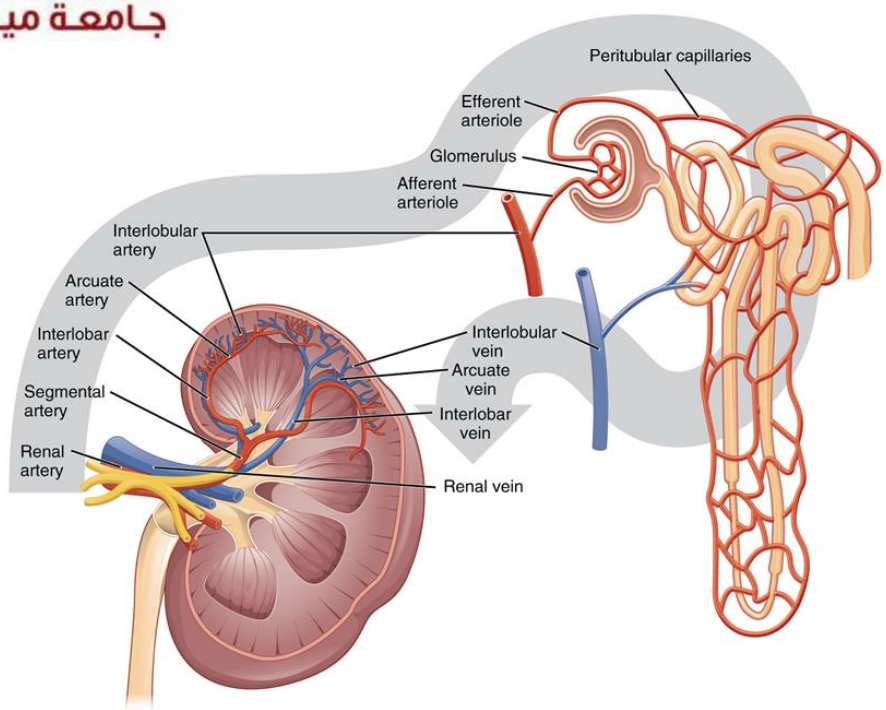


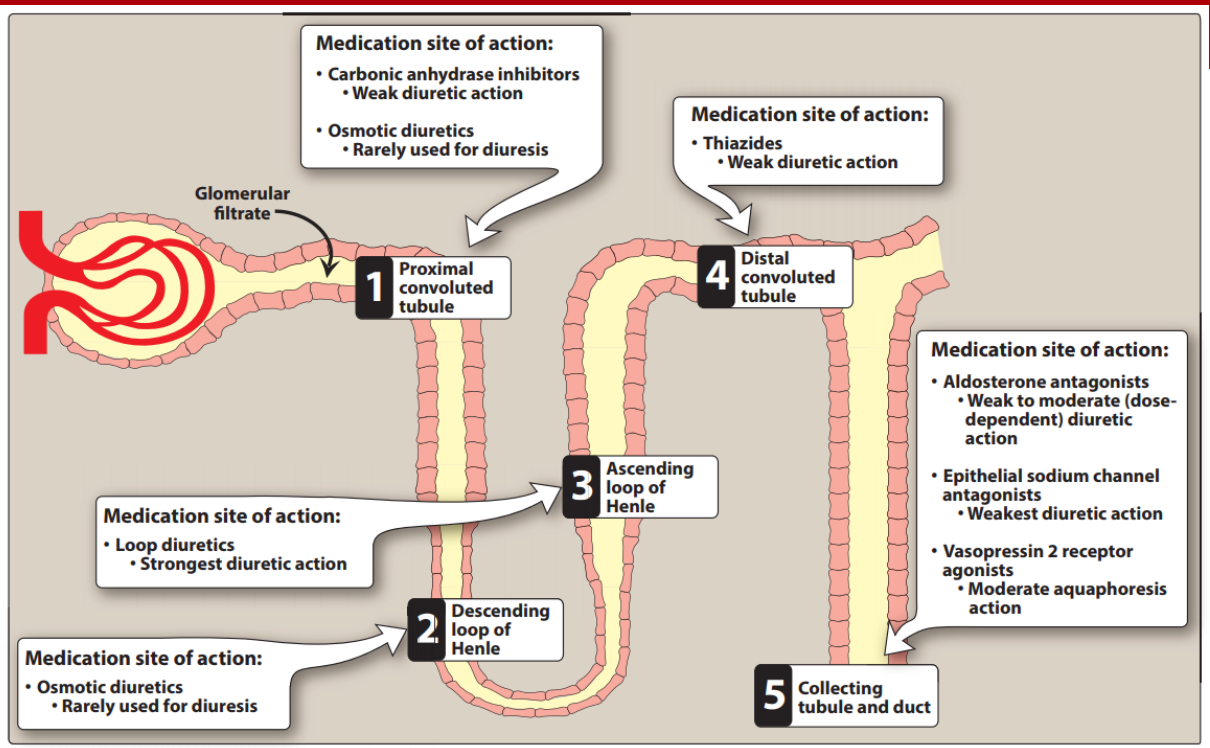
Diuretics

Dr Lobna Aly Abdelzaher

Associate Professor of pharmacology

Faculty of medicine

2025–2026



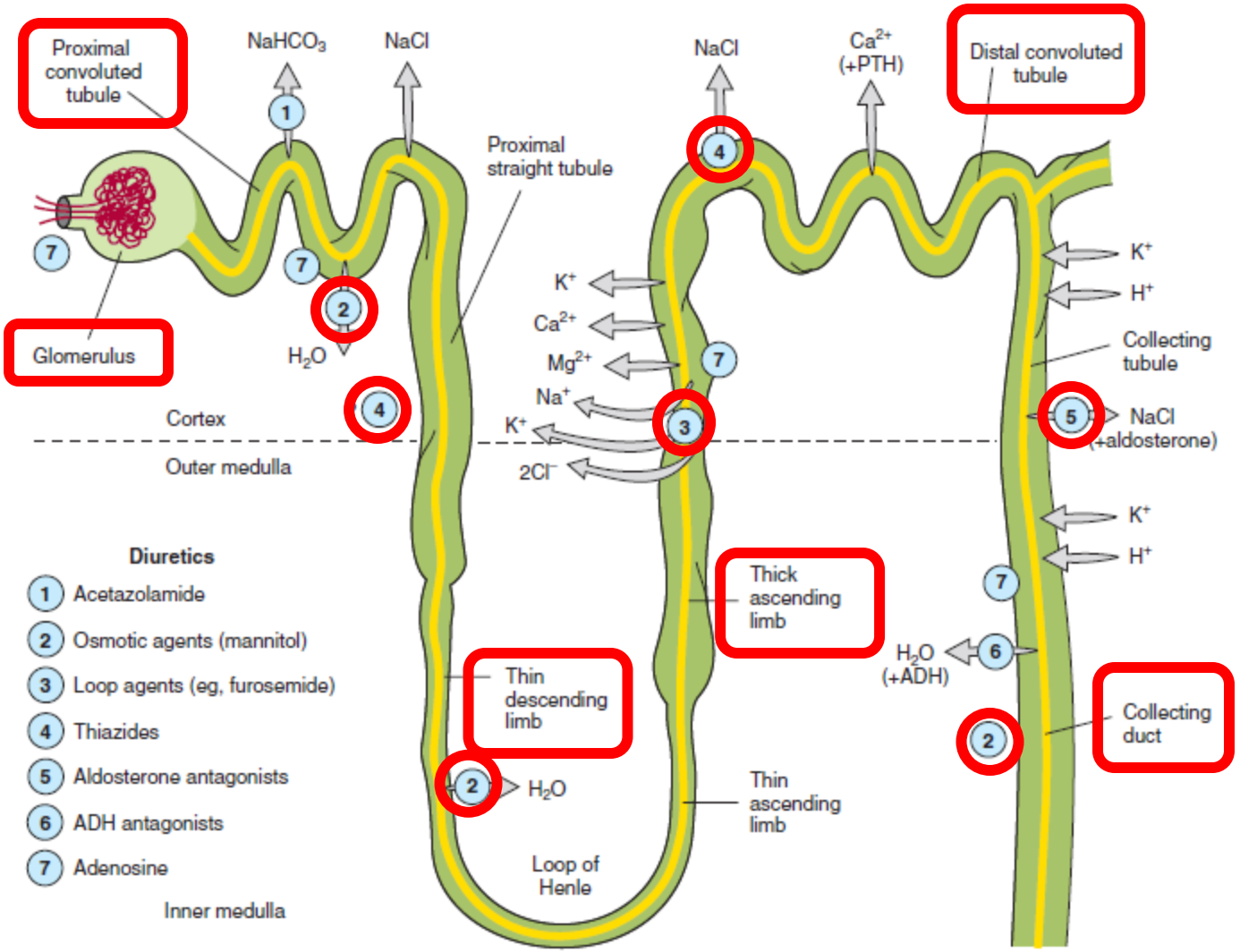
- ***"Diuretics"*** are agents that **increase urine volume by promoting excretion of salt & water from kidneys**.
- They are used in **variety of conditions** as:
  - high blood pressure,
  - glaucoma &
  - edema.

Classification: according to their natriuretic capacity:

a) ***High efficacy:*** excretes 15-25 % of the filtrated sodium as *loop diuretics*.

b) ***Moderate efficacy:*** excretes 5-10 % of the filtrated sodium as *thiazides*.

