YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 1 - Pharmacology

Lec. Title : Diuretics Agents I

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Diuretics agents I

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Faculty of Medicine

Objectives

1. List major types of diuretics and relate them to their sites of action.
2. List the major applications, toxicities, and the efficacy of thiazides, loop diuretics and potassium -sparing diuretics.
3. Describe drugs that reduce potassium loss during diuresis

Introduction

- Diuretics increase urine production by acting on the kidney. (direct or indirect)
- **Most** agents affect water balance indirectly by altering electrolyte reabsorption or secretion.
- Osmotic agents affect water balance directly.
- **Natriuretic diuretics produce diuresis, associated with increased sodium (Na)** excretion, which results in a concomitant loss of water and a reduction in extracellular volume.

- Direct effect: Is the hydrostatic pressure and plasma, this creates driving force for water (low → high) concentration.
- I give a drug which increase osmotic pressure of the urine.
- Indirect effect: sodium always followed by water, (inhibit the reabsorption of sodium → followed by water)

OR

- Increase sodium or potassium secretion which also followed by water.
- It is named Natriuretic because most of them was work on sodium → secretion of sodium followed by secretion of water.

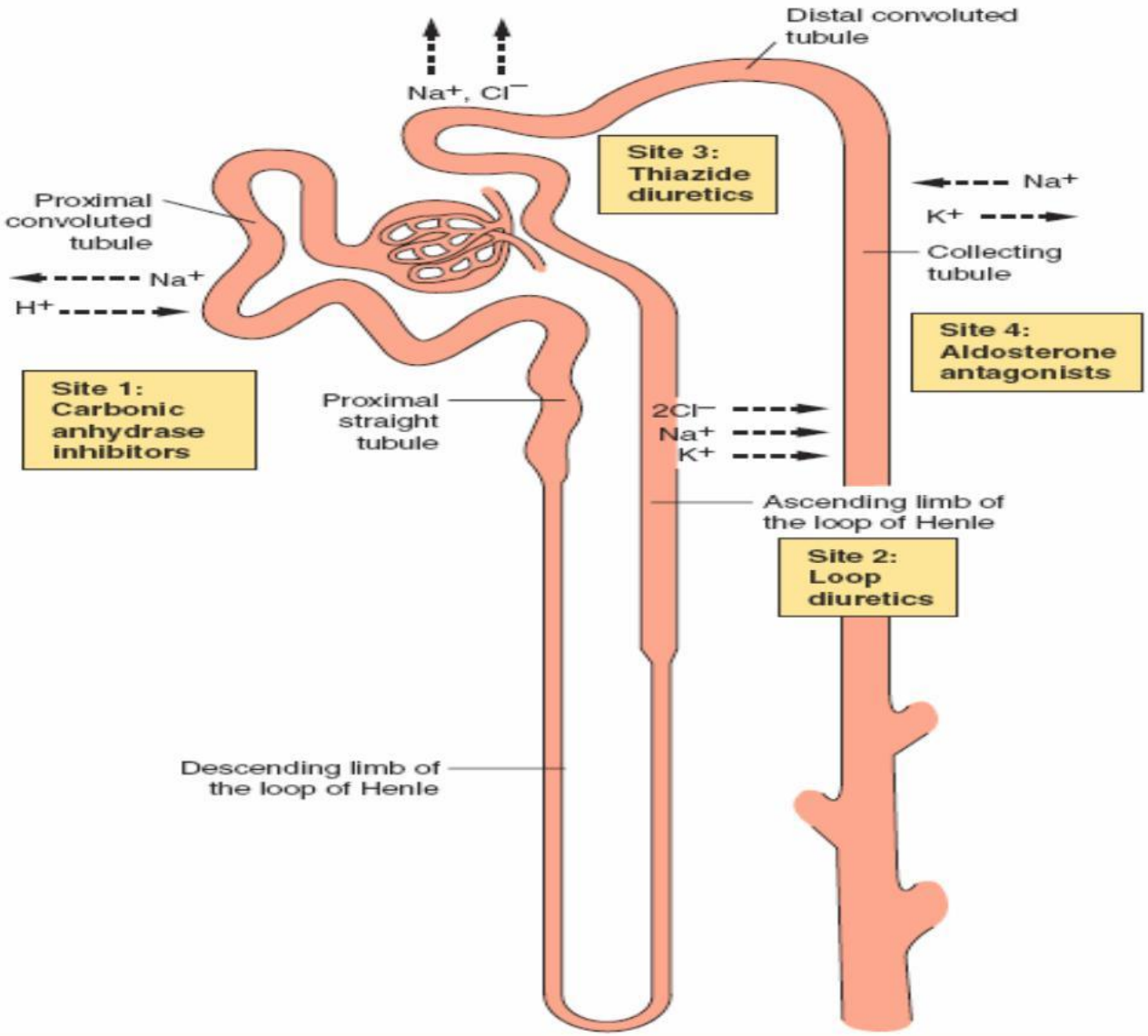
Introduction

- **Therapeutic uses.** Any abnormality in our bodies with fluid distribution.

