# Diuretics

## Objectives:

- Define and classify diuretics
- Identify the site of action of each class of diuretics in the nephron
- Describe the mechanism of action of diuretics
- Detail on the pharmacodynamic actions and pharmacokinetic aspects of diuretics
- List ADRs, therapeutic uses, contraindications, and drug-drug interactions of diuretics

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

Notes

helpful video

Editing file

Studying this lecture requires full understanding of tubular reabsorption

# Diuretics

**Diuretics**: are drugs that increase(urine volume) renal flow rate. They act by↑the quantity of sodium in urine (natriuretic diuretics). Used to remove excess extracellular fluid (oedema)→ water diuresis

**Diuresis:** is the process of excretion of water in the urine. Water can be used as diuretic.

Water↑ blood volume→ ↑ renal blood flow→ ↑GFR→ ↑urine excretion

**Natriuresis**: is the process of **sodium** excretion in water. All diuretics have natriuretic effect

## Definitions

## Indications

-Edema of any origin Ex:pulmonary edema
-Congestive heart failure
-Hypertension
-Elimination of toxins

## MAO

Most diuretics act by interfering **with the normal sodium reabsorption** by the renal tubules resulting into sodium and water excretion.

## Site of action

Target molecules for diuretics are **carriers** or **transporters** in luminal membrane of renal tubular cells required for **tubular reabsorption of sodium** from filtrate back into blood so diuretics inhibit these carriers therefore inhibit reabsorption

## Main Classes of Diuretics

1. Carbonic Anhydrase inhibitors
2. Loop Diuretics
3. Thiazide Diuretics
4. K+ sparing diuretics
5. Osmotic Diuretics

### Classification of diuretics

**According to efficacy**

- High efficacy → Loop diuretics
- Moderate efficacy → Thiazides
- Low efficacy → K+ sparing (-Spironolactone -Triamterin -Amiloride), Osmotic, Carbonic anhydrase inhibitors

**According to protein**

Main function: excreting Na

Target protein

- Transporter → Loop diuretics, Thiazides
- Ion channel → Triamterene, Amiloride
- Enzyme → Carbonic Anhydrase inhibitors
- Receptor → Spironolactone

Main function: excreting water

No target protein → Osmotic Diuretics

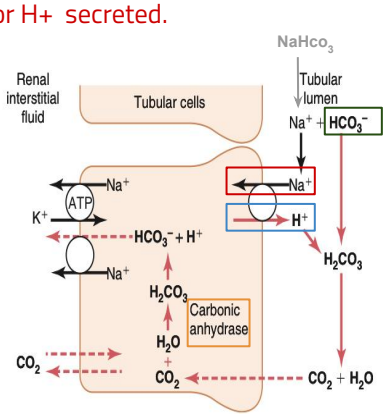
These drugs act without any receptor but they give an action because of their osmotic properties(pressure) which will attract water and increase water excretion.

# Site of action of Diuretics

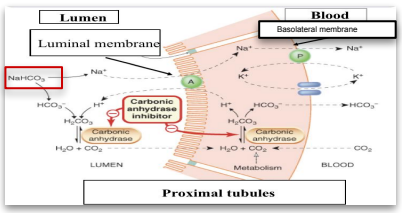
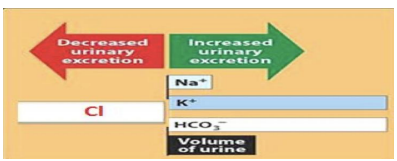
| Segment | Normal reabsorbed Na | Transporter | Diuretics |
|---|---|---|---|
| **Proximal convoluted tubules** | -65% NaHCO3 | -Na/H transporter<br>-Carbonic anhydrase enzyme | Carbonic anhydrase inhibitors |
| **Thick ascending loop** | -Active reabsorption of 20-30% Na,K,Cl. | Na/K/2Cl transporter | Loop diuretics |
| **Distal convoluted tubules** | Active tubular reabsorption of 5-10% Na, Cl, Ca | Na and Cl cotransporter | Thiazide diuretics |
| **Collecting tubules** | -5% Na reabsorption<br>-K & H secretion | -Na channels<br>-K & H transporter<br>-Aldosterone when aldosterone binds to its intracellular receptor, the receptor sends signals that stimulate the opening of Na channels<br>-Antidiuretic hormone ADH release cause the opening of aquaporin channels which will reabsorb water | K-sparing diuretics |

Reminder:
**Transporter(pumps)** ⟶ transport molecules against concentration gradient
**Cotransporters**⟶ transport one molecule down its concentration gradient and another molecule against its concentration gradient.
**Ion channels**⟶ transport ions down their concentration gradient
**Receptor**⟶ send signals inside the cell which activate enzymes in the cytoplasm when a molecule from outside of the cell binds to the receptor.
**Enzyme**⟶ transform one molecule from one form to another( substrates to products). Enzymes can be in the cytoplasm or along the membrane.

