PHARMACOLOGY

- SHEET NO. 3
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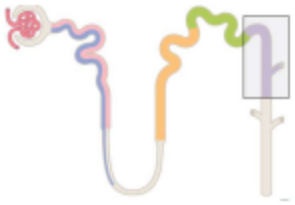
Diuretics 3



1-Potassium-Sparing Diuretics

*Low efficacy diuretics (usually used not alone but rather in combination with other diuretics to correct the levels of K^+)

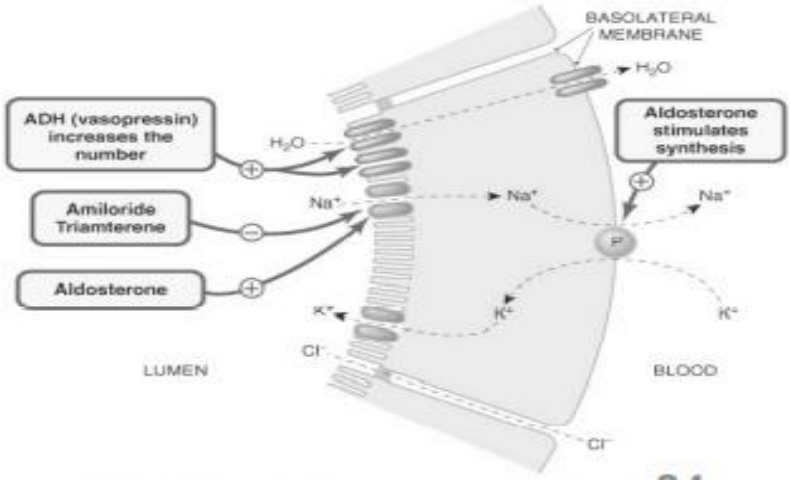
-Act on the distal portion of the distal tubule & the cortical collecting tubule (CCT), (Where Na+ is exchanged for K+).

- Aldosterone promotes reabsorption of Na+ in exchange for K+ upregulates the Na+/K+ pump and sodium channels)

↑ Na+ reabsorption,

↓ reabsorption of K+

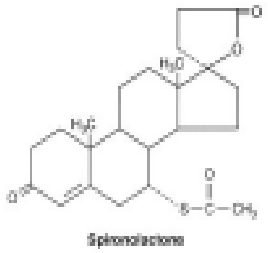
Net effect: - (↑excretion of K+ & H+)



Aldosterone antagonists (by blocking aldosterone receptors) →↑ Na+ excretion & ↓ K+ & H+ excretion (that's why they are called potassium sparing diuretics).

-There are 2 types of potassium sparing drugs:

A- the type that blocks aldosterone (mineralocorticoid) receptors like: Spironolactone; Eplerenone



-Only effective in presence of aldosterone (competitive antagonists), if aldosterone level is low, they're ineffective because the receptors are inactive

-Given orally; have delayed onset of action requires several days

-Weak diuretics, usually combined with other diuretics (like thiazides or loop diuretics)

- Have great benefit in improving myocardial function in patients with heart failure (patients with heart failure have high aldosterone levels because of activation of renin-angiotensin-aldosterone system)

- Eplerenone is more potent than Spironolactone (and has a fewer side effects)

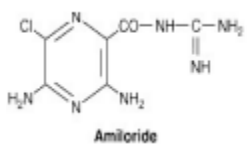
-**Eplerenone** is a spironolactone analog with much greater selectivity and potency for the mineralocorticoid receptor.

-It is several hundred-fold less active on androgen and progesterone receptors than spironolactone, and therefore has fewer adverse effects (like gynecomastia and impotency).

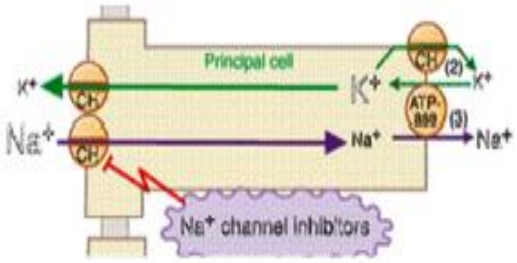
B- Amiloride and triamterene

Are none steroidal potassium sparing diuretics. **They do not block aldosterone receptors, but instead directly interfere with Na+ entry through the epithelial Na+ channels (ENaC) in the apical membrane of the collecting tubule.**

-Triamterene is metabolized in the liver, but renal excretion is a major route of elimination for the active form and the metabolites. it has a shorter half-life and must be given more frequently than amiloride (not metabolized/ longer half-life).



-They are available alone or combined with thiazides



• The actions of the aldosterone antagonists depend on renal prostaglandin production.

• The action of K+ -sparing diuretics can be inhibited by NSAIDs under certain conditions.

