Week 1 Pharmacology Notes – Pharmacodynamics

1. **Definitions**
   - **Receptors** – the components of a cell or organism that interact with a drug and initiate the chain of events leading to the drugs observed effects. Typically a protein.
   - **Potency-** Potency refers to the affinity or attraction between an agonist and its receptor. A good measure of potency is the concentration (EC_{50}) or dose (ED_{50}) of a drug required to produce 50% of that drugs maximal effect. The "ED50" of a drug is the dose required to produce effect in 50% of people. If the ED50's of two drugs are 5mg and 500mg respectively, we can say that the first drug is 100 times more potent than the second for that particular effect.
   - **Efficacy-** the maximal level of response to the drug
   - **Agonist-** activate the receptor to signal as a direct result of binding to it
   - **Partial agonist-** produce a lower response at full receptor occupancy than **full agonists**
   - **Antagonist-** Bind to receptors but do not activate the generation of a signal, consequently interfering with the ability of an agonist to trigger the signal
   - **Allosteric modulator-** Binds to a different site than the agonist and alter the receptor either positive or negative
   - **Orphan receptor-** receptors that have been discovered via genome sequencing, whose natural ligands have not been found yet
   - **Coupling** – The overall transduction that links drug occupancy of receptors with pharmacological effect. Determined by downstream biochemical events. Can be linear or non-linear.
   - **Spare receptor-** a term used to describe receptors involved in a drug response where the maximal effect of a drug can be achieved without the full occupancy of all receptors. E.g; the same maximal inotropic response can be elicited in cardiac muscle even when 90% of β-adrenoceptors are bound by an irreversible antagonist. Therefore, myocardial cells are said to have a lot of spare receptors.

2. **Outline the role of receptors in relation to drugs**
   - Determine the quantitative relation between dose/concentration of a drug and the pharmacological effect. i.e. the affinity for binding determines the concentration of drug required to form the needed number of complexes to exert effects. The receptor can be the limiting factor in the drug reaction.
   - Receptors are responsible for the selectivity of drug action. This can be altered with changing the molecular size, shape and charge of the molecule.
   - Receptors mediate the action of agonists and antagonists as key determinants of the therapeutic and toxic effects in patients

3. **Name different types of antagonist, and give examples**
   - **Competitive antagonist** – propranolol (at rest) blocks the effects of basal levels of norepinephrine, and the heart rate is decreased. Increased NE i.e. exercise or postural changes can overcome the propranolol.
   - **Non-competitive antagonist**- typically irreversible binding. The duration of effect doesn't depend on its own elimination but on the regeneration of new receptors? Aspirin
   - **Irreversible**- phenoxybenzamine, a drug used to prevent hypertension in pheochromocytoma. Administration lowers blood pressure and the blockade will remain steady even if bursts of catecholamines are released.
   - **Chemical** – i.e protamine, negatively charged at physiological pH, counteracts heparin which is negatively charged. Ionic binding prevents heparin acting on other proteins involved in blood clotting.
   - **Physiological antagonism-** between endogenous regulatory pathways mediated by different receptors. i.e. glucocorticoids send BSL up via catabolism and insulin dose may need to be increased as a result. Less specific and harder to control.
   - Enzymes may be inhibited by binding a drug. E.g dihydrofolate reductase – the receptor for methotrexate; HMG-CoA-reductase, the target receptor for statins.
   - Transport proteins- Na/K/ATPase as a target for digoxin, serotonin transporter proteins for antidepressants.
   - Tubulin protein as a target for colchicine