## Extra explanation from gyton

| | Normal function | Carbonic anhydrase inhibitor (Acetazolamide) |
|---|---|---|
| Proximal tubule | (1) active secretion of H+ into the renal tubule;<br>(2) tubular reabsorption of HCO3– by combination with H+ to form carbonic acid, which dissociates to form carbon dioxide and water; and<br>(3) sodium ion reabsorption in exchange for H+ secreted.<br>  | inhibit the enzyme **carbonic anhydrase**, which is critical for the reabsorption of bicarbonate. Because hydrogen ion (H+) secretion and HCO3– reabsorption are coupled to **sodium reabsorption** through the sodium-hydrogen ion counter transport mechanism in the luminal membrane, decreasing HCO3– reabsorption also reduces sodium reabsorption (water follows sodium which causes diuresis. #osmosis) which causes these ions to remain in the tubules and act as an osmotic diuretic.<br><br>1) HCO3– reabsorption ( it used to make the blood alkaline = acidosis) #lost an alkali ( goes from blood into urine which causes urine alkalosis)<br><br>2) (H+) secretion into urine ( now it's going to stay in the blood = acidosis) #gain of an acid<br><br>3) sodium reabsorption⟶ with CA inhibitors sodium secretion is increased (natriuresis) ⟶ water follows sodium (dieresis) |

# Carbonic Anhydrase Inhibitors

| Drug | 1-Acetazolamide ممكن نقرأ الاسم بالمقلوب : "متي الزولية يا ستي" |
|---|---|
| **M.O.A (common with Dorzolamide)** | -Inhibit carbonic anhydrase (CA) enzyme in proximal convoluted tubules thus interferes with NaHCO3 reabsorption and causes diuresis.<br>-Carbonic anhydrase required for reversible reaction (accelerates the attainment of equilibrium in the reaction), in which<br>$CO2 + H2O \leftrightharpoons H2CO3 \leftrightharpoons H^+ + HCO3^-$ |
| **P.k** | -Given orally once a day so it has a long duration of action<br>-Onset of action is rapid (30 min)<br>-Duration of action (9-12h)<br>- t ½ 6-9h<br>-Excreted by active secretion in proximal convoluted tubule<br>- produces alkaline urine because NaHCO3 is an alkaline<br>( only CA inhibitors cause alkaline urine) Alkaline = "رحت بيت الخال يوريني الزولية"<br>  |
| **P.D** | -Potent specific inhibitor of carbonic anhydrase, enzyme inhibition is non competitive.<br>- It ↓ reabsorption of bicarbonate in the proximal tubule & prevent the acidification of urine in the distal tubule.<br>-Self- limiting action of acetazolamide restrict its use to mild oedema. |
| **Pharmacological actions** | -↑mild increase in urine volume<br>-↑urinary excretion of sodium,potassium, bicarbonate (alkaline urine) normally, these ions are reabsorbed at the proximal convoluted tubules.<br>-Metabolic acidosis due to the continuous loss of NaHCO3 from the blood. Metabolic acidosis = "متى اسدد لك دين الزولية" **Ac**etazolamide = **Ac**idosis<br>-↑ Urinary phosphate excretion. Phosphate excretion increases with acidosis of the blood<br>-Promotes K+ excretion by ↑ the load of Na delivered to the distal tubules<br>1-Increased Na delivery to distal tubules will lead to its passive diffusion into cells through specialized Na channels (ENaC), increased flow of sodium through this channel will create a negative potential inside the lumen, and positivity inside the cells that are just adequate to drive potassium outside of the cells. (Team 438)<br>2-part of the sodium in the filtrate will be reabsorbed in the collecting tubules which is controlled by aldosterone ( sodium reabsorption & potassium **excretion)** |
| **Notes** | <u>Why do CA inhibitors have **weak diuretic** properties?</u><br><br>Diuretic properties decreases after several days as the blood bicarbonate falls.<br>with repeated dosage the diuretic action is lost → loss of $HCO3^-$ & development of acidosis<br>because as we know, the main target for carbonic anhydrase inhibitors is the bicarbonate and when there's a constant usage of Acetazolamide the amount of bicarbonate decreases after a period of time thus decreasing the efficacy. (Team 438)<br>  |

