DIURETICS-4

Dr. Shariq Syed

Pop Quiz !!

- Loop diuretics act on which transporter

PKCC

NKCC2

AIKTCC

I Don't know

Pop Quiz !!

- Loop diuretics are _____ diuretics

Strong

Medium

weak

I Don't know

Pop Quiz !!

- Thiazide diuretics act on which transporter

ACC

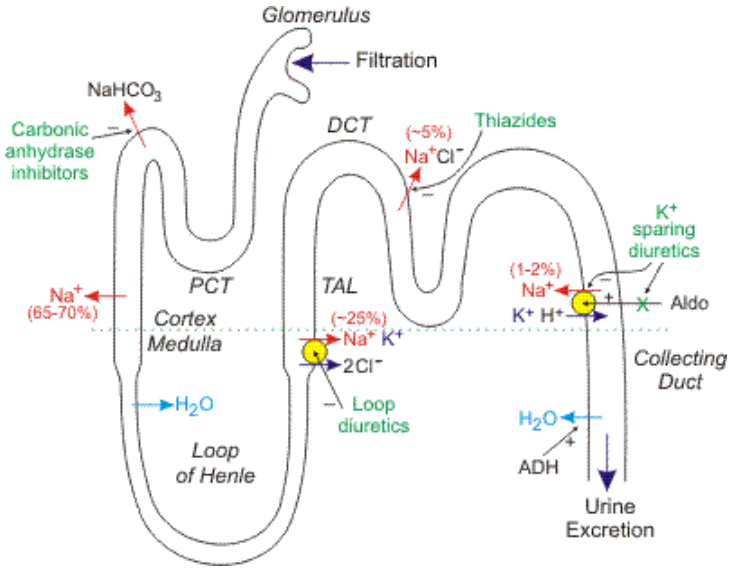
NCC

KCC

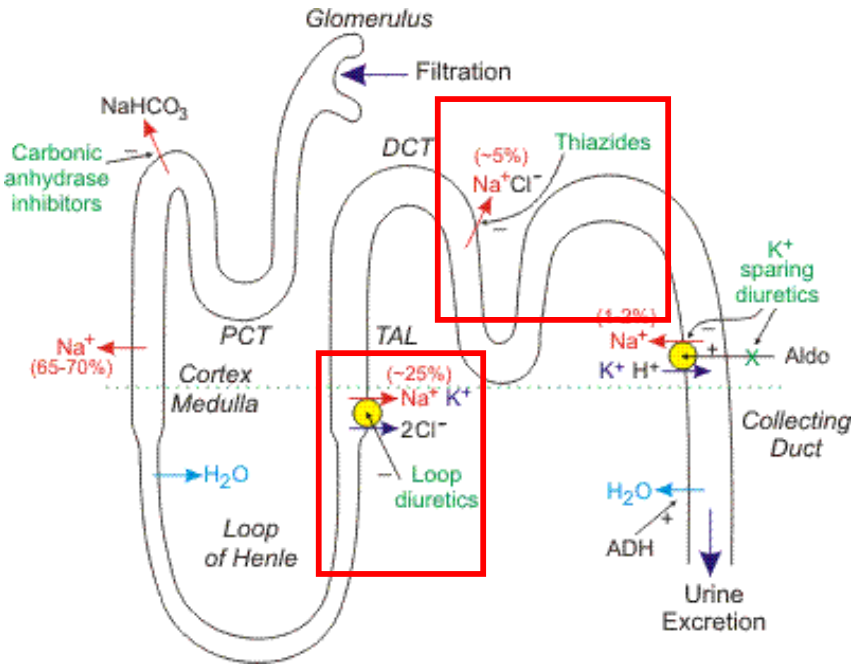
I Don't know

Recap of what we did last time

- Reviewed the structure/function of Nephron
- Basic concept of how diuretics work
- Introduced different classes of Diuretics
- Looked in detail at Carbonic Anhydrase inhibitors

