Drugs used in treatment of Cardiovascular System

Diuretics

Dr Qutaiba Ghanim Karwi
Department of Pharmacology
College of Medicine
University of Diyala

Diuretics are act through two mechanism:

- **Renal**: through increasing the excretion of Na^+ and water.
- **Extra-renal**: that increase excretion of urine:

1. ↑ C.O. that lead to ↑ glomerular filteration.
2. ↓ in ADH release.
3. Mobilizing peripheral edema fluid.

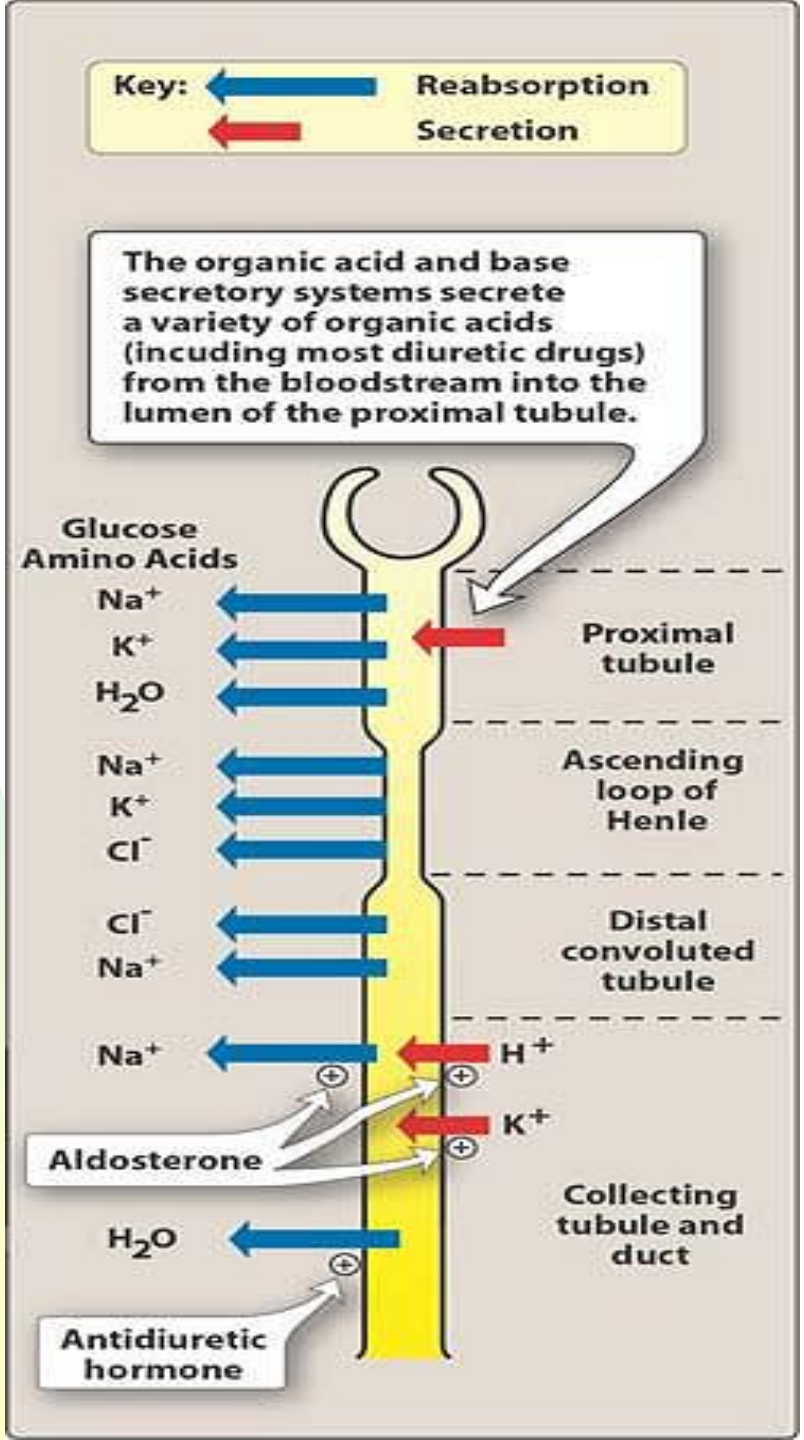
Division of Nephron:

1. ***Proximal convoluted tubule (PCT):*** 60-70% of the filtered Na^+, Cl^-, H_2O are reabsorbed activity in such rapidity that osmotic balance is kept between intraluminal and interstitial fluid.

