PHARMACOLOGY

RR-8.0

Contents

GENERAL PHARMACOLOGY : PART 1

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Types of Drugs

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Orphan drugs :

Used for rare diseases → ↓Profitability (↓Development of drug).

Note : Orphan receptor → Receptor with unknown ligand.

Essential drugs :

Meets healthcare needs of the majority of a population :

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

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

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

Misbranded drugs : Incorrect or missing information on drug label.

Adulterated drug : Unwanted additive in drug.

Rational Drug Use :

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

Movement of Drug Through the Body (ADME)

00:08:00

Note : Pharmacodynamics → Drug induced change in body via receptor binding (Drug receptor effect).

Drug Absorption

00:10:10

- M/c mechanism : Passive diffusion along concentration gradient.
  - (Lipid soluble; Unionised drugs → pH of drug = pH of medium).
- Maximum absorption of drug in GIT : Small intestine (D/t large surface area).
- Poor oral absorption : Drugs with large size (Eg : Proteins → Drugs with -tide/-ase/-mab).

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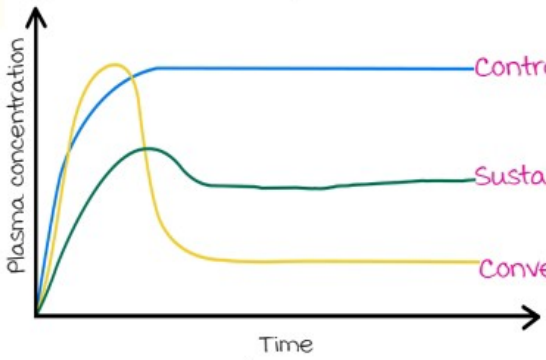
Types of Tablets/Capsules :



Controlled release : Drug covered with a membrane.

Sustained release : Over a period of time; drug embedded within layers.

Conventional release : Peak present.

Uses of controlled/sustained release :

- ↑Duration of effect → ↓no. of doses. (Useful if t1/2/< 4h).
- ↓Risk of acute toxicity : D/t lower/absent peak concentration.

Enteric coated drugs :

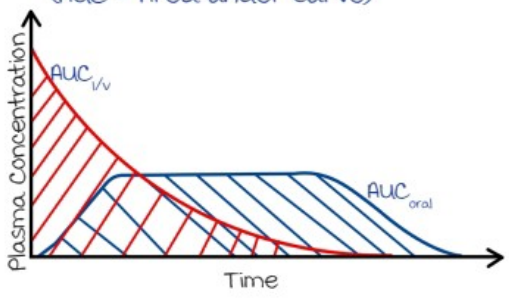
- HCl-resistant membrane coating used.
- Prevents drug breakdown in acidic pH of stomach.

Extent of Absorption :

- Amount of drug absorbed.
- AKA bioavailability.
- Formula :

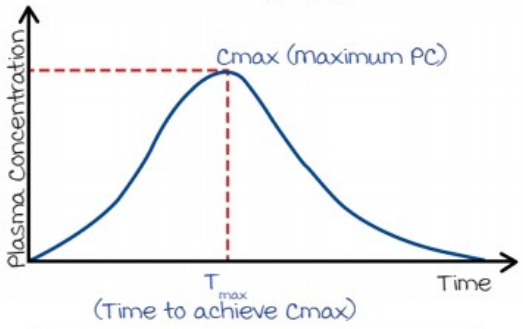
$$\text{Bioavailability} = \frac{AUC_{oral}}{AUC_{i/v}}$$

(AUC = Area under curve)



Rate of Absorption :

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



(Time to achieve Cmax)

Note → RATE : Rate → T_{max}
AUC → Extent

ATP-binding Cassette (ABC) :

AKA : p-glycoprotein/multi-drug resistance (MDR)-1 pumps.

Physiological functions :

1. Intestine/liver : Drug efflux (Eg : Digoxin).
   ↓Drug concentration in systemic circulation due to removal.
2. Blood brain barrier : Limit drug exposure to central nervous system.
   Removes drugs that cross the BBB → No central effects (Eg : Loperamide).
3. In liver : Excretion of bile acids.