| Drug | 2- Dorzolamide "درسوا للميد" |
|---|---|
| Info. | • Is a carbonic anhydrase inhibitor<br>• Used topically for treatment of ↑ IOP in open-angle glaucoma.<br>• no diuretic or systemic side effects (Why?) Because of the **topical use.** |
| Therapeutic uses | 1. **Open angle glaucoma:** "درسو للميد زين وفتحوا عيونكم"<br>Aqueous humor contains a high concentration of bicarbonates, carbonic anhydrase inhibitors ↓ Carbonic Anhydrase ↓ rate of aqueous humor formation ↓ IOP by reducing aqueous humor formation in ciliary body of eye **(tolerance does not develop to this effect)**<br>2. **As prophylactic therapy, in acute mountain sickness ↓ CSF of brain:** given nightly 5 days before the ascent ↓ weakness, breathlessness, dizziness, nausea, cerebral & pulmonary oedema. In acute mountain sickness which happens during the ascending of a mountain, the brain can swell so we reduce the pressure around it by decreasing the formation of CSF. Also, as the mountain climbers ascends, decreased oxygen in the atmosphere can cause hyperventilation, which can result in increased $CO_2$ washout and then cause alkalosis. As Dorzolamide usually increases the excretion of bicarbonate, it can compensate for the resulting alkalosis.<br>3. **Formation of CSF:**<br>↓ of carbonic anhydrase in the choroid plexus→↓formation of CSF. Useful in treating benign intracranial hypertension).<br>4. **Urinary alkalinization to enhance renal excretion of acidic substances:**<br>(uric acid, methotrexate and cysteine in cystinuria) are relatively insoluble in acid urine. Renal excretion can be ↑by ↑ urinary bicarbonate excretion. Effect is short lived & require bicarbonate infusion.<br>5. **Hyperphosphatemia**<br>6. **Adjunct for treatment of epilepsy**<br>glial cells contain carbonic anhydrase. Nerves are highly responsive to rise in pH. ↑7.4→ 7.8 causes convulsions. ↓of neuronal carbonic anhydrase →↓ pH in the vicinity of neurons→↓ convulsions.<br>7. **Metabolic alkalosis**<br>Useful for correcting a metabolic alkalosis, especially an alkalosis caused by diuretic-induced increases in $H^+$ excretion & metabolic alkalosis of heart failure |
| ADRs | • Hypokalemia (potassium loss).<br>• Metabolic acidosis.(lossing of bicarbonate will increase H and decrease PH (acidosis).<br>• Renal stone formation (calcium phosphate stones). (calcium phosphate stones precipitate in alkaline urine)<br>• Hypersensitivity reaction. Because the drug is similar in structure to sulfonamides and sulfonamides are known to cause allergic reactions.<br>• Drowsiness<br>• Numbness<br>• Disturbance of vision<br>• Tingling sensation of the face & extremities |
| Contraindications | • Contraindicated in patients with liver cirrhosis (alkaline urine ↓excretion of NH4→ hyperammonemia & hepatic encephalopathy (Ammonia (NH3), is metabolized in the liver to urea and NH4 (ammonium) to be excreted, in liver cirrhosis there is less conversion of ammonia to ammonium, and ammonia accumulates and cause toxic effects on brain cells. CA inhibitors decrease excretion of NH4 because it is an acid, which in high pH environment can be turned back into NH3, the toxic metabolite) #438<br>• Pts with Hyperchloremic acidosis or severe COPD |

