PHARMACOKINETICS

(a) **To explain the concept of pharmacokinetic modeling of single and multiple compartment models and define:**
- **Half life**
- **Clearance**
- **Zero and first order kinetics**
- **Volume of distribution**
- **Bio-availability**
- **Area under the plasma concentration time-curve**
- **Extraction ratio**

(b) **To describe absorption and factors that will influence it with reference to clinically utilized sites of administration**

(c) **To describe factors influencing the distribution of drugs (Eg. protein binding, lipid solubility, pH, pKa) and their alteration in physiological and pathological disturbance.**

(d) **To describe the mechanisms of drug clearance and how physiological and pathological disturbance may effect these.**

(e) **To describe the mechanisms of non-hepatic and hepatic metabolism of drugs. To describe Phase 1 and Phase 2 reactions, hepatic extraction ratio and its significance, first pass effect, enzyme induction and inhibition.**

(f) **To explain and apply concepts related to intravenous and infusion kinetics. To describe the concepts of effect-site and effect-site equilibration time and their clinical applications. To describe the concept of context sensitive half time and its clinical applications.**

(g) **To calculate loading and maintenance dosage regimens.**

(h) **To describe the pharmacokinetics of drugs administered in the epidural and subarachnoid space.**

(i) **To explain clinical drug monitoring with regard to peak and trough concentrations, minimum therapeutic concentration and toxicity.**

(A) **Overview of Pharmacokinetics**:

Pharmacokinetics is the study of absorption, distribution, metabolism and excretion of drugs by the body (Ie. "way the body handles drugs")

Based on a given drug dose, it help determines the [drug] in plasma and at the effect site → this is then used to:

- (i) Determine drug effect with time
- (ii) Determine inter-individual variability in drug responses
- (iii) Form the basis for rational drug dosage schedules
- (iv) Aid interpretation of measured plasma [drug] with regards to drug effect/toxicity

(B) **<u>Drug Transport across a Cell Membrane</u>**:

Drugs need to pass through cell membranes to reach its "effect-site" to exert its actions

> Aside – Cell membrane
> - A phospholipid bi-layer (10 nm thick) → each layer consists of phospholipids arranged with their hydrophilic heads on outside and lipophilic chains facing inwards, such that the bilayer effectively comprises of 2x hydrophilic layers surrounding a central hydrophobic one
> - Glycoproteins either span the bi-layer, or are attached to outside or inside of it → they form ion channels, receptors, G-proteins, enzymes, Etc.

<u>Methods of drug transport across a cell membrane</u>:

(1) Passive diffusion (MOST common method)
- Drugs move across the cell membrane down its [ ] gradient across without the use of energy
- Drugs that are lipid-soluble and non-polar diffuse across cell membrane easily → in particular, only the "unionized" form of drug can diffuse across the cell membrane
- Rate of transport dependent on "Fick's Law of diffusion":

$$\frac{dQ}{dt} = \frac{(-D)(A)(dc)}{(dx)}$$

dQ/dt = Rate of drug flux across a membrane
D = Diffusion constant, which is = (Solubility in membrane)/√MWT)
A = Surface area available for diffusion
dc = [ ] gradient across the membrane
dx = Membrane thickness

> Rate of drug diffusion across a membrane is:
> - (1) Proportional to the [ ] gradient of "diffusible fraction" of drug (Ie. unionised and not bound to protein) across the membrane
> - (2) Proportional to the "surface area available for diffusion"
> - (3) Proportional to the "solubility of drug in membrane", which is dependent on:
>   - (i) Lipid solubility → non-polar and lipid-soluble drugs cross membrane easily
>   - (ii) Ionisation state → only unionised form of drug can cross membrane
> - (4) Inversely proportional to the square-root of the "molecular size" of the drug
> - (5) Inversely proportional to the "membrane thickness"

(2) Passive filtration
- H_2O, small ions and low MWT drugs are transported across membrane pores/channels via "bulk flow" (Ie. balance of $P_{HYDROSTATIC}$ and $P_{ONCOTIC}$ across the membrane)
- Note – There are some vascular beds (esp kidneys) that have large pores that permit high MWT drugs to pass through

(3) Facilitated (carrier-mediate) diffusion
- Drugs moves across the cell membrane using a membrane-bound carrier protein → movement occurs down its [ ] gradient and without the use of energy
- Rate of transport also dependent on "Fick's Law of diffusion" (see above) → but it occurs at a FASTER rate than passive diffusion

(4) Active transport
- Drugs moves across the cell membrane using a membrane-bound carrier protein → movement occurs against its [ ] gradient and with the use of energy
- Can be either:

- (i) 1° active transport – Energy supplied to carrier protein that directly transports the drug across the membrane
- (ii) 2° active transport – Energy is supplied to a carrier protein that generates an ionic gradient required to transport the drug across the membrane (Ie. drug-ion co-transporter)

Important to note – "Carrier proteins" used in facilitated diffusion and active transport exhibit:
- (i) Specificity → carrier protein is specific for a type of drug
- (ii) Saturation → carrier protein has a fixed number of binding sites for transport
- (iii) Competition → different drugs compete for the binding sites on the carrier protein

(5) Endocytosis
- Energy-dependent process by which the cell membrane invaginates around the drug and moves it into the cell where it is either released into the cell or retained in a vacuole
- Reserved for drugs that are too large to cross membrane by aforementioned mechanisms

(C) **Drug Handling by the Body**:

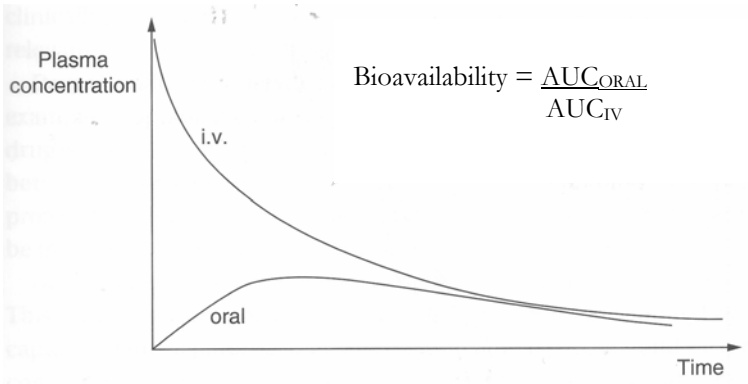
(I) **Absorption**:

Overview of absorption:

Absorption → process by which a drug enters the systemic circulation from its site of administration

Rate and extent of absorption is determined by:
- (1) Route of administration
- (2) Local factors at absorption site (Eg. pH, tissue blood flow, area/thickness of site)
- (3) Drug factors (Eg. dose, pKa, solubility)

Important to note – "Bioavailability":
- Defined as the fraction of drug dose reaching the systemic circulation, as compared with the same dose given intravenously
- It is determined by the route of administration → for example, oral route has the lowest bioavailability, while IV route has the highest
- It is measured by the ratio of areas under the [ ]-vs-time curves for an identical bolus given both IV and via the route in which bioavailability is being measured (Eg. oral)



$$\text{Bioavailability} = \frac{AUC_{ORAL}}{AUC_{IV}}$$

- Factors that determine bioavailability::
  - (1) Rate of absorption
    - (i) Pharmaceutical preparation – Small particle size or liquid → ↑ rapid dispersion and ↑ absorption; large particle size or binding agents (Eg. enteric-coated) → ↓ dispersion and ↓ absorption
    - (ii) Physicochemical interactions – Drugs/food can interact and inactivate or bind drug (Eg. Ca^{2+} in milk can sequester tetracycline) → ↓ absorption
    - (iii) Patient factors – ↓ absorption due to malabsorption syndromes, gastric stasis, ↓ regional blood flow, Etc.
  - (2) Degree of first pass clearance
    - Drugs absorbed via GIT undergoes first-pass metabolism (due to gut wall or hepatic metabolism) → ↑ first-pass metabolism leads to ↓ absorption

Routes for drug administration:

Important to note – Route of administration chosen is determined by:
- (1) Desired site of action (local vs systemic effects)
- (2) Type of drug preparation available
- (3) Factors that influence the systemic absorption of drug (see above) → this determines the intensity and duration of action of the drug

(1) Alimentary routes (Ie. involves GI tract):

Important to note – "First-pass metabolism" (FPM):

- Drugs absorbed from GIT (except buccal and rectal mucosal) enter portal venous blood and pass through liver before entering systemic circulation → in doing so, they are metabolised by enzymes within the (i) liver (main) and (ii) gut wall (minor)
- FPM is a main reason why plasma [ ] after an oral dose is less cf. similar IV dose → as a result, it is a key determinant of oral bioavailability:

$F_B = F_A \times F_G \times F_H$

F_B = Bioavailable fraction
F_A = Fraction absorbed
F_G = Fraction remaining after gut mucosal metabolism
F_H = Fraction remaining after hepatic metabolism

Since $F_G \times F_H = (1 - \text{Extraction ratio})$ ⟶ thus, $F_B = F_A \times (1 - \text{Extraction ratio})$

- Significance – Drugs with ↓ FPM are either well-absorbed, stable in GIT, and/or have minimal hepatic metabolism → thus, have ↑ oral bioavailability (and ↑ plasma [ ]). The opposite is true for drugs with ↑ FPM

- (a) Oral:
  - Orally administered drugs are absorbed 1°ly through the gut mucosa of the small intestines (due to its ↑↑↑ mucosal surface area)
  - For drugs without a transport mechanism (Ie. relies on passive diffusion), only the unionized form is absorbed → thus, Δs in pH of GIT fluid favour the ↑ presence of the unionised fraction in certain parts of GI, resulting in ↑ absorption there:
    - Acidic drugs (Eg. aspirin) – Unionized in acidic gastric juice → thus, absorbed mainly in stomach
    - Basic drugs (Eg. propanolol) – Ionized in gastric juice, but unionized in duodenum → thus, absorbed mainly in small intestines

