SOS in Pharmaceutical Sciences, Jiwaji University, Gwalior

Diuretics- Introduction, Classification and Mechanism of Action

SUBJECT- PHARMACEUTICAL CHEMISTRY-VII (4T2)

PRESENTED BY:

JAGDEESH AHIRWAR

ASST. PROF. (CONTRACT)

Introduction

- Diuretics are chemicals that increase the rate of urine formation. By increasing the urine flow rate, diuretic usage leads to increased excretion of electrolytes (especially sodium and chloride ions) and water from the body without affecting protein, vitamin, glucose, or amino acid reabsorption.
- These pharmacologic properties have led to the use of diuretics in the treatment of edematous conditions resulting from a variety of causes (e.g., congestive heart failure, nephrotic syndrome, and chronic liver disease) and in the management of hypertension.
- Diuretic drugs also are useful as the sole agent or as adjunct therapy in the treatment of a wide range of clinical conditions, including hypercalcemia, diabetes insipidus, acute mountain sickness, primary hyperaldosteronism, and glaucoma.

- Diuretics (natriuretics) are drugs which cause a net loss of Na^+ and water in urine. However, Na^+ balance is soon restored, even with continuing diuretic action, by compensatory homeostatic mechanisms of the body, albeit with a certain degree of persisting Na^+ deficit and reduction in extracellular fluid volume.
- The primary target organ for diuretics is the kidney, where these drugs interfere with the reabsorption of sodium and other ions from the lumina of the nephrons, which are the functional units of the kidney.
- The amount of ions and accompanying water that are excreted as urine following administration of a diuretic, however, is determined by many factors, including
    - ✓ Chemical structure of the diuretic,
    - ✓ Site or sites of action of the agent,
    - ✓ Salt intake of the patient, and
    - ✓ Amount of extracellular fluid present.

- In addition to the direct effect of diuretics to impair solute and water reabsorption from the nephron, diuretics also can trigger compensatory physiologic events that have an impact on either the magnitude or the duration of the diuretic response. Thus, it is important to be aware of the **normal mechanisms of urine formation and renal control mechanisms** to understand clearly the ability of chemicals to induce diuresis.
- Urine formation begins with the filtration of blood at the glomerulus. Approximately 1,200 mL of blood per minute flows through both kidneys and reaches the nephron by way of afferent arterioles.
- Approximately 20% of the blood entering the glomerulus is filtered into Bowman's capsule to form the glomerular filtrate.
- The glomerular filtrate is composed of blood components with a molecular weight less than that of albumin (~69,000 daltons) and not bound to plasma proteins.
- The glomerular filtration rate (GFR) averages 125 mL/ min in humans but can vary widely even in normal functional states.