1. used for the management of edema,
2. hypertension,
3. congestive heart failure (CHF),
4. abnormalities in body fluid distribution.
5. glaucoma: increasing intraocular pressure. (Acetazolamide).

The drug reduces water accumulation behind the cornea

-also used for Ménière disease(water accumulation in the inner ear).


Distal convoluted tubule
Na+, Cl−
Site 3: Thiazide diuretics
Na+
K+
Collecting tubule
Proximal convoluted tubule
Na+
H+
Site 4: Aldosterone antagonists
Site 1: Carbonic anhydrase inhibitors
Proximal straight tubule
2Cl−
Na+
K+
Ascending limb of the loop of Henle
Site 2: Loop diuretics
Descending limb of the loop of Henle

There are 4 groups based on the place where it works:

1. Proximal convoluted tubule: carbonic anhydrase inhibitors.

2. Loop of Henle: loop diuretics (furosemide).

The most potent diuretics.

3. Distal convoluted tubule: Thiazide

(act on Na+/K+ co-transporter)

4. Aldosterone antagonist.

- → Directly aldosterone antagonist
- → Directly Na+-/K+ channel blockers

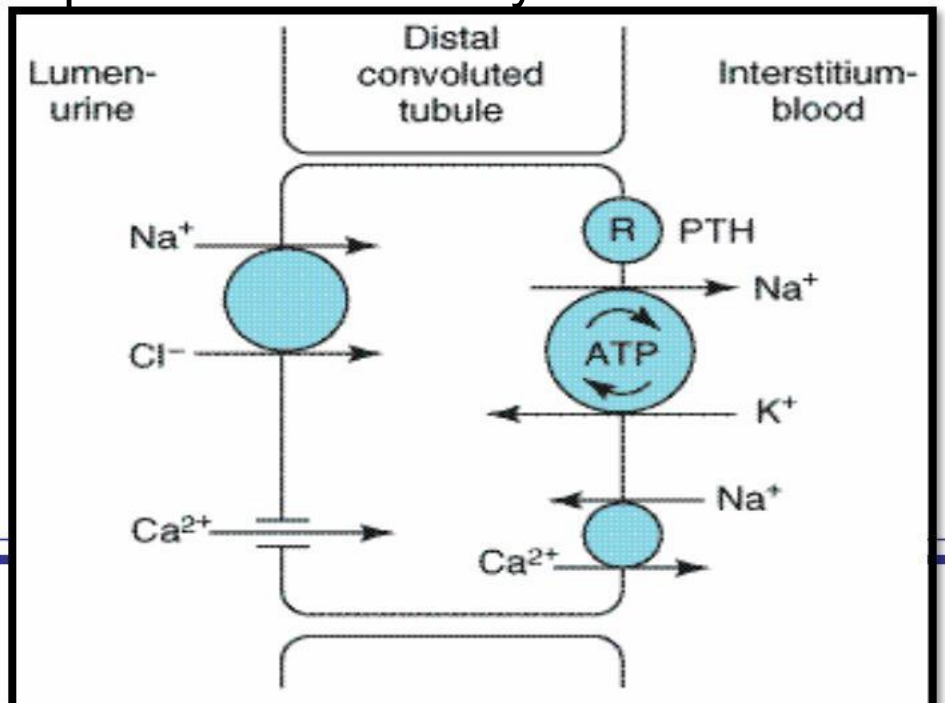
Diuretics:

1. Thiazides: Chlorothiazide, Hydrochlorothiazide, chlorthalidone
2. Loop diuretics: Furosemide, Bumetanide
3. K+ sparing: Spironolactone, Triamterene And Amiloride
4. Carbonic anhydrase inhibitors: Acetazolamide
5. Osmotic Diuretics (mannitol). لكن ممكن, ضعيفة

ما بحتاج مدر بول قوي, احتاجها لاستخدامات محددة مثل الغلوكوما.

Thiazide diuretics

- Only about 10% of the filtered NaCl is reabsorbed in the distal convoluted tubule.
- The mechanism of NaCl transport in the distal convoluted tubule is electrically neutral Na+ and Cl- cotransport
- This NaCl transporter is blocked by diuretics of the thiazide class.



Simply, Na+/cl- transporters are inhibited, block the reabsorption of these it.

As all other transporters will be blocked, we will loss all electrolytes in the urine except the calcium

As a consequence, Thiazides cause hypo(Natremia, Chloremia, kalemia).

So, there is electrolytes disturbance especially K+.