2. ***Ascending Loop of Henle:*** there is active reabsorption of 20-30% of Na^+ and Cl^- with No water (Diluting Segment).

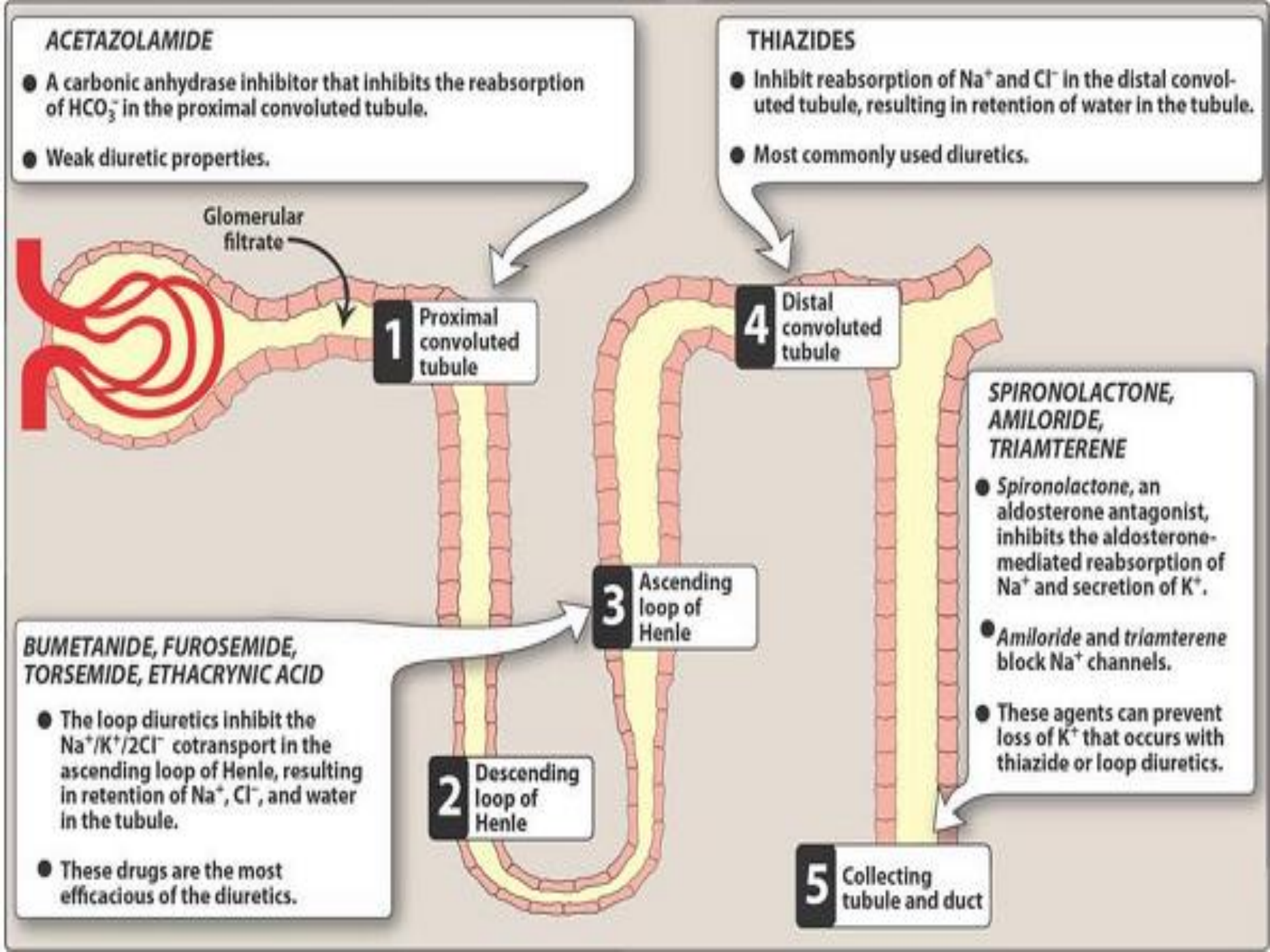
3. ***Distal Convoluted tubules (DCT):*** 5% of Na^+ is actively reabsorbed in exchange with K^+ and H^+ under Aldosterone influence.