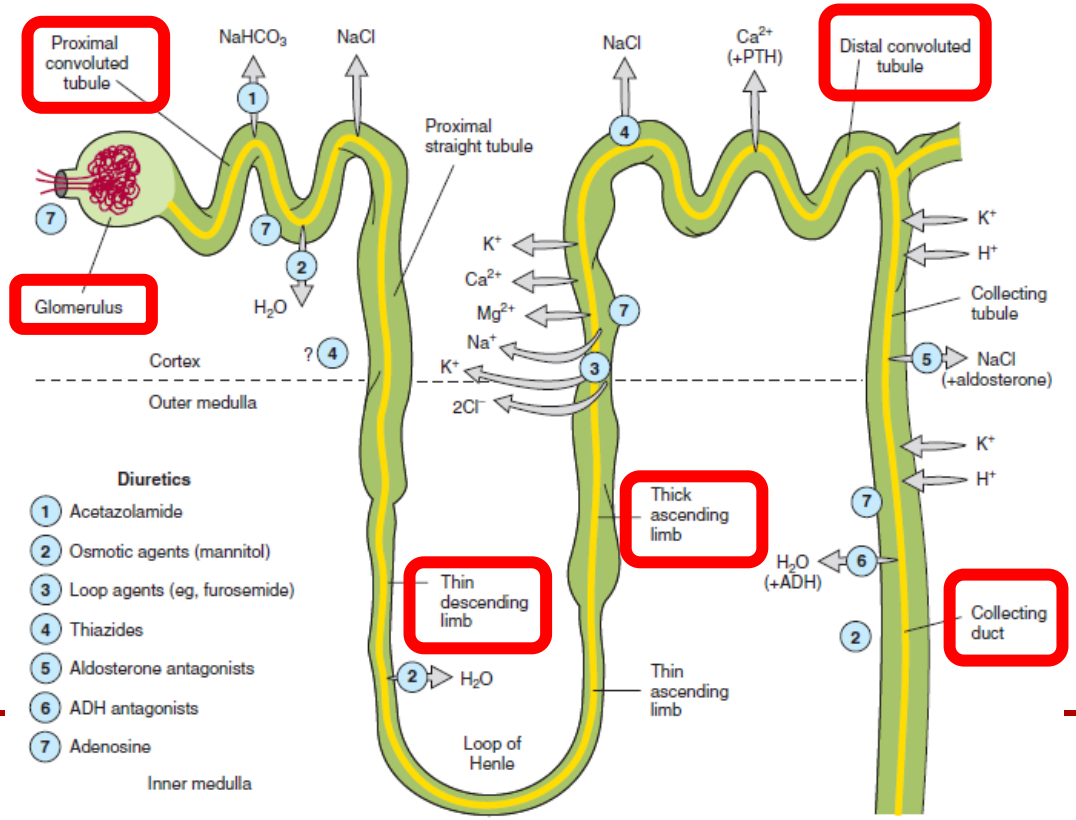
c) ***Low efficacy:*** excretes less than 5 % of the filtrated sodium as *K-sparing diuretics & osmotic* diuretics.



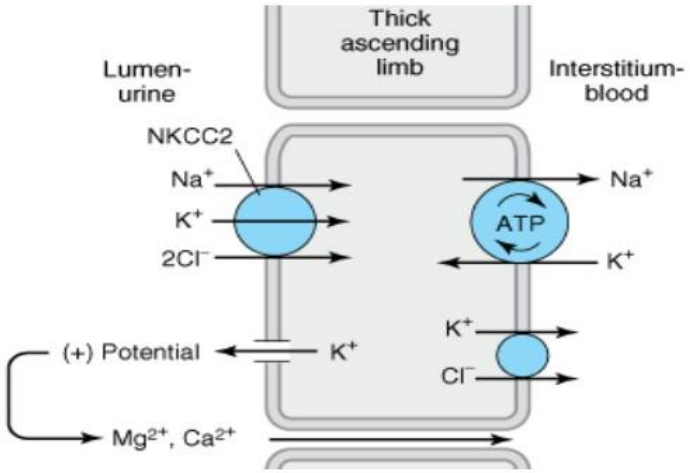
Sites of transport of solutes and water along the nephron

➢ Major segments of the nephron and their function:-

Segment	Function	Water permeability	Diuretic with major action
Glomerulus	- Formation of glomerular filtrate	Extremely high	None
Proximal convoluted tubule (PCT)	- Reabsorption of 65% of filtered Na^+, K^+, Ca^{2+} & Mg^{2+}. - Reabsorption of 85% of $NaHCO_3$. - Reabsorption of 100% of glucose and amino acids.	Very high	Carbonic anhydrase inhibitors
Thin descending limb of Henle's loop	- Passive reabsorption of water.	High	None
Thick ascending limb of Henle's loop (TAL)	- Active reabsorption of 15-25% of filtered Na^+, K^+ & Cl^-. - Secondary reabsorption of Ca^{2+} and Mg^{2+}.	Low	Loop diuretics
Distal convoluted tubule (DCT)	- Active reabsorption of 4-8% of filtered Na^+ & Cl^-. - Ca^{2+} reabsorption under parathyroid hormone control.	Very low	Thiazides
Cortical collecting tubule (CCT)	- Na^+ reabsorption (2-5%) coupled to K^+ and H^+ secretion.	Variable	K^+-sparing diuretics



1- LOOP DIURETICS
(HIGH CEILING DIURETICS)



- ***e.g.*** ***Furosemide (Lasix), Bumetanide, torsemide, Ethacrynic acid*** (Edecrine).
- They act by inhibition of **Na+ / K+ / 2Cl- co-transport** mechanism in thick part of the ascending limb of loop of Henle. They also increase the excretion of Ca++ and Mg++.
- Rapid onset of action within 1 hour of oral use, peak effect within 30 min. after I.V. use with Short duration (3-6 h.) **so suitable in emergency situations.**

Therapeutic Uses

1- Acute pulmonary edema: they improve pulmonary edema and left ventricular pressure before the diuresis.

