

# Pharmacology

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# GENERAL PHARMACOLOGY : PART 1

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## Types of Drugs

00:00:07

Orphan drugs : used for **rare diseases** → ↓ Profitability.

Essential drugs : meets healthcare needs of the majority of a population.

- Inexpensive.
- Easily available.
- Efficacious.
- Safe.
- **Single molecule** (Not fixed dose combination).

Prescription/legend drugs : Require prescription (under **Schedule H**).

Spurious drugs : Do not produce expected effect as drug component is falsified.

Misbranded drugs : Incorrect or missing information on drug label (Produces adequate effect).

Adulterated drug : Unwanted **additive** in drug (Cough syrup : Glycerine contaminated with diethylene glycol → Renal failure).

P-drug :

- 'Personal drug' for any disease.
- **STEP** criteria to choose P-drug :
  - Safe.
  - Tolerable.
  - Efficacy.
  - ↓ Price.

Rational Drug Use :

use of right drug for right disease & patient; at right dose, duration & route with right dispensation & monitoring ("Right price" **not included**).

## Pharmacokinetics and Pharmacodynamics

00:14:05

Pharmacokinetics :

Movement of drug through the body (**ADME**) :

- Absorption.
- Distribution.
- Metabolism.
- Excretion.

Pharmacodynamics :

Drug induced changes in body via target (**DRE** : Drug receptor effect).

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## Drug Absorption

00:17:24

- m/c mechanism: **Passive diffusion**.
- ↑ Diffusion: **Unionized drug** (Same pH of drug and medium) d/t ↑ **lipid solubility**.
- **maximum absorption** → **Small intestine** (Large surface area).

**Pka**: pH where drug → 50% ionized & 50% unionized.

### Oral Absorption:

Good oral absorption drugs :

Drugs with :

- **Small size**.
- ↑ **Lipid solubility**.

Poor oral absorption drugs :

- **Proteins** d/t large size.
- Drugs ending with :
  - tide (Octreotide).
  - ase (Asparaginase).
  - mab (Trastuzumab).

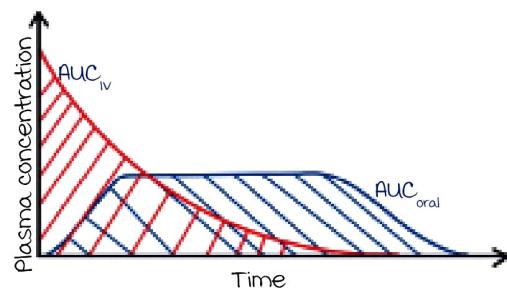
### Extent and Rate of Absorption:

Extent of absorption :

- Amount of drug absorbed.
- AKA **bioavailability** (f: Fraction).
- Formula :

$$\text{Bioavailability (BA)} = \frac{\text{AUC}_{\text{oral}}}{\text{AUC}_{\text{IV}}}$$

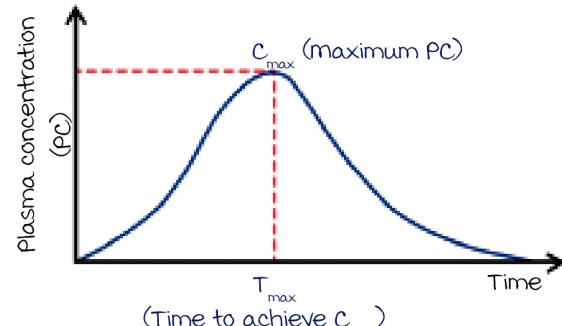
(AUC = Area under curve)



- Normal range of BA: 0 to 1.
- 100% BA: IV and **inhalational gas**.
- BA depends on :
  - Bypassing 1<sup>st</sup> pass metabolism.
  - Absorption.

Rate of absorption :

- Amount of drug absorbed per unit of time.
- Determined by **T<sub>max</sub>**.



