue and masking of hypoglycemia symptoms including (main side effects),

USES
Dose dependent
hypertension, angina, heart failure(,more common)
arrhythmia, migraine or murmur
.

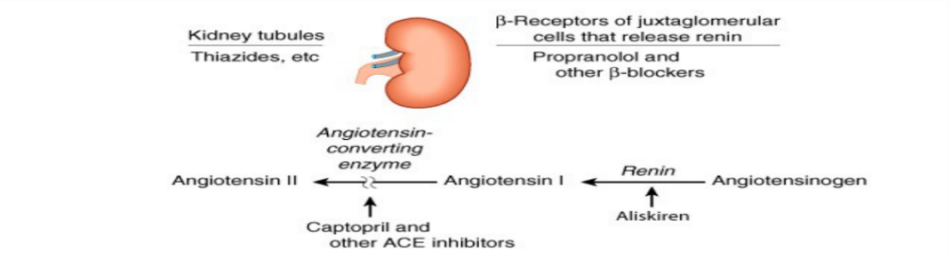
ALPHA RECEPTORS OF VESSELS (ALPHA ANTAGONIST)

Prazosin and Doxazosin

MOA
Alpha-1 receptors antagonist
blood vessels dilate (widen), which leads to lower blood pressure.

SIDE EFFECTS
Orthostatic hypotension that happens in the arteries and veins(main side effect)
First-dose syncope (or first-dose hypotension)
alpha-1 antagonists only given in hospital under surveillance , for two hours until the renin-angiotensin system and other system start work and compensate.

the Kidney (Renal):



DIURETICS

Thiazides (Chlorothiazide, ,Hydrochlorothiazide)

SITE OF ACTION

Thiazides work on distal tubules of nephron

* distal tubules are responsible for 5-7% of Na reabsorption

MOA

Thiazides:work on distal tubules, on sodium channels and potassium channels, inhibiting the reabsorption of sodium, decreasing water retention, which will cause diuresis.

depleting body sodium stores-- > excret water --> reduces blood volume --> decrease in cardiac output

Effect on cardiovascular system

a. acute decrease in plasma volume

b. chronically, decrease in **T**otal **P**eriphral **R**esistance , **C**ardiac **O**utput returns to normalmechanism unknown

c. often used to compensate for Na+ retaining reflex induced by other antihypertensive agents.

USES

•this drug remains the First-line, as it has a nice effect with no serious side effects.like orthostatic hypotension

•adequate treatment for mild or moderate essential hypertension.

THIAZIDES SIDE EFFECT

hypokalemia in 70% of pts/common??

Potassium loss is coupled to reabsorption of sodium, and restriction of dietary sodium intake therefore minimizes potassium loss.

Mild and can be tolerated by many patients

hazardous in persons taking digitalis, those who have chronic arrhythmias.

hyperuricemia in 70%of pts/common??

Uric acid and thiazides compete for the same excretion site

Thyazides are contraindicated with gout pt

hyperglycemia in 10%of pts ??

interfere with the conversion of pro-insulin to insulin

NOTES about Thiazides

▪ Patients should avoid salt(**Na**Cl) intake

why hypertension patients should not take salts?

1- it increases tension

2- make drug drug interaction causing rebuild of sodium in vessels

3- increases secretion of potassium --> increasing hypokalemia

▪ *Initially*, diuretics reduce blood pressure by **reducing blood volume** and cardiac output; peripheral *vascular resistance may increase.*

▪ *After 6–8 weeks*, cardiac output returns toward normal while *peripheral vascular resistance declines*

*When sodium reabsorption is inhibited by thiazide diuretics, other channels, such as sodium-calcium exchangers, may compensate by reabsorbing sodium. So, with time, water and sodium will return to normal, but blood pressure will remain decreased.

*During the first 6-8 weeks, sodium is removed from the vessels, leading to a depletion of sodium in the patient's body. Stopping the drug will cause the body to return to its normal state.

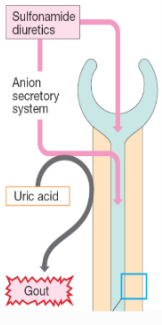
*Therefore, the patient must continue taking the drug and avoid consuming salt. This is one of the most important reasons why we advise hypertensive patients not to take salt: because salt (sodium) will rebuild sodium levels in the vessels.

▪ **Sodium** is believed to contribute to **vascular resistance** by increasingvessel stiffness and neural reactivity, possibly related to altered level of sodium.

Thiazides are dose-independent

lower doses (25–50 mg) exert as much antihypertensive effect as do higher doses.

Hydrochlorothiazideits diuretic effect plateaus after a few weeks



DIURETICS

Loop diuretics

• Furosemide "lasix" , ethacrynic acid, and bumetanide,

SITE OF ACTION

Loop of Henle has pumps that are responsible for reabsorption of sodium (25%), so this is a substantial effect.

