Toppersnotes
Unleash the topper in you

RAJASTHAN PHARMACIST

Rajasthan Subordinate & Ministerial Services Selection Board

Part – B
Volume – 6

Pharmacology and Toxicology

SIERRA INNOVATIONS

RAJASTHAN PHARMACIST

CONTENTS

Pharmacology and Toxicology

Pharmacology and Toxicology

Pharmacology

Pharmacon + logus

Pharmacon → Durg

Logus → Study

Pharmacology is the branch of biology which deal with the study of drugs action.

Drug → Substance or material that is used or intended to be used to modify or explore physiological system or pathological states, for benefit of the recipient.

Branch of Pharmacology

Pharmacokinetic → Pharmacon + kinetic

Pharmacon → drug

Kinetic → movement

Pharmacokinetic is the branch of pharmacology which deal with study of movement of drug within the body.

It include → Absorption (A)

→ Distribution (D)

→ Metabolism (M)

→ Excretion (E) of drug or shortly we can say ADME of drugs it means what the body does to the drugs.

Pharmacodynemic → Pharmacon + dynemic

Pharmacon → drug

dynemic → power

* Pharmacodynemic is the branch of pharmacology which deal with the study of drug, their mechanism of action. Pharmacological action & their adverse effect or what the drug does to the body.
* Clinical pharmacology – It deal with study of drug in human volunteers.
* Toxicology – Study of Toxic effect of drugs.
* Chemotherapy – Treatment of infectious disease with antimicrobial & drugs used to treat cancer.

Various discovery by scientist

i. Father of Modern pharmacology – Oswald schmiedbberg.
ii. Father of Indian pharmacology – RamNath Chopda
iii. Father of chemotherapy – Paul Ehrlich.
iv. Discovery of penicillin – Alexander Flaming (in 1928)
v. Discovery of insulin – Banting & Best
vi. Father of Pharmacy – Galen

ORPHAN drugs

Drugs that one used for the diagnosis treatment & prevention of rare disease.
E.g.

Rifabutin (Anti T.B. drug)
Sumatriptan (Treat migran)
Digoxin toxicity (Treat overdose of Digitalis)
Fomipizole (Antidote for methanol poisoning)
Amphotercin B (Antibiotic)

Prescription Drugs: It is a pharmaceutical drug that legally requires a medical prescription to be dispensed.
E.g. Antidepressant drug
Antibiotic

Non- prescription Drugs

Also called over the counter (OTC) drugs
Drug that can buy without a doctor's prescription
e.g. ENO
Paracetamol
Strepsil etc.

Route of Administration of drugs

Factor affecting Route of drug administration

* Physical & chemical properties of drug
* Emergency / Routine use (Fast or slow)
* Condition of the patient
E.g. Unconscious, diarrheas Vomiting

* Age of Patient
* Effect of 1st pass metabolism.

Route of drug Administration

i. Local Route
ii. Systemic Route

Local Route – Higher concentration is attained at desired site without exposing the rest of the body.

Topical – Application of the drugs on the surface of the body or mucous membranes.
Poorly absorption by oral route like Nystatin, Streptomycin
Drug inhaled – Salbutamol
Terbutaline

Injection at Local site -
Like – Intra-articular injection (into joint)
Intra- thecal injection (into CSF)
Intra – arterial injection (into fine arterial bed)

Systemic Route

Oral:

Most commonly used but not suitable
For – Unpalatable drugs like – Paraldehyde

* Irritable drug like emetine cause nausea & vomiting
* Drug destroyed by digestive juice
  e.g. pen. G
  Hormones
* Drugs with high 1st pass metabolism
  e.g. Amino glycoside

Sublingual or Buccal:
Suitable for non-irritating & lipid soluble drugs
e.g. Nitroglycerine
Liver is by passed

Rectal: Suitable for administration of irritant & unpleasant drugs.
About 50% of drugs by pass liver.

Cutaneous:
Drugs are applied as patch over skin.
Local irritation & erythema may occur
e.g. Fentanyl
Nicotine etc.

Inhalation:
Suitable for volatile gases & liquid.
e.g. Halothan
Amyl Nitrate

Nasal: Liver is by passed
e.g. Decompressing

Parenteral:

(a) Subcutaneous (S.C.)

* Suitable for depot preparation
* Dermojet – A device used for S.C. administration.

(b) Intramuscular (I.M.)