Thiazide diuretics

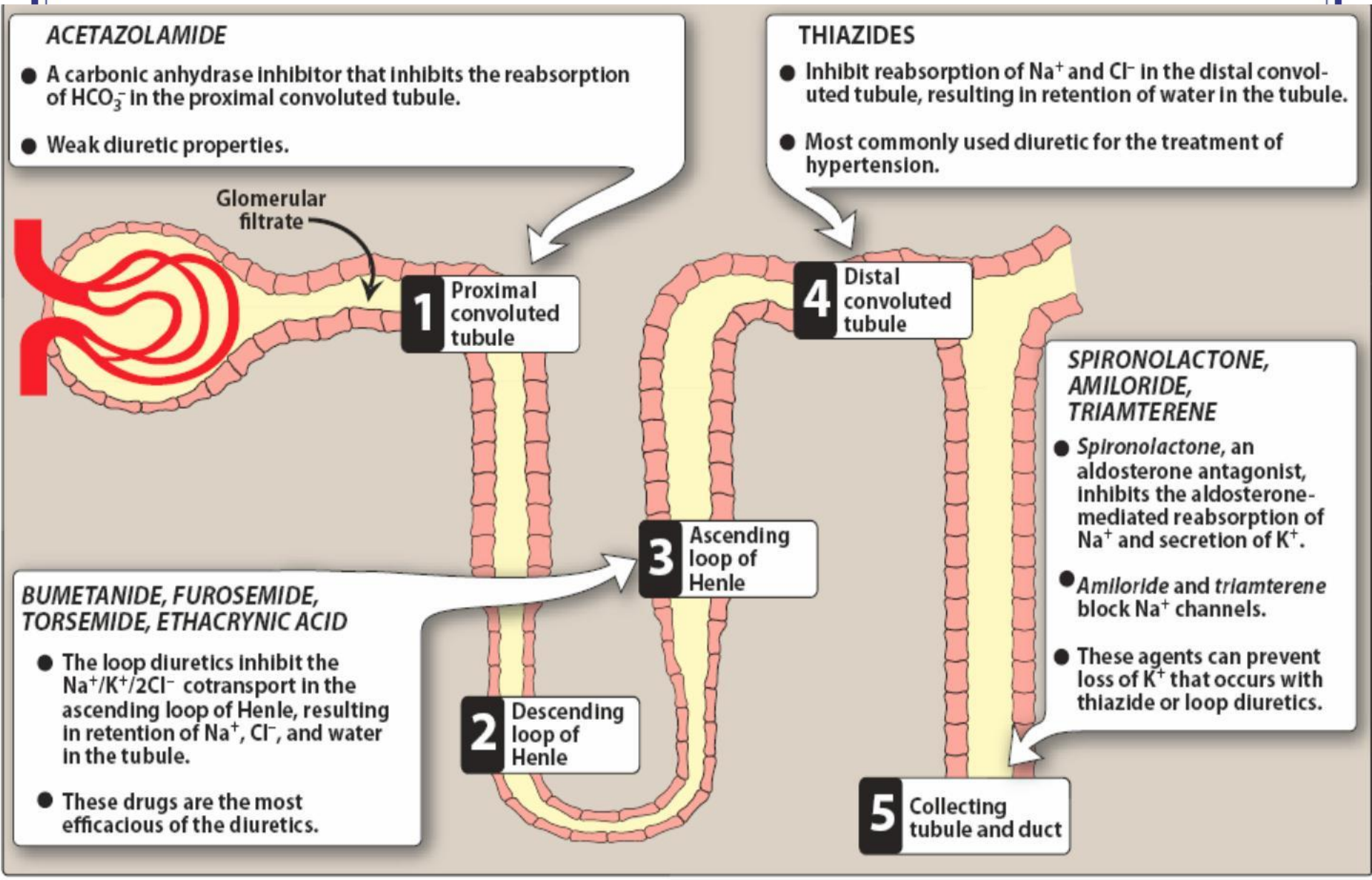
- MOA:

a. These agents inhibit active reabsorption of sodium chloride (NaCl) in the distal convoluted tubule by interfering with Na/Cl cotransporter (**NCC),**resulting in the net excretion of Na and an accompanying volume of water.

