PHARMACOLOGY

Lectures 4,5,6: diuretics

- **OBJECTIVES:**

By the end of these lectures, student should be able to:

- Identify the different classes of diuretics
- Identify major locations of ion and water exchange in the nephron
- Understand sites of action for each class
- know molecular target of actions for each.
- Understand the pharmacokinetics and pharmacodynamics of each class of diuretics.
- Discuss the clinical applications of diuretics in special diseases.
- Know what are the major adverse effects of each group especially those of clinical importance.

PHARMACOLOGY
435

- Important.
- Extra notes.
- Mnemonics

Diuretics

Definition:

Diuretics are drugs that increase renal excretion of sodium and water resulting in increase in urine volume.

Diuresis:
is the process of excretion of water in the urine.

Natriuresis:
is the process of excretion of sodium in the urine.

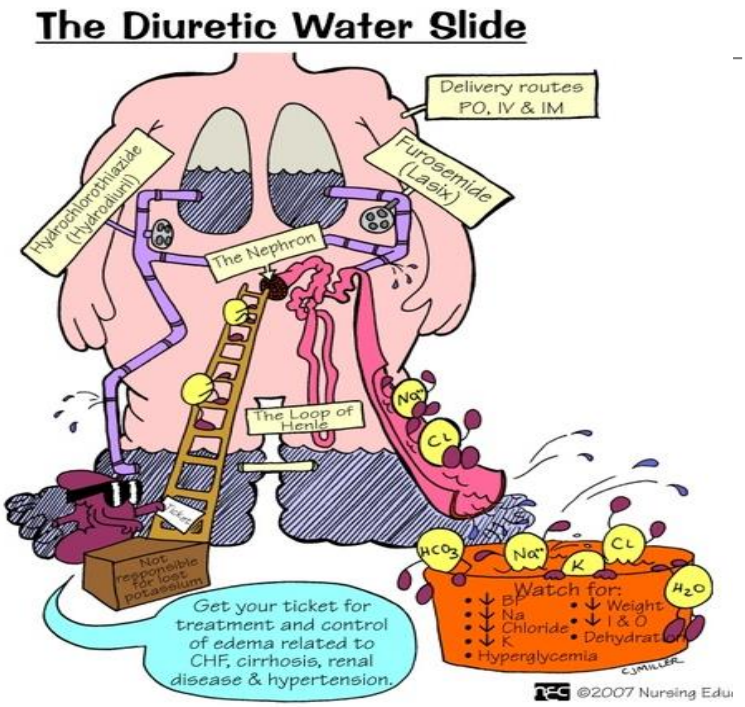
Mechanism of action:

Most diuretics act by inhibiting normal sodium reabsorption by the renal tubules resulting in sodium and water excretion.

Sites of action:

Target molecules for most diuretics are carriers or transporters in luminal membrane of renal tubular cells required for tubular reabsorption of sodium from filtrate back into blood. In addition to the ion transport inhibitors, other types of diuretics include osmotic diuretics, aldosterone antagonists, and carbonic anhydrase inhibitors.

Notes:
*Na is important For body, so is usually filtered but it has to be reabsorbed
*Natriuretics are diuretics that inhibit Na as NaCl reabsorption and then lead to diuresis , As a result, greater amount of Na^+ and other ions, such as Cl^-, stay in the urine and don't get reabsorbed, which in turn greater amount of H_2O stays in urine due to osmolarity changes.



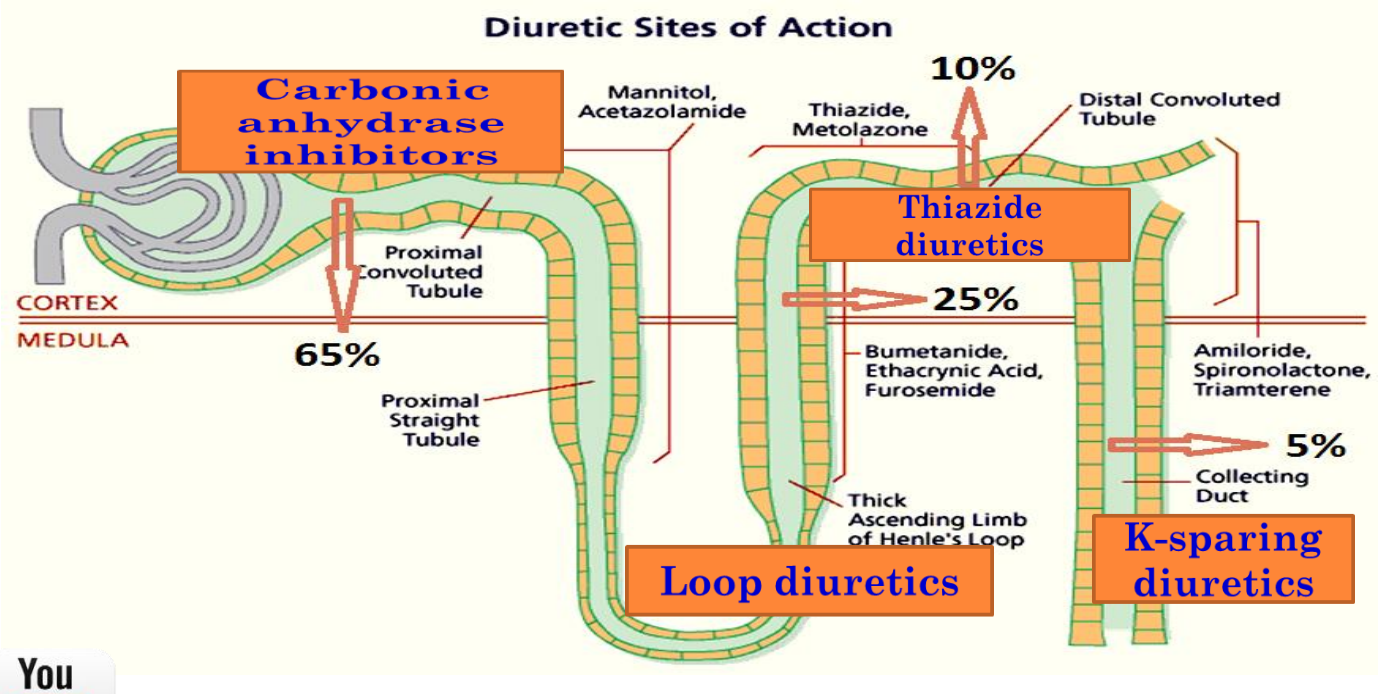
Diuretic action in the kidney

Different nephron segments

Nephron Segment	Na+ Transporter\ Transporter	Filtered Na+ re-absorbed	Diuretics	Function
Proximal convoluted tubules	Na+/H+ transporter Carbonic anhydrase enzyme	85 % As Na,HCO3 65 % As NaHCO3	Carbonic anhydrase inhibitors	Re-absorption of -100% glucose and amino acids. -66% Na, K, Ca, Mg. -85% NaHCO3.
Proximal straight tubules	Acid & base transporter	-----	None	Secretion and re-absorption of organic acids and bases
Ascending Loop of Henle	Na+/K+/2Cl- transporter	20-30% Active reabsorption Na, K, Cl, Ca and mg	Loop diuretics	Active reabsorption 25% Na, K, Cl Secondary re-absorption Ca, Mg
Distal convoluted tubules	Na+/Cl- cotransporter	5-10% Active reabsorption Na, Cl	Thiazide diuretics	Active tubular reabsorption of 5% Na, Cl, Ca
Cortical Collecting Tubules	Na+ channel K&H transporter Aldosterone Antidiuretic hormone	5% Na reabsorption K & H secretion	K-sparing diuretics	Na reabsorption K & H secretion

Classification of diuretics

Classification	Mechanism of Action	Examples
Carbonic anhydrase inhibitors	Inhibits carbonic anhydrase (CA) enzyme in **proximal convoluted tubules** thus interferes with NaHCO3 re-absorption and causes diuresis.	Acetazolamide & dorzolamide
Loop diuretics	• Inhibit Na+ / K+ / 2 Cl- co-transporter in the luminal membrane of the thick ascending loop of Henle (TAL) • Inhibit Ca++ and Mg ++ re-absorption.	Furosemide, bumetanide , ethacrynic Acid
Thiazide diuretics	acts via inhibition of Na/Cl co-transporter on the luminal membrane of distal convoluted tubules.	Chlorothiazide , Hydrochlorothiazide, Metolazone, Chlorthalidone, Indapamide
Potassium sparing diuretics	Act in collecting tubules and ducts by inhibiting Na re-absorption and K & H excretion (blocking NA channels + antagonizing aldosterone)	Spironolactone, triamterene , amiloride
Osmotic diuretics	↑ urine output by osmosis, drawing water out of cells and into the blood stream.	Mannitol (sugar)



Diuretics - Learn with Visual Mnemonics!