* Injected into skeletal muscle like deltoid, gluteus maximums rectus femora's etc.

(C) I.V. (Intra venous)

* Drug bio availibity is 100

(d) Intra dermal

* Used for BCG, small pox vaccine, T.B. Testing, leporine test, Sensitivity test.

Pharmacokinetics

* It is the study of movement of drug within the body.
* It deal with absorption (A)
  Distribution (D)
  Metabolism (M)
  Excretion of drag (E)
  or ADME of drugs.

Absorption: Movement of drug from site of administration into the systemic circulation.

Passive diffusion

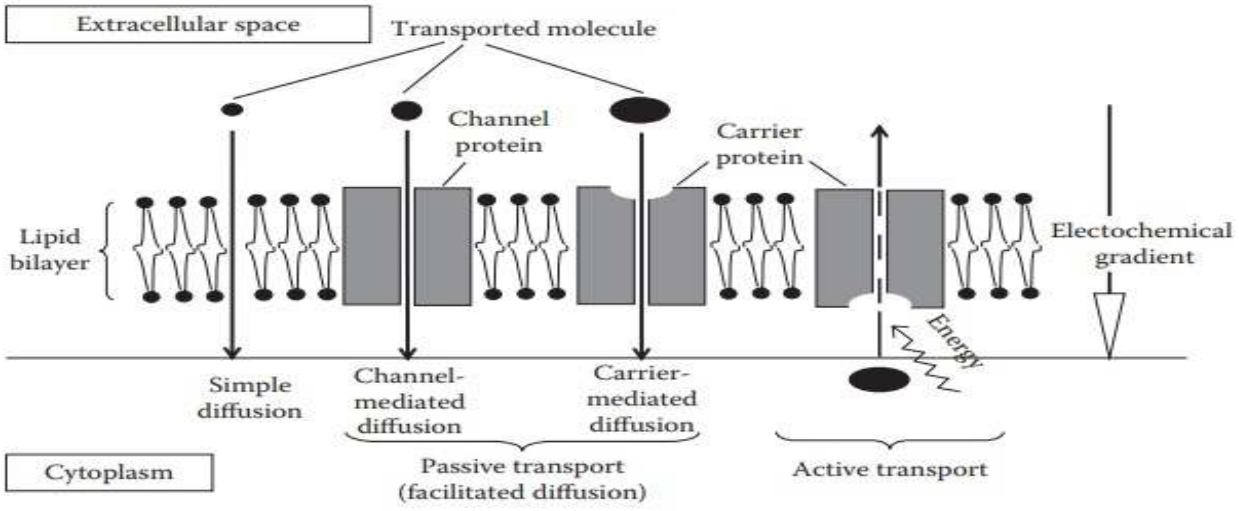
* Drug transport in the direction of concentration gradient.
* More lipid soluble drug diffuses quickly.
* No energy Require.
* No carrier require.
* Follow 1st order kinetic.
* Follow Fick's first low.

Filtration: - Drug Having low MW are easily filtered.

Specialized transport :-

Active transport

* In active transport drug movement against concentration gradiant.
* Energy & carrier required.
* Symport (Cotrasport) – Na^+ & Glucose
* Antiport (exchange transport) Na^+ K^+ Atpase



Facilitated diffusion

* Transport of Glucose across muscle cell membrane by transporter GLUTU.
* Drug transport in the direction of concentration gradient.
* No ATP consumed
* No carrier required.

