Pharmacology

Marrow Edition 8

MARROW

Instructions

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// ME821-PPL

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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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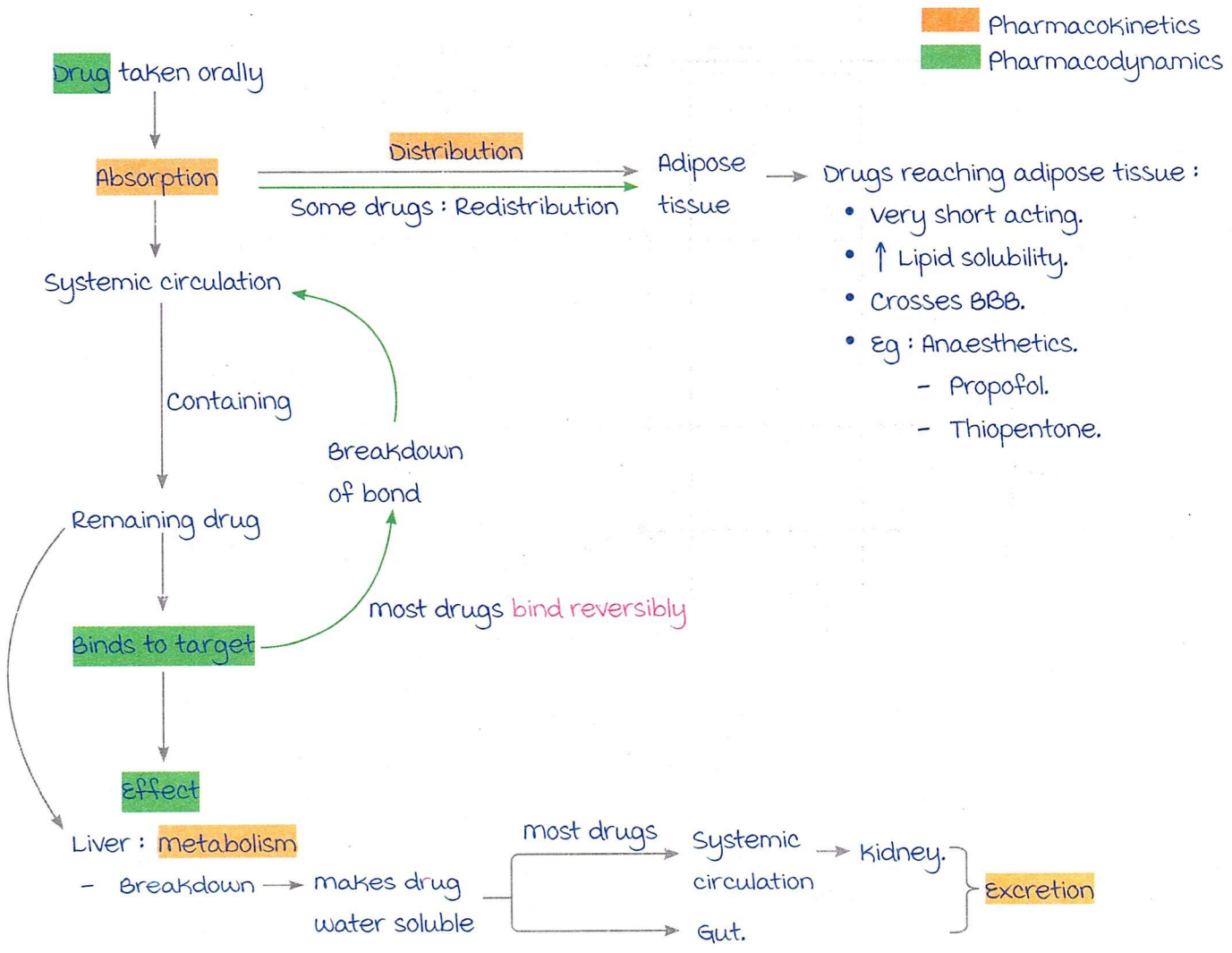

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PHARMACOKINETICS : ABSORPTION - PART 1

