

Genitourinary System Module

Pharmacology

Diuretics (1)

Faculty of Medicine
The Hashemite University

Ola Ebbeni (BDS, MSc, PhD)

Diuretics: Overview

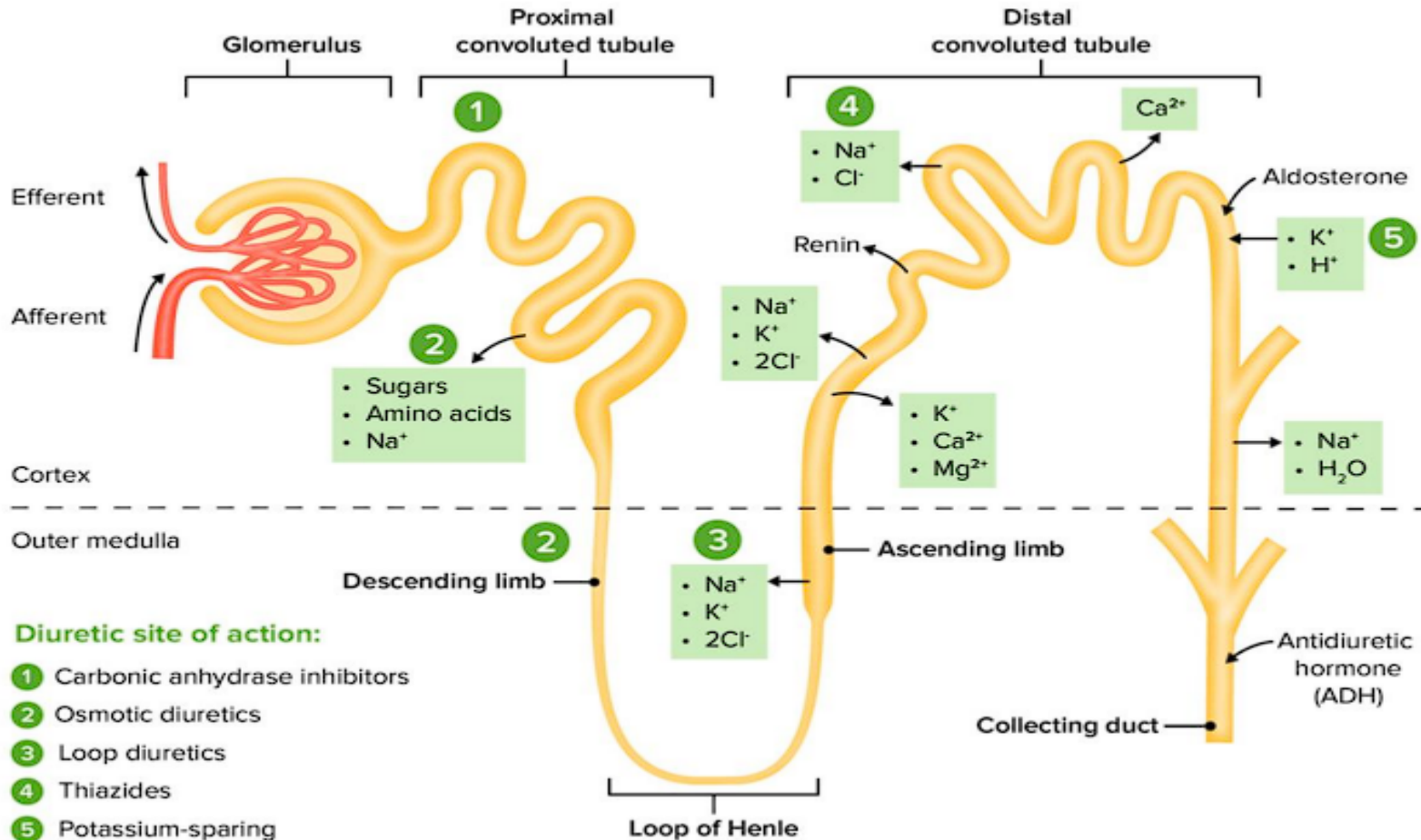
- Diuretics promotes excretion of water and electrolytes by the kidneys
- Increase the rate of urine flow and the 24h-urine volume
- Most diuretic acts by inhibiting renal ion transporters that decrease the reabsorption of Na^+ at different sites in the nephron. As a result, Na^+ and other ions enter the urine in greater than normal amounts along with water.
- They often change urine pH and ionic composition of urine and blood
- Indications: edema, hypertension, glaucoma, heart failure.

