Bioavailability

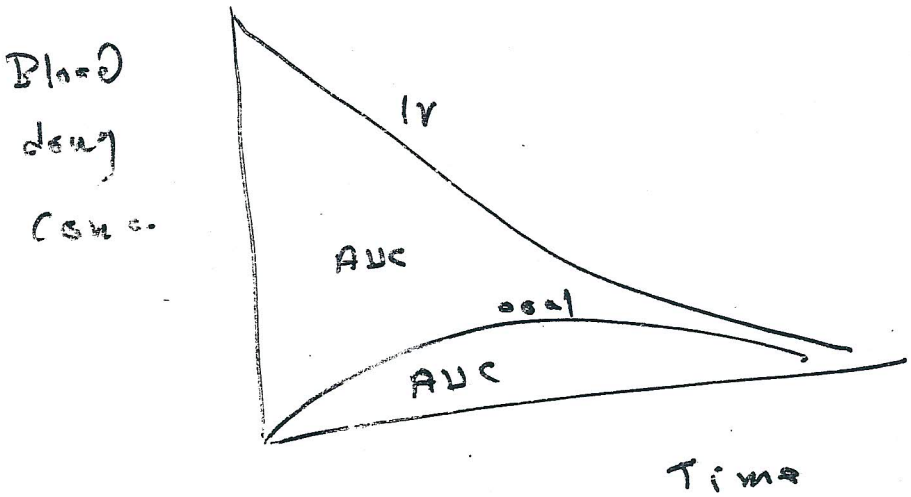
Definition:

The fraction of administered drug that reaches systemic circulation unchanged chemically.

Determination:

IV - administration = All bioavailable

others → oral, IM etc. = all or fraction



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

= fraction absorbed.

Factors that influence bioavailability

1- First - pass effect :-

oral drugs : → portal circulation → liver

liver → unchanged drug in blood

liver → metabolized drug (metabolites)

for the first time

2- physical properties of drugs :-

solubility → water → poorly absorbed
→ lipid → poorly absorbed
→ both → well absorbed

3- chemical properties

e.g. penicillins = acid unstable → cannot be useful.

insulin = pt^n digested

4- formulation :

- particle size → tablet
  → capsules
- salt form → . sodium salts → soluble
  . calcium salts → insoluble ?
  aluminium " → insoluble ?
- crystal polymorphism : penicill G -
  procain P. et.
- excipients → binders agents = sustained release
  disintegrating agents - effervescent

Bioequivelence

- two different formulas → same active ingridient
- AUC → extent of absorption.
- Cmax } → rate of absorption.
- Tmax }

Therapeutic equivalence :

Compare efficacy : - safty :-

Depend on : . pharmacokinetic parameters = Dong conc.

. " dynamic parameters.

- different formulas = pharmacokinetic parameter.
  some active ingridients

= different chemicals : same mechanism of action
  different " " "

Absorption & Distribution.

Absorption = irriversible transportation of drugs from site of administration to central compartment (blood).

Distribution: reversible movement of drugs from central compartment to peripheral tissues:-

a- target tissues

b- elimination organs - kidney
- liver
- etc.

Central compartment => 1) blood

2) well perfused tissues
a) lungs
b) kidney
c) liver etc.

Note: 1) Drug concentrations in blood can equilibrate quickly with highly perfused tissues e.g. lung, kidney etc. considered part of central comp.

2) poorly perfused tissues = fat tissues = will only take up and release drugs slowly

3- once drug arrive at a tissue, it must pass out of the blood capillaries and possibly cross cell membrane barriers, either to:-
a- its target tissue
b- pass into urine or bile

4- [illegible] Drug's ability to cross cell membranes is [illegible] pharmacoki[illegible]

Membrane permeation by drugs

membrane permeability by Drugs

The plasma membrane of cells constitutes a hydrophobic lipid barrier and drug permeation can occur by:-

1- direct diffusion through the lipid.

2- carrier-mediated transport.

3- diffusion through aqueous pores.

4- pinocytosis.

Note: 1) Direc diffusion & carrier-mediated are most important.

2) aqueous pores are too small to allow the passage of most drugs.
(molecular weights in the range of 200-1000)

3) pinocytosis is thought to be important for only few large molecules.
e.g. insulin penetration of the blood-brain barrier)

Diffusion through membrane lipid

Diffusion of drug depends on:-

a- concentration gradient

b- diffusion coefficient

Drugs lipid/water partitioning coefficient

Estimated by : Drug distribution between water and simple organic solvent e.g. heptane

Ionization:

- most drugs are either:- a- weak acids
  b- " basis

- So in aqueous solution they exist in ionized & non-ionized forms

- The ionized form is lipophobic.

- So that ionization impedes passive membrane permeation.

- Headerson - Hasserbalch equation

for wea acids = $\text{Log}_{10} \frac{c_i}{c_u} = pH - pKa$

" " basis = $\text{Log}_{10} \frac{c_i}{c_u} = pKa - pH$

- unionized form

ion trapping

- lipid membrane seperates solution of different pH.
- Differences in ionization of the two sides can lead to uneven distribution
- The ionized molecules do not readily cross the membrane.
- an effective trapping of ionized drug form on the side promoting ionization.
- A weak base such as morphine will achieve a higher concentration in the acid gastric lumen.
- a weak acid such as phenobarbital will achieve a higher concentration in urine that can be alkalinized after toxication.

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Active transport

- Carriers are important for membrane transport of essential nutrients that have Low lipid solubility

- most drugs are exogenous substance of No nutritional values

* Absorption
* ~~des~~ Elimination of drugs from liver & kidney.

- features of active transport mechanism.
  = uphil transport
  = saturation
  = Competition between drugs for transport.

Enternal administration =

via gut

- oral administration: absorption =
  (most convenient & acceptable route)
  - stomach
  - small intestin
  - Larg intestin

- portal circulation → liver
  (major site of drug metabolism)

- first pass effect:

- sublingual → rapid → direct to systemic circul.
- rectal → cause irritation, vomiting, unsure children → systemic circulation

Drug Distribution

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- most drugs entering the body Don't spread rapidly throughout the whole of body water to achieve a uniform concentration.

- Large molecules = heparin
  = insulin
  } cannot easily enter interstitial and intracellular spaces

- Small & lipid-soluble molecules can reach interstitial & intracellular fluids.

- apparent volume of distribution (Vd)

$$Vd = \frac{Dose}{Cp}$$

- examples: - heparin = 0.05 - 0.1 (L/kg)
  - tubocurarine = 0.2 - 0.4 "
  - ethanol 1.0 "
  - propranolol 2-5 "
  - Nortriptaline > 20.0 "

Binding to protein & other tissues

- Tetracyclines → Ca^{++} → bone & teeth.

- plasma proteins:
  - albumin → most important.
  - α-acid glycoprotein – basic drugs
    e.g. propranolol
  - Low specificity.
  - Bound drug → inactive
  - ↓ free drug → ↓ elimination kidney.
  - drug-drug interactions
    - highly bound drugs
      e.g. warfarine.

- Accumulation in lipid.
  lipid-soluble drugs → adipose tissues
  e.g. halothane

- BBB.
- joint.
- eyes
- fœtus etc..