Absorption

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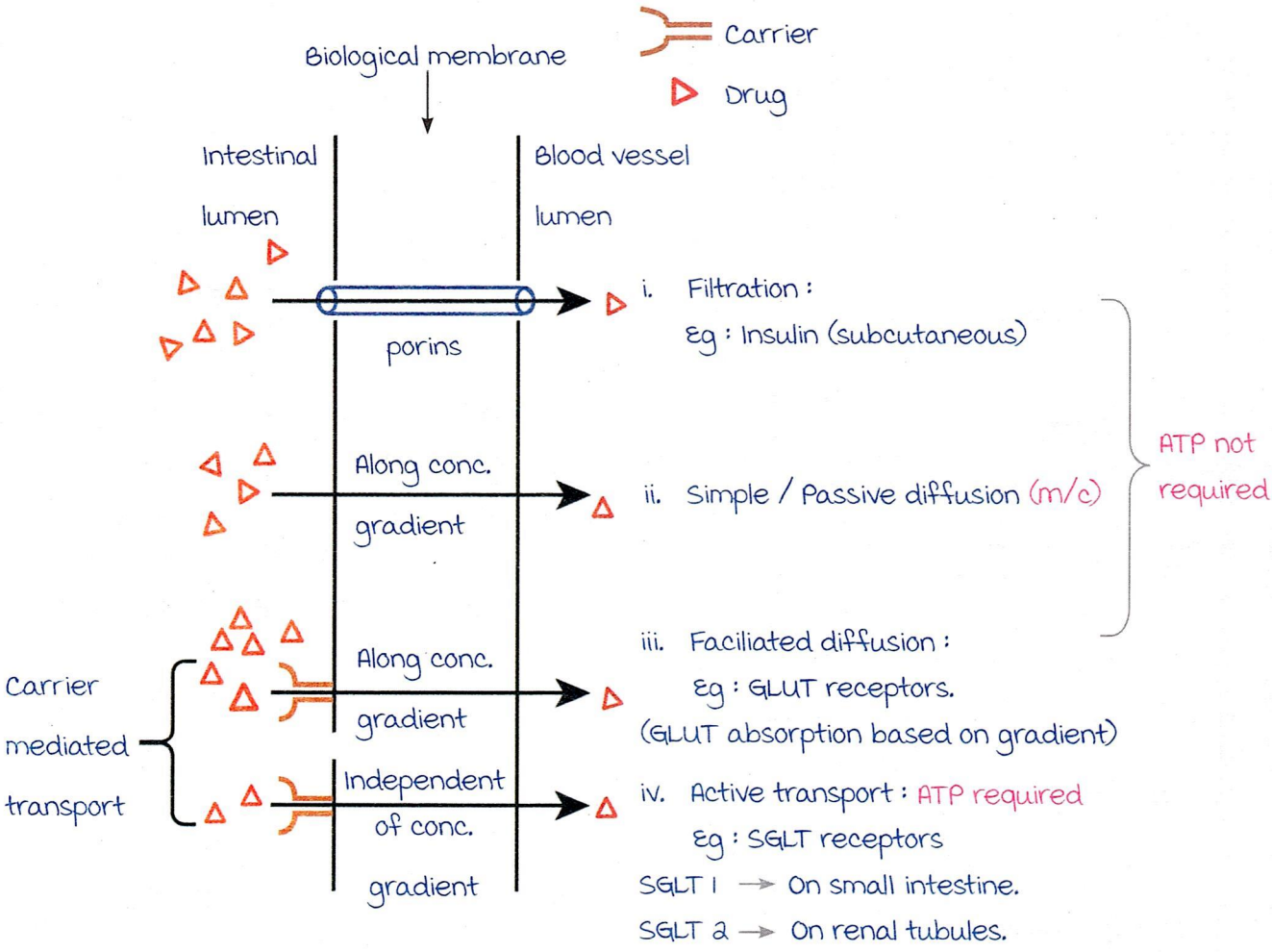

Active transport : P - glycoprotein pump (pgp)/ MDR_1 pump

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m/c type of ABC pump

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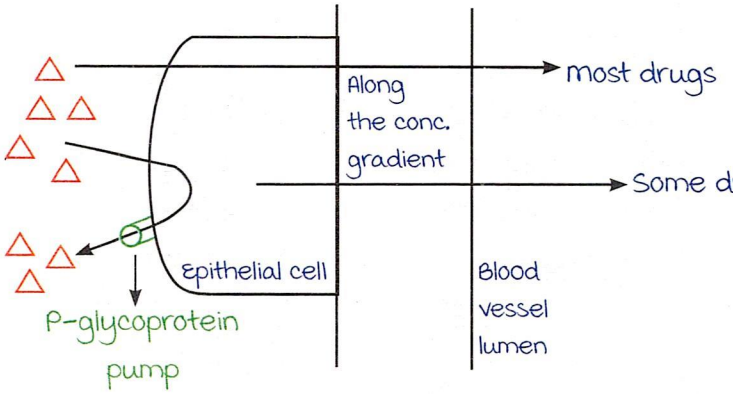
Function :

