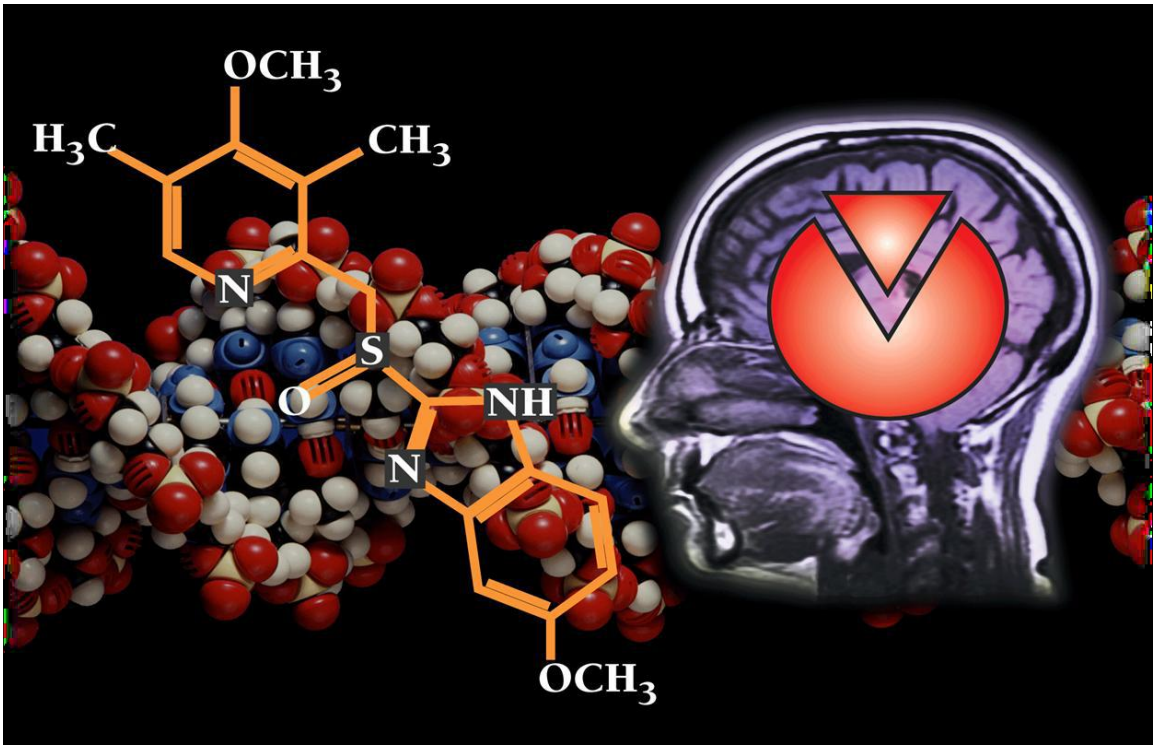
King Saud University
College Of Medicine
Pharmacology Team 430
Renal Block

DIURETICS



Important: To understand this lecture you should know these things about the anatomy and physiology of the kidney. Although these points won't come as pharmacology question, we **highly recommend** that you print the **Nephron Table** attached along with this file, and hold it with you while you are studying from this lesson

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Background & Physiology

Kidney (nephron) is responsible for regulation of fluids and electrolytes.

Kidney does its function through three processes:

1. Glomerular filtration: Filtrate contains water, glucose, amino acids, sodium bicarbonates, organic solutes and electrolytes (sodium, potassium, chloride).
2. Passive tubular re-absorption**.**
3. Active tubular secretion**.**

How could urine output be increased?

↑ Glomerular filtration Vs ↓ Tubular reabsorption (the most important clinically)

Purpose of Using Diuretics:

- To maintain urine volume (e.g.: renal failure)
- To mobilize edema fluid (e.g.: heart failure, liver failure; nephrotic syndrome)
- To control high blood pressure.

Nephron is the structural unit of the kidney It is composed of :

1-Glomerulus:

Where ultrafiltration occurs.

2-Proximal convoluted tubule:

— Responsible for re-absorption of all glucose and amino acids, organic solutes, electrolytes as sodium chloride, Potassium and sodium bicarbonate. HCO3- is reabsorbed by action of enzyme **carbonic anhydrase** luminal membrane of proximal tubular cells. Water (passively following salts to maintain osmolarity in tubular fluids (60%).

PCT is the site of organic acids or bases secretory systems: It secretes organic acids and drugs.

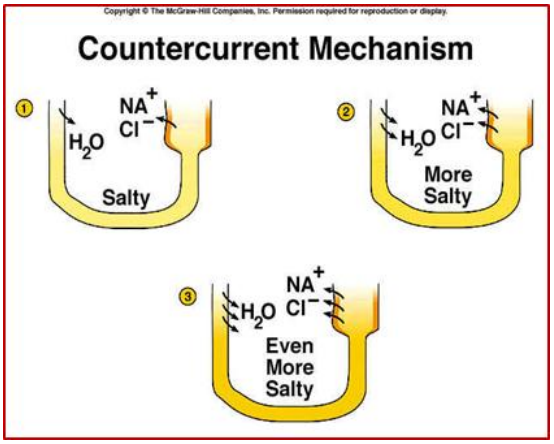
> **Note:** Organic acid secretory system is usually saturated by organics acids such as Uric acids. Drugs in the blood stream compete with these endogenous acids. These drugs are secreted instead, and leaving these endogenous Organic acids in the blood. This explains why some diuretics like furosemide

3-(Thin) Descending loop of Henle: (high Osmolarity)

- Located in the medulla.
- It is the site of water reabsorption.
- No handling of electrolytes occurs here.

Why does water gets reabsorbed here?