**Fastest rate** : **Inhalational route**.

Role of ATP Binding Cassette (ABC) :

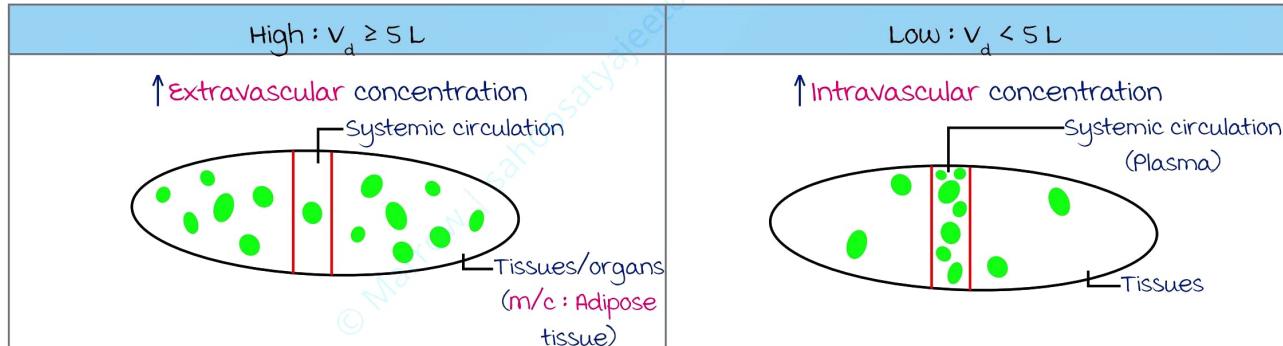
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- AKA p-glycoprotein (p-GP)/multidrug resistance-1 (MDR-1) pumps.
- Helps in drug efflux.

	Substance excreted by p-GP	Drugs & action on p-GP	Effect of drug
Intestinal cell	Digoxin	Clarithromycin : (−)	Digoxin toxicity
		Rifampicin : (+)	Digoxin failure
BBB	Loperamide	Quinidine : (−)	Loperamide induced respiratory depression
Hepatocyte	Bile acids	Cyclosporine : (−)	Cholestasis
Tumor cell/ bacteria	Anticancer/antibiotics (Cause resistance)	Verapamil : (−) (Competitive)	(−) Development of resistance

Drug Distribution

00:41:47

volume of distribution ( $V_d$ ) : $\alpha V_d$  :

$$\alpha V_d = \frac{D}{C_0} = \frac{\text{Dose of drug via IV route}}{\text{Initial PC} (C_{max})}$$

$$D = \alpha V_d \times C_T \text{ (Target PC)}$$

Significance :

## i. Loading dose (LD) :

i. In IV route :

$$LD = \alpha V_d \times C_T$$

ii. Other route :

$$D \times f = \alpha V_d \times C_T$$

$$LD = \frac{\alpha V_d \times C_T}{f}$$

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2. Dialysis : Not effective against high  $V_d$  drugs.

Drugs with $\uparrow V_d$ (BAD DOC)	Antidote
Benzodiazepine	Flumazenil
$\beta$ -blocker	Glucagon
Amphetamines	Ammonium chloride
Digoxin	Digibind
Opioids	Naloxone
Organophosphates	Atropine
Calcium channel blockers	Calcium gluconate

### Plasma Protein Binding :

Proteins :

Albumin (m/c)	Alpha-1-acid glycoprotein
Binds to <b>acidic</b> drugs	Binds to <b>basic</b> drugs
<ul style="list-style-type: none"> <li>• Aspirin</li> <li>• Anti-coagulant (warfarin)</li> <li>• Anti-epileptics/ anti-psychotics/ anti-depressants</li> <li>• Antibiotics (Sulfonamides)</li> </ul>	<ul style="list-style-type: none"> <li>• Opioids</li> <li>• Tricyclic anti-depressants</li> <li>• <math>\beta</math>-blockers</li> <li>• Anti-arrhythmics (Amiodarone/Lidocaine)</li> </ul>

Significance :

Hypoalbuminemia d/t :

i)  $\downarrow$  Synthesis :

- $\downarrow$  Drug binding

$\uparrow$  Free drug

$\uparrow$  Toxicity.

- Seen in cirrhosis.

ii)  $\uparrow$  Excretion :

- $\uparrow$  Drug excretion (Albumin bound)

$\uparrow$  Failure.

- Seen in :

- Nephrotic syndrome.
- Diabetes mellitus.
- Chronic kidney disease.