Diuretics: Classes

- Thiazides
- Loop diuretics
- Potassium sparing diuretics
- Carbonic anhydrase inhibitors
- Mannitol (Osmotic Diuretics)

- *(will be discussed according to the frequency of their use)*

Site of action



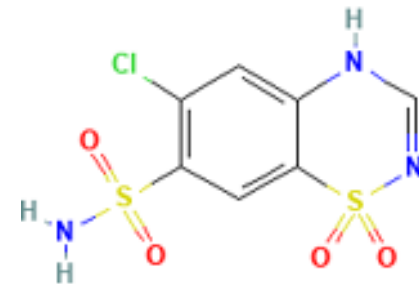
16% to 20% of the blood plasma entering the kidneys is filtered into Bowman's capsule. The filtrate, contains most of the low molecular weight plasma components in concentrations similar to that in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, as well as electrolytes, such as Na^+ , K^+ , and Cl^- . The kidney regulates the ionic composition and volume of urine by active reabsorption or secretion of ions and/or passive reabsorption of water

Thiazides

- Thiazides are the most widely used diuretics because of their antihypertensive effects.
- They are sulfonamide related organic acids that do not generally cause hypersensitivity reactions in patients with allergies to sulfonamide antimicrobials

Thiazides:

- Chlorothiazides
- Hydrochlorothiazide



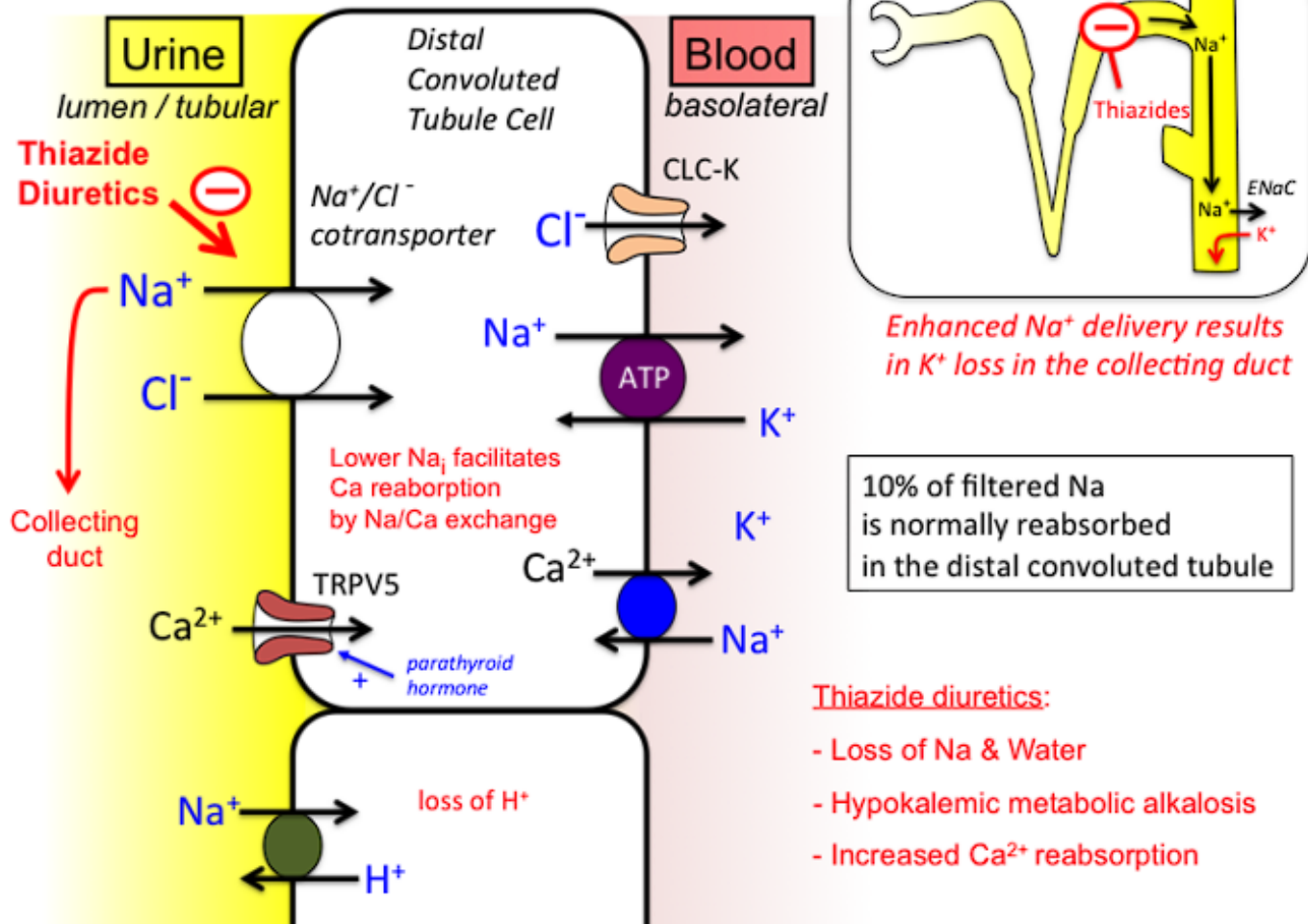
Chlorothiazides

Thiazide-like diuretics:

- Chlorthalidone
- Indapamide
- Metolazone

Mechanism

- **Secreted into the proximal tubule by an organic secretory mechanism.** (Thiazides compete for the same secretory process by which uric acid is secreted into the proximal tubule).