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Pathological function :

Cancer cells/bacteria : use the pump to remove drug. (Confers resistance → AKA MDR-1 pump).

p-GP/MDR-1 substrates	
• Loperamide	• Digoxin
• Methadone	• Erythromycin, Clarithromycin
• Nelfinavir	• Quinidine
• Cyclosporine	• Ranolazine
• CCB (Verapamil)	• Sotagliflozin

p-GP/MDR-1 inducers
Enzyme inducers like :
• Rifampicin
• Phenytoin
• Carbamazepine

Significance :

1. pGP substrates competitively inhibit each other → ↑Toxicity of either drug.
   Eg :
   - Clarithromycin + Digoxin → Digoxin toxicity.
   - Quinidine → Loperamide induced CNS toxicity (Crosses BBB).
2. pGP inducers cause drug failure.
   Eg : Rifampicin + Digoxin → ↑Digoxin efflux → Rx failure.
3. pGP substrates can cause cholestatic jaundice :
   D/t competitive inhibition of bile acid excretion. Eg : Cyclosporine.
4. pGP inhibitors can be used to reverse drug resistance.
   m/c used : Verapamil.

Drug Distribution

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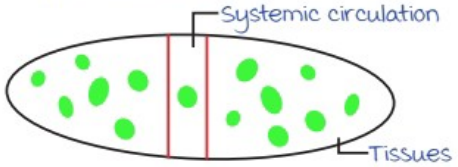
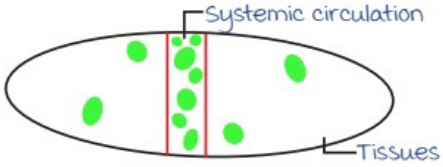
Volume of Distribution (V_d) :

High volume of distribution	Low volume of distribution
↑Extravascular concentration.	↑Intravascular concentration.
	

Formulae :

$$\text{Apparent } V_d \ (aV_d) \text{ (Liters)} = \frac{D}{C_0} = \frac{\text{Dose via IV route}}{\text{Initial PC}}$$

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

Note : Loading dose $\propto aV_d$.

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Significance :

Dialysis : Not effective for 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 :

1. Liver cirrhosis :
   ↓Albumin production → ↓Drug binding → ↑Free drug → ↑Toxicity.
2. Nephrotic syndrome/Chronic kidney disease :
   ↑Albumin excretion → ↑Drug excretion → Drug failure.
3. ↑Alpha-1-acid glycoprotein :
   Seen in RA, IBD, MI → ↓Free drug → Drug failure.

Drug Metabolism

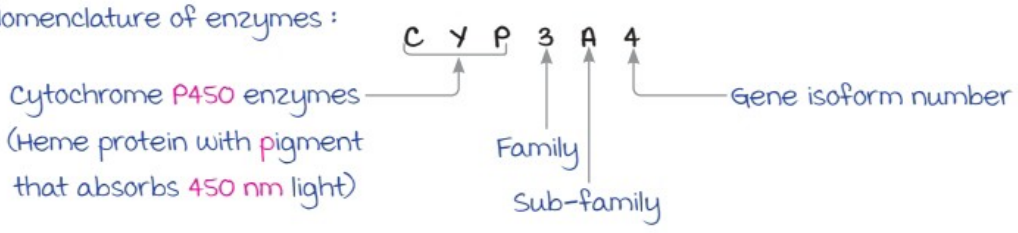
00:45:12

Phase I vs. Phase II Reactions :

	Phase I reactions	Phase II reactions
Purpose	Drug inactivation	Make drug water soluble
m/c reaction	Oxidation	Glucuronidation
m/c enzyme	CYP3A4	Glucuronyl transferase (GT)

Note :

- Nomenclature of enzymes :



- Crigler-Najjar syndrome : ↓GT → ↑Toxicity of → Irinotecan (Anti-cancer).
  → Atazanavir (Anti-HIV).

