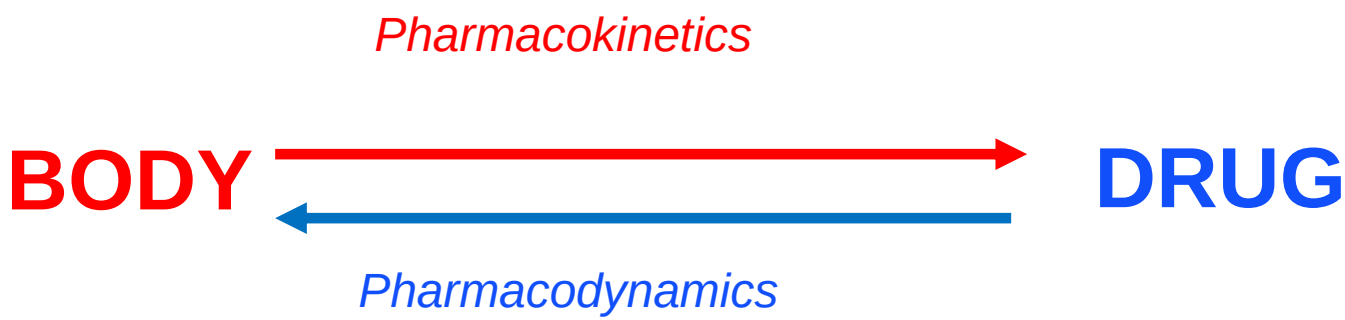
# Pharmacokinetics and Psychotropic medication

Dr Jonathan Keay

(additional material Dr Cathy Symonds, Dr Rachel Thomasson and Dr Jane Wilson)

# Pharmacokinetics - definition

- The study of the time course of a drug's passage through body fluids and tissues
- "what the body does to the drug"



# Pharmacokinetics

allows:

- Calculation of drug dosage
- Uses concepts of loading and maintenance dosing
- Individualised drug dosage (“personalised medicine”)
- Dose adjusting
- Understanding what happens to a drug

# The pharmacokinetic processes – the 4 principles to understand

**Absorption**

- the processes of getting into the body (not necessarily the systemic circulation)

**Distribution**

- the processes of distribution to the tissues

**Elimination**

- the processes removing drug from the plasma
- generally makes drug products more water soluble and hence easily excreted

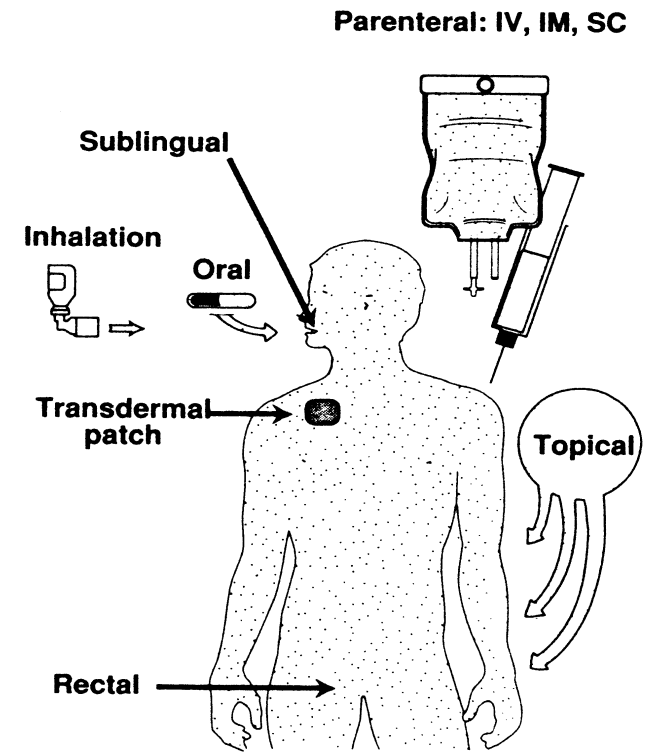
**Excretion**

- the processes removing drug from the body (mainly via urine & faeces)

# Absorption

# Routes of Administration

- Oral – slow, unpredictable, dependent on pH, gastric emptying plus many other factors
- Intravenous (iv)- fastest , 100%
- Intramuscular (im) – slower than IV
  can be unpredictable (eg diazepam)
- Subcutaneous (sc) – rapid but can be variable
- Inhalation – fast locally
- Rectal – usually local
- Topical – usually local




*Determined primarily by the properties of the drug and the therapeutic objectives*