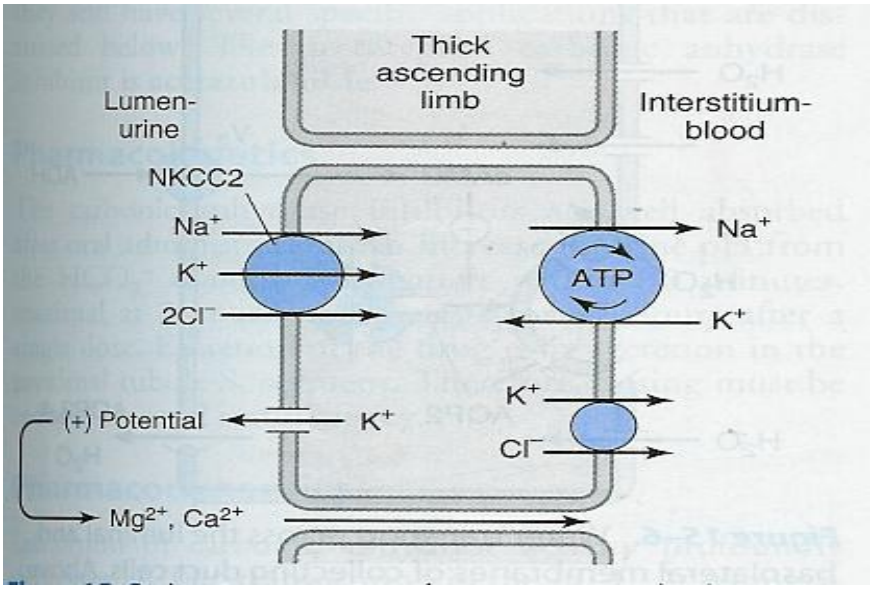
Because of the osmotic forces in hypertonic medullary interstitium since it is located in the medulla as mentioned before. This mechanism is known as (counter current mechanism).



> **Note:** in (Thin) Descending loop of Henle water is getting reabsorbed by counter current mechanism where water molecules are moving from a site of low concentration of water molecules t site of high concentration of water molecules (osmosis) thus, the filtrate is getting salty more and more.

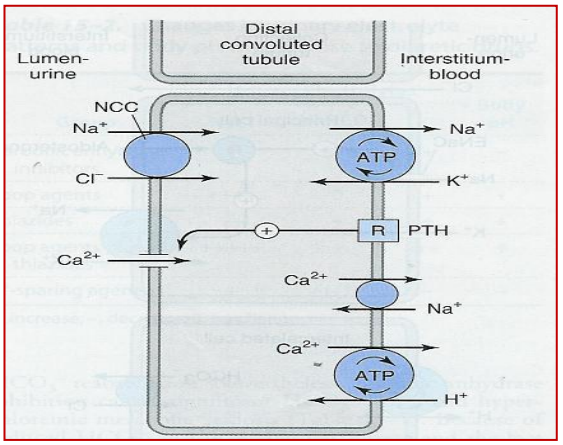
4-(Thick) Ascending loop of Henle:

- It is impermeable to water.
- It is responsible for sodium-chloride (sodium by 25-30 %) and potassium-chloride reabsorption via transport system called **Na+/ K+ / 2Cl- co-transporter.**
- This is a protein (enzyme) located on the luminal membrane called Na+/ K+ / 2Cl- co-transporter (sodium-potassium-dichloride transporter). It transports 1 Na, 1K, 2Cl at a time. Inhibition of this enzyme results in diuresis action. For that reason, it is called the diluting segment.



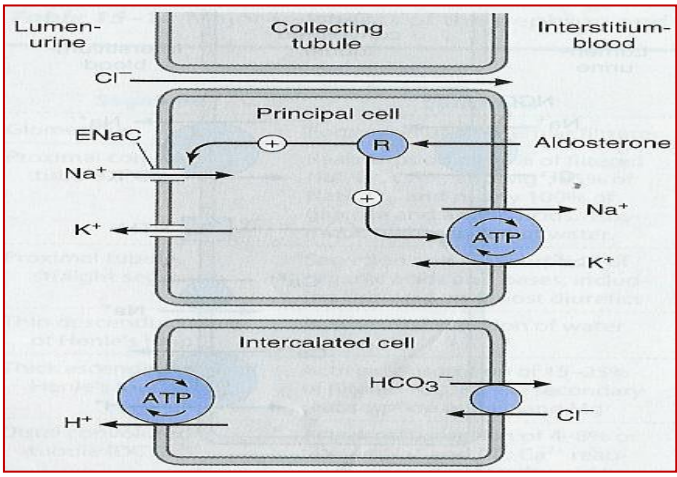
5-Distal convoluted tubule:

- Is impermeable to water.
- Responsible for active reabsorption of the remaining NaCl (5 to 10%) via transport system Na/Cl transporter in luminal membrane (Na/Cl carrier).
- Parathyroid hormone acts on DCT to stimulate active reabsorption of Ca via Ca channel and Na+/Ca2+ exchanger in basolateral membrane.



