Genitourinary System Module

Pharmacology
Lecture (2)

Diuretics (2)

Faculty of Medicine
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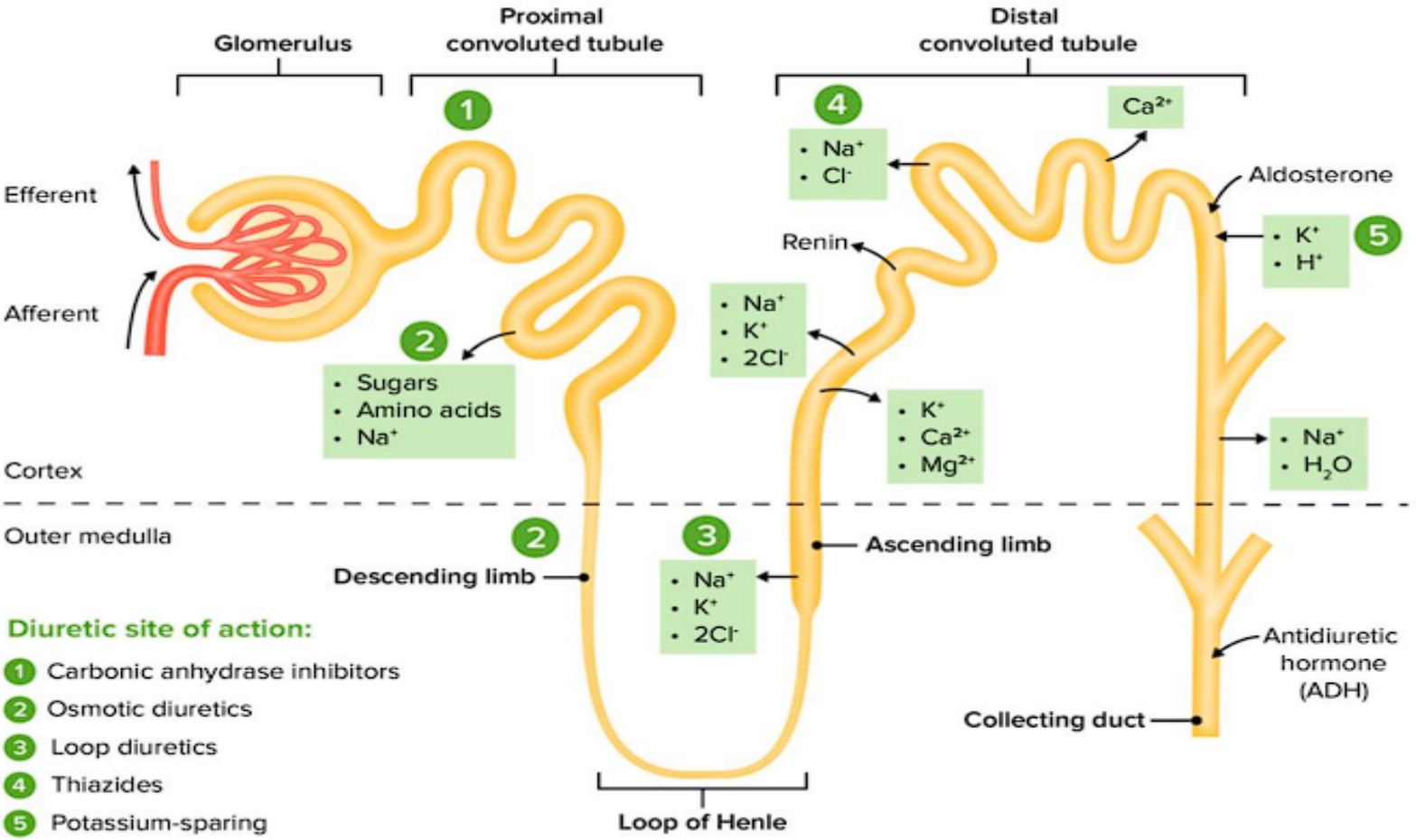
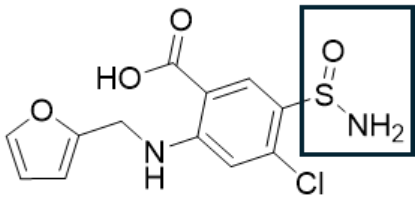

