PHARMACOLOGY

ED.08

INTRODUCTION TO PHARMACOKINETICS AND PHARMACODYNAMICS

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Pharmacokinetics :

- Study of movement of drugs in the body after intake through any route.

Pharmacodynamics :

- Drug induced change in the body.

Course of drug through the body

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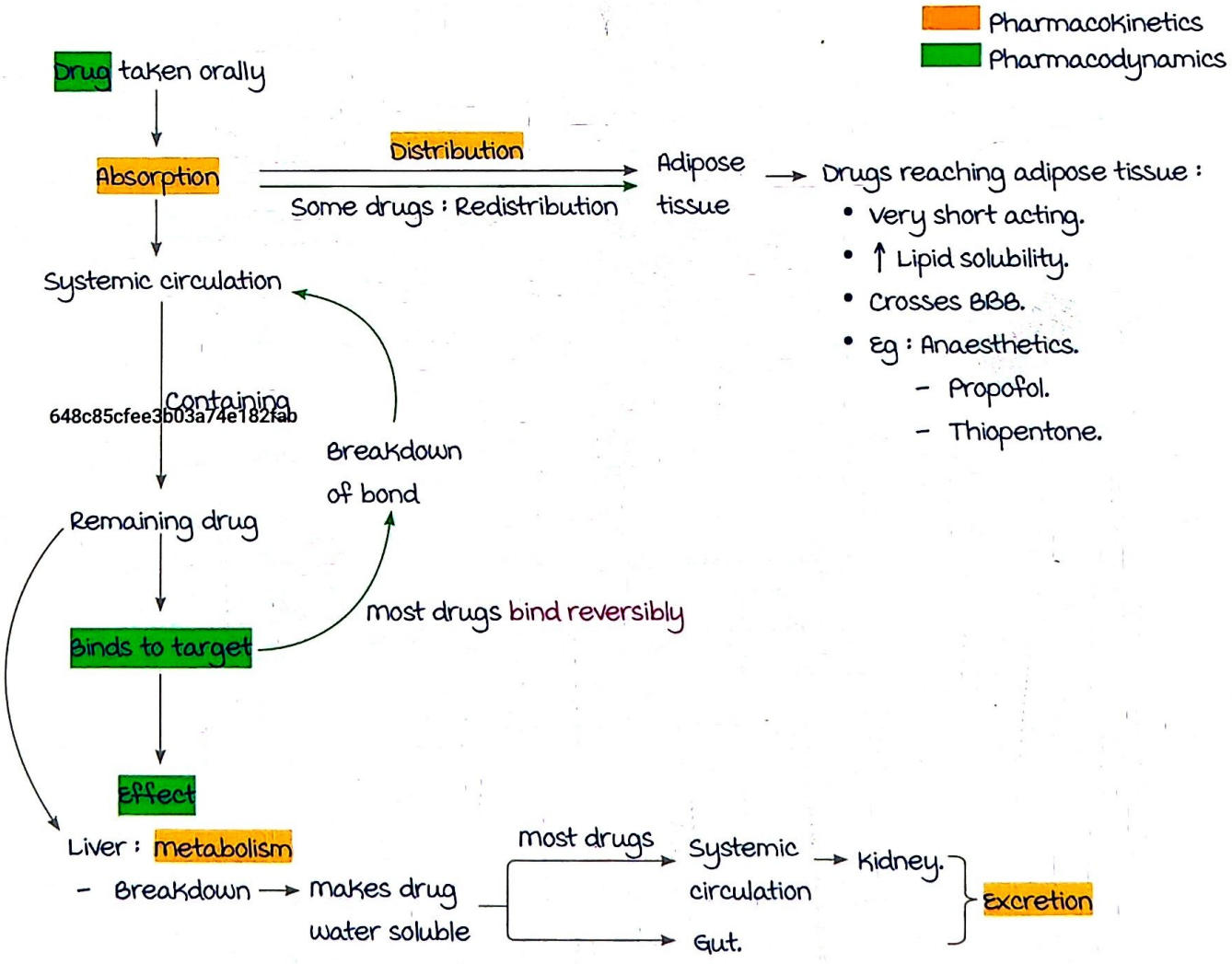

Feedback

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PHARMACOKINETICS : ABSORPTION - PART 1

