Clinical Pharmacology

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Low Efficacy Diuretics

1. Potassium sparing diuretics
2. Carbonic anhydrase inhibitors
3. Osmotic diuretics
4. Miscellaneous

Potassium sparing diuretics

1. **Aldosterone antagonists**
   - Spironolactone
   - Eplerenone
2. **Renal epithelial Na+ channel inhibitors**
   - Triamterene
   - Amiloride

Miscellaneous

- CCBs
- ARBs
- Dopamine
- Adenosin Receptor Antagonists

Potassium sparing diuretics

- *Spironolactone:*
- It acts by competitive inhibition with aldosterone for specific intracellular receptors on DCT leading to NaCl loss and decrease K excretion.
- It increases calcium excretion by direct action on the tubules
- Action is dependent on aldosterone

Spironolactone: PKs

- Spironolactone : oral bioavailability ~75 %
- Converted into metabolite (canrenone).
- Delayed onset of action (max. diuretic effect 4 days)

Spironolactone: Uses

- It is a weak diuretic
- More useful in refractory edema which is associated with hyperaldosteronism in cases of liver cirrhosis, CHF and nephrotic syndrome.
- Resistant HT
- It is used (as K-sparing) to counteract the K+ loss due to thiazides or loop diuretics.
- Polycystic ovary syndrome: blocks androgen receptors and inhibits steroid synthesis

Spironolactone: Side Effects

- Hyperkalemia especially in patient with renal diseases or co-therapy with ACIs, ARBs or with NSAIDs and B-blockers (reduced renin).
- Gynaecomastia
- Menstrual irregularities
- Impotence
- Metabolic acidosis
- GI upset, confusion and skin rash

Eplerenone

- Eplerenone is the first of a new class of drugs known as selective aldosterone receptor antagonists (SARA), which selectively block the aldosterone receptor with minimal effect at other steroid receptors.
- like spironolactone, is a competitive antagonist of the aldosterone receptor.
- Oral eplerenone is approved for use in patients with LV systolic dysfunction following MI.

Eplerenone: PKs

- It is 50% - 75% as potent as spironolactone
- It is cleared primarily via metabolism by CYP3A4 to inactive metabolites, with an elimination half-life of 4 to 6 hours

Eplerenone: Side Effects

- Hyperkalemia and sex hormone–related side effects appear to be lower than with spironolactone.
- Mild dose dependent increases in cholesterol
- Elevated serum transaminases and Thyroid-stimulating hormone was reported
- Drug/Drug interaction with hepatic enzyme inducers/inhibitors

Eplerenone vs. Spironolactone

Parameter	Eplerenone	Spironolactone
Receptor Selectivity	SARA	Non-SARA
Potency	Less	More
metabolite	inactive	active
Duration of action	shorter	longer
Side effect profile	Less	high
Hepatic enzyme iducer/inhibitors I	Yes	No

Renal epithelial Na+ channel inhibitors

- **Triamterene and Amiloride**
- They non-aldosterone antagonists
- Both are used in conjunction with thiazides and loop diuretics
- Hyperkalemia is potential risk

Triamterene

- Triamterene
- Half life ~ 4 hrs
- Leg cramps, renal stone, impaired glucose tolerance and photosensitivity are noted side effects

Amiloride

- Its structurally related to but 10 times more potent than the triamterene
- It decreases calcium excretion and increases urate excretion (uricosuric effect)
- Half life ~ 15 hrs
- Blocks entry of lithium into renal cells and mitigate DI caused by lithium
- As aerosol – symptomatic improvement in cystic fibrosis by increasing fluidity of respiratory secretions

Carbonic anhydrase inhibitors, Acetazolamide

Acetazolamide

- The net effect is inhibition of HCO3 reabsorption in PCT.
- The secretion of H+ is inhibited.
- The distal Na+ is exchanged with K. So K+ loss in urine.
- The urine produced is rich in bicarbonate -- alkaline urine – depletes body of HCO3---- producing acidosis.

Carbonic anhydrase inhibitors

Extra – renal actions:

- Lowering of IOP due to decreased formation of aqueous humor.
- Decreased gastric acid and bicarbonate secretion.
- Raised levels of CO2 in brain and lowering of pH – raising seizure threshold and sedation

Acetazolamide: Uses

- Very weak diuretic
- Glaucoma
- To alkalinize urine (salycilate poisoning)
- Epilepsy
- Acute mountain sickness

Acetazolamide: Side effects

- Drowsiness, Parasthesia and Headache
- Acidosis
- Hypokalemia
- Crystalurea and stone formation
- Contraindicated in liver disease – interfere with elimination of ammonia

Osmotic diuretics: Mannitol

- It is a non-electrolyte – pharmacologically inert
- Not metabolized, freely filtered in the glomerulus, undergoes no (limited) reabsorption
- Inhibits water and electrolyte reabsorption
- Expands extracellular fluid and increases GFR
- Increases renal blood flow - salt reabsorption is reduced
- Primary action is to increase urinary volume
- Not absorbed orally – given I.V

Osmotic diuretics: Mannitol

Uses (by its osmotic activity):

- To maintain GFR and urine flow in renal failure
- Forced diuresis in poisoning
- To reduced ICT (head injury)
- To reduced IOP (glaucoma)

- Side effects: Headache, Nausea, Vomiting and allergy

Miscellaneous

- ARBs and ACIs: as they have antialdosterone effect, they act as K-retaining agent. They should not be combined with other K-retainers especially in patients with renal impairment
- CCBs (DHPs group) have direct (intrinsic) diuretic effect.
- Dopamine: *Indirect diuretic action*, improvement in COP and cardiac function, so increase renal perfusion and *Direct effect*, in case of fluid retention, stimulation of DA1 receptor on renal tubular cells which appose the effect of ADH

Special problems with diuretics

- Overdiuresis
- Resistance
- Hyponatremia

Aquaretics

- **Vaptans**
- They are antagonists of AVP-2 receptors in the kidney to promote solute-free excretion to correct hyponatremia..
- Tolvaptan (oral V2 antagonist) , conivaptan (IV combined V1/V2 antagonist), satavaptan

THANK YOU

FOR YOUR ATTENTION