STUCK IN MEMORIZING THEM IN ORDER ? Nothing to worry about, our team will help you ;)

"COLT Pee:"

Diuretics make patient pee like a horse, hence "Colt Pee"

- According to their sequential site of action along the nephron:

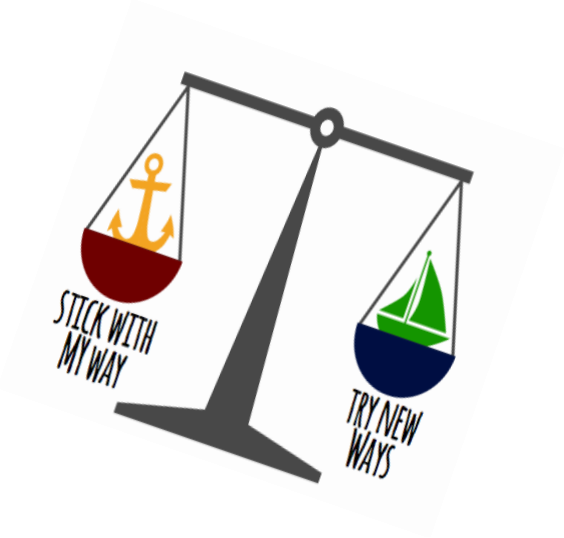
Carbonic anhydrase inhibitors (at the proximal tubule)
Osmotic diuretics (Act in proximal tubules and descending loop of Henle)
Loop diuretics (at the ascending loop of Henle)
Thiazides (at the distal tubule)
Potassium-sparing diuretics (at the collecting tubules)

"Leak Over The CAN"

"leak" is slang for urination and "can" is slang for a toilet.

Diuretics:

Loop diuretics
Osmotics
Thiazides
Carbonic anhydrase inhibitors
K-sparing diuretics:
- **A**ldosterone inhibitors
- **N**a (sodium) channel blockers

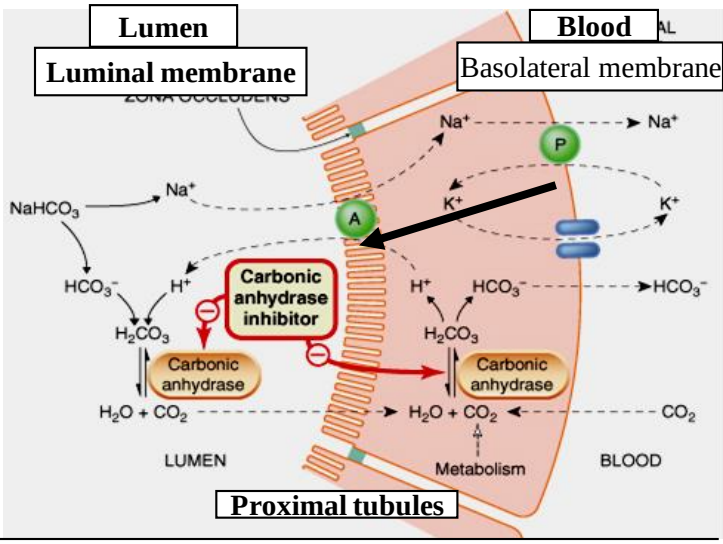


Carbonic Anhydrase Inhibitors

Carbonic Anhydrase Inhibitors : sulfonamides derivatives.

Function of Carbonic Anhydrase CA :

CA is required for reversible reaction, in which CO2 +H2O ↔ H2CO3 (H^+ + $HCO3^-$). H2CO3 spontaneously ionizes into HCO_3^- + H^+ in the proximal tubular cells. H^+ is then secreted to the lumen in exchange for Na. thus, to reabsorb Na to the proximal tubules from the lumen we need this enzyme. CA is present in the kidney, aqueous humor in eye, & CSF. In the kidney, it is found in the cytoplasm of proximal tubules + luminal membrane.



NOTE : اللي يدخل لل لويمنال ميمبراين معناه نبغاه يطلع مع البول لكن اللي نرجعه للبروكسيمل توبيول نبيه يعاد إمتصاصه

	Acetazolamide (diuretic)	Dorzolamide (eye drops for OAG)
Mechanism of action:	**Site of action:** proximal convoluted tubules. Inhibit **carbonic anhydrase (CA) enzyme** in proximal convoluted tubules, thus interfere with **NaHCO3 re-absorption** and cause diuresis. **NaHCO3** will be execrated with water in the urine.	
Pharmacokinetics:	• Produces **alkaline urine** because of the bicarbonate " but the state of the **blood is acidosis** due to the lose of the bicarbonate which make the H ions has the upper hand in plasma". • given **orally** once a day. **Except for Dorzolamide** given by eye drops. • Onset of action is **rapid (30 min).** • Duration of action **(12 h).** " long " • Excreted by active secretion in **proximal convoluted tubules.**	
Pharmacological actions:	• **↑ urine volume** • ↑ urinary excretion of **sodium**, **potassium , bicarbonate** (causing alkaline urine). • **Metabolic acidosis.** " due to lose of bicarbonate " • **↑ Urinary phosphate excretion**." لان البول لما يكون قاعدي يطلع معه الفسفور • Promotes **K+ excretion** by ↑ the load of **Na**+ delivered to **the distal tubules.** Aldosterone transport K into tubule and Na out of tubule to endothelium, which leads H_2O to follow Na.	

Carbonic Anhydrase Inhibitors (cont.)

Therapeutic uses:

- **Open angle glaucoma " HOW?** carbonic anhydrase inhibitors cause ↓ IOP by reducing aqueous humor formation in ciliary body of eye. "more explanation: أغلب مكونات الخليط المائي هذا عبارة عن بيكربونات ومن أجل تكوين هذا الخليط نحتاج الإنزيم carbonic anhydrase "
- **As prophylactic therapy, in acute mountain sickness to ↓ CSF of brain** "given nightly 5 days before the ascent to reduce symptoms of mountain sickness (↓ weakness, breathlessness , dizziness, nausea, cerebral & pulmonary oedema)
- **Epilepsy.** Epilepsy happen when pH Changes to be in the alkaline range, so CA inhibitor is used as adjuvent to decrease the risk as it **causes acidosis + decreases cerebrospinal fluid (CSF).**
- **Urinary alkalinization** to enhance renal excretion of acidic substances accumulated in the body **(e.g. cysteine in cystinuria).**
- **Hyperphosphatemia.**
- **Metabolic alkalosis.**treated with CA inhibitors because they cause metabolic acidosis.

Adverse effects:

All these AE are NOT for Dorzolamide because the route of administration.

- **Hypokalemia (potassium loss).**
- **Metabolic acidosis.**
- **Renal stone formation (calcium phosphate" not soluble " stones).**
- **Hypersensitivity reaction. " "مو مميزه لان كل مجموعة السلفون امايد تسبب نفس الشيء**

Question: Why do CA inhibitors have weak diuretic properties?

