

Pharmacology

Edition 8.5

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Instructions

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Immunomodulators

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INTRODUCTION TO PHARMACOKINETICS AND PHARMACODYNAMICS

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Pharmacokinetics :

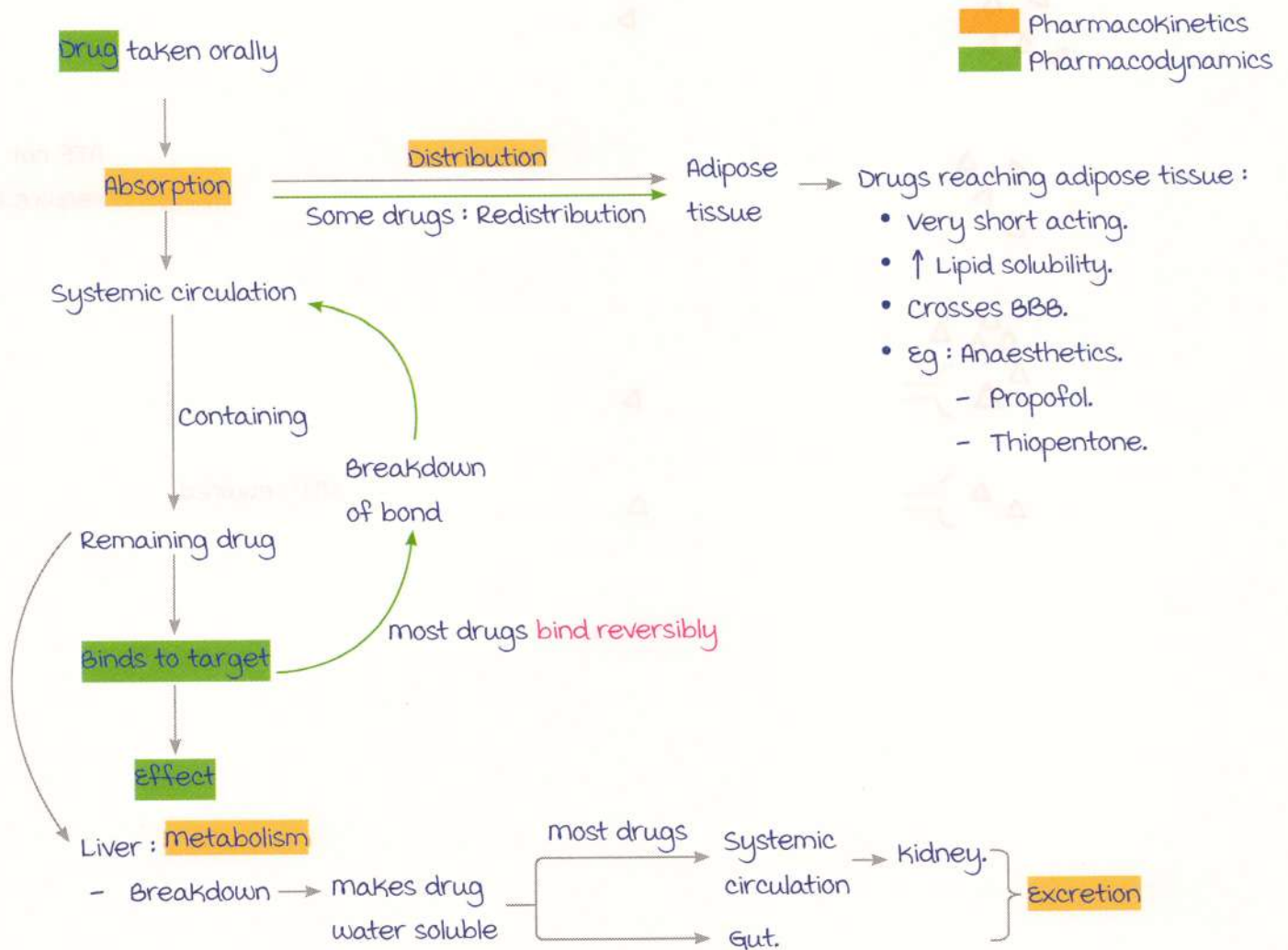
- Study of movement of drugs in the body after intake through any route.