4. ***Collecting duct:*** it is the site of ADH. If it is presence, this part become permeable to water and urine become hypertonic. If not, The urine become hypotonic.


Key:
Reabsorption
Secretion
The organic acid and base secretory systems secrete a variety of organic acids (incuding most diuretic drugs) from the bloodstream into the lumen of the proximal tubule.
Glucose
Amino Acids
Na+
K+
H2O
Proximal tubule
Na+
K+
Cl-
Ascending loop of Henle
Cl-
Na+
Distal convoluted tubule
Na+
H+
K+
Aldosterone
Collecting tubule and duct
H2O
Antidiuretic hormone

Group of Diuretics:

1. High Efficacy Diuretics (HED).
2. Moderate Efficacy Diuretics (MED).
3. Low Efficacy Diuretics (LED).


ACETAZOLAMIDE
A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
Weak diuretic properties.
THIAZIDES
Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
Most commonly used diuretics.
Glomerular filtrate
1 Proximal convoluted tubule
2 Descending loop of Henle
3 Ascending loop of Henle
4 Distal convoluted tubule
5 Collecting tubule and duct
BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID
The loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+, Cl^-, and water in the tubule.
These drugs are the most efficacious of the diuretics.
SPIRONOLACTONE, AMILORIDE, TRIAMTERENE
Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+.
Amiloride and triamterene block Na^+ channels.
These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.

High Efficacy Diuretics:

Furosemide, Ethacrynic a., Bumetanide, Piretanide and Torasemide

- HED can cause 5-25% of filtered Na+ to be excreted.
- They are called loop D. due to their action on ascending loop of Henle, also it has slight effect on proximal C.T.
- HED work even if the GER is below 10 ml/min in case of Oliquria. (normal GFR is 120ml/min).
- Their maximum diuresis:

Frusemide – Bumetanide, Etharcynic a is less than both.

Mechnism of Action:

- HED are act by inhibiting Na+ & Cl- reabsorption lead to excretion of both in urine which is usually accompanied with water and large amount of urine.
- K+ is also excreted lead to hypokalemia because of large amount of Na+ subjected to the distal CT where it has more chance to be exchange with K+.
- The onset of action of HED is within 2-10 min if given I.V. and 1 hr if given orally.

Indications of HED:

1. Acute pulmonary edema: but the relief occure before diuresis occurs, so this is an indicate on their effect on blood vessels.
2. Hypertension crisis.
3. All types of heart failure.
4. Chronic renal failure.
5. Refractory edema.
6. Nephrotic syndrome.
7. Oligouric state.
8. Hypercalcemia.
9. Forced alkaline diuresis to get rid of some drugs from body like salcylate and barbiturates

Side effects:

1. Metabolic alkalosis: might result as Cl- loss is relatively more than HCO3-.
2. Hyperuricemia: because the HED and uric acid have the same secretory mechanism on tubule.
3. Decrease CHO tolerance in diabetics and prediabetics, suger level increased with less extent than Thiazides.
4. Hypokalemia: HED produced hypokalemia less serious than that produced by MED because of their short duration of action in comparison with MED.
5. Might cause renal interstitial nephritis lead to reverible renal failure.
6. Deafness might be occure:
   - *Transient with Furosemide.*
   - *Infrequent with Bumetanide.*
7. *Permenant with Ethacrynic a.*
8. GIT disturbance.
9. Hypomagnesemia.
10. Hypotension.
11. Skin rash and parasthesia.

Route of Administration:

- **Furesemide and Bumetanide:** I.V., I.M. and orally.
- **Ethacrynic a.**: I.V. and orally.
- HED inhibit 15-20% of filterated load.

Moderate Efficacy Diuretics (MED)

Chlorthiazide, Hydrochlorthiazide, Chlorthalidone, Indapamide, Metolazone

- It has moderate uricouric effect (i.e. uric a. excretion activity).
- MED inhibit 5-10% of filterated load of Na+.
- MED doesn't work if GFR is below (20ml/min).
- MED site of action is Distal CT.
- They have similar qualitatively similar properties but they differ quantitatively and this is reflected on the doses used and their potency.

