Drug	medium			Cross
A	A	Non ionize.	LS	✓
A	B	ionized	WS	X
B	B	Nonionized	LS	✓
B	A	ionized	WS	X.

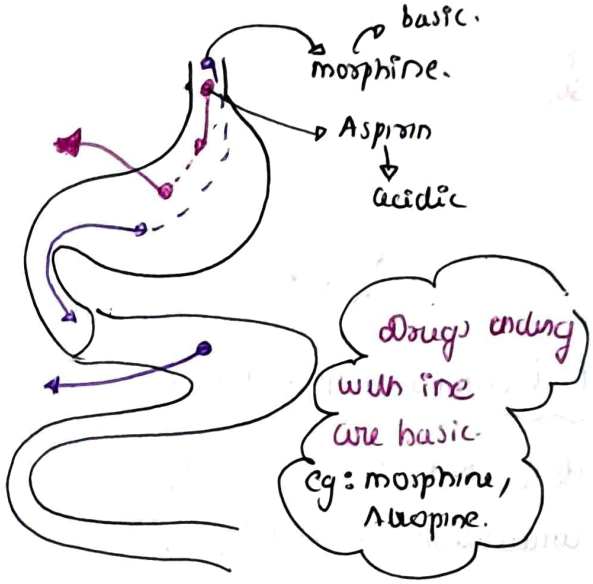
Henderson - Hasselbach eq

$$pH = pKa + \log \frac{[\text{ionized}]}{[\text{Nonionized}]}$$

• When we say, Acidic drug crosses in acidic medium, we do not mean that 100% of acidic drug will cross

never 0/100% $\xrightarrow{X}$ more/less → pH dependent.

• pH @ which 50% is ionized & 50% unionized = pKa.



eg: PKa = 6.

PH	Cross X WS/ ionized	will cross LS/ unionized.
3	0.1%	99.9%
4	1%	99%
5	10%	90%
6	50%	50%
7	90%	10%
	99.9%	0.1%
8	99.99	0.01
	99.999	0.001

• Calculate with 1 unit difference of PH

10	1	0.1	0.01	0.001
90	99	99.9	99.99	99.999

⇒ According to Henderson - Hasselbach eq, acidic drugs are absorbed from stomach and basic drugs from Intestine.

⚠ according to Henderson - Hasselbach only! practically! all drugs are better absorbed from Intestine than from stomach, be it acidic / basic.

• gastric emptying time - 30 min

• Intestine → many hours.

↓

greater surface area, rapidly absorbed.

Pharmakokinetics.
(ADME).

ABSORPTION

pharmacokinetics — 4 points *.

- Quantitative study of (1) drug movement, - in, through and out of body
- deals with what the body does to drug. (2)
- consists of absorption, distribution, metabolism and Excretion. (3)

All pharmacokinetic process involve transport of drug across biological membrane (4)

Biological membrane

- phospholipid bilayer + cholesterol.
  ↓
  adsorbed proteins.
  - Intrinsic
    ↓
    Extend full length of membrane
    ↓
    Surround fine aqueous pores.
  - Extrinsic.

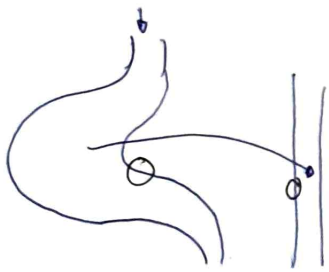
others → enzymatic / carriers, receptor / signal transduction.

Drugs are transported across membrane by

- passive diffusion and filtration.
- Specialized transport.
  - Carrier transport
    - facilitated diffusion
    - active transport.
  - vesicular transport.

GRG

- absorption



- movement of drug from site of administration to blood
- it will have to cross membran
- so, the easier it can cross mem the better it will be absorbed
- It's crossing depends on it's lipid solubility.
- L.S cross drugs ✓
  W.S will not cross drugs ✗

$HA \longrightarrow H^+ + A^-$

Non polar — polar.

