UNIT

VIII

EXCRETION

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INTRODUCTION

The process through which drugs and/or their metabolites are removed from the body is known as excretion. Drugs can be excreted in their original (unchanged) form as well as in their active or inactive metabolites.

Kidneys are the primary site of excretion of the drugs. Thus, renal excretion refers to the excretion of the drug through kidneys, whereas non-renal excretion is the excretion of drugs through other routes of excretion other than kidneys, such as lungs, intestine, breast milk, biliary system, sweat glands, and salivary glands.

Renal Excretion of Drugs

It is clearly understood that most of the drugs and their metabolites are excreted through the kidneys to some extent or another. The kidneys can readily eliminate the agents in urine that are water-soluble, polarized, non-volatile, and having small molecular size (less than 500 Daltons). For the lipid-soluble drugs to be excreted through kidneys, it should first undergo biotransformation in the liver that helps to transform it into a more water-soluble drug, which can be easily eliminated from the kidneys.

Nephron is the basic and functional unit of the kidney that consists of glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct, which are involved in the excretion process. The major mechanisms through which urinary excretion of a drug takes place are: (a) Glomerular filtration; (b) Active tubular secretion; and (c) Active or passive tubular reabsorption.

Thus, in simple terms, the rate of excretion can be estimated by the following equation:

Rate of Excretion = Rate of Filtration + Rate of Secretion – Rate of Re-absoprtion

1. **Glomerular Filtration**

It is a non-selective and unidirectional process in which most ionised or unionised substances, excluding those bound to plasma proteins or blood cells and so acting as macromolecules, are filtered. The glomeruli filters only 10% of the total renal flow (about 120 to 130 mL/min), the rate being referred to as the glomerular filtration rate (GFR).

2. **Active Tubular Secretion**

The tubular secretion is a carrier-mediated active process that needs the energy to transfer the compounds against the concentration gradient. The system is saturable and capacity limited. There are two active tubular secretion processes known:

i. For the secretion of organic acids/anions like penicillin, glucuronides, salicylates, sulphates etc.

ii. For the secretion of organic bases/cations like morphine, hexamethonium, mecamylamine, and endogenous amines such as catecholamines etc.

3. **Tubular Reabsorption**

Following the glomerular filtration of drugs, tubular reabsorption occurs along the entire length of the renal tubule. Reabsorption, in contrast to tubular secretion, causes a drug's half-life to increase as the drug substances will be reabsorbed. Tubular reabsorption can be active (reabsorption of endogenous substances or nutrients such as electrolytes, vitamins, amino acids, glucose, and so on) or passive (reabsorption of several exogenous substances as well as drugs).

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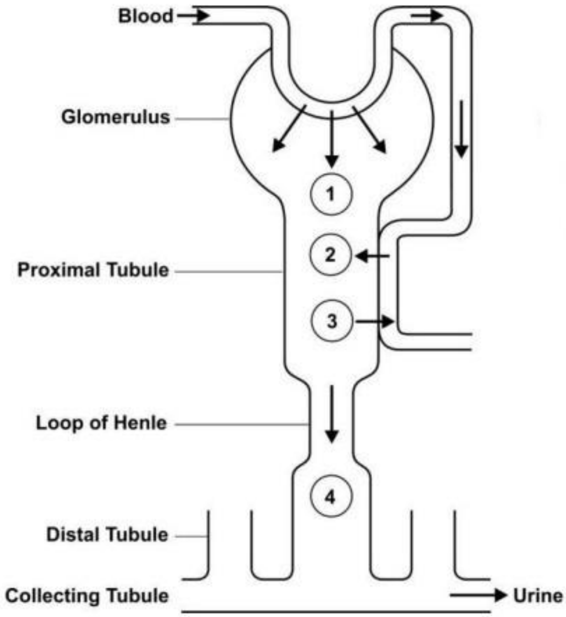

Figure 8.1: Renal excretion of drugs, where, **(1)** represents the glomerular filtration of water and unbound drugs and metabolites; **(2)** Active tubular secretion of acidic and basic drugs and metabolites; **(3)** Active reabsorption of acidic and basic endogenous compounds and passive reabsorption of lipophilic drugs; and **(4)** urinary excretion of drugs and metabolites that are filtered and/or actively secreted and not reabsorbed.

CONCEPT OF CLEARANCE

The hypothetical volume of drug-containing body fluids from which the drug is eliminated or cleared completely in a specific time period is referred to as clearance. It is a constant for any given plasma drug concentration and expressed in millilitres per minute (mL/min) or litres per hour (L/hr).

$$Clearance\ (Cl) = \frac{Elimination\ rate}{Plasma\ drug\ concentration}$$

Total Systemic Clearance (Cl_T): *Total body clearance, also known as total systemic clearance, is the sum of individual clearances by all eliminating organs.* It is calculated as the sum of renal and non-renal clearances.

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Renal Clearance (Cl_R): *It is the volume of blood or plasma that is entirely cleared of the unmodified drug by the kidney per unit time.* It is mathematically stated as:

$$Renal\ Clearance\ (Cl_R) = \frac{Rate\ of\ urinary\ excretion}{Plasma\ drug\ concentration}$$

Physiologically speaking, **renal clearance** is the ratio of rate of excretion by kidney to plasma drug concentration, *C*.

$$Cl_R = \frac{Rate\ filtration + Rate\ of\ secretion - Rate\ of\ reabsorption}{Plasma\ drug\ concentration}$$

Non-renal Clearance (Cl_{NR}): Clearance of the drug by all organs other than kidney is sometimes, referred to as non-renal clearance.

$$Hepatic\ Clearance\ (Cl_H) = \frac{Rate\ of\ elimination\ by\ liver}{Plasma\ drug\ concentration}$$

$$Other\ organ\ Clearance\ (Cl_{Others}) = \frac{Rate\ of\ elimination\ by\ other\ organs}{Plasma\ drug\ concentration}$$

Thus, the total body clearance, Cl_T, also referred to as total systemic clearance, is an additive property of individual organ clearances.

$$Cl_T = Cl_R + Cl_H + Cl_{others}$$

Clearance by all organs other than kidney is sometimes known as nonrenal clearance, Cl_{NR}.

$$Cl_T = Cl_R + Cl_H + Cl_{others}$$