



Renal block.

Additional note : Grey color Important: Red color



For any correction, suggestions or any useful information do not hesitate to contact as: pharmacology434@gmail.com

Diuretics:

- **Definition:** It is a group of drugs that increase renal excretion of <u>sodium</u> and <u>water</u> resulting in increase in urine volume
- How do diuretics work?

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

- How could urine output be increased ?
- **1-** ↑ Glomerular filtration

- 2-↓ Tubular reabsorption
- What is the Purpose of Using Diuretics?
- 1- To maintain urine volume (e.g.: renal failure)
- 2- To mobilize edema fluid (e.g.: heart failure, liver failure; nephrotic syndrome)
- 3- To control high blood pressure.
- What is the site of action of Diuretics?

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.

- What is the clinical uses of Diuretics ?
- 1- Edema of any origin
 - in 2- Congestive heart failure
- 3- Elimination of toxins
- 4- Hypertension
- Classification of Diuretic According to site of Action (Best Classification) :

Classification of Drug	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
Osmotic diuretics	\uparrow urine output by osmosis, drawing water out of cells and into the blood stream.	Mannitol
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 , Metolazone, Chlorthalidone, Hydrochlorothiazide, Indapamide
Potassium sparing diuretics	Act in collecting tubules and ducts by inhibiting Na re-absorption and K & H excretion	Spironolactone, triamterene , amiloride



New terms :

- **Diuresis:** is the process of excretion of water in the urine.
- <u>Natriuresis</u>: is the process of excretion of sodium in the urine.

segment	segment Function		Diuretics	
Proximal convoluted tubules	Re-absorption of 66% Na, K, Ca, Mg, 100% glucose and amino acids; 85% NaHCO3	Na/H transporter, Carbonic anhydra enzyme	se Carbonic anhydrase inhibitors	
Proximal Straight Tubules	Secretion and re-absorption of organic acids and ba	ases Acid & base transporter	NONE	
Thick ascending loop	Active reabsorption 25% Na, K, Cl Secondary reabsorption Ca, Mg	Na/K/2Cl transporter	Loop diuretics	
Distal convoluted tubules	Active tubular reabsorption of 5%Na, Cl, Ca	Na and Cl cotransporter	Thiazide diuretics	
Collecting tubules	Na reabsorption K & H secretion	Na channels K & H transporter	K-sparing diuretics	
Segment of nephron				
PCT Ascen		cending loop of H	DCT	
Lumen- urime NIa^{+} NIa^{+} H^{+} H^{+} H^{-} $H^{$		Thick ascending limb Interstitium- blood Na ⁺ K ⁺ CI	Lumen- urine Na ⁺ CI Ca ²⁺ Ca ²⁺ Ca ²⁺ H ⁺	
СТ				
Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collecting Collec			This slide is physiology but we need to take looks at transporter , different Electrolytic diffuse to understand pharmacology	



Diuretics that inhibit transport in the Convoluted Proximal Tubule



to be used I.V. !

Osmotic Diuretics

<u>Site of action</u>: in proximal tubules & descending loop of Henle

	Mannitol
Mechanism of action	 ↑ urine output by osmosis, drawing water out of cells and into the blood stream. Expand the extracellular fluid volume, decrease blood viscosity and ↑renal blood flow. ↑ water excretion with relatively less effect on Na+ (water diuresis).
Pharmacokinetics	✓ Poorly absorbed
	\checkmark If given orally \rightarrow osmotic diarrhea
	✓ Given intravenously.
	✓ Not metabolized.
	 Excreted by glomerular filtration within 30-60 min without being re-absorbed or secreted.
Therapeutic Uses:	 <u>Acute renal failure</u> due to shock or trauma → to maintain urine flow/ preserve kidney function. <u>Acute drug poisoning</u> → To eliminate drugs that are reabsorbed from the renal tubules e.g. salicylates.
	barbiturates.
	➤ TO I Intraocular & intracranial pressure before ophthalmic or brain procedures (cerebraledema).
Side effect	> Headache, nausea, vomiting
	Extracellular volume expansion, complicates heart failure & pulmonary oedema.
	$ ightarrow$ Excessive use \rightarrow dehydration & hypernatraemia (Adequate water replacement is required).