# Choice of route

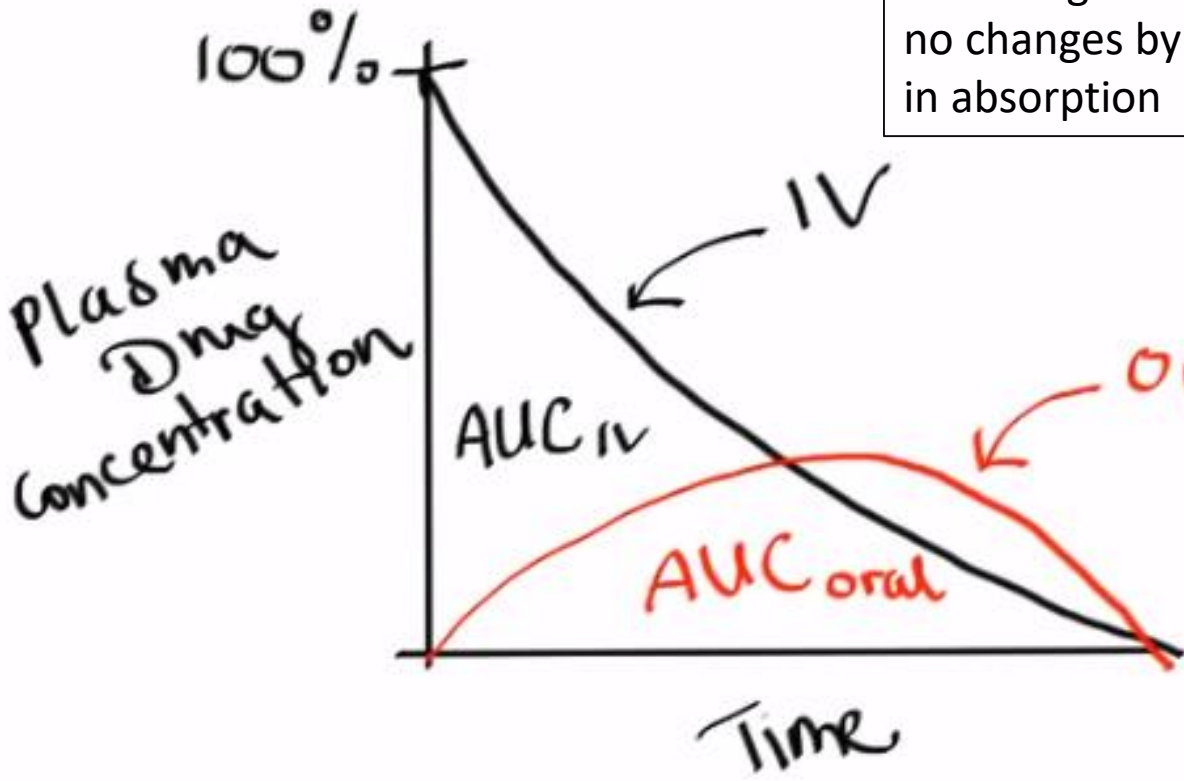
- For a drug to be absorbed after oral administration, it must
- cross  intestinal cell membranes (favours lipophilic drugs eg olanzapine, although some absorption of hydrophilic drugs between cells in upper intestine)
- dissolve (favours hydrophilic drugs eg amisulpride, lithium)

- Parenteral administration avoids this stage eg Rapid Tranq when speed of onset and accuracy of dosing is needed
- IM can be fast eg olanzapine or slow eg depots or unreliable eg diazepam depending on chemistry of drug
- IV fastest and more reliable but not practical in RT

# Bioavailability

- The proportion of an administered dose which reaches the *systemic circulation (F)*
- Ranges between 0 and 100%
- Is affected by
  - *Chemical nature of drug*
  - *first-pass metabolism*
    - the proportion of an absorbed dose which escapes metabolism before it reaches the systemic circulation (hepatic extraction ratio)
    - therefore high (hepatic) clearance drugs will have low bioavailability

Iv = straight line as no changes by body in absorption



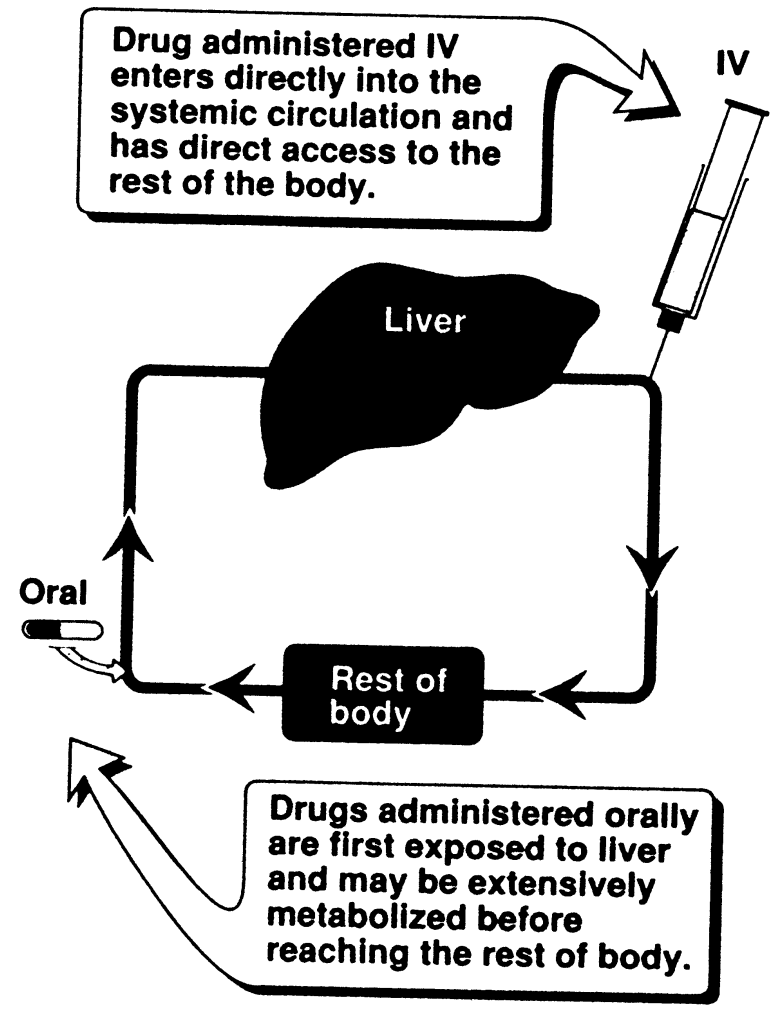

Oral= drug affected by gut, skin etc so not straight line

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

# Factors Affecting Bioavailability

- First-pass Hepatic Metabolism
- Solubility of the drug
- Chemical Instability
- Nature of the drug formulation