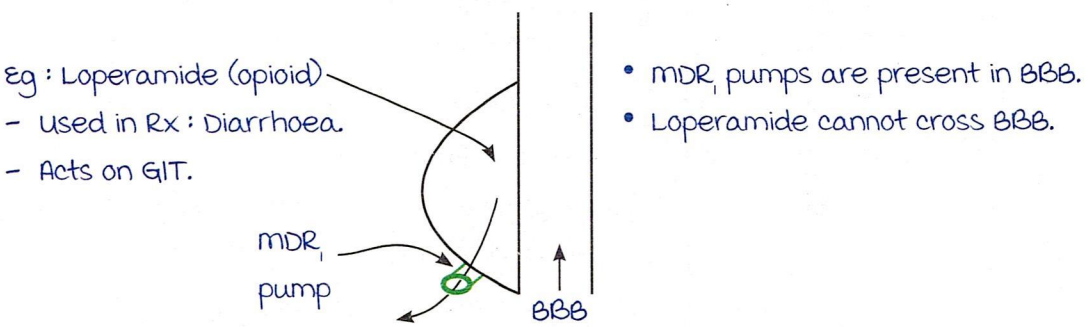
Small intestine/liver



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 MDR_1 pumps in placenta.

Bile acid excretion : D/t presence of MDR_1 pumps on hepatocytes.

In Bacteria / Tumor cell :

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

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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 toxicity
• Cyclosporine	Cholestatic jaundice
• Verapamil	Used in reversal of drug resistance (Cancer, bacteria)
• Quinidine	Loperamide induced central S/E

Passive Diffusion

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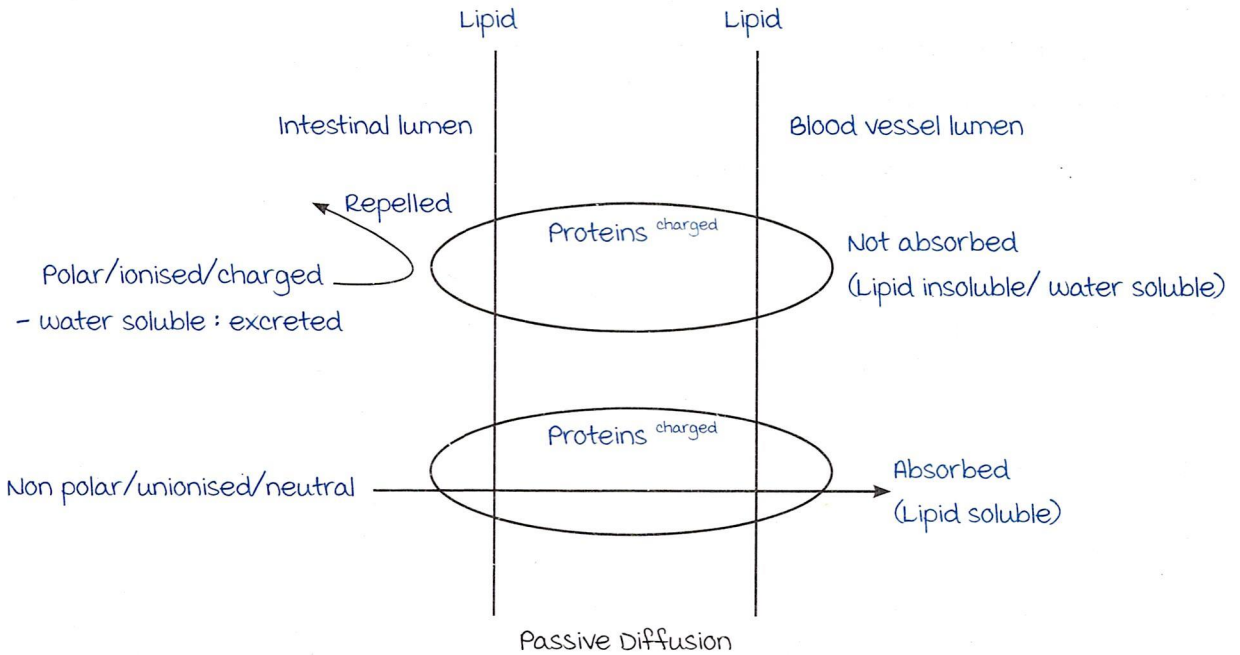

