Toppersnotes
Unleash the topper in you

NEET - MDS

MASTERS OF DENTAL SURGERY

BY NBE

NATIONAL ELIGIBILITY CUM ENTRANCE TEST

Volume – 3

General & Dental Pharmacology and Therapeutics

SIERRA INNOVATIONS

CONTENT

GENERAL AND DENTAL PHARMACOLOGY AND THERAPEUTICS

General Pharmacology

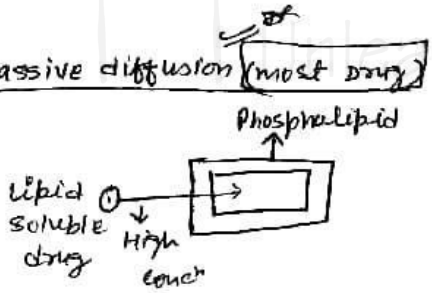
- **Pharmakokineties**
  - movement of the drug inside the body.
  - Body does to → Drug
- **Pharmacodynamics**
  - Drug + effect produce by the drug
  - Drug does to → body
- **Drugs- All topic**

Pharmacokinetics :- ADME study

- Absorption → B.A
- Distribution → V.d
- Metabolism → C.L
- Elimination → C.L

Absorption :- cellular barries a drug has to cross to reach systemic circulation (Veins) → Heart

- ? cross cell wall
  - ① simple/passive diffusion (most drug)



- ✓ No ATP/energy
- ✓ Along conc gradient
- Lipid soluble drug cross

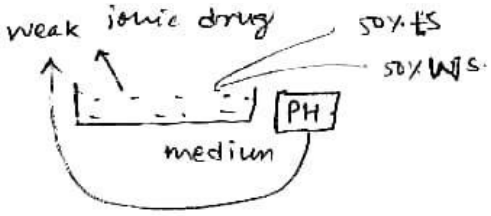
- Bioavailability (B.A)

- How to find lipid solubility of drug?
- by P.K value.

100% lipid soluble / strong Non Ionic — 100% water soluble strong Ionic / Polar

- non polar → ✓ cross
- weak ionic drug → PK value
- Ionic / Polar → ✗ cross

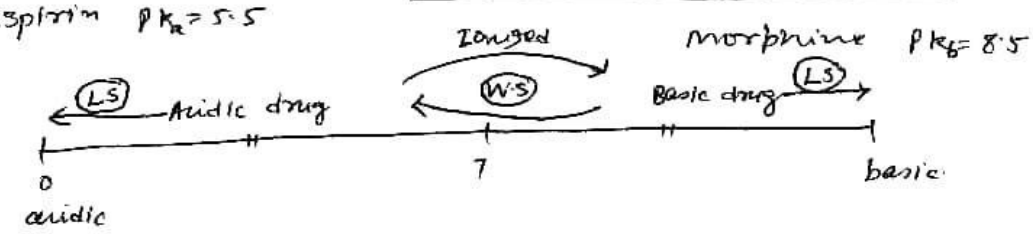
Pk value :- That PH at which drug is 50% Ionised & 50% Non Ionized.



