

ELIMINATION/ EXCRETION OF DRUGS

- Excretion is defined as the process where drugs or their metabolites are irreversibly transferred from internal (body) to external environment through rectal or non-rectal routes.
- Excretion, along with metabolism and drug distribution is important in determining both the duration of drug action and rate of drug elimination.

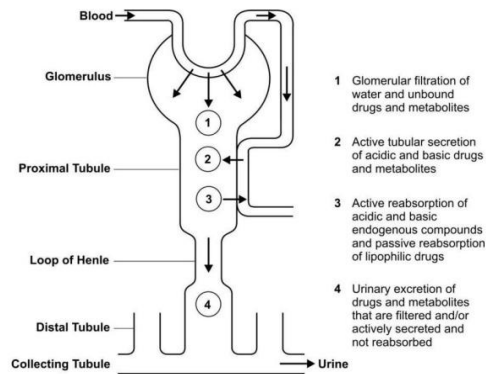
PRINCIPAL ORGANS INVOLVED IN EXCRETION-

Drugs and their metabolites are excreted in:

1. **Urine**-Through the kidney. It is the most important channel of excretion for majority of drugs.
2. **Faeces**-Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Relatively larger molecules (MW > 300) are preferentially eliminated in the bile. Most of the free drug in the gut, including that released by deconjugation of glucuronides by enteric bacteria is reabsorbed (enterohepatic cycling) and ultimate excretion occurs in urine. Only the remaining is excreted in the faeces.
3. **Exhaled air**- Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility. Alveolar transfer of the gas/vapour depends on its partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter that enters circulation.
4. **Saliva and sweat**- These are of minor importance for drug excretion. Lithium, potassium iodide, rifampin and heavy metals are present in these secretions in significant amounts. Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drugs.
5. **Milk**- The excretion of drug in milk is not important for the mother, but the infant inadvertently receives the drug. Most drugs enter by passive diffusion. As such, more lipid soluble and less protein bound drugs cross better. Milk has a lower pH (7.0) than plasma, basic drugs are somewhat more concentrated in it.

RENAL EXCRETION-

- Drugs are eliminated from the body primarily by kidneys. The kidney is responsible for excreting all water soluble substances.
 - Agents that are excreted in urine are – Water-soluble, non-volatile and small in molecular size (less than 500 Daltons).
 - The basic functional unit of the kidney involved in excretion is the nephron. Each kidney comprises one million nephrons. Each nephron is made up of the glomerulus, the proximal tubule, the loop of Henle, the distal tubule and the collecting tubule.
 - The principal renal mechanisms involved in the excretion of drugs are Glomerular filtration, tubular reabsorption and tubular secretion. Glomerular filtration and active tubular secretion tend to increase the concentration of drugs in lumen and hence facilitate excretion whereas tubular reabsorption decreases it and prevents the movement of drug out of the body.
- Net renal excretion= (Glomerular filtration + tubular secretion) – tubular reabsorption



Glomerular filtration-

- Glomerular filtration is a non-selective, unidirectional process whereby most compounds, ionised or unionised, are filtered except those that are bound to plasma proteins or blood cells and thus behave as macromolecules.
- The driving force for filtration through the glomerulus is the hydrostatic pressure of the blood flowing in the capillaries. Out of the 25% of cardiac output or 1.2 litres of blood/min that goes to the kidneys via renal artery, only 10% or 120 to 130 ml/min is filtered through the glomeruli, the rate being called as the glomerular filtration rate (GFR).

Tubular reabsorption-

- Tubular reabsorption occurs after the glomerular filtration of drugs.
- This occurs by passive diffusion and depends on lipid solubility and ionization of the drug at the existing urinary pH.
- Tubular reabsorption can either be an active process, or passive process. Active tubular reabsorption is commonly seen with high threshold endogenous substances or nutrients that the body needs to conserve such as electrolytes, glucose, vitamins, amino acids, etc. Passive tubular reabsorption is common for a large number of exogenous substances including drugs. The driving force for such a process i.e. the concentration gradient is established by the back diffusion or reabsorption of water along with sodium and other inorganic ions.
- Changes in urinary pH affect tubular reabsorption of drugs that are partially ionized—Weak bases ionize more and are less reabsorbed in acidic urine. Weak acids ionize more and are less reabsorbed in alkaline urine.

Tubular secretion-

- It is a carrier-mediated process which requires energy for transportation of compounds against the concentration gradient. The system is capacity-limited and saturable. Two active tubular secretion mechanisms have been identified:
 - System for secretion of organic acids/anions like penicillins, salicylates, glucuronides, sulphates, etc (through Organic anion transporting polypeptides or OATPs).
 - System for secretion of organic bases/cations like morphine, mecamylamine, hexamethonium and endogenous amines such as catecholamines, choline, histamine, etc (through organic cation transporter).

- Both the systems are relatively non-selective and independent of each other but both can be bidirectional i.e. agents may both be secreted as well as reabsorbed actively, for example, uric acid.

KINETICS OF ELIMINATION

- The knowledge of kinetics of elimination of a drug provides the basis for, as well as serves to devise rational dosage regimens and to modify them according to individual needs.
- Drug elimination is the sumtotal of metabolic inactivation and excretion.

TYPES OF ELIMINATION KINETICS-

1. **First-order kinetics:** Elimination of a constant percentage (or fraction) of the drug per unit time.
 - For most drugs, the elimination occurs at a rate directly proportional to the concentration of the drug—i.e the higher the drug concentration, the higher its elimination rate. First-order kinetics is also referred to as non-saturable or linear kinetics.
 - CL remains constant.
2. **Zero-order kinetics:** Elimination of a constant quantity of the drug per unit time independent of the concentration of the drug.
 - With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large. Therefore, the plasma drug concentration is much greater. Drug metabolism is constant and independent of the dose. Zero-order kinetics is also known as saturable, dose- or concentration independent or nonlinear kinetics.
 - CL decreases with increase in concentration.

CLEARANCE OF DRUG-

- Clearance is a pharmacokinetic measurement of the volume of plasma from which a substance is completely removed per unit time.
- Usually, clearance is measured in L/h or mL/min.
- $CL = \text{Rate of elimination}/C$ where C is the plasma concentration.

PLASMA HALF-LIFE

- The Plasma half-life ($t_{1/2}$) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.
- Half-life is expressed in minutes or hours.
- The half-life determines the length of the drug's effect.

BIOAVAILABILITY

- It refers to the amount of the drug that is absorbed from its site of administration and reaches the systemic circulation.
- Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.
- When administered intravenously, the bioavailability of the drug is assumed to be 100%. When administered orally, the bioavailability of the drug is usually less than 100% – this is because of the following main factors:

- Extent of absorption
- First-pass metabolism
- Volume of distribution
- Bioavailability differs not only among drugs and routes of administration, but also between different formulations of the same drug. When two drug formulations have similar bioavailability, they are called bioequivalent.
- Relative bioavailability is when the bioavailability of an oral drug (for example tablet) is compared with other oral formulations (for example suspension) of the same drug.

BIOCONCENTRATION-

- Bioconcentration is the specific bioaccumulation process by which the concentration of a chemical in an organism becomes higher than its concentration in the air or water around the organism.
- Bioaccumulation refers to increase in concentration of a substance in certain tissues of an organism's body.
- Bioaccumulation occurs when an organism absorbs a toxic substance from all sources at a rate greater than that at which the substance is lost. Bioconcentration occurs when an organism absorbs a toxic substance from ONLY Water at a rate greater than that at which the substance is lost.