

## Medical

Background

*Pharmacology Team*

### *Loop and Thiazide Diuretics*

*Content:*

- \* Explanation.*
- \* Summary.*
- \* Questions.*

## Loop Diuretics

- **The most efficacious diuretics**

**Efficacy:** High 25-30% **natriuresis**. (Excretion of Na in urine)

**Drugs as:**

- **Furosemide** - torsemide
- **Bumetanide** - Ethacrynic acid

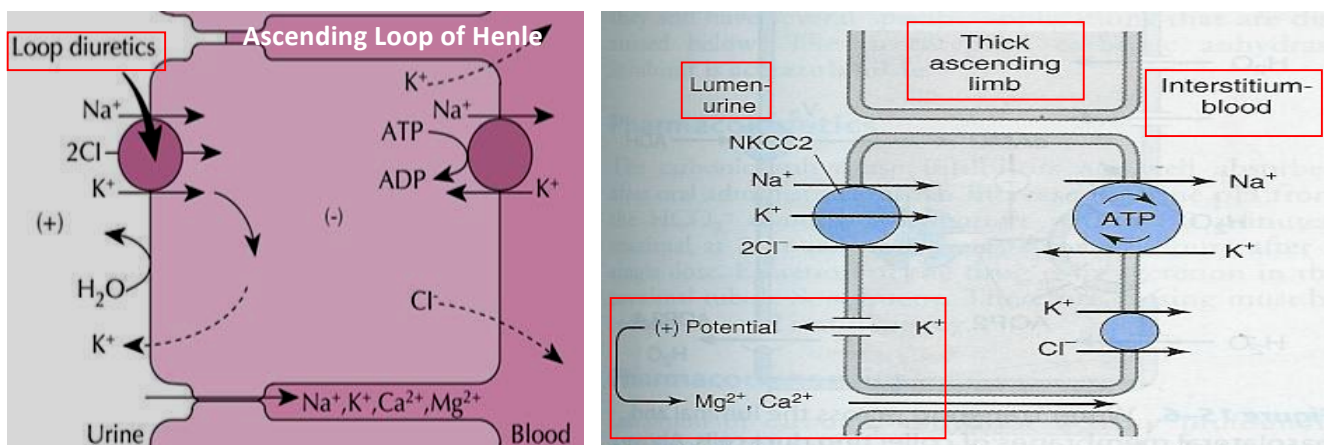
**Mechanism of Action:**

- Inhibit  $\text{Na}^+ / \text{K}^+ / 2 \text{Cl}^-$  Co-transporter (**NKCC2**) in the luminal membrane of the thick ascending loop of Henle (TAL).
- Inhibit  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$  re-absorption.

Re-absorption of Ca and Mg is via: paracellular pathway

The driving force is: Difference in potential

By inhibiting the co-transporter > Back diffusion of K is inhibited > Potential is inhibited



**An Additional Mechanism Of Action:**

Increase synthesis of Prostaglandins > Increase renal blood flow > Increase urine volume

\***Prostaglandins:** Lipid compounds derived from fatty acids, one of their functions is vasodilation.

### Pharmacokinetics:

- Given orally or I. V.
- Has fast onset of action. (suitable for emergency)
- Have short duration of action.
- Excreted by active tubular secretion of weak acids into urine. (competes with uric acid for renal secretory system)

Both Loop and Thiazide diuretics are acidic in nature (their structure is related to Sulfonamide) so, they are excreted by active tubular secretion of weak acids (requires a carrier and energy). Uric acid is also acidic and requires the **same carrier** to be excreted in urine. So if a patient with Gout (Hyperuricemia) takes Loop or Thiazide diuretics, they will compete with Uric acid for the same carrier resulting in: secretion of Loop/Thiazide and retaining uric acid > increase gouty attacks.

Therefore, a patient with Gout SHOULD NOT be given Loop or Thiazide diuretics.

### Pharmacological Effects:

- ↑ Urinary excretion of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$  and  $\text{Mg}^{++}$  (In other words: **Hyponatremia**, **Hypokalemia**, **Hypocalcemia**, **Hypomagnesemia**.) \*If electrolytes are high in the urine, they will be low in the serum)
- ↑ Urine volume.
- ↑ Renal blood flow.

### Uses:

**Drug of choice for emergency situations** as:

- Acute pulmonary edema. (Because they have potent pulmonary vasodilating effects)
- Edema associated with heart failure, nephrotic syndrome.
- Acute hyperkalemia.
- Acute hypercalcemia.

