MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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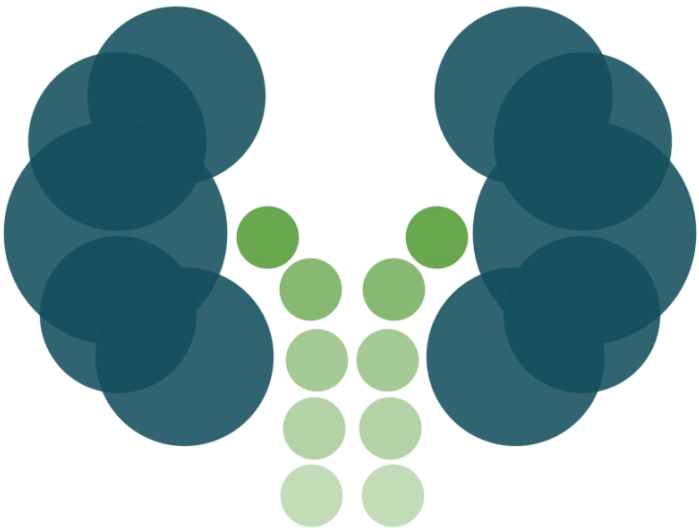


Renal Block

Pharmacology Team 438

Diuretics

Editing File

Objectives:

By the end of this lecture, students should be able to:

- 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

Color Index:

Red : important

Black :Main content

Pink : in female's slides only

Blue : in male's slides only

Green : Dr's notes

Grey: Extra information , explanation

Diuretics

Definitions

-Diuretics: Drugs that increase renal flow rate(urine volume).
-Diuresis:The process of excretion of water in the urine. ,water can be used as diuretic.
-Natriuresis: is the process of excretion of sodium in the urine.
-All Diuretics have natriuretic effect.

Indications

-Edema of any origin.
-Congestive heart failure.
-Hypertension.
-Elimination of toxins.

M.O.A

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

Site of action

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

The main classes are[1]:

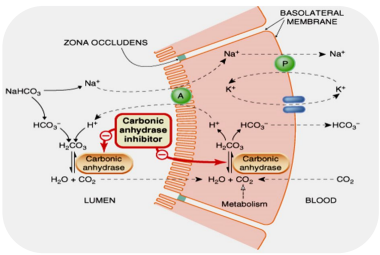
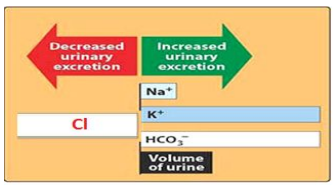
1. Carbonic anhydrase inhibitors
2. Loop diuretics
3. Thiazide diuretics
4. K+ sparing diuretics
5. Osmotic diuretics

Site of action of diuretics

Segment	Normal filtered Na + reabsorbed	Transporter	Diuretics
Proximal convoluted tubules	65 % As $NaHCO_3$.[2]	-Na/H transporter -Carbonic anhydrase enzyme.	-Carbonic anhydrase inhibitors.
Thick ascending loop	20-30% Active reabsorption Na, K, Cl.	Na/K/2Cl cotransporter.	-Loop diuretics
Distal convoluted tubule	5-10% Active reabsorption Na,Cl.	Na/Cl Cotransporter.	-Thiazide diuretics.
Collecting tubules	-5% Na reabsorption , K & H secretion.	-Na channels -K and H transporter -Aldosterone -Antidiuretic hormone.	-K-sparing diuretics.

1- First 4 classes their target is a protein and their goal is to excrete Na+, unlike osmotic diuretics which depends on physical properties and its goal is to excrete water (has less effect on Na+ excretion).
2- Bicarbonate is the conjugate base of carbonic acid (conjugate bases are formed when acids lose their H ions), it has an exactly (-1) negative charge, therefore it tends to bind with Na, and K, which have a +1 charge to reach chemical stability, but more with Na due to its abundance therefore we may always notice $KHCO_3$, $NaCO_3$ being formed and bound to Na or K.