- They block the sodium-chloride (Na/Cl) channel expressed in the proximal segment of the distal convoluted tubule (DCT), resulting in increased excretion of Na,Cl ions.
- Thiazides enhance Ca^{2+} reabsorption in the distal convoluted tubule, by increasing $\text{Na}^{+}/\text{Ca}^{2+}$ exchange. Thiazide diuretics also reduce the urinary excretion of Ca^{2+} .
- Natriuresis (excretion of sodium in the urine) may be accompanied by some loss of potassium and H^{+} .

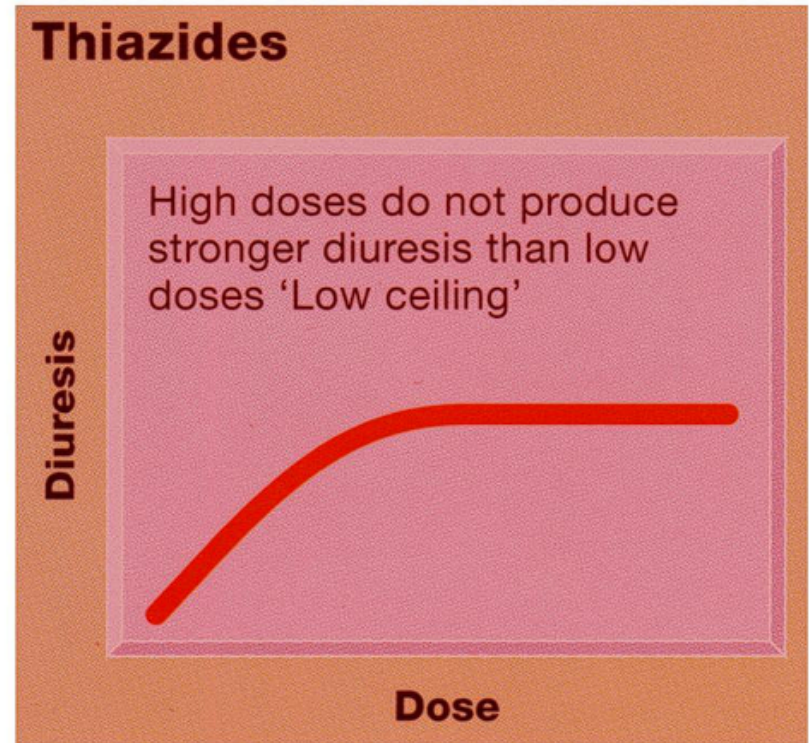


Thiazide diuretics compete for the chloride binding site on the **Na/Cl cotransporter** that is **selectively expressed in the distal convoluted tubule**, inhibiting its ability to transport ions. Inhibition of this cotransporter lowers intracellular Na, which in turn results in a lowering of intracellular calcium mediated by Na/Ca exchange expressed on the basolateral membrane. This **facilitates the diffusion of calcium** through calcium ion channels expressed on the lumen membrane. The inhibition of Na transport in this segment results in greater delivery of sodium to the collecting duct, where enhanced Na influx through epithelial Na channels stimulates potassium efflux, which can result in the **development of hypokalemia**.

Thiazides are 'low ceiling diuretics'

Thiazides have moderate efficacy as diuretics, as 90% of glomerular filtrate has already been reabsorbed.