Unionized. — Ionized

↓ Lipid soluble form. — ↓ Ionized form combine with water

↓ soluble in water

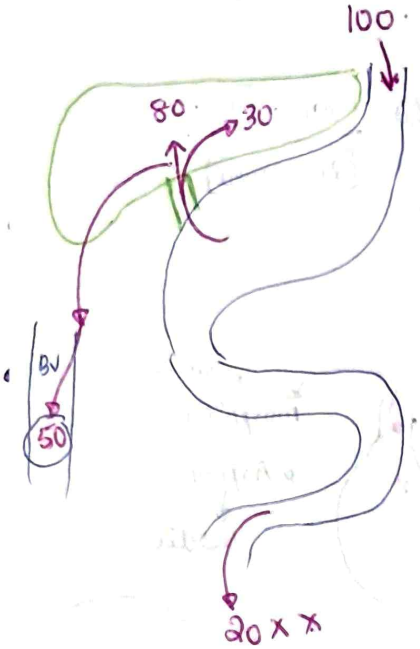
---

weak acids and bases, ionize depending on pH.

- acidic substance.
  ↓
  unionized in acidic medium.
  ↓
  Cross membrane.

same → cross

ie, acidic drug in acidic gastric pH will be absorbed not alkaline intestine.



Bioavailability → % of given dose that reach systemic circulation in unchanged form.

↓

It will determine dose of drug.