Because diuretic properties decreases after several days as the blood bicarbonate falls. This means that Na is excreted in association with HCO3, when HCO3 plasma concentration decreases in metabolic acidosis, Na excretion will also decrease. they are thus "self- limiting diuretics".

Another reason is that Action of diuresis is blunted by NaCl reabsorption in distal portion. The reabsorption mechanism in the ascending loop of Henle & distal convoluted tubules is load-dependent. This means that the more Na delivered there, the more it is reabsorbed.

NOTE THAT Dorzolamide:

- **Is a carbonic anhydrase inhibitor**
- **Used topically (eye drops) for treatment of open-angle glaucoma.**
- **Thus no diuretic or systemic side effects**

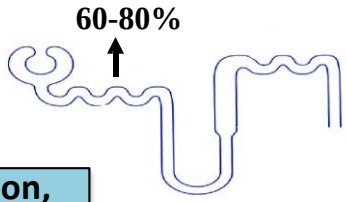
Osmotic Diuretics

Mannitol

Pharmacokinetics	Pharmacodynamics	Therapeutic uses
●Poorly absorbed ●Given I.V ●If given orally --> osmotic diarrhea ●Not metabolized ●Excreted by glomerular filtration, without being reabsorbed or secreted ,within 30-60 minutes.	●Acts in proximal tubules and descending loop of Henle by osmotic effect. ●↑ Urine output by osmosis, drawing water out of cells and into blood stream. ●Expand the ECF volume, decrease blood viscosity and inhibit renin release ↑ renal blood flow. ●↑ Water excretion with relatively less effect on Na+ (water diuresis)	• **Acute renal failure due to shock or trauma** (maintain urine flow – preserve kidney function) • **In acute drug poisoning:** to eliminate drugs that are reabsorbed from renal tubules e.g. salicylates, barbiturates. • To ↓ intraocular &intracranial pressure before ophthalmic or brain procedures **(cerebral edema)**

ADRs

- Headache, nausea, vomiting
- **Extracellular volume expansion,** complicates heart failure and pulmonary edema
- **Excessive use** → dehydration & hypernatremia (adequate water replacement is required).



[1]If given orally → increases water in the GIT → osmotic diarrhea

[2] The presence of osmotic diuretics in filtrate results in a higher osmolarity of the tubular fluid and thus prevents further water reabsorption, resulting in osmotic diuresis. Only a small amount of additional salt may also be excreted. (no natriuraesis)

[3] Drags water out of the cells and into the ECF (because the presence of *mannitol* in the extracellular fluid) →↓ blood viscosity → increase renal blood flow.

[4] It drags water out of the cells without affecting sodium receptors

[5] Hypernatremia is probably caused following excessive loss of water, which leads to the increase in Na concentration in plasma.

Loop Diuretics

Loop diuretics are The most potent diuretics (thus termed: High Ceiling Diuretic).

They work even in patients with poor renal function or lack of response to other diuretics. These agents have the greatest diuretic effect of all the diuretic drugs, since the **ascending limb** accounts for reabsorption of 25% to 30% of filtered NaCl, and downstream sites are unable to compensate for the increased Na+ load (Na inhibited from reabsorption).

Drugs as:

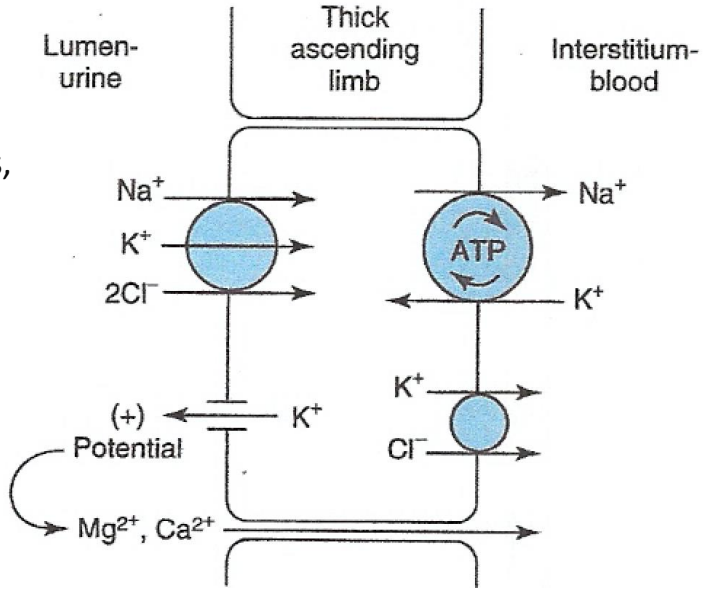
Bumetanide Potency 40, t 1/2 =0.8 h (Most potent)	Ethacrynic Acid Potency 0.7, t 1/2 = 1 h (Most toxic, less used)
Furosemide Potency 1, t 1/2 = 1.5 h (Most used)	Torsemide Potency 3, t 1/2 = 3.5 h (Longest duration)

Physiology of the Ascending loop of Henle (TAL)

1. It is impermeable to water.
2. TAL is responsible for active re-absorption of Na, K and Cl, 25-30% of Na+ is reabsorbed via transport system in luminal membrane called Na+/k+/2CL- co-transporter.
3. Ca and Mg are reabsorbed and enter the interstitial fluid via paracellular pathway.

Mechanism of action:

- Inhibit NA+/K+/2Cl- co-transport in the luminal membrane of the thick ascending loop of Henle (TAL). Causing High natriuresis, as 25-30% Na+ is normally reabsorbed from the ascending loop of Henle.
- Additional effect: Inhibit Ca++ and Mg++ re-absorption (Unlike thiazides, loop diuretics increase the $Ca+^{2}$ content of urine. In patients with normal serum $Ca+^{2}$ concentrations, hypocalcemia does not result, because Ca^{2+} is reabsorbed in the distal convoluted tubule).



Loop Diuretics (cont.)

	Pharmacokinetics	Pharmacological Actions	Uses: (As drug of choice for emergency/acute situations)
Loop diuretics	Given IV or orally, and have a short duration of action (2 to 4 hrs.)	↑ Urinary excretion of Na+ and K+	Edema associated with: congestive heart failure, nephrotic syndrome
	Have fast onset of action (suitable for emergency)	↑ Urinary excretion of Ca++ and Mg++	**Acute** pulmonary edema (and peripheral edema)
	Excreted by active tubular secretion of week acids into urine. Uric acid is also secreted by the same transporter, thus, competition with loop diuretics Interferes with uric acid secretion (causing hyperuricemia)	↑ Urine volume	**Acute** hyperkalemia Because they cause hypokalemia
		↑ Renal blood flow *	**Acute** hypercalcemia. Because they increase the Ca^{+2} content of urine

Adverse effects:

Ototoxicity [1] (more seen with ethacrynic acid!) (Risk increased if combined with **aminoglycoside,** because they also cause ototoxicity)

Hyper-uricemia [2] (Increase blood uric acid and gouty attacks)

Hypokalemia [4] (↓ Blood K+) *Dietary K supplementation or K-sparing diuretics should be given to avoid it.

Hypomagnesemia [4] (↓ Blood Mg++) & Hyperglycemia

Hypocalcemia [4] (↓ Blood Ca++) Avoid in pts with risk of osteoporosis

Metabolic Alkalosis [5]

Postural hypotension

Hyponatremia [4] (↓ Blood Na+)

Hypovolemia (volume depletion) [6]

allergic reactions (as all derivatives of sulfa drugs)

Notes:

*Loop diuretics may increase renal blood flow, possibly by enhancing prostaglandin synthesis. NSAIDs inhibit renal prostaglandin synthesis and can reduce the diuretic action of loop diuretics (so contraindicated).