Absorption

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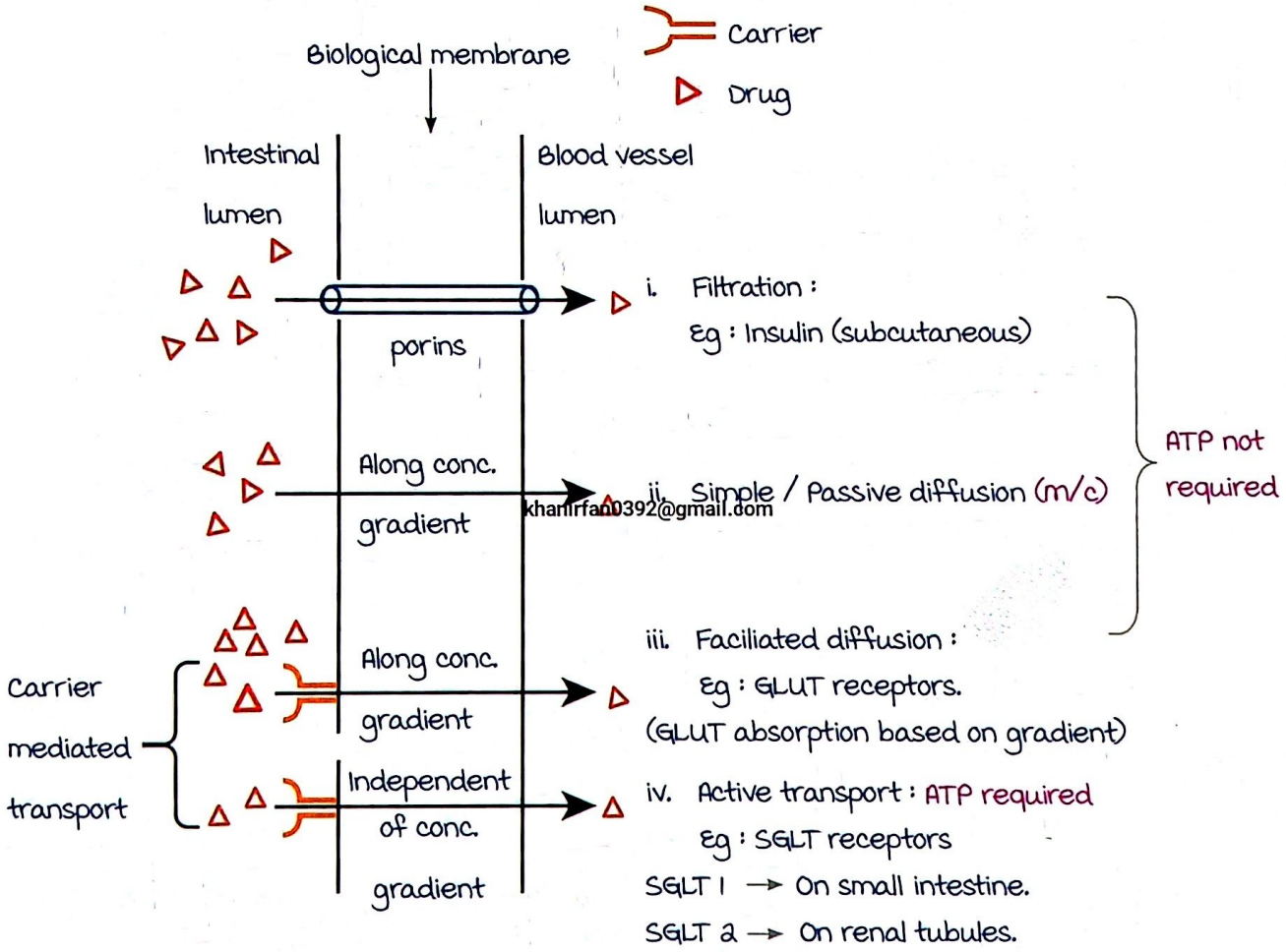

Active transport : P - glycoprotein pump (pgp)/ MDR_1 pump

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m/c type of ABC pump

Function :

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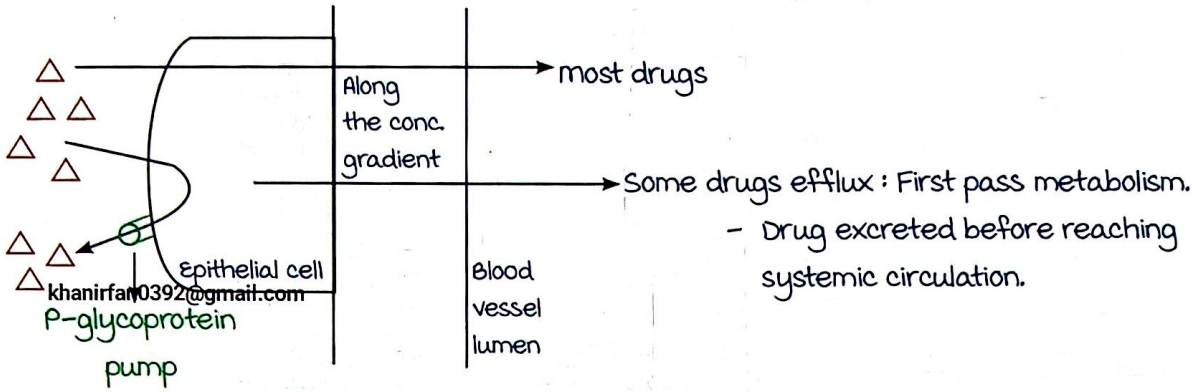
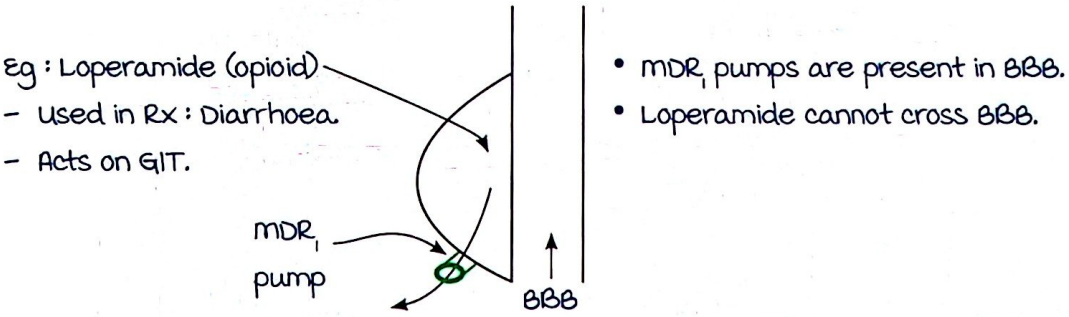
Small intestine/liver



Significance :

Eg : Digoxin dosage is calculated based on amount being lost d/t drug efflux.