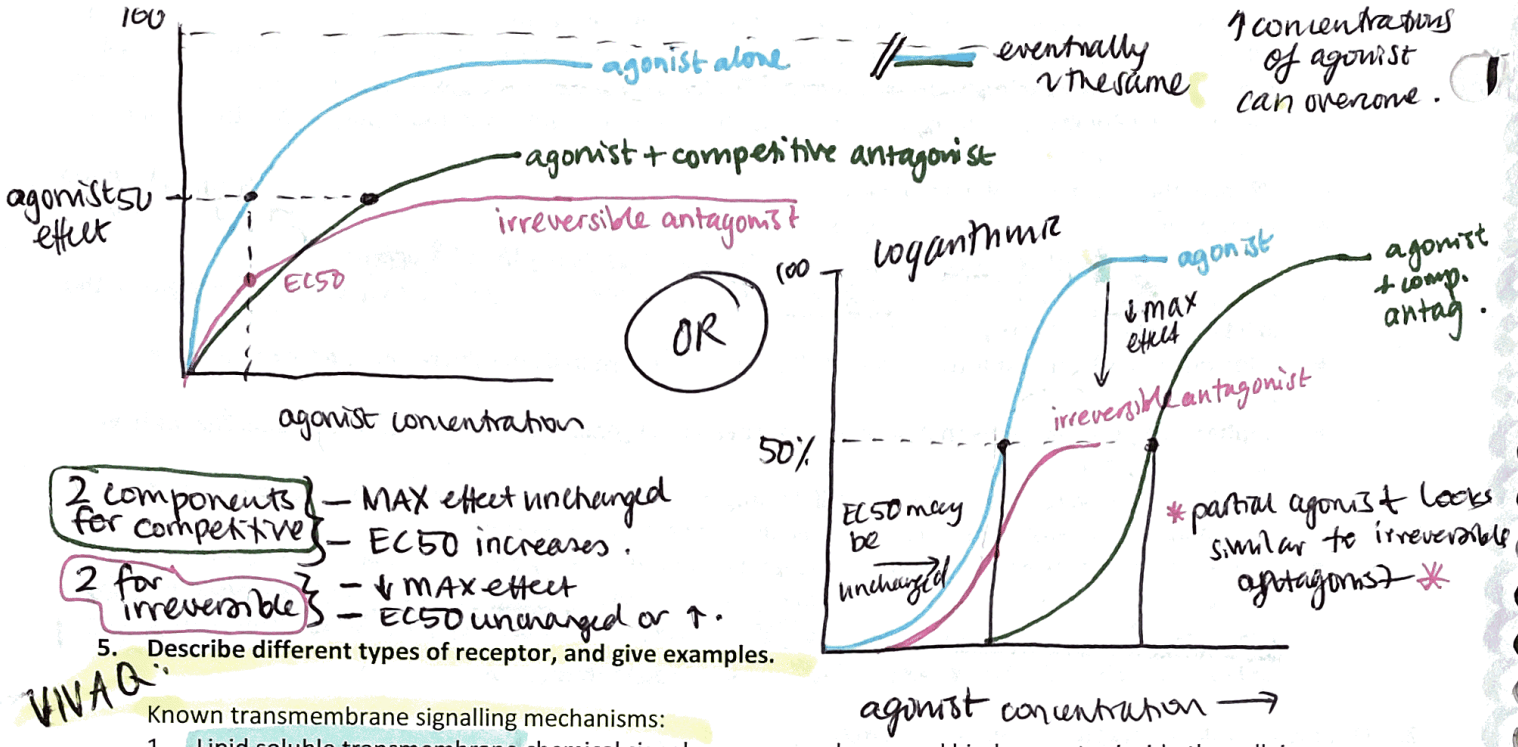
4. **Draw – Dose response curves for agonist/antagonist/partial agonist**

   The relation between dose of a drug and the observed effects is complicated in patients, but simple in in vitro experiments.

$$E = \frac{E_{max} \times C}{C + EC_{50}}$$

E = effect observed at concentration C, Emax is the maximal response that can be reproduced by the drug and EC50 is the concentration of the drug that produces 50% response.

This dose response curve mimics the mass action law that describes the relationship between two molecules of a given affinity. The resemblance suggests that the drug acts by binding or occupying a receptor site.



2 components for competitive } – MAX effect unchanged
– EC50 increases.

2 for irreversible } – ↓ MAX effect
– EC50 unchanged or ↑.

VIVA Q:

5. Describe different types of receptor, and give examples.

Known transmembrane signalling mechanisms:

1. Lipid soluble transmembrane chemical signal crosses membrane and binds receptor inside the cell. i.e an enzyme involved in gene transcription. i.e. steroids
2. Signal binds to extracellular domain of transmembrane protein, activating enzymatic activity of its intracellular/cytoplasmic domain
3. Signal binds to extracellular domain of receptor bound to tyrosine kinase, which it activates. i.e. insulin acts via TK to trigger uptake of glucose and amino acids. Inhibitors of TK are used for antineoplastic agents. i.e trastuzumab. Sometimes they are endocytosed after activation at a rate higher than receptor production i.e. down regulation
4. The signal binds to and causes the opening of an ion channel. i.e. nicotinic ACh receptor opens and allows Na into nerve cell to depolarise
5. The signal binds to cell surface receptor linked to effector enzyme via G protein

3 examples of LIGANDS THAT work by 2nd msngr:

① B-adrenergic amines → ↑camp.
② glucagon
③ ~~opioids~~ opiates / opioids.