[1] The heavy load of Na+ presented to the collecting tubule results in increased exchange of tubular Na+ for K+, causing hypokalemia.

[1] Mechanism unknown

[2] Loop and thiazide diuretics interfere with uric acid secretion.

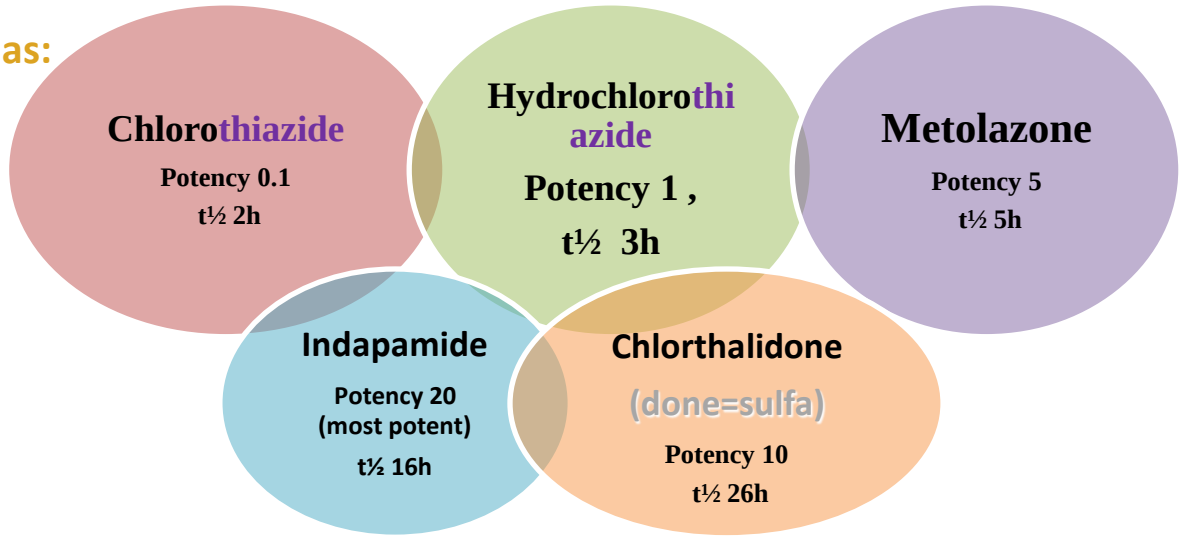
[4] When you block the Na, K, Cl cotransporter in the TAL the gradient that drives Mg, Na, K, and Ca into the blood is lost, therefore there will be no reabsorption of either of these which will cause, hyponatremia, hypocalcemia, hypomagnesaemia, and hypokalemia.

[5] Metabolic alkalosis is caused by hypovolemia, which results in activation of RAAS & thus Increases aldosterone. Which contributes significantly to urinary H+ & K+ losses.

[6] Hypovolemia causes a severe and rapid reduction in blood volume, with the possibility of hypotension, shock, and cardiac arrhythmia.

THIAZIDE DIURETICS

Drugs as:



Notes:

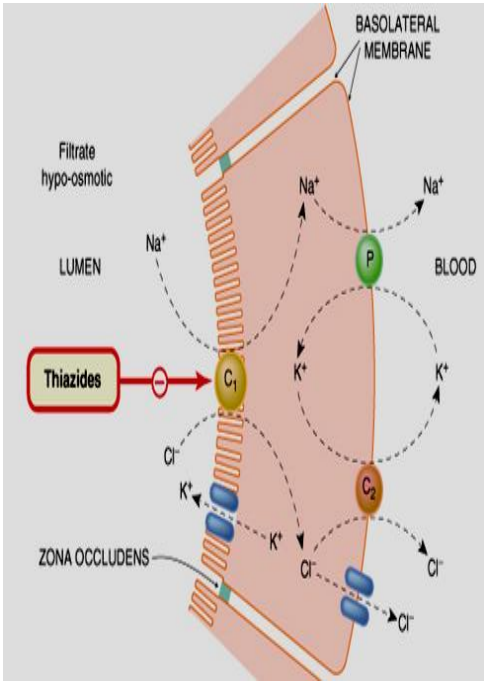
- Thiazides are also sulfa derivatives. They are the most widely used diuretics.
- Potency= معيار الجرعة. The more potent a drug is, the more it is effective at lower doses
- Chlorthalidone, indapamide, and metolazone are referred to as thiazide-like diuretics, because they contain the sulfonamide residue in their chemical structures, and their mechanism of action is similar. However, they are not truly thiazides.
- Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.
- The efficacy of these agents may be diminished with concomitant use of NSAIDs, which inhibit production of renal prostaglandins, thereby reducing renal blood flow.

Mechanism of action:

Act via inhibition of Na/Cl co-transporter on the luminal membrane of distal convoluted tubules.

- Ca is reabsorbed by the action of parathyroid hormone (Which is responsible for maintaining normal Ca concentrations, if there's any deficiency in Ca, Parathyroid hormone will increase Ca reabsorption in the kidneys).

Efficacy: Thiazides have moderate natriuresis, as only 5-10% of filtered load of sodium is reabsorbed in DCT.



THIAZIDE DIURETICS (cont.)

Pharmacokinetics

- **Given orally, slow of onset.** Thus not used in acute situations
- **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)
  Recall: lecture (renal excretion of drugs)

Pharmacological Effects

↑Urinary NaCl Excretion

↑Urinary K Excretion (Hypokalemia). Because thiazides increase Na+ in the filtrate arriving at the distal tubule, more K+ is also exchanged for Na+, resulting in a continual loss of K+ from the body with prolonged use of these drugs (increasing aldosterone activity) . Thus, we need to prescribe K supplements when taking these diuretics.

↑Urinary Magnesium Excretion

↓Urinary Calcium Excretion & ↑Calcium Re-absorption (Hypercalcemia).
(Thiazides enhance parathyroid hormone activity, which is responsible for Ca reabsorption).

Uses

Mnemonic for indications of thiazide diuretics: "CHIC"

- **CHF: Treatment of <u>mild</u> congestive heart failure (to reduce extracellular volume).**
- **Hypertension: FIRST CHOICE for Treatment of essential hypertension (cheap & well tolerated).** Add beta blockers to reduce BP further more.
- **Insipidus: Nephrogenic diabetes insipidus (decrease blood volume and GFR)** due to pathology of the kidney, Patients with Nephrogenic diabetes insipidus suffer from Polyuria (production of abnormally large volumes of dilute urine & thirst). In this case, thiazides cause initial increase in urine output, then it returns to the normal rate by compensatory mechanisms.
- **Ca calculi: Calcium nephrolithiasis due to hypercalciuria (to increase calcium re-absorption and decrease renal calcium stones)**

The thiazides can be useful in treating idiopathic hypercalciuria, because they inhibit urinary Ca2+ excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract. They can also be safely used in pts with osteoporosis (unlike loop diuretics).

Mechanism of antidiuretic effect of thiazide in diabetes insipidus

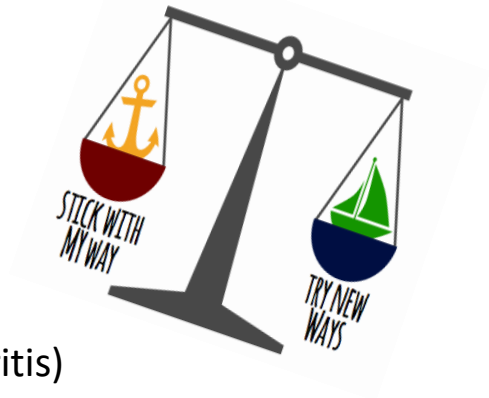
Thiazide → ↓Distal tubular Na+ reabsorption → ↑Urinary excretion → ↓Extracellular volume → ↑Proximal Na+ & Water reabsorption → ↓Distal delivery of Na+ & water → ↓Urine volume (initial increase then it returns to the normal rate)

THIAZIDE DIURETICS (cont.)