Blood Brain Barrier (BBB) :



Note : Another cause of drugs not crossing BBB → Water solubility.

Placenta : Certain drugs cannot cross from maternal circulation to fetal circulation d/t presence of MDR1 pumps in placenta.

Bile acid excretion : D/t presence of MDR1 pumps on hepatocytes.

In Bacteria / Tumor cell :

Cell —develops→ Pgp pump → Drug efflux → Resistance.

Feedback

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Pharmacological significance :

Substrate :
Undergoes efflux by pump
- Loperamide
- Cyclosporine
- Digoxin

Inducers :
↑ no. of pump
(Causes drug failure)
≈ Enzyme inducers
- Rifampicin
- Phenytoin
- Phenobarbitol

Inhibitors :
↓ no. of pumps
(Causes drug toxicity)
- Verapamil
- Amiodarone
- Quinidine
- Cyclosporine
- Itraconazole
- Neratinib
- Erythromycin/ Clarithromycin

Effects of blockade :

Drug blocking PGP	Effect
• Rifampicin	Digoxin failure
• Clarithromycin	Digoxin failure
• Cyclosporine	Cholestatic jaundice
• Verapamil	Used in reversal of drug resistance (Cancer, bacteria)
• Quinidine	Loperamide induced central S/E

Passive Diffusion

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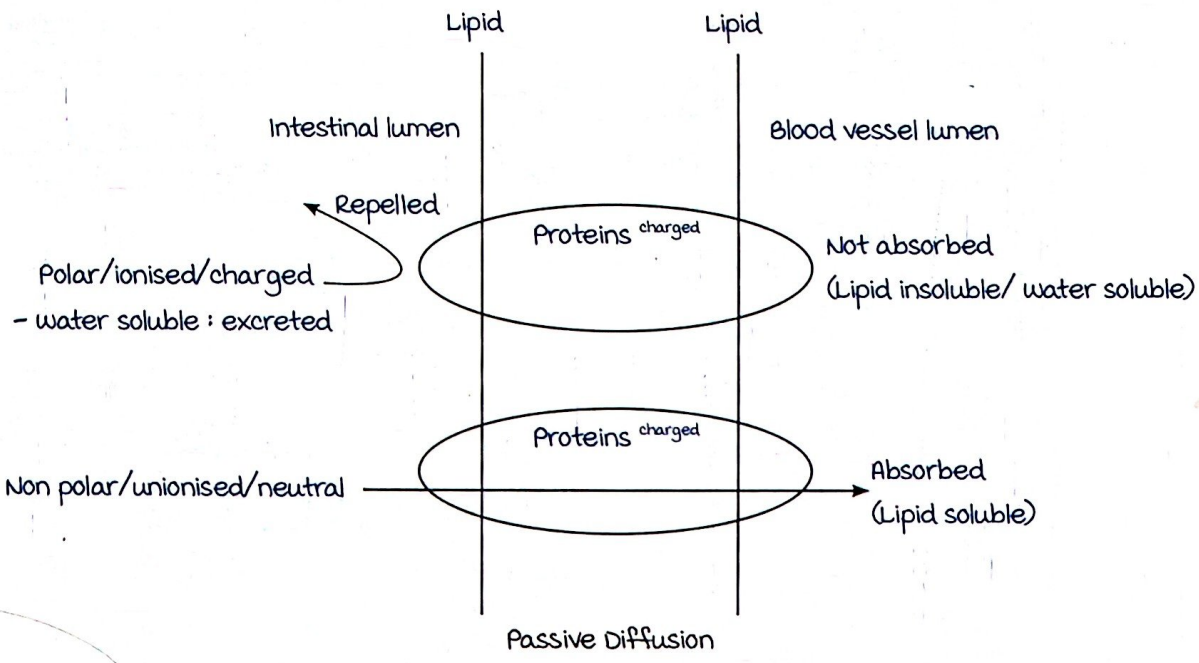

Feedback

PHARMACOKINETICS : ABSORPTION PART 2

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Ionization of drugs

00:00:10

CRITERIA

	Absorption	Excretion
Solubility	Lipid	Water
Ionization	Unionised	Ionised
Relation of pH of medium	Equal	Unequal
Polarity	Non polar	Polar

Mnemonic : LUNA Mnemonic : WIPE

UNIONIZATION

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- Acidic drug – Acidic medium : Stomach.
- Basic drug – Basic medium : Small Intestine.

Eg : Aspirin (Acidic drug) is unionized in stomach.

But max absorption of unionized drug (Both Acidic & Basic) happens in Small intestine : Duodenum (D/t large surface area).

Note : Short bowel syndrome

- Resection of small intestine → ↓ Absorption of drug.
- Mx : ↑ Dosage of drug or change route.

