# Pharmacology Team

## Diuretics

"Our notes are in Blue  "

### Made By

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Special thanx to Badra'a 

# Diuretics

- **Diuretics : drugs that increase urine volume.**

**Natriuretics: drugs that increase urinary excretion of sodium.**
**(Natriuretics will result in diuretic effect because when u increase Na excretion that increase water excretion )**
- **Increased urinary sodium excretion result in increased water excretion.**

**الملح يجر معه الماء, in other words: water follows solutes –passively-**

## DIURETICS
**are classified into**

- **Carbonic Anhydrase (CA) Inhibitors** ( PCT)
- **Loop Diuretics** ( TAL)
- **Thiazides** (DCT)
- **Potassium-Sparing Diuretics** (CCT)
- **Osmotic Diuretics** ( D loop)

## *1- CARBONIC ANHYDRASE IHIBITORS*
**ACETAZOLAMIDE**

### *Chemistry:*

**Sulphonamide derivative** ( acidic character )

### *Mechanism of action:*
**Inhibits carbonic anhydrase enzyme in PCT thus interferes with $NaHCO_3$ reabsorption.**

### *Pharmacodynamics:*

- **Increase excretion of bicarbonate, sodium, potassium "alkaline diuresis"** ( bicarbonate is alkaline , it excreted in urine so the urine will be the same, opposite to blood which will be acidosis ) *Always keep in mind, **if the urine pH is acidosis, blood pH is alkaline**, and vice versa ;)*
- **Metabolic acidosis.**
- **Phosphate excretion is increased** ( unknown mechanism )
- **Weak diuretics.** Because it depends on inhibition of $HCO_3$ **( the most effective diuretic is LOOOOOOP DUIERTICS )**
- **Decreases after several days (*self-limiting as the blood bicarbonate falls* ).**

## ***Pharmacokinetics:***

•**given orally or parenterally. ( most common is orally )**

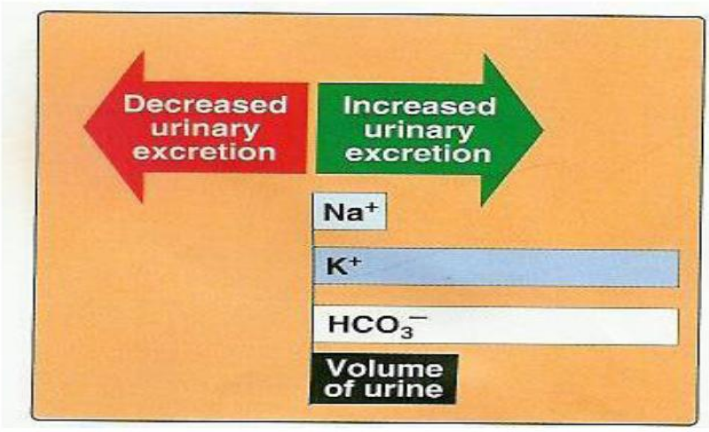
•**Onset of action is rapid (30 min).**

•**Duration of action12 h.**

•**Excreted by active secreted in proximal convoluted tubules**
**(active: needs energy – ATP molecules. passive: no need for energy or a carrier, it happens due to difference in concentration & pressure gradient)**

•***(dose should be reduced in renal insufficiency) (coz it's excreted by the kidneys)***

**PHARMACODYNAMICS OF CA INHIBITORS:**




## ***Therapeutic uses:***

•**Open angle glaucoma (*reduce formation of aqueous humor by blocking carbonic anhydrase in ciliary body of eye*).**

**Glaucoma** : increase intraocular pressure of aqueous humor

•**Epilepsy *(decrease cerebrospinal fluid –CSF)***
CA : in kidney ( drug act here has low diuretic effect ) , eye (drug decrease secretion of aqueous humor so treat glaucoma ) , brain ( drug decrease secretion of CSF treat epilepsy )
•**Urinary alkalinization to enhance excretion of uric acid and cystine which are soluble in alkaline urine**.

(normally ph in urine 5.3 , acidic substance best execrated in alkaline urine and the opposite is true )

•**In prophylaxis of acute mountain sickness (*to decrease CSF and pH of brain).* Given five days before the ascent .**

•**Acute mountain sickness is characterized by nausea, headache, weakness, pulmonary and cerebral edema.**

•**Hyperphosphatemia** ( cause it increase secretion of phosphate ) → ?

•**Metabolic alkalosis** ( cause the drug make bl. Acidosis ) → ?

## ***Adverse effects:***

**•Metabolic acidosis.**

**•Renal stones (calcium phosphate)** ( result from increase secretion of phosphate & make the urine alkaline cause Ca can't dissolute except in acidic urine )

**•Hypokalemia (potassium loss).**

**•Drowsiness, Paresthesia** تنميل

***All diuretic cause hypoookalemia except :::: K sparing***

## ***Contraindication***

**•liver cirrhosis: it decrease $NH_4$ excretion & hepatic encephalopathy**

Liver cirrhosis is disease which is characterize by elevated amount of ammonia (alkaline ) and urine become alkaline by CA inhibitor so NH4 can't execrated which result in hepatic encephalopathy.