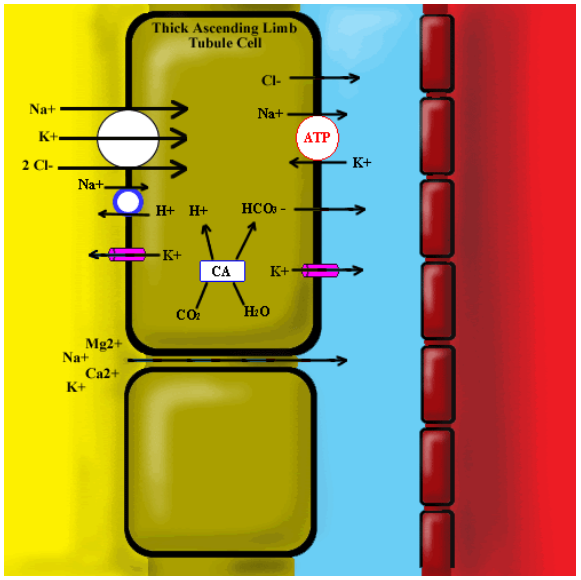


Plan for today



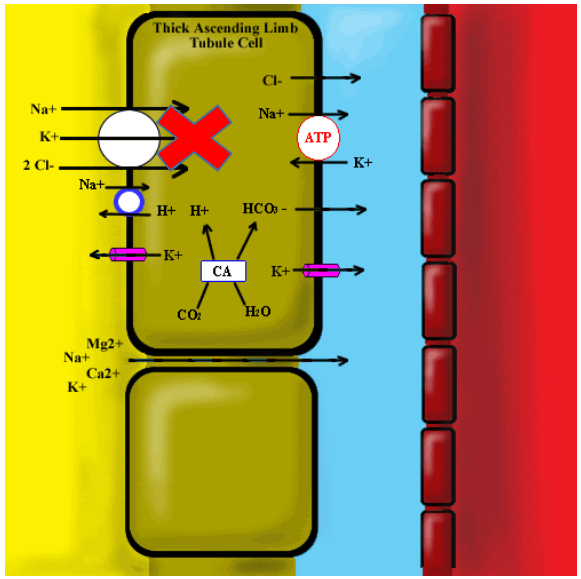
Action at TAL, close look at NKCC2

- NKCC2 electrically neutral transporter (2^+, 2^-)
- Leads to excess accumulation of K^+ in cells, gets diffused back in lumen
- Positive potential in lumen drive Ca^{2+}, Mg^{2+} reabsorbed via paracellular path

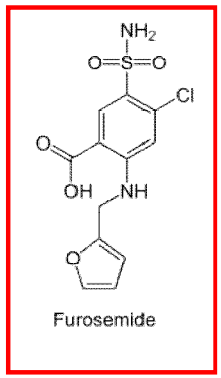


Loop Diuretics, MOA, Site

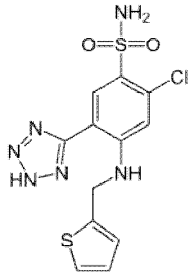
- Loop diuretics blocks the NKCC2 transporter leading to
  - Decreased reabsorption of Na^+ along with Ca^{2+}, Mg^{2+}
  - By disrupting the reabsorption of these ions, loop diuretics prevent the generation of a hypertonic renal medulla
  - Without such a concentrated medulla, water has less of an osmotic driving force to leave the collecting duct system, ultimately resulting in increased urine production