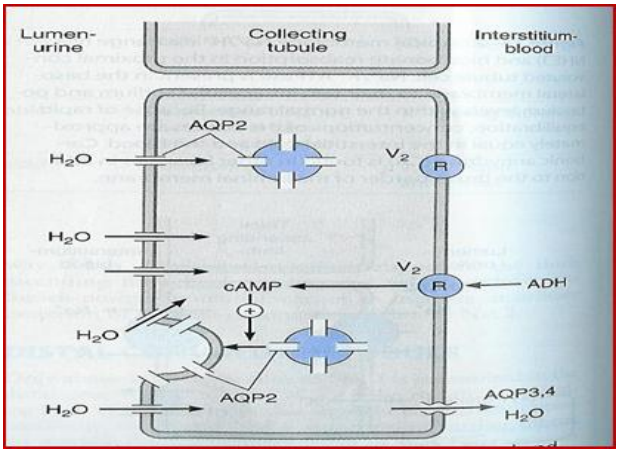
6-Collecting duct:

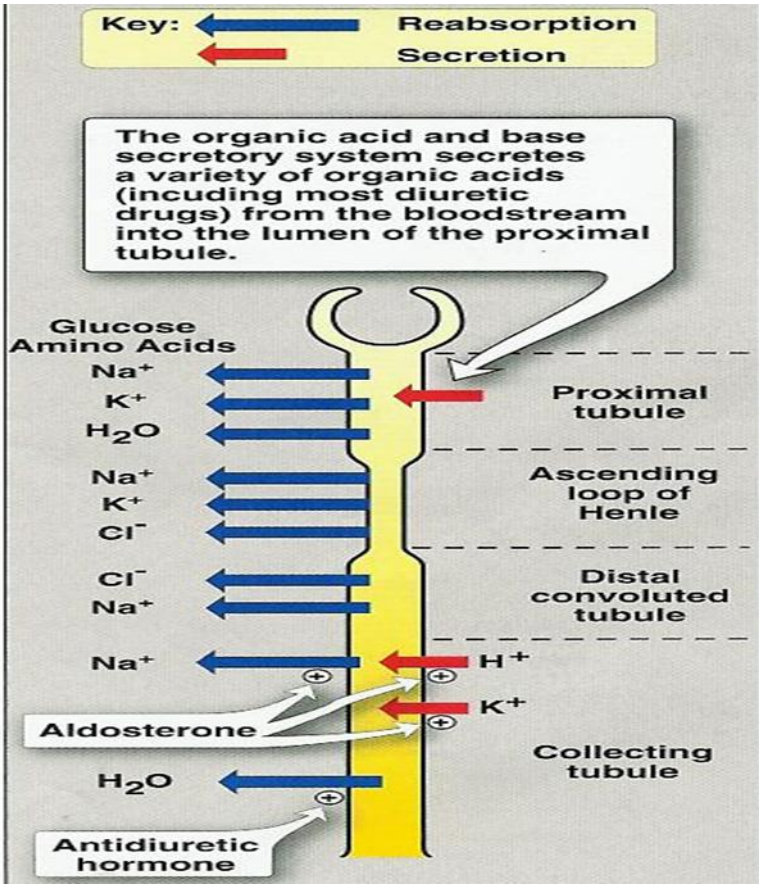
- It is the site of action of two hormones: *1.aldosterone 2.anti diuretic hormone (ADH)*.
- Its cells are of two distinct functional types: Principal and intercalated cells.
- Principal cells permeability to water and solutes is regulated by hormones (the previous hormones).
- Intercalated cells secretion of hydrogen ions for acid/base balancing.
- Principal cells are responsible for reabsorption of Na (in exchange for K via Na/K-ATPase) and water.
- Aldosterone receptors located in the principle cells influence Na re-absorption and K secretion.
- ADH is responsible for water reabsorption.
- Water reabsorption (antidiuretic hormone, ADH



To Understand The Role of ADH:

- Water reabsorbed from collecting duct (by osmosis) is determined by the hormone ADH (anti-diuretic hormone).
- Osmoreceptors in the hypothalamus detect the low levels of water (high osmolarity), so the hypothalamus sends an impulse to the pituitary gland which releases ADH into the bloodstream.
- ADH makes the wall of the collecting duct more permeable to water.
- In the present of ADH more water is reabsorbed and less is excreted.





Sites for solutes and water transport along the nephron

Sodium Excretion Regulation

Nephron Segment	Filtered Na^+ reabsorbed	Na^+ Transporter
Proximal CT	60-70%	Na^+- H^+ transporter
Ascending Loop of Henle	20-30%	Na^+-K^+-2Cl^- transporter
Distal CT	5-10%	Na^+-Cl^- transporter
Cortical Collecting Tubules	5%	Na^+ channel Aldosterone ADH

Note: The only thing you should know in this schedule is: the highest % of reabsorption is in the proximal convoluted tubule and the lowest % is in the collecting tubules.

Organic acids or bases secretory systems:

- Organic base secretory system responsible for secretion of bases into luminal fluid e.g. choline and creatinine.
- Organic acid secretory system responsible for secretion of acids into luminal tubular fluid e.g. Uric acid, NSAIDs, antibiotics and diuretics.
- So from the previous part different diuretics act by inhibiting deferent protein throughout the nephron:

segment	Function	transporter	Diuretics
Proximal convoluted tubules	Reabsorption of 66% Na, K, Ca, Mg, 100% glucose and amino acids; 85% NaHCO3	Na/H transporter, Carbonic anhydrase enzyme	Carbonic anhydrase inhibitors
Proximal Straight Tubules	Secretion and reabsorption of organic acids and bases	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