Carbonic Anhydrase Inhibitors

Drug	1) Acetazolamide (Prototype)
M.O.A	• Carbonic anhydrase accelerates the attainment of equilibrium in the reaction: $CO2 + H2O \leftrightharpoons H2CO3 \leftrightharpoons H^+ + HCO3^-$ Bicarbonate acts as buffer to maintain the pH • Inhibits carbonic anhydrase (CA) enzyme in the proximal convoluted tubules thus interferes with NaHCO3 reabsorption and causes diuresis • Acetazolamide is a **potent specific inhibitor** of carbonic anhydrase, enzyme inhibition is non competitive. • **It ↓ reabsorption of bicarbonate in the proximal tubule** & prevent the acidification of urine in the distal tubule. • **Self- limiting action of acetazolamide restrict its use to mild oedema .** 
P.K	• given orally once a day. • Onset of action is rapid (30 min). • Duration of action (9-12 h). • t ½ 6-9h • Excreted by active secretion in proximal convoluted tubules. • Produces alkaline urine. Since it Inhibits the reabsorption of bicarbonate, urine will have excess bicarbonate
Pharmaco-logical actions	• ↑ Mild increase in urine volume. • ↑ urinary excretion of sodium, potassium , bicarbonate (alkaline urine). • Metabolic acidosis. • ↑ Urinary phosphate excretion. Due to the change of urine pH "alkaline" • Promotes K+ excretion by ↑the load of Na+ delivered to the distal tubules[1].
★ Notes	-Why do CA inhibitors have weak diuretic properties? • Diuretic properties decreases after several days as the blood bicarbonate falls 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. 

Drug	2) Dorzolamide
Info	• Is a carbonic anhydrase inhibitor • Used topically for treatment of increased intraocular pressure in open-angle glaucoma. • No diuretic or systemic side effects , why? Because it has low volume of distribution therefore used locally.

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.

Carbonic Anhydrase Inhibitors (cont...)

Therapeutic uses	**1.Open angle glaucoma** -aqueous humor contains a high concentration of bicarbonates. ↓of carbonic anhydrase ↓ rate of aqueous humor formation in ciliary body of eye→ ↓intraocular pressure (tolerance does not develop to this effect) **2.As <u>prophylactic</u> therapy, in acute mountain sickness [1] ↓ CSF of brain** -Given nightly 5 days <u>before</u> the ascent↓ weakness, breathlessness, dizziness, nausea, cerebral and pulmonary oedema. **3.Formation of CSF** ↓ of carbonic anhydrase in the choroid plexus → ↓ formation of CSF. Useful in treating benign intracranial hypertension **4.Urinary alkalinization to enhance renal excretion of acidic substances:** uric acid, Methotrexate [2] and cysteine in cystinuria;Renal excretion can be ↑by ↑ urinary bicarbonate excretion. Effect is short lived & require bicarbonate infusion. **5.Hyperphosphatemia** **6.Adjunct for treatment of epilepsy**. -Glial cells contain carbonic anhydrase. Nerves are highly responsive to rise in pH 7.4→7.8 which causes convulsions. ↓ in neuronal carbonic anhydrase → ↓ pH in the vicinity of neurons → ↓ convulsion. **7.Metabolic alkalosis** -Useful for correcting a metabolic alkalosis, especially an alkalosis caused by diuretic-induced increases in H+ excretion & metabolic alkalosis of heart failure.
ADRs	• Drowsiness • Numbness • Tingling sensation of the face and extremities • Disturbance of vision • Hypokalemia(K+ loss) • Metabolic acidosis • Renal stone formation (calcium phosphate stones). • Hypersensitivity reaction • Hypovolemia • Hyponatremia
Contra-indications	In patient with liver cirrhosis (alkaline urine ↓ Excretion of NH4 → Hyperammonemia and hepatic encephalopathy)[3]

1: In high altitude, low oxygen is inhaled which is compensated by hyperventilation, resulting in huge amounts of CO_2 exhaled, CO_2 is a lewis acid therefore alkalosis will develop. Inducing an acidic environment with CA inhibitors before ascent can help to fight off respiratory alkalosis and its deleterious effects.
2: TNF-alpha receptor blocker for treatment of rheumatoid arthritis, inhibits nucleic acid synthesis so it is also used in cancer therapy.
3: Ammonia (NH_3), is metabolized in the liver to urea and NH_4 (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 NH_4 because it is an acid, which in high pH environment can be turned back into NH_3, the toxic metabolite. .

