# Pharmacokinetics

**Pharmacokinetics is,** generally, what the body does to the drug after being taken: absorption, distribution, metabolism, excretion.

**Pharmacokinetic**, therefore, is concerned with the time course **(the rate)** at which drug molecules cross cell membranes to enter the body (**absorption**), to **distribute** within it and to leave the body **(excretion)** as well as with the structural changes **(metabolism)** to which they are subjected

## I. Absorption

### Drug passage across cell membrane

Cell membranes are essentially **bilayers of lipid** molecules with islands of proteins in between. Therefore, lipid-soluble substances can diffuse readily

**Water-soluble** substances of small molecular size may filter through **water-filled** channels between some epithelial and endothelial cells e.g. jejunum and proximal renal tubules

### Mechanisms of passage of drugs across cell membrane

1. **Passive diffusion** (the most important)

It is the natural tendency to move passively from an area of high concentration to one of low concentration**.** The rate is concentration dependent**.** Cellular energy is **not** required

**Lipid or water solubility is influenced by: structural** properties of the molecules **and** environmental **pH**

### Drugs are classified according to their ionization in response to environmental pH

**A.** Those that their **ionization is dependent on the environmental pH** (unionized=lipid soluble, ionized=water soluble)

**B.** Those that are **unionized** whatever the environmental pH (unionized, lipid-soluble, non-polar compounds)

**C.** Those that are **ionized** whatever the environmental pH (ionized, water soluble, polar compounds)

**A. <u>Drugs ionized according to environmental pH</u>**

The extent to which a molecule has a tendency to ionize is given by the dissociation (ionization) constant, usually expressed as the **pKa** (i.e. negative logarithm of the Ka)

- **Acidic** drugs in an **acidic** environment become: **unionized,** lipid soluble, easily diffusible
- **Acidic** drugs in an **alkaline** environment become: **ionized,** water soluble, non-diffusible

**pKa is the pH at which 50% of the drug is ionized** i.e. when aspirin pKa is 3.5, this means that at pH 3.5, 50% of aspirin is ionized

**Gut pH varies**: stomach 1.5, upper intestine 6.8, lower intestine 7.6, and pH inside the body 7.4. Therefore, aspirin in stomach (acid in acid medium): **un-ionized, lipid soluble, diffuse easily** into gastric epithelial cells. Inside epithelial cells, pH is 7.4, aspirin becomes ionized, less diffusible, and localize there **(ion trapping) (this is one mechanism for aspirin-induced gastric injury)**

B. **<u>Drugs that are unionized whatever the environmental pH</u>**

**Example**: digoxin, steroids (e.g.prednisolone), chloramphenicol

- Unaffected by environmental pH
- Lipid soluble (non-polar compounds)
- Diffuse readily across tissues (good oral absorption)

**C. <u>Drugs that are permanently ionized drugs whatever the environmental pH</u>**

- Water-soluble (polar)
- Limited capacity to cross membranes, poor GIT absorption, usually given parenterally
- Does not cross placenta; useful in pregnancy (heparin compared with warfarin)

They are either**: negatively charged** (acidic, e.g. heparin), or **Positively charged** (basic, e.g. ipratropium, tubocurarine, suxamethonium)

2. **<u>Carrier-mediated transport</u>**

**<u>Active transport</u>**: In active transport, drugs are capable to move against concentration gradient, requires cellular energy, more rapid than diffusion, shows high degree of specificity, subjected to saturation and can be inhibited by other compounds, and is important for some drugs with structural similarity for endogenous molecules.
**Examples**: Levodopa across blood brain barrier and secretion of many weak organic acids and bases through renal tubules and biliary ducts e.g. penicillins, probenecid and uric acid are actively transported in renal tubules

Large molecules can, sometimes, pass from area of high concentration to an area of low concentration through the help of specialized carrier proteins without the need for energy. This type of diffusion is called **facilitated diffusion**. Facilitated diffusion can be saturated and can be inhibited by other competitive compounds e.g. glucose and amino acid transport across cell membranes, retinols.

3. **<u>Filtration</u>** plays a minor role in drug transfer except for glomerular filtration. It occurs through water (aqueous) channels allowing passage of water soluble substances.