    Note – Oral acidic drugs have advantage over oral basic drugs → there is rapid initial absorption in stomach 2° to ↑ unionised fraction (causing rapid onset from ingestion) and continued absorption in the small intestines b/c of its large SA (in spite of its highly ionized fraction there)

  - Advantages:
    - (i) Most convenient and economical route
    - (ii) Drugs can be given for local effects (Eg. antacids for gastric reflux) or systemic effects (Eg. anti-hypertensives)
    - (iii) Sterility not required
  - Disadvantages:
    - (i) Issues with patient compliance
    - (ii) Variable absorption (Ie. irregularities due to presence of food/drug, emesis due to irritation of GIT mucosa, drug destruction by digestive enzymes/acidic gastric fluid)
    - (iii) Lowest bioavailability due to effects of FPM
- (b) Sublingual, nasal and buccal:
  - Drugs given by these routes avoids effects of FBM → results in (i) ↑ rapid onset and (ii) ↑ bioavailability
  - Eg. S/L GTN spray for angina is absorbed directly into SVC (cf. PO GTN which is extensive metabolised by hepatic FPM)
- (c) Rectal:
  - Considered when oral route unavailable

- Advantages:
  - (i) Potentially ↑ bioavailability cf. oral → b/c it can avoid FPM
  - (ii) Drugs can be given for local effects (Eg. steroids for IBD) or systemic effects (Eg. diclofenac for analgesia)
- Disadvantages:
  - (i) Little evidence that it is more efficacious than oral route
  - (ii) ↓ surface area → slow and incomplete absorption
  - (iii) Unpredictable response due to variable FPM – Drugs given into proximal rectum absorbed into superior haemorrhoidal veins are transported via portal venous system to liver for FPM ; drugs given into distal rectum below these veins avoids this
  - (iv) PR drugs can also cause irritation of rectal mucosa

(2) Parental routes (Ie. avoids GI tract):

- (a) Intravenous:
  - Advantages:
    - (i) Most direct and reliable route of systemic drug therapy → rapidly achieves desired plasma [drug] and has the highest bioavailability
    - (ii) No systemic absorption required → plasma [drug] is independent of factors such as GI absorption and skin/muscle perfusion
    - (iii) Less irritant (cf. S/C or IM) as blood vessel walls are insensate and IV drugs are rapidly diluted in blood
  - Disadvantages:
    - (i) Drug preparations more expensive
    - (ii) Requires sterility
    - (iii) Can produce high plasma [drug] → undesired adverse effects
    - (iv) Some require CVC access (which carries risks of insertion)
- (b) Intramuscular:
  - Rate of absorption depends on muscle perfusion:
    - Well-perfused muscles (Eg. deltoid, quadriceps) → ↑ absorption rate
    - Poorly-perfused muscle (Ie. due to local vasoconstriction or systemic hypotension) → delayed absorption due to ↓ absorption rate, until muscle perfusion restored → this has two consequences – (i) drug ineffective within expected time, leading to 2nd dose given, and (ii) when perfusion is restored, plasma levels may ↑↑↑ leading to toxicity due to sudden ↑ absorption
  - Advantages:
    - (i) Bioavailability approaches 1
    - (ii) Rapid rate of onset (can ≈ IV)
  - Disadvantages:
    - (i) Not all drugs can be given IM
    - (ii) Painful
    - (iii) Can cause local abscess or haematoma (esp in coagulopathic patient)
    - (iv) Risk of inadvertent IVI
- (c) Subcutaneous:
  - Advantages:
    - (i) Bioavailability approaches 1
    - (ii) Some drugs well absorbed from subcutaneous tissues (Eg. heparin, insulin)
    - (iii) Allows for depot preparation in non-compliant patients (Eg. anti-psychotics)
    - (iv) Absorption can be delayed to allow for sustained plasma [drug] (Eg. insulin with zinc/protamine)

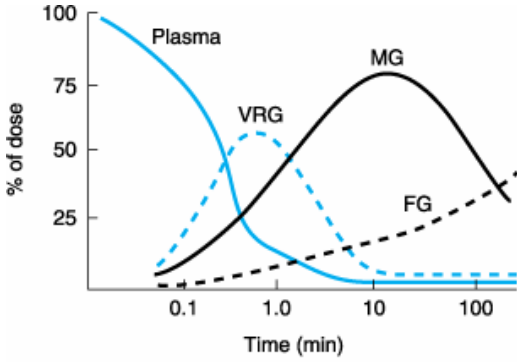
    - Disadvantage – Rate of absorption dependent on local blood flow → faces similar issues with poor tissue perfusion as IMI (see above)
- (d) Transdermal:
    - Rate-limiting step to absorption is diffusion across the stratum corneum (epidermis)
    - Advantages:
        - (i) Can be used for local effects (Eg. topical steroids) or systemic effects (Eg. fentanyl, GTN, scopolamine, clonidine)
        - (ii) ↑ bioavailability (as it avoids FPM)
        - (iii) Patches can produce slow and constant drug release → provides sustained therapeutic plasma [drug] and avoids loss of drug effect due to fluctuations in plasma drug levels
        - (iv) Low incidence of adverse effects (as small amounts of drugs are released)
        - (v) ↑ patient compliance
    - Disadvantages:
        - (i) Issues with absorption – Drugs need to have ↑ lipid solubility, site needs to have good regional blood flow (Eg. thorax, abdomen), variations in thickness of stratum corneum across the body
        - (ii) Need to use potent drugs if systemic effects desired (as small amounts of drugs are released at a time)
        - (iii) Contact dermatitis
        - (iv) Limited duration of adhesion (7 days max) → due to sloughing/regeneration of stratum corneum
- (e) Neuraxial:
    - Epidural
        - Speed of onset – Determined by % unionized drug → LA with ↓ pKa (Eg. lignocaine) or ↑ pH at site of administration (Ie. adding HCO_3^-) will ↑ % unionised drug and ↑ speed of onset
        - Duration of drug effect – Determined by loss of drug to systemic vascular absorption → LA with ↑ tissue protein binding (Eg. bupivacaine) or use of vasoconstrictors (Eg. adrenaline) will ↑ duration of LA block
        - Note – Significant amounts of drugs (LA and opioids) can be absorbed form epidural space into systemic circulation (esp during infusions) → carry significant morbidity when toxic systemic levels reached
    - Intrathecal
        - Amount of drug given is very small cf. epidural route → little reaches systemic circulation, thus minimizing unwanted systemic effects of drug
        - Spread of intrathecal drug (Eg. LA) depends on – (i) Volume of solution used, and (ii) Type of soluble used (Ie. hyper- vs hypobaric solution spread is dependent on patient positioning)
- (f) Inhalational
    - Site of drug action depends on the particle size:
        - Local effect (Eg. inhaled bronchodilators) – Large droplets reach AW mucosa only (from larynx to bronchioles)
        - Systemic effect (Eg. volatiles, nebulised bronchodilators) – Small droplets (< 1 um) reach alveolus and are absorbed systemically (Nb. lungs have large SA (70 m^2) and results in rapid absorption of a large amount of drugs → rapid onset of effects and ↑ degree of systemic effects)

(II) **<u>Distribution</u>**:

Overview of drug distribution:

Distribution → process by which drugs are distributed into interstitial or cellular fluids

Following systemic absorption of drug into plasma, drug is distributed in the following pattern:
- (1) Initially distributed to tissues with highest blood flow (brain, heart, lung, liver, kidney)
- (2) Then redistributes to tissue with moderate blood flow (muscle, fat)
- (3) Then finally redistributed to tissue with very low blood flow (bone, cartilage)



Note – As plasma [drug] falls below the [drug] within each tissue group → drug is "leached" out of tissue back into plasma along its [ ] gradient → drug in plasma is then either (i) redistributed to less-perfused sites or (ii) eliminated from the body (by metabolism/excretion)

Factors influencing drug distribution:

Uptake of drug by tissues → determined by:
- (1) Cardiac output and tissue blood flow (MAIN factor) – ↑ C.O. and tissue BF means more drug penetrates tissue membranes more rapidly
- (2) [ ] gradient for "diffusible fraction" of drug (Ie. unionized and unbound form) – ↑ $[\ ]_{GRADIENT}$ means ↑ diffusion and uptake of drug
- (3) Physicochemical properties of drug:
  - (a) Ionization state – ↑ % unionised state allows ↑ diffusion and uptake of drug
  - (b) Lipid solubility – ↑ lipid-solubility of drug allows ↑ diffusion and uptake of drug
  - (c) Protein binding – ↑ % of drug unbound/free allows ↑ diffusion and uptake of drug
  - (d) Molecular size – ↓ drug MWT allows ↑ diffusion and uptake of drug
- (4) Capillary permeability in various tissues (Ie. BBB, placenta) – ↑ capillary permeability to drug allows for ↑ diffusion and uptake of drug

Tissue capacity to store a drug → determined by:
- (1) Drug solubility in tissue – ↑ solubility allows for ↑ tissue drug storage
- (2) Tissue mass (esp muscle (50% of body) and fat (20% of body)) – ↑ mass allows for ↑ tissue drug storage
- (3) Drug binding to macromolecules within tissue – ↑ binding allows for ↑ tissue drug storage
- (4) pH within tissue – "Ion trapping" of drug allows for ↑ tissue drug storage