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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, Clarithromycin • Grapefruit juice • DEC, Delavirdine, Disulfiram
Important drug interactions	Rifampicin : • OCP failure • C/I in HIV with TB	• Erythromycin → Theophylline toxicity • Clarithromycin → Statin toxicity

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.
- Clevidipine.
- Remifentanil, Remimazolam.
- Mivacurium.
- Succinylcholine.
- Acetylcholine.

Drug Excretion

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m/c organ : Kidney (Drug needs to be ionized & water soluble).
→ (Acidic drug → Basic media and vice versa).

Significance :

Drug toxicity :

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

Mechanisms :

- Filtration : Only free drug excreted.
- Tubular secretion : Free + plasma protein bound drug excreted.

Calculations :

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

Rate = P.C. x clearance (in mg/hr)

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Infusion rate (IR) : Amount of drug to be administered per unit of time.

IR : Rate of drug elimination = P.C. x clearance

Maintenance dose : Dose required to maintain steady state of drug P.C.

MD = P.C. x clearance x time

Half-life :

$$t_{1/2} = \frac{0.693 \times V_d}{\text{Clearance}} = \frac{0.693}{K_{\text{elimination}}}$$

Note : Infusion rate & maintenance dose ∝ Clearance.

Order of Kinetics :

	Zero order Kinetics	First order Kinetics
Definition	Constant amount eliminated per hour	Constant proportion eliminated per hour
Effect of ↑sing dose	• $T_{1/2}$ ↑ • Clearance ↓ • P.C. : Disproportionate ↑	• $T_{1/2}$ constant • Clearance constant • P.C. : Proportionate ↑
Risk of toxicity on overdosing	Higher	Lower
Examples	Zero ATP Has Made Weak : • Alcohol • Theophylline, Tolbutamide • Phenytoin • Heparin • Methanol • Warfarin	Most drugs

GENERAL PHARMACOLOGY : PART 2

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Drug $\xrightarrow{\text{Binds to}}$ Receptor $\xrightarrow{\text{Causes}}$ Effect.

Factors Affecting Pharmacodynamics :

Affinity :

- Tendency of a drug to bind to its receptor.
- Marker of dose $\left[\text{Affinity } \alpha \frac{1}{\text{Dose}}\right]$.

Efficacy :

- Maximum clinical effect produced by a drug (most important factor).
- Marker of effect of drug.

Potency :

- Relative dose of a drug required to produce particular effect.
- Potency $\alpha \frac{1}{\text{Dose}}$.

Dose-Response Curve (DRC)

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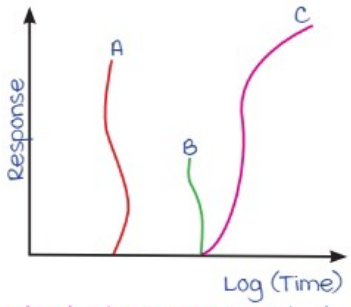
Graded Curve :

Response is graded.



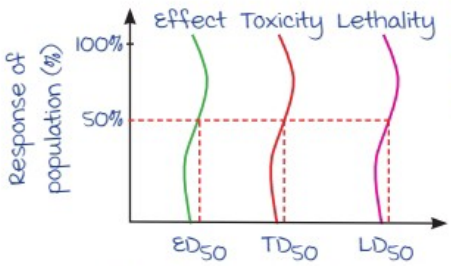
Individual responses noted.

- Efficacy : Height of curve.
  - C > A > B.
- Potency : Left shift.
  - A > B > C.

HELP

- Affinity :
  Compared only if acting on the same receptor.
  - Parallel graphs = Same receptor.
  - A > B.

Quantal Curve :



- Response : Binary (Yes/No) → Eg : Sedation.
- Population response noted.
- In 50% population, dose required to cause :
  - Effect : ED_{50} (marker of potency).
  - Toxicity : TD_{50}
  - Lethality : LD_{50}

} marker of toxicity.

Note : Lethality checked only in animals.