4. **Endocytosis**

Endocytosis occurs through binding to specialized components on cell membranes with subsequent engulfment (infolding of the membrane) e.g.

- large polar molecules such as peptides
- small polar substances such as vitamin B12 and iron combine with special proteins (intrinsic factor or transferrin) and the complexes enter the cell by this mechanism.

**The order of the pharmacokinetic processes**

**First order processes**

A constant **fraction** (**proportion**, **percentage)** of the drug is processed per unit time e.g. 10**%** of the dose is metabolized per hour

**Zero-order processes**

A constant **amount** of the drug is processed per unit time e.g. 10**mg** of the dose is metabolized per hour

**In first order kinetics:**

The rate of the pharmacokinetic process of a drug (A D M E ) is **directly proportional** to the amount of the drug administered or to its concentration in the blood (high at high concentration, low at low concentration).The plasma half-life (t1/2) (which is the time for any plasma concentration to fall by 50%) is **always the same** (**constant**) when different therapeutic doses are given. The majority of drugs in doses used clinically follow first order kinetics, but in overdose, their kinetic processes may get saturated

**In zero-order (saturation) kinetics,** the process may become easily saturated e.g. limited amount of metabolizing enzymes.

A **small** increase in the dose can result in a **steep** and disproportionate increase in plasma concentration

**Examples** of drugs following zero-order kinetics in **metabolism**:
Phenytoin, theophylline, ethanol and also aspirin in high therapeutic doses

Zero-order **absorption** applies to iron, also to depot formulation and to drug implants e.g. antipsychotics and sex hormones

**Plasma half life and steady state concentration**

**Plasma elimination half life**

is the time taken for any plasma concentration to fall by half of its original value. It is constant if elimination follows first order kinetics

**Half life can be used**: to determine the dosing frequency if drug effect is directly related to plasma concentration, to calculate the time taken to reach a steady state, to calculate the time for the decline in plasma concentration after dosing ceases and to calculate the clearance and volume of distribution

$$t_{1/2} = \frac{0.693 \times Vd}{Cl} = \frac{0.693}{K}$$

**The steady state concentration**

When a drug is given at a constant rate, the time to reach a steady state depends on the drug half life and is practically reached after **five half lives**

**In a steady state:** The rate of administration is equal to the rate of elimination and the plasma concentration will be at a plateau

Any increase or decrease in drug dosing, the new steady state is reached after **five** half-lives.

For example; the time required to reach a steady state concentration for dobutamine (t1/2 is 2 minutes) is 10 minutes, and for digoxin (half life is 36 hours) is 7.5 days (here, a loading dose is required to reach SS state quickly).

Half-life **varies** in the population over a range of values but a single average half life is given for clarity, **examples**:

| | | | |
|---|---|---|---|
| Adenosine | < 2 seconds | Paracetamol | 2 hours |
| Dobutamine | 2 minutes | Diazepam | 40 hours |
| Benzylpenicillin | 30 minutes | Piroxicam | 45 hours |

Plasma concentration can be measured for therapeutic purposes **(Therapeutic Drug Monitoring, TDM)** if the drug effect is related to drug concentration at receptors in the tissues

## Individual Pharmacokinetic processes

### Absorption

**Absorption from GIT**

*Small intestine is the **main site** of absorption of drugs**.**

*Stomach does not play a major role in absorbing drugs **(small surface area, rapid gastric emptying),** even with acidic drugs; the **onset** of absorption occurs in stomach, but the main part of the dose is absorbed in the small intestine.

*The colon is also capable of absorbing drugs particularly slow-release formulations (SR).

*Buccal absorption is rapid for lipid-soluble drugs; blood flow is abundant, entry into systemic circulation avoiding first pass metabolism

**Enterohepatic circulation**

Bile salts are conserved about 8 times a day. A number of drugs form conjugates with glucuronic acid and are excreted in bile.

Glucuronides are polar (ionized) and are not absorbed, but the parent drugs are released by being hydrolyzed by intestinal enzymes and bacteria.

Recycling helps to sustain plasma concentration and increase duration of action.