IONIZATION (EXCRETION)

- pH of drug and pH of medium are different.

Clinical Application :

- Acidic drug toxicity ——→ Make urine Basic
  - Aspirin ——→ By bicarbonate : Urine Alkalinizer.
  - Phenobarbital.
  - Methotrexate.
- Basic drug toxicity ——→ Make urine Acidic
  - Amphetamine ——→ By Ammonium chloride : Urine Acidifier.

Note : Other examples for Urine acidifiers are Vit C, Cranberry Juice.

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Henderson - Hasselbach Equation

00:13:28

Quantification of Ionization.

- Acidic drug → $\log \frac{[\text{Unionized}]}{[\text{Ionized}]}$ = pKa − pH (Of medium).
- Basic drug → $\log \frac{[\text{Ionized}]}{[\text{Unionized}]}$ = pKa − pH
- E.g : Ionization of acidic drug with pKa = 4 in stomach (pH = 2).

  $\log \frac{[UI]}{[I]} = 4 - 2$

  $\log \frac{[UI]}{[I]} = 2 \rightarrow \frac{UI}{I} = 10^2 \rightarrow \frac{UI}{I} = 100$ } 99% unionized & 1% ionized.
- pKa : pH of the medium at which 50% drug is ionized & 50 is Unionised

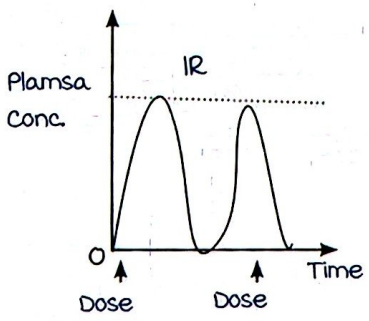
Absorption of oral drugs

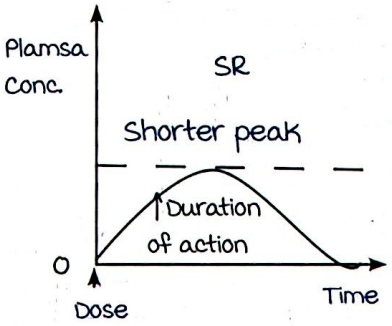
00:21:30

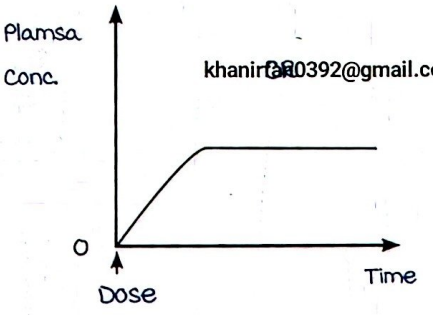
1. Delayed absorption of Oral drugs :

Tablet /Capsule

- IR : Immediate release
- ER : Extended Release
  - SR : Sustained Release
  - CR : Controlled Release
    AKA zero order CR







Mechanism : Frequent dosing : ↓Compliance.

Example : Indomethacin TID.

- Better compliance.
- Polymer coating present.
- SR Indomethacin.
- Polymer coating of pores.
- CR Zolpidem.

Feedback

2. Drugs bypassing the stomach :

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Delayed release :
- Release of drug in SI instead in stomach.
- Eg: Sulfasalazine → For ulcerative colitis.

Enteric coated :
E.g : PPI → Protect from gastric HCl.

Rate and Extent of Absorption

00:31:00

BIOAVAILABILITY (f)

Fraction of drug reaches systemic circulation unchanged.

Factors determining f :

- 100% of drug → Intestinal absorption → Liver → Fraction that reaches systemic circulation
  - Intestinal absorption → Excretion of a fraction
  - Liver → Fraction undergoes first pass metabolism

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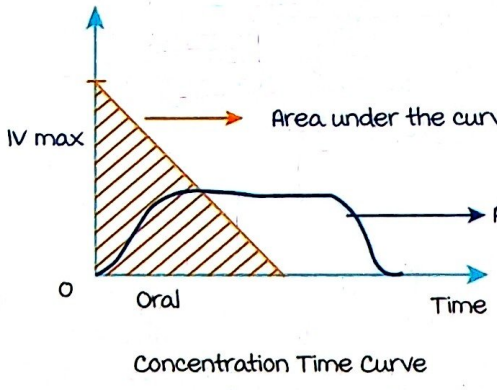
- ↑f if → Drug bypasses liver. / ↑Absorption occurs.

Plasma concentration :



Concentration Time Curve

$$\text{Bioavailability} : \frac{AUC_{oral}}{AUC_{I/V}} \times 100$$

Extent of Drug Absorption →
Only route with 100% B.V : I/V

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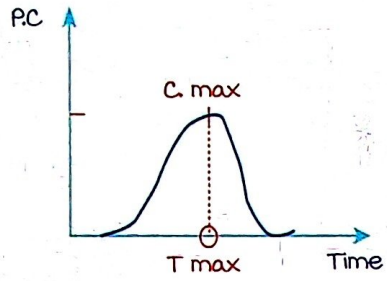
Route of administration	Bioavailability
IV	1
Im/SC	0.75-1.0
Oral	0.50-1.0

Note : f does not indicate rate of drug absorption.