Diuretics

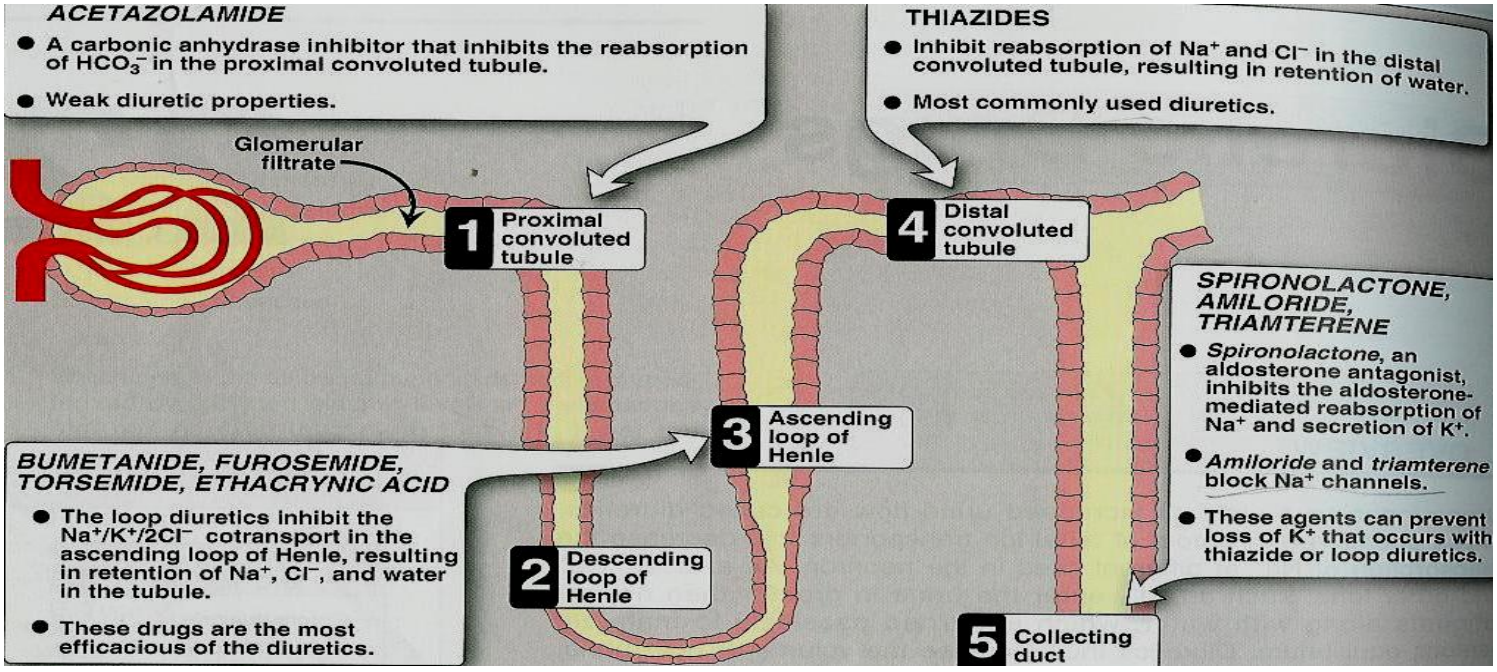
What are diuretics?

- They are drugs that increase the urine volume by increasing the sodium excretion.
- So when sodium get excreted, water get exerted along with it (increase urine flow).-
- They are agents that inhibit renal ion transporters thus decrease the reabsorption of ions at different site of the nephron, in other word the site of action of most diuretics act on transporter proteins which are located in the renal tubular cells.

Classification of diuretics:

- The best way to classify diuretics is to look for their Site of action in the nephron:
- Diuretics that inhibit transport in the Proximal Convoluted Tubule **(Osmotic diuretics M; Carbonic Anhydrase Inhibitors).**
- Diuretics that inhibit transport in the Medullary Ascending Limb of the Loop of Henle **(Loop diuretics).**
- Diuretics that inhibit transport in the Distal Convoluted Tubule **(Thiazides- Indapamide- Metolazone).**
- Diuretics that inhibit transport in the Cortical Collecting Tubule **(Potassium spring diuretics).**

SITES OF ACTION OF DIURETICS



1- Diuretics that inhibit transport in the Convoluted Proximal Tubule: **Osmotic Diuretics: (e.g.: Mannitol)**

Mechanism of Action:

They are hydrophilic compounds that are easily filtered through the glomerulus with little re-absorption and thus increase urinary output via osmosis.

Pharmacokinetics: Given i.v , and is not absorbed orally.

Indications:

- To decrease intracranial pressure in neurological condition.

- To decrease intraocular pressure in acute glaucoma.
- The **best choice** to maintain high urine flow in acute renal failure during shock,trauma & drug toxicities

Note: Because osmotic diuretics have the potent effect of more water secretion, and not the effect of NA excretion. They are not used in cases of NA retention, like hyperaldosteronisim

Adverse Effects:

- **Extracellular water expansion and dehydration.**
- **Hypernatremia** due to loss more water than sodium(due to loss more water than sodium cause the Mannitol has a secondary effect on reducing Na+ reabsorbtion not like other diuretics)
- **Hyperkalemia**(water is extracted from cells, intracellular K+ concentration rises)

Note: The extracellular expansions occur due to presence of Mannitol in extracellular fluid. It extracts water from cells. This causes **hyponatremia** until diuresis occurs. Dehydration occurs if water is not replaced adequately.

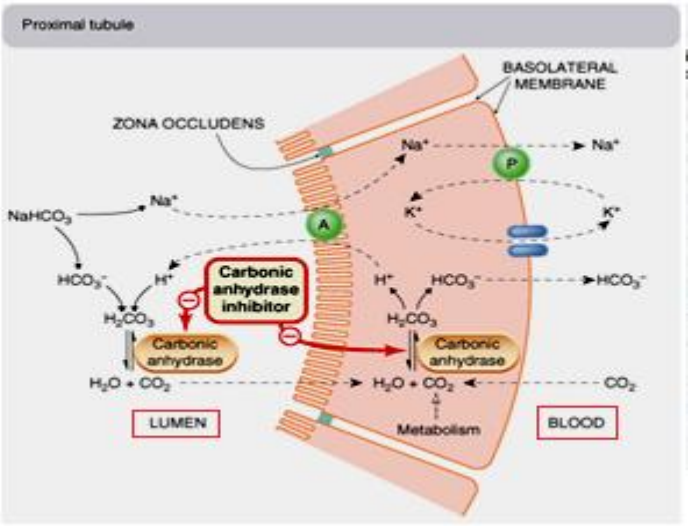
2- Carbonic Anhydrase Inhibitors :(Acetazolamide (Oral) ; Dorsolamide (Ocular) ; Brinzolamide (Ocular)