Pharmacodynamics :

- Drug induced change in the body.

Course of Drug Through the Body

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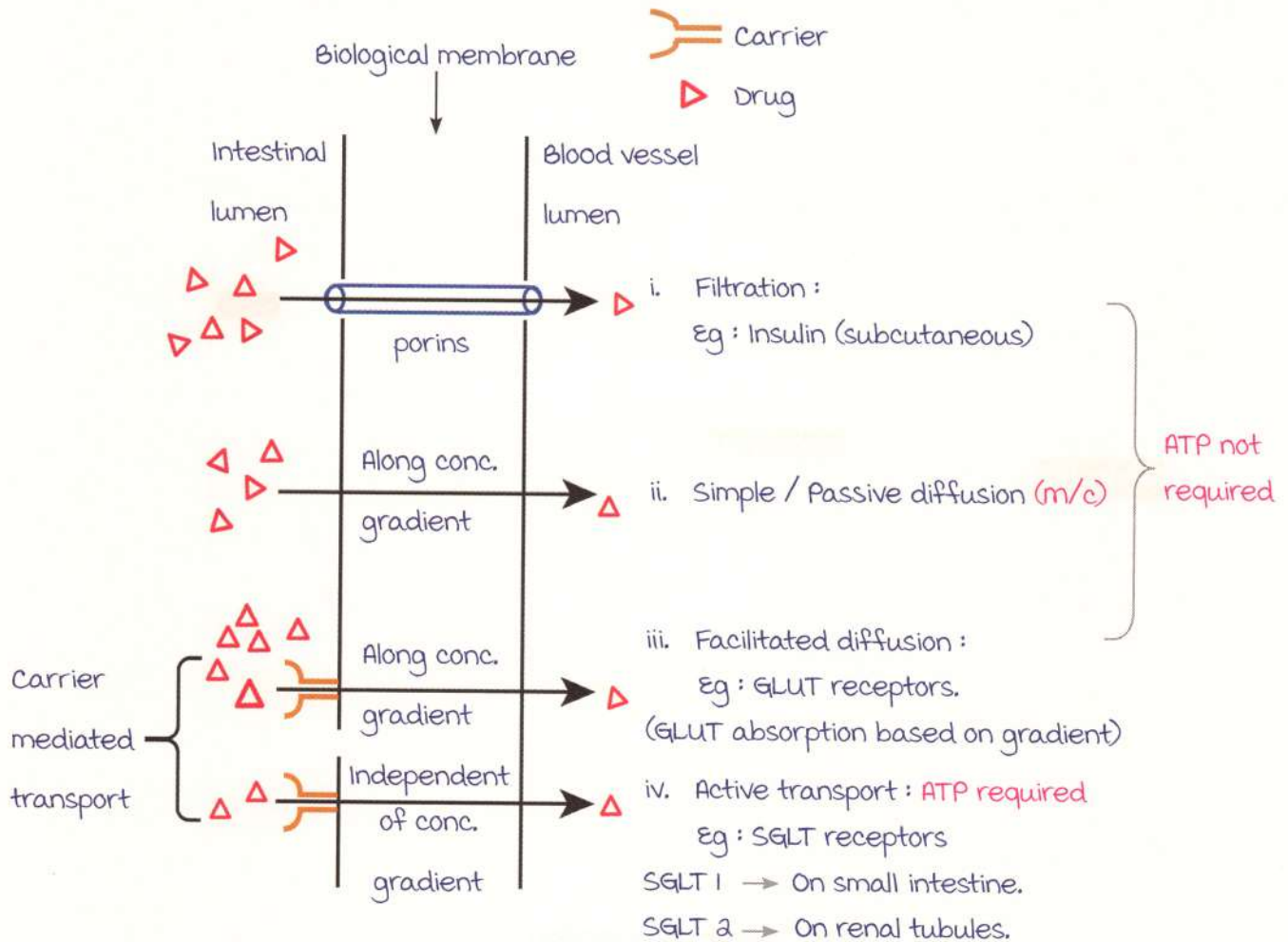