Adverse Effects

1. **Fluid and electrolyte imbalance**
2. **Metabolic alkalosis** (excretion of potassium due to aldosterone effect will cause loss of hydrogen too)
3. **Hypovolemia (volume depletion).** This can cause orthostatic hypotension or light-headedness.
4. **Hyponatremia**
5. **Hypokalemia.** Thiazides decrease the intravascular volume, resulting in activation of the renin–angiotensin–aldosterone system. Increased aldosterone contributes significantly to urinary K+ losses.
6. **Hyperuricaemia (contraindicated in gout)** because of reabsorption of uric acid
7. **Hypercalcemia (characteristic).** (they enhance parathyroid hormone).
8. **Hyperglycaemia.** possibly due to impaired release of insulin and tissue uptake of glucose
9. **Hyperlipidemia**
10. **Hypomagnesaemia.** The mechanism for the magnesuria is not understood.

MEMORIZING STATION



Thiazides diuretics Hyper / Hypo effects:

HYPER effects in serum: (**U**gly **G**irls **L**ike **Cars**)

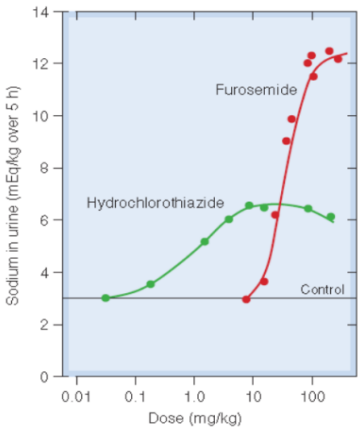
- **HYPER**uricemia (precipitate acute gouty arthritis)
- **HYPER**glycemia
- **HYPER**lipidemia (increase cholesterol and LDL)
- **HYPER**calcemia (renal calcium resorption, decrease calcium in urine)

HYPO effects in serum: (**M**iss **N**ora **V**olunteered in **K**uwait)

- **Hypo**magnesaemia
- **Hypo**natremia
- **Hypo**volemia and thus **HYPO**tension (decreases blood volume and peripheral vascular resistance)
- **HYPO**kalemia

Extra slide

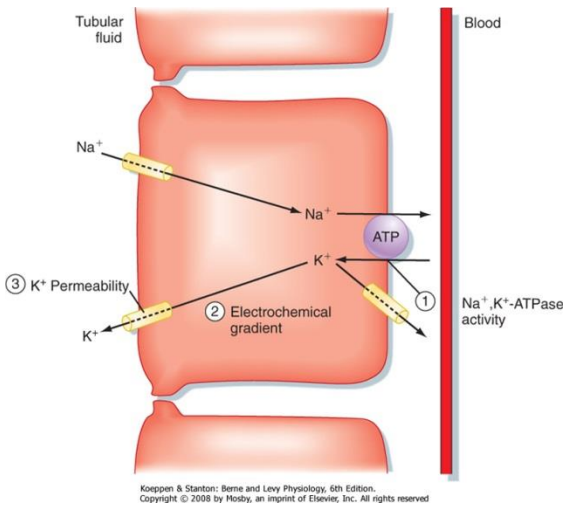
Ceiling: The maximum biological effect that can be induced in a tissue by a given drug, regardless of how large a dose is administered.
Thiazides are sometimes called “low ceiling diuretics,” because increasing the dose above normal therapeutic doses does not promote further diuretic response.
It is the opposite for loop diuretics, thus are the most potent diuretics.



Thiazide diuretics VS. loop diuretics	
Loop diuretics	Thiazide diuretics
High ceiling diuretics	Low ceiling diuretics
The most Effective	Not as effective as loop
used in emergency and acute situations (Have fast onset and short duration of action)	Not used in emergency (has long duration but slow onset)
hypocalcemia	Hypercalcemia

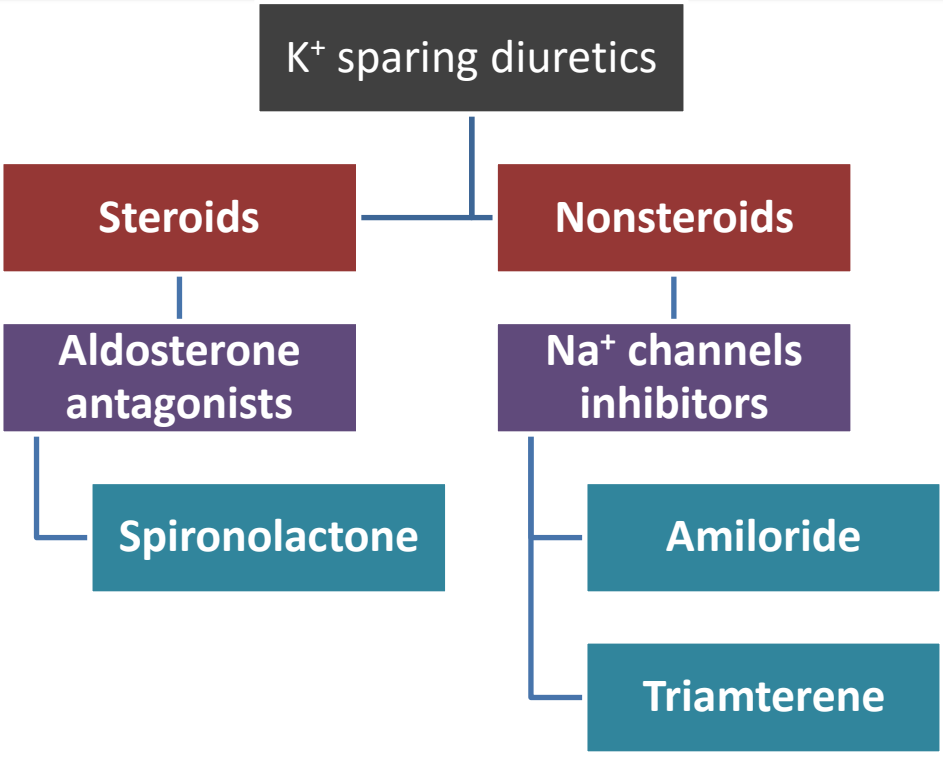
All diuretics which work before the collecting tubules cause hypokalemia, why?

1. More Na reaches the principal cells → more Na is reabsorbed there → more Na/K pumped in the basolateral membrane → more intracellular K → increase conc. Gradient between cell and lumen → K excretion
2. **Hypovolemia → RAAS activation → aldosterone exchanges K for Na to correct the hypovolemia → some Na reabsorption and K excretion**



3. More anions reaching the principal cells (HCO3/Cl) → electronegative luminal membrane → increase electrochemical gradient → more K excreted into lumen
4. More water reaching the principal cells → less conc. Of K in lumen → increase conc. Gradient between cell and lumen → K excretion

Potassium-sparing diuretics



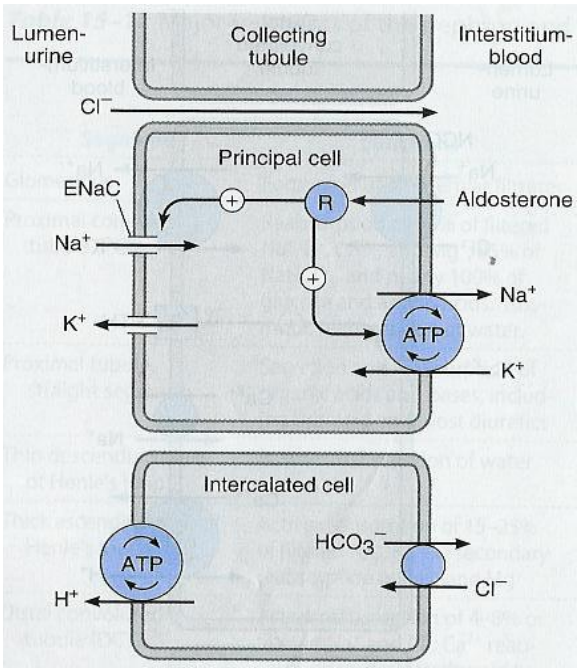
K^+ sparing diuretics make the K^+ stay (not go down in the urine)
STAy
Spironolactone
Triamterene
Amiloride

Mechanism of action

Act in collecting tubules and ducts by inhibiting Na re-absorption and K & H excretion (K-sparing effect) by either:

Steroids	Non-Steroids
Aldosterone antagonists Spironolactone (a synthetic steroid)	**Na^+ channels inhibitors** Triamterene and Amiloride
produces its diuretic effect by antagonizing cytoplasmic aldosterone receptors.	Inhibition of Na^+ influx through epithelial Na^+ channels in the luminal membrane.