Henderson - Hassel bach eqn :-

$$Pk = PH + \log \frac{[\text{Non ionic conc}]}{[\text{Ionic conc}]}$$

Aspirin $Pk_a = 5.5$

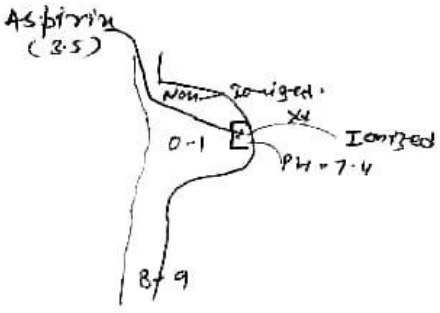


Weak acidic drug
- Non ionized (LS) in Acidic media
- Ionized (WS) → Basic media

Weak basic drug
- Non ionized → basic media
- Ionized → Acidic media

Strong acidic / Basic drug → - Not influenced by PH
- Always water soluble

Clinical imp :-



Aspirin shows ion trapping inside stomach cell

↓

- cox enzyme

↓

peptic ulcer

All drug

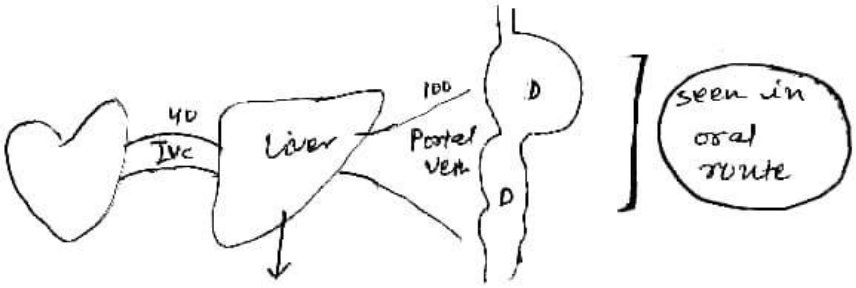
Absorb from

Basic drug :- SI (duodenum) >>>> Stomach

Acidic drug :- SI (" ") > Stomach

↓

Greater surface area



metaboliged a drug before reach systemic circulation

** Drug Having high first pass metabolism ?

Not given orally

✓ Natural steroid :- Hydro cortisone
Aldosteron
Testosteron
Estrogen

✓ Lignocaine :-

High oral dose

Propranolol
Morphine
Verapamil
Pethidine
Salbutamol
Imipramine
Nitrates

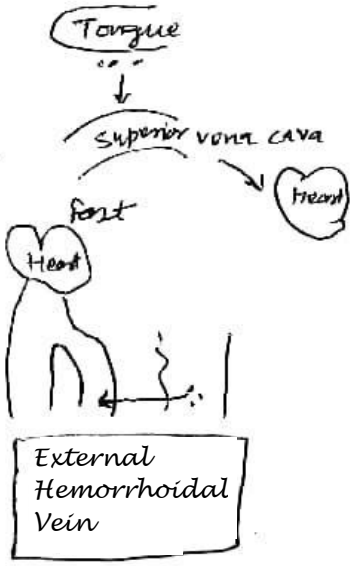
How to Avoid / by pass first pass metabolism of liver ?

✓ by all other systemic routes (except - oral)

ex. (1) sublingual :-

by pass FPM in Liver

(2) Rectal :-



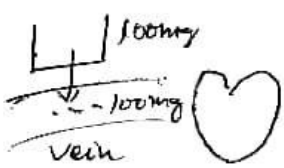
ex S/L Nitrates

DOC - Acute Angina

ex. Rectal Diazepam

DOC :- febrile seizure.

(3) Intravenous :-



✓ 100% Bioavailability

✓ No cellular barriers.

Bio-availability (B.A) :- fraction of drug that reaches systemic circulation in unchange form with time.

B.A I/V route :- 100% → standard for calculating.

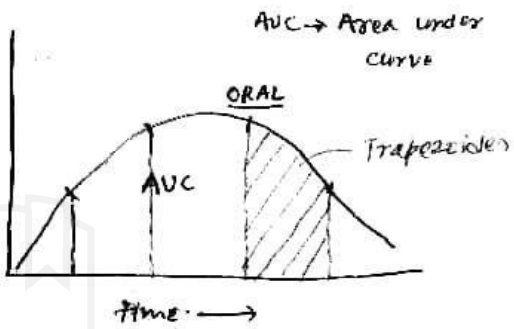
All other routes → < 100%

Calculate B.A :-

B.A[F] :- AUC of conc^n – time graph (oral) / AUC of conc^n time graph (I/V)

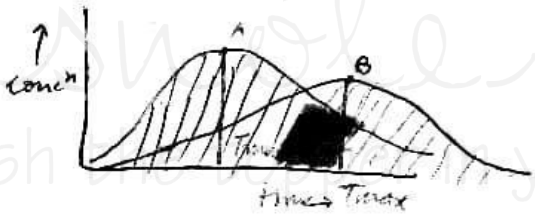
↓

fraction → No units.