**•Renal failure: it accumulates to produce nervous system toxicity**

## ***NEW CARBONIC ANHYDRASE INHIBITORS***

**o Dorzolamide**

**•Topically active.** ( to avoid all the side effects )

**•Reduce introcular pressure equal to oral agents.**

**•Have no diuretic or systemic metabolic effects.**

***-amide ::: CA inhibitor***

## 2- Osmotic Diuretics (e.g.: Mannitol)

**MOA:**

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

- Hydrophilic drug means poorly absorbed only given IV
- Not metabolize ; excreted unchanged ( glomerouls filtration no secretion: ***no reabsorption*** = so increase osmotic pressure of ( lumen ) urine leads to the retention of water in lumen = excreted in urine & little effect of Na excretion )
- ACTs on : proximal tubules & mainly Descending loop of henle .

**PK:** Given i.v Can it be given orally?

**Indications:**

- to decrease intracranial pressure in neurological condition ( cerebral edema )
- to decrease intraocular pressure in acute glaucoma
- to maintain high urine flow in acute renal failure during shock. ( make the kidney function more GFR more urine )

**Adverse Reactions:**

- Extracellular water expansion ( by osmotic make water go from intracellular to extracellular ) and dehydration
- Hypernatremia due to loss more water than sodium

## 3- Diuretics Acting on the Thick Ascending Loop of Henle (loop diuretics) High ceiling

► e.g. Furosemide (Lasix$^{R}$), Torsemide, Bumetanide (Burex$^{R}$), Ethacrynic acid.

1) **Mechanism of Action** : Simply inhibit the coupled NA/K/2Cl transport inthe loop of Henle. Also, they have potent pulmonary vasodilating effects (via PGs).

- **Ascending loop of henle impermeable to water, only electrolyte**
- Loop diuretic is the Most effective cause it acts on the segment where the most(25%-30%) Nacl reabsorbed opposite to thiazide which work on DCT just 5%
- Although in PCT there are absorption of Nacl but there is no drug inhibit it.

- Also Mg , Ca reabsorption paracellular is inhibited by loop diuretic so there is hypocalciema opposite to thiazide where there is hypercalciema )

***ACTIONS***:

Hypovolumia ( increase urine volume )
Hyponatriema ( increase Na in urine )
Hypokalemia
Hypocalciema ( hypercalciurea)
Hypomagnesemia
Increase renal bl flow & reduce renal vascular resistance= later can cause decrease BP

What are the compensatory mechanisms?
**Why furosemide is a better diuretic than acetazolamide despite the fact that only 25% of the reabsorption occurs at the ascending loop of Henle?**

**•A: Because (A) works on PCT, and thus it can be easily compensated by the pumps later on in the nephron, while loop diuretics can have the majority of effects on water and sodium depletion. ((F) is not affected by compensatory mechanisms as Acetazolamide does)**

## Side effects:.

**Ototoxicity;** loss of hearing
**Hypokalemic metabolic alkalalosis;**
**Hypocalcemia**
**hypomagnesemia** especially in old patient **;**
**hypochloremia;**
**Hypovolemia;**
**hyperuricemia (How?);**
**hypersensitivity reactions.** Due to sulphonamide

- Hyperuricemia : cause it excreted by (active tubular secretion) Organic acid secretory system same as uric acid so the drug secreted and the uric acid stay in bl. So it is Contraindicated in gouty patient.

- Hyperuricema is also a side effect with thiazide diuretic .
- Usually ( hypokalemia with metabolic alkalosis & hyperkalemia with metabolic acidosis ; WHY**??!! Thazide which work on DCT & loop diuretic works on ATL cause more excretion of Na & K when more Na go to CT that enhance reabsorption of Na & excretion of K & H+ result in metabolic alkalosis )**

- To avoid Hypovolumia tell patient to drink water

- To avoid hypokalemia take K supplementation & or take with loop diuretic K sparing .

- Usually K sparing is given with thiazide; or loop diuretic .