Collecting tubules (CT) :



Notes: Aldosterone increase **Na^+** reabsorption and release K^+ →loss of H^+. When we antagonize the action of Aldosterone, **Na^+** is released in the urine and K^+ is reabsorbed → H^+ is also reabsorbed.
So the net result is hyperkalemia (which is a result only this group of diuretics can achieve), in addition to acidosis (caused by the H^+ reabsorption) and subsequent alkalosis of urine.

Potassium-sparing diuretics (cont.)

Pharmaco-dynamics

↑ urinary Na^+ excretion (Amount of Na normally reabsorbed from the collecting tubules & ducts =5% , thus Potassium-sparing diuretics are weak diuretics.)

↓ urinary K^+ excretion (hyperkalemia)

↓ urinary H^+ excretion (acidosis)

Therapeutic uses

1-To prevent hypokalemia in treatment of hypertension (combined with thiazide or loop diuretics to correct hypokalemia).

2-Drug of choice for patients with hepatic cirrhosis Patient with hepatic cirrhosis have ↑ aldosterone which is antagonized by Spironolactone.

3-Secondary hyperaldosteronism

(Congestive heart failure, hepatic cirrhosis and nephrotic syndrome)

In primary hyperaldosteronism, there are abnormalities of the adrenal gland causing over production of aldosterone. In secondary hyperaldosteronism, there is stimulation of RAAS due to another disease e.g. hypoalbuminemia in nephrotic syndrome. hypoalbuminemia and hypovolemia > stimulation of RAAS > net increase in aldosterone > antagonized by Spironolactone

Adverse Effects

1-Hyperkaliemia

2-Metabolic acidosis decreased excretion of H^+ and K^+

3-Gynecomastia (tenderness of the breast in males). Caused by Anti-androgenic action (against testosterone) only by Spironolactone. May also cause sexual dysfunction.

4-GIT upset and peptic ulcer (Idiopathic)

Contraindication

1- Hyperkalemia: due to disease or administration of drugs that already cause hyperkalemia. As in:

- Chronic renal failure (hyperkalemia due to electrolyte balance problem)
- K^+ supplementation
- β-blockers or ACE inhibitors (increase serum potassium)

2- Liver Disease (dose adjustment is needed).

Therapeutic applications of diuretics

Hypertension

- **Thiazide diuretics:** used alone or in combination with beta blockers at low doses (fewer side effects)
- Loop diuretics are used in the **presence of renal failure**[1]

Edema states

- Mild edema with normal renal function → Thiazide diuretics
- Impaired renal function → Loop diuretics

Congestive heart Failure

- **Mild cases:** thiazides may be used with well preserved renal function
- **Severe cases:** loop diuretics are much preferred, especially when GFR is lowered. E.g. In life-threatening acute pulmonary edema, furosemide is given I.V

Renal failure

- Thiazides are used till GFR ≥ 40-50 ml/min
- Loop diuretics are used below given values, with increasing the dose as GFR goes down.

Nephrogenic diabetes insipidus

- In nephrogenic DI, Large volume (>10 L/day) of dilute urine → thiazide diuretics are used to reduce urine volume.

Hepatic cirrhosis with ascites

- Spironolactone is the drug of choice

[1]Because they increase PGs → vasodilation

Summary

Tubular segment	Proximal convoluted tubules	Proximal Straight Tubules	Thick ascending loop	Distal convoluted tubules	Collecting tubules	proximal tubules & descending loop of Henle
Function	Re-absorption of 66% Na, K, Ca, Mg, 100% glucose and amino acids; 85% $NaHCO_3$	Secretion and re-absorption of organic acids and bases	Active reabsorption 25% Na, K, Cl Secondary reabsorption Ca, Mg	Active tubular reabsorption of 5%Na, Cl, Ca	Na reabsorption K & H secretion	
Transporter	Na/H transporter, Carbonic anhydrase enzyme	Acid & base transporter	Na/K/2Cl transporter	Na and Cl cotransporter	Na channels K & H transporter	
Diuretic acting on this segment	Carbonic anhydrase inhibitors Acetazolamide Dorzolamide	None	Loop diuretics Furosemide	Thiazide diuretics hydrochlorothiazide	K-sparing diuretics Spironolactone	Osmotic diuretic Mannitol
Mechanism of action	Inhibition of $NaHCO_3$ reabsorption in PCT		Na/K/2Cl transporter in TAL the most effective	Na and Cl cotransporter in DCT	competitive antagonist of aldosterone in CCT	Osmotic effect in PCT
Effects	↑Urinary $NaHCO_3$, K ↑Urinary alkalosis ↑Metabolic acidosis		↑Urinary Na, K, Ca, Mg -Metabolic alkalosis	↑Urinary Na, K, Mg BUT↓ urinary Ca (hypercalcemia) -Metabolic alkalosis	↑ Urinary Na ↓ K, H secretion Metabolic acidosis	↑Urine excretion ↑ Little Na
Uses	Glaucoma (Dorzolamide topically), epilepsy Mountain sickness Alkalosis Phosphatemia		Acute pulmonary edema (Drug of choice) Heart failure Hyperkalemia, Hypercalcemia	Commonly used Hypertension, mild heart failure, nephrolithiasis, diabetes insipidus	Hepatic cirrhosis (Drug of choice)	•Cerebral edema, glaucoma • Acute renal failure, drug toxicities

Summary - Adverse effects

Carbonic anhydrase inhibitors

Acetazolamide

Dorzolamide

- **Metabolic acidosis**
- **Urinary alkalosis**
- **Hypokalemia**
- **Renal stone formation**
- **Hypersensitivity reactions**

Osmotic diuretic

Mannitol

- Headache, nausea, vomiting
- **Extracellular water expansion**
- **Dehydration**
- **Hypernatremia**

K-sparing diuretics

Spironolactone

- **Gynecomastia (spironolactone)**
- **Hyperkaliemia**
- **Metabolic acidosis.**
- **GIT upset and peptic ulcer**