RATE OF DRUG ABSORPTION



- C.max : Maximum plasma conc achieved by a drug.
- T.max : Marker of rate of drug absorption.

Bioequivalence in drug industry :

- Bioequivalence : Two pharmaceutically equivalent compound with similar rate (Tmax) and extent (AUC) of absorption.
- Branded drug : One which is invented, patented for 20 years.
- Generic drug : Legal copy of a new drug (Done after patent expires).
  - Benefit of a generic drug : Cheaper.
  - For generic drug approval : ANDA (Abbreviated New Drug Application).
- Criteria for approval :

  Generic drug = Bioequivalent to Branded drug ± 20%.

PHARMACOKINETICS : DISTRIBUTION

Apparent Volume of Distribution (AVd)

00:00:20

DEFINITION

- Hypothetical volume of plasma in litres necessary to account for the total amount of drug (intravascularly and extravascularly) in the patient's body.
- Drug with ↑ AVd → Mostly in Extravascular compartment/Tissue.
- Drug with ↓ AVd → Mostly in Intravascular compartment/Systemic.

CALCULATION

$AVd = \frac{D(dose)}{Co} \times f$ ⇒

Co → Initial plasma concentration

- f : Bioavailability
- f = 1 in intravenous route

Loading dose :

$D = \frac{AVd \times C_T}{f}$

C_T → Target plasma concentration (constant)

- $D \propto AVd/f$
  - If AVd of a drug is ↑, Dose is increased to maintain C_T

FACTORS DETERMINING APPARENT VOLUME OF DISTRIBUTION

- Fat content
  - Obesity : ↑ Volume of distribution (Vd)
  - Athletes : ↓ Vd
  - Sex : F(↑ Fat content) > M

  } ∝Vd
- Lipia Soluble (Pka).
- Albumin binding (Plasma proten binding) $\propto \frac{1}{Vd}$
- Tissue binding.

Eg :

- Distribution of Digoxin → Skeletal muscle > Heart
  (D/t ↑ mass) (Target organ)
  - Hence loading dose is determined by lean body mass (Not total body mass)

Significance in toxicity :

↑↑ Vd
- ↑ Extravascular concentration
- ↓ Intravascular concentration

} Dialysis is ineffective

Antidotes are given in toxicity.

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Drugs with ↑ Vd :

Mnemonic : BADDOC.

Drugs not cleared by dialysis	Antidotes
Benzodiazepines	Flumazenil
Beta blockers (Blocks GPCR)	Glucagon (↑ cAMP)
Amphetamines	Ammonium Chloride
Digoxin	Digibind
Opoids	Naloxone
Organophosphates	Atropine
Calcium channel blockers	Calcium gluconate

Plasma protein binding

00:22:13

Important plasma proteins :

- Albumin → Binds to Acidic drugs (m/c).
- α1 acid glycoprotein : Basic drugs.

	Albumin	α1 acid glycoprotein
Drugs bound	• Antipsychotics • Antidepressants • Antiepileptics • Antibiotics : Sulfonamides • Anticoagulant : Warfarin • Aspirin } Increase each others plasma conc. if used together ↓ ↑Bleeding	• Tricyclic antidepressants • Opioids • Antiarrythmic – β blocker – Amiodarone – Lidocaine
Effect on drugs	↓ Albumin ↓ ↑ Free drug ↓ ↑ Risk of toxicity	↑ α1 glycoprotien ↓ ↓ Free drug ↓ ↓ Effect
Clinical Application	↓ Albumin : – Nephrotic syndrome – CKD – Liver Cirrhosis – Diabetes mellitus	↑ α1 gp : • Inflammatory : – Rheumatoid arthritis – Inflammatory bowel disease • myocardial infarction

PHARMACOKINETICS : METABOLISM

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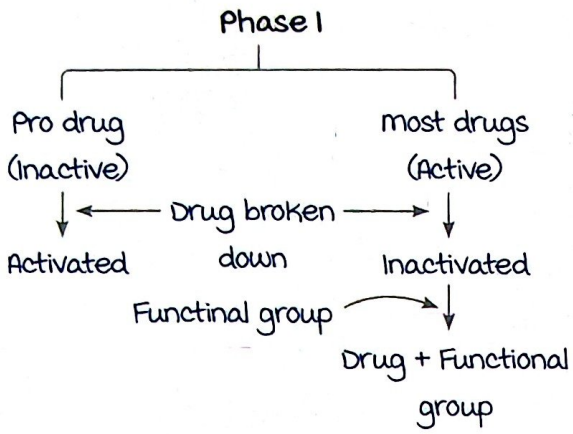

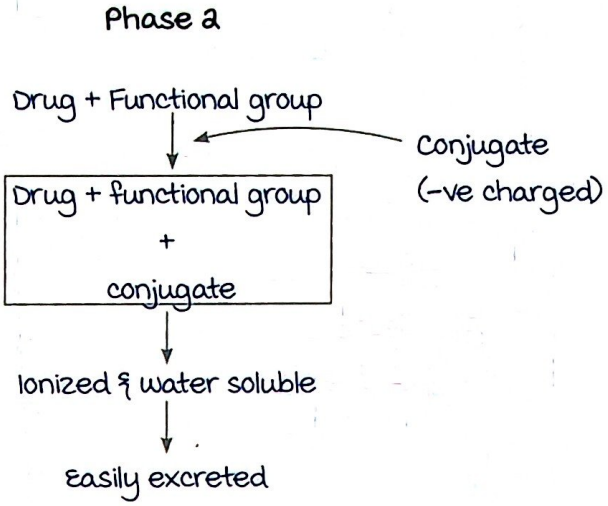

Prodrugs :

- Proguanil.
- Ramipril & other ACEi (Except Captopril, Lisinopril).
- Oxcarbazepine , Omeprazole.
- Depivefrine, Levodopa.
- Racecadotril.
- 5- Fluorouracil.
- Gemcitabine.