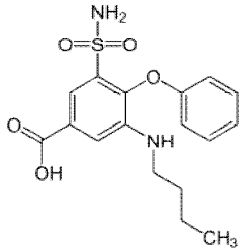
Loop Diuretics, Structures



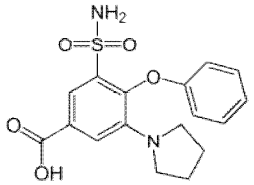
Furosemide



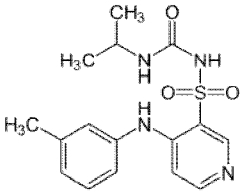
Azosemide



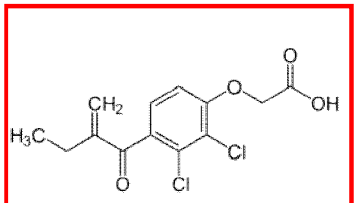
Bumetanide



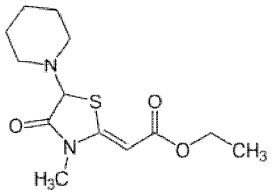
Piretanide



Torasemide



Ethacrynic acid



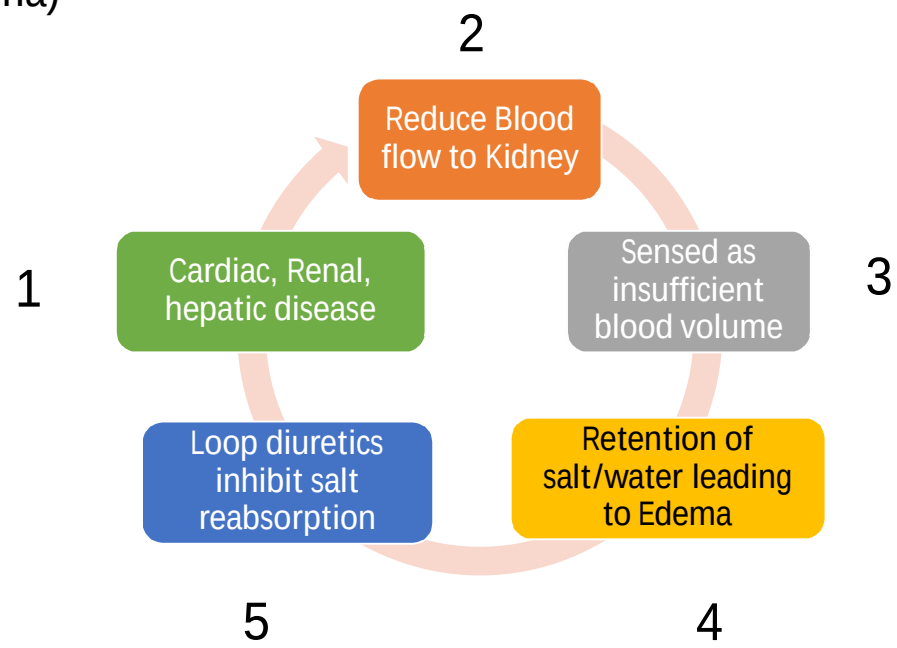
Etozolin

Pharmacokinetics of Diuretics

- Loop diuretics are rapidly absorbed (1-3 hours)
- Eliminated by glomerular filtration and secretion
- Duration of effect is 2- 3 hours
- Half life depends on renal function

Clinical Indications

- Most important use of loop diuretics in treating EDEMATOUS conditions (peripheral or pulmonary edema)



Clinical Indications

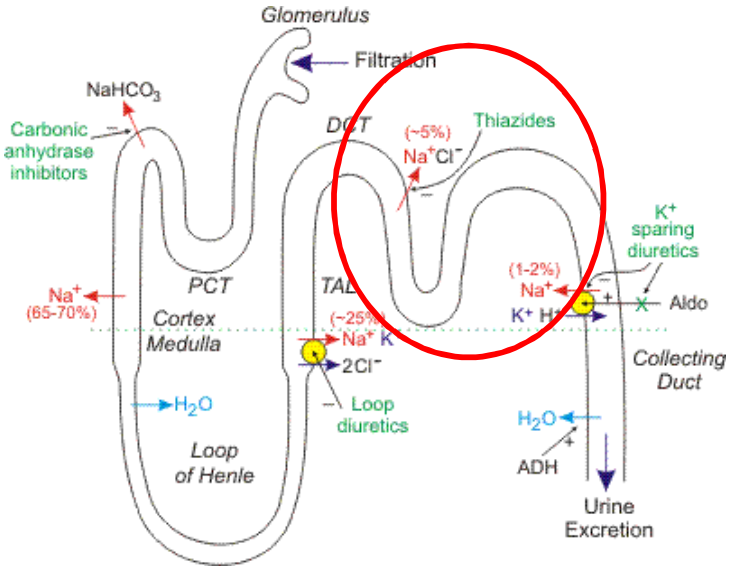
- Hyperkalemia:
  - Loop diuretics significantly enhance urinary excretion of K^+
- Acute renal failure
  - Increase in urinary flow to flush out intra-tubular casts , obstructions
- Anion overdose
  - Br, Fl, I
  - Saline must be co-administered to replenish Na, Cl loss