Important to note – Tissues that accumulate drug preferentially act as reservoir of drug (Eg. lung takes up basic lipophilic amines (pK 8), such as lignocaine, fentanyl, alfentanil, pethidine, propranolol) → later release drug back into systemic circulation → maintains plasma [drug] and prolongs its duration of action

"*Ionisation*":

- Drugs exist as either:
  - (i) Weak acid – Can donate a proton (H^+) to form a –ve anion
  - (ii) Weak base – Can accept a proton to form a +ve cation
- As a result, a drug (whether it is a weak acid or weak base) will be present in both ionized and unionized forms in solution → its degree of ionization depends on (i) pKa of drug and (ii) pH of solution it is dissolved in (as per Henderson-Hasselbach equation):

$$pH = pKa - \log \frac{[\text{protonated form}]}{[\text{unprotonated form}]}$$

> Note: "pKa" – pH at which [ ] of unionized and ionized drug are equal (Ie. 50% of drug is ionized, and 50% of drug is unionized) → value of pKa is dependent on the drug's molecular structure (and NOT on whether it is acidic or basic)

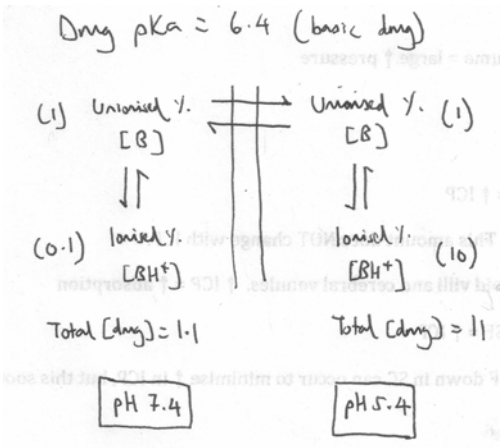
For an acidic drug: $pH = pKa - \log \frac{[HA]}{[A^-]}$ → pH < pKa → ↑ unionised % of drug; pH > pKa → ↑ ionized % of drug

For a basic drug: $pH = pKa - \log \frac{[BH^+]}{[B]}$ → pH < pKa → ↑ ionized % of drug; pH > pKa → ↑ unionised % of drug

- Significance of ionization state of drug:
  - Unionised state of drug is lipid-soluble → able to cross cell membranes to exert effect → thus, "pharmacologically active" (Ie. absorbed from GIT, metabolised in liver, reabsorbed within renal tubules, cross barriers (Eg. BBB, placenta))
  - Ionised state of drug is poorly lipid-soluble → unable to cross cell membranes to exert drug effect → thus, "pharmacologically inactive" (Ie. unable to be absorbed from GIT, not metabolised in liver, unable to cross barriers, excreted in urine)

"*Ion trapping*":

- Definition – Phenomenon where a difference in [total drug] develops on two sides of membrane that separates fluids with different pH
- Mechanism – Only the unionised state of the drug can cross the membrane, such that at steady state, the [ ] of unionised drug on both sides equilibrates and becomes the same → however, the pH difference across the membrane alters the [ ] of ionized drug on each side → this leads to the difference in [total drug] on both sides of the membrane



> Example – LA is a weak base that is readily transferred across the placenta from mother to foetus b/c foetal blood is more acidic than maternal blood → unionized (lipid-soluble) form of LA crosses placenta and is converted to ionized (less lipid-soluble) form due to the acidic environment and remains trapped there → conversion of unionized to ionized form maintains a [ ] gradient for further diffusion of LA into foetus resulting in ↑ total [LA] in the foetus → LA toxicity

"*Protein binding*:

- Drugs bind to two types of proteins:
  - (1) Albumin → binds neutral and acidic drugs (Note – Albumin has 2 important bind sites → (i) warfarin and (ii) diazepam)
  - (2) Globulin (esp α1-acid glycoprotein) → binds basic drugs
- Protein-drug interaction:
  - Occurs by weak bonds (ionic bonds, hydrogen bonds and van der Waals forces) that can be formed/unformed rapidly and reversibly
  - Extent of protein binding is determined by:
    - (i) Lipid solubility of drug – Determines affinity of drug for protein (Ie. ↑ lipid solubility → ↑ affinity for drug for protein → ↑ protein binding)
    - (ii) Plasma [ ] of drug (Ie. ↑ [drug] = ↑ protein binding)
    - (iii) Plasma [ ] of binding protein – Determines # of available drug binding sites (Ie. ↑ [protein] → ↑ # available drug bind sites → ↑ protein binding)
  - Protein binding is non-selective – Competition for bind sites b/t different drugs and/or endogenous substances (Eg. sulphonamides and bilirubin binding to albumin) occur → results in alteration of % unbound of each substance

Note – Protein binding is altered by pathology:

- Albumin – ↓ binding occurs with inflammation, infection, cirrhosis, renal failure → results in ↑ fraction of unbound drug and ↑ drug effects
- α1AGP (acute phase protein) – ↑ levels with surgery, inflammatory diseases, chronic pain states → results in ↓ fraction of unbound drug and ↓ drug effects; ↓ levels with neonates → results in ↑ fraction of unbound drugs and ↑ drug effects

- Significance of protein binding of drugs:
  - (1) Only unbound (free) fraction of drug crosses cell membrane and exerts effect → "pharmacologically active"
  - (2) Affects volume of distribution (V_D) in an inverse manner (Ie. ↑ protein binding → ↓ V_D as it limits drug transfer into tissue)
  - (3) Affects drug clearance (Cl) in an inverse manner (Ie. ↑ protein binding → ↓ Cl as only unbound drug can be metabolised by liver or filtered by kidney)

Important to note – Protein binding is clinically important if drug is highly bound (> 90%), such as with warfarin, phenytoin, diazepam, propranolol, Etc.:

- This is b/c small Δ in bound fraction produces large Δ in the amount of unbound drug (Ie. ↓ from 98% to 96% binding doubles the plasma % of unbound drug!) → BUT this does necessarily result in ↑↑↑ [ ] of free drug or clinically significant effect b/c (i) therapeutic [ ] of drug is much less than protein [ ], (ii) more free drug distributes into the entire V_D, and (iii) there is ↑ drug metabolism/clearance (as with 1st order kinetics)
- HOWEVER, significant ↑ [ ] of free drug and toxic effects are seen where drug metabolism/clearance involve zero-order kinetics (Eg. phenytoin)

"*Lipid solubility*""

- Determined by "lipid-water" partition coefficient → property of a substance independent of its pKa/ionization state
- Reflects ability to pass through cell membrane (Ie. ↑ lipid solubility → ↑ transport across cell membrane)

"*Capillary permeability in various tissues*"

- Blood-brain barrier:
  - An anatomical and functional barrier b/t circulation and CNS:
    - Substances transported across via – (i) Active transport (Eg. hormones), (ii) Facilitated diffusion (Eg. glucose, low MWT lipid-soluble drugs), (iii) Passive diffusion (Eg. inhaled/IV anaesthetic agents)
    - Large, water-soluble and ionized drugs cannot cross BBB (Eg. NMBD)
    - Contains enzymes (Eg. MAO) that metabolise drugs passing through it
  - Permeability of BBB can vary – (i) ↑↑↑ drug doses → ↑ permeability, (ii) Acute head injury, infection, inflammation, hypoxaemia → ↑ permeability
- Placenta:
  - Barrier consists of phospholipids membrane that is easily crossed by lipid-soluble substances → thus, less selective than BBB
  - Rate of transfer determined by:
    - (i) Maternal and placental blood flows
    - (ii) $[\ ]_{GRADIENT}$ of free drug
    - (iii) Degree of protein binding in foetus cf. mother (Ie. ↑ foetal protein binding = ↑ transfer)
    - (iv) Degree of ionization in foetal blood cf. maternal blood (Ie. ion trapping)
    - (v) Rate of foetal drug metabolism

(III) **Metabolism**:

Overview of metabolism:

Metabolism → process of chemically altering a drug within the body

Effect of metabolism:

- (1) ↓ drug activity (main effect)
  - Process of metabolism generally converts a "pharmacologically active" form of drug (Ie. non-polar and lipid soluble) into a "pharmacologically inactive" form (Ie. more polar and water-soluble) that can be excreted from the body (esp in bile or urine)
- (2) ↑ drug activity
  - "Prodrug" → drugs with no inherent activity, but are converted by metabolism in the body to an active moiety (Eg. enalapril → enalaprilat; parecoxib → valdecoxib)
- (3) Produce metabolites with equal activity to parent compound (Eg. diazepam, propranolol)

Location of metabolism – Mainly occurs in liver (by hepatic microsomal enzymes), but also in kidneys, GIT, adrenal glands, lung and plasma (Eg. Hofmann, ester hydrolysis, Etc.)