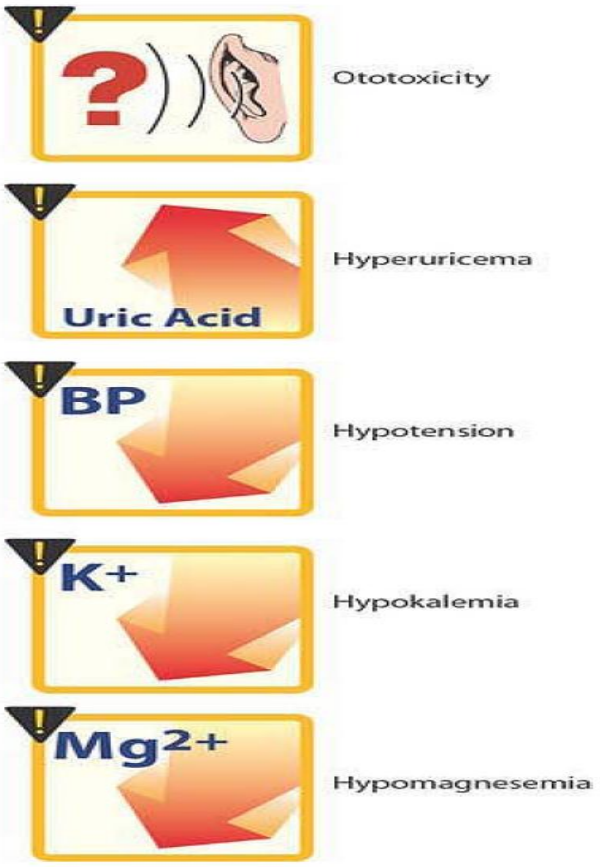



Figure 22.7 Summary of some adverse effects c‹

# Therapeutic Uses

**a) Edema (Like What?) → acute pulmonary edema of HF**
**b) Acute renal failure**
**c) Hyperkalemia**
**d) Hypercalcemia**
**e) CHF**

( most drug use as diuretic are thiazide & loop ; loop diuretic in emergency = rapid onset of action + can take IV & thiazide as antihypertensive )

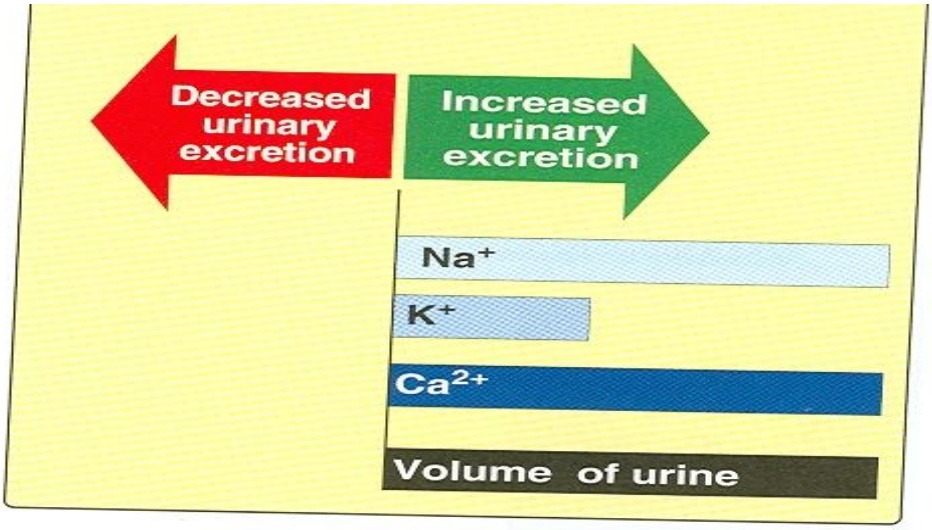



**Figure 22.6**
Relative changes in the composition of urine induced by loop diuretics.

## 3- THIAZIDES DIURETICS

### Chemistry:

- **are sulphonamide derivatives.** ( acidic character )
- **Chlorothiazide, hydrochlorothiazide**
- **Chlorthalidone, indapamide are *thiazide-like diuretics*.**

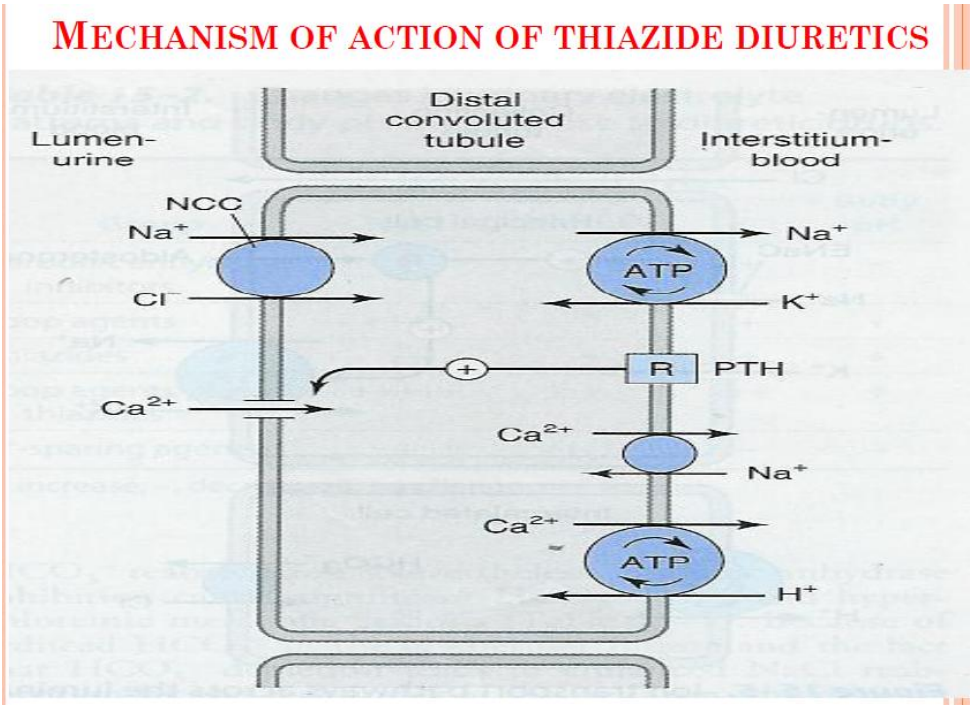
### Pharmacokinetics:

- **given orally.**
- **Chlorothiazide-injection available.**
- **Chlorothiazide is the least potent**. ( require high dose )
- **All have slow of onset. ( not used in emergency opposite to loop diuretic )**
- **All have long duration of action (40 h)**
- **All are secreted by active tubular secretion (organic acid secretory system) *may interfere with uric acid secretion and cause hyperuricemia*.**

( diuretic go to secretion by organic acid secretory system and let the uric acid stay in body cause hyperuricema ; so be attention with gouty patient)

### MECHANISM OF ACTION

- **Affect distal convoluted tubules (DCT)**
- **Decreases NaCl reabsorption via inhibition of Na/Cl co-transporter on the luminal membrane of DCT.**



## ***PHARMACODYNAMICS:***

**•Increased NaCl excretion in urine**

**•loss of K in urine (Hypokalemia)**

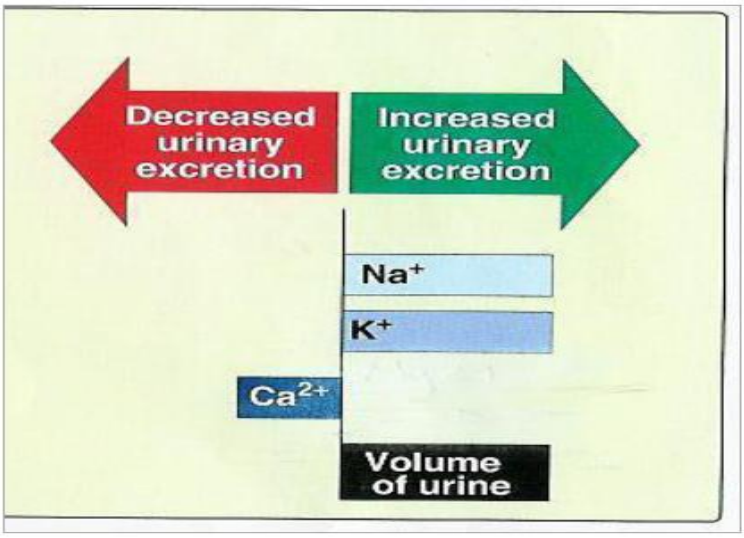
**•loss of magnesium in urine** ( unknown mechanism )

**•Increase calcium reabsorption** ( because the drug act mainly on Nacl not Ca )

**•Mild vasodilator action.** ( hypotensive action )

**•Hyperglycemia: impaired release of insulin, decreased tissue utilization of glucose.**

## EFFECTS OF THIAZIDE DIURETICS




## ***THERAPEUTIC USES:***

**omost widely used**

**•Essential hypertension** ***(cheap-well tolerated)*** ( vasodilatation & decrease bl . volume)

**•Heart Failure** ***(to reduce extracellular volume)***

**•Severe edema of cirrhosis. ( BUT drug of choice in cirrhosis is K sparing)**

**•Nephrolithiasis or hypercalciuria** ***(to prevent kidney stone formation of calcium)***

**•Nephrogenic diabetes insipidus** ***(decrease blood volume and GFR)***

diabetes insipidus : always thirst and needs much amount of water which will excreted)

# ADVERS EEFFECTS:

•**Fluid and electrolyte imbalance**

•**Hypokalemia (Potassium depletion)**

•**Hyponatremia**

•**Hypovolemia (volume depletion)**

•**Metabolic alkalosis.**

•**Hyperuricaemia (gout)**

•**Hypercalcemia**

•**Hyperglycaemia:**

•**Hyperlipidemia: increased plasma cholesterol.**

•**Hypersensitivity**

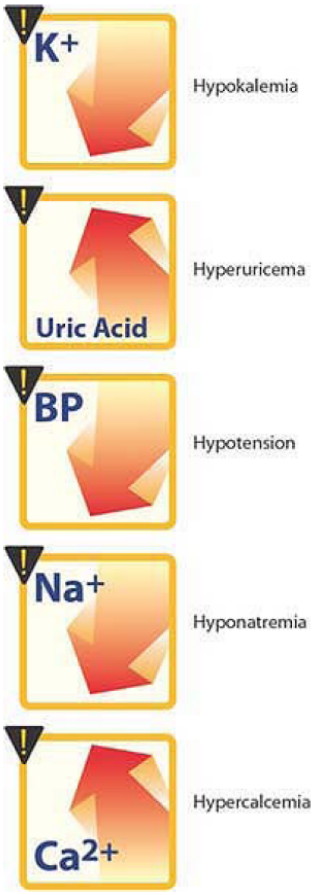



Figure 22.5 Summary of some adverse effects commonly observed with thiazide diuretics.