(1) **These agents increase excretion of Cl, Na, potassium (K), and, at high doses HCO3**

(2) **They reduce excretion of calcium (Ca+2).**

MOA: Diuretics



Thiazides: Specific agents

- **Prototype true thiazides**
  - **chlorothiazide and hydrochlorothiazide. methyclothiazide.**
  - Chlorothiazide is the only thiazide available for parenteral (IV) use.
- **Thiazide-like drugs.** 2nd generation (not truly).
  - **metolazone, chlorthalidone, and indapamide**
  - Unlike thiazides, these agents may be effective in the presence of some renal impairment.

newly agents, more active and potent

Thiazides: Therapeutic uses

1. **Thiazide diuretics are the preferred class of diuretic for the treatment of essential hypertension when renal function is normal;**
   - **they are often used in combination with** other antihypertensive agents to enhance their blood pressure-lowering effects.
   - They reduce plasma volume and total peripheral resistance.
2. **These agents reduce the formation of new calcium stones in idiopathic hypercalciuria.**
3. **Thiazide diuretics may be useful in patients with diabetes insipidus that is not** responsive to antidiuretic hormone (ADH).
4. **These agents are often used in combination with a potassium-sparing diuretic to** manage **mild cardiac edema, cirrhotic or nephrotic edema, and edema produced by hormone imbalances.**
5. **They are frequently used in the treatment of Ménière disease**

1- Not only reduce stroke volume and cardiac output, it also reduce the peripheral resistance,

By decreasing Na+ → decrease rigidity.

2- about Ca+2 → it will reduce excretion of Ca+2 . So, hypercalcemia in plasma, hypocalcemia in urine.

ما رح يصرفلي الكالسيوم لبرا ف رح يمنع تراكمه بالنفرون.

3- Thiazide used for diabetes insipidus (the urine here is hypo osmotic and the plasma is hyper osmotic)

Ao, the thiazides secretes electrolytes to maintain plasma osmolarity.

- Ménière disease: is the accumulation of fluids in the inner ear.

Thiazides: contraindications

- ***Thiazide diuretics should be used cautiously in the*** presence of: **renal or hepatic diseases such as cirrhosis**, and they should be used only as an ancillary treatment in nephrotic syndrome.

This drug can be metabolized in the liver, so in hepatic disease there will be accumulation of it.

بستخدمه بس بعد ما اعدل الدوز.

In chronic renal failure (the Creatinine clearance < 15mg/min) , here the new potent indapamide may be the only drug of choice.

Thiazides: Adverse effects

1. **Electrolyte imbalances** such as **hypokalemia, hyponatremia, Hypomagnesemia** and **hypochloremic alkalosis.**
2. These imbalances are often accompanied: by central nervous system (CNS) disturbances, including **dizziness, confusion, and irritability;**
3. Hypokalaemia – **muscle weakness; fatigue and cardiac arrhythmias**;
   - by decreasing plasma K, **increased sensitivity to digitalis.**
   - **Diets low in Na and high in K are recommended;**
   - **K supplementation** may be required.

Hypokalaemia

→ arrhythmia

→ muscle fatigue

→ if the patient takes digoxin : increase digoxin toxicity

خصوصا انه اغلب المرضى الي بتعامل معهم بكونوا مرضى قلب فمعرضين يكونوا بياخدوا ديجوكسين.

-The side effects may be reversible. اذا وقفت الدوا تخف.

-All these side effects are dose related (as the dose ↑ the side effects ↑)

-Also it depends on the patient (patient with high risk for goat, ↑ blood glucose, ↑ cholesterol)

Thiazides: Adverse effects

4. **Gout-like symptoms may appear: elevate serum urate, presumably as a result of competition for the** organic anion carriers (which also eliminates uric acid)
5. **Hyperglycemia**: Inhibition of insulin release due to K+ depletion (decrease proinsulin to insulin) – precipitation of diabetes **(especially in patients with diabetes) (pseudodiabetes)**
6. **hypertriglyceridemia, hypercholesterolemia** rise in total LDL level

– risk of stroke

7. **hypercalcemia**
8. **hypersensitivity reactions (sulfa groups).**

- All the above metabolic side effects – higher doses (50 – 100mg per day
- But, its observed that these adverse effects are minimal with low doses (12.5 to 25 mg)

About the point 4:

Not with all patients, some patients have high risk (person has high uric acid but isn't a gout patient), this patient will has Goat-like symptoms.

The cause is that the diuretic that he takes also will inhibit uric acid secretion.

Thiazides

- **Thiazide diuretics are absorbed from the gastrointestinal (GI) tract and**

Drug	Chemical Class	Potency	Half-Life (h)
Chlorothiazide	Benzothiadiazide	0.1	2
Hydrochlorothiazide	Benzothiadiazide	1.0	3
Metolazone	Quinazoline	5	5
Chlorthalidone	Quinazoline	10	26
Indapamide	Indoline	20	16

Most potent, long-acting, so it is the most preferable.

Loop diuretics

انسحب بسبب اعراضه الجانبية

- **Prototype drugs include:**
  - **Furosemide, Bumetanide, Ethacrynic Acid and Torsemide**.
- They are administered either orally or parenterally.
- Diuresis occurs within 5 minutes of intravenous (IV) administration and within 30 minutes of oral administration

Table 15–2. Loop Diuretics: Dosages.