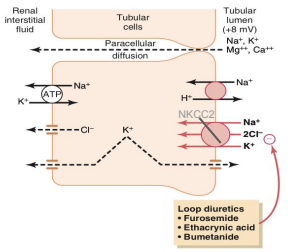
# Osmotic Diuretics

| Drug | Mannitol (A sugar) |
|---|---|
| P.K | • Poorly absorbed<br>• If given orally → osmotic diarrhea<br>• Given intravenously<br>• Excreted by glomerular filtration without being reabsorbed or secreted within 30-60 min.<br>• Mainly excreted unchanged in urine<br>• Mannitol, IV, not absorbed from the GIT, ↑**water** excretion with relatively **less** effect on **Na**+ [aquaretic]<br>• Little \ Not metabolized<br>• T½ 0.25-1.7h, prolonged in renal failure to 36h |
| P.D | **In systemic circulation:**<br><br>1-Mannitol increases urine output by osmosis, drawing water out of cells and into the bloodstream.<br><br>**2-Expand** the **extracellular fluid volume**, decrease blood viscosity, and **inhibit renin** release, ↑renal blood flow→ ↑GFR→ ↑urine volume.<br><br>Renin is released to cause vasoconstriction which fixes hypotension, but when blood volume is ↑ hypotension won't occur so renin release will be inhibited.<br><br>**In the kidney tubule:**<br><br>1-Acts in proximal tubules & descending loop of Henle by osmotic effect.<br><br>2-IV administration of any solute filtered by glomeruli may produce osmotic diuresis when the amount delivered to tubules exceeds their absorptive capacity, IV administration of mannitol (the dissolved compound) exert an osmotic pressure→↓ water & Na+ reabsorption.<br><br>*↑water excretion with relatively less effect on Na+. |
| Therapeutic uses | • **Acute renal failure due to shock or trauma** (maintain urine flow- preserve kidney function).<br>A hemorrhagic shock might lead to renal failure due to decreased renal blood flow. Decreased renal blood flow will cause a deterioration in the kidney's function. So we give an osmotic diuretic to maintain the renal blood flow by directing more blood volume to the kidney which will maintain the kidney's function.<br>• To maintain urine volume & prevent **anuria** resulting from large pigmentation load to the kidney **e.g. haemolysis, rhabdomyolysis**<br>• **In acute drug poisoning:** To eliminate drugs that are reabsorbed from the renal tubules e.g. salicylates, barbiturates, and bromides.<br>• To ↓ intracranial & intraocular pressure before ophthalmic or brain procedures (**cerebral edema**).<br>• To prevent acute renal necrosis after severe injury , haemorrhage, hypovolaemia, →↓ GFR, absorption of water & salts is complete , distal part dries up→ irreversible damage |
| ADRs | • **Headache, nausea, vomiting** → hyponatremia<br>• **Extracellular volume expansion,** complicates heart failure & pulmonary oedema<br>• **Excessive use** → **dehydration & hypernatraemia** (Adequate water replacement is required). It causes hypernatremia because the volume of water is reduced so the concentration of Na is increased. |
| Contraindications | • Chronic heart failure<br>• Anuric patients or patients not responding to a test dose of mannitol<br>• Pulmonary edema |

# Loop Diuretics

E.T is FABulous

| Drug | Bumetanide (Most potent) | Torsemide (Longest duration) | Furosemide | Ethacrynic Acid |
|---|---|---|---|---|
| Potency , t ½ | B ume tanide = "بامي تنادي"<br>Potency 40,<br>t½ 0.8 hrs | Tor semide = "ثور صامد"<br>Potency 3,<br>t½ 3.5 hrs | Fur semide = "لأجل صامد"<br>Potency 1,<br>t½ 1.5 hrs | Etha cry nic acid = "إذا بكي نسي"<br>Potency 0.7,<br>t½ 1hr |
| Efficacy | - High natriuresis as 25-30% of glomerular filtrate of Na+ is reabsorbed.<br>- The most potent diuretic, termed "high ceiling diuretic" use in emergency state | | | |
| M.A.O | - Inhibit **Na+ /K+ /2 Cl- co-transporter** in the luminal membrane of the thick segment of the ascending loop of Henle (TAL).<br>- Inihbit Ca++ and Mg++ reabsorption. | | | |
| P.K | - Given orally or I.V (reserved for emergency situations)<br>- Have fast onset of action (for emergency)<br>- Have short duration of action<br>- Excreted by active tubular secretion of **weak acids** into urine (avidly bound to plasma proteins)<br>- Interfere with uric acid secretion (hyperuricemia) contraindicated in gout* | | | |
| Pharmaco-logical actions | - ↑ Urinary excretion of Na , K+ , Ca++ and Mg++.<br>- ↑ Urine volume<br>- Induce expression of COX, PGE↓ salt transport in TAL.<br>- ↓ Renal vascular resistance & ↑renal blood flow (which increases the urine volume) because of PG<br>- Furosemide and ethacrynic acid reduce pulmonary congestion and left ventricular filling pressure in heart failure →↑venous capacitance | | | |
| Uses | Drugs of choice for emergency (acute) situations such as :<br>- severe Edema associated with congestive heart failure, nephrotic syndrome.<br>- increase venous capacitance → **Acute** Pulmonary Edema<br>- Increase Ca excretion → **Acute** Hypercalcemia<br>- Increase $K^+$ excretion → **Acute** Hyperkalemia<br>- Increase urine volume → Oliguric ARF<br>- Anion overdose → Toxicity of Br, F & I (anion overdose) | | | |
| ADRs | • **HYPO**:<br>-Volemia.<br>-Kalemia<br>-Magnesemia<br>**-Calcaemia** contraidicatio with Osteoporosis<br>-Natremia<br>• **HYPER**:<br>-Glycemia [1]<br>-Uricemia [5]<br>• Postural hypotension[2]<br>• Allergic reactions<br>• **Ototoxicity**[3] (aminoglycosides ↑the risk)<br>• **Metabolic alkalosis** [4] OtO toxicity = Loop diuretics<br>• Profound ECFV Depletion<br>Dietary k supplementation or k-sparing diuretics should be used to avoid hypokalemia | | | |
| Contra-indications | - Severe Na and volume depletion<br>- Hypersensitivity to sulfonamides (Thiazides and loop diuretics are sulfonamide derivatives, except ethacrynic acid.).<br>- Anuria unresponsive to a trial dose of loop diuretic | | | |
| Drug-Drug interaction | - NSAIDs → ↓ Diuretic response (loop diuretics increase PGs, while NSAIDs decrease PGs)<br>- Digitalis → Arrhythmias (both cause hypokalemia)<br>- Aminoglycosides → ↑ Ototoxicity of loop diuretic<br>- Loop diuretic →↑Nephrotoxicity of aminoglycosides | | | |