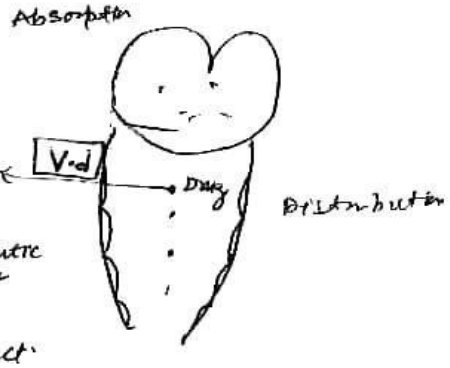


✓ AUC is calculated by Trapezoidal rule.

Rate of Absorption (speed) ← *Tmax



Distribution :-



Target organ :- Therapeutic effect

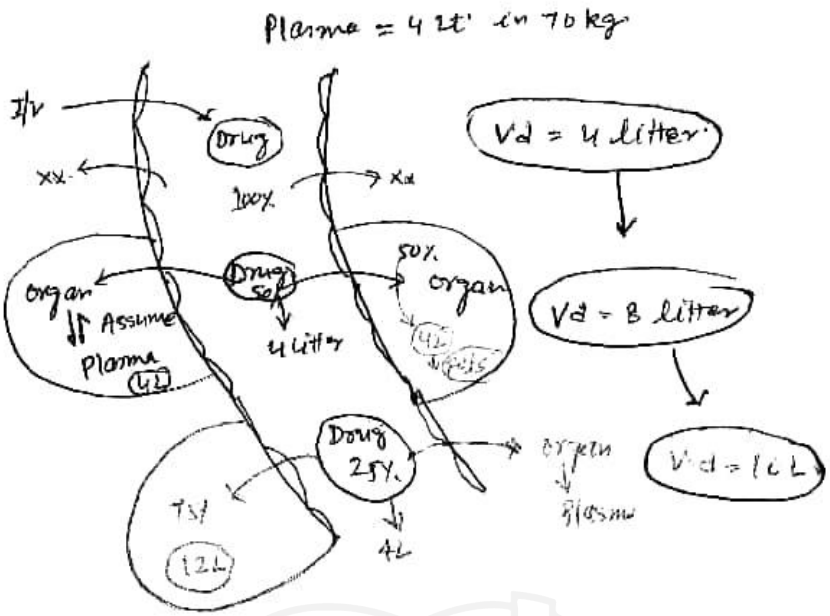
Other :- Adverse effect.

Volume of distribution (V.d) :- or (Apparent V.d)

✓ Extravascular deposition of drug into organ

✓ Apparent / false volume (not a true Vd)

✓ **Def^n :-** Vol^n of Plasma (lt) req. to contain a drug in equal conc^n



calculate V.d :-

$$V.d = \frac{\text{Dose given (I/v)}}{\text{Plasma conc}^{n}}$$

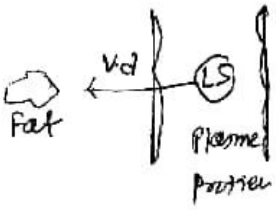
Q 100mg of dose a plasma conc^{n} is 5 mg/Lt.

calculate V.d → 20 litter.

Factor affecting V.d :-

(1) Lipid solubility :- (Pk) $\propto$ V.d ↑

(2) Plasma protein binding :- $\propto \frac{1}{V.d}$



(3) Physiological factor :- Age, Gender, Pregnancy

Disease :- liver DIS, kidney disease (nephrotic syndrom), shock, blood loss.] Alter plasma protein & plasma vol.