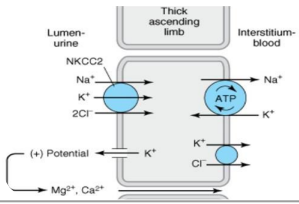
Osmotic Diuretics

(Aquaretics)

Drug	Mannitol
P.K	• Poorly absorbed • Given I.V, not absorbed from the GIT, ↑water excretion with relatively less effect on Na+. • If given orally it will cause osmotic diarrhea. • Little/ not metabolized • Excreted by glomerular filtration without being reabsorbed or secreted, within 30-60 minutes. • t½ 0.25 -1.7 hours, prolonged in renal failure to 36 hours .
Pharmaco-logical actions	• Acts in proximal tubules and descending loop of Henle by **osmotic effect .** **In Systemic circulation:** • Mannitol increases urine output by osmosis, drawing water out of the cells and into the bloodstream. • Expand the extracellular fluid volume, decreasing blood viscosity, and inhibit renin release, increases renal blood flow. **In the kidney tubules:** • IV administration of any solute filtered by glomeruli may produce osmotic diuresis when the amount delivered to the tubules exceeds their absorptive capacity. • The dissolved compound exert an osmotic pressure → ↓Water and Na+ reabsorption.
Therapeutic uses	• **Acute renal failure due to shock or trauma** (maintain urine flow - preserve kidney function) ○ To maintain urine volume and prevent anuria resulting from large pigmentation load to the kidney. E.g, hemolysis [1] & rhabdomyolysis. • To **prevent** acute renal necrosis after severe injury, hemorrhage, hypovolemia → ↓ GFR ,absorption of water & salt is complete, distal part dries up → irreversible damage • **In acute drug poisoning** : to eliminate drugs that are reabsorbed from renal tubules e.g salicyaltes, barbiturates and bromides. • To decrease intraocular & intracranial pressure before ophthalmic or brain procedure (cerebral edema).
ADRs	• Headache, nausea, vomiting →Hyponatremia (loss of electrolytes when vomiting) • Extracellular volume expansion , complicates heart failure & pulmonary edema • Excessive use → dehydration & hypernatremia (adequate water replacement is required).
Contra-indication	• Chronic heart failure • Anuric patients or patients not responding to a test dose on mannitol.

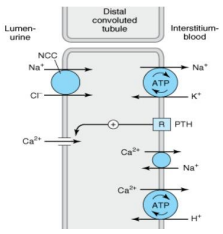
1: rupture of the RBCs → hyperbilirubinemia. RBCs contain hemoglobin, and muscle cells contain myoglobin, both of which contain heme which is a pigment that gives the red color to RBCs. Heme is toxic to kidney cells.