**Examples**: sulindac, ethinylestradiol

**Bioavailability (Systemic availability)**

**Systemic availability** is the percentage of the administered dose that reaches the systemic circulation intact. In simple terms, bioavailability is how much of the drug dose is available to produce a biological effect

**Bioavailability is useful to:**

1. Determine the dose and route of administration
   e.g. propranolol i.v. 1-10mg, oral 10-320mg (because of FPM); a drug with oral bioavailability of 5% should not be given orally
2. Compare between different formulations of a drug e.g. sublingual GTN >90%, oral GTN <10%
3. To know the large number of factors that might increase or

decrease the systemic availability of a drug and lead to failure of therapy or to toxicity

Oral bioavailability is calculated from the equation:

$$\frac{\text{AUC oral}}{\text{AUC i.v.}} \times \frac{\text{Dose i.v.}}{\text{Dose oral}} \times 100$$

AUC = Area under plasma concentration-time curve

A drug injected i.v. is 100% available to exert its biological effect

**Factors affecting systemic availability**

1. **Pharmacological factors**

a. **Drug properties**: e.g. instability in gastric acid such as benzylpenicillin in gastric acid

b. **Pharmaceutical factors**: type of ingredients, compression force,….affecting disintegration and dissolution of the tablets e.g. tablets containing same amount of digoxin made by different companies may produce different plasma concentrations and therefore different effects

c. **Interaction** with other substances in the gut e.g. food and drugs (such as tetracycline binding to calcium and iron)

2. **Patient characteristics**

- disease e.g. (malabsorption, hepatic dysfunction)
- GI factors e.g. motility, pH, blood flow
- genetic factors e.g. acetylator status: fast and slow

3. **Pre-systemic (first-pass) elimination (FPM)**

It is the extent of drug metabolism which takes place after oral

administration during **first passage** of the drug through the gut wall and mainly through the liver **before reaching** the systemic circulation

**Examples of drugs undergoing extensive (>50%) first pass metabolism (FPM)**

**Hepatic**: Beta blockers (e.g. propranolol, metoprolol)
Opioids (e.g. morphine, pethidine)
Antiarrhythmics (e.g. lignocaine, verapamil)
Others (e.g. GTN, imipramine)

**Gut wall**: Estrogens, levodopa, isoprenaline

**The importance of extensive FPM**

1. It is a major **source of variations** between individuals in response to drugs. A small change in first pass metabolism will have a relatively large effect on systemic availability if the drug is extensively metabolized.
2. If the FPM is over 95% e.g. lignocaine, then the **oral route is not** suitable
3. In severe **hepatic disease** e.g. cirrhosis with both impaired liver cell function and shunting of blood into systemic circulation; FPM is reduced and systemic availability is increased (i.e. exaggerated response to normal doses)

**The effect of food on drug kinetics**

1. Changes in gastric emptying (slower absorption of most drugs)
2. Drug chelation (tetracycline and dietary calcium; iron and tannic acid in tea and coffee)
3. Changes in drug metabolizing enzymes (induction by alcohol, charcoal grilled beef, brussel sprout)
4. Changes in splanchnic blood flow (increased after food), FPM is reduced.

**Food can <u>decrease</u> bioavailability of certain drugs**: **Examples**

Ampicillin **(markedly reduced)**

Erythromycins **(except erythromycin estolate)**

Rifampicin and INH (anti-Tb)

Atenolol and captopril

**Food can <u>increase</u> bioavailability of certain drugs: Examples**

- propranolol, metoprolol, hydralazine
- griseofulvin, nitrofurantoin, mebendazole (particularly by fatty food)
- Erythromycin estolate

## II. <u>Distribution</u>

**The extent of distribution depends on:** water/lipid solubility**,** protein and tissue binding**,** ability to cross cell membrane passively or actively

**<u>The volume of distribution (Vd)</u>**

It is a theoretical **(apparent)** volume of fluid in which the drug dose appears to distribute with a concentration equal to that in plasma

$$Vd = \frac{\text{Dose}}{C_o}$$

$C_o$ is the initial plasma concentration, i.e. at time zero

**Vd is small**: if the drug remains mostly in plasma e.g. warfarin which is highly protein bound (also tolbutamide, salicylates)

**Vd is large**: if the drug is present mainly in the tissues e.g. digoxin, pethidine, nortriptyline, chloroquine

**The significance of the Vd**

1. In drug overdose; removal of a drug by hemodialysis is appropriate for drugs with small Vd i.e. a major proportion of the dose is present in plasma
2. Drug interaction is likely to occur between those with small Vd e.g. displacement from protein binding