Plasma protein

Albumin
(Basic protein)
↓
Bind to acidic drug

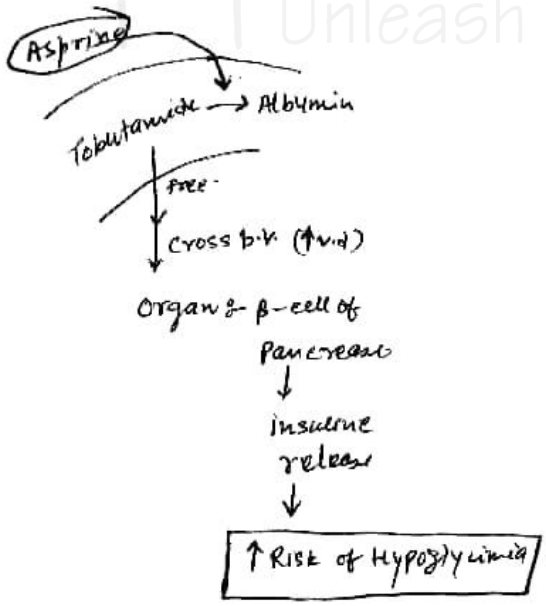
ex
- Aspirin (NSAIDs)
- Barbiturates
- Anti epileptics
- Sulfonamides
- Warfarin

α_1 Acid glycoprotein
(Acidic protein)
↓
Bind to basic Drug.

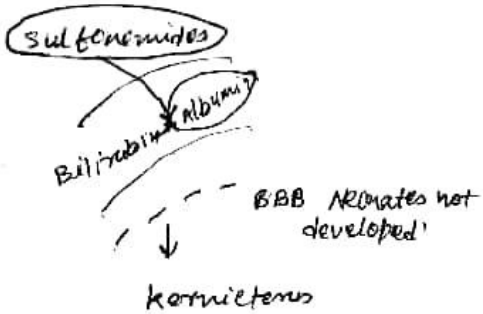
ex. - Anti Arrythmemics
- Beta-blocker (-lol)
- CCB (Verapamil)
- Lignocaine (Local Anesthesia)

Plasma protein binding → Non specific & Reversible.
- Non specific → multiple drug can bind at same site
- Reversible → Displace each other

Ex. ✓Aspirin displace Tobutamide from albumin ✓ Sulfonamides are C/I in Neonates

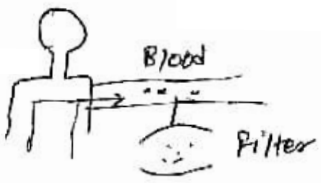


Reason - Displace bilirubin from albumin
↓
cross BBB of Neonates (not fully developed)
↓
CNS toxicity
K/s - kernicterus.



✓ All Anti epileptic → Displace each other from Albumin
↓
↑ each other toxicity.

(4) Hemodialysis :- T/t for poisoning of a drug.



(1) High Vd drugs → No role of Hemodialysis
(are not present in plasma)
ex. Digoxin → Vd - 450 Lt of Plasma.

(2) Low V.d + High protein binding → No role of HD.
↓
Not allow drug to filter
ex. Warfarin → 99% Albumin bound

(3) Low V.d + Low plasma protein binding → ✓ H.D.
(in plasma) (in free form)

☆ Hemodialysis [H.D]

✓ Do [H.D]
ex. Barbiturates (ex. Phenobarbiture)
Lithium
Alcohol
Aspirin
Salicylates
Theophylline

✗ No role of [H.D.]
ex.
Amfetamin
Verapamil / warfarin
Organophosphate
Imipramine
✓ Digoxin
Amiodarone
Benzodiazepin (Diazepam)
Chloroquine.

✓ Chloroquine - Highest V.d among all drugs.
↓
✓ 15000 Lt of plasm
(Deposites in all organs)
↓
Retina
↓
Chloroquine ring
↓
☆ Bull's eye Retinopathy.
↓ causes
(Permanent blindness)

Metabolism

- k/s bio-transformation
- k/s Xenobiotics.

lipid soluble → Metabolism → water soluble → elimination

- Non ionic
- Non polar

- Ionic
- Polar

Metabolism depends on
- Activity of drug
- Site of metabolism

(1) Active drug —(M)→ Inactive (most drug)

(2) Active drug —(M)→ Active form. ex Fluoxetine → Nor fluoxetin

(3) Inactive drug —(M)→ Active drug
- ↳ k/s (Pro-drug)
- ex. Inactive —(M)→ Active (Plasma-esD)
  - Prednisone → Prednisolone
  - Levodopa → Dopamine
  - ACE inhibitor (-PRIL) → -PRILAT
    - ex Enalapril → Enalaprilat

Allopurinol → Oxypurinol

Diazepam → Oxazepam

Spironolactone → Canrenone

Codein → morphine.

primidone → Phenobarbitone

all "ACEI" are pro drug
except → captopril, Lisinopril } are not pro drug.