Remember:

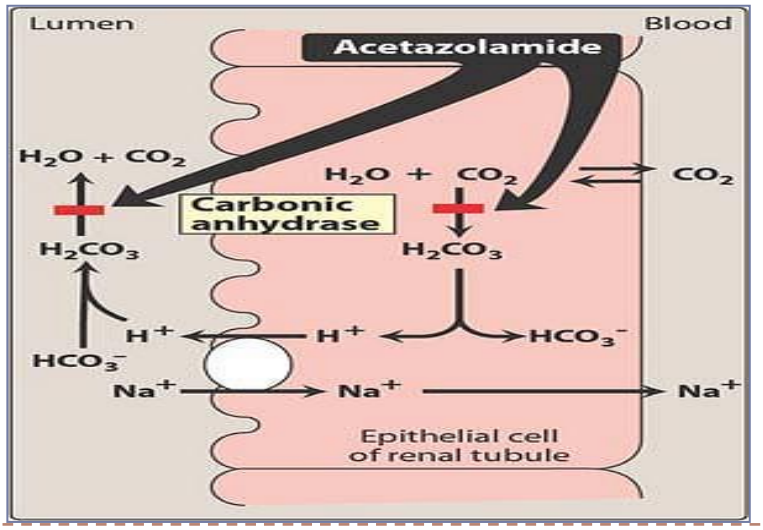
- Carbonic Anhydrase enzyme (CA) is Located in PCT (proximal convoluted tubules).
- Responsible for reabsorption of $HCO3^-$ (in the luminal membrane of proximal tubular cells).
- Water (passively following salts to maintain osmolarity in tubular fluids (60%).
- PCT is the site of organic acids or bases secretory systems.

Mechanism of action: Simply inhibit reabsorption of sodium and bicarbonate

Inhibits carbonic anhydrase enzyme in PCT thus interferes with NaHCO3 (sodium Bicarbonate) reabsorption.



Here we can see that CAI will inhibit CA enzyme in PCT which prevent HCO_3^- from being transported inside the blood (prevent reabsorption) which leads to increase in HCO_3^- excretion -->metabolic acidosis.



Here also we can see that CAI will inhibit H_2CO_3 to convert into $H_2O + CO_2$ so it can't enter the cell. It also prevents the conversion of $H_2O + CO_2$ into H_2CO_3 (carbonic Acid) inside the cell. This decreases the ability to exchange NA+ for H+. Leaving more NA in the lumen of renal tubules, which thin gives a weak diuretic action.

Pharmacological actions:

- ↑ urinary excretion of bicarbonate, sodium, potassium "alkaline diuresis"
- Metabolic acidosis.
- ↑ Urinary phosphate excretion. **(unknown mechanism)**
- Weak diuretics.
- Decreases after several days (self-limiting as the blood bicarbonate falls).

Pharmacokinetics:

- Given orally once a day.-
- Rapid onset of action (30 min).-
- Duration of action12 h.-
- Excreted by active secretion in proximal convoluted tubules.

Therapeutic uses:

NB: Acetazolamide is not used as a diuretic.

- **Epilepsy**(decrease cerebrospinal fluid) (CSF)
- **Urinary alkalinization** to enhance excretion of acidic substances (uric acid and cysteine).
- **In acute mountain sickness (**prophylaxis, to decrease CSF and pH of brain).
- **Hyperphosphatemia.**
- **Metabolic alkalosis.**
- **Open angle glaucoma** (↓ Intraocular pressure (IOP) by reducing aqueous humor formation via blocking carbonic anhydrase in ciliary body of eye).

Note: Epilepsy is a common chronic neurological disorder characterized by seizures (Benign intracranial hypertension)

Note: They are useful in the chronic treatment of Glaucoma, but not used in acute attacks of glaucoma.

Adverse effects of Acetazolamide:

- **Sedation**
- **Drowsiness.**
- **Hypersensitivity reaction.**
- **Hyperchloremia.**
- **Hyponatremia.**
- **Hypokalemia (potassium loss).**
- **Hyperchloremic Metabolic Acidosis** (due to Acidosis predictably results from chronic reduction of body HCO3– stores by carbonic anhydrase inhibitors)
- **Renal stone formation.**(Phosphaturia and hypercalciuria occur during the bicarbonaturic response to inhibitors of carbonic anhydrase, which may then lead to formation of stones)

Note: Potassium wasting can occur because Na+ presented to the collecting tubule is partially reabsorbed, increasing the lumen-negative electrical potential in that segment and enhancing K+ secretion.

Dorzolamide, Brinzolamide:

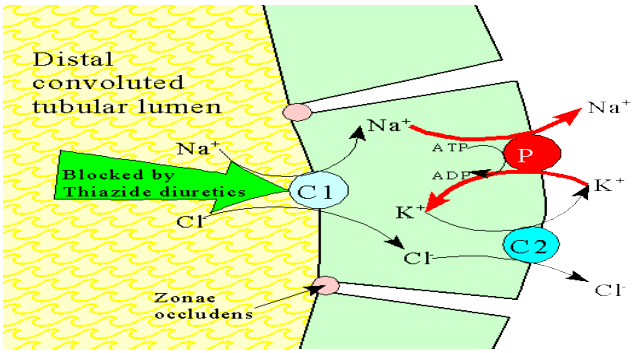
- Used for treatment of glaucoma (applied topically to eye).
- Have no diuretic or systemic side effects.