Loop Diuretics

Drug	Bumetanide (Most potent)	Torsemide (Longest duration)	Furosemide	Ethacrynic Acid
Potency, t½	Potency 40, t½ 0.8 hrs	Potency 3, t½ 3.5 hrs	Potency 1, t½ 1.5 hrs	Potency 0.7, t½ 1hr
Efficacy	• High natriuresis as 25-30% Na+ is reabsorbed. • The most potent diuretic, termed "high ceiling diuretic"			
M.O.A	• Inhibit Na+ /K+ /2 Cl- co-transporter in the luminal membrane of the thick ascending loop of Henle (TAL). • Inihbit Ca++ and Mg++ reabsorption. 			
P.K	• Given orally or I.V • Have fast onset of action (for emergency) • Have short duration of action • Excreted by active tubular secretion of weak acids into urine • Interfere with uric acid secretion (hyperuricemia)			
Pharmaco-logical effects	• ↑ Urinary excretion of Na , K+ , Ca++ and Mg++. • ↑ Urine volume • **Induce expression of COX, PGE**↓ salt transport in TAL. • ↓ Renal vascular resistance & ↑**renal blood flow** because of PGs • Furosemide and ethacrynic acid reduce pulmonary congestion and left ventricular filling pressure in heart failure →↑venous capacitance			
Uses	**Drugs of choice for emergency situations such as :** • Edema associated with congestive heart failure, nephrotic syndrome. • Acute Pulmonary Edema • Acute Hypercalcemia • Acute Hyperkalemia • Oliguric ARF • Toxicity of Br, F & I (anion overdose)			
ADRs	• **HYPO**: -Volemia -Kalemia -Magnesemia -Calcaemia -Natremia	• **HYPER**: -Glycemia [1] -Uricemia	• Postural hypotension • Allergic reactions • Ototoxicity [2] • Metabolic alkalosis [3]	
Contra-indications	• Severe Na and volume depletion • Hypersensitivity to sulfonamides (ethacrynic acid is the only loop diuretic which does not contain a sulfonamide group). [4] • Anuria unresponsive to a trial dose of loop diuretic			
Drug-drug interaction	• NSAIDs → ↓ Diuretic response [5] • Digitalis → Arrhythmias [6] • Aminoglycosides → ↑ Ototoxicity of loop diuretic • Loop diuretic →↑Nephrotoxicity of aminoglycosides			

1)interferes with insulin sensitivity.
2)affects the triple co-transporter that's located in the inner ear. Ethacrynic acid is the most severe.
3)potassium secretion is accompanied with hydrogen secretion.
4) Thiazides and loop diuretics are sulfonamide derivatives, except ethacrynic acid.
5) loop diuretics increase PGs, while NSAIDs decrease PGs.
6) both cause hypokalemia.

Thiazide diuretics

Drug	Chlorothiazide	Hydrochloro thiazide	Metolazone	Chlorthalidone	Indapamide
Potency [1] t ½	Potency 0.1 t ½ 2h	Potency 1 t ½ 3h	Potency 5 t ½ 5h	Potency 10 t ½ 26h	Potency 20 t ½ 16h
M.O.A	Acts via inhibition of Na/Cl co-transporter [2] on the luminal membrane of distal convoluted tubules. 				
Efficacy	• Moderate natriuresis (5-10% of filtered load of sodium is reabsorbed).				
P.K	• Thiazides are lipid soluble • Given orally,efficiently absorbed from the GIT • Eliminated by glomerular filtration & active tubular secretion , some is reabsorbed • Long duration of action (40 h) , with slow onset • May interfere with uric acid secretion and cause **hyperuricemia**				
Pharmaco-logical actions	• ↑urinary excretion of: -NaCl -K+ -Mg++ • ↓urinary excretion of: - Uric acid - Ca++ **"With increase in its reabsorption"** • May give rise to hypokalemic alkalosis • Causes vasodilatation , diazoxide , non diuretic thiazide is a potent vasodilator • ↓ of urine volume in case of diabetes insipidus.				
Uses	• Treatment of essential hypertension (cheap-well tolerated). • Treatment of **mild** heart failure (to reduce extracellular volume). • Treatment of Osteoporosis • Calcium nephrolithiasis due to hypercalciuria (to increase calcium reabsorption and decrease renal calcium stones) • Nephrogenic diabetes insipidus (decrease blood volume + GFR) , **How?** Thiazide→ ↓Distal tubular Na+ reabsorption → ↑ Urinary Excretion→ ↓Extracellular Volume → ↑ Proximal Na+ & water reabsorption→↓Distal Delivery of Na+ & Water → ↓Urine Volume				
ADRs	• **HYPO**: -Natremia -Volemia -Kalemia -Magnesemia • **HYPER**: -Uricemia (gout) -Calcemia -Glycaemia -Lipidemia • Fluid and electrolyte imbalance • Metabolic alkalosis				
Drug-Drug Interaction	• Uricosurics , Sulphonylurea → Thiazides Diminish effect • Digitalis , Diazoxide → Thiazides Increase effect • NSAIDs → Reduce thiazide efficacy.				