PHARMACOKINETICS : ABSORPTION PART 2

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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 → 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

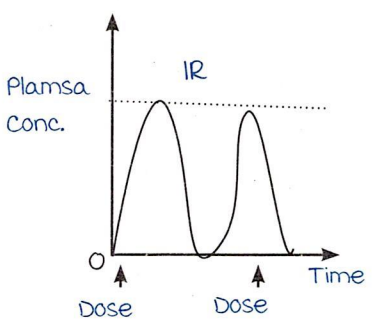
Absorption of oral drugs

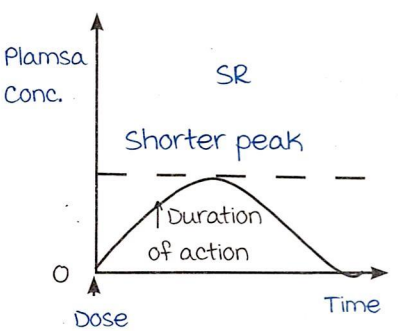
00:21:30

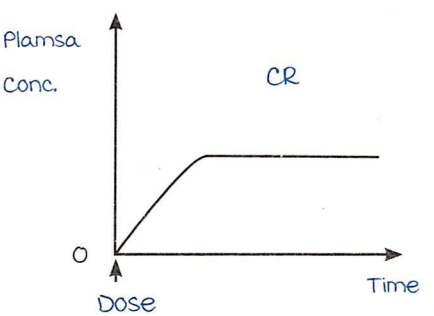
1. Delayed absorption of Oral drugs :

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.

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

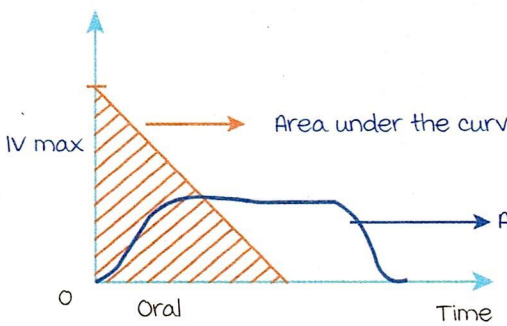
BIOAVAILABILITY (f)

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

Plasma concentration :



Concentration Time Curve

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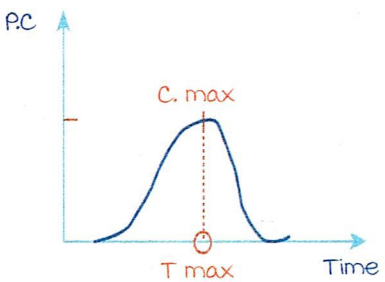
Route of administration	Bioavailability
IV	1
Im/SC	0.75–1.0
Oral	0.50–1.0

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

$$AVd = \frac{D(dose)}{Co} \times f \Rightarrow$$

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
- Lipid 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 • Antiarrhythmic – 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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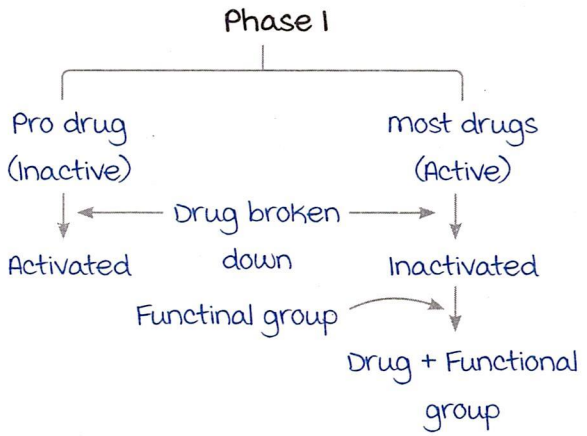

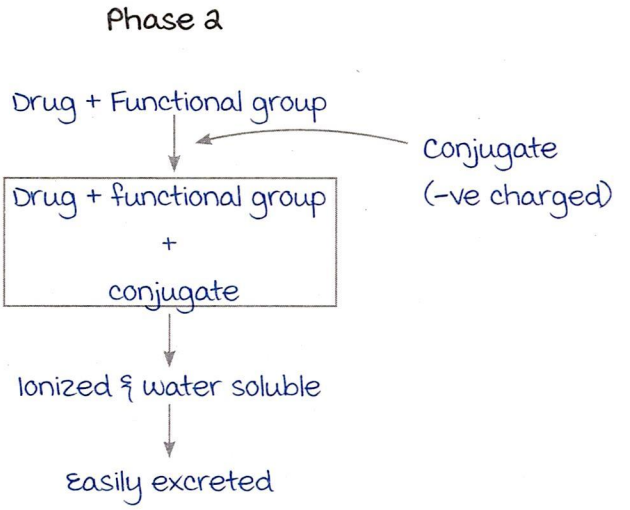

Prodrugs :