Clinical uses of potassium sparing diuretics:

• Spironolactone is particularly useful in the treatment of resistant hypertension due to **primary hyperaldosteronism** and of refractory edema associated with **secondary aldosteronism** (**cardiac failure** (activation of sympathetic system-release of renin), **hepatic cirrhosis**, **nephrotic syndrome**, and **severe ascites**)

• to correct Hypokalemia

• Hirsutism (antiandrogenic effect).

Hirsutism is growth of facial hair in females

Toxicity

1-Hyperkalemia

-Can cause mild, moderate, or even life-threatening hyperkalemia. → cardiac arrhythmias.

-More severe with eplerenone.

-More common in patients with diabetes, chronic renal disease, or patients on ACE inhibitors

-Combinations of K+-sparing and thiazide diuretics, the thiazide-induced hypokalemia and metabolic alkalosis are ameliorated.

Hyperchloremic Metabolic Acidosis

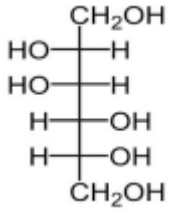
By inhibiting H+ secretion in parallel with K+ secretion, the K+-sparing diuretics can cause acidosis.

2-Gynecomastia

Spironolactone may cause Gynecomastia, impotence, benign prostatic hyperplasia in males and breast tenderness and menstrual abnormalities in females (rare with Eplerenone)

3-Acute Renal Failure

The combination of triamterene with indomethacin may cause acute renal failure. This has not been reported with other K+-sparing diuretics.



4-Kidney Stones Triamterene is only slightly soluble and may precipitate in the urine, causing kidney stones.

Contraindications:

● Oral K+ administration should be discontinued if K+-sparing diuretics are administered (otherwise hyperkalemia might develop).

● Concomitant use of other agents that blunt the renin-angiotensin system (β blockers or ACE inhibitors) increases the likelihood of hyperkalemia.

● Patients with liver disease may have impaired metabolism of triamterene and spironolactone, so dosing must be carefully adjusted.

● Strong CYP3A4 inhibitors (e.g., ketoconazole) can markedly increase blood levels of Eplerenone.

2-Agents That Alter Water Excretion/Osmotic diuretics/ Mannitol, urea, glycerol

*Mannitol is the prototype and the most commonly used

-The proximal tubule and descending limb of Henle's loop are freely permeable to water. Any osmotically active agent that is filtered by the glomerulus but not reabsorbed promotes a water diuresis.

-**Mannitol** is a sugar, not absorbed by kidney tubules (if given orally by the same osmotic manner it causes diarrhea but has no effect on the kidneys), has no systemic effects and not metabolized

Pharmacokinetics

-Not absorbed by the GI tract & must be given parenterally.

-Mannitol is not metabolized and is excreted by glomerular filtration within 30–60 minutes, without any important tubular reabsorption or secretion.

Pharmacodynamics

-Osmotic diuretics have their major effect in the proximal tubule and the descending limb of Henle's loop.

-Through osmotic effects, they also oppose the action of ADH in the collecting tubule.

-As a result, urine volume increases.

-The increase in urine flow rate decreases the contact time between fluid and the tubular epithelium, thus reducing Na+ as well as water reabsorption.

-The resulting natriuresis is of lesser magnitude than the water diuresis, leading eventually to excessive water loss and hypernatremia.

Clinical Indications & Dosage

Increase of Urine Volume

used to maintain urine volume and to prevent anuria when using a large pigment loads to the kidney. (used to visualize arteries in atherosclerosis) ;they help clear these pigments fast.

Reduction of Intracranial and Intraocular Pressure

-Osmotic diuretics are used to reduce intracranial pressure, cerebral edema and brain mass before and after neurosurgery. and to reduce intraocular pressure in glaucoma before ophthalmologic procedures.

-The above therapeutic uses are based on the fact that osmotic diuretics increase the osmotic pressure of plasma thus extract water from the eye and brain.

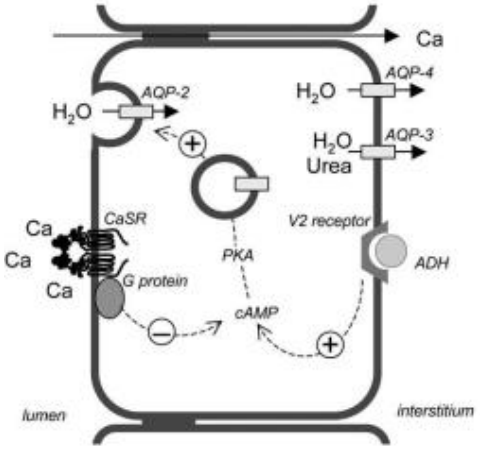
Toxicity

Extracellular Volume Expansion: Mannitol extracts water from cells prior to the diuresis. This leads to expansion of the extracellular volume and hyponatremia (dilution of sodium in blood).

Headache, nausea, and vomiting.