*by definition, IV injection bypasses all these factors and absorption is 100%. It is not 100% by other routes*



# Bioequivalence

- **Bioequivalence** When two different formulations of the same active compound, given at the same dose and by the same route, achieve comparable plasma levels within a given timeframe (eg different formulations of lithium)

- **Chemical equivalence** indicates that drug products contain the same active compound in the same amount and meet current official standards
  - Inactive ingredients in drug products may differ.
  - Eg Prozac and generic fluoxetine

# Distribution

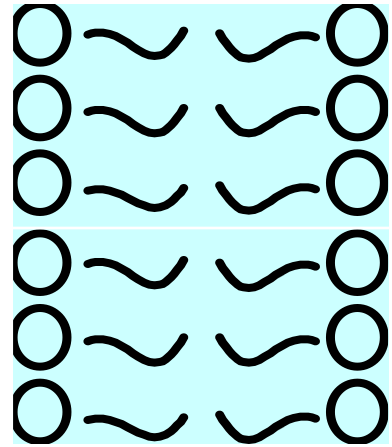
# Drug Distribution

- Process by which a drug reversibly leaves the site of administration and is distributed to the tissues in the body.

- Distribution depends on various factors such as:
  - blood flow (brain>liver>skeletal muscle>adipose tissue) influences choice of route
  - capillary permeability (kidney is high & brain low)
  - degree of reversible protein binding (binding to albumin)
  - water/lipid solubility of the drug can vary with formulation eg depots

# Drugs Crossing Membranes

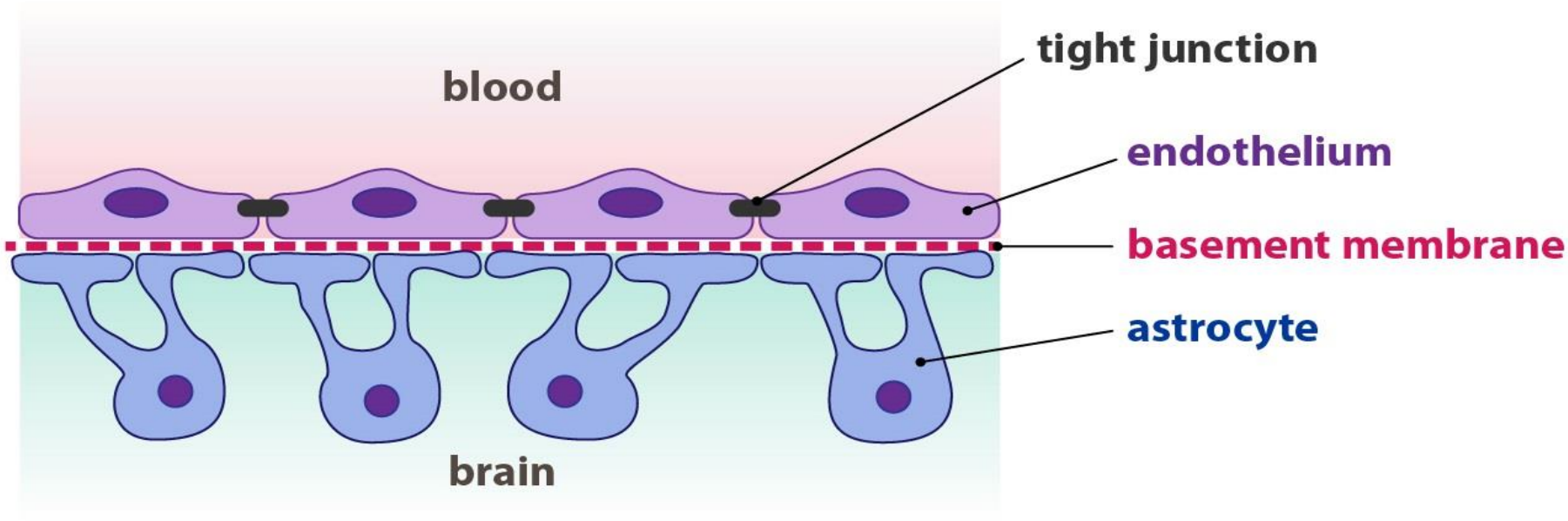
- chemical properties of drugs.
  - polarity (-OH, C=O)
  - ionization (pKa)
  - size (Mol. Wt.)



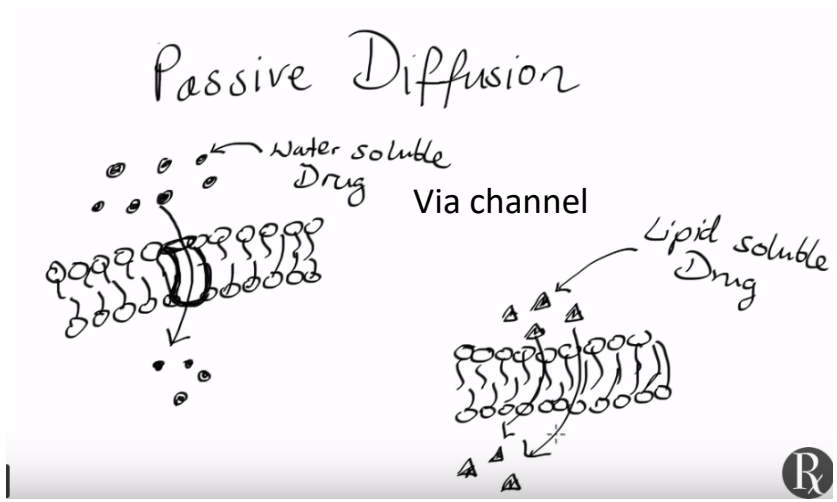
*like dissolves like so lipophilic drug cross the lipoid cell membranes easily*
*lipophilic drugs require hepatic metabolism to be excreted renally, in order to be filtered by the glomerulus*