Normal Mechanisms of Urine Formation

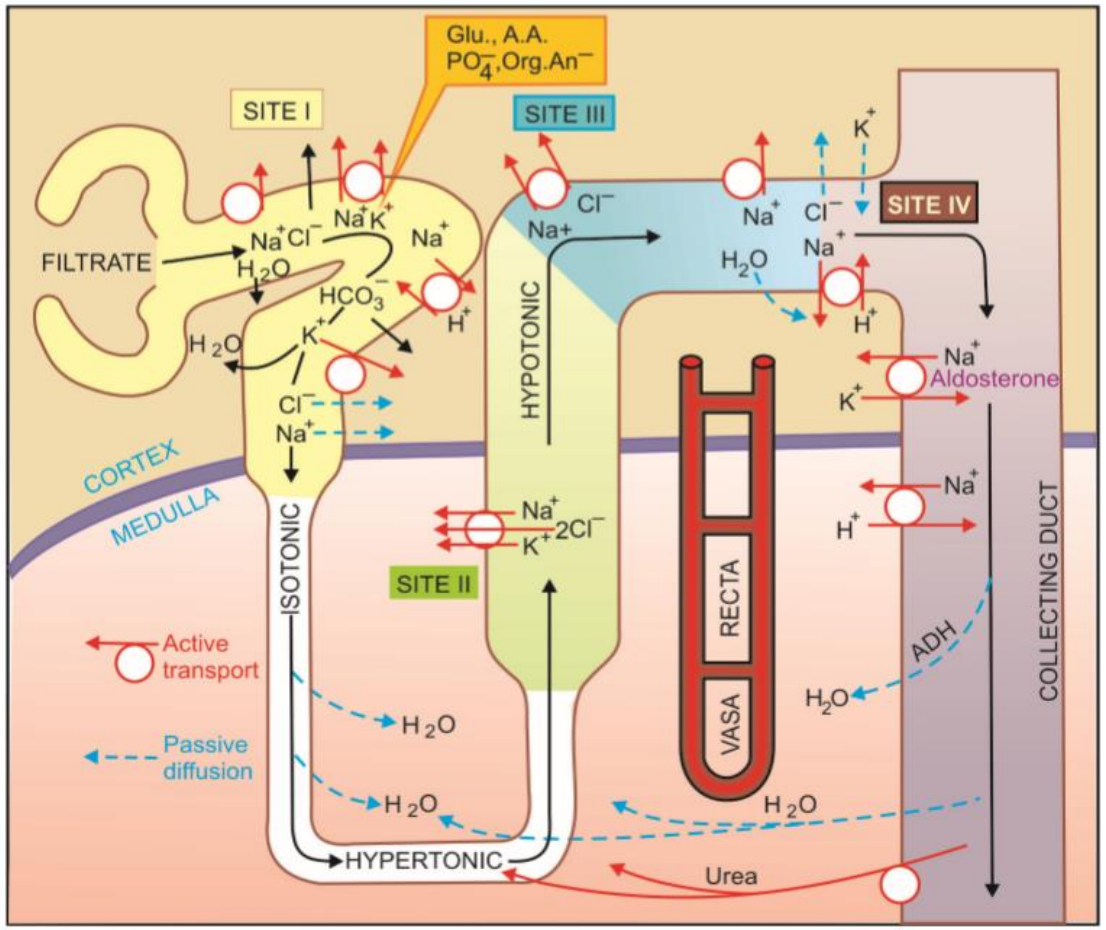


Fig. IX.1: Diagrammatic representation of nephron showing the four sites of solute reabsorption. The thick ascending limb of loop of Henle is impermeable to water; Glu.—Glucose; A.A.—Amino acid; Org. An.—Organic anions.

Classification

1. High efficacy diuretics (Inhibitors of Na^+K^+-$2Cl^-$ cotransport)

Sulphamoyl derivatives-

Furosemide, Bumetanide, Torasemide

2. Medium efficacy diuretics (Inhibitors of Na+-Cl^- symport)

(a) Benzothiadiazines (thiazides)-

Hydrochlorothiazide, Benzthiazide, Hydroflumethiazide, Bendroflumethiazide

(b) Thiazide like (related heterocyclics)-

Chlorthalidone, Metolazone, Xipamide, Indapamide, Clopamide

3. Weak or adjunctive diuretics

(a) Carbonic anhydrase inhibitors-

Acetazolamide

(b) Potassium sparing diuretics-

(i) Aldosterone antagonist:

Spironolactone, Eplerenone

(ii) Inhibitors of renal epithelial Na^+ channel:

Triamterene, Amiloride.

(c) Osmotic diuretics-

Mannitol, Isosorbide, Glycerol

Medium efficacy diuretics (Inhibitors of Na^+-Cl^- symport)

- These diuretics **(thiazides diuretics)** are actively secreted in the proximal tubule and are carried to the loop of Henle and to the distal tubule. The major site of action of these compounds is in the distal convoluted tubule, where these drugs compete for the chloride binding site of the Na^+/ Cl^- symporter and inhibit the reabsorption of sodium and chloride ions. For this reason, they are referred to as saluretics.