*Both are weak acids, the diuretic competes with uric acid on the carrier required for uric acid secretion ; which causes hyperuricemia

remember HEHe:
HEart failure
Hyper (tension, calcemia, kalemia)
Edema

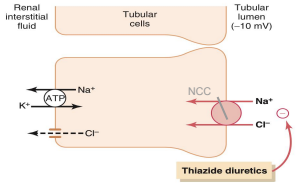
1) interferes with insulin sensitivity. 2)due to sever hypovolemia ( that's why they're reserved for emergencies)
3)affects the triple co-transporter that's located in the inner ear. Ethacrynic acid is the most severe,
4) potassium secretion is accompanied with hydrogen secretion. 5)increase blood uric acid and gouty attack so it is contraindicated with gout patient

# Thiazide Diuretics

| Drug | Chlorothiazide | Hydrochlorothiazide | Metolazone | Chlorthalidone | Indapamide |
|---|---|---|---|---|---|
| Potency<br>t ½<br>Not important | Potency = 0.1<br>t ½ =2h | Potency = 1<br>t ½ = 3h | Potency = 5<br>t ½ = 5h | Potency = 10<br>t ½ = 26h | Potency = 20<br>t ½ = 16h |

## M.A.O

Acts On luminal membrane of early distal tubule
via inhibition of Na/Cl co-transporter (NCC)
(This will activates Na/Ca exchanger, so the Ca will be reabsorbed)
Efficacy: Moderate natriuresis not for emergency
(5-10% of filtered load os Na is reabsorbed)
Week inhibitors of carbonic anhydrase, but this does not contribute to their action

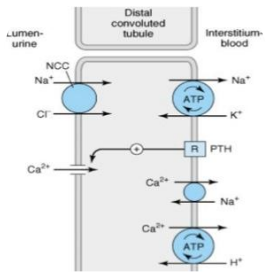



## P.K

- Given orally, efficiently absorbed from the GIT
- Slow onset, with Long duration of action (40h)(unlike loop diuretics 1)short duration 2)used for emergencies)
- Eliminated by glomerular filtration & active tubular secretion (in the proximal tubules), some is reabsorbed
- May interfere with uric acid secretion and cause Hyperuricemia.(caution with gout patients). Same mechanism in loop diuretics ( competition...)
- Lipid soluble

## Pharmaco-logical actions

- ↑Urinary excretion of: 1-NaCl 2-K+ 3-Mg++
- ↓Urinary excretion of: 1-Uric acid 2-Ca++ (With increase reabsorption)
- May give rise to hypokalemic alkalosis.
- Cause vasodilatation, non diuretic thiazide is a potent vasodilator.
- ↓Of urine volume in case of diabetes insipidus.




## Uses

remember Oh! CHIC! :
-Osteoporosis
-CHF
-Hypertension
-Insidious
-Calcium calculi

- Treatment of essential Hypertension (cheap-well tolerated)
- Treatment of mild heart failure ( to reduce extracellular volume)
- **Treatment of Osteoporosis (decreased Ca excretion)**
- Calcium nephrolithiasis due to hypercalciuria (decreased Ca excretion) (to increase calcium reabsorption and decrease renal calcium stones)
- Nephrogenic diabetes insipidus* (decrease blood volume and GFR)

Thiazide→↓Distal tubular Na+ **reabsorption**→↑urinary excretion (initially)→↓extracellular volume as a result →↑proximal Na+ & water reabsorption due to↓renal blood flow and GFR →↓distal **delivery** of Na+ & water→↓Urinary volume

- Treatment for mild edema

*Diabetes insidipidus (DI) is a condition characterized by large amounts of dilute urine and increased thirst.