Diuretics that inhibit transport in the Convoluted Proximal Tubule



Diuretics that inhibit transport in the Convoluted Proximal Tubule

Carbonic Anhydrase Inhibitors

pharmacokinetics	 Given orally once a day. Onset of action is rapid (30m). Duration of action (12h). Excreted by active secretion in proximal convoluted tubules. Produces alkaline urine.
Pharmacological actions	 个 urine volume. ↑ urinary excretion of sodium, potassium, bicarbonate (alkaline urine). Metabolic acidosis. ↑ urinary phosphate excretion. Promotes K+ excretion by the load of Na+ delivered to the distal tubules.
Indications	 Open angle glaucoma: carbonic anhydrase inhibitors cause IOP ↑ by reducing aqueous humor formation in ciliary body of eye. As prophylactic therapy, in acute mountain sickness ↓ CSF of brain: given nightly 5 days before the ascent ↓ weakness, breathlessness, dizziness, nausea, cerebral & pulmonary oedema. Epilepsy (decrease cerebrospinal fluid, CSF). Urinary alkalinization to enhance renal excretion of acidic substances (cystenie in cystinuria). Hyperphosphatemia. Metabolic alkalosis. IOP: intraocular pressure. CSF: cerebrospinal fluid.

Loop Diuretics

Basic Concept

Water follows sodium Block re-absorption of Na \rightarrow diuresis

Review of normal physiology related to loop diuretics

Na,K,2Cl transporter:

- Located in the thick ascending limb of loop of Henle Is impermeable to water
- It has two important functions:
- 1) Reabsorb Na \rightarrow Reabsorb water (water follows Na)
- 2) Enables the reabsorption of Mg++, & Ca++
- What is the mechanism of the reabsorbtion of calcium & magnesium?
- 1) Na,K,2Cl transporter normally transports Na, K, &2Cl into the cell
- 2) K concentration in the cell
- 3) K must find a way to leave the cell
- 4) K leaves the cell by going to the **luminal membrane** or basolateral membrane via facilitated diffusion
- 5) When K leaves the cell & goes into the luminal membrane, it maintains a positive charge in the lumen (because K is positive)
- 6) When Mg++ & Ca++ want to enter the lumen of the thick ascending limb of the loop of Henle, they find it filled with positively charged potassium
- 7) Mg & Ca are repelled & pushed through the spaces between the cells (paracellular route) to re-renter the body
- Inhibition of Na,K,2Cl will inhibit the recycling of potassium & will wash it out → the positive charge in the lumen is now lost → Mg & Ca will not be repelled → loss of Mg & Ca in urine → hypocalcemia & hypomagnesemia



Loop Divretics

Include Furo semide , Tor semide , Bumeta nide , Ethacrynic ac id		
Pharmacokinetics	Given orally or I. V. Have fast onset of action (suitable for emergency) Have short duration of action. Excreted by active tubular secretion of weak acids into urine Interfere with uric acid secretion (hyperuricemia).	
Mechanism of action	 Loops inhibit Na,K,2Cl transporter in the TAL of loop of Henle Loops also release vasodilators (prostaglandins PGE2) which cause vasodilation, particularly in the pulmonary circulation Loops are the most potent diuretics because most of the Na is reabsorbed by this transporter, & because there is little compensation Compensation means that other parts of the nephron would work harder to reabsorb Na High natriuresis as 25-30% Na⁺ is reabsorbed. & inhibit Ca⁺⁺ and Mg ⁺⁺ re-absorption. 	
Adverse effects	 Hypocalcemia & hypomagnesemia Due to decreased positive potential in TAL of loop of Henle Hypokalemia which leads to alkalosis Hypokalemia is due to decreased reabsorbtion of K because of inhibition of Na,K,2Cl transporter Metabolic alkalosis secondary to hypokalemia (transcellular shifting) Sulfonamide hypersensitivity 	
Clinical uses	 Acute pulmonary edema Because loops cause diuresis Because loops secrete prostaglandins which are vasodilators → ↑ renal blood flow. Heart failure (Diuresis → decrease preload → work done by heart) Hypertention (Mainly because loops secrete PGs which cause vasodilation) Edemas Pts. with hypercalcemia Pts. with hyperkalemia Acute renal failure (Because they increase urine volume → increase renal blood flow) 	

Thiazide Divretics

(Chlorothiazide t¹/₂ 2h, Chlorthalidonet¹/₂26h, Metolazone t¹/₂ 5h, Hydrochlorothiazide t¹/₂ 3h, Indapamide t¹/₂ 16h)