Glomerulus
Proximal convoluted tubule
Distal convoluted tubule
Efferent
Afferent
Cortex
Outer medulla
1
2
• Sugars
• Amino acids
• Na+
4
• Na+
• Cl-
Ca2+
Aldosterone
5
• K+
• H+
Renin
• Na+
• K+
• 2Cl-
• K+
• Ca2+
• Mg2+
• Na+
• H2O
2
Descending limb
3
• Na+
• K+
• 2Cl-
Ascending limb
Antidiuretic hormone (ADH)
Collecting duct
Loop of Henle
Diuretic site of action:
1 Carbonic anhydrase inhibitors
2 Osmotic diuretics
3 Loop diuretics
4 Thiazides
5 Potassium-sparing

Loop Diuretics

- Diuretics inhibit the cotransport of Na + /K+ /2Cl− in the luminal membrane in the thick ascending limb of the loop of Henle
- They reach their target site by active secretion from the blood into the urine by the organic acid transporters present in the proximal tubules.

- Drugs:
  - Furosemide(Lasix): most commonly used
  - Bumetanide
  - Torsemide
  - Ethacrynic acid: used infrequently due to its adverse effect profile.



Furosemide

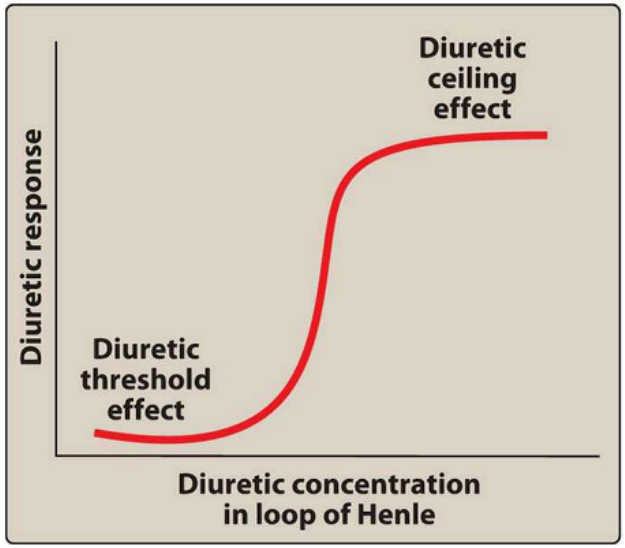
All, but ethacrynic acid contain sulfonamide group, but generally don't cause allergic rxn in patients who are allergic to sulfonamide antibiotics.

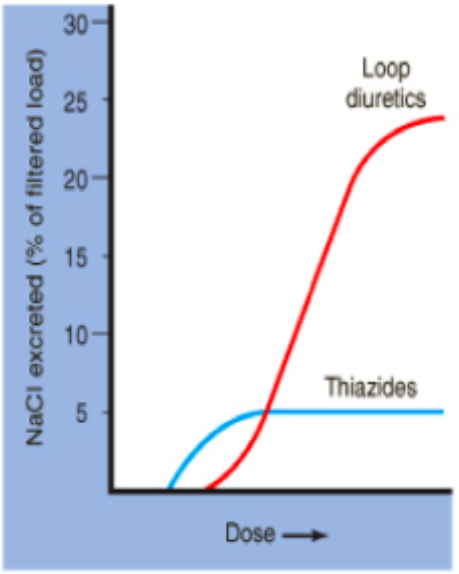
Actions

1. **Diuresis:** inhibition of Na/K/2Cl cotransporter results in reduced reabsorption of these ions into the renal medulla, creating a lower osmotic pressure in the medulla, which then reduces water reabsorption in water permeable segments.