Drug	Daily Oral Dose[1]
Bumetanide	0.5–2 mg
Ethacrynic acid	50–200 mg
Furosemide	20–80 mg
Torsemide	2.5–20 mg

[1] As single dose or in two divided doses.

Patients with high blood pressure ,more than 160 (acute hypertension), should take furosemide (first onset of action).

Even if he takes it orally within 30 minutes the pressure will be corrected.

While the thiazides need days → months to reach constant blood pressure.

For this cause, Thiazides on the long term is more preferable because it is moderate diuretic.

Thiazide doesn't result in hypovolemia, while loop diuretic does → more water secretion → high diuresis.

Loop diuretics

- **Mechanism.**

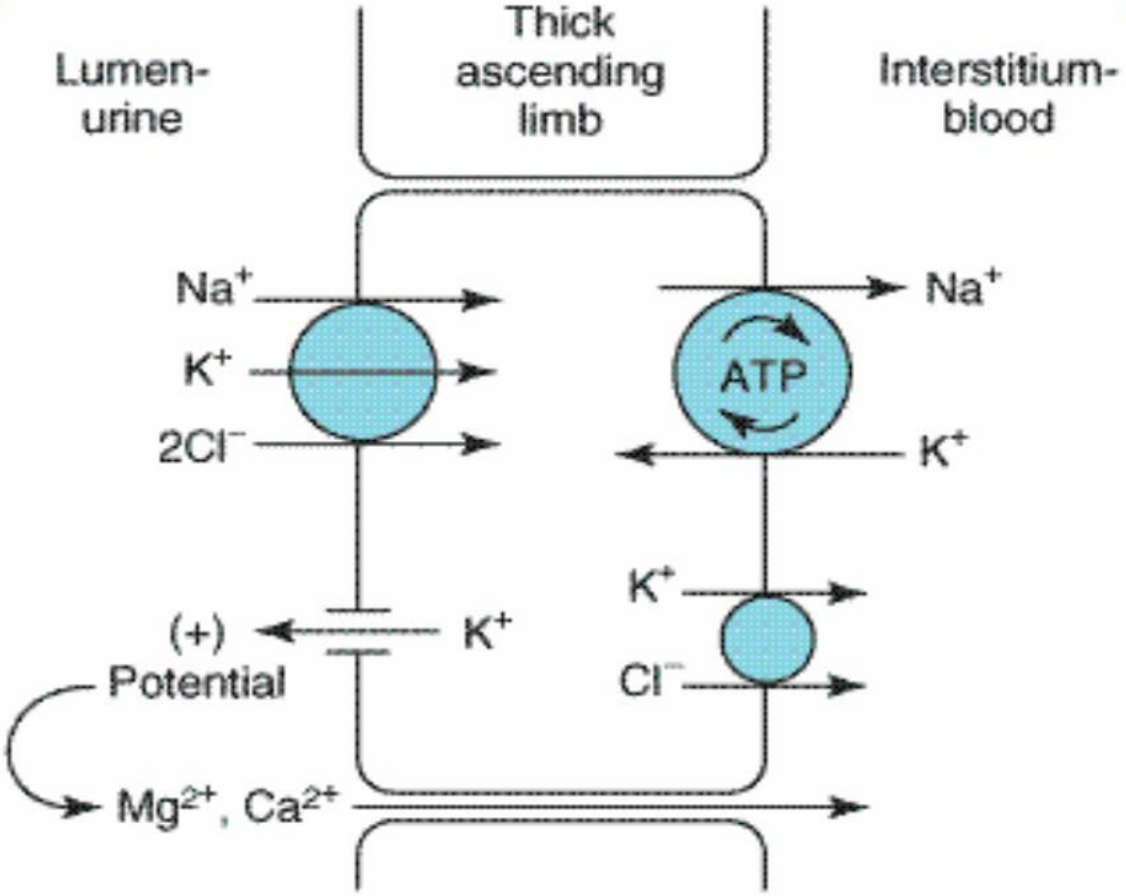
a. **Loop diuretics inhibit active Na/K/Cl reabsorption in the thick ascending limb of the loop** of Henle by inhibiting **specific** Na+/K+/2Cl- **co-transporter.**

- This results in back diffusion of K+ into the tubular lumen and development of a lumen-positive electrical potential
- This electrical potential provides the driving force for reabsorption of cations—including Mg2+ and Ca2+

- **Because of** the high capacity for Na/Cl reabsorption in this segment, agents active at this site markedly increase water and electrolyte excretion and are referred to as **high-ceiling diuretics.**

- The loop diuretics are the most efficacious diuretic drugs. Reduce reabsorption by 25%.

Loop diuretics



-Work on Na+/K+/cl- co-transporter and inhibit it.

-Inhibit the reabsorption of sodium, potassium and chloride.