# Psychotrophic drugs must cross the blood brain barrier

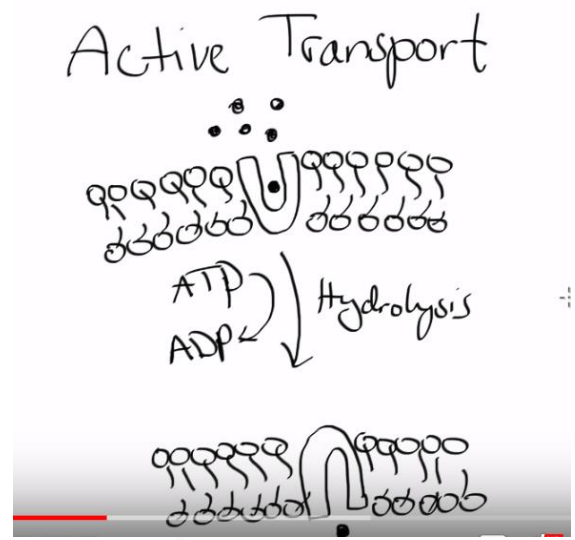
- Tight junctions between capillary endothelial cells and Astrocytes
  - Regulates entry and exit of large molecules
  - Maintains careful osmotic gradient
  - Enables high intracerebral concentration of glucose