The dose-response curve flattens rapidly



Pharmacokinetics

- Thiazides are effective orally with bioavailability of 60%–70%, (except for chlorothiazide is given IV due its low bioavailability (15-30%))
- Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure
- exhibit a prolonged half-life (approximately 10 to 15 hours).
- Excretion: unmodified in the urine ((except indapamide it undergoes hepatic metabolism and is excreted in both urine and bile))

Therapeutic uses

1. Hypertension: 1st line drugs for uncomplicated hypertension. They have low cost and well tolerated

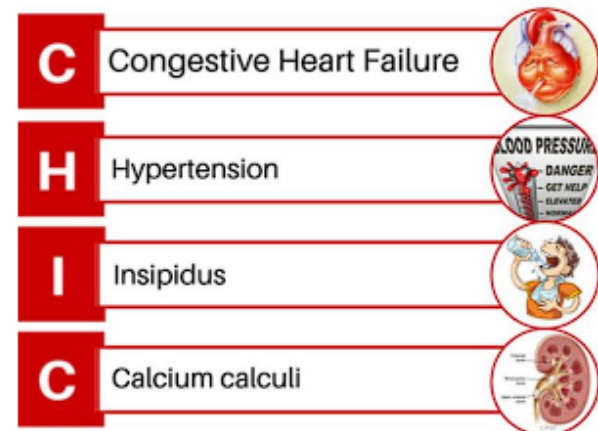
An initial reduction in blood pressure results from a decrease in blood volume and, therefore, a decrease in cardiac output. With continued therapy, blood volume returns to baseline. However, antihypertensive effects continue, resulting from reduced total peripheral vascular resistance (unclear mechanism).

2. Heart failure: Loop diuretics are the diuretics of choice for reducing extracellular volume in heart failure. However, thiazide diuretics can be added to patients with resistance to loop diuretics. It requires careful monitoring of hypokalemia.

Therapeutic uses

3. Hypercalciuria: used in idiopathic hypercalciuria and calcium oxalate stones in the urinary tract, because they inhibit urinary Ca^{2+} excretion.
4. Nephrogenic Diabetes insipidus: caused by the collecting ducts not responding to ADH. Patients present with polyuria (increased urination rate) and polydipsia (increased thirst). The paradoxical effect of diuretics in reducing urine output is not clear. The urine volume of such individuals may drop from 11 to about 3 L/d when treated with thiazides.

Thiazides Indications "CHIC"

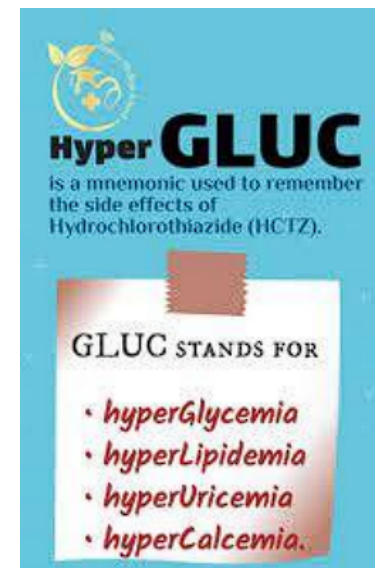


Side effects

- Hypokalemia: the most frequent problem with the thiazide diuretics. serum K^+ should be measured periodically (more frequently at the beginning of therapy). Potassium supplementation or combination with a potassium-sparing diuretic may be required. Low-sodium diets blunt the potassium depletion caused by thiazide diuretics.
- Hypomagnesemia
- Hyponatremia
- Hypovolemia: This can cause orthostatic hypotension or light-headedness.

Side effects

- Hyperglycemia possibly due to impaired release of insulin related to hypokalemia. Patients with diabetes still benefit from thiazide therapy, but should monitor glucose to assess the need for an adjustment in diabetes therapy if thiazides are initiated.
- Hyperlipidemia: Dyslipidemia can be produced by high doses of thiazides (not typically used).
- Hyperuricemia (Why?) uric acid deposits in the joints and may precipitate a gouty attack in predisposed individuals. Therefore, thiazides should be used with caution in patients with gout or high levels of uric acid.
- Hypercalcemia



Thiazide efficacy

- Drug and diseases that affects thiazides efficacy:

- 1-Renal failure and heart failure: results in decreased renal blood flow, which reduces the diuretic effects as thiazides must be secreted into the proximal tubule to be effective.

- 2-Concomitant use of NSAIDs inhibits the production of prostaglandins, which inhibits renal blood flow.

- Lithium: thiazide reduces renal clearance of lithium and can cause rapid increase in lithium serum level.