Pharmacology - GUS

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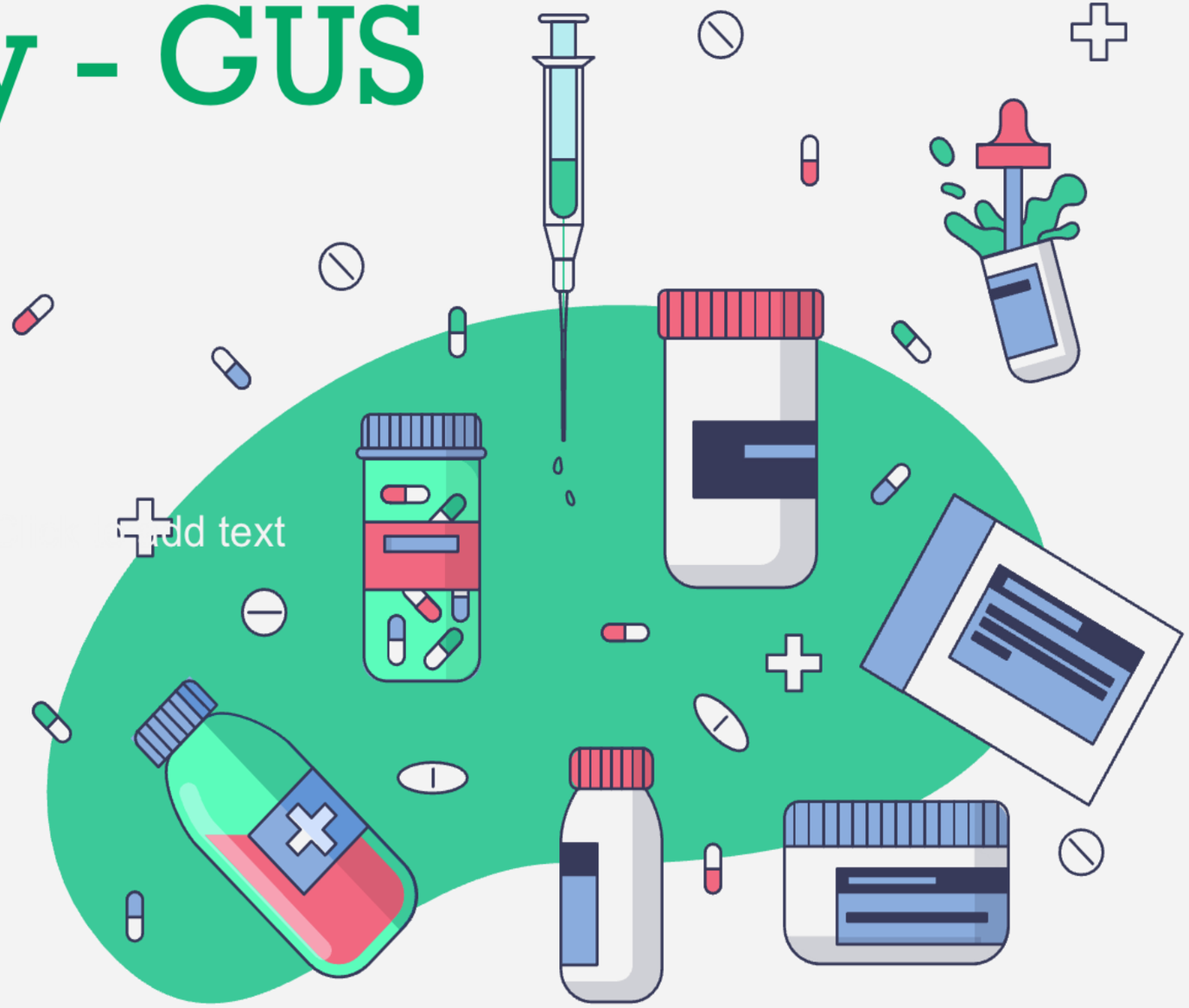

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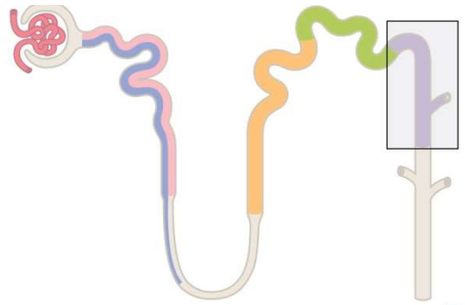
Diuretic Agents