Mechanism of action	acts via inhibition of Na/Cl co-transporter on the luminal membrane of distal convoluted tubules. Efficacy: Moderate natriuresis (loss of Na+ in the urine) as 5-10% of filtered load of sodium is reabsorbed	
Pharmacokinetics	Given orally, slow of onset , long duration of action.	
	may interfere with uric acid secretion and cause hyperuricemia	
Pharmacological	Increase urinary NaCl excretion	
effects	Increase urinary K excretion (Hypokalemia)	
	Increase urinary magnesium excretion	
	Decrease urinary calcium excretion	
	Increase calcium re-absorption (hypercalcemia)	
Clinical uses	1-Hypertension Drug of Choice (Hydrochlorthiazide, Indapamide)	
	2-Refractory Edema together with the Loop diuretics(Metolazone) (to reduce extracellular volume)	
	3-Calcium nephrolithiasis due to hypercalciuria (to increase calcium re-absorption and decrease renal calcium stones)	
	4-Nephrogenic diabetes insipidus (decrease blood volume and GFR)	
	5-Treatment of mild heart failure (to reduce extracellular volume).	
Adverse effects	No ototoxicity, more hyponatremia than loop diuretics, Hypokalemia Hypomagnesaemia , Hyperlipidemia , Hyperglycemia , Metabolic Alkalosis, volume depletion, Hyperuricaemia (gout), Hypercalcemia	



Potassium-sparing diuretics (STAys (

Site of action : collecting tubules and ducts

A- (Steroids() Aldosterone antagonists(B- (Nonsteroids()Na ⁺ channels inhibitors(
	Spironolactone	Triamterene & Amiloride
Mechanism of action)K-sparing effect) by	 oproduces its diuretic effect by antagonizing cytoplasmic oby Inhibition of Na influx through Na channels in the luminal membrane 	
Pharmacodynamics	1. ↑urinary Na ⁺ excretion	
	2. ↓urinary K ⁺ excretion O hyperkalemia	
	3. ψ urinary H ⁺ excretion Q cidosis	
	In hypertension (as thiazide diuretic(
	prevent hypokalemia (combined with thiazide or loop diuretics to correct for hypokalemia.)	
Uses	Drug of choice for patients with <u>hepatic cirrhosis*</u> (by spironolactone as aldosterone antagonist)	
	Secondary hyperaldosteronism (CHF, hepatic cirrhosis, nephrotic syndrome(
Adverse Effects	Adverse Effects OHyperkalaemia.	
	OMetabolic acidosis.	
	OGynaecomastia) تثدي Spironolactone(
	•GIT upset and peptic ulcer	
Contraindications	• Hyperkalaemia: as in chronic renal failure, K+ supplementation, ®-blockers or ACE inhibitors.	

*It is a chronic degenerative disease in which normal **liver** cells are damaged and are then replaced by scar tissue.

Therapeutic applications of diuretics

N	Aedical condition	Thiazides Diuretic	Loop Diuretics	Notes
	.1Treatment of hypertension :	used alone or in combination with beta- blockers at low-dose (fewer side effects (Used in presence of renal failure.) to increase blood flow(
	.2Edema States	Used in mild edema with normal renal function .	Used in cases with impaired renal function .	
	.3Congestive Heart failure	Used in only mild cases with well- preserved renal function	Much more preferred in severe cases especially when GF is lowered .	In life-threatening acute pulmonary edema , Furosemide (loop duretic) is given IV .
3	.4Renal failure	Used if : GFR ≥ 40-50 ml/ min	Used if : GFR < 40	
	.5Diabetes inspidus	Reduces urine volume		Large volume(>10 L/day) of dilute urine in diabetes inspidus .
	.6Hepatic cirrhosis with ascites			Spironolactone (K-sparing diuretic) is the drug of choice .