Thiazide diuretics

hydrochlorothiazide

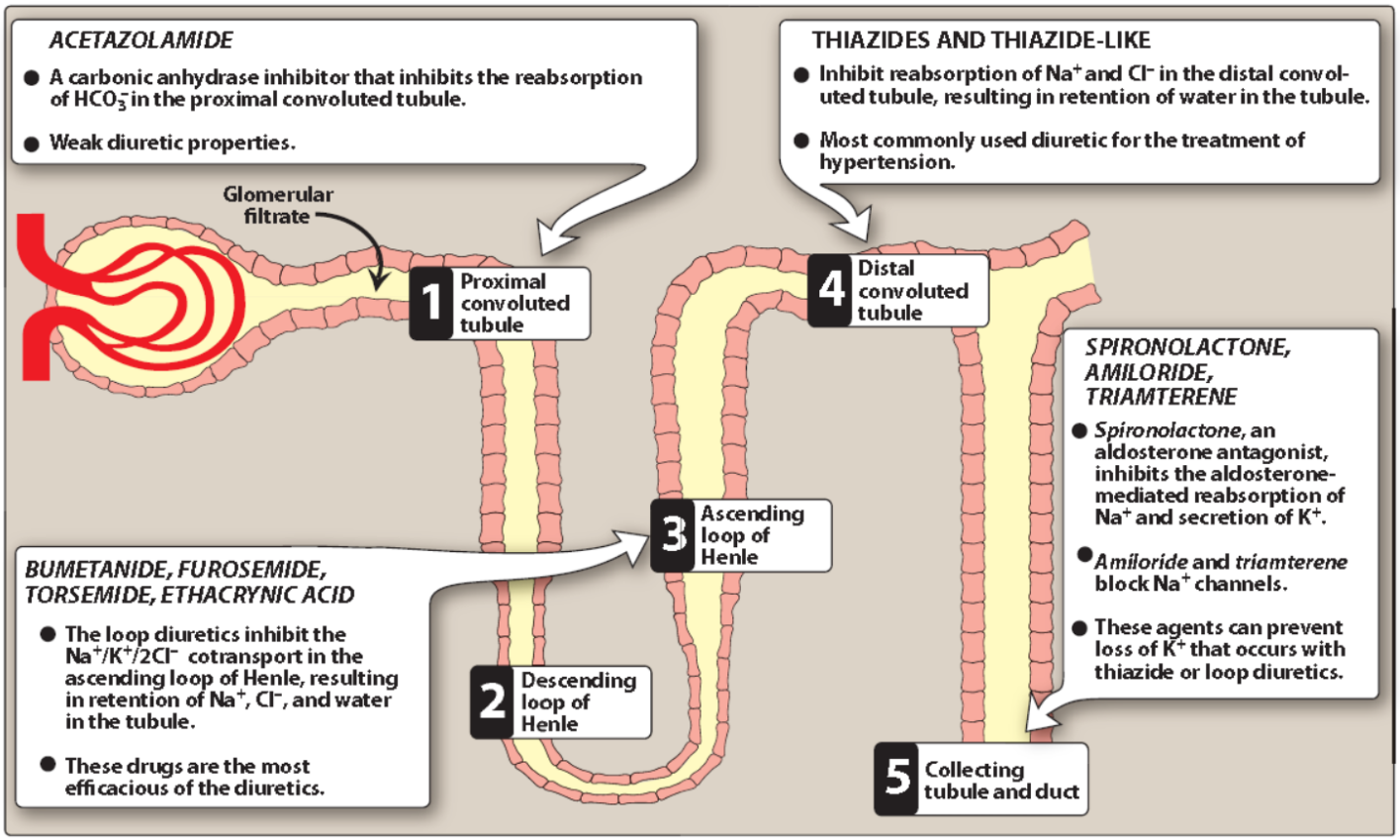
- **Hypokalemia**
- **hyponatremia, hypovolemia,**
- **hypomagnesemia, hypercalcemia**
- **Alkalosis, precipitate gout**
- **Hyperlipidemia, hyperglycemia**

Loop diuretics

Furosemide

- **Hypokalemia,**
- **hypovolemia, hyponatremia,**
- **hypomagnesemia, hypocalcemia**
- **Precipitate gout, alkalosis**
- Ototoxicity

Summary



Diuretics Comparison

Diuretic class	Major site of action	Special Side effect (s)
1. Carbonic anhydrase inhibitor	Proximal tubule	Acidosis
2. Thiazide and thiazide like	Proximal tubule	Hyperuricemia Hypokalemia
3. Loop diuretics	Loop of Henle	Hypokalemia Ototoxicity
4. Potassium sparing	Distal tubule	Hyperkalemia
5. Osmotic diuretic	Glomerulus	Hypovolemia & hypotension

Summary


DIURETICS
Osmotic diuretics
Mannitol
Excreted by glomerular filtration without being re-absorbed or secreted within 30-60 min
used to treat patients with Acute renal failure due to shock or trauma and In acute drug poisoning
ADR:Headache, nausea, vomiting and Extracellular volume expansion
Expand the extracellular fluid volume, decrease blood viscosity, and inhibit renin release, increase renal blood flow
Carbonic Anhydrase Inhibitors
Site of action: proximal convoluted tubules
Produces alkaline urine
Dorzolamide Has no diuretic or systemic side effects
used to treat patient with Open angle glaucoma
Used As prophylactic therapy, in acute mountain sickness
ADR :Renal stone formation (calcium phosphate stones and Hypersensitivity reaction
PDF
Diuretics
Loop Diuretics
The most potent diuretic , termed "high ceiling diuretic
Given orally or I. V and Have fast onset of action (suitable for emergency)
Used for Emergency satiation such as Edema associated with congestive heart failure, nephrotic syndrome Acute pulmonary edema Acute hyperkalaemia. Acute hypercalcemia
inhibit Na+ / K+ / 2 Cl- co-transporter in the luminal membrane of the TAL
inhibit Ca++ and Mg ++ re-absorption
Interfere with uric acid secretion (hyperuricemia).
Excreted by active tubular secretion of weak acids into urine
increase urinary excretion of K , Na , Ca , Mg
increase urine volume and Renal blood flow
ADR :Hyponatraemia ,Hypokalemia, Hypomagnesaemia ,Hypocalcaemia, Metabolic alkalosis Postural hypotension , Hypovolemia , Hyperuricemia , Ototoxicity and Allergic reactions
Thiazide diuretics
acts via inhibition of Na/Cl co-transporter on the luminal membrane of distal convoluted tubules.
are secreted by active tubular secretory system of the kidney
may interfere with uric acid secretion and cause hyperuricemia
Increase urinary excretion of NaCl , Mg , K and increase Ca reabsorption
Used to treat essential hypertension and mild heart failure
ADR : Fluid and electrolyte imbalance Hyponatremia , Hypovolemia, Hypokalemia , Metabolic alkalosis , Hyperuricaemia, Hypercalcemia , Hyperglycaemia and Hyperlipidemia
Used to treat essential hypertension , mild heart failure , Calcium nephrolithiasis due to hypercalciuria and Nephrogenic diabetes insipidus
PDF

Summary

Potassium- sparing diuretics

- Spironolactone: act by antagonizing cytoplasmic aldosterone receptors
- Hyperkalemia
- they decrease H+ excretion (acidosis)
- Used to treat hypertension (combined with thiazide or loop diuretics to correct for hypokalemia).
- Spironolactone is used for secondary hyperaldosteronism e.g. hepatic cirrohsis.
- ADR: Hyperkalaemia. Metabolic acidosis. Gynaecomastia GIT upset and peptic ulcer
- Contraindicatedin case of Hyperkalaemia: as in chronic renal failure, K+ supplementation, beta-blockers or ACE inhibitors.

