Renal Pharmacology

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Diuretics

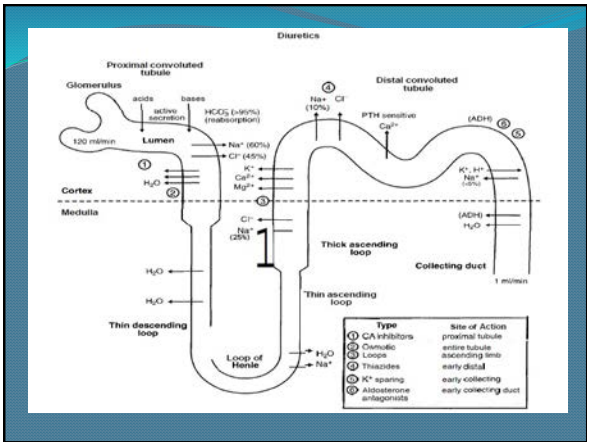
- Clinical uses:
  - HTN,
  - heart failure,
  - edematous states,
  - renal dysfunction,
  - hypercalcemias,
  - nephrolithiasis,
  - glaucoma, and
  - mountain sickness

Approximate Percentage of Sodium Reabsorption in Renal Tubular Segments:

- Proximal convoluted tubule (PCT >60%).
- Thick ascending limb of the loop of Henle (TAL <25%).
- Distal convoluted tubule (DCT < 10%).
- The collecting tubules and ducts (CT <4%).

Hypokalemia and Alkalosis

- Diuretics that block Na reabsorption at segments above the CT will increase sodium load to the collecting tubules and ducts ("downstream").
- This results in increased loss of K → hypokalemia, and in the case of both loop and thiazide diuretics the associated loss of H→ results in alkalosis.

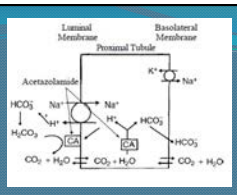


OSMOTIC DIURETICS

- Mannitol (IV only) inhibits water reabsorption in the proximal convoluted tubule (PCT) (main site), the thin descending limb of the loop of Henle, and the collecting ducts.
- It increases urine volume, preventing anuria in hemolysis and rhabdomyolysis, and facilitates elimination of toxic drugs (e.g., cisplatin). Similar osmotic actions in the ECF of other tissues → decrease intraocular and intracerebral pressure.
- Adverse effects:
  - nausea and vomiting,
  - chills,
  - electrolyte imbalance,
  - hypovolemia,
  - chest pain.

CARBONIC ANHYDRASE INHIBITORS

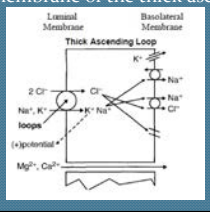
- Actions
  - Acetazolamide and dorzolamide inhibit CA on both the luminal membrane and in the PCT cell.
  - Inhibition of CO_2, formation in the lumen decreases its intracellular availability. This, together with inhibition of formation of carbonic acid (CA is reversible), decreases intracellular bicarbonate and H+ levels.
  - Na+ reabsorption across the luminal membrane is decreased because of decrease availability of protons needed for the Na/H antiporter.
  - Filtered bicarbonate and Na+ ions continue down the tubule, leading to bicarbonaturia (with resulting acidosis) and presenting a major Na+ load downstream.



- Clinical Uses
  - Glaucoma (decreases formation of aqueous humor decrease IOP), acute mountain sickness (decrease pulmonary and cerebral edema),
  - metabolic alkalosis (e.g., thiazide-induced),
  - elimination of acidic drugs (e.g., ASA, uric acid).
- Adverse Effects
  - Acidosis,
  - bicarbonaturia,
  - hypokalemia,
  - hyperchloremia,
  - paresthesias, and
  - renal stones (hypercalciuria, phosphaturia).