## ADRs

- **Hypo:**
  - Magnesemia
  - Natremia
  - Volemia
  - Kalemia

Miss Noura Volunteered in Kuwait

- **Hyper:** GLUC
  - **G**lycemia
  - **L**ipidemia (LDL)
  - **U**ricemia (gout)
  - **C**alcemia 3)unlike loop diuretics which cause HYPOcalcemia
- **Metabolic alkalosis**
- Fluid and electrolyte imbalance
- ECFV Depletion
- Impotence

## Drug-Drug interaction

- **Uricosuric**, Sulphonylurea → Thiazide diminish effect
- **Digitalis**, Diazoxide → Thiazide increase effect
- **NSAID** → Reduce thiazide efficacy(PGs maintain renal blood flow, NSAIDs decrease PGs)

# Potassium sparing diuretics

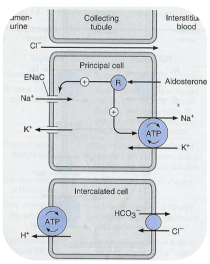
**1 Steroids**
**Competitive Aldosterone Antagonist:**
Also called K-sparing diuretics or mineralocorticoid receptor antagonist
➔ Spironolact**one**
➔ Epleren**one**

**2 Non-Steroids**
**Na+ channel inhibitors:**
➔ amiloride
➔ Triamterene

remember SEAT:
-Spironolactone
-Eplerenone
-Amiloride
-Triamterene

## A) Aldosterone antagonist

Also called mineralocorticoid receptor antagonist

| Drug | 1) Spironolactone |
|---|---|
| M.O.A | - Acts at the **collecting duct** by competitive inhibition of cytoplasmic aldosterone receptors →↑ Excretion of $Na^+$,Cl & ↓Excretion of $K^+$,$H^+$,NH4<br>- Actions depend on renal PGs production |
| P.k | - Well absorbed from the GIT , t½=16h<br>- Highly protein-bound<br>- Undergoes enterohepatic recycling<br>- Delayed onset of action(nuclear receptor), maximum diuretic action 4 days<br>- Converted in gut & liver to Canrenone (active metabolite), t½=16h<br>- It binds androgen receptors with high affinity<br>  <br>Normally:<br>- In the principal cells sodium is reabsorbed by stimulating a nuclear receptor which stimulates sodium reabsorption in exchange for **potassium**.<br>- in the intercalated cells the excretion of sodium is accompanied by loss of hydrogen |
| P.D | - ↑urinary $Na^+$ excretion<br>- ↓urinary $K^+$ excretion (Hyperkalemia)<br>- ↓ $H^+$ excretion (Acidosis)<br>- Has antiandrogenic action[1] |
| Uses | - **Treatment of** resistant **hypertension** ;usually used combined with **thiazide** or **loop diuretics** to :<br>1- Enhance natriuresis caused by other diuretics 2- Correct / prevent **hypokalemia**<br>- **Treatment of primary**[2] **hyperaldosteronism** (Conn's syndrome)<br>- **Treatment of secondary hyperaldosteronism** in diseases as CHF (improve survival), Edema of hepatic cirrhosis and Nephrotic syndrome.<br>- **Treatment of hirsutism**[3], acne due to the antiandrogenic effects |
| ADRs | (hyper) كبير (kalaemia) كلام (no) مان بلا ( Spiro) سبرو<br>- Hyperkalaemia<br>- Gynecomastia (male breast enlargement)<br>- Impotence(sexual disfunction )<br>- Metabolic acidosis in cirrhotic patients (↑$H^+$)<br>- Menstrual irregularities<br>- GIT upset and peptic ulcer<br>- Deepening of voice<br>- CNS side effects<br>- Hirsutism<br>- Gastritis |

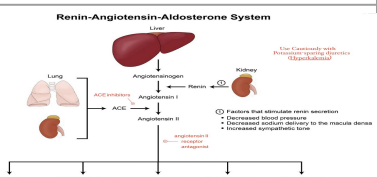
1: Aldosterone antagonists structure is similar to testosterone → blockage of testosterone receptors
2: hyperaldosteronism means excessive aldosterone secretion from adrenal cortex ; primary ( due to tumors in the adrenal gland) , secondary ( due to overstimulation to RAAS )
3: overproduction of hair in inappropriate places.