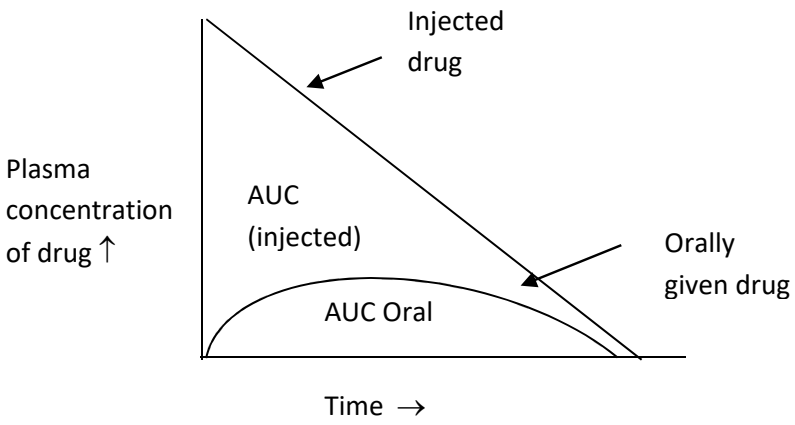
Factor Affecting absorption of drug

* Weakly acidic drugs like aspirin batter absorbed from the stomach as unionized form.
* Weakly Basic drugs like Morphine, Quinine are batter absorbed from intestine as unionized form.
* Aqueous solubility – Solution absorbed faster than solid.
* Concentration of drug :- Concentrated solution absorbed faster than dilute solution.
* Area of absorption surface – More area faster absorption.
* Blood Flow - ↑ Blood flow remain the drug from the site of the absorption so reduce absorption.
* Empty Stomach - ↑ absorption of drugs
* Presence of food → Retard drug absorption
  → Except – Halofentrine
* Ionization of drug – Drug is absorbed in unionized state so ionization decreases drug absorption.
* Too lipophilic drug or too hydrophilic drug have poor absorption.

Bioavailability of drug

* Rate & Extent (fraction) of drug that is reaches in systemic circulation is called bioavailability.
  e.g If two unit of a drug is administered by any route & 70% unit reaches in the systemic circulation, than bioavailability of drug is 70%.
* Bioavailability of I.V. Route is 100%
* Disintegration time & dissolution Rate affect bioavailability.
* Calculated by relating area under curve plasma concentration – Time i.v. route & for that particular route.

$$\text{Bioavailability} = \frac{\text{AUC oral}}{\text{AUC Injected}} \times 100$$



First Pass metabolism

* When drugs are administered orally, they have to pass via gut wall. Portal vein-liver systemic circulation.
* Drug with high hepatic 1st pass Metabolism are salbutamol, Verapamil, Propranolol, Nitroglycerin, Amitrptyline, Pethidine, Methyl testosterone

Distribution

After the drug reaches into the blood circulation, it may be distributed to various tissue & organs.

Distribution is determined by hypothetical parameter volume of distribution (Vd)

$$\boldsymbol{Vd = \frac{Total\ amount\ of\ drug\ in\ body}{concentration\ of\ drug\ in\ Plasma}}$$

Factor affecting volume of distribution

1. Lipid: Water partition coefficient of drug (lipid solubility) :-
   Highly lipid soluble drugs easily cross blood vessel wall & are distributed to the tissue I make volume of distribution.

2. pka value of drug: Highly ionized drug being lipid insoluble, remain inside the blood vessel so less volume of distribution occur.

3. Plasma protein binding: Highly plasma protein bound drug remain inside the blood vessel → less Volume of distribution occur.

4. Degree of blood flow

5. Affinity for different tissue

6. Disease like CHF, Uremia & cirrhosis

7. Pregnancy.

Barrier of Drug

BBB (Blood brain barrier)

Only lipid soluble drug can cross BBB

e.g. levodopa,

propranolol

Physostigmine

They cross BBB & act on brain.

Placental barrier :- competitively weak as compared to BBB.

Placental barrier are lipoidal & allow free passes of lipophilic drugs, while Restring hydrophilic drugs.

Plasma protein Binding (PPB)

Acidic drug generally bind to Plasma albumine

* Basic drug generally bind to α-acid glycoprotein
* Lipid soluble drug are highly plass protein bound.
* Highly PPB drug within vascular compartment → Small Vd. (volume of distribution).
* Plasma Bound Fraction of drug is inactive & equilibrium with free drugs.
* Generally concentration of drug refers to bound as well as free drug.
* PPb drug neither act nor excrete out the body.
* Highly PPB drug are difficult to remove by haemodialysis in case of their poisoning.

Redistribution

When highly lipid soluble drugs are administered → Initially distributed to highly perused organs.

Then redistributed to adipose tissue because of their affinity.

e.g. Thio pentone

Its anesthetic effect terminated within few minute due to redistribution.

