PHARMACOKINETICS – I
Absorption & Distribution

Dr Ruwan Parakramawansha
MBBS, MD, MRCP(UK),MRCPE, DMT(UK)
(2013/08/21)

LEARNING OUTCOMES

By the end of the lecture students will be able to..

- Define pharmacokinetics, bioavailability, bioequivalence and volume of distribution
- Outline different methods of transfer of drugs across membranes
- Describe factors affecting diffusion through lipid membrane
- Describe factors affecting distribution into different body compartments
- Mention clinical relevance of bioavailability, bioequivalence and volume of distribution

DEFINITION - PHARMACOKINETICS

"what the body does to the drug".

...the study of the time course of the drug and metabolite concentration in biological fluids

DEFINITION

A branch of pharmacology that describes drug,

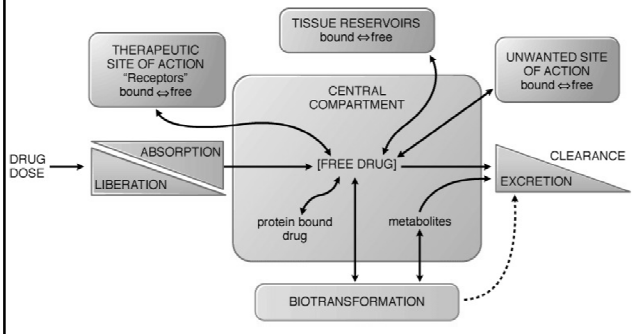
A – Absorption
D – Distribution
M - Metabolism
E – Excretion

WHY....

- To know how much drug will reach the site(s) of drug action/unwanted site(s)
- To know when a drug will reach the site(s) of action//unwanted site(s)

Help to understand and control the therapeutic action of drugs/adverse effects in the human body

ADME AND THERAPEUIC ACTION



DRUG DISPOSITION

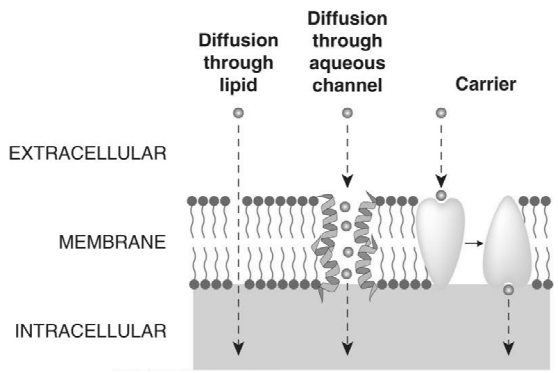
Drug molecules move around the body in two ways:

I. Bulk flow (i.e. in the bloodstream, lymphatics or cerebrospinal fluid)
II. Movement across cell membrane/s

TRANSFER OF DRUGS ACROSS MEMBRANES

Four main ways...

1) By diffusing directly through the lipid
2) By diffusing through aqueous pores formed by special proteins
3) By combination with a membrane transporter
4) By *pinocytosis*.



FACTORS AFFECTING DIFFUSION THROUGH LIPID

For non-ionized forms of drugs...

- Magnitude of the concentration gradient across the membrane
- Permeability coefficient of the drug ~ **LIPID SOLUBILITY**
- The membrane surface area exposed to the drug

FACTORS AFFECTING DIFFUSION THROUGH LIPID

- Many drugs are weak acids or bases that are present in solution as both the non-ionized and ionized species.

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

- The non-ionized molecules usually are more lipid soluble and can diffuse readily across the cell membrane

FACTORS AFFECTING DIFFUSION THROUGH LIPID

For ionized forms of drugs...

- pK_a ....the pH at which half the drug (weak acid or base electrolyte) is in its ionized form
- pH gradient across the membrane

At steady state, an acidic drug will accumulate on the more basic side of the membrane and a basic drug on the more acidic side....**ION TRAPPING**

ION TRAPPING IN CLINICAL PRACTICE

- 2nd generation antihistamines are ionized molecules at physiological pH that cross the blood-brain barrier poorly compared to first generation antihistamines (uncharged at pH 7.4)

2nd generation antihistamines less sedative

ION TRAPPING IN CLINICAL PRACTICE

- In aspirin toxicity elevation of urine pH (by giving sodium bicarbonate)

promotes urinary excretion of aspirin (a weak acid)

ION TRAPPING IN CLINICAL PRACTICE

Acidic pH of the stomach and absorption of acidic drugs such as aspirin.....