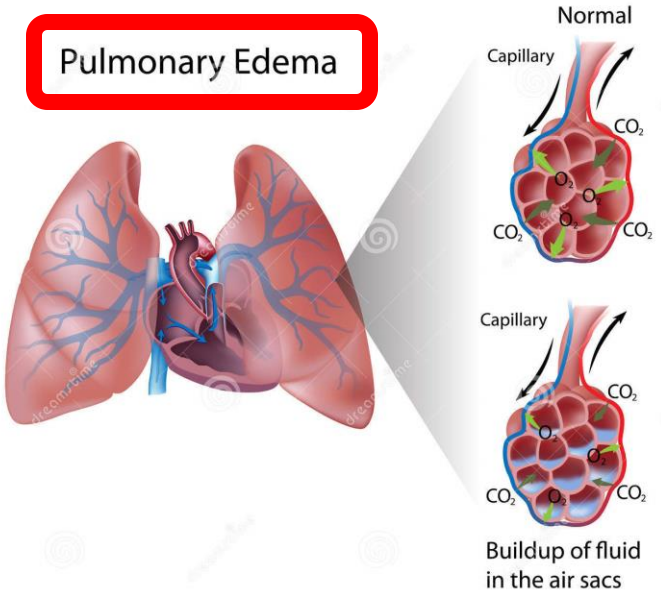
2- Generalized Edema: due to renal, hepatic and heart failure**.** They are useful in patients with renal dysfunction.

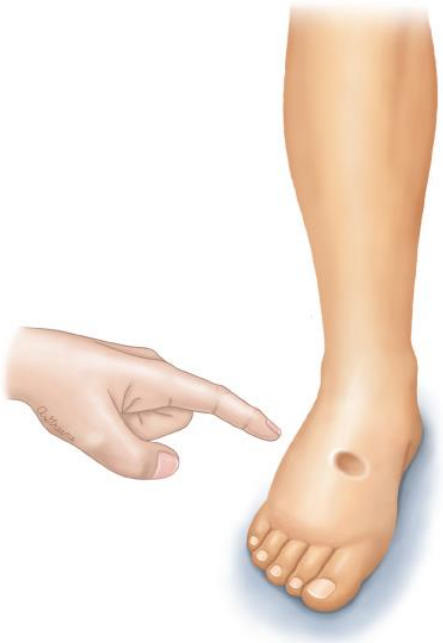
3- Hyperkalemia & hypercalcemia.

4- Acute Renal Failure: they increase the rate of urine flow and enhance K+ excretion in acute renal failure.

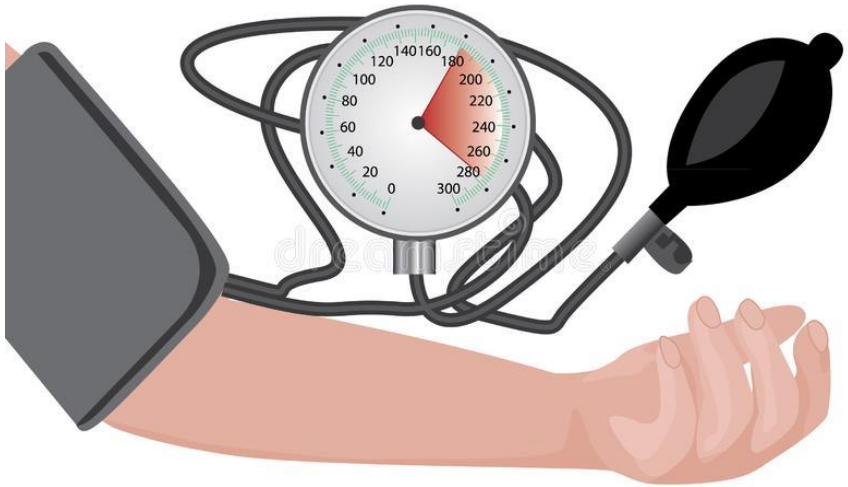
5- Hypertension: they are indicated in hypertensive crisis as a short term treatment (due to their rapid onset of action) and in presence of renal dysfunction. They are not suitable for chronic use due to their short duration and they causes severe electrolytes disturbance.

6- Anion Overdose: Loop diuretics are useful in treating toxic ingestions of bromide, fluoride, and iodide.