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PHARMACOKINETICS : ABSORPTION - PART 1

Absorption

00:00:25



Active Transport : P-Glycoprotein Pump (pgp)/MDR₁ Pump

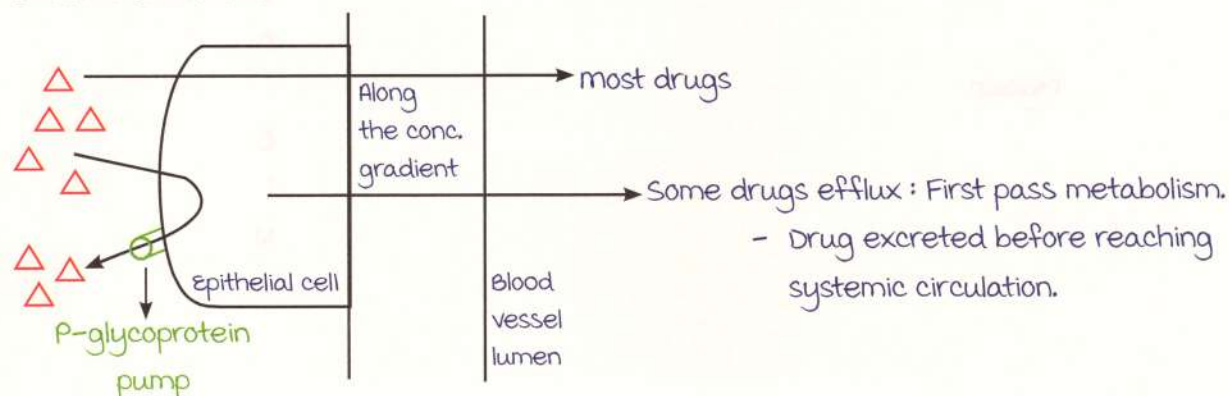
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m/c type of ABC pump.

Function :

Small intestine/liver

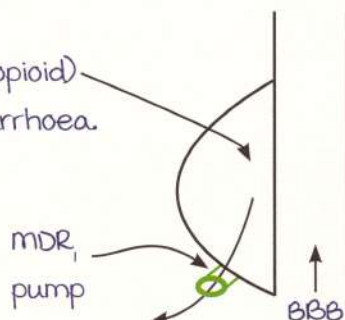
**Significance :**

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

Blood Brain Barrier (BBB) :

Eg : Loperamide (opioid)

- Used in Rx : Diarrhoea.
- Acts on GIT.



- MDR₁ pumps are present in BBB.
- Loperamide cannot cross 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 $\xrightarrow{\text{develops}}$ Pgp pump $\longrightarrow$ Drug efflux $\longrightarrow$ Resistance.

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

Pharmacological Significance :

Substrate :
undergoes efflux
by pump

- Loperamide
- Cyclosporine
- Digoxin

Inducers :
↑ no. of pump
(Causes drug failure)

- ≈ Enzyme inducers
- Rifampicin
 - Phenytoin
 - Phenobarbital

Inhibitors :
↓ no. of pumps
(Causes drug toxicity)