Toxicity

- Hypokalemia Metabolic Alkalosis
  - Increased excretion of K^+ due to increased excretion of Na^+
- Hypomagnesaemia
  - Increased excretion of Mg^+
- Allergic and other reactions

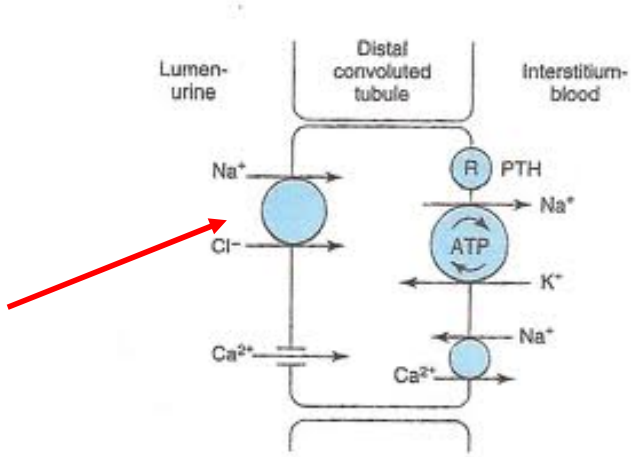
Thiazide Diuretics

- 5- 10 % Na reabsorbed at DCT
- Impermeable to water, leads to dilution
- Thiazide diuretics originally synthesized to create more potent carbonic anhydrase inhibitors
- Act at DCT

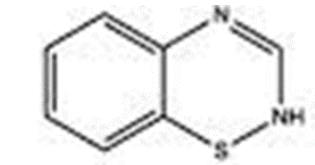


Thiazide action at DCT

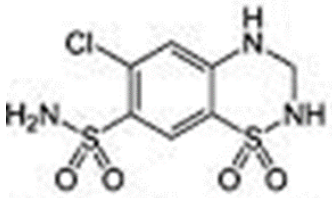
- Na^+, Cl^- reabsorbed by Na^+/Cl^- co-transporter (NCC)
- Ca^{++} actively reabsorbed by Ca^{++} channel & basolateral Na^+/Ca^{++} exchanger
- Thiazides bind to Cl^- inhibiting NCC & thus prevent Na^+ reabsorption