- If absorption ↑ B.A ↑
- If first pass ↑ metabolism (Liver) B.A ↓

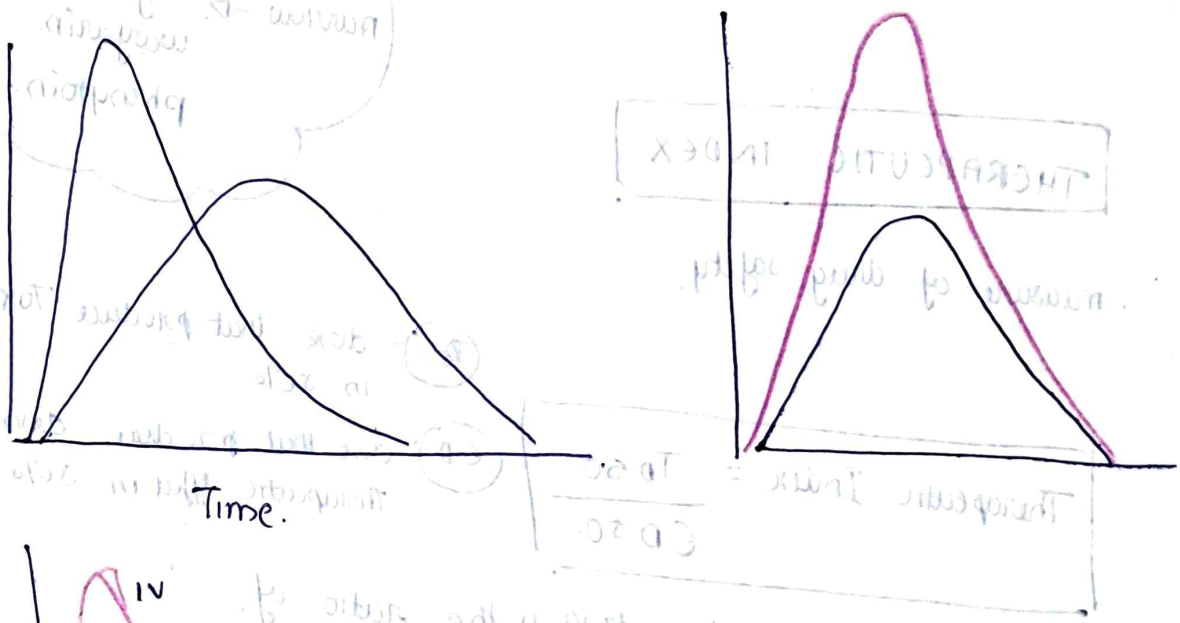
Drugs having high first pass metabolism

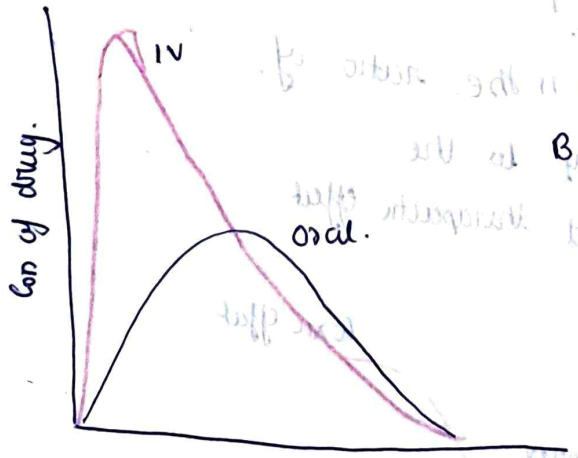
- Lignocaine
- propanolol
- GTN (nitroglycerine)

Bioavailability.

Bioavailability (F) is fraction of administered dose of drug that reaches the systemic circulation in an unchanged form.

$$F\% = \frac{AUC\ (oral.)}{AUC\ (IV)} \times 100$$





$$B = \frac{AUC\ oral.}{AUC\ IV} \times 100.$$

- IV = 100% B.A
- oral - less due to → ① First pass metabolism ✓
  ② decreased absorption. ✓

Factors affecting B.A

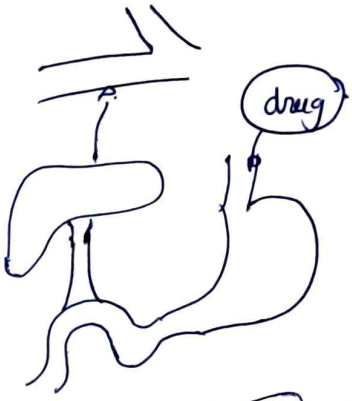
1. first pass metabolism
2. Hepatic ds.
3. Enterohepatic cycling.
4. physicochemical ppts of drug.
5. PH & ionization
6. food.
7. drugs
8. area of absorbing surface.
9. GI disorders.

NIL By Mouth

Nitroglycerin
Lignocaine
β-blocker
Morphine.

First pass metabolism with suitable eg.

- pre-systemic metabolism.
- Initial metabolism of drug by the liver before it reaches systemic circulation.



Not given orally

→ lignocaine
→ testosterone
→ hydrocortisone.

Result : ↓ B.A of orally administered drug.

Consequence.

- oral dose needs to be higher than IV dose.
- If oral B.A ↓ → needs to give by other routes.

Examples

	B.A	so given
Nitroglycerin	1% oral.	sublingual.
Lidocaine	35%	IV. - not given orally.
propranolol	25-35%	orally high dose needed.
morphine	20-40%	oral B.A lower than IV.

Pharmacokinetics

- plasma half life of a drug is the time taken for it's plasma concentration to be reduced to half of it's original value.

$$T1/2 = \frac{0.693 \times Vd}{CL}$$

Vd - Volume of distribution.
CL - Clearance.

Types - distribution T/2.
elimination T1/2

USES

1. to estimate time to reach steady state ~ 4-5 T1/2
2. Time required for elimination of drug from body.
   4-5 T1/2 of >96% removal.
3. drug dosing interval.
4. relationship between loading dose & maintenance dose.