LOOP DIURETICS

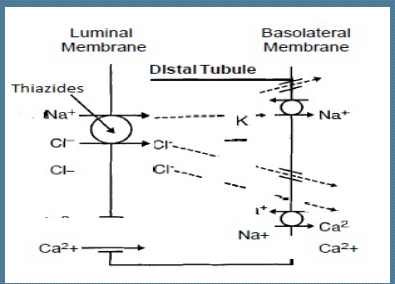
- Actions
  - Ethacrynic acid and furosemide are weak acids that are both filtered and secreted, so they achieve high levels in the tubular lumen.
  - Loop diuretics inhibit the Na/K/2Cl cotransporter on the luminal membrane of the thick ascending loop (TAL).



- **Clinical Uses**
  - Acute pulmonary edema, acute renal failure, anion overdose, heart failure, hypercalcemic states, hypertension, and refractory edemas.
- **Adverse Effects**
  - Allergies, alkalosis, hypocalcemia, hypokalemia, hypomagnesemia, hyperuricemia, hypovolemia, ototoxicity (ethacrynate > furosemide) enhanced by aminoglycosides.
  - Loop diuretics may decrease lithium clearance.

Thiazides

- Hydrochlorothiazide, indapamide, and metolazone



- Clinical **Uses**
  - Thiazides are widely used in HTN and heart failure with proven long-term efficacy. Their actions are improved by Na restriction.
  - Their activity is reduced at low GFR. Also used in edematous states (+/- loops), including pulmonary edema, nephrolithiasis, and diabetes insipidus (ADH resistance), including that due to lithium
- Adverse Effects
  - Allergies, alkalosis, hypokalemia, hypercalcemia, hyperuricemia, hypovolemia, hyperglycemia, hyperlipidemia and sexual dysfunction.

K+ SPARING AGENTS

- Spironolactone, amiloride, and triamterene act at the level of the collecting tubules and ducts.
- These are weak diuretics because most of the filtered Na+ is reabsorbed before reaching the CT.
- The CT determines final urinary Na+ concentration and is a major site of secretion of K+ ions and protons.
- Normally, aldosterone exerts its mineralocorticoid actions via interaction with its receptors → increase activity of Na/K and H+ exchangers. Na+ diffuses through its channels, increasing intracellular positive charge, which leads to extrusion of K+ into the lumen.
- By mechanisms that are unclear, Na+ entry into cells of the CT leads to an increase in the energy dependent extrusion of protons across the luminal membranes of intercalated cells.
- Spironolactone (aldosterone receptor antagonist) and amiloride and triamterene (Na+ channel blockers) prevent the above effects, leading to minor effects on Na+ reabsorption but major effects on the retention of K ions and protons. Thus, they cause small increases in urinary Na+ and marked decreases in urinary K+, resulting in hyperkalemia and acidosis.

- Clinical Use
  - Spironolactone
    - In hyperaldosteronic states, as an adjunctive with other diuretics in HTN and in heart failure (improves survival when used with ACEIs). It also has antiandrogenic uses (e.g., female hirsutism).
  - Na Channel Blockers
    - As an adjunctive with other diuretics in HTN and heart failure to decrease K loss, and in lithium induced diabetes insipidus (amiloride).
- Adverse Effects
  - Acidosis, hyperkalemia, azotemia, gynecomastia and libido changes (spironolactone), nephrolithiasis (triamterene).

Summary of the Modes of Action and Effects of the Various Classes of Diuretics

Drug	Mechanisms of Action	**Urinary** Electrolytes	Blood Chemistry and **pH**
Acetazolamide	Inhibition of carbonic anhydrase in PCT	↑ Na ↑ K ↑ Ca ↑↑ HCO_3 ↑ PO_4	Hypokalemia, acidosis (↓ pH), hyperchloremia
Ethacrynic acid, furosemide, torsemide	Inhibition of Na/K/2Cl cotransporter in TAL	↑↑ Na ↑ K ↑ Ca ↑ Mg ↑ Cl ↓ HCO_3	Hypokalemia, alkalosis (↑ pH), hypomagnesemia
Hydrochlorothiazide, indapamide, metolazone	Inhibition of Na/Cl cotransporter in DCT	↑ Na ↑ K ↑ Cl ↓ Ca	Hypokalemia, alkalosis (↑ pH), hypercalcemia
Amiloride, triamterene, spironolactone	Block Na channels, block aldosterone receptors in CT	↑ Na (small) ↓ K	Hyperkalemia, acidosis (↓ pH)