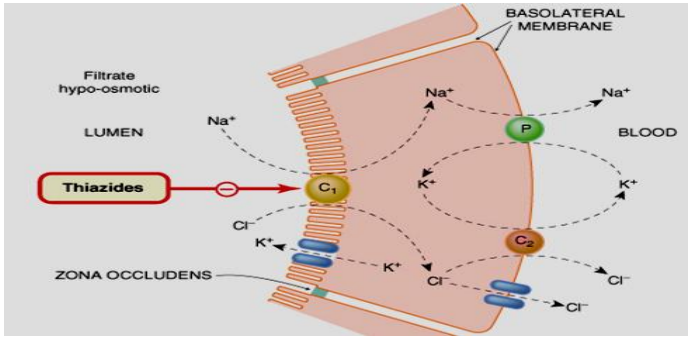
3- THIAZIDES DIURETICS

Examples: **Hydrochlorothiazide**(prototype) – **Indapamide**(Is a lipid soluble non- thiazide diuretic that have long duration of action. At low doses shows significant anti-hypertensive effect with minimal diuresis) – **Metolazone**(retain significant carbonic anhydrase inhibitory activity, which means it act on PCT)

MOA:

They work by inhibiting reabsorption of sodium (Na+) and chloride (Cl−) ions from the luminal membrane of the distal convoluted tubules in the kidneys**.**
They also cause loss of potassium and an increase in serum uric acid (Hypokalemia and hyperuricemia).
Efficacy is Moderate: 5% natriuresis.**(Natriuresis is the process of excretion of sodium in the urine via action of the kidneys).**





Pharmacokinetics:

- Slow onset, given orally, long duration of action (40h).
- are secreted by organic acid secretory system of the kidney (may interfere with uric acid secretion and cause hyperuricemia).

Pharmacological effects:

For your information: Thiazides lower urinary calcium excretion, making them useful in preventing calcium-containing kidney stones. This effect is associated with positive calcium balance and is associated with an increase in bone mineral density and reductions in fracture rates attributable to osteoporosis.

- **Increase NaCl (salt) excretion in the urine.(**this produces a hyperosmolar urine)
- **Increase K (potassium) excretion in the urine and that leads to Hypokalemia**.(since they increase NA excretion at the DCT more K+ is going to be exchanged with NA+)
- **Increase Mg (magnesium) excretion in the urine.**
- **Decrease Ca (calcium) excretion in the urine** and that in some cases leads to increase in the re-absorption of Ca leading to Hypercalcemia.
- **Increase uric acid in the blood (hyperuricemia).**
- **Increase glucose in the blood (hyperglycemia).**
- **Increase in the volume of the urine.**

Note: Thiazides mildly impair the release of insulin. Patients suffering from diabetes mellitus may become hyperglycemic due to the s impaired release of insulin and tissue uptake of glucose

Uses:

1. **Drug of choice for essential hypertension (cheap-well tolerated).(Hydrochlorthiazide; Indapamide)**

Explanation : When administered thiazides first lower blood pressure by causing diuresis, a fall in plasma volume and a reduction in cardiac output. However, after chronic (3 to 7) use of thiazides cause a reduction in blood pressure by lowering peripheral resistance (i.e. vasodilation).

2. **Treatment of mild heart failure** (to reduce extracellular volume).
3. **Severe edema of cirrhosis, Refractory Edema together with the Loop diuretics.** (Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis). **(E.g. Metolazone).**
4. **Nephrolithiasis with or without hypercalciuria :** (to increase calcium re-absorption and decrease renal calcium stone).

Nephrolithiasis : the process of forming a kidney stone.
Hypercalciuria : excessive urinary calcium excretion.

5. **Nephrogenic diabetes insipidus:** (decrease blood volume and GFR).

Note: Diabetes insipidus is due to deficient production of ADH (neurogenic or central diabetes insipidus) or inadequate responsiveness to ADH (nephrogenic diabetes insipidus). Administration of supplementary ADH or one of its analogs is only effective in central diabetes insipidus. Thiazide diuretics can reduce polyuria and polydipsia (excessive thirst) in both types of diabetes insipidus. This effect is mediated through plasma volume reduction with a fall in glomerular filtration rate, and enhanced proximal reabsorption of NaCl and water, and decreased delivery of fluid to the downstream diluting segments. (So thiazides enhances ADH activity)

Adverse Effects:

- **Fluid and electrolyte imbalance.**
- **Hypokalemia** (Potassium depletion).
- **Hyponatremia** (Low Na in the blood) It is due to a combination of hypovolemia-induced elevation of ADH, reduction in the diluting capacity of the kidney, and increased thirst. It can be prevented by reducing the dose of the drug or limiting water intake.
- **Hypovolemia** (volume depletion)**.**

- **Metabolic alkalosis .**
- **Hyperuricaemia might lead to gout.** (High uric acid in the blood)
- **Hypercalcemia** (High Ca in the blood due to increased PTH reabsorption of Ca)**.**
- **Hyperglycaemia** (High glucose in the blood)**.**
- **Hyperlipidemia** (High lipid in the blood, and after prolonged the lipid level is back to normal)**.**

4- LOOP DIURETICS (High Ceiling diuretics)

