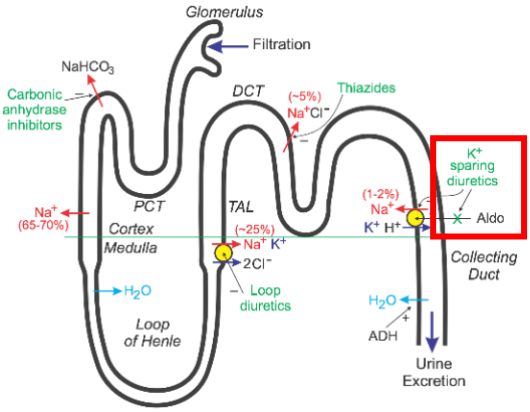
Clinical Pharmacology & Toxicology Pearl of the Week

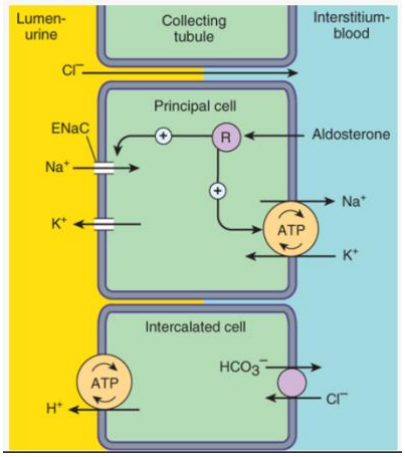
The following are a series of Pearls of the Week pertaining to anti-hypertensives and their clinical pharmacology with key points to drive effective prescribing.

Part 4- Hypertension Series: Mineralocorticoid Receptor Antagonists (MRAs)



- ✓ MRAs are synthetic steroids that competitively antagonizes aldosterone
- ✓ Members: Spironolactone and eplerenone
- ✓ Cardiovascular indications:
  - Heart failure
  - Myocardial infarction
  - **Resistant hypertension** (After: Thiazide/thiazide-like diuretic, ACEi/ARB, CCB, MRA)
  - **Aldosterone-mediated hypertension** (e.g., primary hyperaldosteronism, secondary aldosterone excess – metabolic syndrome, OSA, cirrhosis, etc)

Mechanism of action: (Blood pressure)



- ✓ RAAS system: Objective - maintain kidney perfusion. Renin is secreted by the kidney → converts angiotensinogen to angiotensin I → endothelial angiotensin converting enzyme (ACE) coverts angiotensin I → angiotensin II → adrenal cortex release of aldosterone
- ✓ Aldosterone is a steroid hormone – predominant site of action is the distal convoluted tubule
  - Upregulate Na+/K+ ATP pump on basolateral membrane (3Na: 2K)
  - Migration of ENAC sodium channels to apical membrane
  - Result: sodium is pumped out of the principle cell creating a concentration gradient that promotes reabsorption of sodium from the tubule
  - Increased sodium reabsorption causes water to be re-absorbed from the tubule in the collecting duct (via aquaporins).
  - Result: Increased salt and fluid retention → increased blood volume (pressure)
  - MRAs antagonize aldosterone: Result –A reduced sodium concentration gradient at the distal convoluted tubule → reduced potassium efflux (Potassium sparing) and less sodium reabsorption → increased sodium excretion → lower blood pressure
  - Effect: Natriuresis (and decreased blood pressure), potassium sparing, and mild diuresis

Pharmacokinetics/Pharmacodynamics:

- ✓ Spironolactone → metabolized (Deacteylated) to canrenone and 7-α-spirolactone (metabolites are active)
  - Spironolactone half-life: ~4hrs
  - Metabolite half-life: (12-20hrs)
- ✓ Eplerenone → metabolized by CYP 3A4 (Metabolites inactive)
  - Half-life: 4-6hrs
- ✓ Effect on blood pressure is longer than the half-life of agents (Blocks the hormone aldosterone, which triggers multiple downstream effects).
  - After cessation: medication effect can be prolonged (up to 4 weeks)
- ✓ Typical dosing: (for hypertension)
  - Spironolactone: 50-300mg Po Daily
  - Eplerenone: 25-150mg Po BID
  - Dosing: Linear dose response (the higher the dose, the greater the anti-hypertensive effect)

Adverse effects/Toxicity:

- ✓ Spironolactone: Cross affinity to androgen-receptors, which results in androgen blockade → Can result in gynecomastia and low-libido
  - Eplerenone has less affinity for androgen receptors and so less androgen-blockade associated side-effects (e.g. Gynecomastia and low libido)
- ✓ Hyperkalemia (Potassium 'sparing' diuretic)
- ✓ Acidosis (Type IV RTA) Aldosterone mediates H^+ excretion and $HCO3^-$ synthesis at intercalated cells
- ✓ Volume depletion and acute kidney injury (rare)
- ✓ Other: Diarrhea, nausea, vomiting
- ✓ Drug interactions: Caution when using with other agents that increase serum potassium, e.g. ACEi/AEB, amiloride, septra, NSAIDs

Take-home points:

- ✓ Antagonizes effect of aldosterone
- ✓ Effective anti-hypertensive for aldosterone-excess hypertension
- ✓ Spironolactone has partial affinity to androgen receptors; blockade leads to gynecomastia/low libido. Eplerenone has much higher specificity for aldosterone receptors
- ✓ Linear dose response curve (the higher the dose, the greater the anti-hypertensive effect)

The Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 and select option 1.

References:

1. Reilly RF, Jackson EK. Regulation of Renal Function and Vascular Volume. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. McGraw-Hill
2. Benowitz NL. Antihypertensive Agents. In: Katzung BG. eds. *Basic & Clinical Pharmacology, 14e*. McGraw-Hill
3. Drugbank: https://go.drugbank.com/drugs
4. Micromedex: https://www-micromedexsolutions-com.ahs.idm.oclc.org
5. Indiana University Department of Medicine Clinical Pharmacology - Flockhart Tables: https://drug-interactions.medicine.iu.edu/MainTable.aspx