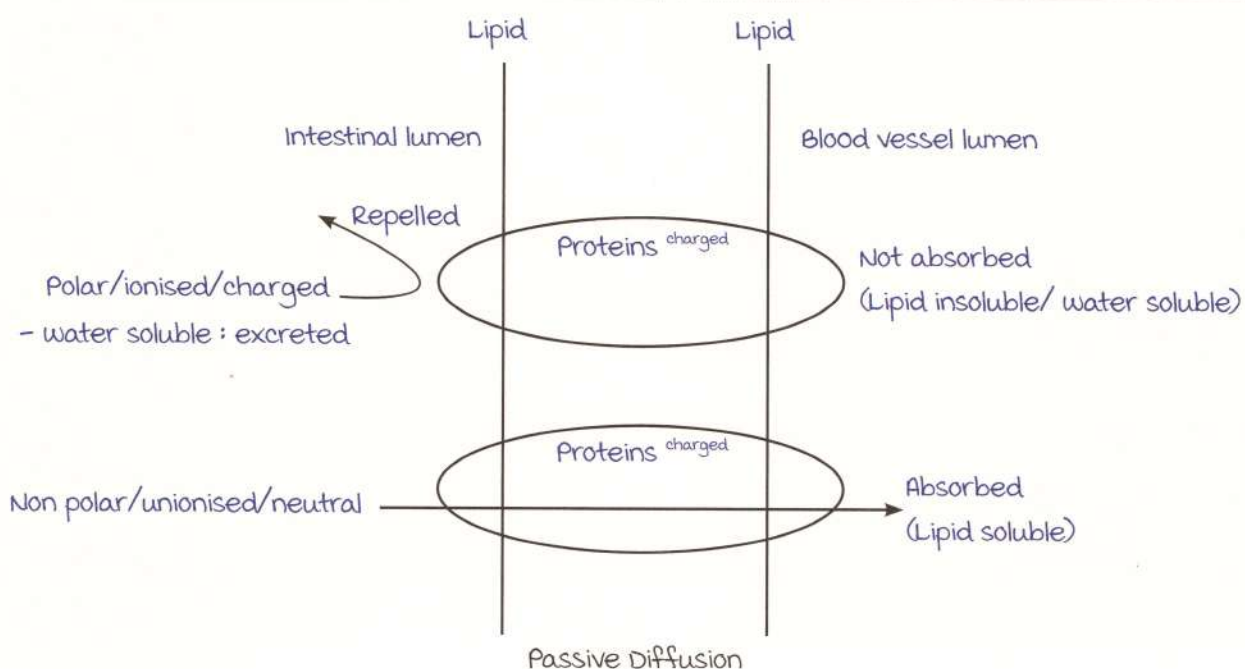
- Verapamil
- Amiodarone
- Quinidine
- Cyclosporine
- Itraconazole
- Neratinib
- Erythromycin/
Clarithromycin

effects of blockade :

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

Passive Diffusion

00:27:35



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 :

- 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
 - Phenobarbital
 - methotrexate
 By bicarbonate : urine Alkalinizer.
- 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 - Hasselbalch Equation

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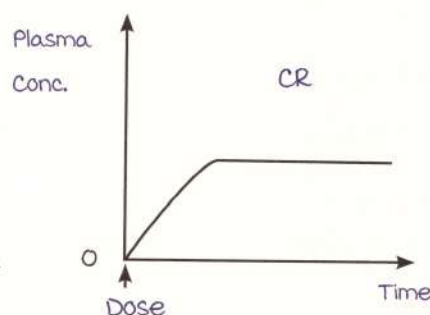
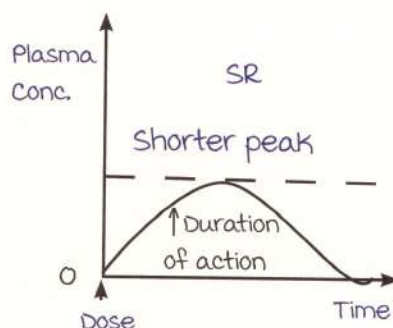
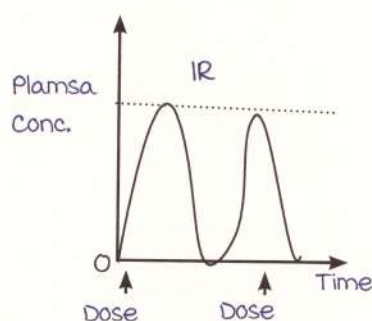
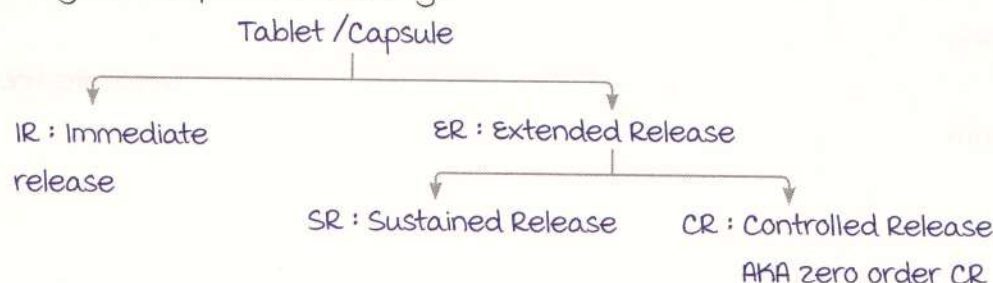
Quantification of Ionization.