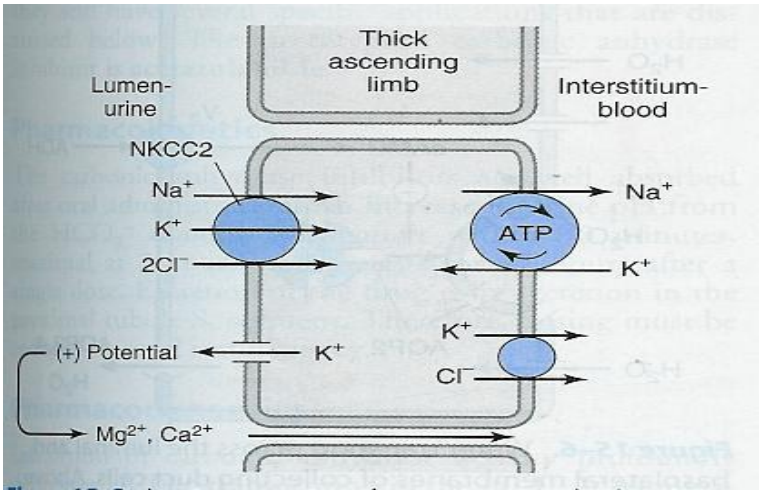
Examples : **Furosemide - torsemide - Bumetanide - Ethcrynic acid** .

MOA:

The effect is rapid, intense, and brief (high-ceiling diuresis).
They inhibit Na+/K+/2Cl– cotransport in the luminal membrane of the thick ascending limb of Henle's loop . As a result, these electrolytes, together with water, are excreted in larger amounts. Excretion of Ca2+ and Mg2+ also increases.
Also, they have potent pulmonary vasodilating effects (via PGs).
Efficacy is High : 25-30% natriuresis .

Pharmacokinetics :

- **Given orally or I. V.** (for your information: when given orally, a strong diuresis occurs within 1 h but persists for only about 4 h)
- **Has fast onset of action (<u>suitable for emergency</u>)**
- **Have short duration of action.**
- **Excreted by active tubular secretion of weak acids into urine (*compete with uric acid for renal secretory system)*.**



Pharmacological effects:

- **↑ urinary excretion of Na+ , K,+Ca++ and Mg ++.**
- **↑ urine volume.**
- **↑ renal blood flow.**

For your information:
While thiazide diuretics are more effective in patients with normal kidney function, loop diuretics are more effective in patients with impaired kidney function

Uses:

- **Acute pulmonary edema.**
- **Congestive heart failure.**
- **Acute hyperkalaemia.**
- **Acute hypercalcemia.**
- **Acute renal failure.(Given IV)**

Note: Loop agents can increase the rate of urine flow and enhance K+ excretion in acute renal failure. However, they do not shorten the duration of renal failure. If a large pigment load has precipitated acute renal failure (or threatens to), loop agents may help flush out intratubular casts and ameliorate intratubular obstruction.

<u>Further Explanation</u> : When treating heart failure with diuretics, care must be taken to not unload too much volume because this can depress cardiac output. Most patients in heart failure are prescribed a loop diuretic because they are more effective in unloading sodium and water than thiazide diuretics.

- **Hypokalemia** (dietary K supplementation or K-sparing diuretics).
- **Metabolic alkalosis.**
- **Acute Hypovolemia**
- **Hyponatraemia.**
- **Hypomagnesaemia**
- **Hyperuricemia** (increase gouty attack).
- **Ototoxicity (**usually with large parenteral doses and rapid administration and in renal impairment or using them with aminoglycosides)**.**

Note: Loop diuretics cause hypokalemic metabolic alkalosis by inhibiting salt reabsorption in the thick ascending loop, this increases delivery to the collecting duct. Increased delivery leads to increased secretion of K+ and H+.

Note: Except for ethacrynic acid, the loop diuretics are sulfonamides that may lead to **hypersensitivity**

What are the differences between furosemide and torsemide?
Simply oral torsemide considers as i.v of furesemide. Because only 50% of furesemide is absorped in the intestine.
What are the advantages of bumetanide (Bumex) over that of furosemide?
Potent (40 times) with very fast onset and short duration.
How do thiazides differ from furosemide in their side effects?
No ototoxicity

5- POTASSIUM-SPARING DIURETICS

A) Direct antagonist of mineralocorticoid receptors (Aldosterone Antagonists e.g. **spironolactone** (AldactoneR) or
B) Indirect via inhibition of Na+ influx in luminal membrane (e.g. **Triametrene, Amiloride**)

Note:
All diuretic drugs cause hypokalemia except (k-sparing diuretic eg: Spironolactone causes K retention-hyperkalimia.

PHARMACOKINETICS:

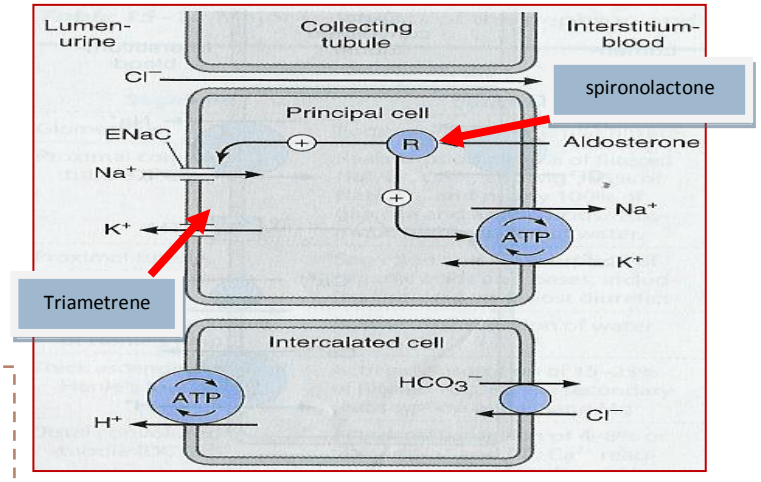
- — Spironolactone
- — Rapidly absorbed orally
- — Has slow onset of action, takes several days
- — Converted into active metabolite
- — Induces CYT P450