Rate of metabolism:

Determined by:

- (1) [drug] at site of metabolism → influenced 1°ly by HBF (as it determines drug delivery to liver for metabolism)
- (2) Intrinsic metabolism rate → influenced by genetics and enzyme induction/inhibition

Important to note:
- Most drug metabolism follows "1st order kinetics" (see below) – Constant fraction of drug is metabolised in a given time period → rate of metabolism dependent on plasma [drug] (Ie. highest rate of metabolism occurs when plasma [drug] is highest)
- Some drug metabolism follows "zero order kinetics" (Eg. EtOH, aspirin, phenytoin; see below) – Constant amount of drug is metabolised in a given time period → rate of metabolism is independent on plasma [drug]

Phases of metabolism:

(1) Phase I (functionalisation or non-synthetic)
- Role – Alter drug reactivity for phase II reaction and to ↑ drug polarity/water-solubility
- Involves:
  - (a) Oxidation
    - Hepatic microsomal enzymes (esp CYP450) causes the loss of electrons from the drug → requires NAD^+ ([O] agent) and O_2
    - Includes – Hydroxylation (Eg. propofol), desulphation (Eg. STP), dealkylation (Eg. vecuronium), dehalogenation (Eg. volatiles), deamination
  - (b) Reduction
    - Hepatic microsomal enzymes (esp CYP450) causes the gain of electrons to drug under ↓ PO_2 conditions
  - (c) Hydrolysis
    - Non-microsomal enzymes (Eg. plasma esterases) hydrolyse ester bonds

(2) Phase II (conjugation or synthetic)
- Role – ↑ water solubility of drug or its metabolite by conjugating it to a polar endogenous moiety (Eg. sulphate, glucuronyl, methyl, Etc.) → permits excretion in urine or bile
- Involves:
  - (a) Glucuronidation via glucuronosyltransferase (Eg. morphine, propofol)
    - UDP-glucuronic acid is conjugated to the drug → conjugate is inactive and water-soluble → excreted in urine/bile
    - Conjugated undergoes "enterohepatic recirculation" if eliminated in bile → intestinal bacterial glucuronidases hydrolyses glucuronide → liberates free drug which is reabsorbed back into circulation → results in prolonged drug action
  - (b) Sulphation via sulfotransferase (Eg. propofol quinol metabolite)
  - (c) Acetylation via N-acetyl transferase (Eg. isoniazid)
  - (d) Methylation via a O-methyl transferase (Eg. catechoalmines)
  - (e) Glutathione via glutathione-S-transferase (Eg. EtOH)
- Note – All these reactions involve non-microsomal enzymes, EXCEPT for glucuronidation (requires hepatic CYP450 microsomal enzymes)

Metabolic enzyme systems:

(1) Microsomal enzyme system (CYP450)
- CYP450 is a superfamily of membrane-bound haeme proteins that catalyses metabolism of most drugs → via oxidation, reduction and conjugation reactions

Aside: CYP450 is named after wavelength (in nm) of maximal light absorption when its reduced state is combined with carbon monoxide

- It is usually found in liver (within SER), but is also found in GIT (esp small intestines), adrenal cortex, kidney, lung and brain
- CYP450 are classified according to their degree of shared a.a. sequences:
    - (i) Families (Eg. CYP1, CYP2, Etc.) → CYP share > 40% a.a. sequence homology
    - (ii) Subfamilies (Eg. CYP1A, CYP1B, Etc.) → CYP share > 55% a.a. sequence homology
    - (iii) Isoforms (Eg. CYP1A1, CYP1A2, Etc.)

Examples of relevant CYP450's:
- CYP2B6: Propofol
- CYP2D6: Codeine, flecainide, metoprolol
- CYP2E1: Halogenated volatiles, paracetamol
- CYP3A4: Diazepam, temazepam, midazolam, fentanyl, vecuronium, lignocaine

Key CYP450 – CYP 3A4/3A5 (metabolise > 50% drugs) and CYP2D6 (metabolise 25% drugs)

- Important to note:
    - (i) Drugs can be metabolised by > 1 CYP450 isozyme (Eg. midazolam is metabolised by CYP3A5 and 3A4)
    - (ii) Genetic variations occur (Eg. CYP2D6 and codeine → poor metabolisers)
    - (iii) CYP450 have low substrate specificity → each isozyme can metabolise several types of drugs (Eg. CYP3A4 metabolises Bz, fentanyl, lignocaine, vecuronium)

(2) Non-microsomal enzyme system (non-CYP450)
- Various enzymes that catalyse 1°ly hydrolysis and conjugation (less oxidation and reduction) reactions
- Includes – Esterases (plasma, hepatic, GIT), mitochondrial MAO, cytoplasmic EtOH dehydrogenase, ACE, sulfotransferase, N-acetyl transferase, glutathione-S-transferase, catechol-O-methyl transferase

Important to note – Metabolic enzyme systems are affected by:
- (1) Enzyme inhibition/induction (* Affects ONLY CYP450 (microsomal) system *)
    - Enzyme induction – Certain drugs can induce CYP450 enzyme synthesis → ↑ enzyme activity and drug metabolism → resulting in ↓ plasma [drug]

      Examples – A/Bs (rifampicin), chronic EtOH, volatiles (halothane, enflurane), barbiturates (STP, Phenobarbital), AEDs (phenytoin, carbamazepine), cigarette smoking, hormones (steroids)

    - Enzyme inhibition – Certain drugs inhibit CYP450 enzyme by competitive inhibition → ↓ enzyme activity and drug metabolism → resulting in ↑ plasma [drug]

      Examples – A/Bs (metronidazole, isoniazid, chloramphenicol), H2RB (cimetidine), MAOis (phenelzine, tranylcypromine), amiodarone, grapefruit juice)

    - Note – Enzyme induction is SLOWER cf. inhibition b/c enzyme synthesis is required
- (2) Genetic polymorphism (* Affects both CYP450 and non-CYP450 system *)
    - Inherited differences in enzyme structure alter the metabolism of drugs

      Examples:
      - Plasma cholinesterase – Several AR-inherited genes contribute to ↓ levels of SCh hydrolysis in plasma → resulting in prolonged paralysis with SCh
      - Acetylation – Genetically-encoded "fast" acetylators metabolise drugs (Eg. isoniazid and hydrallazine) quickly → absence of therapeutic response; "slow" acetylators → ↑ therapeutic response to drugs and ↑ risk of side-effects (Eg. lupus with hydrallazine)
      - CYP2D6 variants – Genetic deficiencies in CYP2D6 levels (such as in HK Chinese) result in defect metabolism of codeine

"*Hepatic clearance*" → determined by:

- (1) Hepatic blood flow (HBF) – Rate at which drug is delivered to the liver
- (2) Hepatic extraction ration (HER) – Fraction of drug that is irreversibly removed during 1st pass of blood through the liver → determined by (i) intrinsic clearance (enzyme activity) and (ii) unbound % of drug

Hepatic clearance = HBF x HER = HBF x [(% unbound) x (intrinsic clearance)]

Important to note:

- (1) Drugs with HER > 0.7 (↑ enzyme activity or "flow-limited"), such as GTN:
  - Hepatic drug clearance is dependent on HBF ("perfusion-dependent elimination") → ↑ HBF will lead to ↑ hepatic drug clearance
  - Changes in HER (intrinsic enzyme activity or unbound %) have minimal effect on hepatic drug clearance as heaps of drug is already removed at a given time

Ie. Hepatic clearance ≈ HBF

- (2) Drugs with HER < 0.3 (↓ enzyme activity or "capacity-limited"), such as diazepam:
  - Hepatic drug clearance is dependent on protein binding and intrinsic enzyme activity ("capacity-dependent clearance") → ↑ enzyme activity and/or ↓ protein binding will ↑ hepatic drug clearance
  - Changes in HBF will have minimal effect on hepatic drug clearance as only a small % of drug is ever removed at a given time

Ie. Hepatic clearance ≈ HER = (unbound %) x (intrinsic clearance)

(IV) **Excretion**:

"Excretion" – process by which a drug or its metabolite is removed from the body

Important to note – "Elimination" → process by which drug is removed from plasma (includes both distribution and metabolism/excretion)

Routes of excretion:

- (1) Renal (most important route)
  - Drugs or metabolites that are renally excreted are generally:
    - (i) Water-soluble → drugs are metabolised from a lipid-soluble for to a water-soluble metabolite (via phase I and II reactions above)
    - (ii) Low MWT (< 30 kDa)
  - Involves:
    - (a) Glomerular filtration
      - Amount of drug filtered into the renal tubular lumen depends on – (i) % unbound to protein and (ii) GFR
    - (b) Proximal tubular secretion
      - Drugs (esp organic acids) are actively secreted into renal tubules against their [ ] gradients
      - Different carrier systems exist for acidic and basic drugs → each are capacity-limited for their respective drug type (Ie. max. clearance of one acidic drug is limited by clearance of another, but not by basic drug)
    - (c) Passive tubular reabsorption

- Lipid-soluble fraction of drugs in the distal tubules are reabsorbed via passive diffusion → prevented from excretion in urine
- Rate of reabsorption depends on:
    - (i) Urine pH → "ion trapping" where ionized (water-soluble) form of drug cannot be reabsorbed and is excreted in urine (Ie. acidic drugs are trapped in alkaline tubular fluid and excreted in urine; basic drugs are trapped in acidic tubular fluid and excreted in urine)
    - (ii) Rate of renal tubular flow → ↑ flow rate = ↑ excretion

- (2) Biliary
    - Drugs or metabolites that are excreted in bile are generally:
        - (i) Water-soluble → drugs are metabolised from a lipid-soluble for to a water-soluble metabolite (via phase I and II reactions above)
        - (ii) High MWT (> 30 kDa)
    - Involves "active secretion" of unchanged drug (Eg. rifampicin) or metabolite (Eg. glucuronidated morphine) from hepatocytes into biliary canaliculus → passed into small bowels where it is then excreted in faeces

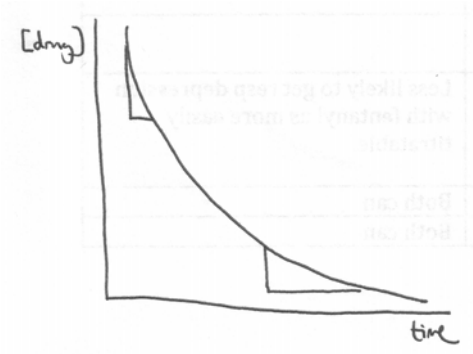
> Important to note – "Enterohepatic circulation":
> - Metabolites (esp glucuronidated drugs) excreted in bile may be hydrolysed in small bowel by glucuronidase secreted by bacteria → liberates the active lipid-soluble form of drug, which can be reabsorbed
> - Reabsorbed fraction passes through portal circulation to liver where some is reconjugated and re-excreted in bile, while the rest returns back to the systemic circulation