Note : Placebo does not contain any drug.

Reactions of Drugs in the Phases

00:06:20

Phase I Reactions :

Mnemonic : ORCHID

- Oxidation (m/c).
- Reduction.
- Cyclization.
- Hydrolysis.
- Hydrolysis.
- Aliphatic hydroxylation.
- Aromatic hydroxylation.
- Deamination.

Phase II Reaction :

Named after the conjugate :

- Glucuronidation (m/c) : Microsomal.
- Glycination.
- Glutathionation.
- Acetylation.
- Methylation.
- Sulfation.

} Non microsomal reactions.

Phase I reactions are enabled by microsomal CYP450 enzymes.

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CYP450 enzyme group

- CY (Cytochrome) : Heme protein that binds oxygen → Facilitates metabolism.
- P450 : Enzymes discovered in plant pigment, absorbs light of 450nm wavelength.
- Eg : CYP1A2

  1 → Denotes the family. A → Subfamily. 2 → Geneisoform number.

DRUGS METABOLISED IN PHASE I (BY CYP450 TYPES)

CYP1A2 :

- Paracetamol.
- Tacrine.
- Theophylline.

CYP2B6 :

- b-mercaptopurine.
- methyldopa.

CYP2C9 : Phenytoin, Warfarin.

CYP2C19 :

- metabolises Omeprazole.
- Activates Clopidogrel.

} Competitive Inhibitors (2 substrates, 1 enzyme) : Omeprazole decreases the effect of clopidogrel.

CYP2D6 :

- metabolizes :
  - Psychiatric drugs (Antidepressant, Antipsychotics).
  - Opioids.
  - β-blockers.
- Activates : Tamoxifen.

CYP2E1 :

- Ethanol —Chronic consumption→ CYP2E1 Upregulation

  ↓

  Paracetamol → ↑NAPQI → Hepatotoxicity

  (Paracetamol metabolised by CYP2E1 >> CYP2E2)

CYP3A4 (m/c) :

metabolises >50% of drugs (Eg : Mifepristone).

DRUGS METABOLISED IN PHASE II

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

Glucuronidation :

- Atazanavir (Antiviral) —Cause→ Steven Johnson Syndrome.
- Irinotecan (Anticancer) → Toxicity.

} Both drugs are C/I in Crigler Najjar syndrome.

- Estrogen :

Estrogen
↓
Liver :
- Phase I with CYP3A4
- Phase II : Glucuronidation

↓
Estrogen + Glucuronic acid (water soluble)
↓
Small intestine
↓
Glucuronidase action by gut bacteria
↓
Estrogen broken down + lipid soluble

Enterohepatic Circulation : Extension of normal $T_{1/2}$

Antibiotics ⊘ → ✕ Glucuronidase action by gut bacteria

↓ Enterohepatic circulation of estrogen
↓
↓ $T_{1/2}$
↓
OCP failure

Acetylation :

Mnemonic : HIPS Dance.

- Hydralazine..
- Isoniazid.
- Procainamide
- Sulfanamide.
- Dapsone.

} Can cause drug induced SLE.

Feedback

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

Drug Interactions

00:27:00

D/t microsomal enzymes induction or Inhibition.

	Enzyme inducers	Enzyme Inhibitors
Effect	↑ enzyme ↓ ↑ metabolism ↓ Plasma concentration ↓ ↓ Drug failure	↓ enzyme ↓ ↓metabolism ↓ ↑ Plasma concentration ↓ Drug Toxicity
Examples	• Griseofulvin • Rifampicin • Alcohol (Chronic) • Benzopyrene • Phenobarbital • Carbamazepine • St. John's wart (Plant used to treat depression)	• Acute alcohol consumption • Quinidine • Isoniazid • Cimetidine • Ciprofloxacin • Ketoconazole • Valproate • Erythromycin/Clarithromycin • Grapefruit juice • Diethylcarbamazine
Clinical Significance	In case of OCP failure d/t Rifampicin : ↓ • Change the method of contraception (IUD or condoms) or • Avoid enzyme inducers or • ↑The dose of drugs (Eg. Phenytoin & Retigabine)	1. Erythromycin → Theophyllin toxicity (↓ Arrhythmia, ↓ fibrillation) 2. Clarithromycin → Statin toxicity.

Feedback

PHARMACOKINETICS : EXCRETION

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

- Ionised / water soluble / polar drug.
- The major organs of excretion.

Kidneys (m/c organ for excretion) Liver

Note :
m/c organ involved in metabolism
↓
Liver

	Filtration (20%)	Tubular secretion (80%)
Unbound drug	+	-
Plasma protein (negative charge) bound drug	- (d/t -ve charge of basement membrane)	+

- Some drugs are excreted through saliva & sweat.