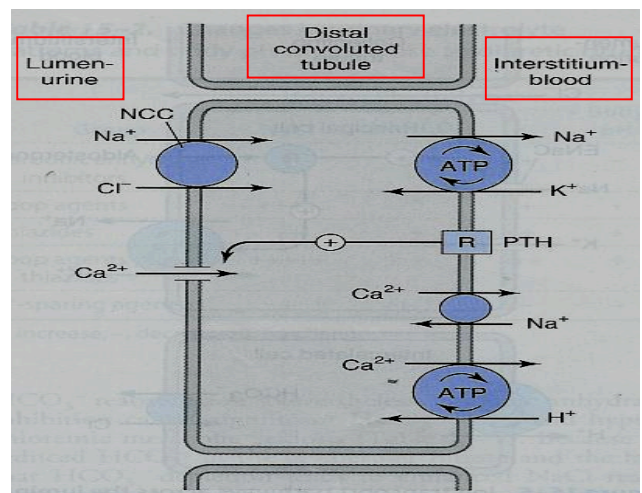
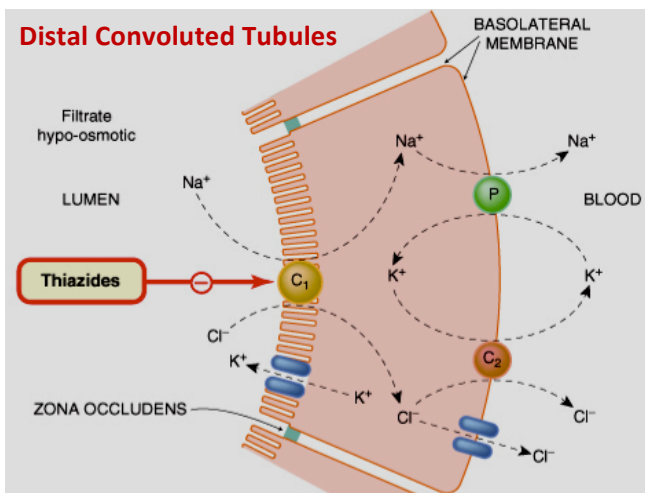
### Adverse Effects:

- Hypokalemia. (Treated by: dietary K supplementation or in combination with K-sparing diuretics)
  - Metabolic alkalosis. (As a result of K secretion in urine which leads to secretion of H)
  - Acute Hypovolemia, postural hypotension. (As a result of **Hyponatremia**)
  - Hyponatremia.
  - Hypomagnesaemia.
  - Hyperuricemia. (increase gouty attack)
  - Ototoxicity. (risk increased if combined with aminoglycosides)
  - Allergic reactions.
-

## Thiazide Diuretics

### Mechanism of action:

- Acts via inhibition of Na/Cl Co-transporter (NCC) on the luminal membrane of distal convoluted tubules.
- **Efficacy:** Moderate 5% natriuresis.
- **Drugs as:** Hydrochlorothiazide - metolazone



### Pharmacokinetics:

- Given orally, slow of onset.
- Long duration of action. (40 h)
- Are secreted by active tubular secretory system of the kidney *may interfere with uric acid secretion and cause hyperuricemia. (Just like Loop diuretics)*

### Pharmacological Effects:

- ↓ Urinary calcium excretion.

\*Ca is re-absorbed in Loop of Henle and Distal Convoluted Tubules through Ca channels and under the effect of Parathyroid hormone (PTH)

Thiazide produces Hypercalcemia by 2 mechanisms:

- 1) Stimulate NA/Ca ATPase > re-absorption of Ca through the Ca channels & extrusion of Na in tubular cells.
- 2) Stimulation of PTH > Stimulation of Ca channels > Stimulation of Ca re-absorption.

- ↑ Calcium re-absorption. (**Hypercalcemia**)
- ↑ Urinary NaCl excretion.
- ↑ Urinary K excretion. (**Hypokalemia**)
- ↑ Urinary magnesium excretion.
- ↑ Uric acid in blood. (**Hyperuricemia**)
- ↑ Glucose in blood. (**Hyperglycemia**: As a result of reduction in releases of Insulin. It is more noticed in diabetic patients)

### Uses:

- Treatment of essential (primary) hypertension. (**cheap-well tolerated**) (If severe, combination with B blockers OR with ACE)
- Treatment of mild heart failure. (**to reduce extracellular volume**) (If severe, we use Loop)
- Nephrolithiasis due to hypercalciuria. (**to increase calcium re-absorption and decrease renal calcium stones**)
- Nephrogenic diabetes insipidus. (**It decrease blood volume and GFR**)

### Adverse Effects:

- Fluid and electrolyte imbalance.
- Hyponatremia.
- Hypovolemia (volume depletion).
- Hypokalemia.
- Metabolic alkalosis.
- Hyperuricaemia (gout).
- **Hypercalcemia.**
- **Hyperglycemia.**

#### **Nephrogenic diabetes insipidus (NDI):**

A disorder in which the kidney tubules do not respond to antidiuretic hormone "vasopressin", resulting in polyuria "passing a large amount of urine".

#### **How is NDI "an extreme diuresis" treated with a diuretic "Thiazide"?!**

The thiazide diuretics will decrease distal convoluted tubule reabsorption of Na and water, thereby causing **diuresis**. This **decreases plasma volume**, thus **lowering GFR** and **enhancing the absorption** of Na and water in the **proximal** nephron. Less fluid reaches the distal nephron, so overall fluid conservation is obtained.

**N.B.** Loop and Thiazide diuretics share most effects and adverse effects, BUT:

Loop: More potent – used in emergencies

Thiazide's adverse effects include: Hypercalcemia & Hyperglycemia

## Questions

Q1) Blockade of the Na/K/2Cl co-transporter is the mechanism of action of:

- A) Metolazone.
- B) Dorzolamide.
- C) Bumetanide.
- D) Mannitol.

Q2) A patient taking diuretics developed hyperglycemia, which of these drugs is the most likely cause?

- A) Furosemide.
- B) Ethcrylic acid.
- C) Spironolactone.
- D) Hydrochlorothiazide

Q3) Loop diuretics effects on ionic excretion:

- A) Increased sodium excretion.
- B) Decreased sodium loss.
- C) Decreased magnesium loss.
- D) Decreased potassium loss.

---

## Answers:

- 1)C
- 2)D
- 3)A