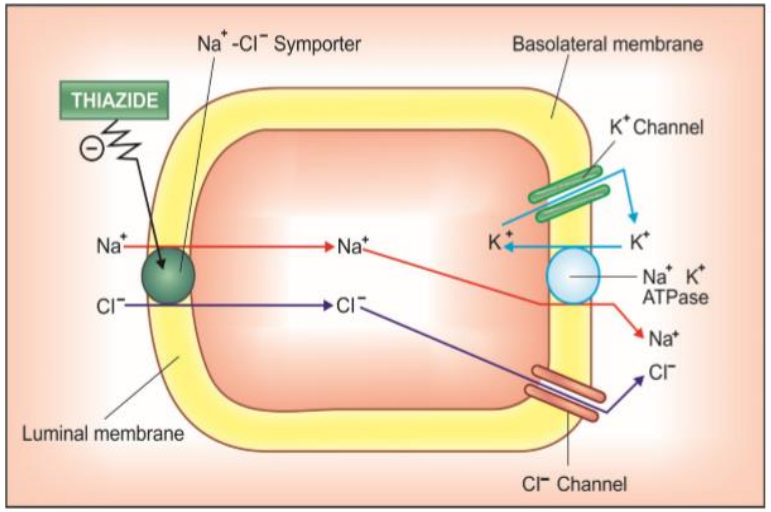


Fig. 41.2: Mechanism of salt reabsorption in early distal tubular cell and site of action of thiazide diuretics on Na^+Cl^- symporter

High-Ceiling or Loop Diuretic

- These drugs produce a peak diuresis much greater than that observed with the other commonly used diuretics, hence the name high-ceiling diuretics. Their main site of action is believed to be on the thick ascending limb of the loop of Henle, where they inhibit the luminal Na^+/ K^+/$2Cl^-$ symporter. These diuretics are commonly referred to as loop diuretics. Examples include furosemide, bumetanide, torsemide, and ethacrynic acid.

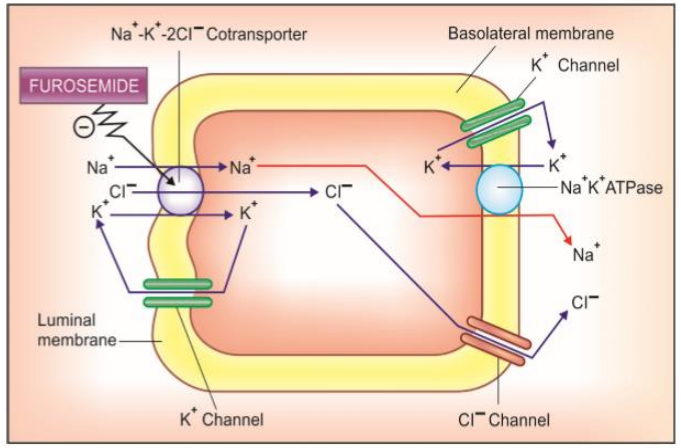
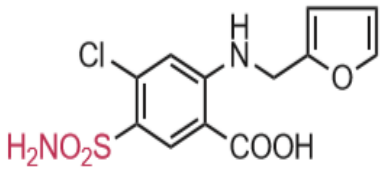
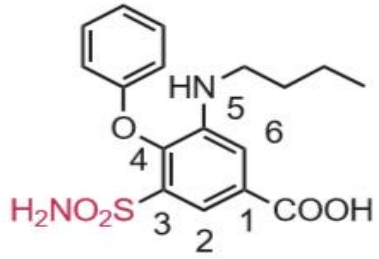


Fig. 41.1: Mechanism of salt reabsorption in the thick ascending limb of loop of Henle (AscLH) cell, and site of action of furosemide on the Na^+-K^+-$2Cl^-$ cotransporter



Furosemide



Bumetanide

Carbonic anhydrase inhibitors

- Carbonic anhydrase inhibitors induce diuresis by inhibiting the formation of carbonic acid within proximal (proximal convoluted tubule) and distal tubular cells to limit the number of hydrogen ions available to promote sodium reabsorption. For a diuretic response to be observed, more than 99% of the carbonic anhydrase must be inhibited. Although carbonic anhydrase activity in the proximal tubule regulates the reabsorption of approximately 20% to 25% of the filtered load of sodium, the carbonic anhydrase inhibitors are not highly efficacious diuretics.