EERA

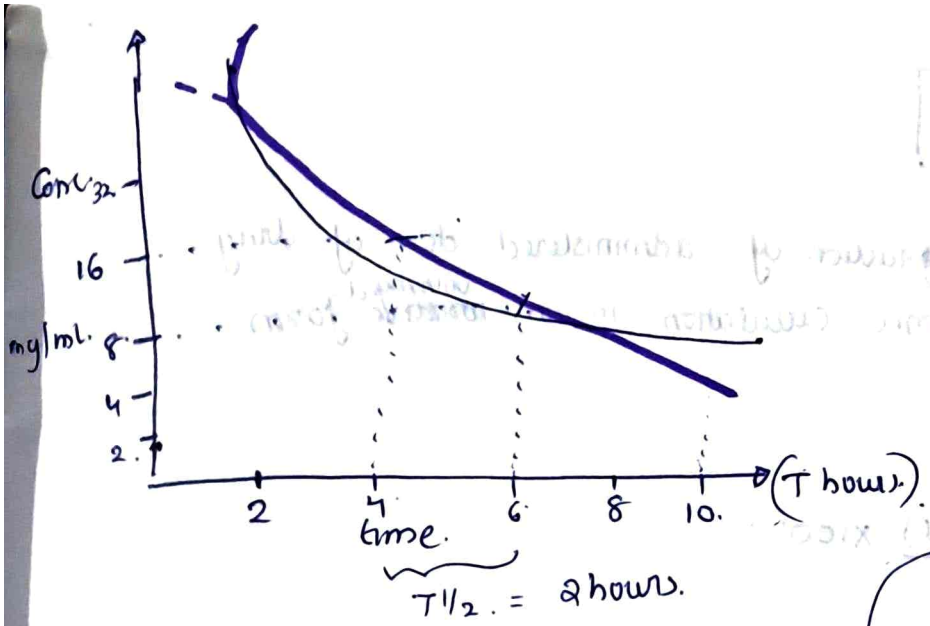
Short T1/2

- aminoglycosides
- Adenosine
- Remifentanil
- Esmolol.
- Edrophonium.

WDAD

Long acting.

- amiodarone - 50 days.
- diazepam - 20-40 h.
- Digitoxin 7 days.
- warfarin 36-42 hours.



wide → D.
paracetamol
Penicillin or
amlodipine.
sildenafil.

narrow → D.
Lithium.
Digoxin
warfarin.
phenytoin.

THERAPEUTIC INDEX

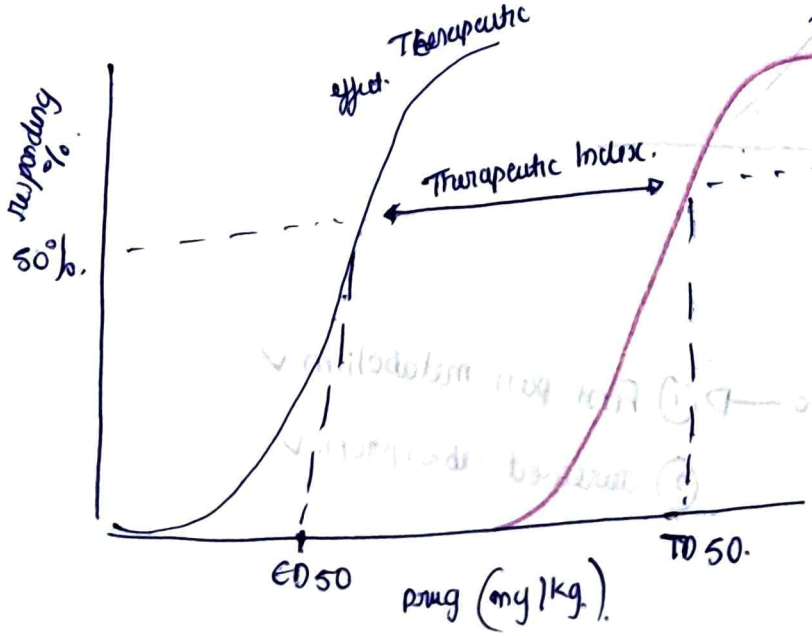
- measure of drug safety.

TD50 = dose that produce Toxic response in 50%.

ED = dose that produce desired. Therapeutic effect in 50% of population.

$$\text{Therapeutic Index} = \frac{TD\,50}{ED\,50}$$

Therapeutic index of a drug is the ratio of.
dose that produces toxicity to the
dose that produce desired therapeutic effect



narrow → low safety
monitoring ✓

wide: safe ✓.