ACTIVATION
* extracellular receptor
* cytoplasmic G protein
* changes enzyme / ion channel
* changes [ ] of intracellular 2nd msngr which mediates response.

6. Describe mechanism of action of 2nd Messengers with examples

Almost all secondary messenger signalling involves reversible phosphorylation. This phosphorylation causes amplification of the signal from the original ligand. Flexible regulation occurs when secondary messengers act on different downstream proteins, providing various branches through with the signalling pathway can be controlled.

G protein coupled receptors: ↑HR + contractility

↑Cyclic AMP (via ↑adenylyl cyclase) – for mobilising CHO breakdown via b-adrenergic amines, vasopressin induced water conservation by the kidney, calcium homeostasis via parathyroid hormone, glucagon, serotonin.

↓cAMP via ↓adenylyl cyclase – opioids
NB: caffeine inhibits cAMP degratation

Phosphoinositides & Calcium
Phospholipase C → ↑IP3, diacylglycerol, IP3 triggers release & ↑ of cytoplasmic Ca from intracellular storage vesicles– muscarinic ACh receptors

Cyclic GMP
↑cGMP phosphodiasterase → ↓cGMP = phototranduction in the retina
↑cGMP causes relaxation of smooth muscle via dephosphorylation of myosin light chains. This is how NO works in cardiac vessels and how GTN works. → goes straight into cell as NO.

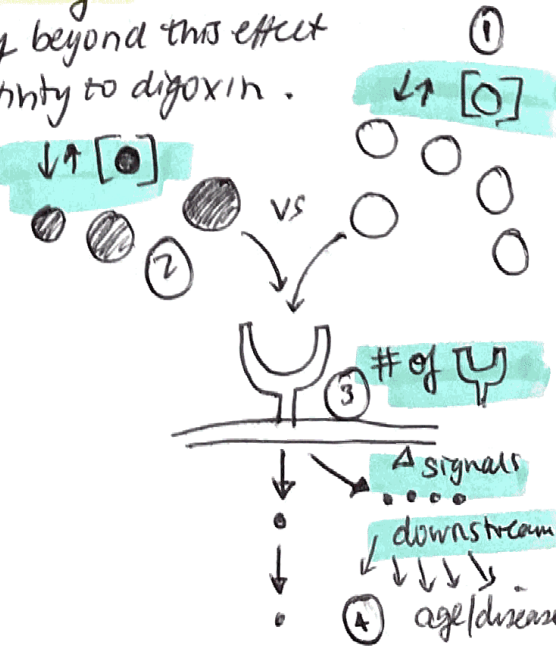
7. **How do these signalling mechanisms work together? Examples?**
cAMP and calcium-phosphoinositide pathways work together in the liver to increase glucose release.
In smooth muscle, vasopressors cause contraction via IP3 mediated mobilisation of Ca, whereas agents that relax smooth muscle work via cAMP

8. **What is the therapeutic index of a drug? How is it calculated? What are the implications for practice? How does it differ from the therapeutic window?**
   - A measure which relates the dose of a drug required to produce a desired effect to that which produces an undesired effect.
   - Described as the ratio of the median toxic dose (dose at which 50% of people have toxic effects TD_{50}) to the median effective dose (ED_{50}) for a therapeutically relevant effect.
   - Therapeutic window is the range between the minimum therapeutic dose & the minimum toxic dose – this has greater practical value for choosing a dose for your patient.

9. **What are the four general mechanisms that contribute to variation in drug responsiveness in patients at different times?**
   - **Alteration in concentration of drug that reaches the receptor** – absorption, distribution, clearance (quick or slow). Drug metabolising enzymes. Active transport of drug from the cytoplasm of target tissue i.e. MDR genes in cancer cells.
   - **Variation in concentration of receptor ligand** – propranolol (beta adrenergic antagonist) slows the HR of a patient whose endogenous catecholamines are raised but would not have any effect on the HR of a relaxed marathon runner.
   - **Alteration in number or function of receptors** – increased or decreased number or reduced coupling between ligand and downstream effects of receptor activation. i.e. in thyrotoxicosis the thyroid hormones increase the number of beta adrenoceptors on the heart muscle and sensitivity to catecholamines.
   - **Changes of components distal to the receptor** – compensatory mechanisms in the patient i.e increased sympathetic tone and and fluid retention by the kidney when given a vasodilator

RAS → mitogenic signal "emperor RAS divided the nation".