Metabolism (Biotrans formation)

Biotransformation of drug may lead to:-:

(i) Activation of drug (pro drug)
(ii) Inactivation of drug & its metabolite
(iii) Active metabolite for active drug

Most of the drug after metabolism convert into - water soluble ↑ polarity

SO they can easily excrete out through kidney

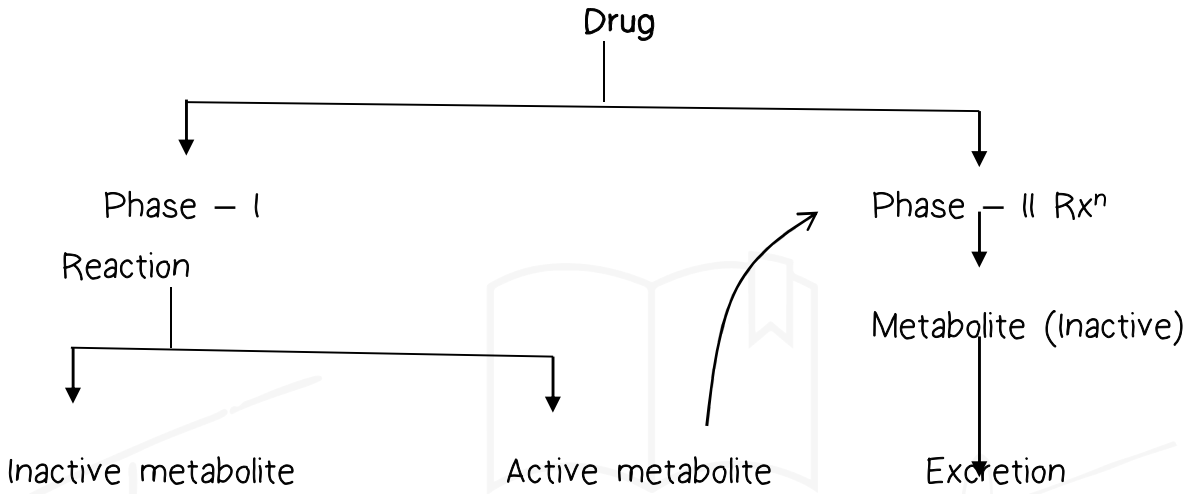
Active drug	Active metabolite
1. Amitripty line	Nortryptyline
2. Codein	Morphine
3. Diazepam	Oxazepam
4. Digitoxin	Digoxin
5. Imipromine	Desipramine
6. Phenacetin	Paracetamol
7. Primidone	Phenobarbiton
8. Spironolactne	Canrenone
9. Allpurinol	Alloxanthine
10. Morphine	Morphine – 6 – glucornide

Activation of drug

Inactive Drug (Pro drug)	Active form
1. Progunil	Cycloguanil
2. Levodopa	Dopamine
3. Fnalapril	Enalaprilat
4. Dipsvefrine	Epinephrine
5. Sulindac	Sulfide metabolite
6. Prednisone	Prednisolone
7. Bacampicillin	Ampicillin

8. Sulfasalazine — Sulfa pyridine + 5-Amino salicylic acid
9. Acyclovir — Acyclovir triphosphate
10. Cylophosphamide — Aldopnosphamide
11. Benorylate — Aspirn +PCM

Type of Bio transformation Rxⁿ.



There are mainly two type of Bio transform.

1. Phase – 1 Rxⁿ / Non synthetic
2. Phase – 2 Rxⁿ / synthetic

(1) Phase – 1 Rxⁿ

Example –

(i) Oxidation
(ii) Reduction
(iii) Hydrolysis
(iv) Cycliztion
(V) Decyclization

(i) **Oxidation**:

Addition of oxygen or removal of Hydrogen.

e.g. Phenytoin
Phenobarbiton
Propranolol

Most of the drug metabolized by oxidation in phase -1 Rxⁿ.

Reduction

Removal of oxygen or addition of Hydrogen
e.g. Chloramphenicol,
Methadon.

(iii) Hydrolysis:
Breakdown of the compound by addition of water is called Hydrolysis.

This is common among drug which have ester group (R-CWR) or Amide group ($RCONH_2$)
E.g. - *Procaine*
succinylcholine
Lignocaine
procainamide,
Aspirin,
Pethidine
Oxytocin

(iv) Cyclization:
Conversion of a straight Chain compound into Ring Structure.
E.g. Proguanil
↓
Cycloguanil (Cyclic)

(v) Decyclization:
Breaking up of the ring structure of the drugs.
e.g. – Pheno barbiton
phenytoin

(2) Phase -II Rx^n / conjugation Rx^n / synthetic Rx^n

Example
(i) Glucuronide Conjugation
(ii) Glycinc Conjugation
(iii) Glutathion conjugation
(iv) Acetylation
(v) Methylation
(Vi) Sulfate conjugation

(i) **Glucuronide Conjugation**:

Responsible Enzyme → UDP Glucuronosyl transferase.

e.g. Chloramphenicol

Aspirin,

Phenacetin.