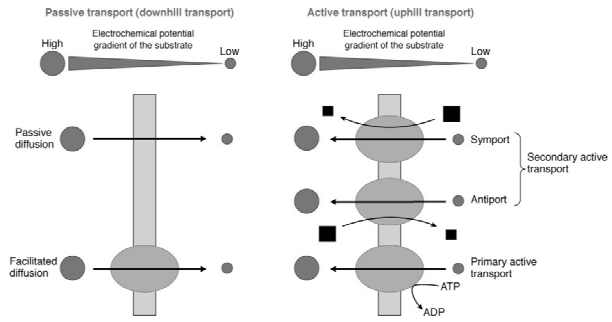
- Enormous absorptive surface area of the villi and microvilli in the ileum compared with the much smaller surface area in the stomach overrides the importance of pH partition
- ∴ absorption of an acidic drug such as aspirin is promoted by drugs that accelerate gastric emptying (e.g. metoclopramide) > acidic stomach pH

CARRIER-MEDIATED MEMBRANE TRANSPORT

- Membrane transporters may mediate either drug uptake or efflux (creating a barrier to prevent the intracellular accumulation of potentially toxic substances)
- Two major super-families:
  I. ABC (ATP binding cassette) transporters
  II. SLC (solute carrier) transporters

CARRIER-MEDIATED MEMBRANE TRANSPORT

- ABC proteins are primary active transporters, which rely on ATP hydrolysis to actively pump their substrates across membranes
- SLC super-family includes genes that encode facilitated transporters and ion-coupled secondary active transporters



P-GLYCOPROTEINS

- P-glycoproteins (P for 'permeability') belong to the ABC transporter super-family
- P-glycoprotein is overexpressed in tumor cells after exposure to cytotoxic anticancer agents and pumps out the anticancer drugs, rendering cells resistant to their cytotoxic effects

DRUG ABSORPTION

- .....passage of a drug from its site of administration into the plasma
- Absorption - complete by definition for intravenous route
- For topical administration – absorption not required for the drug to act

BIOAVAILABILITY

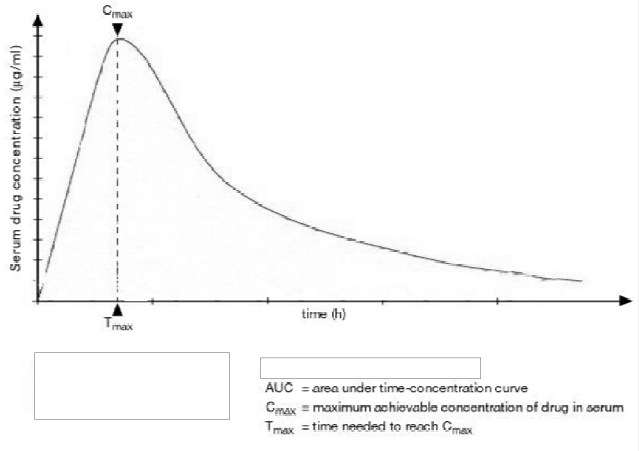
- **... the fraction of unchanged drug reaching the systemic circulation following administration by any route**
- Bioavailability for i.v. Route is 100%

BIOAVAILABILITY

- Bioavailability for oral route may be limited by...
  - the characteristics of the dosage form
  - the drug's physicochemical properties
  - intestinal and liver metabolism
  - by transporter export back into the intestinal lumen

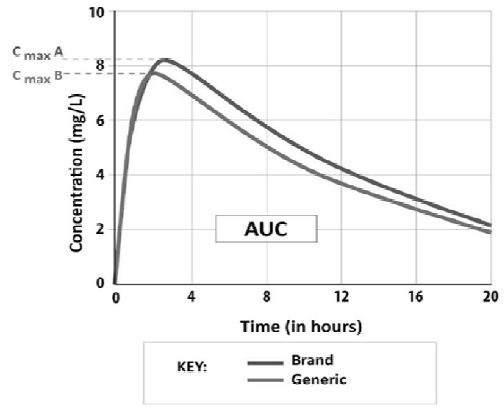
PHARMACEUTICAL EQUIVALENCE VS. BIOEQUIVALENCE

- **Pharmaceutical equivalents** - contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration
- **Bioequivalence** – rates of absorption and extents of bioavailability of the active ingredient are same



AREA UNDER THE CURVE (AUC)

- An index of the drug exposure of the body
- Closely dependent on the drug amount that enter into the systemic circulation and on the ability that the system has to eliminate the drug(clearance)