Mechanism of Action:

- The thiazide derivatives act mainly in the distal tubule to decrease the reabsorption of Na^+apparently by inhibition of a Na^+/Cl^- cotransporter on the luminal membrane of the distal convoluted tubule.

- They have a lesser effect in the proximal tubule. As a result, these drugs increase the concentration of Na^+ and Cl^- in the tubular fluid. The acid-base balance is not usually affected.

- Note: Because the site of action of the thiazide derivatives is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.

Therapeutical Indications:

- Chronic renal failure.
- Edema due to chronic hepatic disease.
- Hypertension.
- Hypocalcemia.(↓ Ca+ secretion)
- Nephrogenic diabetes insipidus: ↓volume of urine or substitute ADH).

Side Effects:

1. Hypokalemia: more serious than HED.
2. Hyperuricemia.
3. D.M. aggrevation, glucose in blood. They do so either by inhibiting insulin secretion or inhibiting glcose peripheral utilization.
4. Hypercalcemia.
5. Thrombocytopenic purpura.

Low Efficacy Diuretics (LED)

Amiloride, Eplerenone, Spironolactone, Triamterene

- They are called K-conserving or K-sparing.
- They lead to excrete 5% of filtrated Na+.
- The site of action is Collecting CT.

Spironolactone

- Spironolactone is a synthetic steroid that antagonizes aldosterone at intracellular cytoplasmic receptor sites. The spironolactone-receptor complex is inactive. That is, it prevents translocation of the receptor complex into the nucleus of the target cell; thus, it cannot bind to DNA. This results in a failure to produce proteins that are normally synthesized in response to aldosterone. These mediator proteins normally stimulate the Na^+/K^+-exchange sites of the collecting tubule. Thus, a lack of mediator proteins prevents Na^+ reabsorption and, therefore, K^+ and H^+ secretion.

Indications:

1. The 1st use is to combined it with diuretics that lead to K+ depletion.
2. Nephrotic Syndrom.
3. Hepatic cirrhosis.
4. Refractory edema that doesn’t respond to other drugs.

Side effects:

- Abdominal pain.
- Slight hyperurecemia.
- Gynecomastia in males.
- Menstural disturbances.

Triamterene & Amiloride

- Triamterene and Amiloride block Na^+ transport channels, resulting in a decrease in Na^+/K^+ exchange.
- Although they have a K^+-sparing diuretic action similar to that of spironolactone, their ability to block the Na^+/K^+-exchange site in the collecting tubule does not depend on the presence of aldosterone. Thus, they have diuretic activity even in individuals with Addison's disease.
- Like spironolactone, they are not very efficacious diuretics.
- Both triamterene and amiloride are frequently used in combination with other diuretics, usually for their potassium-sparing properties.
- The side effects of triamterene are leg cramps and the possibility of increased blood urea nitrogen as well as uric acid and K^+ retention.

Osmotic Diuretics

- They are weak diuretics such as Mannitol and Urea.
- Their site of action is Proximal, Distal CT and Collecting duct.
- They are not electric substances, that mean:

1. They are freely filterated from glomerulus.
2. They undergo limited absorption in the renal tubule.
3. Pharmacologically, they are inert substances.

- The cause osmotic balance between the tubular fluid and peritubular fluid that limits backward movement of water and increase the volume of urine.

Therapeutic uses:

1. Prophylaxis of acute renal failure but nowaday, their use is less because of HED.
2. Eliminate some drugs that rae reabsorbed in renal tubules in acute poisoning of salicylates, barbiturates, bromides.
3. Reduce intracranial or intraocular pressure.
4. Rarely used in resistance edema.

Carbonic Anhydrase Inhibitors

Acetazolamide

- Acetazolamide inhibits the enzyme carbonic anhydrase in the proximal tubular epithelial cells. It is weak diuretic.

- **Mechanism of action:**

  Acetazolamide inhibits carbonic anhydrase located in proximal tubular epithelium. Carbonic anhydrase catalyzes the reaction of CO_2 and H_2O, leading to H_2CO_3, which spontaneously ionizes to H^+ and HCO_3^- (bicarbonate). The decreased ability to exchange Na^+ for H^+ in the presence of acetazolamide results in a mild diuresis.

- Additionally, HCO_3^- is retained in the lumen, with marked elevation in urinary pH. The loss of HCO_3^- causes a hyperchloremic metabolic acidosis and decreased diuretic efficacy following several days of therapy.

End of Diuretics