1: less potent but longer duration of action than loop diuretics.
2: This activates Na+/Ca++ exchanger.

Potassium Sparing Diuretics

Steroids

Competitive Aldosterone Antagonist:
Also called K-sparing diuretics or mineralocorticoid receptor antagonist

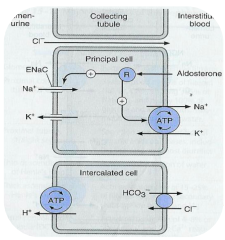
- ➔ Spironolactone
- ➔ Eplerenone

Non-Steroids

Na+ Channel Inhibitors:

- ➔ Amiloride
- ➔ Triamterene

A) Aldosterone 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 • Actions depend on renal PGs production 
P.K	• Well absorbed from the GIT , t½=1.6h • Highly protein-bound • Undergoes enterohepatic recycling • Delayed onset of action (nuclear receptor), maximum diuretic action 4 days. • Converted in gut & liver to Canrenone (active metabolite), t½=16h • It binds androgen receptors with high affinity
Pharmaco-dynamics	• ↑urinary Na+ excretion • ↓urinary K+ excretion (Hyperkalemia) • ↓ H+ excretion (Acidosis) • Has antiandrogenic action [1]
Uses	• **Treatment of hypertension** ;usually used combined with **thiazide** or **loop diuretics** to: 1- Enhance natriuresis caused by other diuretics 2 - Correct for hypokalemia • Treatment of **primary** [2] hyperaldosteronism (Conn's syndrome Adrenal tumor) • Treatment of **secondary** hyperaldosteronism in diseases as CHF, Edema of hepatic cirrhosis and Nephrotic syndrome. • Treatment of hirsutism [3], acne due to the antiandrogenic effects

1: Aldosterone antagonists structure is similar to testosterone → blockage of testosterone receptors
2: we differentiate between primary and secondary hyperaldosteronism by the level of renin: normal or low → primary, high → secondary.
3: overproduction of hair in inappropriate places.

Aldosterone Antagonist (cont...)

ADRs	• Hyperkalaemia • Gynecomastia (male breast enlargement) • CNS side effects • Metabolic acidosis in cirrhotic patients • Menstrual irregularities • Hirsutism • Impotence • Gastritis and peptic ulcer • Deepening of voice
Contra-indication	• Hyperkalemia ○ Chronic renal failure ○ K+ supplement use ○ B-blocker ○ ACEI. ○ Other k sparing diuretics • Liver disease (dose adjustment is needed).
Inter-actions	• ACEI , B-blocker , K+ supplement , K+ sparing diuretic and Aliskiren→↑Hyperkalemia-induced by k+ Sparing diuretics • Salicylates → decrease secretion of canrenone and decrease efficacy of spironolactone • Digitalis → Spironolactone alters its clearance

Drug	**2) Eplerenone**
Info	• Eliminated by metabolism(CYP3A4),t½ 5h • Low affinity for progesterone and androgen receptors • Both ineffective in adrenalectomized patients

B) Na+ Channels Inhibitors

Drug	**Triamterene** (Potency 0.1, t ½ 4.2h)	**Amiloride** (Potency 1, t ½ 21h)
M.O.A	Inhibition of Na influx through direct blockade of the epithelial sodium channel (ENaC) on the lumen side of the kidney (collecting tubule)	
Uses	-Used in Combination with Loop & Thiazide Diuretics -Treatment of lithium -Induced Diabetes Insipidus.[1] -Treatment for Liddle's Syndrome	
ADRs	-Hyperkalemia -Renal stones (promotes crystallization and stability of Ca-oxalate complexes) -Interstitial nephritis[2] -Megaloblastosis in cirrhotic patients	-Hyperkalemia
Contra-indication	The risk of developing **hyperkalemia** is increased in patients who are also on ACE inhibitors, angiotensin II receptor antagonists, other potassium- sparing diuretics, or any potassium-containing supplements.	
Inter-actions	ACE Inhibitors, Beta-Blockers K Supplements, K-Sparing Diuretics, ,Aliskiren (renin antagonist) ⟹	↑Hyperkalemia-induced by K-Sparing diuretics