   - 25% to 30% of filtered NaCl is filtered in the ascending loop therefore loop diuretics have the greatest diuretic effect .
   - They show ‘high celling effect’ with great diuretic response to a small change in the dose.

High Vs low ceiling diuretics



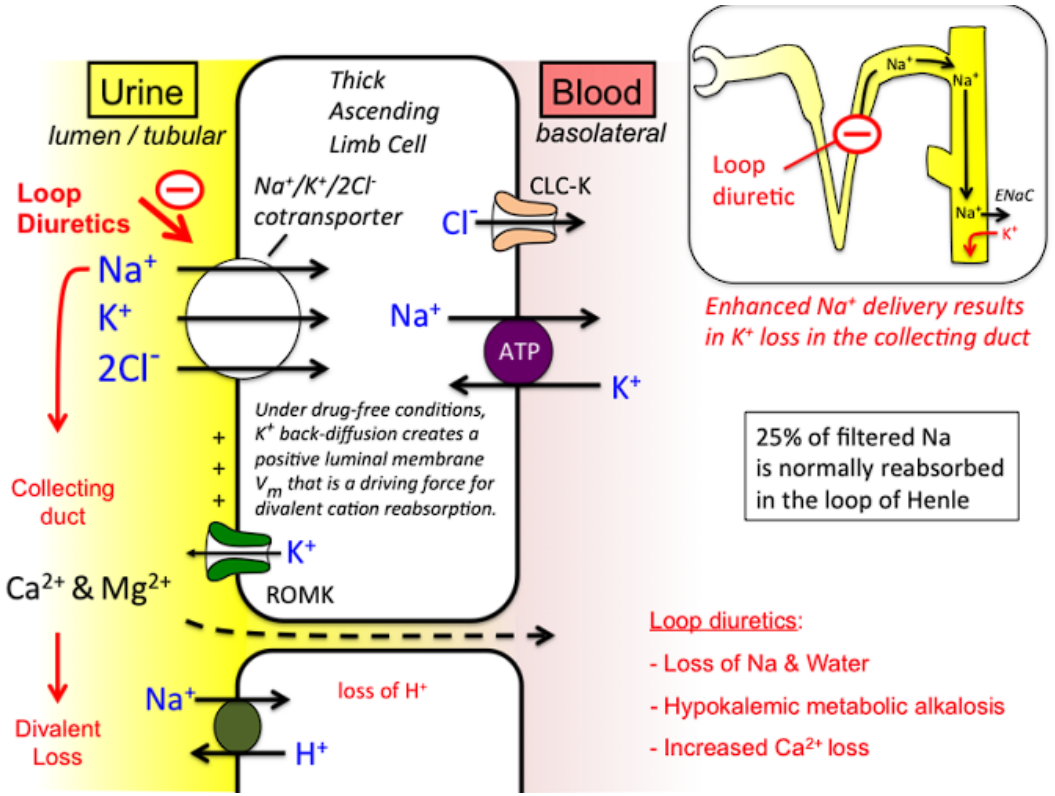


Actions

2. Increased urinary calcium excretion: Unlike thiazides, loop diuretics increase the Ca^{2+} content of urine. They are used in hypercalcemia treatment
3. Venodilatation : loop diuretics cause acute venodilatation and reduce left ventricular filling pressures via enhanced prostaglandin synthesis.

Effects of loop diuretics on ion composition of urine and blood

Urine	Blood
↑Na+	Hyponatremia
↑Cl-	Hypochloremia
↑ H2O	Hypovolemia
↑K+	Hypokalemia
↑ H+	Alkalosis
↑Mg++	Hypomagnesemia
↑Ca++	Hypocalcemia



Loop diuretics: Pharmacokinetics

- Loop diuretics are administered orally or parenterally.
- Furosemide has unpredictable bioavailability of 10% to 90% after oral administration.
- Bumetanide and torsemide have reliable bioavailability of 80% to 100%, which makes these agents preferred for oral therapy.
- Furosemide and bumetanide DoA is ˜ 6h, and moderately longer for torsemide.

