

Pharmacology

World of Revision

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GENERAL PHARMACOLOGY : PART 1

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Types of Drugs

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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 causes → 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

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Pharmacokinetics :

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

- Absorption.
- Distribution.
- metabolism.
- Excretion.

Pharmacodynamics :

Drug induced changes in body via target (**DRE** : **D**rug **r**eceptor **e**ffect).

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Drug Absorption

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- **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).

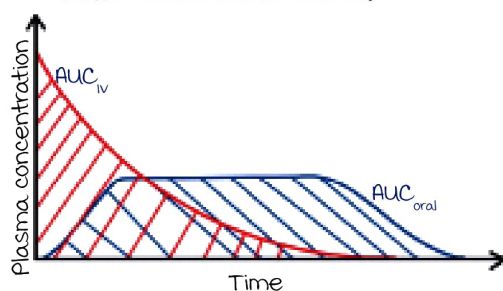
Extent and Rate of Absorption :

Extent of absorption :

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

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

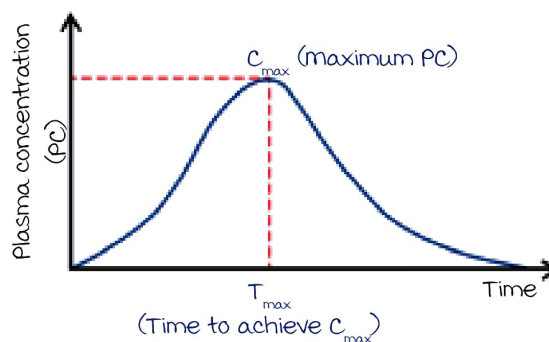
(AUC = Area under curve)



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

Rate of absorption :

- Amount of drug absorbed per unit of time.
- Determined by **T_{max}**.



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 : \ominus	Digoxin toxicity
		Rifampicin : \oplus	Digoxin failure
BBB	Loperamide	Quinidine : \ominus	Loperamide induced respiratory depression
Hepatocyte	Bile acids	Cyclosporine : \ominus	Cholestasis
Tumor cell/ bacteria	Anticancer/antibiotics (Cause resistance)	Verapamil : \ominus (Competitive)	\ominus Development of resistance

Drug Distribution

00:41:47

Volume of Distribution (V_d) :

High : $V_d \geq 5L$	Low : $V_d < 5L$
<p>\uparrow Extravascular concentration</p> <p>Systemic circulation</p> <p>Tissues/organs (m/c: Adipose tissue)</p>	<p>\uparrow Intravascular concentration</p> <p>Systemic circulation (Plasma)</p> <p>Tissues</p>

 aV_d :

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

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

Significance :i. **Loading dose (LD) :**

i. In IV route :

$$LD = aV_d \times C_T$$

ii. Other route :

$$D \times f = aV_d \times C_T$$

$$LD = \frac{aV_d \times C_T}{f}$$

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2. Dialysis : Not effective against high V_d drugs.

Drugs with ↑ V_d (BAD DOC)	Antidote
Benzodiazepine	Flumazenil
β-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 acidic drugs	Binds to basic drugs
<ul style="list-style-type: none"> Aspirin Anti-coagulant (Warfarin) Anti-epileptics/anti-psychotics/anti-depressants Antibiotics (Sulfonamides) 	<ul style="list-style-type: none"> Opioids Tricyclic anti-depressants β-blockers Anti-arrhythmics (Amiodarone/Lidocaine)

Significance :

Hypoalbuminemia d/t :

i) ↓ **Synthesis** :

- ↓ Drug binding

↓
↑ Free drug↓
↑ **Toxicity.**

- Seen in cirrhosis.

ii) ↑ **Excretion** :

- ↑ Drug excretion (Albumin bound)

↓
↑ **Failure.**

- Seen in :

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

Drug Metabolism

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Phases :

	Phase I	Phase II (AKA conjugation)
mechanisms	Breakdown of drug (D) + Addition of functional group (FG)	Conjugate (-ve charged) binds to FG ↓ Ionised/water soluble drugs
Reactions	ORCHAD : <ul style="list-style-type: none"> Oxidation (m/c) Reduction Cyclization Hydrolysis <ul style="list-style-type: none"> Aliphatic and aromatic hydroxylation Deamination 	GAMS (mnemonic) : <ul style="list-style-type: none"> Glucuronidation (m/c) Glycination 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 <ul style="list-style-type: none"> Griseofulvin Rifampicin Alcohol (Chronic consumption) Benzopyrene Phenytoin, Phenobarbital, Primidone Carbamazepine, Cigarettes 	mnemonic : QUICK VEG, DISK <ul style="list-style-type: none"> Quinidine Isoniazid, Protease inhibitors Cimetidine, Chloramphenicol, Ciprofloxacin Ketoconazole, Itraconazole, Fluconazole Valproate Erythromycin Grapefruit juice DEC, Delavirdine, Disulfiram
Important drug interactions	Rifampicin : <ul style="list-style-type: none"> OCP failure C/i in HIV with TB : <ul style="list-style-type: none"> Affects Dolutegravir Rx : Double the dose of Dolutegravir or change Rifampicin to Rifabutin 	<ul style="list-style-type: none"> 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.
- Remifentanyl, Remimazolam.
- mivacurium.
- Succinylcholine.
- Acetylcholine.

Drug Excretion

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

Significance :

Drug toxicity :

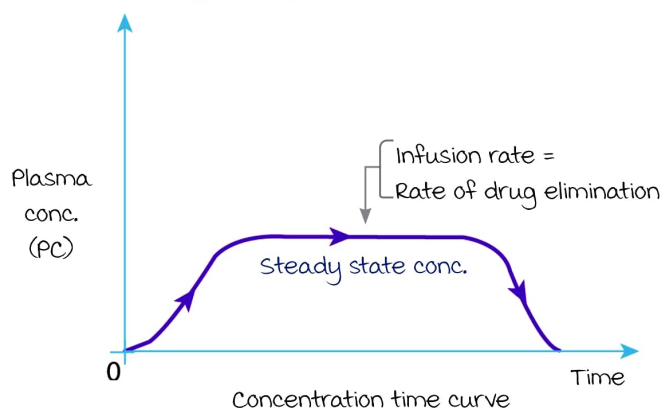
- Acidic drugs (Aspirin, Phenobarbital) \rightarrow Alkalinisation of urine with bicarbonate.
- Basic drugs (Amphetamines) \rightarrow Acidification of urine with ammonium chloride.

Mechanisms :

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

Calculations :

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



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

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