- (3) Others (includes lungs, breast milk, tears, sweat, saliva)

(D) **First-Order and Zero-Order Kinetics**:

First order kinetics:

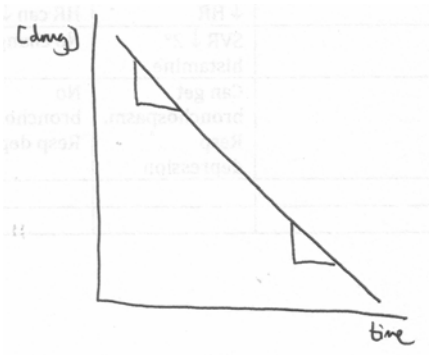
- Defined as a process where the rate of Δ plasma [drug] due to drug clearance from metabolism/excretion is proportional to the plasma [drug] → the greatest rate of Δ plasma [drug] (Ie. highest drug clearance) occurs when plasma [drug] is the greatest
- Describes most enzymatic processes → where there is relative excess of enzyme over substrate (Ie. enzyme activity is NOT the rate-limiting factor), and enzyme activity is dependent on the [substrate]



Important to note – A constant FRACTION of drug is cleared per unit time → this fraction of drug cleared is dependent on the plasma [drug]

Zero order kinetics:

- Defined as a process where the rate of Δ plasma [drug] due to clearance from metabolism/excretion is constant and independent of plasma [drug]
- Describes "saturation kinetics" → where [substrate] exceeds capacity of enzymes (Ie. enzymes are "saturated"), meaning that intrinsic activity of the enzyme is the rate limiting factor



Important to note – A constant AMOUNT of drug is cleared per unit time → this amount of drug cleared is independent of the plasma [drug]

Important to note – Some drugs obey 1st order kinetics at low doses but are cleared by zero order kinetics at higher doses (Eg. EtOH, aspirin, phenytoin and STP infusions) → implications:

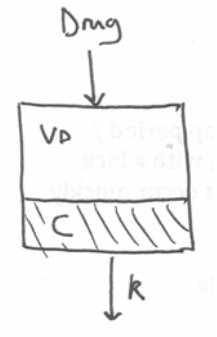
- (i) Small ↑ in drug dose may cause a large ↑ in plasma [drug] (esp at upper limit of therapeutic range) → lead to toxicity
- (ii) No steady-state occurs → if rate of drug delivery exceeds rate of drug excretion, then plasma [drug] will continue to ↑ to toxic levels

(E) **Compartment Models**:

Overview of compartment models:

- "Compartmental models" offer a simplistic view of pharmacokinetics of IV drugs → they predict the effects of IV drugs in a body comprising of a number of "compartments" (Eg. central compartment, peripheral compartment, effect-site compartment) representing theoretical spaces with calculated volumes
- They are derived experimentally by giving IV drugs to a group of healthy patients → then measuring plasma [drug] and fitting a mathematical equation to predict the plasma [drug] under a variety of conditions

Single compartment model:

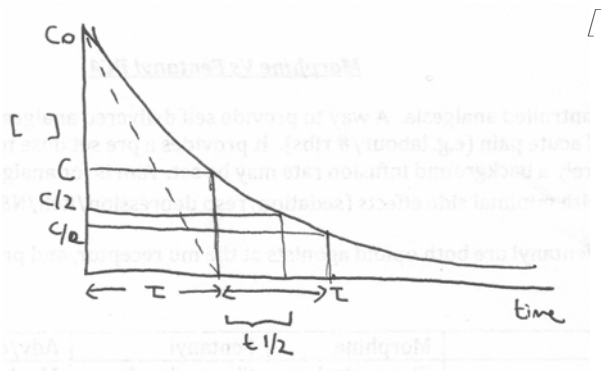


Overview: Single homogenous compartment where the drug enters and leaves

Process:

- (1) Single drug dose is given into the compartment
- (2) Drug disperses evenly through the compartment (according to its V_D) → produces an initial [ ] of drug within it (as C_O)
- (3) Drug is eliminated from the compartment in an "exponential" manner (according to its k)

Nb. For a given drug → model has a constant "k" and "Vd"



[ ] vs time:

- Compartmental [drug] at a given time (C) is described by an exponential equation:

$$C = Co\ e^{-kt}$$

Where:

- C = [drug] at a given time (t)
- Co = [drug] at t = 0
- k = rate constant for elimination

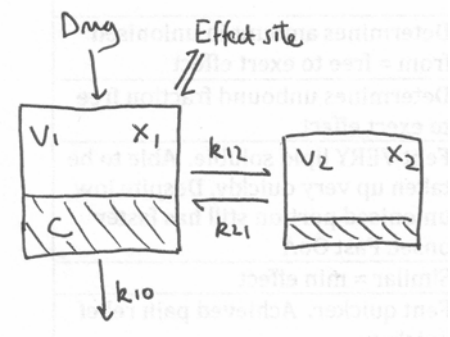
Multi-compartment model:

Overview:

- Different tissues share similar pharmacokinetic properties (Ie. vessel-rich vs vessel-poor; differences in tissue uptake of drug) → form "peripheral compartments"
- Drug can enter into and be eliminated from the body via the "central compartment" only
- "Effect-site" compartment is in equilibrium with the "central compartment → its volume is minute (Ie. does not contribute to total V_D) BUT is useful in predicting the onset/offset of drug response (Ie. observed effect is proportional to effect site [drug])

Examples of multi-compartment models:

(1) Two compartment model:



Overview:

- "Central compartment" (intravascular fluid and vessel-rich tissues with rapid drug uptake (Eg. lungs, heart, brain, kidney, liver, muscle)) interconnects with a "Peripheral compartment" (vessel-poor tissues with slow drug uptake (Eg. fat, bone))
- Drug enters and leaves via the "central compartment" only
- Drug within the "central compartment' can distribute to and from the "peripheral compartment"

Process:

- (1) Single drug dose is given into the "central compartment"
- (2) Drug distributes to the "peripheral compartment" (as per k_{12}) → redistributes back into the "central compartment" (as per k_{21})
- (3) Drug is then eliminated from the "central compartment" (as per k_{10})

Important to note – Drug transfer b/t compartments occurs in an "exponential" manner → it is dependent on:

- (1) Equilibrium rate constant (k) – "Rate constant for intercompartmental transfer" (k_{12} for central to peripheral compartment; k_{21} for peripheral to central compartment) and "Rate constant for elimination" (k_{10} for elimination from central compartment)
- (2) [ ] difference b/t the compartments

Important to note – There are two pathways the drug can be eliminated from the "central compartment" → via (i) Distribution to the "peripheral compartment" or (ii) Elimination of the drug from the body via metabolism/excretion

Important to note – The amount of drug within the "central compartment" following a single bolus is dependent on:

- (i) Drug elimination from body via metabolism/excretion ($k_{10} \bullet X_1$)
- (ii) Drug distribution to "peripheral compartment" ($k_{12} \bullet X_1$)
- (iii) Drug redistribution from "peripheral compartment" ($k_{21} \bullet X_2$)

$$dX_1/dt = -k_{10}X_1 - k_{12}X_1 + k_{21}X_2$$

[ ] vs time:

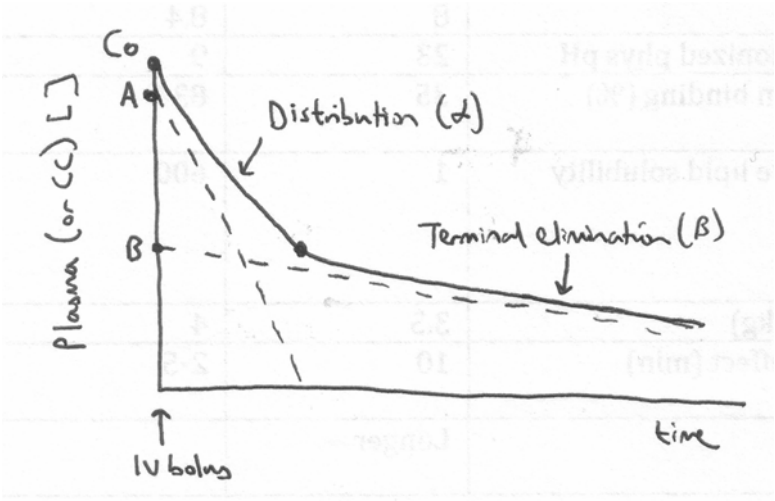
- Following a single IV bolus of a drug, there is a:
  - (i) Initial rapid rate of decline in plasma or central compartment [drug] (α phase) → due to "Distribution" from central to peripheral compartment

Important to note:

- *Rate of drug distribution* – Determined by the steepness of the α phase, which is influenced by k_{12}:k_{21} ratio → ↑ ratio means ↑ steepness of phase and ↑ rapid distribution (Ie. fentanyl has 4:1 ratio cf. 2:1 for propofol, and thus has ↑ steep α phase and ↑ rapid distribution)
- *Contribution of a phase (distribution) to [ ]-vs-time curve* – Determined by absolute k_{12} and k_{21} values → ↑ k values (such as for remifentanyl with k_{12} = 0.4 and k_{21} = 0.2) mean faster distribution and ↓ contribution of α phase to [ ]-vs-time curve (Ie. ↓ degree of drug distribution) → thus, drug conforms more to a single compartment model

- (ii) Late gradual rate of decline in plasma or central compartment [drug] (β phase) → due to "Terminal elimination" (Ie. elimination from body via metabolism/excretion and redistribution from the peripheral compartment) from central compartment