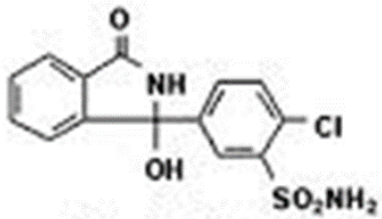
Thiazide Diuretics, Structures



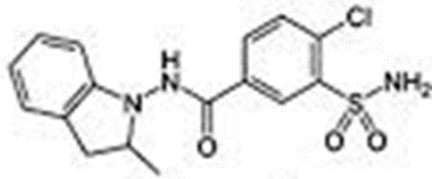
Benzothiadiazine ring



Hydrochlorothiazide



Chlorthalidone



Indapamide

Clinical Indications

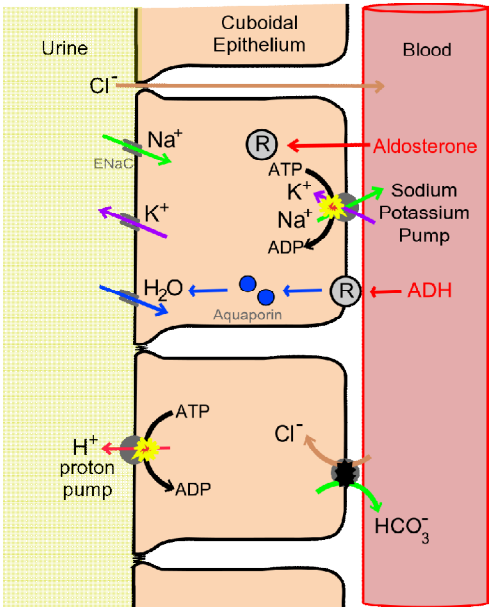
- Less powerful than loop diuretics but preferred in treating Hypertension
  - Decreased blood volume , vasodilation
  - Amongst the group, Hydrochlorothiazide is the most widely used
  - Usually reserved for patients with mild renal insufficiency
- Mild heart failure

Toxicity

- Hypokalemic metabolic acidosis
- Hyperlipidemia
  - Increase in cholesterol and LDL
  - Levels typically return to baseline after prolonged use
- Hyponatremia
  - Important side effect
  - Prevented by reducing the dose or fluid intake

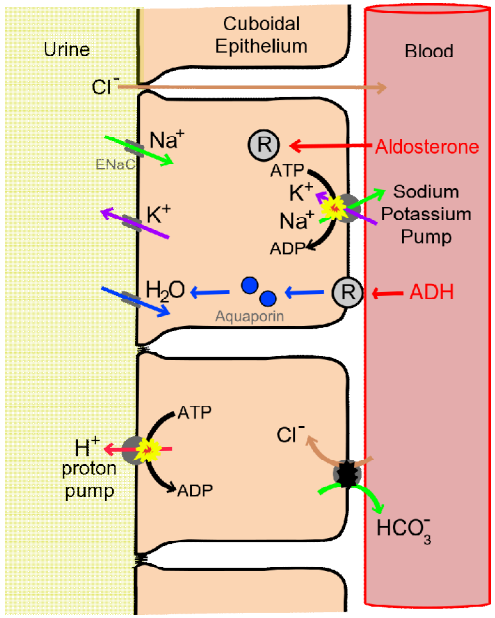
Activity at Collection tubule

- 3 components: connecting tubule, collecting tubule, collecting duct
- 2.5 % Na reabsorption, final site of Na^+ reabsorption
- Mineralocorticoids have the largest influence at this site
- Most important site of K^+ secretion in kidney



Activity at Collection tubule

- Mechanism of ion reabsorption different from other regions
- Separate channels for Na^+ & K^+
- Na^+ entry preferred, movement creates a negative lumen potential
- Cl get's in via paracellular route, K^+ goes out of cell
- Aldosterone increases activity of these channels
- Diuretics and Aldosterone activity leads to K^+ wasting