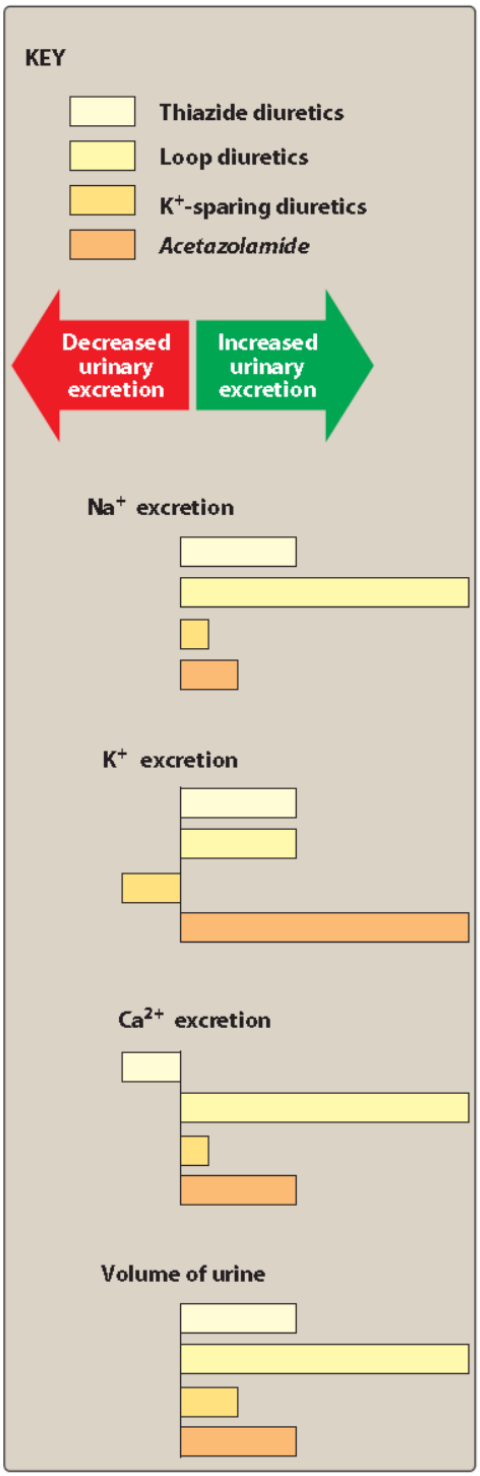


TABLE 15–2 Changes in urinary electrolyte patterns and body pH in response to diuretic drugs.

Group	Urinary Electrolytes			
	NaCl	$NaHCO_3$	K^+	Body pH
Carbonic anhydrase inhibitors	+	+++	+	↓
Loop agents	++++	0	+	↑
Thiazides	++	+	+	↑
Loop agents plus thiazides	+++++	+	++	↑
K^+-sparing agents	+	(+)	–	↓

+, increase; –, decrease; 0, no change; ↓, acidosis; ↑, alkalosis.

Questions

1-A patient came to the clinic complaining of pain in his lower back that started a couple of weeks after using a medication to treat his edema. After doing a few tests the doctor diagnosed him with calcium-phosphate stones. Which one of the following drugs do you think the patient was using?

A-Spironolactone
B-Acetazolamide
C-Torsemide
D-Indapamide

2-A 60-year-old patient came to the clinic, she presented with osteoporosis and edema. Which one of the following is the drug of choice in this case?

A-Ethacrynic acid
B-Dorzolamide
C-Amiloride
D-Indapamide

3-Which one of the following drugs is contraindicated in the previous case?

A-Ethcrynic acid
B-Dorzolamide
C-Amiloride
D-Indapamide

4-A 45-year-old patient came to the nephrology clinic. The doctor asked him to collect a 24-hour urine sample and take it to the lab the next day. The lab results showed a GFR of 32. Which one of the following drugs would you prescribe?

A-Spironolactone
B-Hydrochlorothiazide
C-Torsemide
D-Acetazolamide

5-A 50-year-old patient came to the nephrology clinic, she complained of edema and frothy urine. Which one of the following drugs would you prescribe to relief her edema?

A-Furosemide
B-Chlorothiazide
C-Dorzolamide
D-Mannitol

1-B
2-D
3-A
4-C
5-A

Questions

6-Which one of the following group of diuretics has the least natriuretic effect?
A-Carbonic anhydrase inhibitors
B-Loop diuretics
C-Osmotic diuretics
D-Potassium sparing diuretics

7-Which one of the following group of diuretics are also called high ceiling diuretics?
A-Thiazides
B-Carbonic anhydrase inhibitors
C-Osmotic diuretics
D-Loop diuretics

8-A patient came to the ER with severe life-threatening pulmonary edema. Which one of the following is the drug of choice in this case?
A-Chlorothiazide
B-Furosemide
C-Spironolactone
D-Mannitol

9-What is the route of administration for the drug of choice in previous question?
A-Oral
B-I.M
C-I.V
D-Sublingual

10-A 55-year-old man came to the clinic complaining of joint pain. After asking him a few questions about his pain he explained that it started a couple of weeks ago after he started using a drug for his edema. Which one of the following drugs do you think this patient is using?
A-Indapamide
B-Amiloride
C-Dorzolamide
D-Mannitol

11-Which one of the following drugs should you also avoid in the previous case?
A-Spironolactone
B-Acetazolamide
C-Triamterene
D-Bumetanide

6-C
7-D
8-B
9-C
10-A
11-D

Questions

12-A 35-year-old patient came to the clinic complaining of constant thirst and urination. What is the diuretic of choice in this case?

A-Furosemide
B-Amiloride
C-Mannitol
D-Metolazone

13-A 60-year-old patient came to the clinic complaining of edema. After taking the history it is learned that the patient is hypertensive and he is taking Atenolol. Which one of the following drugs is contraindicated in this case?

A-Spironolactone
B-Ethacrynic acid
D-Mannitol
D-Indapamide

14-Which one of the following drugs works by inhibiting epithelial sodium channels (ENaC)?

A-Spironolactone
B-Triamterene
C-Indapamide
D-Bumetanide

15-Which one of the following thiazide diuretic is the most potent?

A-Chlorothiazide
B-Chlorothalidone
C-Metolazone
D-Indapamide

16-A 23-year-old suicidal patient came into the emergency room after ingesting a handful of aspirin. Which one of the following is the drug of choice in this case?

A-Chlorothalidone
B-Amiloride
C-Mannitol
D-Furosemide

17-A 33-year-old patient came into the ER after a severe hemorrhage caused by a car accident. Which one of the following drugs should be given to preserve kidney function?

A-Amiloride
B-Hydrochlorothiazide
C-Mannitol
D-Furosemide

12-D
13-A
14-B
15-D
16-C
17-C

Explanation

1-Carbonic anhydrase inhibitors increase phosphate excretion which can lead to the formation of calcium-phosphate stones.

2-Thiazides increase the reabsorption of calcium by stimulating parathyroid hormone which is beneficial in osteoporosis.

3-Loop diuretics could cause hypocalcemia which would exacerbate osteoporosis.

4-Loop diuretics are used in renal failure when GFR is below 40

5-Frothy urine and edema indicate nephrotic syndrome. To treat edema associated with nephrotic syndrome we use loop diuretics.

6-Unlike other diuretics, osmotic diuretics do not produce their effect by affecting sodium reabsorption. Therefore, they have the least natriuretic effect.

7-Loop diuretics are the most potent diuretics (explained why earlier) that's why they're also referred to as "high ceiling diuretics".

8-In life-threatening pulmonary edema we use furosemide because it's a highly potent diuretic.

9-In life-threatening pulmonary edema we give furosemide intravenously to get a rapid onset of action.

10-Indapamide (thiazide) has a side effect of hyperuricemia which could lead to gout.

11-Loop diuretics would be contraindicated in this case because they also cause hyperuricemia.

12-Polydipsia (constant thirst) and polyuria (excessive urination) are both important signs of diabetes insipidus. In DI we use thiazide diuretics because over time they will decrease urine output.

13-Potassium sparing diuretics are contraindicated in patients who are using beta blockers because they both increase serum potassium.

14-Triamterene and amiloride both work by blocking ENaC, unlike spironolactone which works by antagonizing aldosterone receptors.

15-Indapamide has a potency of 20 which more than the other thiazide diuretics mentioned in this lecture.

16-Mannitol is used in acute drug poisoning to eliminate drugs that are reabsorbed in the renal tubules e.g. salicylates (like aspirin).

17-Mannitol is given in acute renal failure due to shock (e.g. hemorrhage) to maintain urine flow and preserve kidney function.

THANK YOU FOR CHECKING OUR WORK

THE PHARMACOLOGY TEAM

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For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology.med435@gmail.com

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