- Sulfasalazine → 2
  - sulfapyridine → T/t - Rheumatoid arthritis
  - 5-ASA → T/t - Ulcerative colitis.
- Mycophenolate → mycophenolate.
- Aciclovir/Ganciclovir (A/G) → A/G-6-phosphate.
- Carbimazole → Methimazole.
- Clopidogrel & prasugrel → xy complex ring
- Dipivefrine → Epinephrine

Net urinary clearance (excretion) :- GF + ATS − PR

Glomerular filteration :- passive process (No ATP)

Low molecular wt drug filtered

↑ protein binding → ↓↓ GFR

Acidic Drug (+) >>> Basic Drug (−)

Active tubular secretion :- Active process (↓ ATP)

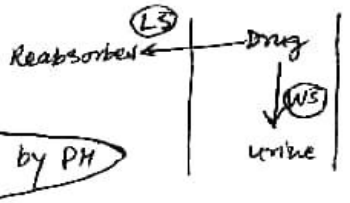
Transporters (+)

- OATP → Acidic drug ex. penicillin
- OCTP → Basic → Tubocurare
- P-gp → Neutral → Digoxin

Probenecid → Inhibit OATP

- makes penicillin longer acting
- Inhibit ATS of penicillin

Passive reabsorption :-



Strong ionic not influenced by PH

Why use weak ?

Weak Ionic drug poisoning

change PH opposite → Drug more (W3) → Urin

- Weak acid → T/t → forced alkaline diuresis. DOC :- Sod. bicarbonate
- weak basic → forced acidic diuresis. DOC :- NH_4Cl

Ex. - Aspirin
- NSAIDS
- Barbiturates
- Methotrexate

- Amphetamine
- Strychnine
- Morphine
- Atropine
- Quinine

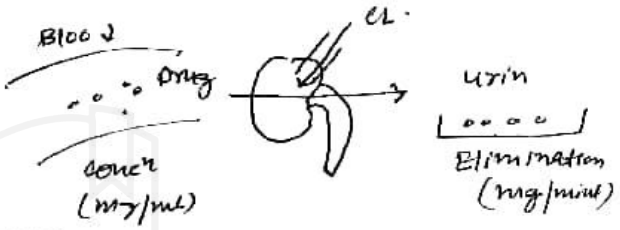
} Plant alkaloids.

Antidote of Aspirin poisoning → Sod. bicarbonates

Antidote of Amfetamine → Ammonium chloride.

kinetics of elimination :-

(i) Clearance capacity :- power of an organ to eliminate a drug.



$E \propto C.L$
$E \propto conc^n$

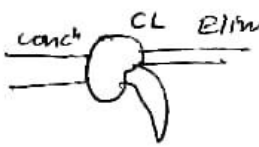
$E = C.L \times conc^n$ — 1st order kinetics.

mg/min = ml/min × mg/ml

Order of kinetics :-

First order (K)

CL capacity High (constant)



Plasma conc^n		Elimination
10	2 min →	5 mg
20	2 min →	10 mg
40	2 min →	20 mg
80	2 min →	40 mg

- Elimination ∝ Plasma conc^n
- constant fraction is eliminated
- $E = CL \times conc^n$
- t1/2 :- constant

zero order (K)

K/S saturation kinetics.

CL - Low (saturated)

max CL — 40mg in 2min

Plasma conc^n		Elimination
80 mg	2 min →	40 mg
100 mg	2 min →	40 mg
200 mg	2 min →	40 mg
500 mg	2 min →	40 mg

- Elimination = constant - independent of plasma conc^n
- constant Amount is eliminated.
- E :- michelis mentel eqn.
- t1/2 = variable

- Acute alcohol → enzyme inhibitor.
- chronic alcohol → enzyme ~~inhibitor~~ Inducer.