**Examples of drugs with their Vd**

| **Drugs** | **Vd (in L/70kg)** | **Drugs** | **Vd (in L/70kg)** |
|---|---|---|---|
| Heparin | 3 | Diazepam | 140 |
| Aspirin | 5 | Digoxin | 420 |
| Amoxicillin | 28 | Nortriptyline | 1000 |
| Atenolol | 77 | Chloroquine | 1300 |

**Selective distribution of drugs**

- to plasma protein: oral anticoagulants
- to melanin-containing tissues including retina: phenothiazines, chloroquine
- to fat: highly lipid soluble drugs e.g. thiopentone
- to thyroid: iodine

**Protein Binding**

Most drugs circulate partly **free** in plasma and partly protein bound

The **free** fraction is the pharmacologically **active** and it is the one removed by metabolism, dialysis and excretion.

*Free and bound fractions are **in equilibrium** i.e. as the free drug

is removed, it will be replaced by drug released from bound fraction.

**Types of proteins available for drug binding**

**Albumin**: is the main binding protein with high capacity and low Affinity**.**

**Globulins:** for hormones such as thyroxine and sex hormones

**Lipoproteins and α1-acid glycoprotein:** for basic drugs such as quinidine, chlorpromazine,imipramine

**Examples of approximate protein binding of drugs**

INH, lithium, ethosuximide (~0%), atenolol (5%), ampicillin (15%), digoxin (25%), phenobarbitone (50%), propranolol (95%), diazepam (98%), tolbutamide (98%), warfarin (99%), ibuprofen (>99%).

**The significance of protein binding**

**1. It is a source of drug interaction**. Displacement may be important for drugs which are highly protein bound and at the same time having small Vd e.g. warfarin and NSAIDs; the free fraction of warfarin is increased leading to bleeding

**2. In renal and liver failure**

The free fraction of drugs may increase and therefore, increase in response or toxicity because of hypo-albuminemia and accumulation of endogenous substances that may cause displacement from protein binding sites

## III. Metabolism

Only few drugs excreted unchanged

Metabolism changes drugs in two major ways:

1. **by reducing lipid solubility (increased elimination)**

2. **by <u>altering biological activity</u> which occurs in 3 possible ways:**

   a. **Conversion of pharmacological <u>active</u> to an <u>inactive</u> substances (most drugs)**

   b. **Conversion of <u>active</u> to another <u>active</u> substance. This prolongs the duration of action**

   diazepam → oxazepam

   codeine → morphine

   amitriptyline → nortriptyline

   c. **Conversion of <u>inactive</u> ( a pro-drug) to <u>active</u>**

levodopa → dopamine

cyclophosphamide →4-ketocyclophosphamide

sulfasalazine → 5-aminosalicylic acid

**<u>Sites of metabolism</u>**

**<u>Organs</u>**: liver (most important)

Kidney (vitamin D, insulin)

gut mucosa (isoprenaline, levodopa, estrogen and progesterone)

Gut flora (sulfasalazine, hepatic conjugates)

lung (serotonin, noradrenaline, prostaglandins, testesterone, isoprenaline)

skin (vitamin D activation, minoxidil, capsaicin)

**Intracellular sites**

microsomal (mostly), mitochondria, cytoplasm, plasma

**Drug metabolism can occur in two phases:**

**Phase 1:** The most important reaction is oxidation by mixed-function oxidases in the microsomes (the final component of these oxidases is cytochrome P450; mixed means for aliphatic and aromatic)

**Phase 1 metabolism may occur in:**

a) **the endoplasmic reticulum** (microsomal)

b) **cytoplasm**: xanthine oxidase, ethanol metabolism

c) **mitochondria**: monoamine oxidase

d) **plasma**: pseudocholinesterase, histaminase

**N.B.** Not all drugs broken down by enzymes e.g. melphalan which undergoes spontaneous hydroxylation to inactive metabolites

**Phase II metabolism**

involves union of the drug with one of the several polar (water-soluble) endogenous molecules forming water soluble conjugates readily eliminated by kidney or bile e.g. glucuronides, sulfate and others

**Phase II metabolism almost invariably terminates biological activity**

**Examples**

**Glucuronide conjugation**: salicylates, paracetamol, morphine

**Sulfate conjugation**: paracetamol, estrogen, steroids.

**Acetylation** e.g. INH, hydralazine (N-acetyltransferase)

**Glutathione conjugation** e.g. halothane, paracetamol overdose.

**Most drugs undergo both phase I and II reaction; few have no major conjugates e.g. warfarin**

## Enzyme induction

Enzyme induction refers to the increase in enzyme amount and activity as a result of exposure to certain chemicals.