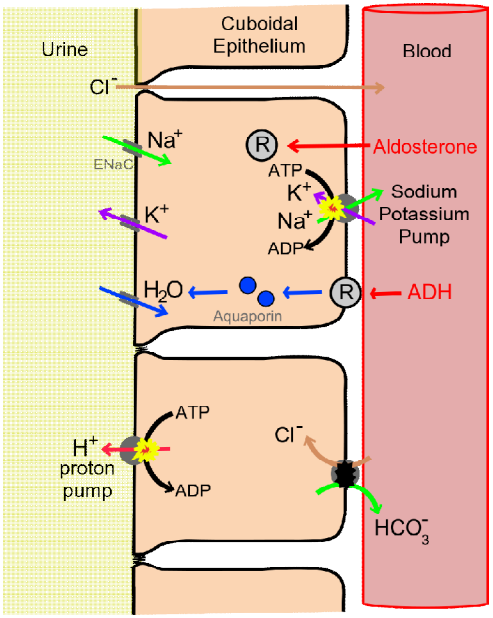


K-Sparing diuretics

- K-Sparing diuretics mainly act by 2 ways

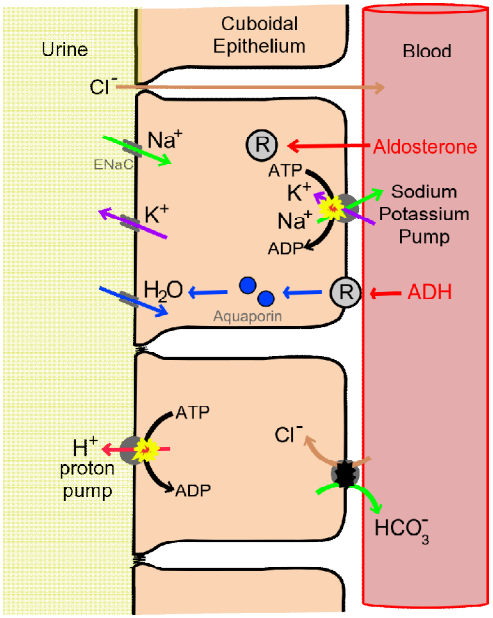
  1. Competitive antagonist of Aldosterone

  2. Directly block Na channels



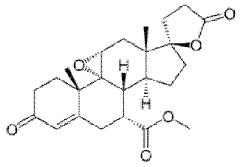
Competitive Aldosterone antagonist

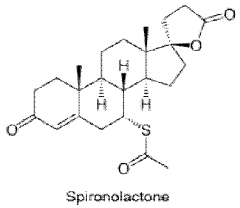
- These directly compete with aldosterone for intracellular cytoplasmic binding sites
- Thus prevent formation of proteins that are normally synthesized in reaction to aldosterone
- As a result mediator proteins are not produced, and so stimulation of sodium-potassium exchange does not occur

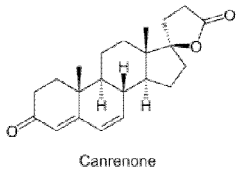


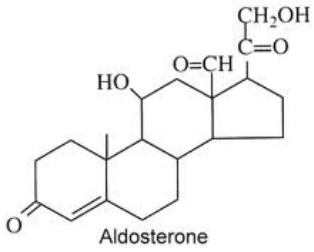
Competitive Aldosterone antagonist

- Synthetic steroidal molecules
- Spironolactone has a slower onset, takes days for full therapeutic effect
- Eplerenone is much selective for ADH receptor, lower side effects