-→ Hypo (natremia, chloremia, kalemia)

-Normally, when the potassium is reabsorbed it will again move toward the lumen , making driving force for the Mg and Ca to move toward the blood.

The drug effect→ they will not go back to the blood. So, we have hypocalcemia and hypomagnesemia.

And this is the difference between it and thiazide , so we can use it to treat hypercalcemia

Loop diuretics

- **Mechanism.**

b. **Loop diuretics cause increased renal prostaglandin production, which accounts for** some of their activity. Nonsteroidal anti-inflammatory drugs (NSAIDs) can reduce the effectiveness of loop diuretics.

c. **Net effects: These agents reduce reabsorption of Cl- and Na+; they increase Ca+2 excretion** and magnesium (Mg).

Loop diuretics: Therapeutic uses

1. Loop diuretics are used in the treatment of **CHF** by reducing **acute pulmonary edema**
2. They are synergistic with thiazide diuretics when coadministered.
3. These agents are used to treat **hypertension**(2nd stage), especially in individuals with **diminished renal function**. They reduce the plasma volume and also the total peripheral resistance.
4. They are also used to treat **acute hypercalcemia**

Loop diuretics: Therapeutic uses

5. Hyperkalemia: loop diuretics can significantly enhance urinary excretion of K+.
6. Acute Renal Failure

- Loop agents can increase the rate of urine f low and enhance K+ excretion in acute renal failure.

7. **halide poisoning**

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

الملخص انه هو بقلل كل ال **electrolytes** لهيك اي حالة عنده ارتفاع ب اي اشي ممكن يعمللله تسمم بقدر استخدمه لحتى اعالج الوضع

Loop diuretics: Adverse effects

- **Hyponatremia**
- **Hypotension and volume depletion,**
- **Hypokalemia**
- They may also produce **alkalosis due to** enhanced H+ secretion. (because it also cause hypo H+)
- **Hypocalcemia**
- **Hypomagnesemia:**

Loop diuretics: Adverse effects

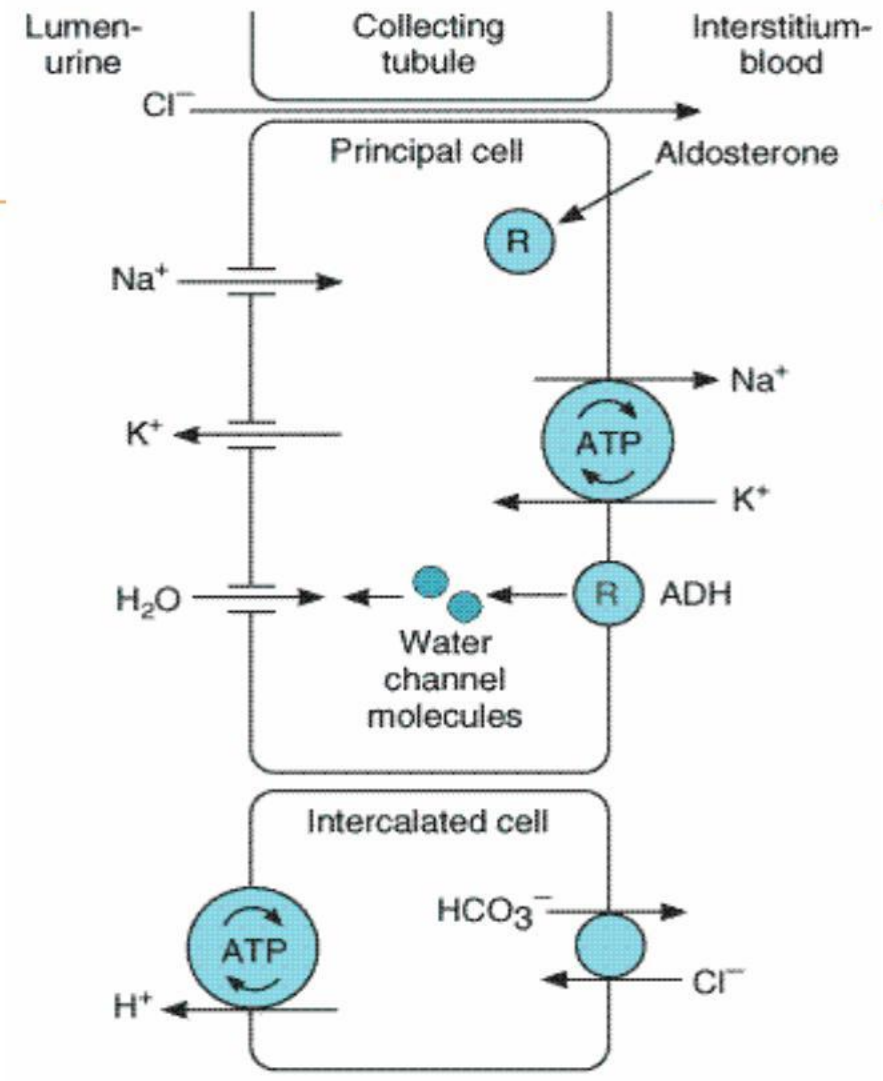
- **Loop diuretics can cause dose-related ototoxicity, more often in individuals with renal impairment.** These effects are more pronounced with **ethacrynic acid** than with furosemide. That's way it is withdrawn.
- These agents should be administered cautiously in the presence of renal disease or with the use of other **ototoxic agents** such as **aminoglycosides.**
- **These agents can cause hypersensitivity reactions.**
- **Ethacrynic acid produces GI** disturbances