# A) Aldosterone antagonist (cont..)

| | |
|---|---|
| Contrain -dication | - **Hyperkalemia** :<br>• Chronic renal failure. • beta-blocker • Other k sparing diuretics<br>• K+ supplement use. • ACEI.<br>- Liver disease ( dose adjustment is needed). (metabolized in liver) |
| Inter-actio ns | - ACEI , β-blocker , K+ supplement , K+ sparing diuretic and Aliskiren →↑Hyperkalemia-induced by K+ Sparing diuretics<br>- Salicylates → ↓ secretion of canrenone and ↓ efficacy of spironolactone<br>- Digitalis → Spironolactone alters its clearance |

| Drug | 2) Eplerenone |
|---|---|
| Information | - Eliminated by metabolism(CYP3A4), t½ 5h<br>- Low affinity for progesterone and androgen receptors<br>- Both ineffective in adrenalectomized patients |

# B) Na+ Channels Inhibitors

| Drug | Triamterene | Amiloride |
|---|---|---|
| Potency | 0.1 (Triamterene = "تراي متَرين = يعني طولي متَرين") | 1 (Amiloride = "أمل وارنَد") |
| T ½ | 4.2h<br>Eliminated by: metabolism | 21h<br>Eliminated by: renal elimination |
| MOA | **Na+ channel inhibitors:**<br>Inhibition of Na influx through direct blockade of the **epithelial sodium channel** (ENaC) on the lumen side of the kidney collecting tubule | |
| Therapeutic uses | • Enhance Natriuresis Caused by Other Diuretics, Prevent Hypokalemia<br>• Used in Combination with Loop & Thiazide Diuretics<br>• Treatment for lithium-Induced Diabetes Insipidus<br>• Treatment for liddle's syndrome | |
| Contra-indic ations | The risk of developing **hyperkalemia** is increased in patients with renal failure & patients also on ACE inhibitors, Aliskiren, angiotensin II receptor antagonists, other potassium-sparing diuretics, or any potassium-containing supplements. | |
| Adverse Effects | **Hyperkalemia** | |
| | Renal Stones<br>Interstitial nephritis<br>Megaloblastosis in cirrhotic patients | - |
| Drug-drug Interactions | ACE Inhibitors<br>Beta-Blockers<br>K Supplements<br>K-Sparing<br>Diuretics<br>→ ↑Hyperkalemia induced by K-Sparing diuretics |  |

# Therapeutic Applications of Diuretics

## Hypertension

- **Thiazide diuretics:**
  used alone or in combination with beta-blockers at low-dose (fewer side effects).

- In presence of renal failure, **loop diuretic** is used.

## Edema States

- **Thiazide diuretic** is used in mild edema with normal renal function.

- **Loop diuretics** are used in cases with impaired renal function.

## Congestive Heart Failure

- **Thiazides** may be used in only mild cases with well-preserved renal function.

- **Loop diuretics** are much preferred in severe cases especially when GF is lowered.

- In life-threatening acute pulmonary edema, **furosemide** is given IV.

## Renal Failure

- **Thiazides** are used till GFR ≥ 40-50 ml/min.

- **Loop diuretic** are used below given values, with increasing the dose as GFR goes down.

## Diabetes Insipidus

Diabetes insipidus: Large volume (>10 L/day) of dilute urine

- **Thiazide** diuretics reduces urine volume

## Hepatic Cirrhosis with Ascites

- **Spironolactone** is the drug of choice.

A woman with dropsy treated by paracentesis

The Bulgarian weightlifting Federation was sanctioned and suspended from participation in the 2000 Olympic summer games in Sydney drug testing revealed the presence of furosemide

## Diuretic doping

To lose weight quickly in order to complete in lower weight classes e.g. wrestling, boxing, and weightlifting.
"Masking" drugs to speed the elimination of banned substances e.g. steroids