Note : Filtration is dependent on GFR → Constant rate of excretion.

Rate of drug elimination (RDE)

00:06:45

- Amount of drug eliminated per hour from the body.
- RDE = plasma concentration x Clearance
  (mg/hr) (mg/ml) (ml/hr)
  - Plasma conc : Conc of drug present in each ml of plasma → mg/ml.
  - Drug clearance : Amount of plasma being cleared of the drugs per hour.

DRUG DOSING

a. Continuous IV infusion.

b. Intermittent dosing.

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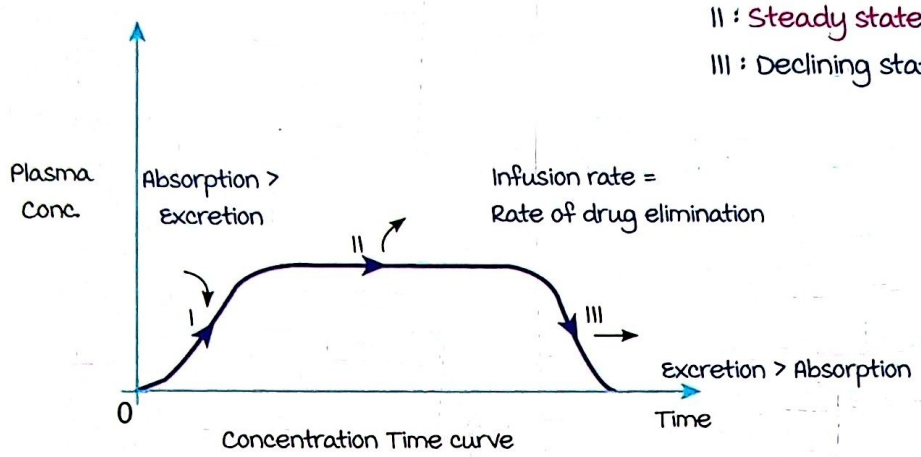
Infusion rate / Dosing rate :

- AKA loading dose.

I : Slowly rising state (Infusion).
II : Steady state plasma concentration.
III : Declining state (elimination).



- Infusion rate = Plasma concentration x clearance
- 4–5 TI/2 are required to attain steady state plasma concentration.
- Depends on Volume of distribution.

Intermittent dosing :

- AKA maintenance dose.
- Dose given after a certain period of time to maintain plasma concentration in steady state.
- Depends on Clearance.

$$\text{Maintenance Dose} = \frac{PC \times CL \times Time}{f}$$

[f : Bioavailability]
f = 1 in IV routes

Half life (TI/2) :

- $TI/2 \propto \frac{\text{Volume of distribution (Vd)}}{\text{Clearance (Cl)}} \rightarrow TI/2 = 0.693 \times \frac{Vd}{Cl} = \frac{0.693}{K_{el}}$
- Elimination constant (K_{el}) = $\frac{Cl}{Vd}$

Feedback

Kinetics of Drug elimination

00:31:40

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

		Zero order kinetics	First order kinetics
Elimination of		Constant amount of drug per hour	Constant proportion of drug per hour
RPE = $(PC)^n \times Cl$		n = 0	n = 1
Dose is constant (Cl is constant)		RDE = constant	RDE ∝ PC
If dose increases	T1/2	↑	Constant
	CL	↓	Constant
	↑ in PC	Disproportionate (risk of toxicity)	Proportionate
Seen in drugs with		Early saturation of elimination	Late saturation of elimination
Exception to the rule at		Lower doses : • Follow first order kinetics until Saturation • Hence aka pseudozero order	Higher doses : • Follows zero order after Saturation
Examples		• Alcohol (true zero order) • Theophylline, Tolbutamide • Phenytion • Heparin • methanol • Warfarin	most drugs

Feedback

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

PHARMACODYNAMICS : POTENCY, EFFICACY AND DOSE RESPONSE CURVE

Affinity, Efficacy and Potency 00:00:37

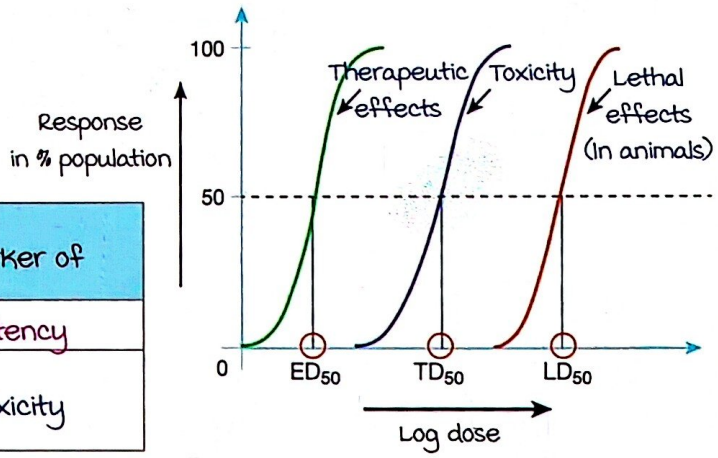
Drug
↓ Binds to } Tendency to bind : Affinity.
Target
↓ Produces } Maximum effect produced : Efficacy → Clinically most important.
Effect

Potency :
Relative dose of a drug required to produce particular effect (Lesser the dose to bring about efficacy → ↑ potency).