Various drug interaction:-

(1) Estrogen (contraceptive) —substrate, CYP3A4 ↑↑→ Inactive

Add:- Rifampicin → cyp inducer ↑↑

(2) Cisapride
Astemizole
Terfinadine
— CYP3A4 ↓↓ (xx) → xx inactive

Add:- Erythromycin/ Ketoconazole → cyp inhibitor ↓↓

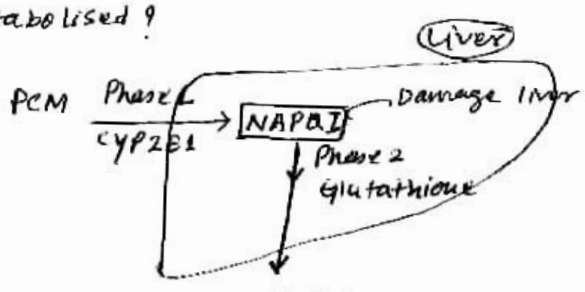
↑Toxicity :- ↑QT interval → Torsades de pointes (fatal arrythmia)
(banned)

(3) Clopidogrel :— CYP 2C19 → active (Antiplatelet) → T/t → MI, Stroke
(Prodrug)
↑ inhibit
Omeprazole

Do not combine
& Omeprazole

(4) Paracetamol (K/s Acetaminophen) — max. Daily dose of Paracetamol :— < 4gm/day

How metabolised ?



main s/E of PCM → "NAPQI" → Hepatotoxicity

Risk of Hepatotoxicity → ✓ chr. Alcoholism ✓ Induce CYP2E1
✓ depletes glutathione (↓)
✓ Isoniazid → Induce CYP2E1

Antidote of PCM toxicity :- ✓ "N acetyle cysteine" (DOC) — Regenerate glutathione
✓ methionine.

Drugs metabolized by Acetylation :-

- SHIP - DP Drug
  - ✓ Sulphonamides
  - ✓ Hydralazine
  - ✓ Isoniazid
  - ✓ Procainamide
  - ✓ Dapsone
  - ✓ Pass

Enzyme :- NAT enzyme
(N - acetyl - Transferase)

Genetic polymorphism

- High quantity → Fast acetylators
- Low quantity → slow acetylators → 2/3rd Indians

✓ Slow acetylators → SHIP-DP Drug → Toxicity

S/E → Drug induced Lupus erythromatosus (DLE)

Elimination :- Rate of Remove of Drug (mg/mint)

Site of elimination

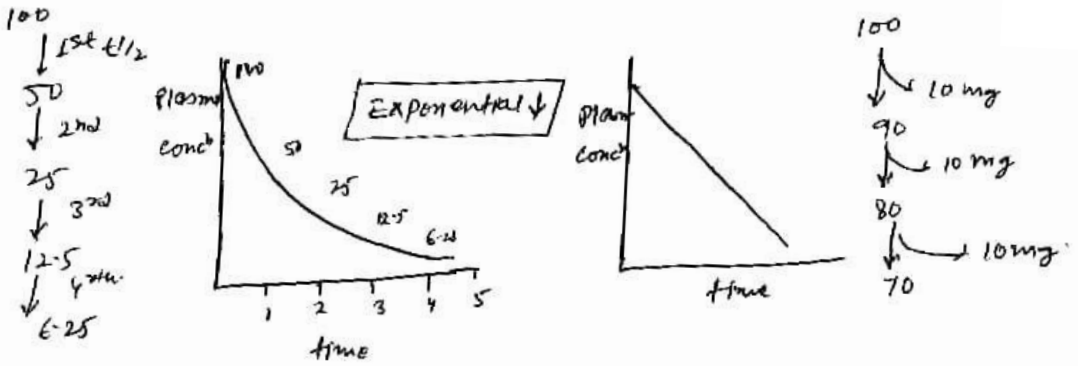
- ✓ Urine (Kidney)
- ✓ sweat, saliva, Tears → eg. Lithium
- ✓ Bile
- ✓ milk → Sulphonamide, Lithium, Aspirin, Methotrexate } C/I During lactation

✓ Drug excreted in bile → reabsorbed ∵ help of colonic bacteria
→ Estrogen (contraceptive)
k/s Entero-hepatic Reabsorption

✓ Anti biotics (Ampicillin, Doxycycline etc)
→ Contraceptive failure

Reason :- kill colonic bacteria
→ Reduce Enterohepatic reabsorption of Estrogen

Kinetics of elimination



✓ most drug — 1st order (K)

✓ few drug — zero order (K)

Examples of zero order kinetics

- Warfarin
- Heparin
- ✓ Alcohol
- ✓ Theophylline
- Salicylate
- ✓ Aspirin (in High dose)
- ✓ Phenytoin
- Phenylbutazone.