# Summary

Diuretic classification in order of site of action **COLT P :**

| Class | M.O.A | Effects | Uses | ADR |
|---|---|---|---|---|
| **CA Inhibitors -Dorzolamide -Acetazolamide** | Inhibition of NaHCO3 reabsorption in PCT | - ↑Urinary NaHCO3, K<br>- Urinary alkalosis<br>- Metabolic acidosis | - Glaucoma<br>- Epilepsy<br>- Mountain sickness<br>- Alkalosis<br>- Phosphatemia | - Metabolic acidosis<br>- Urinary alkalosis<br>- Hypokalemia |
| **Osmotic Diuretics -Mannitol** | Osmotic effect in PCT | - ↑Urine excretion<br>- ↑Little Na | - Cerebral edema<br>- Glaucoma<br>- Acute renal failure<br>- Drug toxicities | - Extracellular water expansion<br>- Dehydration<br>- Hypernatremia |
| **Loop Diuretics -Furosemide** | Inhibit Na/K/2Cl cotransporter in TAL | - ↑Urinary Na,K, Ca,Mg | - **Drug of choice** in Acute pulmonary edema<br>- Heart failure<br>- Hyperkalemia<br>- Hypercalcemia | - **Hypo:** calcemia, volemia, natremia, kalemia, magnesemia<br>-Precipitate gout<br>-Alkalosis |
| **Thiazide Diuretics -Hydrochlorothiazide** | Inhibits Na /Cl cotransporter in DCT | - ↑Urinary Na,K,Mg<br>- ↓ urinary Ca (hypercalcemia)<br>- Metabolic alkalosis | Commonly used<br>- Hypertension<br>- Mild heart failure<br>- Nephrolithiasis<br>- Diabetes insipidus | -**Hyper:** calcemia, lipidemia, glycemia<br>-**Hypo:** kalemia, natremia, volemia, magnesemia.<br>-Precipitate gout<br>-Alkalosis |
| **Potassium-Sparing Diuretics -Spironolactone** | Competitive antagonist of aldosterone in CCT | - ↑Urinary Na<br>- ↓K, H secretion<br>- Metabolic acidosis | - **Drug of choice** in Hepatic cirrhosis | -Hyperkalaemia<br>-Gynaecomastia<br>-Metabolic acidosis<br>-GIT upset and peptic ulcer |

# MCQ

More MCQs [ClickHere]

| 1- Which of the following drugs can be used in lithium induced diabetes insipidus | | | |
|---|---|---|---|
| A- Mannitol | B- Furosemide | C- Amiloride | D- Dorzolamide |

| 2- A patient suffers from hypertension and renal failure. What group of diuretics is appropriate? | | | |
|---|---|---|---|
| A- K+ sparing | B- Loop diuretics | C- Thiazide | D- Osmotic |

| 3-Potassium-sparing diuretics can cause a potentially harmful interaction if taken with ACE inhibitors. | | | |
|---|---|---|---|
| A- True | B- False | | |

| 4- Which class of diuretics work by acting on the proximal tubule? | | | |
|---|---|---|---|
| A- Loop diuretics | B- Carbonic anhydrase inhibitors | C- K+ sparing diuretics | D- Thiazides |

| 5- What kind of acid base change acetazolamide use can produce in urine? | | | |
|---|---|---|---|
| A- Alkalization | B- acidification | C- no change | |

Sodium potassium and chloride after giving the patient Furosemide


# Answers

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

# SAQ

**Q1) A 45 years old patient came to the clinic with symptoms of fatigue, jaundice and oliguria. After investigations, he was diagnosed to have hemolytic anemia. The doctor was worried about his kidneys functions**
**1-What is the drug of choice to preserve kidneys function**
**2- describe its mechanism of action**
**3-mention 3 ADRs**

**Q2) What is the MOA of carbonic anhydrase inhibitors? Mention 2 ADRs and 2 therapeutic uses.**

**Q3) A 34 years old Asian male was diagnosed with diabetes insipidus, his doctor decided to treat him with Diuretics. What is the best group of Diuretics in this case? What's their M.O.A? Mention 4 ADRs of this group.**

**Q4) A patient with kidney failure has a GFR of 30 ml/min. What is the best group of diuretics to be used? What is their MOA? Mention 2 of these drugs.**

**Q5) A male patient is placed on a new medication and notes that his breasts have become enlarged and tender to the touch. Which medication is the most likely taking?**

# Answers

A1) slide 6

A2) They inhibit carbonic anhydrase enzyme at the proximal convoluted tubule so they interfere with $NaHCO_3$ reabsorption and cause diuresis.

ADRs: 1) hypersensitivity 2)hypokalemia. Uses: 1) metabolic alkalosis 2) open angle glaucoma.

A3) Thiazide diuretic., M.O.A:Inhibits Na /Cl cotransporter in DCT,

ADRs:1-Hyper: calcemia, lipidemia, glycemia 2-Hypo: kalemia, natremia, volemia, magnesemia. 3-Precipitate gout 4-Alkalosis

A4) Loop diuretics. MOA:
- Inhibit $Na^+$ /$K^+$ /2 $Cl^-$ co-transporer in the luminal membrane of the thick ascending loop of Henle (TAL).
- Inihbit $Ca^{++}$ and $Mg^{++}$ reabsorption.

e.g. Bumetanide, Torsemide

A5) Spironolactone or Eplerenone, An adverse effect to them is gynecomastia due to its effects on androgens and progesterone in the body.

# GOOD LUCK!

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