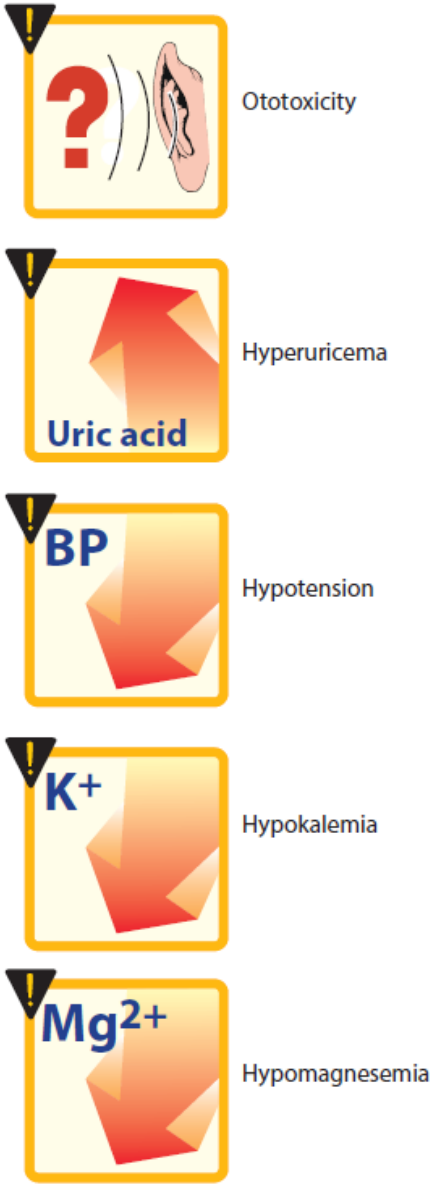


Edema



Hypertension

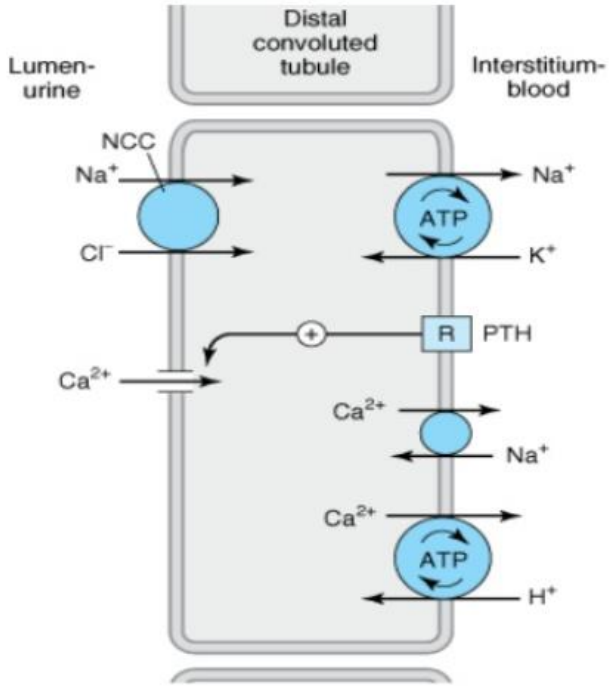
Side Effects



1. **Hypokalemia:** may cause cardiac arrhythmias, particularly in patients taking cardiac glycosides.
2. **Hyponatremia** and extracellular **fluid volume** depletion.
3. **Metabolic Alkalosis.**
4. **Hypocalcemia and calciuric renal stones**
5. **Hypomagnesemia**
6. **Hyperglycemia:** due to decreased insulin release or tissue utilization of glucose.
7. **Hyperlipidemia** as they can increase plasma levels of low-density lipoprotein (LDL) cholesterol and triglycerides while decreasing plasma levels of high-density lipoprotein (HDL) cholesterol.
8. **Hyperuricemia** and precipitate attacks of gout in susceptible patients.
9. **Ototoxicity:** can cause dose-related hearing loss that is usually due to changes in the electrolyte composition in the endolymph of the ear.
10. **Nephrotoxicity:** they potentiate nephrotoxicity of cephalosporin and aminoglycosides.
11. **Teratogenicity:** if used during pregnancy.
12. **Allergic Reactions:** Interstitial nephritis, hepatitis fever and rash as they contain sulfonamide moiety (with all except ethacrynic acid).

2- THIAZIDE & THIAZIDE-LIKE DIURETICS

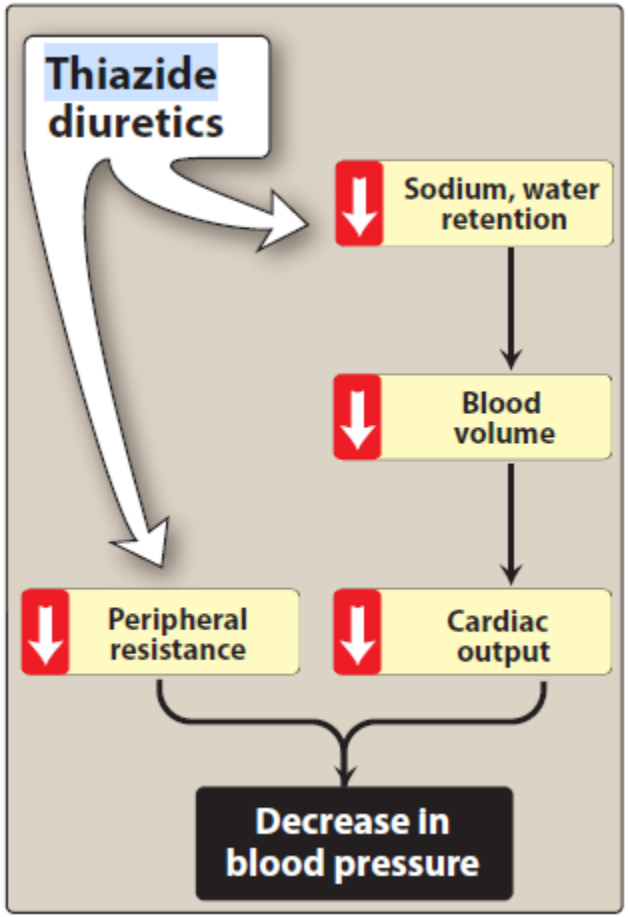
Mechanism of action



- e.g. ***Thiazides***: e.g., chlorothiazide and hydrochlorothiazide, ***Thiazide-like diuretics:*** e.g., chlorthalidone, metolazone and indapamide.
- They act by **inhibition of Na+ / Cl- co-transport mechanism in early segment of distal tubules,** so **they increase the excretion of Na+ Cl-and water. They also increase the excretion of K+.**
- They stimulate **reabsorption of Ca++ in the distal tubules which is under control of parathyroid hormone** (parathormone).
- They increase the excretion of Mg++.

N.B. *Thiazides are ineffective if GFR is less than 30-40 ml / min (except metolazone and indapamide which are effective even the GFR is less than 30 ml / min.), so they are ineffective in severe heart and renal failure.*

Therapeutic Uses



1- Hypertension:

- The first choice for treatment of **mild to moderate hypertension**.
- Can be combined **with other antihypertensive drugs in moderate to severe hypertension**.
- **Not useful in hypertensive patients with renal dysfunction**.