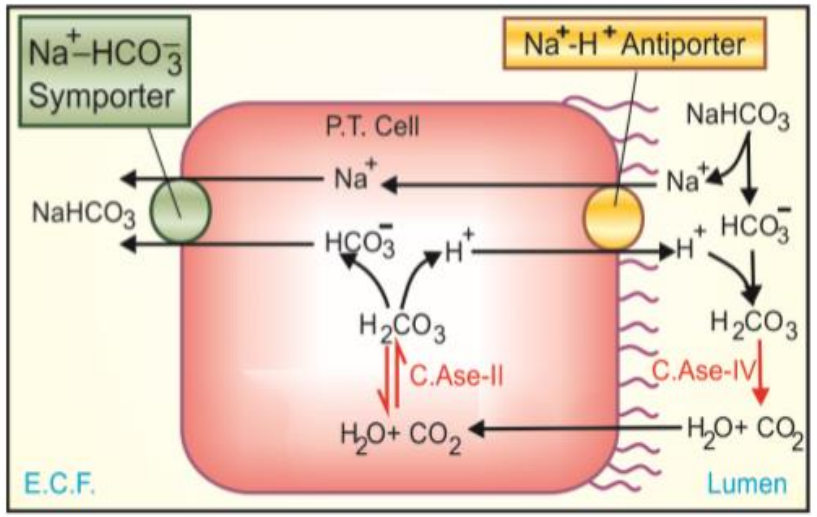
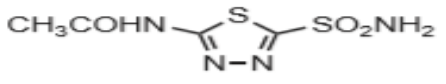
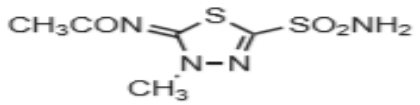


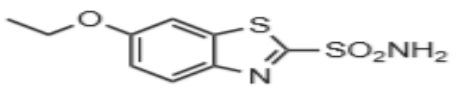
Fig. IX.2: The carbonic anhydrase (C.Ase) mediated bicarbonate absorption in proximal tubule (P.T.)



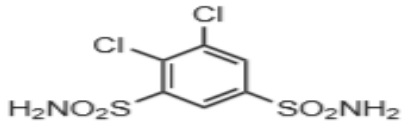
Acetazolamide



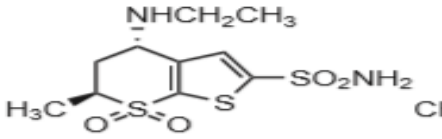
Methazolamide



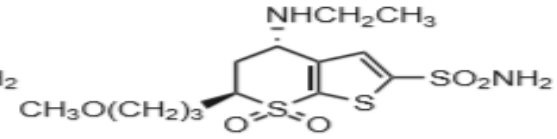
Ethoxzolamide



Dichlorphenamide



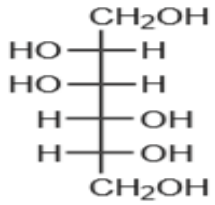
Dorzolamide



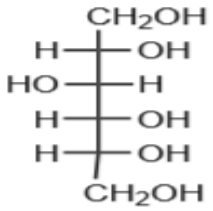
Brinzolamide

Osmotic diuretics

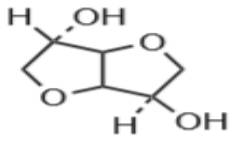
- Osmotic diuretics are low molecular weight compounds that are freely filtered through the Bowman's capsule into the renal tubules, are nonreabsorbable solutes, and are not extensively metabolized except for glycerin and urea. Once in the renal tubule, osmotic diuretics have a limited reabsorption because of their high water solubility. When administered as a hypertonic solution, these agents increase intraluminal osmotic pressure, causing water to pass from the body into the tubule.
- Since the osmotic agent and associated water are not reabsorbed from the nephron, a diuretic effect is observed. Osmotic diuretics increase the volume of urine and the excretion of water and almost all of the electrolytes. Polyols, such as mannitol, sorbitol, and isosorbide, provide this effect.



Mannitol



Sorbitol



Isosorbide

Thank You…