- Proguanil.
- Ramipril & other ACEi (Except Captopril, Lisinopril).
- Oxcarbazepine , Omeprazole.
- 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.
- Hydrolysis.
- Aliphatic hydroxylation.
- Aromatic hydroxylation.
- Deamination.

Phase I reactions are enabled by microsomal CYP450 enzymes.

Phase II Reaction :

Named after the conjugate :

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

} Non microsomal reactions.

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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

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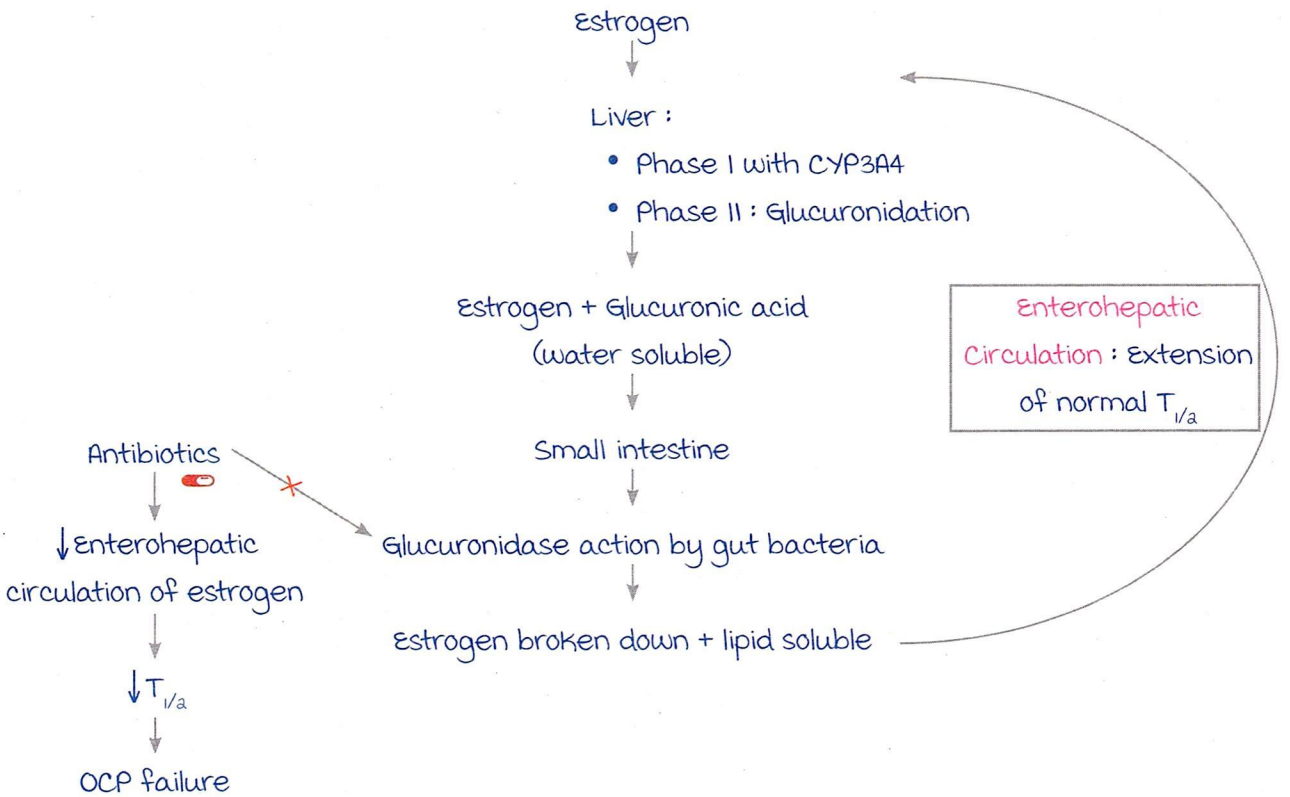
Glucuronidation :

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

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

- Estrogen :



Acetylation :

Mnemonic : HIPS Dance.

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

} Can cause drug induced SLE.

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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.