Therapeutic uses

1. Edema: loop diuretics are used more for the therapy of edema than long term therapy of hypertension. They are the drugs of choice for treatment of pulmonary edema and acute/chronic peripheral edema caused from heart failure or renal impairment. Because of their rapid onset of action, the drugs are useful in emergency situations such as acute pulmonary edema.
2. Hypercalcemia
3. Hyperkalemia

Adverse effects

1. Acute hypovolemia: Loop diuretics can cause a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmias.
2. Hypokalemia: the most common adverse effect of the loop diuretics. The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis. Use of potassium-sparing diuretics or supplementation with K^+ can prevent the development of hypokalemia.
3. Hypomagnesemia
4. Ototoxicity: Reversible or permanent hearing loss may occur with loop diuretics, particularly when at fast rates, at high doses, or when used in conjunction with other ototoxic drugs (for example, aminoglycoside antibiotics). Ethacrynic acid has been known to have a more ototoxic potential than the other members
5. Hyperuricemia: may cause or exacerbate gouty attacks.

Drug-drug interactions

- Aminoglycosides and cephalosporins: Risk of ototoxicity
- Digoxin: combination with loop diuretics (also with thiazide and potassium-sparing diuretics) increases the risk of digoxin toxicity (anorexia, nausea, neurological symptoms, fatal arrhythmias).
- NSAIDs reduces efficacy of diuretics.
- Lithium: can cause lithium retention.

Causes & management of loop diuretics Resistance

Diuretics resistance: can be defined as an unsatisfactory rate of diuresis/ natriuresis despite an adequate diuretic regimen

A. **Pharmacokinetic Causes:**

I. Defective intestinal absorption in decompensated HF (of oral furosemide)

Give the diuretic IV.

II. Defective plasma protein binding in hypoalbuminemic states (liver cirrhosis & nephrotic syndrome) → extravascular diffusion of diuretic →↓ renal excretion

Mix the diuretic with albumin prior to infusion.

III. Defective excretion of diuretics by the acid secretory system in renal impairment due to accumulation of acids.

↑ **Dose of diuretics**

Causes & management of loop diuretics resistance

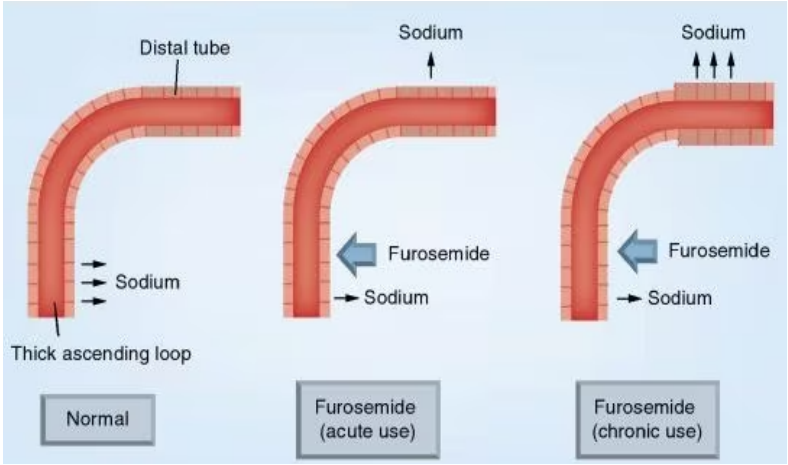
B. Pharmacodynamic Causes

I. Hypertrophy of distal tubular cells (on chronic use →↑ Na+ reabsorption →blunts the action of the diuretic)

Add thiazides

II. activation Na retaining mechanism such as aldosterone. Na^+ lost by loop diuretics reabsorbed in exchange with K^+ in distal tubules (under the effect of aldosterone):

Add the aldosterone antagonist spironolactone.