furosemide → 40 up to 80 mg

اول م المريض يحس ب طنين بالاذن لازم براجعني عشان اقلل الدوز

Potassium-sparing diuretics

- The mechanism of NaCl reabsorption in the collecting tubule is distinct from the mechanisms found in other tubule segments.
- The **principal cells are the major sites of Na+, K+, and H2O transport and** the **intercalated cells are the primary sites of proton secretion**
- **Mechanism:**
  - **reduce Na+ reabsorption and reduce K+ secretion in the** distal part of the nephron (collecting tubule).
- **These are not potent diuretics when used alone; they are primarily used in combination** with other diuretics


Lumen-
urine
Collecting
tubule
Interstitium-
blood
Cl⁻
Principal cell
Aldosterone
R
Na⁺
Na⁺
K⁺
ATP
K⁺
H₂O
R
ADH
Water
channel
molecules
Intercalated cell
HCO₃⁻
ATP
Cl⁻
H⁺

Normally, aldosterone bind with its receptor and increase Na+ reabsorption and K+ secretion.

- The drug cause reversible effect of that, bind with aldosterone receptor as blockers.

So, I have no Na+, H2O reabsorption and no K+ secretion

→ → Hyperkalemia, Hyponatremia

Potassium-sparing diuretics

1. **Antagonists of the mineralocorticoid (aldosterone) receptor include**
    1. **Eplerenone, which** is highly receptor selective,
    2. **Spironolactone, which binds to other nuclear receptors** such as the androgen receptor

- **MOA*:* These agents inhibit the action of aldosterone by competitively binding** to the mineralocorticoid receptor and preventing subsequent cellular events that regulate K and H secretion and Na reabsorption.
- **These agents are active only when endogenous mineralocorticoid is present;** the effects are enhanced when hormone levels are elevated.
- **These agents are absorbed from the GI tract and are metabolized in the liver**
- therapeutic effects are achieved only after several days

Potassium-sparing diuretics

1. **Antagonists of the mineralocorticoid (aldosterone) receptor**

Therapeutic uses.

- ***These drugs are generally used in combination with a thiazide*** or loop diuretic to treat **hypertension, CHF, and refractory edema.**
- **They are also** used to induce diuresis in clinical situations associated with **hyperaldosteronism,** such as in **adrenal hyperplasia and in the presence of aldosterone-producing adenomas when surgery is not feasible**

About the previous two slides:

slide-35

Spironolactone bind with testosterone receptor and cause, in males, gynecomastia. Even in females, it cause menstrual disturbances.

slide-36

K+ sparing diuretics is the first line for CHF, Why?

The story of disease is → no ejection fraction, no cardiac output → low afferent blood flow for the kidney → high renin, angiotensin, aldosterone → so, the problem is that we have high aldosterone.

لهيك بستخدم ادوية هاي المجموعة

Potassium-sparing diuretics

1. **Antagonists of the mineralocorticoid (aldosterone) receptor:**

Adverse effects

- **hyperkalemia, hyperchloremic metabolic acidosis, and arrhythmias**.
- **Spironolactone** is associated with **gynecomastia and can also** cause menstrual abnormalities in women.

- **These drugs are contraindicated in :**
  - **renal insufficiency, especially in diabetic patients**.
  - They must be used cautiously in the presence of **liver disease**
  - They are contraindicated in the presence of other potassium-sparing diuretics and should be used with extreme **caution in individuals taking an ACEI (e.g., captopril)**