- Acidic drug $\rightarrow \frac{\log [\text{Unionized}]}{[\text{Ionized}]} = \text{pKa} - \text{pH (Of medium)}.$
- Basic drug $\rightarrow \frac{\log [\text{Ionized}]}{[\text{Unionized}]} = \text{pKa} - \text{pH}$
- E.g : Ionization of acidic drug with $\text{pKa} = 4$ in stomach ($\text{pH} = 2$).
 $\log \frac{[U]}{[I]} = 4 - 2$
 $\log \frac{[U]}{[I]} = 2 \rightarrow \frac{U}{I} = 10^2 \rightarrow \frac{U}{I} = 100$ } 99% unionized & 1% ionized.
- pKa : $\text{pH of the medium at which 50\% drug is ionized \& 50\% is unionised.}$

Absorption of Oral Drugs

00:21:30

1. Delayed absorption of Oral drugs :



mechanism : Frequent dosing :

↓ Compliance.

Example : Indomethacin TID.

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

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.

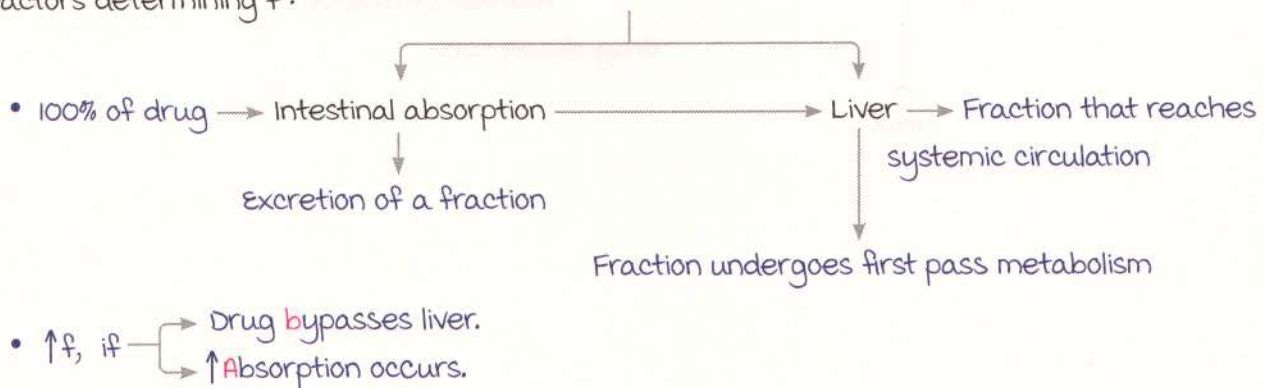
Rate and Extent of Absorption

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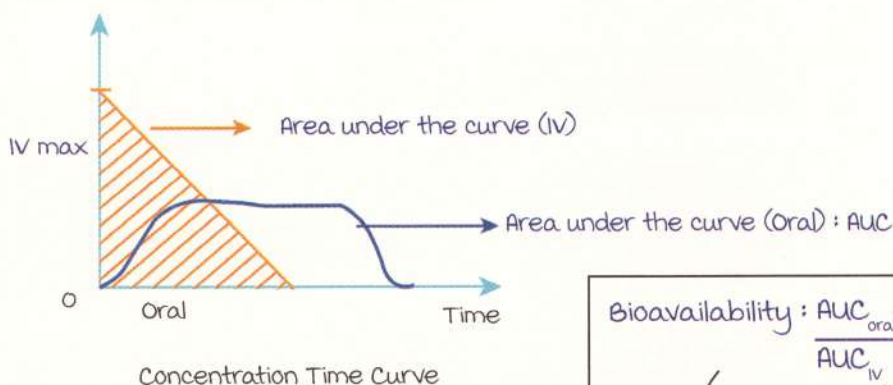
Bioavailability (f) :

Fraction of drug reaches systemic circulation unchanged.

Factors determining f :



Plasma concentration :



$$\text{Bioavailability} : \frac{\text{AUC}_{\text{oral}}}{\text{AUC}_{\text{IV}}} \times 100$$

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

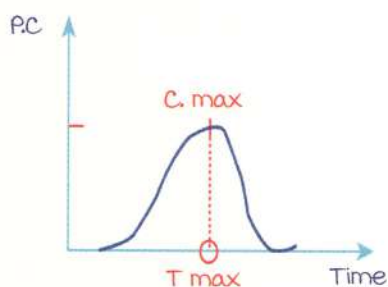
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Route of administration	Bioavailability
IV	1
Im/sc	0.75-1.0
Oral	0.05-1.0

.....