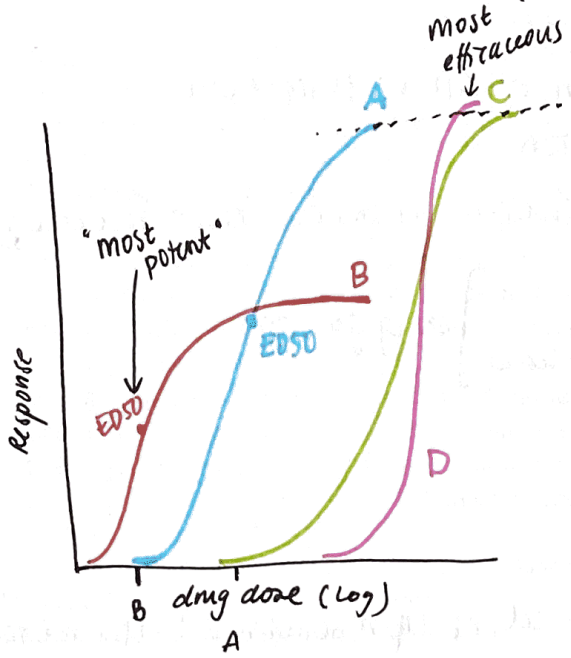
VIVA Q: what pharmacodynamic properties affect drug dosing?
- maximum effect and its relationship to toxicity beyond this effect
- sensitivity (EC50) i.e hyperkalaemia ↓ sensitivity to digoxin.



NOTES

Potency + efficacy

(Emax)



Drugs A & B are more potent because they reach their ED_{50} (dose at which 50% of drug effect is reached) at a lower dose than the others

Potency depends on the affinity (K_d) of receptors for drug & the efficiency with which drug-receptor complex = response

Efficacy is the limit of the dose-response axis.

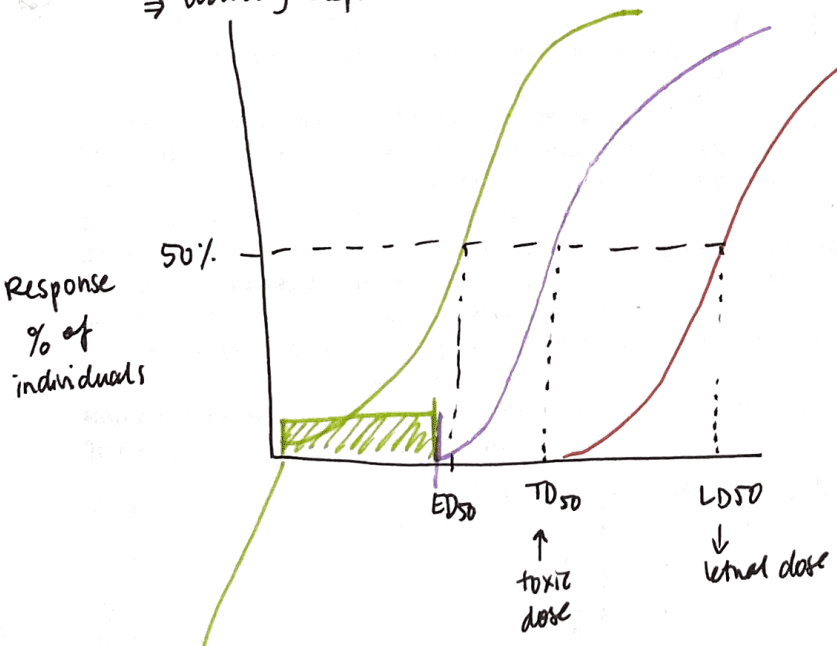
Depends on
- mode of interaction b/w drug + receptor
- characteristics of effector system

NB: "practical efficacy" may be limited by a negative effect.

