Pharmacology

World of Revision

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Contents

Pharmacology

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 $\xrightarrow{\text{Causes}}$ 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

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).

----- Active space -----

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).

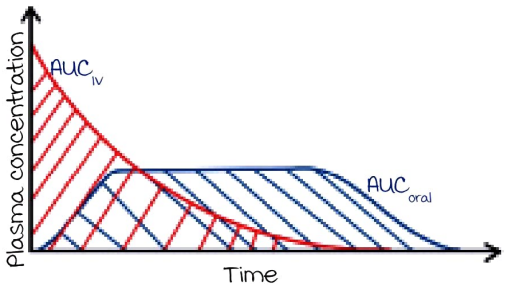
Extent and Rate of Absorption :

Extent of absorption :

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

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

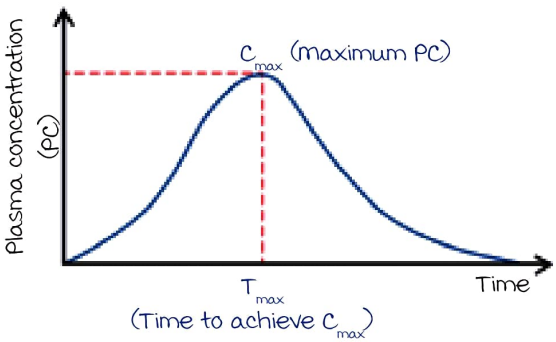
(AUC = Area under curve)



- 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.

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Role of ATP Binding Cassette (ABC) :

- 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

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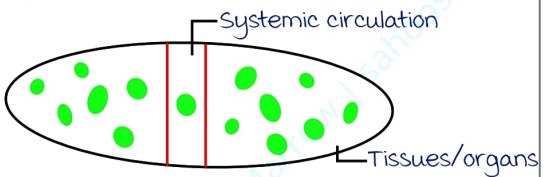
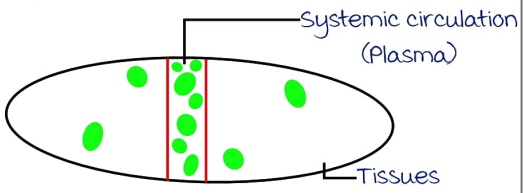
Volume of Distribution (V_d) :

High : $V_d \geq 5$ L	Low : $V_d < 5$ L
↑Extravascular concentration  	↑Intravascular concentration 

aV_d :

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

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

Significance :

1. 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
• Aspirin • Anti-coagulant (Warfarin) • Anti-epileptics/ anti-psychotics/ anti-depressants • Antibiotics (Sulfonamides)	• 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 : • Oxidation (m/c) • Reduction • Cyclization • Hydrolysis • Aliphatic and aromatic hydroxylation • Deamination	GAMS (mnemonic) : • 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 • 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 → 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 → ↑Ionization → ↑Water solubility → ↑Excretion.

Significance :

Drug toxicity :

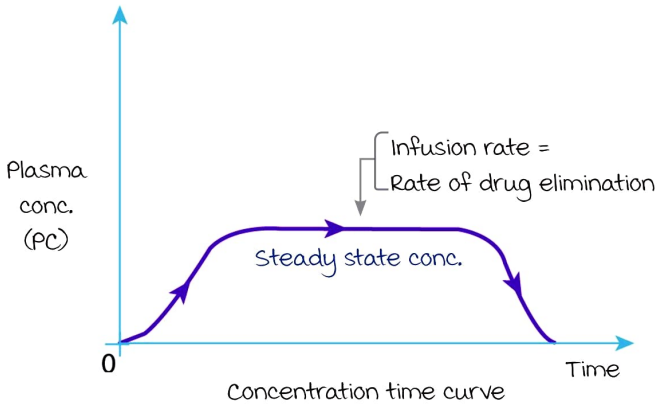
- Acidic drugs (Aspirin, Phenobarbital) → Alkalinisation of urine with bicarbonate.
- Basic drugs (Amphetamines) → Acidification of urine with ammonium chloride.

Mechanisms :

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

Calculations :

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



Concentration time curve

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

Rate (In mg/hr) = PC x clearance