 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 (T_{max}) 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 within $\pm 20\%$.

PHARMACOKINETICS : DISTRIBUTION

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

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 $\uparrow$ Avd $\rightarrow$ mostly in Extravascular compartment/Tissue.
- Drug with $\downarrow$ Avd $\rightarrow$ mostly in Intravascular compartment/Systemic.

Calculation :

$$AVd = \frac{D(\text{dose})}{C_0} \times f$$

Initial plasma concentration

- f : Bioavailability
- $f = 1$ in intravenous route

Loading dose :

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

Target plasma concentration
(constant)

$$D \propto AVd/f$$

- If Avd of a drug is $\uparrow$, Dose is increased to maintain C_T

Factors Determining Apparent volume of Distribution :

- **Fat content**
 - $\rightarrow$ Obesity : $\uparrow$ volume of distribution (V_d)
 - $\rightarrow$ Athletes : $\downarrow V_d$
 - $\rightarrow$ Sex : $F(\uparrow \text{ Fat content}) > m$
- **Lipid Soluble** (P_{ka}).
- **Albumin binding** (Plasma protein binding) $\propto \frac{1}{V_d}$
- **Tissue binding**.

Eg :

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

Significance in toxicity :

- $\uparrow \uparrow V_d$
 - $\rightarrow \uparrow$ Extravascular concentration
 - $\rightarrow \downarrow$ Intravascular concentration
- Antidotes are given in toxicity.

Dialysis is ineffective

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

Drugs with $\uparrow$ v_d :mnemonic : **BADDOC**.