# Contraindications:

•**Liver cirrhosis encephalopathy.**

•**Borderline renal failure.**

## 5- Diuretics that inhibit transport in the Cortical Collecting Tubule (e.g. potassium sparing diuretics).

► **Why does the natriuretic activity of this group has limited range (less than 5%) but d. clinically very important.?**

► **Classification of Potassium Sparing Diuretics:**

A) **Direct** antagonist of mineralocorticoid receptors (Aldosterone Antagonists e.g spironolactone (Aldactone$^{R}$)

B) **Indirect** via inhibition of $Na^+$ flux in luminal membrane (e.g. Triametrene, Amiloride)

## ***Pharmacokinetics***:

- Orally
- Rapid absorbed
- Slow onset of action ( takes several days )
- Converted to active metabolite
- Metabolize in liver
- Induce CYT P450

**Spironolactone (Aldactone$^{R}$)**

► **Synthetic steroids acts as competitive antagonist of adlosterone with slow onset of action.**

► **MOA: Aldosterone enhance $K^+$ secretion by increasing $Na^+/K^+$ ATPase and the same for $H^+$ . Therefore, Spironolactone binds to mineralocorticoid receptors this leads to ???**

- In CT reabsorption of Na , excrete K &H+
- K sparing inhibit **Aldosterone** to produce it effect SO Na excreted in urine & K , H+ reabsorbed .
- Hyperkelemia & metabolic acidosis ( H+ is reabsorbed )

Hyponetremia

**Clinical Uses of $K^+$ sparing Diuretics**:

- As diuretics in states of primary mineralocorticoid excess (e.g. Conn's syndrome; Ectopic ACTH production) or
  to secondary aldosteronism from CHF
  ; Hepatic Cirrhosis
  , Nephrotic syndrome

- Mineralocorticoid hypersecretion ( primary) ; hyperaldosternoism ( conn's syndrome)
- Sometimes hyperaldosternoism ( secondary ) due to other condition like CHF , hepatic cirrhosis, Nephrotic syndrome
- SO the drug of choice to treat hepatic cirrhosis is K sparing

    - To overcome the hypokalemic action of diuretics ( like loop diuretic & thiazide )
    - Hirsutism How?

## Side effects:

- ► Hyperkalemia (increases ) some times useful?
- ► Hyperchloremic metabolic acidosis
- ► Antiandrognic effects (e.g. gynecomastia, impotence) with spironolactone ,
- ► kidney stone with Triametrene

(Aldosterone is similar to testosterone so when you close the effect of Aldosterone it can close effect of testosterone that may cause sexual dysfunction in male like impotence: Erectile dysfunction ; gynecomastia : breast enlargement In male)

- It can also cause GIT upset.

► **Diuretics Combination preparations**

**Examples**:

**Dyazide$^{R}$ = Triametrene 50 mg + Hydrochlorothiazide HCT 25 mg**
**Aldactazide$^{R}$= Spironolactone 25 mg + HCT 25 mg**

**Moduretic$^{R}$ = Amiloride 5 mg + HCT 50 mg**

- ► Why?
- ► Note : thiazides should always be there

► **Contraindications**: Oral K administration

Not given to people who have

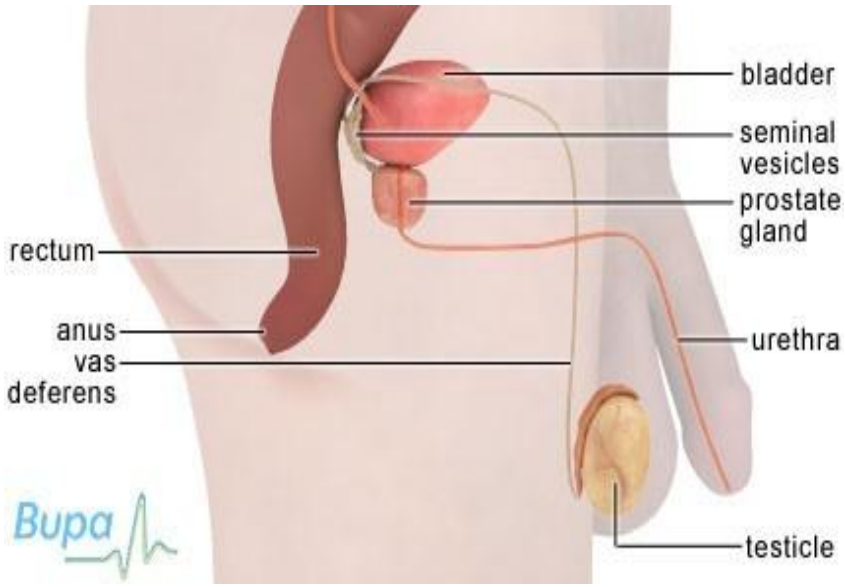
- hyperkelmeia like Chronic Renal Failure ,taking K supplementation
- liver disease because this drug is metabolize in liver