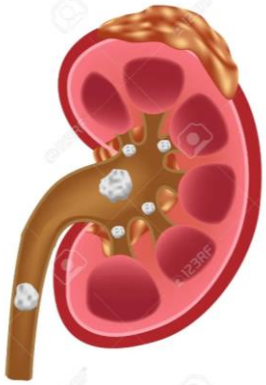
Advantages:

- Safe, inexpensive, effective, well tolerated, once daily dosage, do not require dose titration and have additive or synergistic effects when combined with other antihypertensive agents.

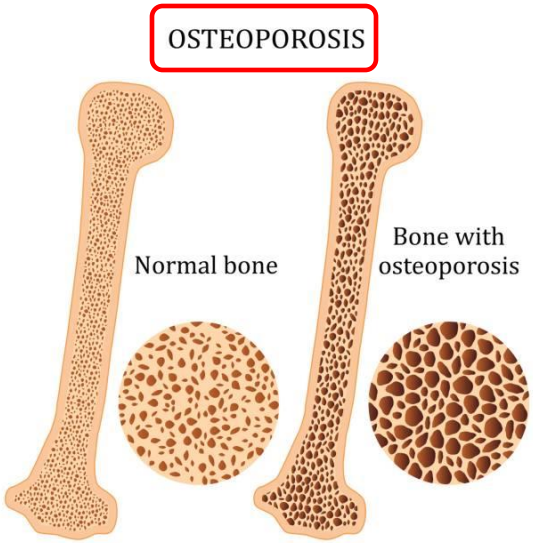
Mechanism:

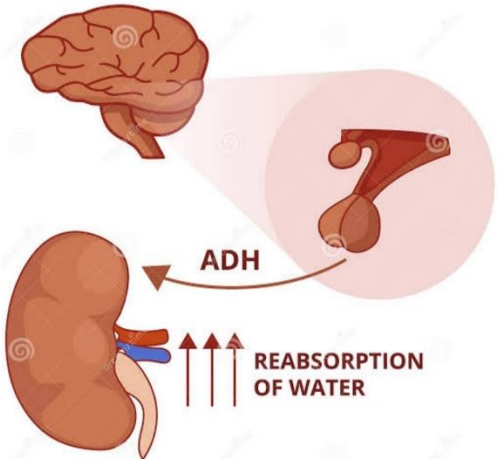
Early, **decrease blood volume (by diuresis),** so decrease COP. Prolonged treatment may be associated with a **decrease in PVR may be due to opening of calcium-dependent potassium channel** (Ca++-dependent k+-channel).

2- ***Generalized edema*** caused by mild to moderate CHF (not severe CHF):
3- ***Idiopathic hypercalciuria*** (as they decrease Ca++ excretion and decrease the incidence of Ca++ renal stones).
4- Treatment of osteoporosis.
5- ***Nephrogenic diabetes insipidus***: It is a paradoxical effect; unknown mechanism.

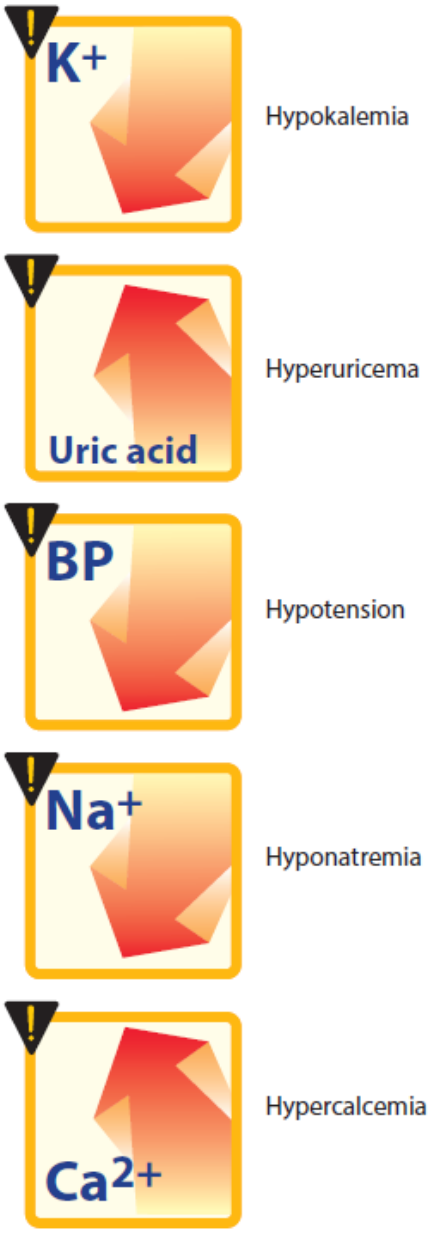


Hypercalciuria





Nephrogenic diabetes insipidus



Side Effects

1)Hypokalemia (may precipitate cardiac arrhythmias in patients using digoxin), need K+ supplements or K-sparing diuretics.

2) Hyponatremia

3) Hypomagnesemia.

4) Impotence.

5) Metabolic alkalosis

6) Hypercalcemia.