Dehydration, Hyperkalemia, and Hypernatremia

As water is extracted from cells, intracellular K+ concentration rises, leading to cellular losses and hyperkalemia.



Hyponatremia

In patients with diminished renal function, mannitol is retained intravenously and causes osmotic extraction of water from cells, leading to hyponatremia. (ECF volume expands leading to dilution of sodium and hyponatremia)

3-Antidiuretic Hormone (ADH)-Vasopressin & desmopressin

-Are used in the treatment of central diabetes insipidus.

-Their renal action is mediated primarily via V2 receptors.

-**Antidiuretic hormone** stimulates water reabsorption by stimulating insertion of "water channels" or **aquaporins** into the membranes of kidney tubules.

-These channels transport solute-free water through tubular cells and back into blood, leading to a decrease in plasma osmolarity and an increase osmolarity of urine.

Antidiuretic Hormone (ADH) Antagonists

Congestive heart failure and syndrome of inappropriate ADH secretion (SIADH), cause water retention as the result of ADH excess.

• Dangerous hyponatremia can result

• **Conivaptan** (available only for IV use) Antagonist to both V1a and V2 receptors.

• Two nonselective agents, **lithium** and **demeclocycline** (a tetracycline antimicrobial drug has anti-ADH effects).

• Both lithium and demeclocycline reduce the formation of cAMP in response to ADH. (which prevents the insertion of aquaporins)

-Conivaptan and demeclocycline have half-lives of 5–10 hours.

Pharmacodynamics

• Antidiuretic hormone antagonists inhibit the effects of ADH in the collecting tubule. **Conivaptan** is a pharmacologic antagonist at V1a and V2 receptors.

Clinical Indications

• Syndrome of Inappropriate ADH Secretion (excessive insuppressible release of ADH) Lithium carbonate used to treat this syndrome, but the response is unpredictable.

• Demeclocycline yields a more predictable result and is less toxic.

• Conivaptan is administered by IV injection, so it is not suitable for chronic use in outpatients.

• water restriction is often the treatment of choice. (although it's difficult)

• Antidiuretic hormone is also elevated in response to diminished effective circulating blood volume, as often occurs in congestive heart failure.

• When treatment by volume replacement is not desirable, hyponatremia may result.

• **Conivaptan** may be particularly useful because blockade of V1a receptors by this drug leads to decreased peripheral vascular resistance and increased cardiac output.

Toxicity

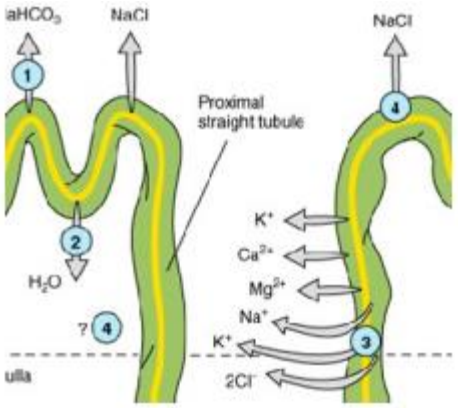
• **Nephrogenic Diabetes Insipidus**

ADH antagonists can cause severe hypernatremia and nephrogenic diabetes insipidus (disorder caused by complete or partial resistance of the kidneys to vasopressin). Nephrogenic diabetes insipidus can be treated with a thiazide diuretic.

• **Renal Failure**

Both lithium and demeclocycline have been reported to cause acute renal failure. Long-term lithium therapy may also cause chronic interstitial nephritis.

• **Other:** Demeclocycline should be avoided in liver disease and in children younger than 12 years. (Problems with bones and teeth remember?)



Diuretic Combinations

1--Loop Agents & Thiazides

• The combination of loop diuretics and thiazides can mobilize large amounts of fluid, even in patients who have not responded to single agents.

• Salt reabsorption in either the TAL or the DCT can increase when the other is blocked. Inhibition of both produces more than an additive diuretic response. -also, thiazides have a weak affect at the proximal tubule which means that thiazides have 2 sites and loop diuretics have 1 site so the combination blocks the reabsorption of sodium at 3 different sites and the action is very strong

• K+-wasting is extremely common & may require parenteral potassium administration with careful monitoring of fluid and electrolyte status.

2--Potassium-Sparing Diuretics & Loop Agents or Thiazides

Hypokalemia develops in many patients taking loop diuretics or thiazides.

This can usually be managed by taking dietary KCl supplements. When hypokalemia cannot be managed in this way, the addition of a K+-sparing diuretic can significantly lower K+ excretion.

It should be avoided in patients with renal insufficiency and in those receiving ACE inhibitors, in whom lifethreatening hyperkalemia can develop in response to K+-sparing diuretics.

سبحان الله و بحمده ،،

سبحان الله العظيم

https://www.youtube.com/watch?v=hvI6u7xytuI