6

Summary For All Diuretics

Side effects	Uses	Effects	Mechanism of action	Diuretics
•Metabolic acidosis , Urinary alkalosis, •Hypokalemia	 Glaucoma, epilepsy Mountain sickness Alkalosis Phosphatemia 	 Urinary Na HCO3, K Urinary alkalosis Metabolic acidosis 	•Inhibition of NaHCO3 reabsorption in PCT	CA inhibitors Acetohexamide Dorzolamide
 Extracellular water expansion Dehydration Hypernatremia 	 Cerebral edema, glaucoma Acute renal failure, drug toxicities 	□Urine excretion □ Little Na	•Osmotic effect in PCT	Osmotic diuretic Mannitol
 Hypokalemia, hypovolemia, hyponatremia, hypomagnesemia, hypocalcemia Precipitate gout, alkalosis 	 Acute pulmonary edema (Drug of choice(Heart failure Hyperkalemia, Hypercalcemia 	□Urinary Na, K, Ca, Mg	• Na/K/2Cl transporter in TAL the most effective	Loop diuretics Furosemide
 Hypokalemia, hyponatremia, hypovolemia, hypomagnesemia, hypercalcemia Alkalosis, precipitate gout Hyperlipidemia, hyperglycemia 	 Commonly used Hypertension, mild heart failure, nephrolithiasis, diabetes inspidus 	 □Urinary Na, K, Mg • BUT↓ urinary Ca (hypercalcemia(• Metabolic alkalosis 	• Na and Cl cotransporter in DCT	Thiazide diuretics hydrochlorothiazide
 Gynaecomastia Hyperkalaemia, Metabolic acidosis. GIT upset and peptic ulcer 	 Hepatic cirrhosis)Drug of choice(↑Urinary Na ↓K, H secretion Metabolic acidosis 	• competitive antagonist of aldosterone in CCT	K-sparing diuretic <mark>Spironolactone</mark> .





Osmotic Diuretics Osmitrol (Manitol) NAT Watch for headaches, edema, CHF, fluid & H2O electrolyte imbalance.

Renal

Disease

V GFR

I think I'm in failure.

iguric

CL-

2+

Check fluid

electrolytes

CIMILLER

Contraindicated in

Pulmonary Edema

Potassium-sparing diuretics



0

1)A 35-year-old woman presents to your office for a regular check-up. She has no complaints. On examination, her blood pressure is slightly elevated at 145/85. She is physically fit and follows a healthy diet. You decide to start her on antihypertensive therapy and prescribe hydrochlorothiazide. How does this agent work?

A) Inhibits reabsorption of sodium chloride in the early distal convoluted tubule

B)Decreases net excretion of chloride, sodium, and potassium

C) Increases excretion of calcium D) Interferes with potassium secretion

E) Inhibits reabsorption of sodium chloride in the thick ascending limb of the loop of Henle

2) A 45-year-old man with a history of medication-controlled hypertension presents to your office with complaints of a painful, swollen big toe on the left foot. You suspect gout and check his uric acid levels, which are elevated. From looking at the list of the medications the patient is taking, you realize that one of the medications may be the cause of hi current symptoms. Which medication might that be ?

A) Acetazolamide C) Spironolactone E)Mannitol B) Amiloride D) Hydrochlorothiazide

3) An 87-year-old woman who is taking multiple medications for her "heart disease" is prescribed gentamicin for diverticulitis. After a few days of taking the antibiotic, she complains of dizziness and tinnitus "ototoxicity". What "heart medication" might she be on?

> A) Spironolactone C) Mannitol E) Urea

B) Hydrochlorothiazide D) Ethacrynic acid

4) A 54-year-old man develops congestive heart failure (CHF) after suffering his second myocardial infarction. His physician puts him on a regimen of several medications, including furosemide. On follow-up, the patient is found to have hypokalemia, likely secondary to furosemide use. The addition of which medication would likely resolve the problem of hypokalemia, while helping to treat the underlying condition,CHF?

A) Allopurinol

C) Spironolactone

E)Ethacrynic acid

B) Hydrochlorothiazide D) Acetazolamide

5) A 45-year-old woman with a long history of alcohol abuse is being treated for cirrhosis associated ascites. Her internist decided to give her amiloride, a diuretic helpful in edema caused by cirrhosis. What common side effect should be monitored in this patient?

A)Hypernatremia C) Hyperphosphatemia E) Hyperkalemia B) HypocalcemiaD) Hypermagnesemia

- 1a

ðG.

34-

р£.

5

18

MCQS

0

6) A 57-year-old man develops progressive vision loss with a sensation of pressure behind his eyes. His ophthalmologist diagnoses the patient with glaucoma. To prevent further progression of the disease and to alleviate current symptoms, What is the drug of choice of diuretics can be use?

A) Furosemide	B) Acetazolamide	
C) Amiloride	D) Spironolactone	E) hydrochlorothiazide

7) A 50-year- old women develops high amount of ADH in the blood, and she diagnosed with nephrogenic diabetes insipidus. Which of the following drug can be used for this condition ?