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

Plasma Protein Binding

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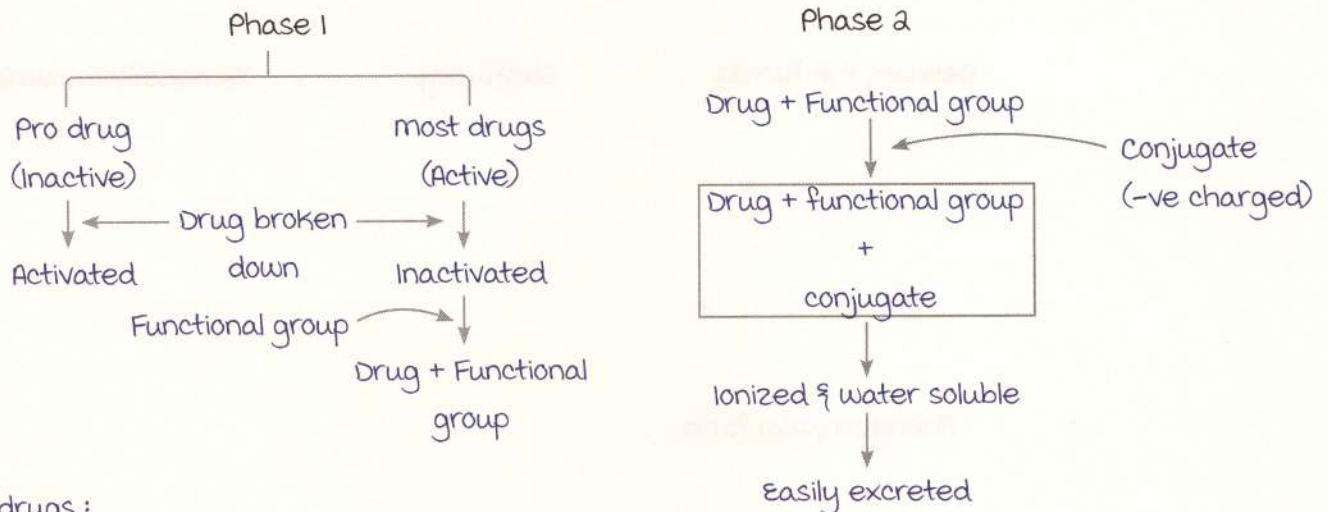
Important plasma proteins :

- Albumin $\rightarrow$ Binds to Acidic drugs (m/c).
- α_1 acid glycoprotein : Basic drugs.

	Albumin	α_1 acid glycoprotein
Drugs bound	• Antipsychotics • Antidepressants • Antiepileptics • Antibiotics : Sulfonamides • Anticoagulant : Warfarin • Aspirin Increase each others plasma conc. if used together $\downarrow$ $\uparrow$ Bleeding	• Tricyclic antidepressants • Opioids • Antiarrhythmic - β blocker - Amiodarone - Lidocaine
Effect on drugs	$\downarrow$ Albumin $\downarrow$ $\uparrow$ Free drug $\downarrow$ $\uparrow$ Risk of toxicity	$\uparrow$ α_1 glycoproteins $\downarrow$ Free drug $\downarrow$ effect
Clinical Application	$\downarrow$ Albumin : - Nephrotic syndrome - CKD - Liver Cirrhosis - Diabetes mellitus	$\uparrow$ α_1 gp : • Inflammatory : - Rheumatoid arthritis - Inflammatory bowel disease • myocardial infarction

PHARMACOKINETICS : METABOLISM

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



Prodrugs :

- Proguanil.
- Ramipril & other ACEi (Except Captopril, Lisinopril).
- Oxcarbazepine, Omeprazole.
- Dipivefrine, 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 : ORCHAD

- Oxidation (m/c).
- Reduction.
- Cyclization.
- 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
 I → Denotes the family. A → Subfamily. 2 → Geneisoform number.

Drugs metabolised in Phase I (By CYP450 types) :

CYP1A2 :

- Paracetamol.
- Tacrine.
- Theophylline.

CYP2B6 :

- 6-mercaptopurine.
- methyl dopa.

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 $\xrightarrow{\text{Chronic consumption}}$ CYP2E1 upregulation
 ↓
 • Paracetamol $\xrightarrow{\text{CYP2E1 upregulation}}$ ↑ NAPQI $\rightarrow$ Hepatotoxicity
 (Paracetamol metabolised by CYP2E1 >> CYP1A2)

CYP3A4 (m/c) :

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