Steps of pharmacokinetics – Absorption, Distribution, Metabolism, and Excretion

For a good pharmacokinetic profile, a medicine must complete 4 steps of pharmacokinetics in the human body, i.e., ADME.

Step 1 Absorption, Bioavailability & Prodrug

The first step of pharmacokinetics is absorption. A medicine can enter the body either directly through blood or indirectly through GIT (stomach/intestine).

When you take medicine orally, it does not directly go to your bloodstream. Before entering your main systemic circulation, medicine has to go through the liver via hepatic portal vein.

Since liver generally receives all the blood by hepatic portal circulation that comes from the stomach and intestine. So, before distribution, the medicine metabolizes first in the liver. It is called **First Pass Metabolism (FPM).**

Some part of medicine gets broken down or metabolized before entering the systemic circulation.

Due to this first pass metabolism, you lose some drugs during metabolism. Whatever amount of medication you get in the systemic circulation represents **bioavailability.**

In other words, bioavailability means the amount (or percentage) of drug that reaches the bloodstream. For example, if you take 100 mg of medicine and your liver break 30 mg of the drug. You get only 70 mg of the absorbed drug into your bloodstream. Here, bioavailability would be 70% of this drug.

The high first-pass metabolism has generally decreased the bioavailability of the drug. Some examples of high first-pass metabolism drugs include Nitrates, Testosterone, Lignocaine, Hydrocortisone, and Remdesivir.

Therefore, these drugs are never given orally.

Intravenous injection has 100 % bioavailability (get absorbed entirely) because it directly goes to your blood and does not involve First Pass Metabolism.

Prodrug -
The liver makes most drugs inactive, but some drugs become active. These drugs are called **prodrugs**.

Generally, Prodrugs are not active initially but become active after First Pass Metabolism. For example –

- All ACE inhibitors are prodrugs except captopril, and lisinopril like enalapril (inactive) converts into enalaprilat (active form)
- All Proton Pump inhibitors are Prodrug like rabeprazole (inactive) converted into sulphenamide (active form)
- Drugs for joints – Allopurinol (inactive) converts into oxypurinol (active form), and azathioprine (inactive) converts into mercaptopurine (active form)
- Steroids – Prednisone (inactive) converts into prednisolone (active)
- CNS agents - Levodopa (inactive) converts into dopamine (active form) and methyldopa (inactive) converts into methyl-norepinephrine (active form)

Step 2 Distribution

The distribution step is only possible if the medicine successfully reaches the bloodstream.

Once medicine reaches the blood, it has to distribute throughout your body, such as the heart, brain, lungs, kidneys, etc.

Distribution describes how much medicine will reach tissues.

Medicine in blood → blood to tissue (or organs) → Pharmacological effects
↓
Desirable effects (Therapeutic action)
Undesirable effects (side effects)
Local drug toxicity (due to accumulation)

When medicine enters your blood, it interacts with various components of blood like **plasma protein** (albumin and globulin).

It depends upon the affinity of drugs. Some drugs bind with plasma protein, and some do not.

If a drug has high plasma protein binding, distribution will decrease, e.g., warfarin, phenytoin, diazepam, etc. Conversely, unbound or free-form drugs (does not bind to plasma protein) will have high distribution, e.g., Gabapentin and pregabalin.

Another crucial pharmacokinetic parameter evaluates how much drug enters your tissues, i.e., **the volume of distribution**.

A high volume of distribution means the maximum amount of drug distributed to the tissues.

Conversely, a low volume of distribution means a minimum amount of drug distributed to the tissues.

The volume of distribution is also a useful pharmacokinetic parameter for calculating **loading dose**. Whereas clearance is a significant pharmacokinetic parameter for calculating **maintenance dose**.

Step 3 Metabolism

Once the drug has done its action (therapeutic and undesirable effects), a medicine has to clear out from the body. But it is difficult for the kidney to eliminate lipophilic (or lipid soluble) drugs from the body.

So, medicine comes back into blood vessels from tissues.

After returning to the blood, medicine goes to the liver for biotransformation. Here, lipid-soluble drugs (non-polar) convert into water-soluble (polar) drugs. This is called the **metabolism** of a drug.

Non-polar drug (lipid soluble) → Polar drug (water soluble) → Kidney

Thus, the primary purpose of metabolism is to make the medicine more polar (or water-soluble) so that it cannot go back to your tissues. When a drug becomes water soluble, it eliminates via urine or stool.

Step 4 Excretion

Once the drug becomes completely polar (or water-soluble), the drug reaches the kidney. The kidney clears the water-soluble drug from the plasma via urine, called **renal excretion**.

Some drugs are removed from the liver via bile, called **non-renal excretion**. Examples include erythromycin, ampicillin, rifampicin, tetracycline, oral contraceptives, vecuronium, and phenolphthalein.

Certain drugs which remove from the body by various routes of excretion –

- Lithium can remove via sweat, urine, saliva, and tear.
- Alcohol removes from the body via respiration
- Lactulose is directly eliminated from the stool.

Acidic medicines are more easily excreted in alkaline urine. While alkaline medications are more easily excreted in acidic urine.

It makes the drug a more ionized compound, polar and water-soluble, so it can dissolve in water and quickly be eliminated from the body.