- [ ]-vs-time curve:



Note that:

- Plasma (or central compartment) [drug] at a given time is the sum of 2 straight lines representing a "bi -exponential" process consisting of → (i) distribution ($Ae^{-\alpha t}$ – with rate constant α) and (ii) terminal elimination ($Be^{-\beta t}$ – with rate constant β)

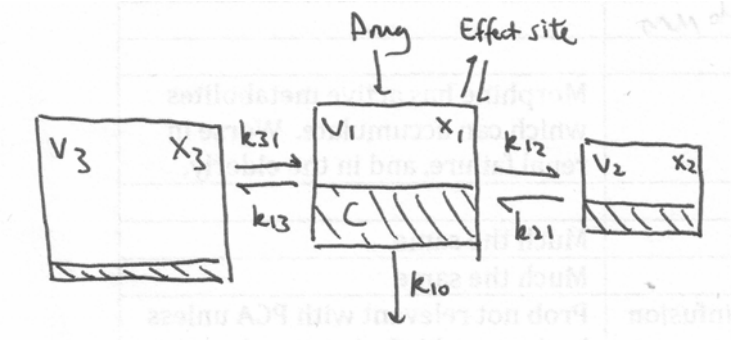
$$C = Ae^{\alpha t} + Be^{-\beta t}$$

- Y-intercepts of these 2 straight lines (Ie. at t = 0) gives 2 constants (A and B) → sum of these constants equals plasma or central compartment [drug] at t = 0:

$$C_O = A + B$$

- Rate constants (α and β) form the gradients of each straight lines → their reciprocals equate to their respective "time constants" (τ_A and τ_B), which are related to their respective "half-lives" (t ½ α and t ½ β)

(2) <u>Three compartment model</u>:



Overview:

- "Central compartment" (intravascular fluid or plasma) interconnects with two "Peripheral compartment" (one compartment as "vessel-rich tissues" with rapid drug uptake (Eg. lungs, heart, brain, kidney, liver, muscle) and the other as "vessel-poor tissues" with slow drug uptake (Eg. fat, bone))
- Drug enters and leaves via the "central compartment" only
- Drug within the "central compartment' can distribute to/from the "peripheral compartments"

Process:

- (1) Single drug dose is given into the "central compartment"
- (2) Drug distributes to the "peripheral compartments" (as per k_{12} and k_{13}) → note that distribution to compartment 2 (vessel-rich) is faster than to compartment 3 (vessel-poor)
- (3) Drug then redistributes back into the "central compartment" (as per k_{21} and k_{31})
- (4) Drug is then eliminated from the "central compartment" (as per k_{10})

Important to note – Drug transfer b/t compartments occurs in an "exponential" manner → it is dependent on:

- (1) Equilibrium rate constant (k) – "Rate constant for intercompartmental transfer" (k_{12} and k_{13} for central to peripheral compartments; k_{21} and k_{31} for peripheral to central compartment) and "Rate constant for elimination" (k_{10} for elimination from central compartment)
- (2) [ ] difference b/t the compartments

Important to note – There are two pathways the drug can be eliminated from the "central compartment" → via (i) Distribution to the "peripheral compartments" or (ii) Elimination of the drug from the body via metabolism/excretion

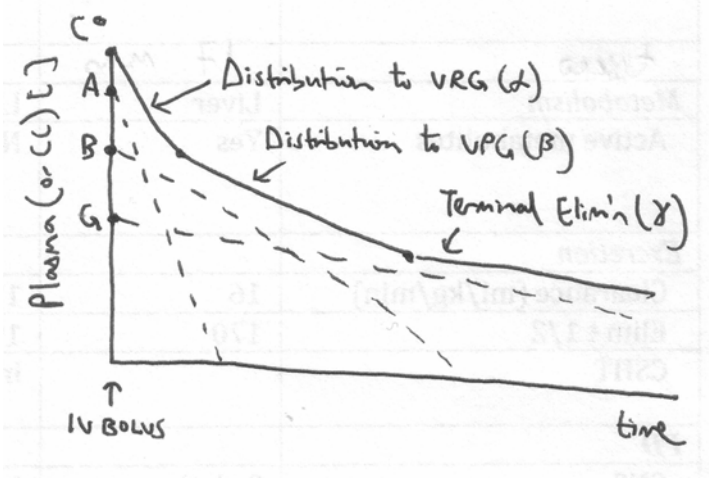
Important to note – The amount of drug within the "central compartment" following a single bolus is dependent on:

- (i) Drug elimination from body via metabolism/excretion ($k_{10} \bullet X_1$)
- (ii) Drug distribution to "peripheral compartments" ($k_{12} \bullet X_1 + k_{13} \bullet X_1$)
- (iii) Drug redistribution from "peripheral compartment" ($+k_{21} \bullet X_2 + k_{31} \bullet X_3$)

$$dX_1/dt = -k_{10}X_1 - (k_{12}X_1 + k_{13}X_1) + (k_{21}X_2 + k_{31}X_3)$$

[ ] vs time:

- Following a single IV bolus of a drug, there is:
  - (i) Initial rapid rate of decline in plasma or central compartment [drug] (α phase) → due to "distribution" from central compartment to compartment 2
  - (ii) Subsequent slower rate of decline in plasma or central compartment [drug] (β phase) → due to "distribution" to compartment 3
  - (iii) Late gradual rate of decline in plasma or central compartment [drug] (γ phase) → due to "Terminal elimination" (Ie. elimination from body via metabolism/excretion and redistribution from the peripheral compartment) from central compartment



Note that:

- Plasma (or central compartment) [drug] at a given time is the sum of 3 straight lines representing a "tri -exponential" process consisting of → (i) 2x distribution phases ($Ae^{-\alpha t}$ – with rate constant α; $Be^{-\beta t}$ – with rate constant β) and (ii) terminal elimination ($Ge^{-\gamma t}$ – with rate constant γ)

$$C = Ae^{-\alpha t} + Be^{-\beta t} + Ge^{-\gamma t}$$

- Y-intercepts of these 3 straight lines (Ie. at t = 0) gives 3 constants (A, B, G) → sum of these constants equals plasma or central compartment [drug] at t = 0:

$$C_O = A + B + G$$

- Rate constants (α, β, γ) form the gradients of each straight lines → their reciprocals equate to their respective "time constants" (τ_A, τ_B, τ_G), which are related to their respective "half-lives" (t ½ α, t ½ β, t ½ γ)

Non-compartmental models:

- These models make no assumptions about specific volumes → instead it derives pharmacokinetic parameters using the AUC (area under curve) of the [drug]-vs-time curve:

$$\text{Clearance} = \frac{\text{Dose}}{\text{AUC}}$$

$$\text{Mean residence time (MRT)} = \frac{\text{AUMC}}{\text{AUC}}$$

$$V_D \text{ at steady-state} = \text{Cl} \times \text{MRT}$$

Note:

- MRT – Measures how long drug stays in body → ≈ time constant in compartmental model
- AUMC – Area under "First moment curve" → derived from plotting [drug]-time on y-axis against time on x-axis

Pharmacokinetic parameters of compartment models:

(1) *Volume of distribution (V_D)*:

- Defined as the apparent volume into which a drug disperses in order to produce the observed plasma [ ] (units – L or L/kg (if indexed to body weight)

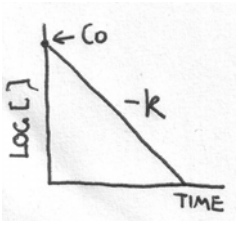
Important to note:

- V_D does NOT correspond to any particular physiological volume → it can be greater than total body water!
- V_D is a CONSTANT value for a given type of drug

- V_D is mainly determined by the physico-chemical properties of the drug:
  - (i) Drug MWT/size
  - (ii) Drug lipid solubility (Ie. lipophilic drugs like propofol have ↑ V_D)
  - (iii) Ionized state of drug (Ie. charged drugs like NMBD have ↓ V_D)
  - (iv) Plasma protein binding of drug (Ie. ↑ binding → ↓ V_D)
  - (v) Tissue binding of drug (Ie. ↑ IC sequestration → ↑ V_D)
  - (vi) Pathology (Ie. renal and hepatic diseases → ↑ Vd)
- Calculating V_D:
  - One-compartment model – V_D is determined by the drug dose given and the plasma [ ] at t = 0 (C_O):

$$V_D = \frac{\text{Dose}}{C_O}$$

Steps:
- (i) Known drug dose is given
- (ii) Log [drug] vs time is plotted → extrapolate to find C_O at t = 0
- (iii) Calculate V_D using above formula



- Multi-compartment model:
  - (i) V_D of the "central compartment" ($V_{INITIAL}$) – Represents the initial volume in which the drug disperses into → determined from the "rapid" distribution phase (α) of the [ ]-vs-time curve:

$$V_{CC} \text{ (or } V_{INITIAL}) = \frac{\text{Dose given (X)}}{\text{Y-intercept of } \alpha \text{ phase (A)}}$$

  - (ii) Total V_D – Represents the sum of all the apparent compartmental volumes within the model (Ie. $V_1 + V_2 + V_3 + \ldots$) → determined via several methods:

(1) V_{EXTRAP}:
- Ignores contribution made by any compartmental volumes apart from that a/w the terminal elimination phase:

$$V_{EXTRAP} = \frac{\text{Dose given}}{\text{Y-intercept of } \beta \text{ phase (B)}}$$

- Issues – Greatly overestimates total V_D (esp if distribution contributes much to drug dispersion)