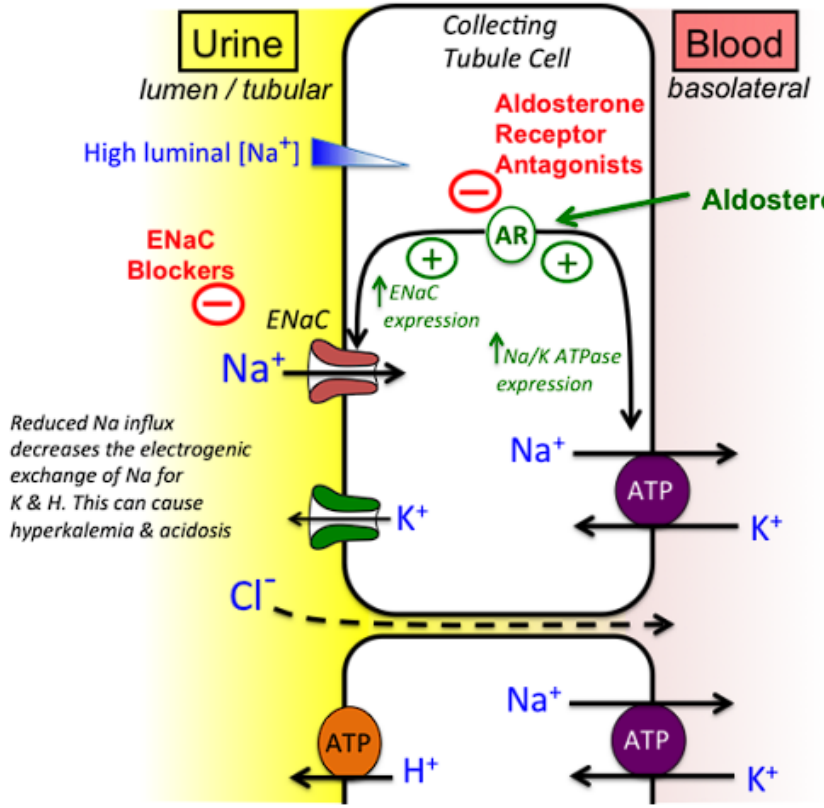


Potassium-Sparing Diuretics

- Potassium-sparing diuretics act in the collecting tubule to inhibit Na^+ reabsorption and K^+ excretion
- Potassium levels must be monitored in patients treated with potassium-sparing diuretics.
- These drugs should be avoided in patients with severe renal dysfunction because of the increased risk of hyperkalemia
- They include: aldosterone antagonists and epithelial sodium channel blockers.

Aldosterone antagonists: spironolactone and eplerenone

- Both synthetic antagonists of aldosterone.
- Aldosterone promotes expression and translocation of ENac (epithelium sodium channel) and expression of Na/K ATPase.
- Aldosterone antagonists prevent Na^+ reabsorption and K+ and H+ secretion.
- Eplerenone is more selective and causes less endocrine effects (gynecomastia) than spironolactone, which also binds to progesterone and androgen receptors.



2-5% of filtered Na
is normally reabsorbed
in the collecting duct

Aldosterone antagonists

- Loss of Na & Water
- Hyperkalemia
- Some risk for acidosis

Therapeutic uses

1. Edema: Given in high doses for trx of edema associated with secondary hyperaldosteronism, such as hepatic cirrhosis and nephrotic syndrome. Spironolactone is the diuretic of choice in patients with hepatic cirrhosis with fluid in the peritoneal cavity (ascites).
2. Hypokalemia: given in conjunction with thiazide or loop diuretics to prevent K+ excretion that occurs with those diuretics.

