Thiazides

*most widely used diuretics because of their antihypertensive effects.
*sulfonamide related organic acids, don't cause hypersensitivity reactions in patients with allergies to sulfonamide antimicrobials

Thiazides:

- Chlorothiazides
- Hydrochlorothiazide

Thiazide-like diuretics:

- Chlorthalidone
- Indapamide
- Metolazone

Pharmacokinetics

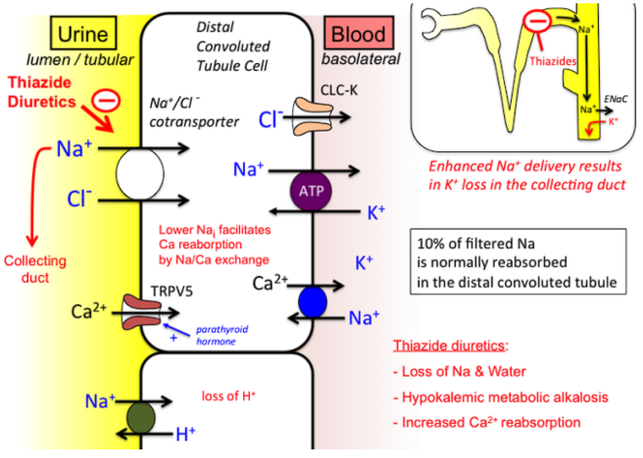
*effective orally with bioavailability of 60%-70%,
(except for chlorothiazide is given IV due its low bioavailability (15-30%)

*Most thiazides take 1 to 3 weeks to produce a stable reduction in BP exhibit a prolonged half-life (approximately 10 - 15 hours).

*Excretion: unmodified in the urine ((except indapamide undergoes hepatic metabolism + excreted in urine and bile))

Mechanism

*Secreted into proximal tubule by organic secretory mechanism.
(compete for the same secretory process of uric acid in proximal tubule).
*block the sodium-chloride (Na/Cl) channel in the prox seg of distal convoluted tubule -> increasing excretion of Na, Cl ions.
*enhance Ca2+ reabsorption in DCT by increasing Na+/Ca2+ exchange.
*reduce the urinary excretion of Ca2+.
*Natriuresis (excretion of sodium in the urine) may be accompanied by some loss of potassium and H+.
*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 hvpokalemia.



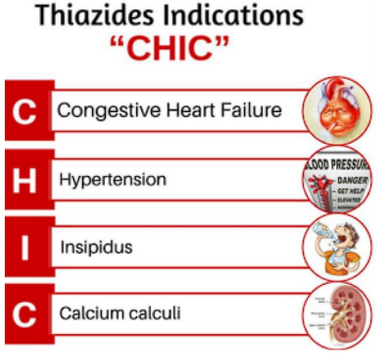
Therapeutic uses

1. Hypertension: 1st line drugs for uncomplicated hypertension (low cost, well tolerated)
Decrease BV -> Decrease CO -> Initial reduction of BP
Continue -> baseline -> reduced total peripheral vascular resistance

2. Heart failure: Loop (diuretics of choice) for reducing extracellular volume in heart failure. Thiazide diuretics can be added to patients with resistance to loop diuretics. It requires careful monitoring of hypokalemia.

3.Hypercalciuria: (idiopathic)+ calcium oxalate stones in UT, they inhibit urinary Ca 2+ excretion.

4.Nephrogenic Diabetes insipidus: when collecting ducts cant respond to ADH. Patients present with polyuria+polydipsia.
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

Side effects

1- 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.

2- Hypomagnesemia.

3- Hyponatremia.

4- Hypovolemia: cause orthostatic hypotension or light-headedness.

5- 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.

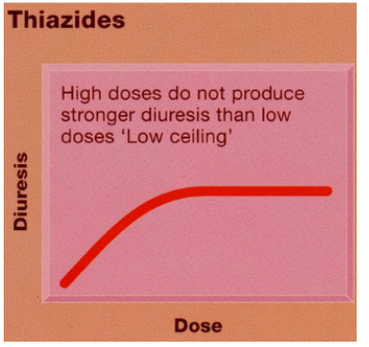
6- Hyperlipidemia: Dyslipidemia can by produced by high doses of thiazides (not typically used).

7- 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.

8- Hypercalcemia

Thiazides are 'low ceiling diuretics'

***moderate efficacy as diuretics, as 90% of glomerular filtrate has already been reabsorbed.**
***The dose-response curve flatten rapidly**



Thiazide efficacy

<u>Drug and diseases that affects thiazides efficacy:</u>
1-<u>Renal failure and heart failure</u>: 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 <u>NSAIDs</u> inhibits the production of prostaglandins, which inhibits renal blood flow.

3-<u>Lithium</u>: thiazide reduces renal clearance of lithium and can cause rapid increase in lithium serum level.