CHAPTER 4

RENAL DRUGS- DIURETICS

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Diuretics are therapeutic agents used in disease conditions like edema, hypertension, and congestive heart failure. They act mainly by impeding renal tubules in the kidney, and the reabsorption of sodium ions. This category of drugs is classified in different ways: based on chemical structure, site of action, mechanism of action, and extent of the natriuretic effect. The classification used nowadays is the combination of all the above-mentioned concepts.

To understand the mechanism of action and effects caused by diuretics we should understand the functioning of the kidney. They are the main organ of excretion and play an important role in homeostasis. The main functions of the kidney are excretion (removal) of water along with various metabolic products, drug substances, and other materials present in the blood. They also have some role in the secretion of renin, erythropoietin, and 1, 2, 5-hydroxycholecalciferol. The other function is the reabsorption of the components which are required by the body, i.e. selectively reabsorbing some of the components like nutrients, water, and electrolytes.

The main divisions of the kidney are the pelvic region, the cortex region, and the medulla region. The main functional unit of the kidney is the nephron. Each kidney contains 1.2 million nephrons. There are two types of nephrons one is known as cortical nephron (about 80%) and the other is juxtamedullary.

The two main functional parts of the nephron are the glomerulus and renal tubules. The glomerulus is surrounded by Bowman's capsule the receiver for filtrate generated by the glomerulus. Approximately 180 L of filtrate is produced every day and about 99% of it is reabsorbed along with electrolytes in renal processes. The major components of the glomerular filtrate are various electrolytic ions like sodium ion, ammonium ion, potassium ion, calcium ion, magnesium ions, chloride ions, and hydrogen phosphate ion. The other components are amino acids, various nitrogenous wastes of metabolism, and glucose. The blood cells are not filtered in the filtrate but are retained.

The next step is the reabsorption of the components (solute and water) which are to be reabsorbed by the nephron. This process takes place by passive or active mechanism, mainly in walls of convoluted tubules (proximal and distal), the loop of Henle, and collecting tubules. The final step is secretion.

Figure 4.1: Reabsorption process of electrolytes, water and other components in different portion of kidney

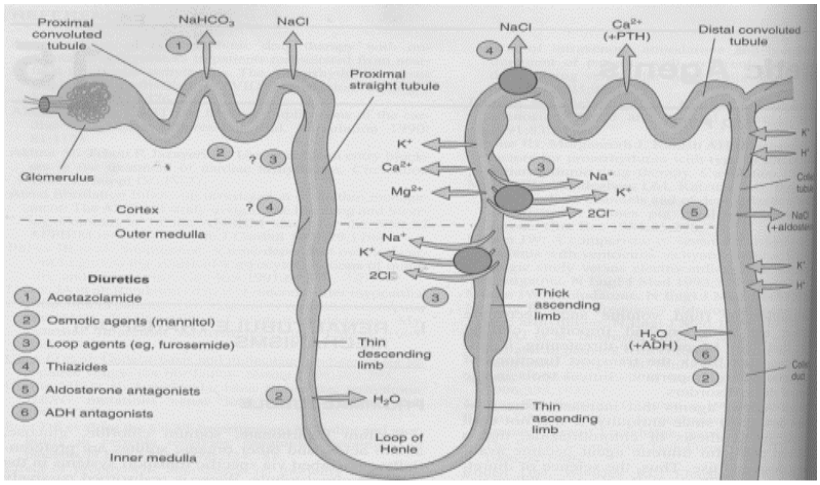

Figure 4.2: Diuretics sites of action in renal tubule.

CLASSIFICATION OF DIURETICS

The major groups of diuretics are as follows:

I. Thiazides and related diuretics, such as hydrochlorothiazide, chlorthalidone, bendrofluazide, and others.

II. Loop diuretics, such as furosemide and ethacrynic acid.

III. Potassium-sparing diuretics, such as triamterene, amiloride, spironolactone, and others.

IV. Carbonic anhydrase inhibitors, such as acetazolamide.

V. Osmotic diuretics, such as mannitol and glycerol.

I. Thiazide diuretics: act by inhibiting NaCl symport at the distal convoluted tubule. The main advantage of this category of compounds is the saluretic effect thus reduction in edema but there is no effect on acid-base balance. The drugs of chlorothiazide and its derivatives have a mild lowering of blood pressure. These compounds increase the sodium and chloride excretion in approximately equal quantity, with the kaliuretic effect also. They reduce calcium excretion while enhancing the excretion of magnesium.

Therapeutic uses: They are mainly used in the treatment of hypertension, and edema of hepatic, renal, and cardiac origin.

Adverse effects: Some of the adverse effects observed are epigastric distress, nausea, vomiting, weakness, fatigue, allergic reactions, hypokalemia, hyperuricemia, and hyperglycemia.

II. Loop diuretics: Loop diuretics (frusemide) have an inhibitory effect on Na+- K – 2Cl symporter specifically in the ascending limb.

Therapeutic uses: This category of drug is used in acute pulmonary edema, edema occurring during cardiac, renal, or hepatic disease, cerebral edema, and hypertension. During drug (anion) overdose this category of drugs can produce forced diuresis which will facilitate very rapid drug elimination.

Adverse effects: Some of the side effects observed by these drugs are hypokalemia, nausea, anorexia, vomiting epigastric distress, fatigue weakness muscle cramps, and drowsiness. Dizziness, and hearing impairment which is usually reversible.

III. Potassium-sparing diuretics: Potassium-sparing diuretics (triamterene, amiloride, spironolactone) are mild diuretics that are causing their diuretic effect by increasing the excretion mainly of sodium, bicarbonate, and calcium but also decrease the excretion of potassium ions.

Therapeutic uses: They are mainly used in conjunction with loop diuretics or thiazides in edema caused by cardiac failure, nephrotic syndrome, and hepatic disease. Adverse effects: The main adverse effects are kidney stones with some of the agents, hyperchloremia, and hyperkaliemia.

IV. **Carbonic anhydrase inhibitors:** The drugs e.g. acetazolamide belonging to this category inhibits the activity of enzyme carbonic anhydrase present in the renal tubular cells thus causing an increase in the excretion of mainly bicarbonate ions, sodium, and potassium ions in urine. Nowadays, the drugs under this category are used for activities other than kidneys.

Therapeutic Use: They have specifically used treatment of acute angle glaucoma, as it causes decreased aqueous humor.

Adverse Effects: Main adverse effects of these agents are drowsiness, hypokalemia, metabolic acidosis, and epigastric distress.

V. **Osmotic diuretics:** The various osmotically active drugs like sorbitol, mannitol, and glycerin (glycerol) is filtered at the glomerulus freely and have very little pharmacologically action, and their reabsorption is limited by the renal tubule. These agents are basically administered to increase the osmolality of plasma and tubular fluid to the extent to cause diuresis. They are mostly given parentally.

Therapeutic uses: They are mostly used in case of cerebral edema and for reduction of intraocular pressure (mainly before surgery). These agents can also be used in the management of poisoning.

Adverse Effects: Osmotic diuretics can cause extracellular volume expansion. Excessive use can lead to dehydration if proper replacement of water is not taken care of. They may cause hyperkalemia, as well as hypernatremia.

Questions

a. Discuss briefly the different classes of diuretic drugs and the basis of classification.
b. Give the mechanism of action and uses of osmotic diuretics.
c. What are the common adverse effects of vasodilators?
d. Discuss loop diuretics' mechanism of action.
e. Discuss the processes taking place in various parts of the nephron.

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