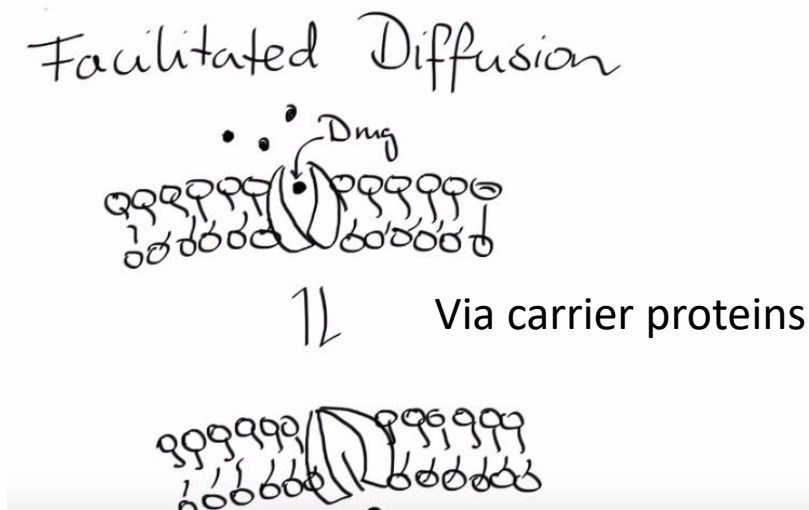


# Drugs cross membranes - absorption

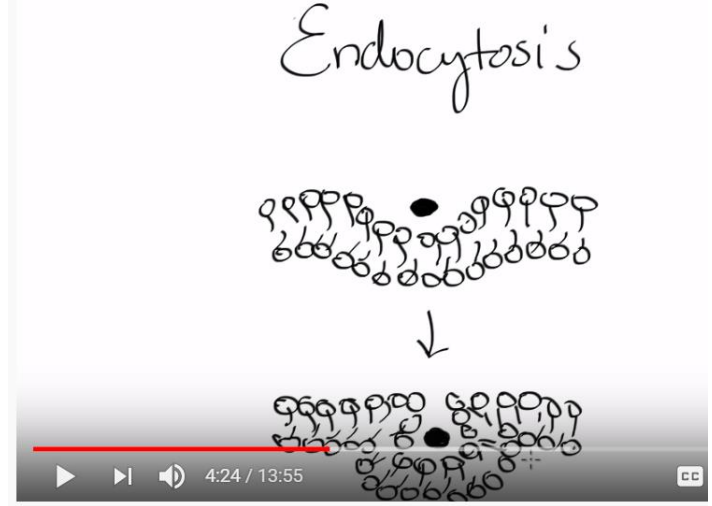



Via channel




Via carrier proteins

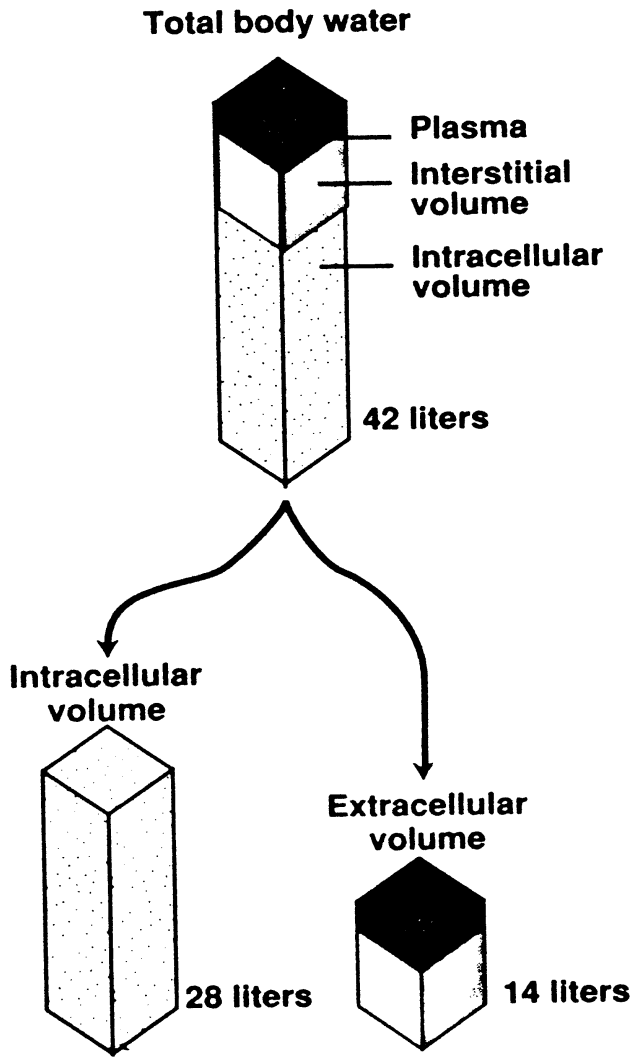



Pharmacology - PHARMACOKINETICS (MADE EASY)

# The Volume of Distribution

- When a drug enters the body it dissolves in body fluids
- Depending on amount of drug and the volume of fluid in the body a concentration will be achieved
- This volume of fluid is known as the volume of distribution for a drug (Vd)
  Lipophilic drugs have are poorly water soluble

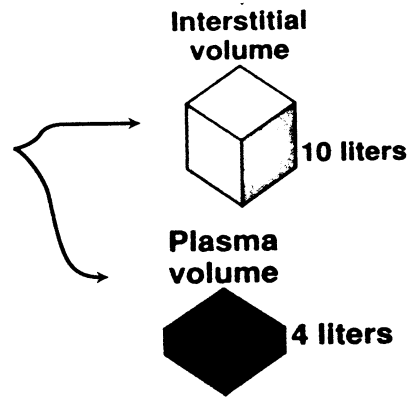
  because of not liking water, often high degree of plasma protein binding  despite this, often have large volumes of distribution, concentrated in brain / fat



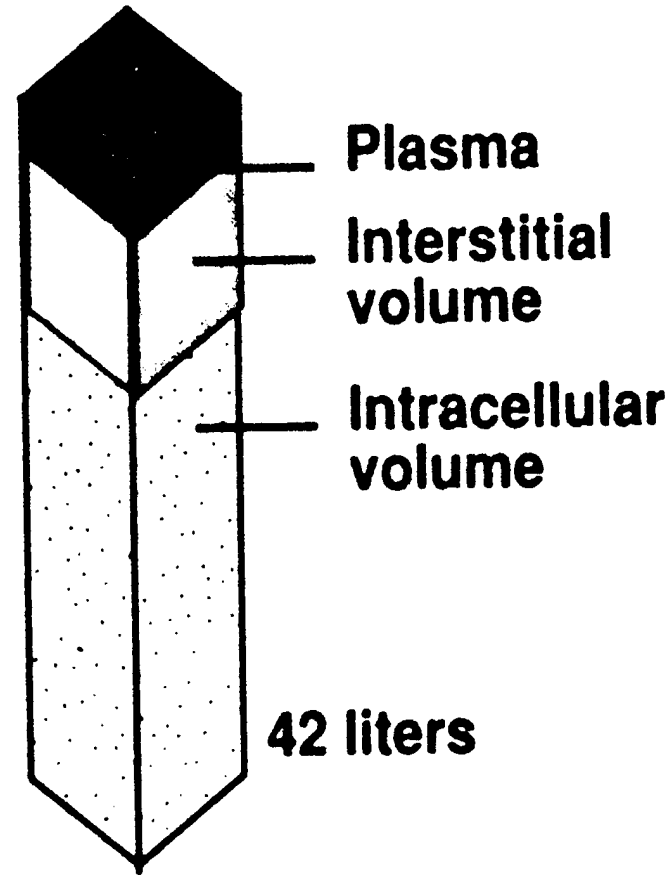

# Volume of distribution Vd

- *H*ypothetical volume of fluid into which the drug is dispersed.
- *Mathematical def*: relates the amount of drug in the body to the concentration in the blood or plasma.

**Vd = Amount in body / Plasma Conc (L)**



- large $V_d$ infers that the drug distributes widely crosses membranes, lipophilic
- small $V_d$ infers that the rug remains in plasma, protein bound, large molecule



# Relevance of distribution phase

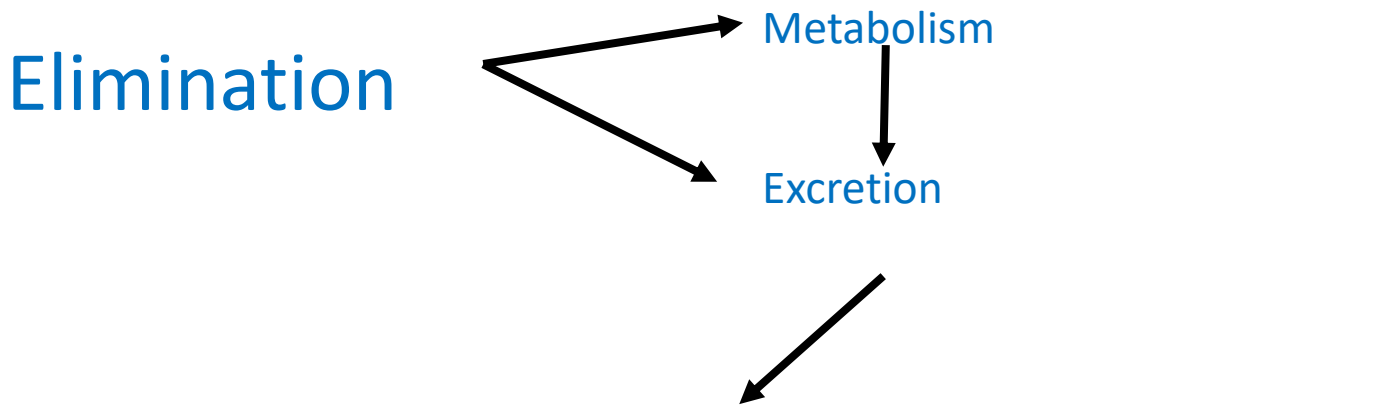
- Blood samples taking during this phase are hard to interpret. Best taken before dose for trough especially with oral drugs