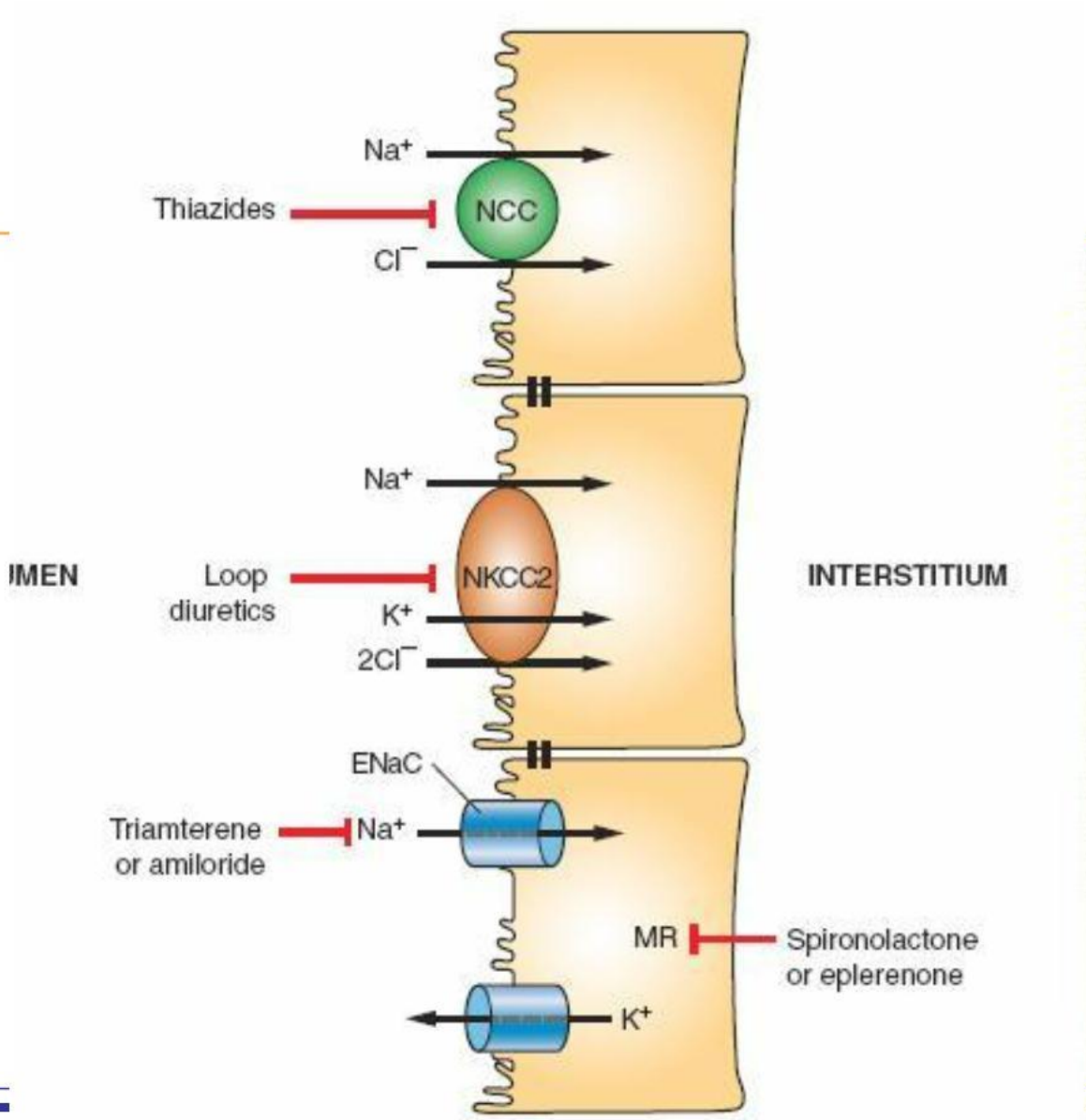
Potassium-sparing diuretics

2. Amiloride and triamterene

- **Mechanism.**
- **Amiloride and triamterene bind to and block Na channel and thereby** decrease absorption of Na and excretion of K in the cortical collecting tubule, independent of the presence of mineralocorticoids.
- **These drugs produce diuretic effects 2–4 hours after oral administration**
- **Triamterene increases urinary excretion of Mg but amiloride does not;**
- **Triamterene and amiloride** are metabolized in the liver.

Potassium-sparing diuretics

- **Therapeutic uses.** as the first group except hyperaldosteronism
  - These agents are used to manage **CHF, cirrhosis, and edema**
  - They are available in combination products containing thiazide or loop diuretics (e.g., triamterene/hydrochlorothiazide, amiloride/hydrochlorothiazide) to treat **hypertension**.
- **Adverse effects and contraindications.**
  - hyperkalemia,
  - ventricular arrhythmias.
  - Dietary potassium intake should be reduced.
  - Minor adverse effects include nausea and vomiting.
- **The use of these drugs is contraindicated in the presence of diminished renal function**.


Na+
Thiazides
NCC
Cl−
Na+
IMEN
Loop
diuretics
NKCC2
INTERSTITIUM
K+
2Cl−
ENaC
Triamterene
or amiloride
Na+
MR
Spironolactone
or eplerenone
K+

As a doctor, you should monitor:

→When you give Thiazides:

-uric acid level.

-electrolytes

→the other groups just monitor plasma electrolytes level.

THANK YOU