2020

Potassium-Sparing Diuretics

low efficacy diuretics

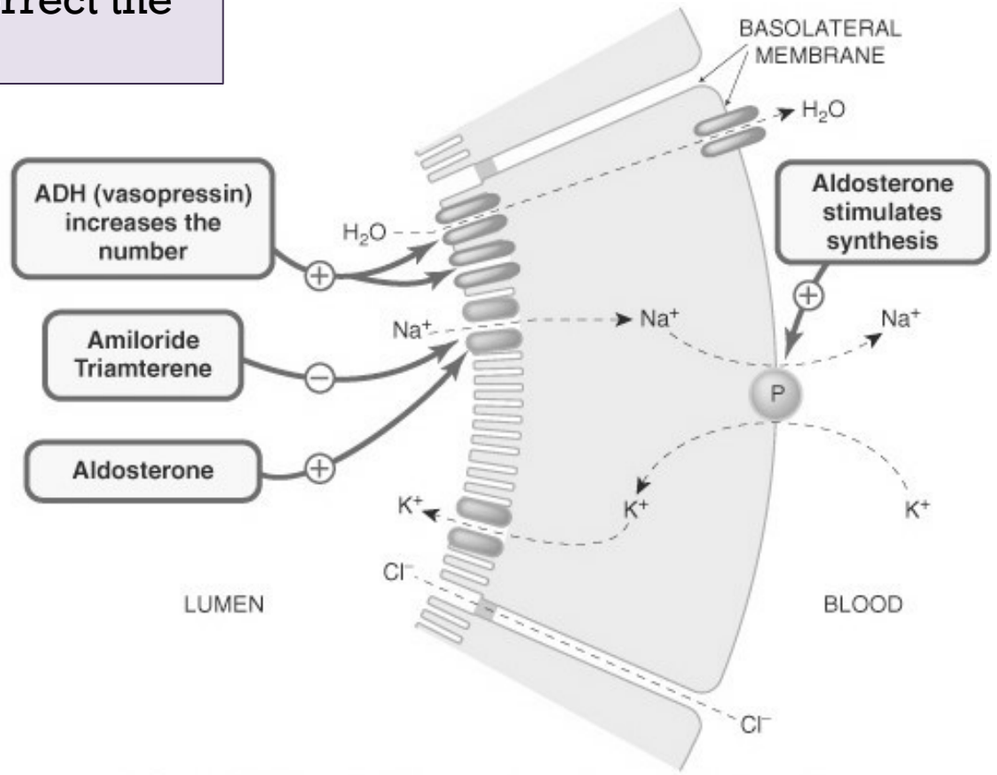
Act on the distal portion of the distal tubule
& the cortical collecting tubule (CCT).
(where Na+ is exchanged for K+)



Usually they aren't used alone , instead they are combined with other agents to correct the level of potassium

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

↑ Na^+ reabsorption,
↓ reabsorption of K^+
(↑excretion of K^+ & H^+)



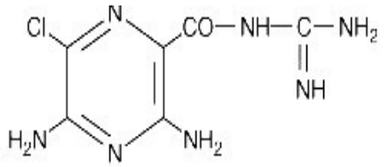
Aldosterone antagonists →↑ Na^+ excretion & ↓ **K^+ &H^+** excretion

That's why their name is potassium sparing diuretics

Spironolactone; Eplerenone

Block aldosterone receptors or mineralcorticoid receptors

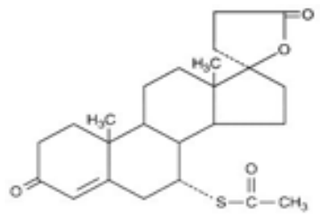
Only effective in presence of aldosterone (competitive antagonists)



Amiloride

Given orally; have delayed onset of action requires several days

Weak diuretics, usually combined with other diuretics (loop diuretics or thiazides) Have great benefit in improving myocardial function in patients with heart failure (because of high aldosterone levels in result of activation of renin-angiotensin system)



Spironolactone

Eplerenone is more potent than Spironolactone (and has 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)

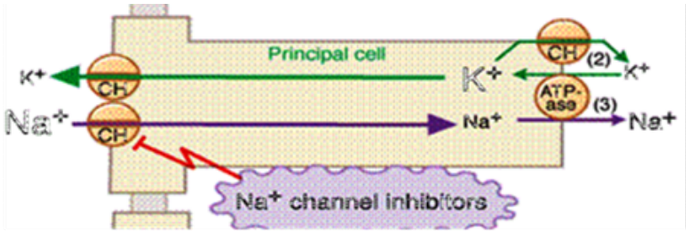
Amiloride and **triamterene**

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).