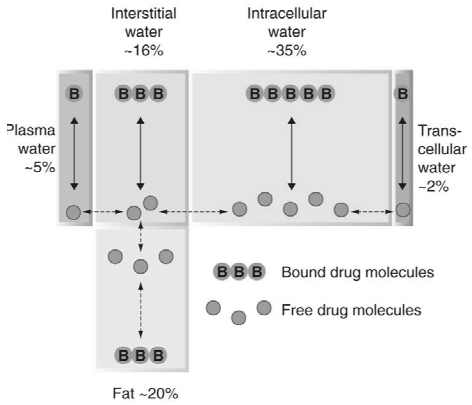
DISTRIBUTION OF DRUGS

- Following absorption or systemic administration into the bloodstream, a drug distributes into interstitial and intracellular fluids
- Initial distribution phase: rapid to well-perfused organs e.g. liver, kidney, brain
- Second distribution phase: slower and accounts for most of the extravascularly distributed drug e.g. muscle, fat, skin (Called **REDISTRIBUTION** when there's no tissue binding during initial distribution phase)

BINDING OF DRUGS TO PLASMA PROTEINS

- Many drugs circulate in the bloodstream bound to plasma proteins
  - e.g. Albumin - acidic drugs
  - α_1-acid glycoprotein - basic drugs
- Binding is usually reversible
- Unbound drug is the pharmacologically active form
- Only unbound drug is in equilibrium across membranes $\Rightarrow$ binding of a drug to plasma proteins limits its concentration in tissues and at its site of action

DISTRIBUTION OF DRUGS



DISTRIBUTION OF DRUGS

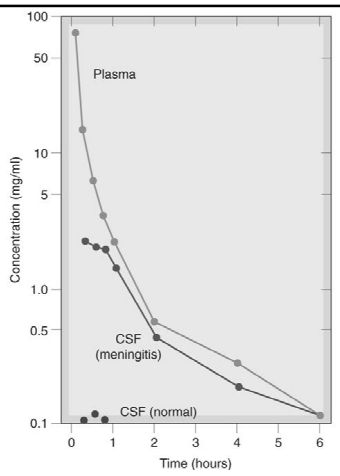
- Diffusion of drug into the interstitial fluid occurs rapidly because of the highly permeable nature of the capillary endothelial membrane
- ∴ Partitioning of drug between blood and the particular tissue depend on,
  - permeability across tissue barriers
  - binding within compartments
  - pH partition
  - fat:water partition

THE BLOOD-BRAIN BARRIER

- The barrier consists of a continuous layer of endothelial cells joined by tight junctions and surrounded by pericytes
- Membrane transporters e.g. P-gp that are efflux carriers present in the brain capillary endothelial cell and capable of removing a large number of chemically diverse drugs from the cell

THE BLOOD-BRAIN BARRIER

- The brain is inaccessible to many drugs with a lipid solubility that is insufficient to allow penetration of the blood-brain barrier
- The more lipophilic a drug, the more likely it is to cross the blood-brain barrier
- Inflammation can disrupt the integrity of the blood-brain barrier, allowing normally impermeant substances to enter the brain



VOLUME OF DISTRIBUTION

- The apparent volume of distribution (V_d), is defined as **the volume of fluid required to contain the total amount of drug in the body at the same concentration as that present in the plasma**
- A hypothetical value ⇒ avoid identifying a given V_d too closely with a particular anatomical compartment

VOLUME OF DISTRIBUTION

- Calculated as the ratio of the dose present in the body and its plasma concentration when the distribution of the drug between the tissues and the plasma is at equilibrium

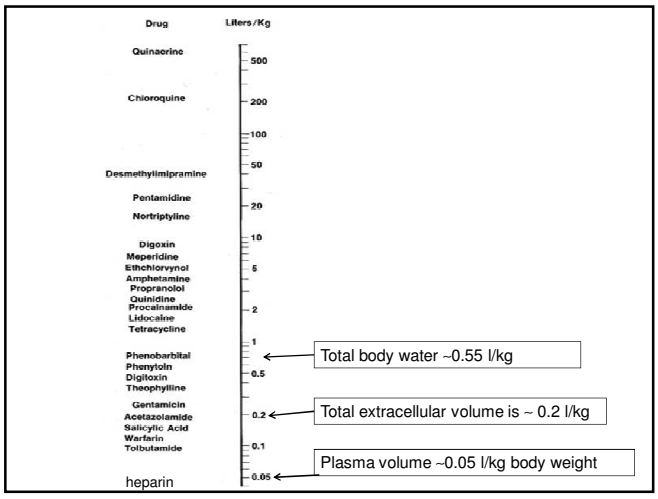
$$Vd = Q/C$$

Q = amount of drug in body (g)
C = unbound plasma drug concentration (g/liter)

- Can be expressed as per kg divided by body weight

CALCULATION

- Calculate Vd when 1 g is administered iv and the plasma drug level is 0.024 g/L
- Vd = 1 g/.024 g/L = 42 L **(Total Body Water)**



VOLUME OF DISTRIBUTION

- Volume of distribution is used to...

1. Compute a loading dose
2. The residual amount of drug in the body knowing plasma concentrations