✓ Alcohol → pure zero order k at all dose.

formulas in Pk :-

(1) Half life
$= 0.693 \frac{Vd}{CL}$

(2) Loading dose
$= Vd \times$ target conc^n

(3) maintenace dose
$= CL \times$ target conc^n.

Half life :- $(t_{1/2})$ Time required to reduce plasma conc^n by 50%.

$$t_{1/2} = 0.693 \frac{Vd}{CL} = \frac{0.693}{k} \qquad k = \frac{CL}{Vd}$$

($0.693 = \ln 2$)

k = Elimination rate constant

$t_{1/2}$	Plasma conc^n	Elimination
0	100%	0%
1st	50%	50%
2nd	25	75%
3rd	12.5	87.5%
4th	6.25	93.75%
5th	3.125	96.875%

Q. 90% elimination ⟶ $t_{1/2}$

A) 2·3
B) 3·3
C) 4·3.

95% elimination $\xrightarrow{4-5\ t_{1/2}}$

100% elimination ⟶ ∞ (Assumption) in PK

If a drug is > 95% elimination Assume, complete elimination of drug (4–5 $t_{1/2}$) ↓ and action of a drug is over

Exception

HIT & RUN Drugs :- They continue to produce action even after complete elimination from blood.

Reason :- bind to target organ → Irreversibly.

ex. MAO inhibitors
Omeprazole (all PPI) → ⊖ H^+K^+ ATPase irreversibly.
Organophosphate
Ecothiopate
Reserpine
Asprin — ⊖ cox enzyme irreversibly

Drug dose in children :-

1) best method of calculating dose in children → body surface area

2) child dose from Adult also
- Young's formula :- $\text{Child dose} = \text{Adult dose} \times \frac{\text{Age}}{\text{Age}+12}$
- clarke's "
- Dilling's

Pharmaco dynamics :-

Drug (k/s Ligands) → Target bind → effect Produce

1) Types of ligand
2) Types of Target
3) Dose – Response curve (DRC)

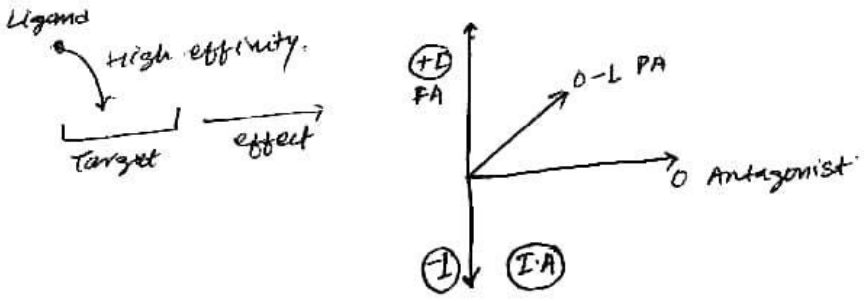
Ligand :- molecule that has **High affinity** for its target.

↓↑

Highly specific

? effect (intrinsic activity)

- **Agonist**
  - Produce effect
    - **Full Agonist** — ↑ max — (+1) Intrinsic activity
    - **Partial Agonist** — ↓ low — (0–1) IA
    - **Iverse Agonist** — ~~↓ opposite~~ — (−1) IA
- **Antagonist** ← k/s Pharmacological blockers
  - Not effect produce.
  - "zero intrinsic activity"



Antagonist :- Inhibit the action of agonist

- Physical
- Chemical
- Physiological
- Pharmacological (k/a blockers)
  - Competative Antagonist
  - Non-competi Antagonist