**Table 15–2.** Electrolyte changes produced by diuretic drugs.

| Drug Group | Urine | | | Body pH |
|---|---|---|---|---|
| | NaCl | $NaHCO_3$ | $K^+$ | |
| Carbonic anhydrase inhibitors | ↑ | ↑↑↑ | ↑ | Acidosis |
| Loop diuretics | ↑↑↑↑ | — | ↑ | Alkalosis |
| Thiazides | ↑↑ | — | ↑ | Alkalosis |
| Potassium-sparing diuretics | ↑ | — | ↓ | Acidosis |

► **What is the prostate?**

The prostate is a gland about the size of a walnut, that is only present in men. It's located just below the bladder and surrounds the urethra, the tube that carries urine from your bladder and out through your penis. One of the main functions of the prostate gland is to produce prostatic fluid, one of the components of semen.

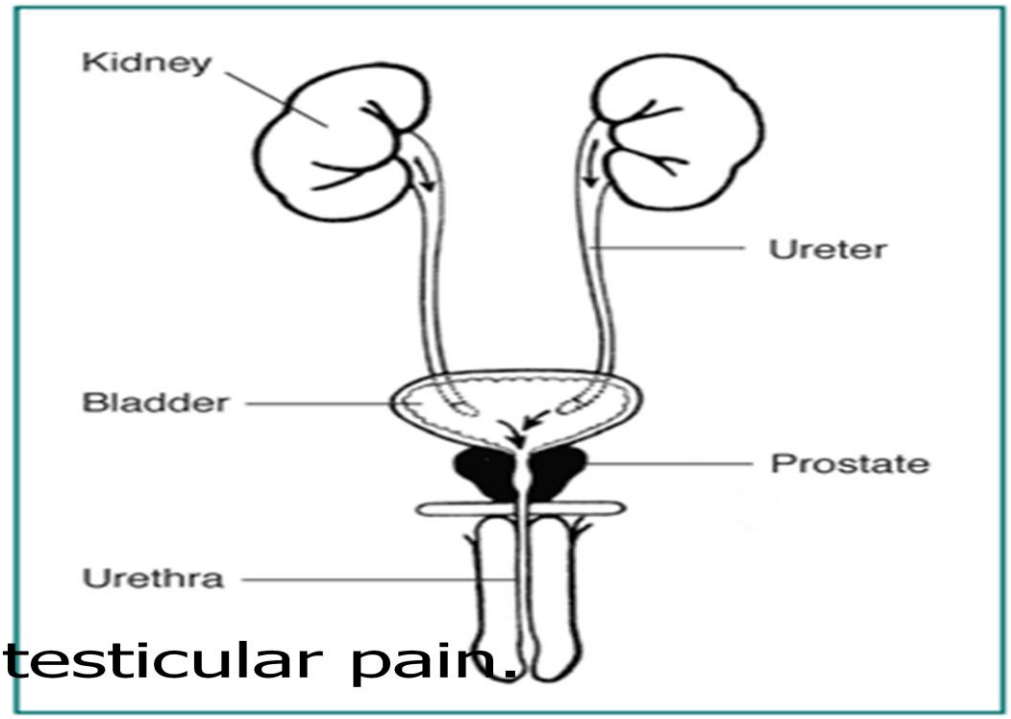


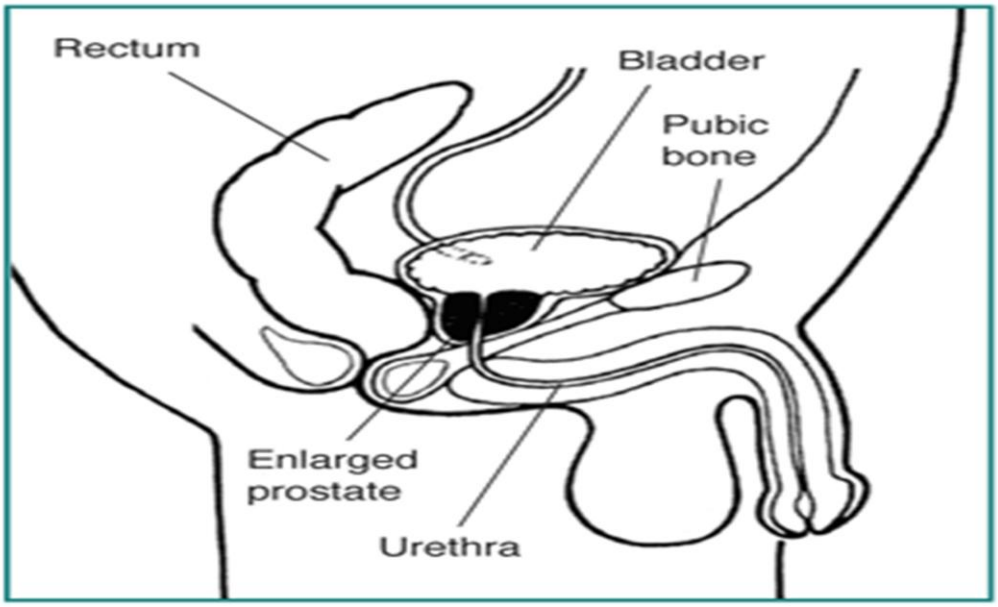

**What is BPH (Benign Prostate Hypertrophy)?**

Refers to the benign increase in size of the prostate in middle-aged and elderly men

Signs and symptoms

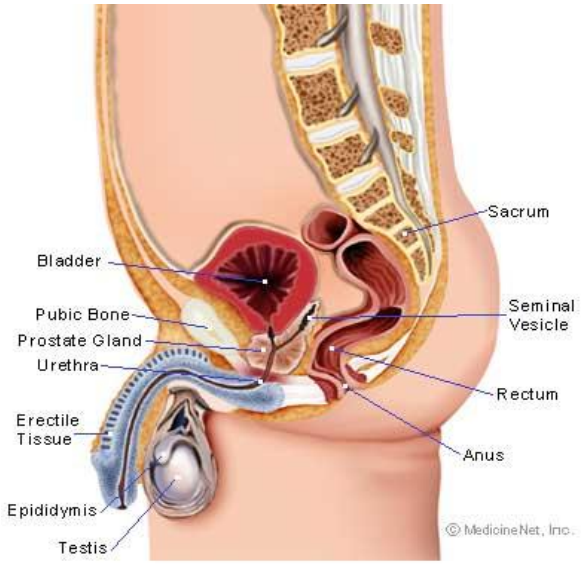
- ► difficulty in starting to pass urine
- ► a weak flow of urine that sometimes starts and stops
- ► dribbling of urine before and after urinating
- ► a frequent or urgent




► What are the drugs that worsen BPH

- Ant icholinergic drugs (Atropine and similar drugs) as side effect can cause urine retention by relaxation of urinary bladder
- Alpha-adrenergic agonists (e.g.; Ephedrine: pseudoephedrine) produce contraction of SM so decrease urine flow




- **Can you suggest drugs that may be used for treatment of BPH?**

  - Alpha1A-adrenergic Blockers (Antagonists) (Tamsulisin (Omnic) Alfuzosin, and Silodosin.