Therapeutic uses

3. Heart failure: given at lower doses to prevent myocardial remodeling mediated by aldosterone. Decrease mortality in patients with reduced ejection fraction.
4. Resistant hypertension: this effect can be seen in those with or without elevated aldosterone levels.
5. Polycystic ovary syndrome Spironolactone is often used off-label for the treatment of polycystic ovary syndrome, it blocks androgen receptors and inhibiting steroid synthesis

Adverse effects

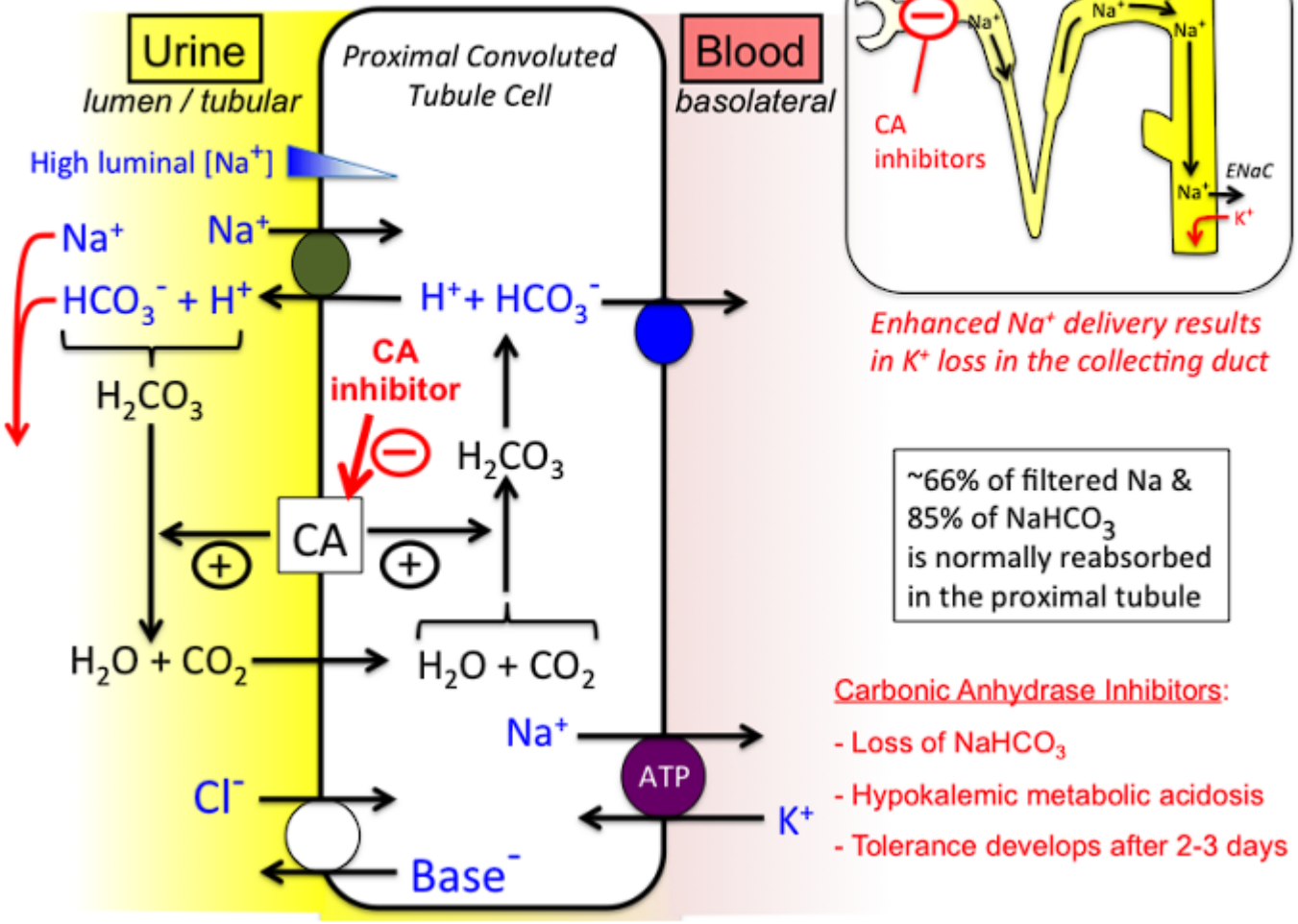
1. Hyperkalemia: The most common side effect. Dose-dependent and increases with renal dysfunction or use of other potassium-sparing agents such as angiotensin-converting enzyme inhibitors and potassium supplements.
2. Gynecomastia in male patients and menstrual irregulation in female: only associated with Spironolactone use.