Most of the drug metabolized by Glucuronid conjugation in phase-II Rx^n.

(ii) **Glycine conjugation**:

Responsible enzyme: Acetyl COA glycene transferase.

This is common among R-COOH

e.g. Salicylate and other drug having R-COOH (Carboxylic acid group)

(iii) **Glutathione conjugation**:

Responsible enzyme:- Glutathione transferees

e.g. PCM

(iv) **Acetylation**:

Responsible enzyme: :-

N - acetyl transferees

* This is most common among amino group contending drug (-NH_2)

e.g. sulfa drug

Sulfonamide

Dapsone

Hydrazine

(v) **Methylation**:

Responsible enzyme → Transimethylase

e.g. Adrenaline,

Histamine,

Nicotinic acid

(vi) **Sulfate conjugation**:

Responsible enzyme → sylpho transferees

e.g. Chloramphenicol

Adrenal and

Sex hormone

Drug metabolizing enzyme :-

(1) Microsomal

(2) Non microsomal

Microsomal enzyme

These are located on smooth endoplasmic Reticulum primary in liver also in kidney, intestinal mucosa & lungs

e.g. Monooxygenase

Cytochrome Pyso

Glucuronyl transferase

Non- Microsomal enzyme

These are present in the cytoplasm & mitochondria of Hepatic cell as well as other tissue including plasma.

e.g. Esterase,

Amidase

Conjugaises

The most important enzyme for oxidation reaction is pyso.

CYP3A4: Carryout biotransformation of *largest number (50%).*
Most common phase -I biotransformation process is Oxidation.
Most common phase-II biotransformation process is - Glucuronidation conjugation.

Enzyme induces & Inhibitor

* Enzyme inducer → Increase the metabolism of other drug. So other drug effect decrease.
  So dose of such other drug should be increase.

Enzyme inhibitor

Trick

G → Griseofulvin, Glucocorticoid

P → Phenytoin, Phenylbytazone

R → Rifampicin

S → Smoking

Cell → Carbamazapine

Chloraldenyde

Phone → Pheno barbitone

Enzyme inhibitor

C_5 → Cimetidine

→ Ciprofloxacin

→ Cyclosporine

→ Clarithromycin

→ Calcium channel blocker

e.g. Amlodipin

Nefadipin

Diltiazem

Varapamil

D → Diltiazem

E → Erythromycin

F_2 → Floxetine

SSRI (Antidepressant)
Fluvoxamine

G → Grape fruit Juice

H → HIV Protease inhibitor

e.g. Indonavir

Ritonavir

Squinavir

I – Itraconazole

K – Ketoconazole

<u>Hoffmann elimination</u> :
In this process drug can be inactivated with need of enzyme.
e.g. :- Natural muscle Relaxant like Atracurium eliminated.

Excretion

* Drugs & their metabolite are excreted in urine, faces, exhaled air, saliva, Milk, sweat etc.
* Most of the drugs are excreted in urine.
* Large molecular weight (7500 da) drugs are eliminated in faces.
* Volatile drugs like alcohol, general anesthetics are eliminated by lung.
* Drug like lithium, Rifampin are exerted is saliva & sweat.

Renal Excretion: Glomerular filtration – Tubular absorption + Tubular secretion

(i) Glomerular Filtration

It depend upon –

(a) Plasma protein binding – Only unbound form is excreted, the drug which is plasma protein bound can't be filtered.

(b) Renal blood flow – GFR increase with increase in renal Blood flow.

(ii) Tubular Reabsorption

99% blood comes back through the reabsorption process.

It depend Upon :-

a. Lipid solubility: Non lipid soluble drugs are excreted more, purpose of metabolism is to make the drug water soluble, so that it can be excreted.
b. Ionization of drug: Highly ionized drug excreted more.
c. Urinary PH for partially ionized drug:
   * Basic drug ionized more on acidic PH & less reabsorbed.
   * Acidic drug are ionized more & reabsorbed less in alkaline PH.

Example :-

* Aspirin Toxicity: Aspirin is a acidic drug.
  So make urine Alkaline (Basic) by $NAHCO_3$, so all the drugs can be excreted completely.

(iii) Tubular secretion

* There are two type of pump present in proximal Tubule, one is Acidic & other one is for basic drugs.
* Only one drug can pass at a time.