Eplerenone


Spironolactone

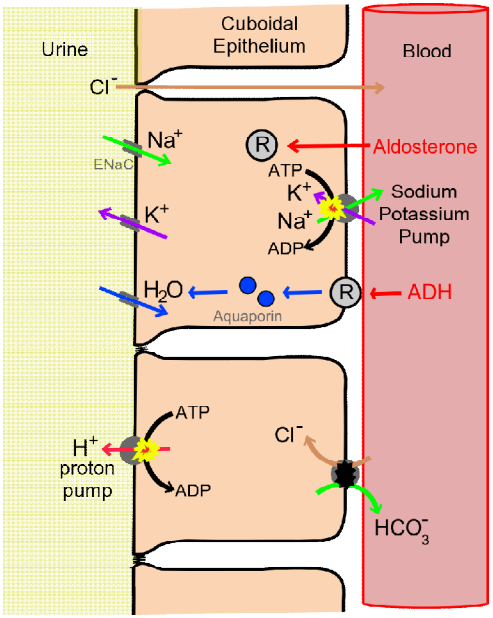

Canrenone



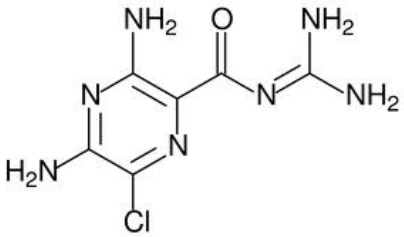
Aldosterone

Direct channel blockers

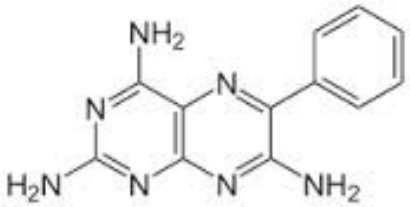
- Directly interfere with Na entry through epithelial Na^+ channels (eNaC)
- Since K^+ secretion is coupled with Na^+ entry in this region
- Both categories are thus K^+ –sparing diuretics



Direct channel blockers



Amiloride



Triamterene

Clinical Indications

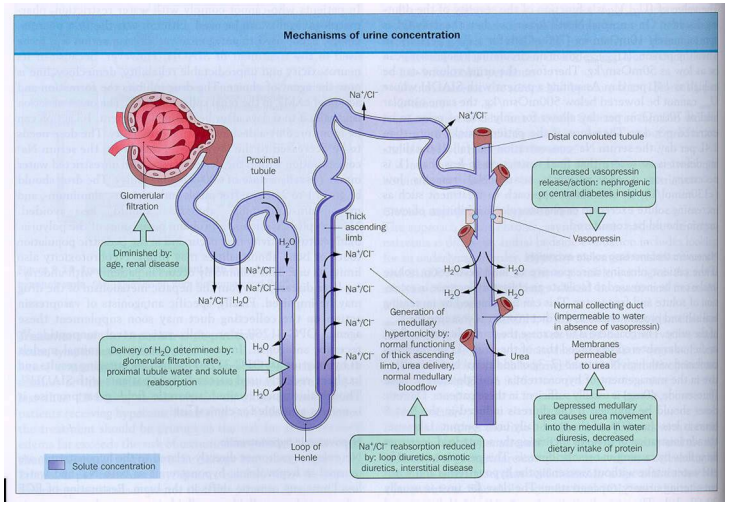
- Most useful in conditions of Aldosterone excess (hyperaldosteronism)
- This excess can be due to
  - Primary hypersecretion (Conn's syndrome .)
  - Secondary hypersecretion (evoked by heart failure, liver cirrhosis etc conditions with lower blood volume)
  - Use of loop, thiazide diuretics exacerbate volume contraction
  - Due to enhanced Aldosterone, higher Na^+ presentation, K^+ wasting occurs, K^+-sparing agents prevent wasting
- These drugs have mild action, should be avoided in conditions where potent diuretic action is desired

Toxicity

- Hyperkalemia
  - Can cause mild, moderate or even life threatening hyperkalemia
  - Risk increased in case of renal disease or renin inhibitors
  - Toxicity more common when used alone
- Hyperchloremic Metabolic Acidosis
  - Inhibit H^+ secretion along with K^+ causing acidosis
- Kidney stones
  - Triamterene is slightly soluble in urine, may ppt causing kidney stones

Agents that alter water excretion
Osmotic Diuretics

- Proximal tubule, descending limb are water permeable
- Any osmotic active agent filtered but not absorbed causes water retention
- Prototype agent : Mannitol