# Elimination & excretion

# Drug Metabolism & Excretion

Drugs have a finite duration of action

Elimination processes largely determine the extent and length of time a drug remains and acts.



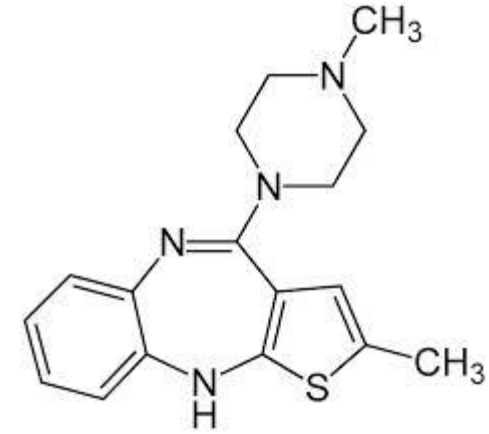

Major Routes: Urine, Bile (eg faeces)

Minor Routes: Saliva, Sweat, Milk,
Expired Air, all body fluids

# Renal vs hepatic function

- Ionic drugs (eg lithium) not metabolised, excreted unchanged by kidney hence renal function most important
- Changes in blood flow, hydration, electrolytes will also have major impact
- Most drugs metabolised by liver hence LFTs more important
- Saturation of capacity of hepatic enzymes eg phenytoin
- Effect of other drugs, alcohol, etc can effect metabolism

# Metabolic routes




- Phase I
  - Oxidation, reduction, hydrolysis carried out by Liver CYP enzymes
  - CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4
  - Active metabolites often produced
- Phase II
  - Produces inactive hydrophilic compounds that are readily excreted
  - Glutathione conjugation, Methylation, Sulphonation, Acetylation, Glucuronidation
  - Drugs do not need phase I metabolism first
    - Lorazepam/oxazepam/temazepam
  - Small compounds excreted via urine
  - Large compounds excreted via bile

# CYP system

- 1A2 – TCAs, Duloxetine, Olanzapine, Clozapine
  - Caffiene and Fluvoxamine inhibits, smoking induces
  - Induction effects take weeks (enzyme synthesis required)
- 2C9 – Lamotrigine, Valproate
  - Fluvoxamine inhibits, CBZ induces
- 2C19 – TCAs, BDZ, citalopram, escitalopram
  - Fluvoxamine inhibits, CBZ induces

# Cytochrome P450

- Mixed function oxidase metabolise most drugs and chemicals including alcohol, tobacco and caffeine
- We used to consider that this enzyme was a single entity and that drugs could inhibit or induce its levels.
- Now we know that this is a multi-gene family of enzymes that have specificity for different drugs
- This type of information allows the selection of safe or at least safer drug combinations.
- Also epigenetic phenemona (have gene but presence of other phenomena make it more/less active eg presence of oestrogen)
- Important genes: CYP1A2, CYP2D6, CYP2C9, CYP2C19, CYP3A4

# CYP system

- 2D6 – Aripiprazole, Clomipramine, Fluoxetine, Galantamine, TCA's, Mianserin, Olanzapine, Risperidone, Clopixol, Venlafaxine
  - Inhibited by TCA's, Duloxetine, Fluoxetine, Paroxetine, Sertraline

- 3A4 – BDZ, CBZ, Aripiprazole, Fluvoxamine, Mirtazepine, Clomipramine, Quetiapine, Trazodone, Z drugs, Methadone
  - Inhibited by Fluoxetine and Paroxetine