## Drug Metabolism

00:54:14

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## Phases :

	Phase I	Phase II (AKA conjugation)
mechanisms	Breakdown of drug (S) + Addition of functional group (FG)	Conjugate (-ve charged) binds to FG ↓ Ionised/water soluble drugs
Reactions	ORCHAD : • Oxidation (m/c) • Reduction • Cyclization • Hydrolysis	GAMS (mnemonic) : • Glucuronidation (m/c) • Glycation • Glutathionation • Acetylation • Methylation • Sulfation
Enzyme involved	CYP450 enzymes : m/c : CYP3A4	Glucuronyl transferase (GT) : Glucuronidation
Clinical significance	-	Crigler Najjar syndrome : ↓ GT → ↑ Toxicity of : i) Irinotecan ii) Atazanavir

## Note :

CYP450 enzymes (m/c : CYP3A4) :

- CY : Cytochrome → Heme protein.
- P : Pigments that absorb light of 450 nm wavelength.
- 3 : Family.
- A : Sub-family.
- 4 : Gene isoform number.

## Drug-Enzyme Interaction :

	Enzyme inducers	Enzyme inhibitors
Effect	Cause drug failure	Cause drug toxicity
Examples	mnemonic : GRAB PC • Griseofulvin • Rifampicin • Alcohol (Chronic consumption) • Benzopyrene • Phenytoin, Phenobarbital, Primidone • Carbamazepine, Cigarettes	mnemonic : QUICK VEG, DISK • Quinidine • Isoniazid, Protease inhibitors • Cimetidine, Chloramphenicol, Ciprofloxacin • Ketoconazole, Itraconazole, Fluconazole • Valproate • Erythromycin • Grapefruit juice • DEC, Delavirdine, Disulfiram
Important drug interactions	Rifampicin : • OCP failure • C/i in HIV with TB : - Affects Dolutegravir - Rx : Double the dose of Dolutegravir or change Rifampicin to Rifabutin	• Erythromycin → Theophylline toxicity • Clarithromycin → Statin toxicity

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Drugs metabolised by Plasma Esterase :Quick action of plasma esterase  $\rightarrow$  Short  $T_{1/2}$  of drugs.

Examples : Plasma Esterase Can Readily metabolise Short Acting drugs.

- Procaine, cocaine.
- Esmolol, Landiolol
- Clevidipine.
- Remifentanil, Remimazolam.
- Mivacurium.
- Succinylcholine.
- Acetylcholine.

Drug Excretion

01:07:50

- m/c organ : Kidney.
- Differing pH b/w drug & medium  $\rightarrow$   $\uparrow$  Ionization  $\rightarrow$   $\uparrow$  water solubility  $\rightarrow$   $\uparrow$  Excretion.

Significance :

Drug toxicity :

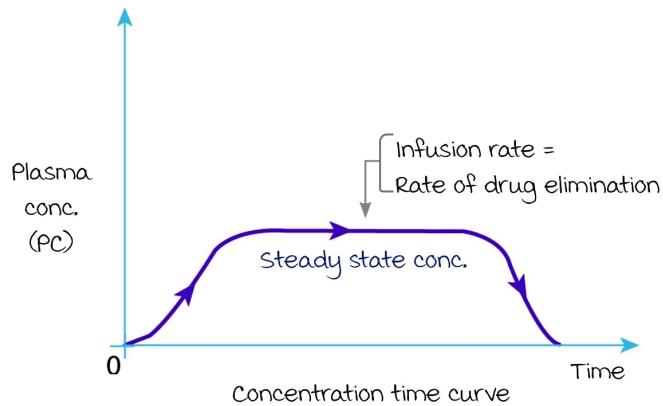
- Acidic drugs (Aspirin, Phenobarbital)  $\rightarrow$  Alkalisation of urine with bicarbonate.
- Basic drugs (Amphetamines)  $\rightarrow$  Acidification of urine with ammonium chloride.

mechanisms :

Tubular secretion (80%) :  $\rightarrow$  Filtration (20%) :  
 Free + plasma protein bound.  $\rightarrow$  Free drug only.

Calculations :

Aim : Achieve &amp; maintain steady state plasma concentration (SSPC).



Rate of drug elimination : Amount of drug excreted per unit of time.

$$\text{Rate (in mg/hr)} = \text{PC} \times \text{clearance}$$