Note:
- It's a prodrug needs to be converted to give its action.
- it induces CYT p450 drug –drug interaction (modulate the other drug by inducing it's metabolism and reducing its effect)

MOA

Aldosterone antagonist (spironolactone)	Triametrene, Amiloride **(indirect antagonism)**
• **Spironolactone is a synthetic steroid that acts as a competitive antagonist to aldosterone at its cytoplasmic receptors** • **—Act in collecting tubules and ducts by inhibiting Na reabsorption and K & H secretion (K-sparing effect).**	Do not block the aldosterone receptor but instead directly **interfere with Na+ entry** through the epithelial sodium ion channels (ENaC) in the apical membrane of the collecting tubule. **(Block the Na/K exchange site in the luminal membrane)**

Note:
Aldosterone is mineral steroidal hormone which lead to retention of Na and water when it's act on the collecting tubules and excrete K,H
So
these k-sparring diuretic drug will block aldosterone receptor and inhibit it's affect causing Na execration and H,K reabsorption.



Note: Using any type of these sub classes would:
- Increase urinary Na excretion
- Decrease urinary K excretion (Hyperkalemia)
- Decrease H secretion (acidosis)

THERAPEUTIC USES

- Drug of choice for patients with **hepatic cirrhosis**.(Since hepatic cirrhosis leads to secondary hyperaldosteronism)
- **In mineralocorticoid hypersecretion** (primary hyperaldosteronism) e.g. Conn's syndrome
- **Secondary hyperaldosteronism:** CHF, hepatic cirrhosis, nephrotic syndrome
- In treatment of **hypertension** (combined with thiazide or loop diuretics to **correct for hypokalemia**).

- Addison's disease (Primarily Adrenal Insufficiency). Only Triametrene or Amiloride are used.
- **Hirsutism** (the presence of coarse pigmented hair on the face, chest, upper back, or abdomen in a female as a result of hyperandrogenism (excessive production of androgen). **Spironolactone is used since it has Anti-Androgenic effects.**

Note: -liver is important to synthesize proteins, so when it's damaged the serum proteins will be low so that will cause edema because of the decrease of oncotic pressure.
-Liver also plays a role in inactivating hormones like Aldosterone (Secondary hyperaldosteronism)
So in the body there is large ECV especially in the abdomen (ascites).

Note: Conn's syndrome is a disease of the adrenal glands involving excess production of mineral steroid (aldosterone) and causes hypertension this drug is effective because it will blocks the aldosterone R then it will decrease serum aldosterone level.

Note:
K –SPARING DIURETIC is not the first choice in the treatment of Hypertension but we combine them with loop or thiazide diuretic to increase the k level. (Loop or thiazide diuretics reduce K+ levels in our body)
So remember that:
First choice in treatment of essential hypertension is thiazide because it's (cheep, well tolerated-minimal gastric upset)
If there is no response (combined with B-blocker, which decreases renin release, so it's preferably not to be used with K sparing diuretics).

Note: in treatment Addison's disease only Triametrene or Amiloride are effective. Since Do not block the aldosterone receptor but instead directly interfere with Na+ entry. (Does not depend on the presence on the presence of Aldosterone)

Adverse Effects

- **Antiandrognic effects** (e.g. gynecomastia (Disease which characterized by breast enlargement) in men, impotence (impairment of sexual function),and menstrual period changes in female with **spironolactone.**
- **GIT upset and peptic ulcer**(give with food)
- **Hyperchloremic metabolic acidosis** (because the increase of H)
- **Hyperkalaemia.** (Complication is greatly increased by renal disease (in which maximal K+ excretion may be reduced) or by the use of other drugs that reduce renin (blockers, NSAIDs) or angiotensin II activity (angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors).
- **Kidney Stones only with Triamterene** (Triamterene is only slightly soluble and may precipitate in the urine, causing kidney stones.)

Note: Spironolactone is a synthetic steroid so it competes with the steroidal substances on binding in their receptor (causes disturbance in the level of sexual hormones (testosterone and estrogen).

Contraindications:—

- **Hyperkalemia:** as in chronic renal failure, K+ supplementation, b-blockers or ACE inhibitors.
- **Patients with liver disease**, dose adjustment is needed.(because this is the site of metabolism of drug)

Note: Using ACE inhibitors, B-blockers , and K+ sparing diuretics would lead excessive hyperkalemia, this leads to Cardiac arrest.

Changes in Urinary Electrolyte Patterns and Body pH in Response to Diuretic Drugs.

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

Summary of Therapeutic uses of diuretics

1-In hypertension:

- Number ONE in HTN is **thiazide diuretics .**
- If the patient is not responding to thiazides then we combine **B-blockers** (Decreases renin) with it.
- In presence of renal failure (decreased GFR) loop diuretics are used.

2-In congestive heart failure (CHF):

- **Thiazide diuretics** are used in mild CHF with well-preserved renal function.
- **Loop diurteics** are used in sever CHF especially when GFR is lowered.
- We may also use K sparing diuretics to suppress the secondary hyperaldosteronism, and to treat hypokalemia induced by Loop diuretics and Thiazide diuretics

3- In edema:

- In mild edema **thiazide** diuretics are used.
- In Pulmonary edema **loop diuretic** are used.
- In Hepatic cirrhosis with ascites **potassium sparing diuretics (ex:Spironolactone**) are used.
- In sever hepatic refractory edema **thiazide and loop diuretics** are used.

4- Hypercalcemia:

- **Loop diuretics** are used since they promote calcium excretion.

5- Diabetes Insipidus:

Thiazides are use since they enhances ADH activity by reducing polyuria and polydipsia.