

THIAZIDES

Introduction

- The thiazides are the most widely used of the diuretic drugs
- Thiazide diuretics are sulfonamide derivatives
- All thiazides affect the distal tubule, and all have equal maximum diuretic effects
- Are moderately potent diuretics.
- They are called ceiling diuretics.

- Act within 1-2 hours of oral administration Duration of action 12-24 hours.
- It take 1-3 weeks to produce a stable reduction of blood pressure.
- Administer early in the day
- Thiazide diuretics include: Chlorothiazide and Hydrochlorothiazide. Bendroflumethiazide. Chlortalidone. Metolazone. Xipamide and Indapamide.

Mechanism of action

- Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule this results in water retention.
- Decrease reabsorption of Sodium by inhibition of Na^+/Cl^- cotransporter on the luminal membrane of the distal convoluted tubule.
- Their effect on the proximal convoluted tubule is less.
- The acid-base balance is not usually affected.

- These drugs must be excreted into the tubular lumen to be effective. Therefore with decreased renal function thiazides are not effective.
- Thiazide diuretics decrease the Ca^{2+} content of urine by promoting the reabsorption of Ca^{2+} .

Indication

- **Hypertension**: reduce systolic and diastolic blood pressure. Either used alone or with B-BKs, ACEI.
- **Heart Failure**: Diuretic of choice in reduction of extracellular volume in mild to moderate heart failure if they fail loop diuretic can be used.

- **Hypercalciuria:** They inhibit urinary Ca^{2+} excretion thus of benefit for patients with calcium oxalate stones in the urinary tract.
- **Diabetes insipidus:** by production of a hyperosmolar urine, they substitute antidiuretic hormone in treatment of nephrogenic diabetes insipidus.

Adverse effect

- 1- Hypokalaemia
- 2- Hyponatremia
- 3- Orthostatic hypotension
- 4- Hypercalcemia
- 5- hyperuricemia

Adverse effect (cont)

- 6- Hyperglycemia
- 7- Hyperlipidemia
- 8- Hypersensitivity
- 9- Renal impairment

Diuretic- thiazides

- **Chlorothiazide**: First orally active thiazide with minimum side effects.
- **Newer derivatives:**
- **Hydrochlorothiazide**
- **Bendroflumethiazide**

Thiazide like analogs

- **1- Chlorthalidone:** is a nonthiazide derivative that behaves pharmacologically like *hydrochlorothiazide*. It has a very long duration of action and, therefore, is often used to treat hypertension.
- **2- Metolazone :** is more potent than the thiazides and, unlike the thiazides, causes Na⁺ excretion in advanced renal failure.

- **3- Xipamide and Indapamide:** chemically related to chlortalidone cause less metabolic disturbances, less diabetes mellitus. At low dose act as anti HT with minimal diuretic effect. they are excreted primarily by the biliary system.

Drug –drug Interactions

- *Many of the interactions of hydrochlorothiazide and other thiazides are due to their effects on fluid and electrolyte balance.*
 1. *Diuretic x digitalis glycosides (hypokalaemia & cardiacarrhythmia)*
 2. *Diuretic x astemizole (non-sedating antihistamine) (arrhythmias) (QT)*
 3. *Diuretic x atracurium (enhance N M blocker) . (hypokalaemia)*

- drug may enhance the hypokalemic effect of diuretic.
- Corticosteroids
- B₂ agonists (salbutamol)
- carbenoxolone, (oral ulcer)
- amphotericin B (anti B)
- Reboxetine (I reuptake noradrenaline)
- **Diuretics X antihypertensives**

may enhance hypotension if used with (α-blockers or ACEI

- Orthostatic hypotension associated with diuretics may be enhanced by alcohol, barbiturates, or opioids.

- The antihypertensive effects of diuretics may be antagonised by drugs that cause fluid retention, such as corticosteroids, NSAIDs, or carbenoxolone
- Thiazides X oral hypoglycaemics adjustment require
- NSAIDs nephrotoxicity enhance by thiazides
- Toxicity of Lithium & tetracyclines enhance
- *trimethoprim .A,B* (hyponatraemia) with thiazid
- hydrochlorothiazide X *carbamazepine*.
(hyponatraemia)
- Bile-acid binding resins X hydrochlorothiazide
- (reduce GIT absorption of thiazide)

- Calcium salts X chlorothiazide
- induce milk-alkali syndrome, characterized by hypocalcaemia, metabolic alkalosis, and renal failure
- Hypercalcaemia may also occur in patients taking thiazides with drugs that increase calcium levels, such as vitamin D.

contraindication

- *Hypotension
- *Allergy to sulphur-containing medications
- *Gout
- *Renal failure
- *Hypokalemia
- *May worsen diabetes
- Thiazides can decrease placental perfusion and adversely affect the fetus so should be avoided in pregnancy.