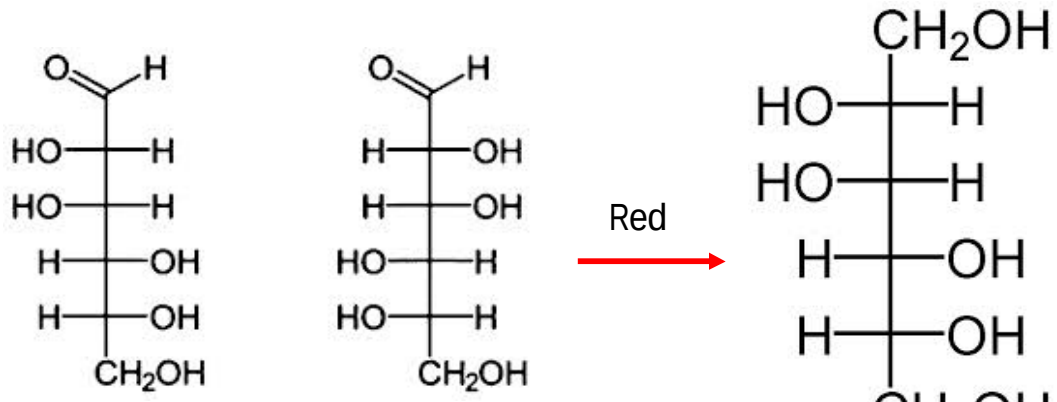


Pharmacodynamics & Pharmacokinetics

- PD:
  - Major effect on Proximal tubule & descending limb
  - Presence of non-absorbable solute counters other osmotic forces
  - Increase in urine flow decreases the contact time for Na^+, water reabsorption
- PK:
  - Mannitol poorly absorbed in GI, given IV
  - Not metabolized, excreted by filtration within 30- 60 min (No reabsorption or secretion)

Mannitol Structure

- Sugar alcohol derived from sugar
- Derived from Mannose by reduction



Mannose

Mannitol

Clinical Indications

- Increase in Urine Volume
  - Used to increase water excretion in preference to Na^+ excretion
  - To maintain urine volume & prevent anuria (No urine formation)
- Reduction of intra-cranial, intra-ocular pressure
  - Osmotic diuretics alter osmotic forces; water leaves cell reducing intra-cellular volume
  - This effect used to lower intra-cranial pressure in neurological conditions
  - & lower intra-ocular pressure before ophthalmic procedures

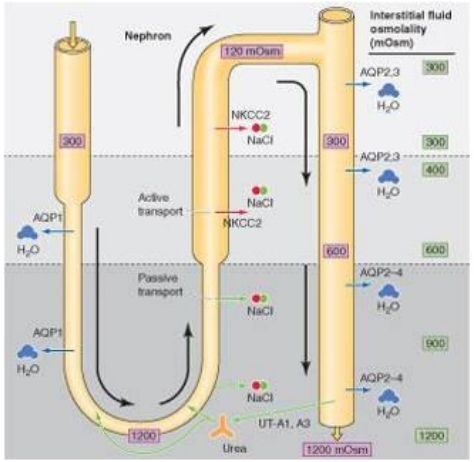
Toxicity

- Extracellular Volume expansion:
  - Mannitol rapidly distributed in extracellular compartment, extracts water from cells
  - Leads to expansion of extracellular volume, hyponatremia
  - This can complicate heart failure, lead to edema

- Dehydration, Hyperkalemia, Hypernatremia:
  - Excessive use leads to water losses leading to dehydration, hypernatremia
  - Water extraction from cells leads to hyperkalemia (increase in K^+ conc)

Water extraction at Collection tubule

- Regulated system of water channels for water reabsorption
- **ADH or arginine vasopressin** controls the movement of water by inserting pre-formed water channels (Aquaporins)
- In absence of ADH, collecting tubule is impermeable to water
- ADH increases water permeability leads to formation of conc urine



ADH Antagonist

- ADH antagonist block effects of ADH leading to diuresis
- Non-selective agents:
  - Lithium, demeclocycline
- Selective agents:
  - Vasopressin receptor (V2) antagonist
  - Conivaptan, tolvaptan, *lixivaptan, satavaptan*
  - Conivaptan is administered IV
  - Tolvaptan is administered orally, half life of 12-24 hrs

Clinical Indications

- Syndrome of Inappropriate ADH secretion (SIADH)
  - Water restriction is preferred choice in SIADH
  - If doesn't work then use ADH antagonist
- Other causes of elevated ADH:
  - Low blood volume due to various reasons leads to elevated ADH levels
  - ADH antagonist useful in this setting