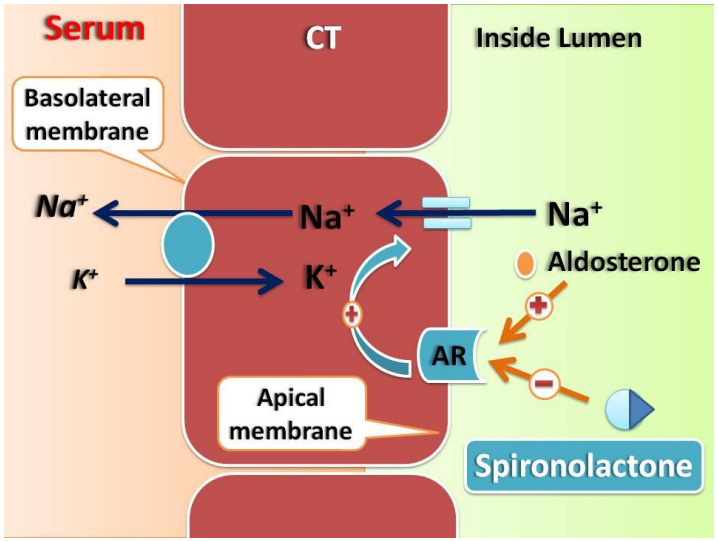
7) Hyperglycemia.

8) Hyperuricemia and may cause gout in susceptible persons.

9) Hyperlipidemia due to increase in plasma cholesterol and triglycerides which may increase the risk of atherosclerosis with chronic use.

10) Allergic reactions: rash, fever, hepatitis and pancreatitis. Thiazide diuretics are contraindicated in individuals who are hypersensitive to sulfonamides.

3- K-SPARING (HYPERKALEMIC) DURETICS



- These **drugs act on collecting tubules and ducts causing increase in Na+ excretion and a decrease in K+ loss in urine**. Therefore, are called K+-sparing or retaining diuretics.
- These drugs are weak diuretics since the amount of Na+-reabsorbed at this site of nephron is only 2-5 % of the filtered Na load.
- They are classified into:
  - Aldosterone antagonist
  - Inhibitors of renal epithelial Na+ -channel

Aldosterone antagonist	Inhibitors of renal epithelial Na+ channel
Spironolactone & Eplerenone	**Triamterene & Amiloride**
• Spironolactone **antagonize aldosterone action at mineralocorticoid receptors (MRs) in the collecting tubules**. Therefore, it **inhibits reabsorption of Na+ and secretion of K+ and H+**.	• They **block renal epithelial Na+ channels at late distal tubules and collecting ducts** leading to **increase in the excretion of NaCl and reduces the net driving force for potassium secretion** (decrease excretion of K+).

4- OSMOTIC DIURETICS

- ***Mannitol*** (prototypical; given IV), ***glycerin and isosorbide (***used orally).
- It increases the renal excretion of water by exerting high osmotic pressure within tubular lumen without Na loss.

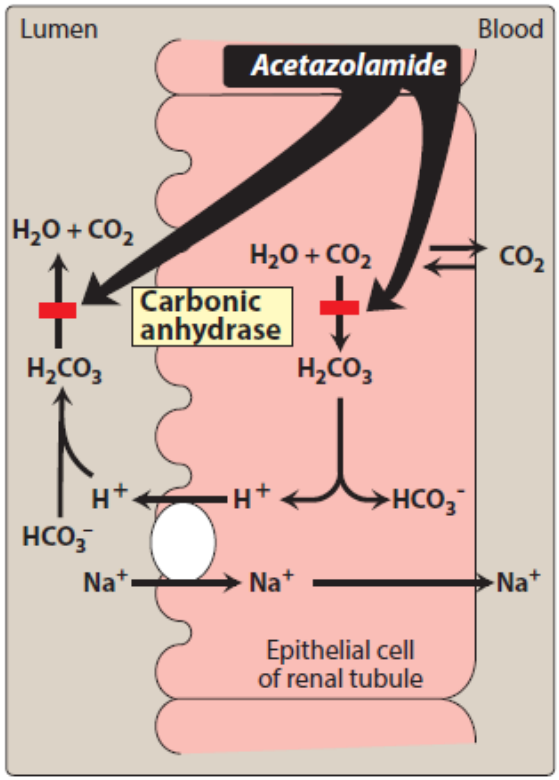
Therapeutic uses:

1. **Increased intracranial pressure** (cerebral edema & cerebral tumors).
2. **Glaucoma:** In cases of acute glaucoma and before eye surgery, it reduce IOP.
3. They are used to **maintain urine flow** in cases acute toxicity-induced acute renal failure
4. **Dialysis disequilibrium syndrome:** Administration of mannitol shifts water back into the extracellular compartment and consequently relieves this syndrome.

Adverse effects:

- Dehydration and extracellular water expansion that cause hyponatremia until diuresis occurs.

5- CARBONIC ANHYDRASE INHIBITORS



- **Acetazolamide** and other carbonic anhydrase inhibitors.
- They act by **inhibition of carbonic anhydrase enzyme in the proximal tubules of kidney,** so they inhibit bicarbonate reabsorption and increase its secretion.
- CAIs can inhibit carbonic anhydrase–dependent bicarbonate transport at the ciliary body of the eye and hence **reduce the formation of aqueous humor** (used in glaucoma).
- They also **block the formation of cerebrospinal fluid by the choroid plexus.**

Therapeutic Uses

1. **Glaucoma:**

Topically (***dorzolamide, brinzolamide***) reduce intraocular pressure without systemic metabolic effects.