Triamterene and amiloride

- Block epithelial sodium channels, resulting in a decrease in Na^+ /K^+ exchange.
- Commonly used in combination with other diuretics, for their potassium-sparing properties.

Carbonic Anhydrase Inhibitor

- Acetazolamide inhibits carbonic anhydrase located intracellularly (cytoplasm) and on the apical membrane of the proximal tubular epithelium.
- There is decreased ability to exchange Na^+ for H^+
- $HCO3^-$ (bicarbonate) is retained in the lumen, with marked elevation in urinary pH.
- The loss of $HCO3^-$ causes a hyperchloremic metabolic acidosis.
- Less efficacious than the thiazide or loop diuretics. Most of the fluid loss is reclaimed in loop of Henle.


Urine
lumen / tubular
Proximal Convoluted Tubule Cell
Blood
basolateral
High luminal [Na+]
Na+
Na+
HCO3- + H+
H+ + HCO3-
H2CO3
CA inhibitor
H2CO3
CA
H2O + CO2
H2O + CO2
Na+
ATP
Cl-
K+
Base-
CA inhibitors
Na+
Na+
Na+
ENaC
K+
Enhanced Na+ delivery results in K+ loss in the collecting duct
~66% of filtered Na & 85% of NaHCO3 is normally reabsorbed in the proximal tubule
Carbonic Anhydrase Inhibitors:
- Loss of NaHCO3
- Hypokalemic metabolic acidosis
- Tolerance develops after 2-3 days

Therapeutic uses

1. Glaucoma: Oral acetazolamide decreases the production of aqueous humor and reduces intraocular pressure in patients with chronic open-angle glaucoma. Dorzolamide & Brinzolamide are given by topical application to minimize systemic and renal side effects
2. Altitude sickness used in the prophylaxis of symptoms of altitude sickness.

Adverse effects

1. Metabolic acidosis (mild)
2. Potassium depletion
3. Renal stone formation
4. Drowsiness
5. Paresthesia (tingling sensation)

The drug should be avoided in patients with hepatic cirrhosis, because it could lead to a decreased excretion of $NH4^+$.

Osmotic Diuretics: Mannitol

- Hydrophilic Sugar alcohol filtered through the glomerulus
- Filtered substances that undergo little or no reabsorption result in a higher osmolarity of the tubular fluid. This prevents further water reabsorption at the descending loop of Henle and proximal convoluted tubule.
- It produces a greater loss of water compared to sodium and potassium.
- These agents are not useful for treating conditions in which Na + retention occurs.

Osmotic Diuretics: Mannitol

Uses:

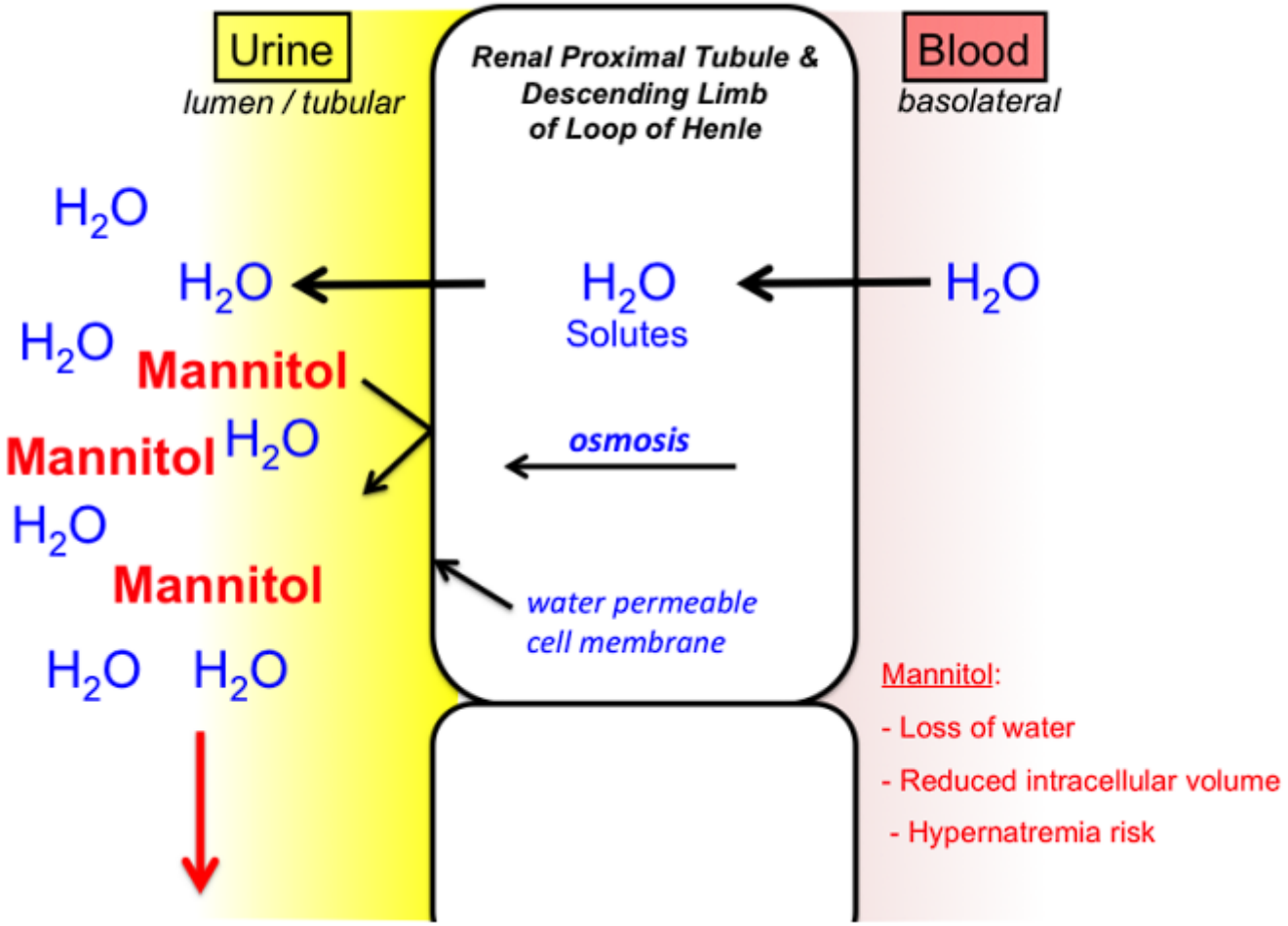
1. Maintenance of urine flow following acute toxic ingestion of substances capable of producing acute renal failure.
2. Mainstay of treatment for patients with increased intracranial pressure.

Mannitol is not absorbed when given orally and should be given intravenously

Adverse effects:

Dehydration and extracellular water expansion from the osmotic effects in the systemic circulation. This causes hyponatremia until diuresis occurs.

Mannitol is not commonly used in patients with edema, because the initially it induces further volume expansion, which can precipitate the development of pulmonary edema in patients with heart failure.


Urine
lumen / tubular
Renal Proximal Tubule & Descending Limb of Loop of Henle
Blood
basolateral
H2O
H2O
H2O
H2O
Solutes
H2O
H2O
Mannitol
Mannitol
H2O
osmosis
H2O
Mannitol
water permeable cell membrane
H2O
H2O
Mannitol:
- Loss of water
- Reduced intracellular volume
- Hypernatremia risk