(2) V_{AREA}:
- Relates both clearance and terminal elimination constant → uses non-compartmental method to calculate clearance (where Cl = dose/AUC), and assumes the "average" rate constant for drug removal from plasma is approximated by the inverse of terminal elimination time constant (β):

$$V_{AREA} = \frac{\text{Clearance}}{\beta} = \frac{\text{Dose}}{(\text{AUC} \times \beta)}$$

- Issues – Can still overestimate total V_D b/c β as an "average" rate constant is an underestimate (esp if there is significant distribution b/t compartments)

(3) V_{SS}:
- Based entirely on non-compartmental models → calculated from product of Cl and MRT

$$Vss = Cl \times MRT = \frac{(\text{Dose})}{(\text{AUC})} \times \frac{(\text{AUMC})}{(\text{AUC})} = \frac{(\text{Dose} \times \text{AUMC})}{\text{AUC}^2}$$

Important to note – $V_{EXTRAP} > V_{AREA} > V_{SS}$

- Significance of V_D:
  - (1) Determines size of loading dose

$$\text{"Loading dose"} = V_D \times \text{desired } [\ ]_{PLASMA}$$

- (2) Depicts the distribution characteristics of drug in within the body
  - (a) Confined to plasma
    - Drugs have a small V_D (≈ plasma) → maintain a very ↑ plasma [ ]
    - Includes drugs that are either (i) too large to cross vascular endothelium (Eg. dextran) and (ii) highly protein bound (Eg. warfarin)
- (b) Limited distribution
  - Drugs have a V_D ≈ ECFV
  - Includes drugs that are polar, bulky and poorly lipid soluble (Eg. NMBD, AChEi) → distribution limited to tissues supplied by capillaries with fenestrae that permit extravascular distribution for their drug effect
- (c) Extensive distribution
  - Drugs have a large V_D (can be = or > TBW) → maintain a very ↓ plasma [ ]
  - Includes drugs that are highly lipid-soluble, small MWT, and limited protein binding (Eg. diazepam, STP, amiodarone) → distribute in peripheral tissues (Eg. fat, thyroid, bone) where they are sequestered

(2) *Clearance (Cl)*:

- Defined as the volume of plasma from which drug is completely removed per unit time (units – mL/min)

> Important to note – Clearance is a CONSTANT value for a given type of drug

- Drug can be cleared from plasma via two routes:
  - (i) "Elimination" from the body – Drug excreted unchanged (via renal or biliary routes) and/or metabolised (by liver or other organ)

Calculating Cl due to "elimination":

- Non-compartmental model: $Cl = \frac{Dose}{AUC}$
- Compartmental model:
  - Single compartment model

$Cl = V_D \times k_{el}$ → as $k_{el} = 1/\tau$, then $Cl = \frac{V_D}{\tau}$

→ as $k_{el} = \frac{\ln 2}{t\,½}$, then $Cl = \frac{V_D (\ln 2)}{t\,½}$

  - Multi-compartment model

$Cl = k_{10} \times V_{CC}$

> Important to note – Cl > HBF suggests extra-hepatic routes of elimination (either extra-hepatic metabolism (Ie. plasma enzymes) or drug excreted unchanged (Ie. lungs or renal))

  - (ii) "Intercompartmental clearance" (* occurs only in multi-compartment model *) – Drug distributes from the central to peripheral compartment(s) → determined by the rate constant for intercompartmental transfer (k_{12}, k_{21}; k_{13}, k_{31}; Etc.)
- Rate of clearance:
  - Most drugs are cleared via 1st order kinetics → drug cleared at rate proportional to plasma [drug] (with highest clearance rate when plasma [drug] is the highest)
  - Few drugs are cleared via zero order kinetics (esp when metabolic/excretory capacity is exceeded – Eg. aspirin, EtOH, phenytoin, STP infusions) → constant amount of drug is cleared per unit time (clearance independent of plasma [drug])
- Significance of clearance:

- Determines maintenance dose rate needed to achieve a plasma [drug] at steady state

"Maintenance dose rate" = Cl x desired $[\ ]_{PLASMA}$

Rationale:

At steady state, for a given plasma [drug] → Rate-in = Rate-el

Rate-in = "Maintenance dose rate" as an infusion (units – mg/min)
Rate-el = "Rate of drug elimination" (units – mg/min)

Since Rate-el = $k \bullet X_t$ (where X_t = amount of drug at a given time)
= $Cl \bullet C_t$ (as $k = Cl/V_D$)

Thus, Rate-in = $Cl \bullet C_t$

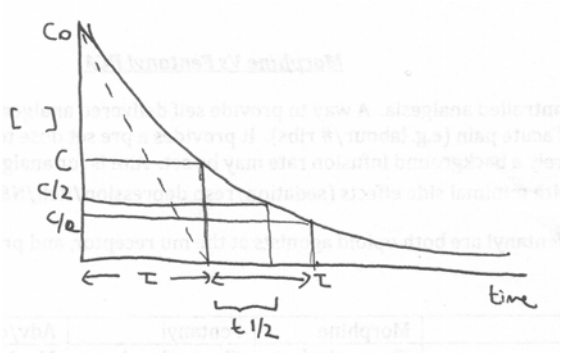
(3) *Rate elimination constant (k_{el} or k_{10})*:

- Defined as the proportion of plasma from which drug is removed per minute (units – $mins^{-1}$) → Ie. k = 0.1 means $1/10^{th}$ compartment will have drug completely removed per minute
- For a single compartment model → k_{el} = slope of the linear ln [drug]-vs-time graph
- It is inversely related to time constant and half-life as follows:

$$k = \frac{1}{\tau} \qquad k = \frac{\ln 2}{t\ ½}$$

Important to note – Rate elimination constant is a CONSTANT value for a given type of drug

(4) *Time constant (τ) and Half-life (t ½)*:



- "Time constant" (τ) – Defined as the time taken for plasma [ ] to fall to zero if original rate of elimination had continued; also defined as the time taken for plasma [ ] to fall by factor of "e" (units – mins)
- "Half-life" (t ½) – Defined as the time taken for plasma [ ] to fall to 50% of initial value (units – mins)

Important to note – Time constants (τ) are LONGER than half-lives (t ½) → t ½ = ln 2 • τ

Important to note – Inverse relationship exists between time constants/half-lives and rate elimination constant:

$$t\ ½ = \frac{\ln 2}{k} \qquad \tau = \frac{1}{k}$$

Important to note:

- Single compartment model – Single exponential relationship exists b/t plasma [drug] and time → time dependency of this process is represented by a "time constant" (τ) or "half life" ($t_{1/2}$)
- Multi-compartment model – Multiple exponential relationships exist b/t plasma [drug] and time → time dependence of this process represented by multiple "time constants" (τ_A, τ_B, τ_G) and "half-lives" ($t_{1/2A}$, $t_{1/2B}$, $t_{1/2G}$) relating to each distinct exponential phase of the process

- Significance of time constants and half-lives – They determine:
  - (1) Duration of drug action after a single IV bolus dose
  - (2) Time needed for a constant drug infusion to reach steady state → 5 x $t_{1/2}$ or 3 x τ
  - (3) Dosing frequency to avoid large fluctuations in plasma [drug]

(F) **<u>Intravenous Infusion Kinetics</u>**:

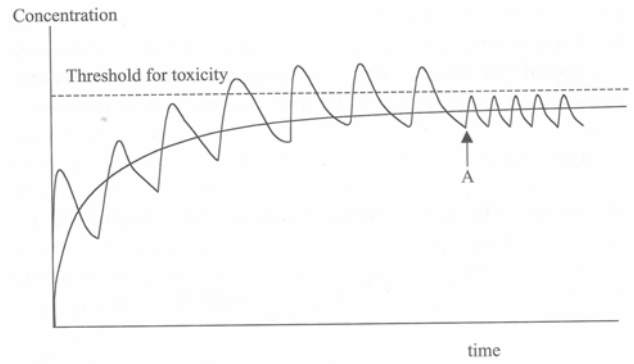
<u>Loading dose and maintaining plasma [ ] of drug</u>:

Loading dose:

$$\text{Dose} = V_1 \bullet [\ ]$$

Where:
- Dose = Drug dose required to give a particular plasma [drug]
- V_1 = Initial V_D of central compartment
- [ ] = Required plasma [drug])

Maintaining plasma [ ] of drug:



- (1) Via repeated drug dosing
  - Produces a "saw tooth" pattern of plasma [drug] (Ie. large swings in plasma [drug]), such that toxic and subtherapeutic levels may occur

$$\text{Maintenance dose} = (\text{Dose}) \times (\text{Dosing frequency})$$

  - Dosing frequency to achieve steady state depends on the rate at which drug is removed from plasma by distribution or elimination – For example, after 1x t ½ plasma [drug] will fall by 50% → if this plasma [ ] is within the therapeutic range, then dose frequency = its elimination t ½. If removal rate is ↑, then frequency of dosing is ↑ (and opposite is true)
  - Rate at which steady state is achieved is influenced by → (i) frequency of dosing and (ii) size of doses

> Important to note – Drug dosing schedule is determined by:
> - (i) Pharmacokinetic factors → frequency of dose and size of dose at start of therapy
> - (ii) Pharmacodynamic factors → size of therapeutic index (Ie. minimal therapeutic [ ] and [ ] that produces adverse effects)

- (2) Via constant drug infusion
  - Produces a constant plasma [drug] within narrow limits (Ie. small swings in plasma [drug]), such drug levels are maintained within therapeutic levels
  - To establish and maintain a steady-state with an infusion (Ie. constant plasma [drug]):

$$\text{Maintenance dose rate} = Cl \times [\ ]_{PLASMA}$$

Where: Cl = Clearance of drug from body
$[\ ]_{PLASMA}$ = Expected plasma [drug]