A) Mannitol	B) Furosemide
C) Dorzolamide	D) Metolazone
E) Ethacrynic acid	

8) which of the following drug can be used as a treatment of Hypertension?

A) AmilorideB) Ethacrynic AcidC)AcetazolamideD)dorzolamide

9) a patient came to you with hepatic cirrhosis, edema due to nephrotic syndrome, which drug of the following is the best drug to

treat his condition?	
A) Spironolactone	B) Hydrochlorothiazide
C)Bumetanide	D)Furosemide

10) a patient is complaining of Hypertension, GIT upset and ulcer, and edema which of the following drugs is the best choice to

A) IndapamideB) AmilorideC) Ethacrynic AcidD)Acetazolamide

treat him?

11) a patient is going to have a brain procedure , which one of the following drugs is best to be given before the procedure?
 A) Mannitol
 B) Amiloride
 C) Ethacrynic Acid
 D) dorzolamide

12)which of the following drugs is contraindicated in patient with pulmonary edema and heart failure?

A) MannitolB) SpironolactoneC) dorzolamideD) Acetazolamide

-12a -11a -8a -7d -7d

- 9 - 6D Answers: 1) GIVE ONE type of diuretics can be used in acute mountain sickness? Acetazolamide

SAOS

2) Which group of diuretics can cause Renal stones as an adverse effect ? Carbonic anhydrase inhibitors

3) Patient with open -angle glaucoma came to mohammed's clinic asking for medication, He has decided to treat him with a diuretic that doesn't have systemic side effect, What is the best drug that mohammad use ? Dorzolamide (used topically)

4) Patient in the ER with acute pulmonary edema, the doctor give a diuretic drug that has fast onset of action with short duration i.v, What is the drug that the doctor used ? Loop diuretics (Furosemide)

5) Gouty patient with CHF, after doing some investigations you find that his blood calcium level is high, Give only ONE drug that is highly contraindicated in this case ? Thiazide diuretics (Chlorothiazide, Hydrochlorothiazide, Metolazone, Chlorthalidone, Indapamide)

6) Give ONE drugs from the diuretics that can cause Ototoxicity? Loop diuretics

7) Patient with hepatic cirrhosis developed Ascites because of excess aldosterone level , What is the drug of choice in this type of edema? Spironolactone (Aldosterone antagonist)

8) Which of type of diuretics can cause diarrhea once it is take orally ? Mannitol

9) Patient with acute pulmonary edema , the consultant decided to treat with diuretics, he asked the intern about what is the best drug can be used and what is the drug that is contraindicated, What the best answer for this question?
USE → Furosemide
Contraindicated → Mannitol

10)Patient with Calcium stones treated with thiazide diuretics, Give Five results of electrolyte blood test can be seen as a side effect? Hyponatremia hypokalemia hypercalcemia metabolic alkalosis hyperuricemia



11) what kind of renal stone does the Carbonic anhydrase inhibitors form? calcium phosphate stones



12) which group of drugs can produce hypersensitivity reaction? Carbonic anhydrase inhibitors (Acetazolamide – dorzolamide(

13) Why do CA inhibitors have weak diuretic properties ? Diuretic properties decreases after several days as the blood bicarbonate falls.

14)what is the mechanism of action of Potassium-sparing diuretics?1. Na+ channels inhibitors2. aldosterone antagonist

15) give an example of Potassium-sparing diuretics which blocks the sodium channels? Amiloride

16) Drugs that work on collecting tubules and ducts? Potassium-sparing diuretics

17) A drug which is used to prevent Hypokalemia? Potassium-sparing diuretics

18) Give the name of the drug that when its given orally the patient will complain of Diarrhea? Mannitol

19) Where does Mannitol acts? in proximal tubules + descending loop of Henle

20) why patients before Opthalmic or brain procedure should be given Mannitol? to decrease intraocular & intracranial pressure



GOOD LUCK!

This Lecture was done by:

- Abdullah Alhamoudi Mohammed Almozini Fahad Alfahad **Mohammed Alkharaz**
- Qassem Alsultan
- Moath alessa

Omar Arahbeeni **Omar Alomar**

- Fetoon alnemari
- Najla aldraiweesh
- sheikh aldosari
- Najla alsabeh
- khulaud Alenzi
- Rana Aljunaidel
- Shima Alduaiji
- Mada albatli