It is accompanied by hypertrophy of liver cell endoplasmic reticulum which contains most drug metabolizing enzymes.

## Non-microsomal enzymes are not inducible

**Examples of enzyme inducers:** barbiturates, rifampicin, phenytoin, carbamazepine, griseofulvin, smoking, chronic (not acute) alcohol ingestion

## The importance of enzyme induction

1. **It can be responsible for clinically important interactions**

**Examples**

a. **contraceptive failure** if potent inducers are taken at the same time
b. **increased breakdown of vitamin D** resulting in osteomalacia and hypocalcemia; and also in megaloblastic anemia due to folate deficiency
c. **failure of anticoagulant therapy** due to reduction of warfarin level

2. **Tolerance** to certain drugs may occur e.g. with antiepileptic drugs which can induce their own metabolism
3. **Drug toxicity** may be more likely e.g. in paracetamol ovcerdose and in patients on rifampicin or INH (hepatotoxicity)
4. **Enzyme inducers can alter liver function tests.** The level of serum bilirubin helps to distinguish the effect of enzyme induction from that of liver disease

5. **Enzyme induction can be used as a therapeutic mean e.g.** phenobarbitone can reduce severe hyperbilirubinemia in neonates by stimulation of fetal hepatic glucuronyl transferase

**Enzyme inhibition**

**Enzyme inhibition is an important mechanism for drug-drug interaction** and can lead to drug accumulation and toxicity particularly with drugs of low therapeutic index

A. **General non-specific inhibition of microsomal enzymes e.g.** cimetidine (inhibits metabolism of warfarin, diazepam, propranolol)

**Other examples:** sodium valproate, chloramphenicol, INH, single large dose of ethanol

B. **Inhibition of specific enzymes could be a mechanism for therapeutic action of drugs**

e.g. captopril inhibits ACE
aspirin inhibits cyclooxygenase
selegiline inhibits MAO(B)
allopurinol inhibits xanthine oxidase

**Elimination**

**Drugs can be eliminated by the following mechanisms**:

1. **Metabolism**
2. **Storage** e.g. highly lipid soluble drugs in fat, heavy metals in bone, phenothiazines and chloroquine in melanin-containing tissues
3. **Excretion**

## IV. Excretion

**Renal excretion**: is the most important route of excretion if the drug is water-soluble and of low molecular weight

**Three mechanisms for excretion**

### a. Glomerular filtration

- binding to plasma proteins slows the filtration rate of drugs

### b. Active tubular secretion

- requires energy
- shows competition and saturation
- occurs in the proximal tubules

**There are two active transport systems:**

For **weak acids** e.g. penicillins, probenecid, phenobarbitone, aspirin

For **weak bases** e.g. amphetamine, imipramine, chloroquine

### c. Tubular reabsorption

- may be active or passive
- the passive is controlled by the pH of the tubular fluid and pKa of the drug
- acids are best eliminated in alkaline urine and bases best in acid urine

**Drug clearance**: is the volume of the body compartments from which the drug is removed in unit time. Total body clearance of the drug is the sum of the clearances by all routes of elimination (usually hepatic and renal)

**Elimination in milk**

Only free (unbound) drug can be excreted in milk according to pH, pKa, and lipid-solubility

Milk pH is toward acidic side and, therefore, basic drugs ionize and may accumulate in milk

Examples of drugs contraindicated during breast feeding: chloramphenicol, anticancer drugs, repeated doses of ergot alkaloids

**Pulmonary elimination**

Important for volatile anesthetics and for alcohol (from medicolegal aspect)from blood to gut lumen

**Fecal elimination**

Either the drug is not absorbed

Passive diffusion

Biliary elimination