2. **Acute Mountain Sickness:**

- Weakness, dizziness, insomnia, headache, and nausea can occur in mountain travelers. In more serious cases, pulmonary or cerebral edema develops.
- Acetazolamide enhances performance status and diminishes symptoms.

Side Effects

Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur. They decrease urinary excretion of NH4 and may contribute to the development of **hyperammonemia** and **hepatic encephalopathy** in patients with cirrhosis.

Acute Mountain Sickness

Dr Lobna Aly Abdelzaher

6- ADH (VASOPRESSIN) ANTAGONISTS

- Demeclocycline is nonspecific ADH antagonists and rarely used in cases of **syndrome of inappropriate secretion of antidiuretic hormone** (SIADH).

7- SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS

Dapagliflozin, canagliflozin, empagliflozin and ipragliflozin

Mechanism of action:

- Almost all filtered glucose is reabsorbed in proximal tubules by SGLT2 transporter.
- Inhibition of SGLT2 results in excretion of glucose by about 30-50 % accompanied by water excretion.

Therapeutic uses:

- The only indication is as **third-line therapy for diabetes mellitus**
- SGLT2 inhibitors reduce the hemoglobin A1c by 0.5–1.0%, similar to other oral hypoglycemic agents.

Adverse effects:

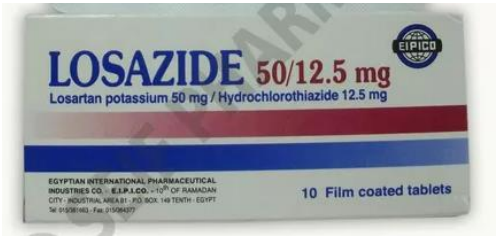
- a low incidence of hypoglycemia (3.5% versus 40.8% with glipizide).
- There is a 6 fold increased incidence of genital fungal infection in women and a slightly higher risk of urinary tract infections.

DIURETIC COMBINATIONS

- Several fixed dose combination of ***K-depleting diuretics*** as thiazides or loop diuretics with ***K-sparing diuretics*** (e.g., spironolactone) or ***ACE inhibitors or ARBs*** is recommended and available in the market e.g., aldactazide, Modiuretics, Capozide, Co-diovan, etc. The value of this combination is that hypokalemia cancel hyperkalemia with additive diuretic activity, i.e., antagonism of side effects and addition of therapeutic effects.
- Combination of ***Thiazides*** and ***loop diuretics*** are hazardous and also combination of K-sparing diuretics and ACE inhibitors or ARBs Explain why?

Commercially Available Drugs


Co-vasotec
Valsartan + Hydrochlorothiazide
160 mg 12.5 mg
Antihypertensive
EIPICO
EGYPTIAN INTERNATIONAL PHARMACEUTICAL INDUSTRIES CO. - E.I.P.I.CO.
14 Film coated tablets
Warnings in the insert leaflet must be revised


LOSAZIDE 50/12.5 mg
Losartan potassium 50 mg / Hydrochlorothiazide 12.5 mg
EIPICO
10 Film coated tablets


30 TABLETS
MODURETIC
AMILORIDE HYDROCHLORIDE 5 MG
HYDROCHLOROTHIAZIDE 50 MG
CAUTION:
Moduretic
موديوريتيك

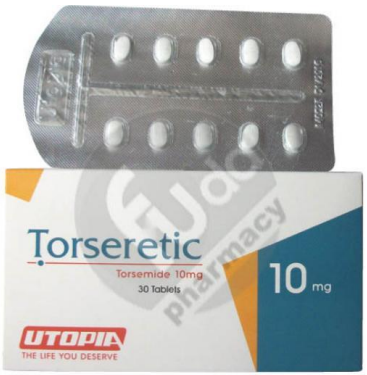

Captopril / Hydrochlorothiazide MYLAN
50 mg / 25 mg
28 comprimés sécables
voie orale
Mylan


20 Film coated tablets
ATENO-C 100/25 mg
Atenolol 100 mg + Chlorthalidone 25 mg
EIPICO


Averothiazide 10/12.5/40mg
Amlodipine 10 mg
Hydrochlorothiazide12.5 mg
Olmesartan medoxomil 40 mg
30 Film Coated Tablets


Tenedone 100
Atenolol 100 mg + Chlorthalidone 25 mg
Cardioselective β-blocker and diuretic, antihypertensive
30 Film Coated Tablets
SIGMA

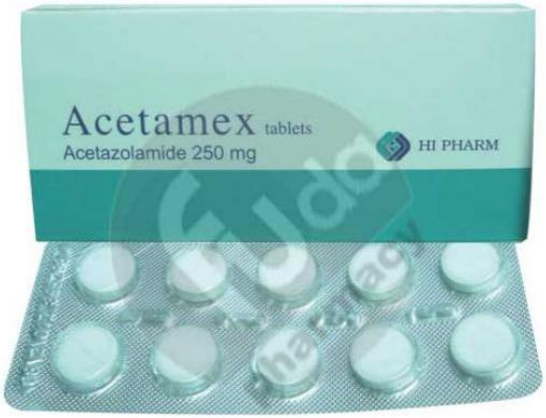
Thiazides



Loop Diuretics

K Sparing Diuretic

Mannitol



Acetazolamide


thank you