MOA

They inhibit reabsorption of water, sodium, magnesium, calcium, and potassium.
inhibition of Na reabsorption depleting body **sodium** stores-- > excret water --> reduces blood volume --> decrease in cardiac output

SIDE-EFFECTS

severe electrolyte imbalance.
Hyponatremia, Hypomagnesemia, Hypocalcemia, Hypokalemia, and hypovolemia.
Respectively

USES

Typically only beneficial in patients with
1. resistant HTN(**hypertension**) and **evidence of fluid (too much fluid in their bodies)**

2. effective if CrCl (creatinine clearance) <30 ml/min || Glomerular Filtration Rate (GFR) under 30
(Kidney failure)
Thiazides are not beneficial in this case ??
must first be secreted and then bind to their receptors from that side.If the GFR is under 30, thiazide is not even secreted, so it can't bind to the pump inhibiting it.

NOTES

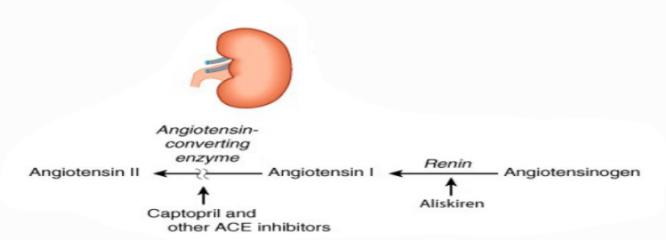
▪ MUST be dosed at least twice daily (Lasix = Lasts six hours)
▪ Administer AM and lunch time to avoid nocturia

* Comparison with Thiazides
produce **greater** diureses than thiazides
but they have **weaker** anti-hypertensive effect and
cause severe electrolyte imbalance.

Loop Diuretics are dose-dependent
continues to increase at doses many times greater than the usual therapeutic dose.

▪ Furosemide has sulfur, and some people have **allergy** to sulfur, so patient with Furosemide sensitivity is given **Ethacrynic Acid**.

RAAS (RENIN -ANGIOTENSIN - ALDOSTERONE SYSTEM)



Aliskiren (it is not effective so forget about it).

ACE inhibitors (ACEI)
"captopril"

NOTES

*ACE :Angiotensin converting enzyme found in the lung , has 2 functions :
metabolism /breakdown of bradykinin
Bradykinin is a inflamatory vasodilator
transformation of Angiotensin I into Angiotensin II
Angiotensin II I a strong vasoconstrictor

MOA of PRILS

inhibits ACE -> Inhibits the transformation of Angiotensin I into Angiotensin II, and the prevent the breakdown of bradykinin.

RESULT

Vasodilation

SIDE-EFFECTS

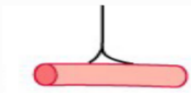
Dry cough ?? First side effect
bradykinin is that it accumulates in the upper and lower respiratory regions,
Angioedema ???
(especially naive patients) they might have high inflammation --> leakage of fluid --> causing Angioedema,
First-dose syncope.
Inhibition of angiotensin which is a potent vasoconstrictor

ARBs
"losartan"

NOTES:
an alternative for ACEI, however, Prils are much better in terms of hypertension because to avoid the dry cough , of their effect on bradykinin, as well as their activity on ADH (antidiuretic hormone).
*(ADH cause retention of water and sodium.)

MOA
Angiotensin II **R**eceptor **B**lockers (**ARBs**),
Result
Vasodilation

Vascular Smooth Muscles



Vascular smooth muscle	
Hydralazine	Verapamil and other calcium channel blockers
Minoxidil	
Nitroprusside	
Diazoxide	Fenoldopam

(1)

- Calcium Channels Blockers "verapamil"

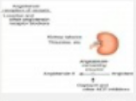
NADA are the most important, they act on calcium channels --> decreasing the entrance of calcium --> relaxation of vessels. mostly our effect on arteries more than veins.

Vasodilation

- ACEI and Calcium Channel Inhibitors are the most used drugs.
- In African Americans, the RAAS functions differently in terms of activity, resulting in stronger vessel contractility. Calcium Channel Blockers are preferred for these patients because they respond better to them than to diuretics, ACE inhibitors, or ARBs.

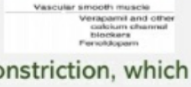
Uses

- First line therapy of hypertension in Jordanian --> diuretics, ACE inhibitors, or ARBs



Drug of Choice

- First line therapy of hypertension in African Americans --> Calcium Channels Blockers "verapamil"



- Different physiology and increased contractility lead to stronger vasoconstriction, which is why calcium channel blockers are more effective in African Americans.

25/

(2)

Drug of choice

- Hydralazine is the drug of choice for heart failure in African Americans, whereas ACE inhibitors are preferred for Jordanians.

Uses

- African Americans starts with Hydralazine because it is vasodilator. Race Based Description
- The drug of choice for congestive heart failure is a combination of hydralazine and one of the nitrates, both of which are vasodilators.

(3)

- Nitroprusside relies on nitric oxide and has equal activity on both arteries and veins, although it may be slightly more effective on veins. This introduces the concept of preload reduction, which is essential in the management of angina.
- Reduction of preload refers to decreasing the amount of blood returning to the heart (specifically, the ventricles) before it contracts. Preload represents the initial stretching of the cardiac muscle fibers at the end of diastole (when the heart is filled with blood).

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