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, hepatic cirrhosis, nephrotic syndrome and severe ascities)
- Hypokalemia
- Hirsutism (antiandrogenic effect).

In cardiac failure because of increased sympathetic stimulation and actin of renin aldosterone system

Sometimes hypertension becomes resistant to the usual anti hypertensive drugs due to high level of aldosterone, spironolactone neutralizes the effect of aldosterone then we can see improvement of blood pressure

Growth of facial hair in females

Toxicity

Hyperkalemia

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

More severe with eplerenone. It has longer effect

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.

Gynecomastia

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

Acute Renal Failure

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

Kidney Stones

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

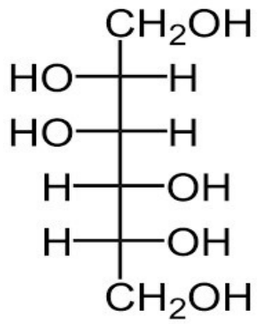
Contraindications

- Oral K+ administration should be discontinued if K+-sparing diuretics are administered.
- 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.

Agents That Alter Water Excretion Osmotic diuretics

Mannitol, urea, glycerole

The prototype, the most 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, 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.

> Sometimes if the patient has arteriosclerosis and we want to check if the coronary arteries are blocked, we inject a pigment to visualize the arteries on x-ray and these pigments are harmful to the kidney so should be cleared

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.

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

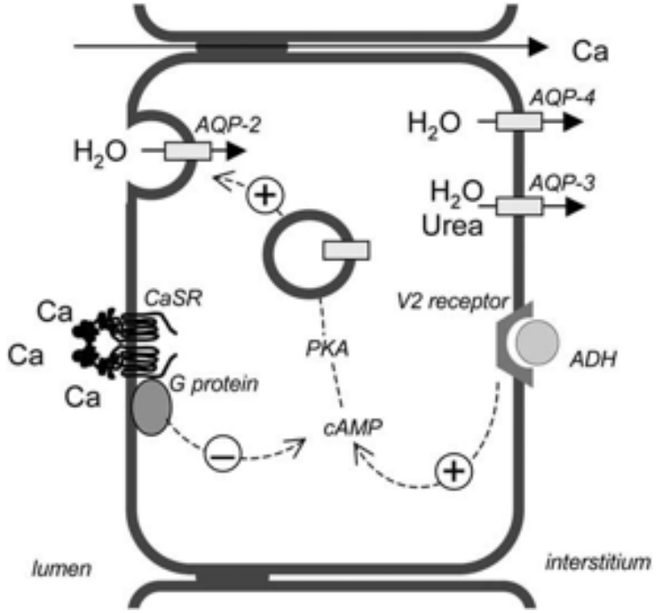
In patients with diminished renal function, mannitol is retained intravenously and causes osmotic extraction of water from cells, leading to hyponatremia.

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 reabsorbtion 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 have anti-ADH effects).
- Both lithium and demeclocycline reduce the formation of cAMP in response to ADH. And this 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 unsuppressible 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.

But this is 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.

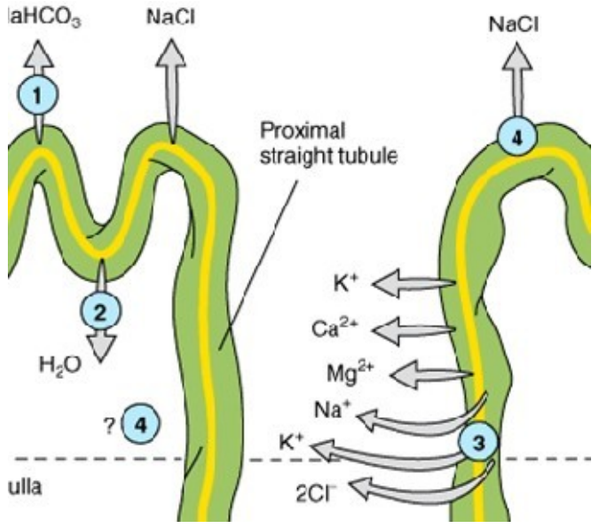
Diuretic Combinations

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.
- K+-wasting is extremely common

& may require parenteral potassium administration with careful monitoring of fluid and electrolyte status.

Thiazides have weak effect on PCT



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 life-threatening hyperkalemia can develop in response to K+-sparing diuretics.