MOA:
Tamsulosin is a selective $\alpha_1$ receptor antagonist that has preferential selectivity for the $\alpha_{1A}$ receptor in the prostate versus the $\alpha_{1B}$ receptor in the blood vessels. This leads to Relaxation (Widening) the sphincter of the bladder.

**Side Effects of alpha-adrenergic blockers:**
Postural hypotension at higher doses
Retrograde ejaculation

## 1) 5-Alpha-reductase inhibitors (Finasteride and Dutasteride)

**MOA:**
These medications inhibit 5a-reductase, which in turn inhibits production of **dihydrotestosterone ( a** hormone responsible for enlarging the prostate). Effects may take longer to appear than alpha blockers, but they persist for many years.

- **Side Effects of Finasteride**
  - impotence
  - gynecomastia (2.2%),
  - erectile dysfunction and
  - testicular pain

  .
- All these side effects are reversible upon discontinuation.

# Qs :

1. **What is the MOA CA inhibitor?**

Inhibit reabsorption of NaHCO3 which result in metabolic acidosis and make urine alkaline

2. **What is the uses of CA inhibitor ?**

It is weak as diuretic but we can use it in glaucoma & epilepsy& acute mountain sickness

3. **Where osmotic drug work ?**

PCT & D.l of henle they increase excretion of water

4. **How osmotic drug given ?**

BY IV and we can use it in acute renal failure

5. **What is MOA thiazide ?**

Inhibit reabsorption OF NaCl and doesn't effect on active reabsorption of Ca so it produce hypercalciemia.

6. **Thiazide is common use as?**

Antihypertensive drug : kidney stones because it is produce hypercalcemia so the Ca in bl. not in kidney.