# Genetics

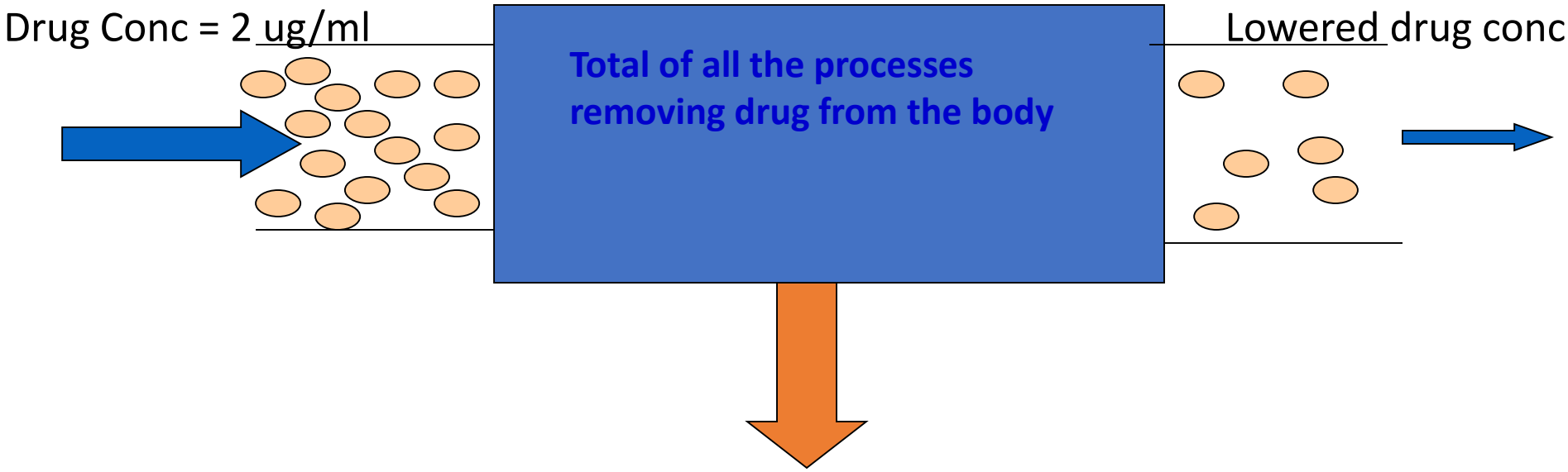
- Poor metabolisers v prone to side effects
- 5-10% caucasians and 1-2% Asians poor 2D6 metabolism
- 33% North Africans, 5% caucasians, 1% Asians – Ultrarapid 2D6 metabolisers
- 15-30% E Asians and 3-6% caucasians poor 2C19 metabolism

- 40% Asians, 60% South American Natives lack Aldehyde Dehydrogenase

# Gender

- Women:
  - Hypoactive 1A2 (TCA, Dlx, Olz)
  - Higher antipsychotic plasma levels
  - Higher rates of acute dystonic reactions
  - Higher rates of Dystonic reactions and Tardive Dyskinesia
  - Higher Vd
  - Longer half life (large lipid compartment)

# Clearance




Drug molecules disappearing from plasma a rate of 400ug per min (clearance is a constant)

$$Cl = \frac{400\ ug/min}{2\ ug/ml} = 200ml/min$$

# Half-life

- Time taken for plasma concentrations to fall by 50%
- determined by **BOTH** volume **AND** clearance

  $t_{1/2}$ = 0.7 Vd/CL

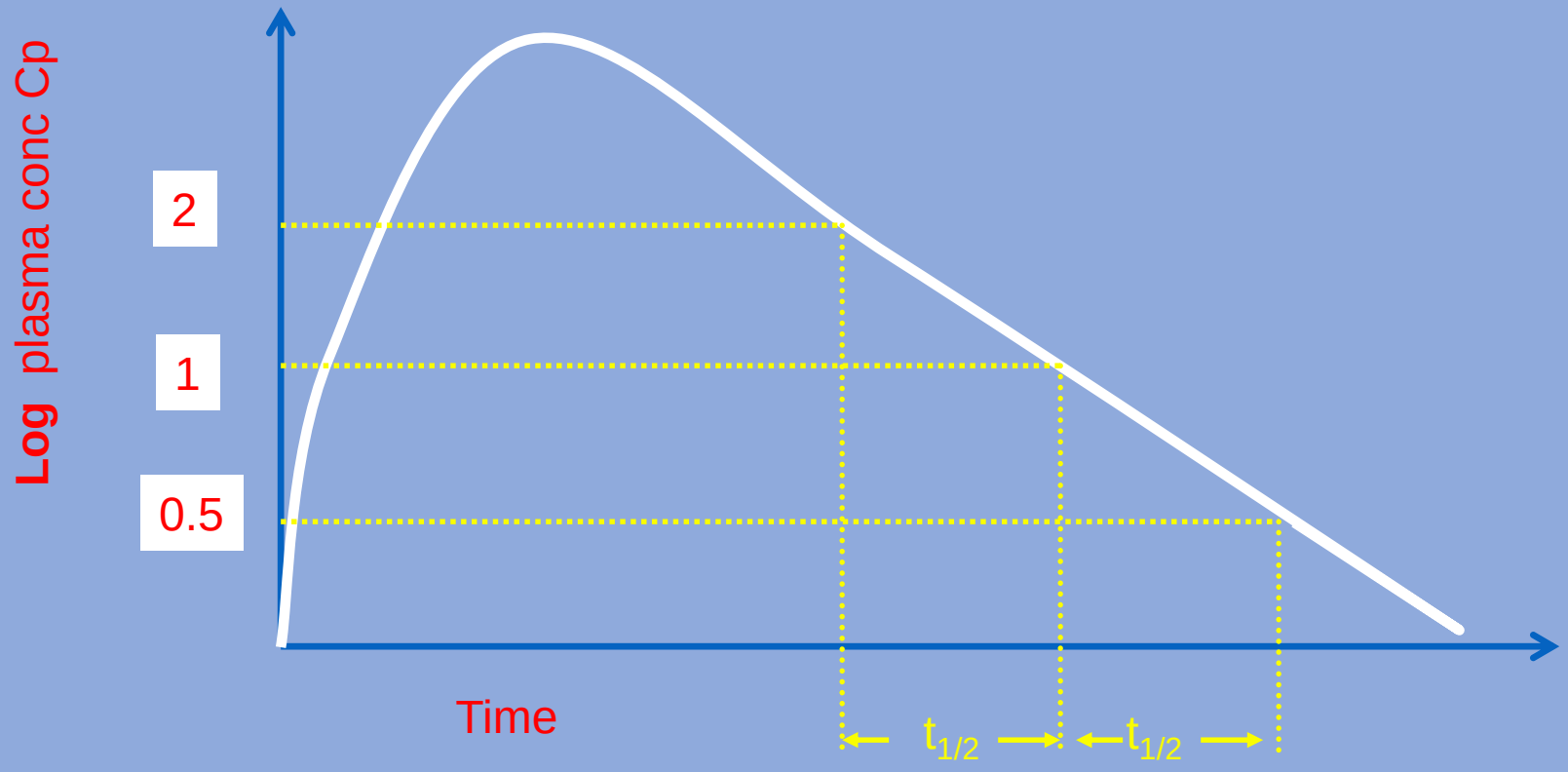
  used in calculation of dosing regimens

  frequency of dosing adjusted to keep interdosing fluctation of concentrations in acceptable limits