> Rationale – At steady state:
> - Rate of drug input (Rate in) = Rate of drug output (Rate of elimination)
> - Since "Rate of elimination" = Cl x $[\ ]_{PLASMA}$ → then "Rate in" must also = Cl x $[\ ]_{PLASMA}$ in order to keep a constant plasma [drug]

- Rate at which steady state is achieved (assuming no loading dose is given and infusion rate is constant) is equal to 5 x half-lives (t ½) OR 3 x time-constants (τ) → this is dependent on the "rate constant for elimination" (k_{el})

> Important to note – Delay in reaching steady state is reduced by (i) giving a loading dose or (ii) starting at higher initial infusion rate (then reducing it back to maintenance levels when desired [ ]PLAMA is reached)

Context sensitive half time (CSHT):

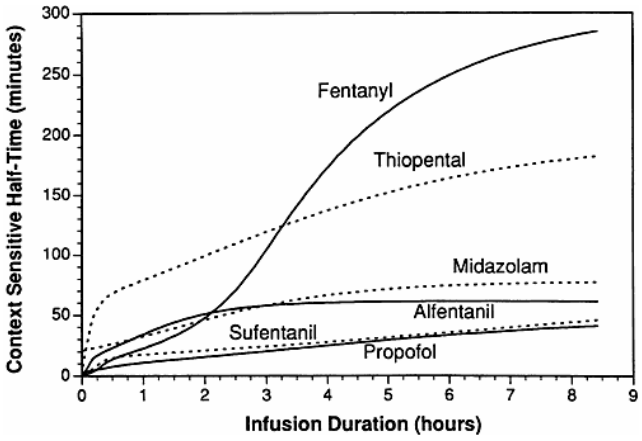
Definition of CSHT – Time for plasma [drug] to fall by 50% after discontinuing a continuous IV drug infusion, with the "context" referring to duration of infusion

Use of CSHT – Describes the pharmacokinetics of continuously infused drugs in a multi-compartmental model → takes into account the effects of (i) drug distribution b/t compartments, (ii) drug elimination from the body (by excretion/metabolism), and (iii) duration of the infusion

Basis of CSHT – Time course for ↓ plasma [drug] in a multi-compartmental model at the end of a drug infusion depends on the duration of the infusion:

- Single IV bolus dose – Produces a rapid ↓ plasma [drug] due to "distribution" to peripheral compartments (rather than "elimination"), which limits the pharmacological actions of the drug → drug "redistribution" back to plasma occurs later but contributes little to maintaining plasma [drug] and does not maintain drug effects
- Prolonged IV infusions run at steady-state – Upon cessation of infusion, [drug] in plasma and peripheral compartments are at equilibrium → elimination of drug from plasma creates a [ ] gradient that causes redistribution of drug back into plasma → maintains plasma [drug] and drug effects

CSHT vs infusion duration:



Important to note:

- (i) CSHT depends on the duration of the infusion (Ie. the "context") → for a given drug, CSHT is the LONGEST when the infusion has reached "steady-state" (Ie. compartments are in equilibrium and infusion rate = elimination rate)
- (ii) Range of CSHT for a drug depends on the ratio of "clearance due to distribution" vs. "clearance due to elimination":

- ↑ "distribution clearance":"elimination clearance" ratio (Eg. fentanyl) → ↑ range of CSHTs → significantly ↑ CSHT with prolonged duration of infusion (Ie. max CSHT for fentanyl is 300 mins)
- ↓ "distribution clearance":"elimination clearance" ratio (Eg. propofol, remifentanyl) → ↓ range of CSHTs → minimal ↑ CSHT with prolonged duration of infusion (Ie. max CSHT for propofol is 20 mins; max CSHT for remifentanyl is 3-5 mins)

- (iii) After 1x CSHT, the next period of time for plasma [drug] to halve is NOT the same CSHT duration → it is likely to be longer due to slower redistribution and metabolism after redistribution has taken place

> Remember – "Half-time" is NOT a constant while "Half-life" is

<u>Elimination half-life and half-time</u>:

- "Elimination half-time" – Defined as the time for plasma [ ] to ↓ to 50% during elimination phase

> Important to note – Elimination half-time is (i) proportional to V_D but (ii) inversely proportional to Cl:
>
> $Cl = k_{el} \bullet V_D \longrightarrow$ as $k_{el} = \frac{\ln 2}{t\,½} \longrightarrow Cl = \frac{\ln 2}{t\,½} \bullet V_D \longrightarrow t\,½ = \frac{\ln 2 \bullet V_D}{Cl}$

> Important to note – The amount of drug remaining in body is related to # elimination half-times elapsed → 5x elimination half-times are needed for total elimination of drug from body (≈ 96.95%)

- "Elimination half-life" – Defined as the time for 50% of drug to be eliminated from the body after rapid IV injection of the drug

> Aside – "Terminal elimination half-life" (TEHL):
> - Defined as the half-life of the "terminal elimination phase", which is the final exponential process in a multi-compartmental model reflecting drug elimination from the body and drug re-distribution from peripheral compartments
> - Of note, the terminal elimination phase is defined by the slope of the line in the log plasma [drug]-vs-time relationship during the final phase of the process
>
> > Note – The "rate constant for elimination" (k_{10} or k_{el}) is NOT the inverse of this TEHL!

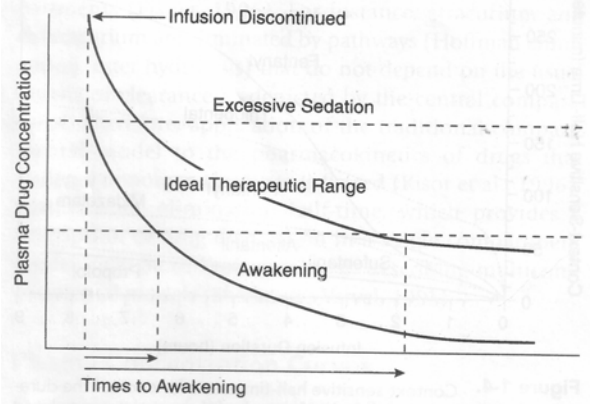
<u>Effect-site equilibration</u>:

- "Effect-site equilibration" → describes the delay b/t IV injection of drug and the onset of its effect due to the time needed for the drug to be delivered via the circulation to the effect site
- "Effect site equilibration time" (t ½ keo) → defined as the half-time of the equilibrium process b/t [drug] in plasma and onset of drug effect

> Importance of "effect site equilibration time" → determines dosing intervals of IV drug administration (esp titrating IV drugs to clinical effects):
> - Drugs with short "effect site equilibration time" (Eg. propofol, remifentanyl, STP) → rapid onset of effects following IV administration
> - Drugs with long "effect site equilibration time" (Eg. midazolam, fentanyl) → slower onset of effects following IV administration

Time to recovery:

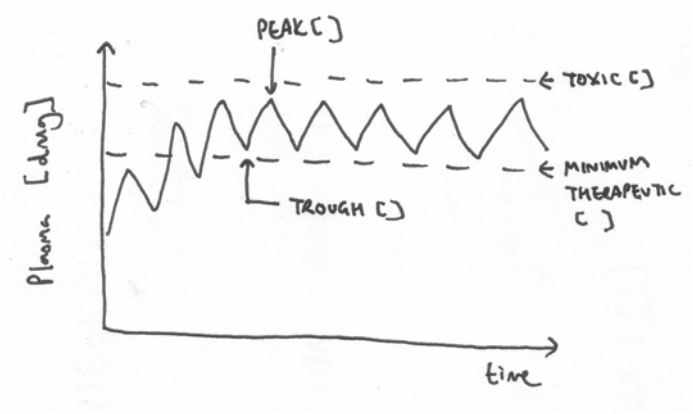
- "Time to recovery" following cessation of a continuous infusion of an anaesthetic agent depends on the difference b/t plasma [drug] at the time of infusion cessation and the plasma [drug] below which awakening is expected
- This is determined indirectly by (i) CSHT and (ii) Elimination half-life of the drug



Note – Time to recovery is FASTER if the plasma [drug] following infusion cessation is just above levels required for awakening (cf. plasma [drug] at much ↑ levels)

(G) **<u>Clincal Monitoring of Plasma Drug Concentrations</u>**:

Clinical monitoring of plasma [drug] is used a monitor for certain drug therapies (Eg. vancomycin, phenytoin, Etc.) → aids development of drug dose scheduling that allows plasma [drug] to be kept within a relatively narrow range (Ie. lessens the toxic effects of drug while maintaining its therapeutic efficacy)



Important points to note regarding monitoring of plasma [drug]:

- (1) Timing of plasma [drug] measurements:
  - (i) Peak serum [ ]'s – Assess drug toxicity (Ie. whether plasma [drug] > toxic levels) → difficult to obtain (Ie. multiple serum samples requires) and detection of peak levels are not very accurate
  - (ii) Trough serum [ ]'s – Assess effectiveness of therapy (Ie. whether plasma [drug] > minimum therapeutic levels) → more practical to obtain (Ie. obtained prior to next dose) and more accurate

    Note – Serial measurements of plasma [drug] is always more informative than a single measurement!
- (2) Plasma [drug] must be measured at "steady-state" → this reflects the [drug] at the effect-site (and receptor site), which provides more information regarding anticipated drug effect
- (3) Measurement technique of plasma [drug]
  - Most techniques measure total plasma [drug] (Ie. bound + free) → BUT only "free" fraction exerts pharmacological activity!
  - Protein binding state must be accounted for with these measurements → esp for drugs with high protein binding, such as phenytoin or diazepam, as small changes in protein binding can have large changes in free fraction of drug
- (4) Plasma [drug] should be interpreted in parallel with clinical course of patient