7. **Hyperuricemia is seen with??!**

Thiazide & loop diuretic

8. **What is most effective drug as diuretic??!**

Loop diuretic

9. **What is the first choice drug to treat liver cirrhosis?**

K sparing diuretic

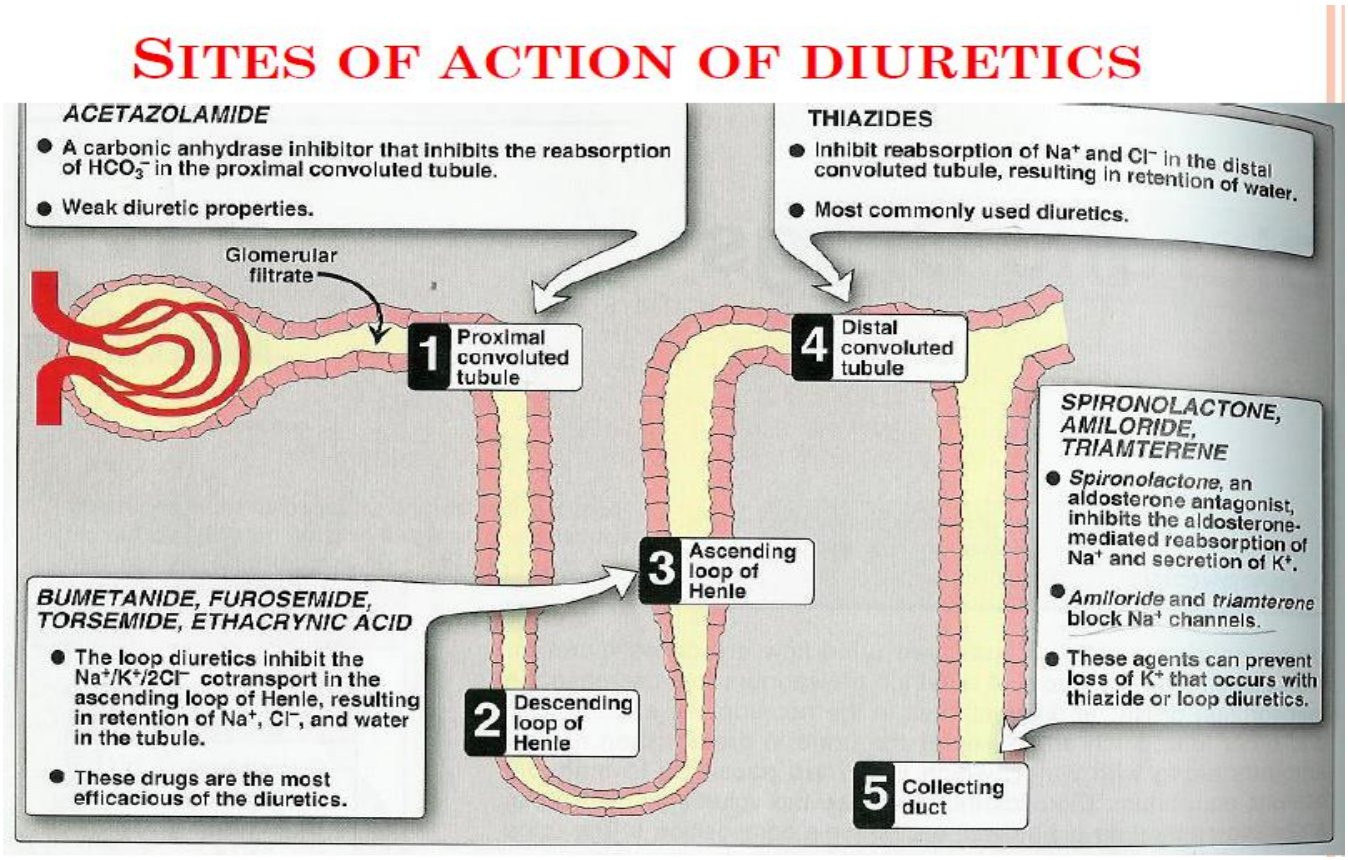
10. **One of the side effect of K sparing is ?**

gynecomastia, impotence

11. **What are the druge use in BPH?**

A1 blocker & 5-Alpha-reductase inhibitors which there effect persist for years.

# Revision




| Drug | Family |
|---|---|
| ACETAZOLAMIDE | CA inhibitor on PCT |
| Dorzolamide | CA inhibitor topically |
| Mannitol | Osmotic diuretic PCT &DLH |
| Furosemide (Lasix®), Torsemide, Bumetanide (Burex®), Ethacrynic acid | Loop diuretic ATL |
| Chlorothiazide, hydrochlorothiazide | Thiazide DCT |
| Chlorthalidone, indapamide | thiazide-like diuretics. |
| spironolactone (Aldactone®) | K sparing(Aldosterone Antagonists) CT |
| Triametrene, Amiloride | K sparing ( inhibit Na influx in luminal membrane ) CT |

## BPH

| | |
|---|---|
| Tamsulisin (Omnic) Alfuzosin, Silodosin. | Alpha1A-adrenergic Blockers (Antagonists) |
| (Finasteride Dutasteride) | 5-Alpha-reductase inhibitors |