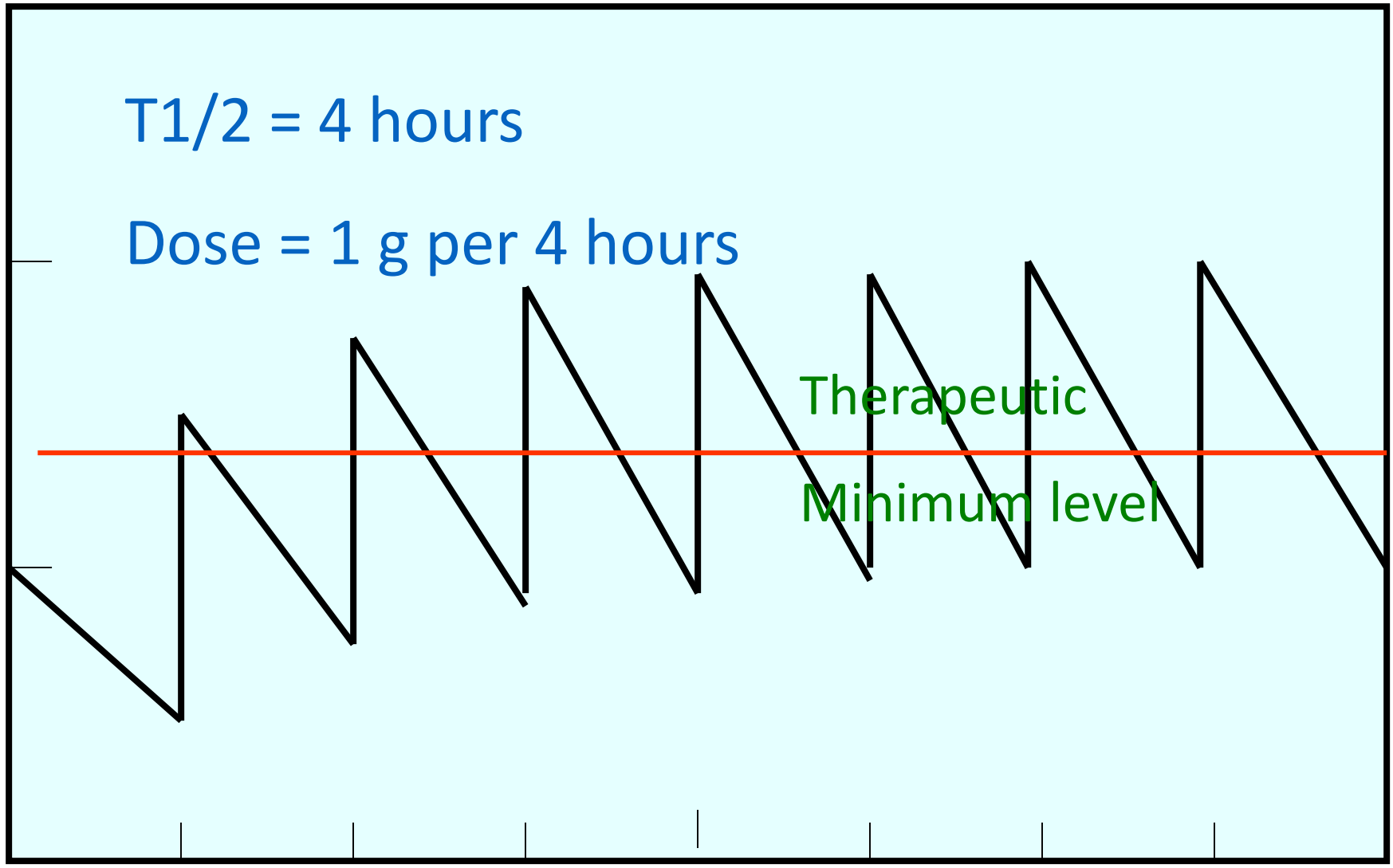
  steady state reached after 4-5 x $t_{1/2}$

  also time to reach 50% of steady state = $t_{1/2}$

# Half-life



# Intermittent dosing



# Use in practice

- Choice of drug for clinical situation eg lorazepam for RT
- Overdoses – interpretation of plasma levels
- Antidotes – flumazenil vs midazolam
- When to increase dose
- Length of washout required when switching eg fluoxetine
- Loading doses eg disulfiram

# Therapeutic Drug Monitoring

- Therapeutic window must be known eg lithium. Atypicals still being determined
- Must take sample at correct time in relation to dose
- Useful for

1. assessing compliance
2. treatment of overdoses
3. high dose prescribing eg above BNF dose

- increasing dose if side effects problematic

Clozapine
- Trough level - 350-500mcg/L

Lithium
- 12h post dose - 0.4-1.0 (0.4-0.8 in over 65's) mmol/L

- Valproate
  - Trough level - 50-100mg/L

**But must treat patient not blood level**

- What knowledge has crossed your blood brain barrier?