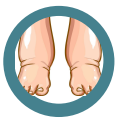
1: Lithium has similar chemical properties to sodium, as they are both in group 1 of the periodic table, therefore Li will compete with sodium reabsorption in ENaC in collecting ducts and DCT, resulting in less sodium reabsorption and frequent urination. The treatment here is mainly to get rid of excess Li. Liddle's syndrome is characterized by increased expression of ENaC channels.
2: Triamterene is a partial folate antagonist, impairing nucleic acid synthesis in RBCs, cirrhotic patients have low folate stores as folate is usually stored in the liver, deficiency in folate results in megaloblastic anemia.

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
because they increase renal blood flow.



Edema

-Thiazide diuretics: used mild edema with normal renal function.

-**Loop diuretics** are used in cases with Impaired renal function

Congestive HF

-**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

Hepatic Cirrhosis with Ascites

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

Nephrogenic Diabetes Insipidus

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

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.

Summary

Class	M.O.A	Effects	Uses	ADR
CA Inhibitors -Dorzolamide -Acetazolamide	Inhibition of NaHCO3 reabsorption in PCT	-↑Urinary NaHCO3, K. -Urinary alkalosis -Metabolic acidosis	-Glaucoma -epilepsy -Mountain sickness -Alkalosis -Phosphatemia	-Metabolic acidosis -Urinary alkalosis -Hypokalemia
Osmotic Diuretic -Mannitol	Osmotic effect in PCT	-↑Urine excretion -↑Little Na	-Cerebral edema -Glaucoma -Acute renal failure -Drug toxicities	-Extra-cellular water expansion -Dehydration - Hypernatremia
Loop Diuretics -Furosemide	Inhibit Na/K/2Cl transporter in TAL	↑Urinary Na,K, Ca,Mg	-Acute pulmonary edema (Drug of choice). -Heart failure -Hyperkalemia -Hypercalcemia	**HYPO:** **-Calcemia**\-Volemia -Natremia\-Kalemia -Magnesemia. -Precipitate gout -Alkalosis
Thiazide Diuretics -Hydrochlorothiazide	Inhibits Na / Cl cotransporter in DCT	-↑Urinary Na,K,Mg -↓ urinary Ca (hypercalcemia) -Metabolic alkalosis	-Commonly used -Hypertension -mild heart failure. -nephrolithiasis -diabetes insipidus	**HYPER:** **-Calcemia**\-lipidemia -Glycemia **HYPO:** -Kalemia\-Natremia -Volemia\ -Magnesemia. -Precipitate gout -Alkalosis
K-sparing Diuretic -Spironolactone	Competitive antagonist of aldosterone in CCT	-↑Urinary Na -↓K, H secretion -metabolic acidosis	Hepatic cirrhosis (Drug of choice)	**-Hyperkalaemia** -Gynaecomastia -Metabolic acidosis -GIT upset -peptic ulcer

Quiz

MCQ

From male's Dr They are important. ClickHere

SAQ

-A 62 year old African-American man who has had poorly controlled hypertension for the past 10 years, presents with signs of ankle edema, a low GFR and a serum creatinine of 2.5 mg/dL.

1) What is the most effective drug for producing diuresis and fall in blood pressure?
2) What is the mechanism of action of this drug?
3) Mention 3 of its adverse effects.

ANS:
1) Loop diuretics
2) Inhibit Na+ /K+ /2Cl cotransporter in the luminal membrane of the thick ascending loop of Henle & Inihbit Ca++ and Mg++ reabsorption
3) Hypokalemia, hyperglycemia, & ototoxicity

pharmacology

Team 438

Good Luck

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Share with us your ideas !