Dose Response Curve (DRC) 00:11:50

QUANTAL DRC :

- Response : Binary (Present/Absent)
  Eg : Sedatives, Fertility drugs.
- Studied in a population.



	Dose at which 50% of the population experiences	marker of
ED_{50}	Therapeutic Effects	Potency
TD_{50}	Toxic Effects	Toxicity
LD_{50}	Lethal Effects on Animals	

Therapeutic Index (TI) :

Measurement of the safety of a drug.

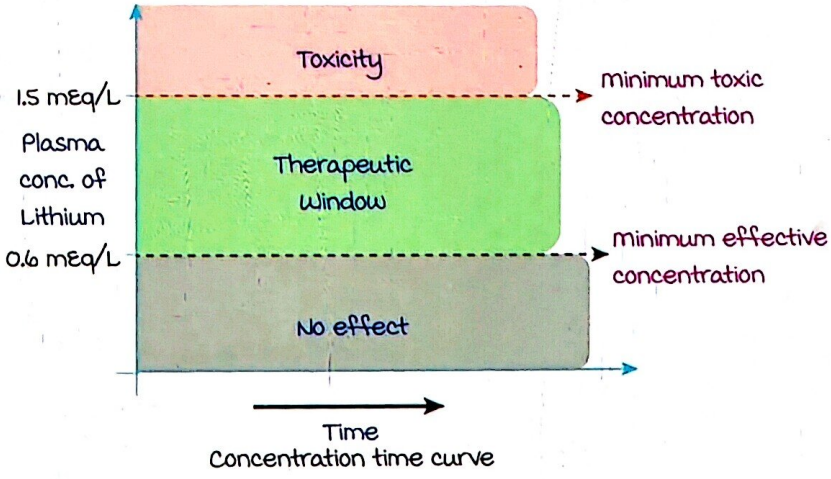
Calculations :

1. Humans : TD_{50}/ED_{50}.
2. Animals: LD_{50}/ED_{50}.

Significance :

- Low TI : Drug safe only in a narrow dosage range.
  ↑ chance of toxicity (E.g : lithium).
- High TI : Drug is safe in wide dosage range.

Therapeutic window/range :



Feedback

Pharmacodynamics : Potency, Efficacy and Dose Response Curve 19

GRADED DRC

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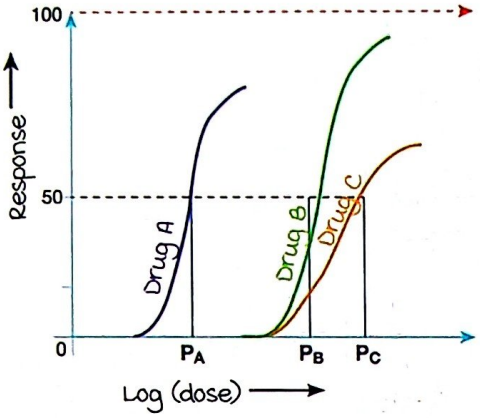
- Graded response (Quantified response) Eg : Drugs modifying BP, HR & blood glucose levels.
- Studied in an individual.



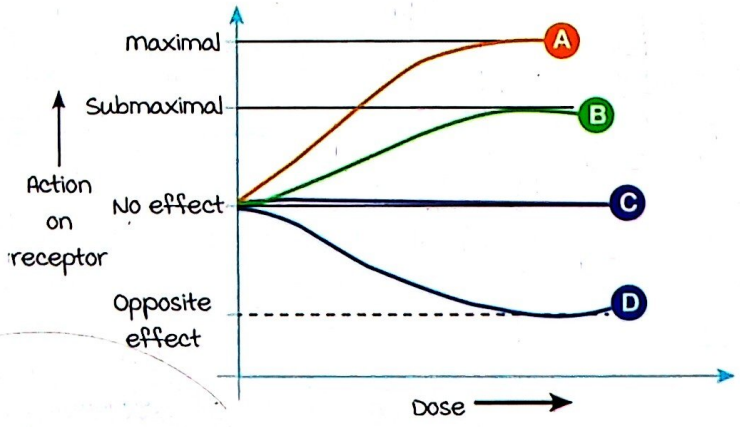
	Description	Determined in a graph via	Comparatively
Efficacy	Determined by response	more the height → ↑ Efficacy	B > A > C
Potency	lesser dose for the same effect → ↑ Potency	more to the left → ↑ Potency	$P_A > P_B > P_C$
Affinity	Comparable between drugs of the same MOA	more to the left → ↑ Affinity (only comparable between parallel lines)	A > B (C is not parallel)

Drug Receptor Interactions

00:38:22

TYPES :

	Full agonists	Partial agonists	Antagonists	Inverse agonist/ Antagonists
Effect upon binding to receptor	Maximum effect (A)	Submaximal effect (B)	No effect (C)	Opposite to the nature of receptors (D)
Net effect in the body (With endogenous full agonists)	-	Mild antagonism (Opposite effect)	Moderate antagonism	Severe antagonism
Intrinsic efficacy ↓ Mathematical representation of efficacy	+1	between 1 & 0	0	-1



Note : Antagonist are m/c used.

Feedback