"Margin of safety"

"Therapeutic Index" ⇒ usually defined as ratio of TD_{50} to ED_{50} for an effect $= \frac{TD50}{ED50}$

↳ depends on the drug + what is considered acceptable i.e chemotherapy vs headache treatment.



i.e $\frac{TD50}{ED50} = \frac{200}{100} = 2 \Rightarrow$ low TI

BUT if $= \frac{200}{10} = 20 \Rightarrow$ high TI so safer drug.

Not affected by potency.

Therapeutic window = minimum toxic dose ↔ min therapeutic dose.

↑ potency drugs: midazolam
fentanyl

VIVA Q: What variables effect the extent + rate of drug absorption?

1 - Route → PO/SC/SL/PR/IV

2 - Nature of the absorbing surface
- → cell membrane i.e epithelium of GIT vs thick skin
- → surface area i.e stomach vs patch

3 - Blood flow → enhances absorption i.e sublingual quicker than subcut.

pt factors

4. Drug solubility
5. Formulation i.e extend coating / slow release

drug factors

What effect does ionisation have?

pKa = pH at which half is ionised.

if pH lower than pKa then drug is unionised % lipid soluble = better absorption.

$$\text{Volume of distribution} = \frac{\text{dose}}{\text{plasma concentration}}$$

APPARENT volume in which the drug is distributed

<5 = blood

5-15 = ECF

>15 = distributed

Week 2 Pharmacology – Pharmacokinetics

1. **Definitions**
   - Absorption- movement of a drug from its site of administration into the systemic circulation
   - **VD** – amount of drug in the body relative to the concentration in blood/plasma. V= amount in body/Concentration. Used to calculate loading doses
   - **Clearance-** Rate of elimination over the concentration in body per unit time. → elimination / concentration (dose bioav)
   - **Half life- (t ½)** = the time required to change the amount of drug in the body by one half during elimination or a constant infusion. T ½ = 0.7 x VD / CL
   - **Bioavailability-** the fraction of unchanged drug reaching the systemic circulation following administration by any route. IV is by definition 100%. PO may be less due to gut absorption and first-pass elimination by the liver. Can estimate the bioavailability of a drug from the difference between oral and IV dose. EG: Metoprolol has such poor bioavailability that the oral dose of 25mg is equal to IV 1mg
   - **Phaemaceutical equivalence-** Two drugs that have the same active ingredients, concentration and route of administration.
   - **Bioequivalence-** when two pharmaceutical equivalent drugs have the same bioavailability
   - **Dosing rate** – clearance x target dose (if poor PO bioavailability the dosing rate is divided by PO bioavailability)
   - **Loading dose** – a dose of a drug that promptly raises the plasma concentration towards steady state. Calculated by the Volume of distribution x the target concentration. Useful for drugs that are eliminated slowly and have a high volume of distribution.
   - **Maintenance dose = dosing rate x dosing interval**

organ fxn, blood flow, protein binding

$$t_{\frac{1}{2}} = 0.7 \times \frac{VD}{CL}$$

2. **What factors affect the volume of distribution**

Drugs affinity for being intravascular vs diffusing onto the rest of the body.

Drug factors
- Molecule size
- Charge
- pKa
- Lipid/water partition coefficient

Patient factors
- Age
- Gender
- Body muscle/fat proportion
- Level of hydration
- Water distribution (oedema, effusions, ascites,

3. **What is zero order and first order kinetics**

zero order elimination – peas + wheels
Phenytoin
Warfarin
Heparin
Ethanol
Aspirin
Theophylline, Tolbutamide
Salicylates.

Zero order absorption- when the rate of absorption is not influenced by concentration. Sustained release drugs are zero order because the rate of absorption is governed by the pre-programmed rate of tablet dissolution. This holds for drugs that depend on stomach emptying rate.

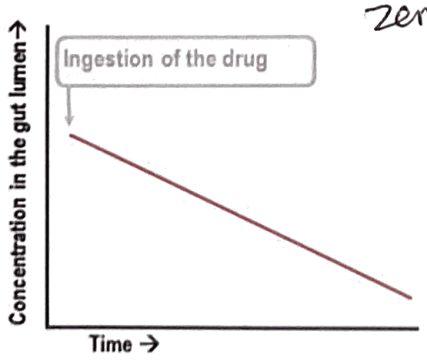
Zero order elimination – a constant amount (i.e. milligrams) is eliminated per unit time. – ethanol, phenytoin, salicylates, cisplatin, fluoxetine, omeprazole

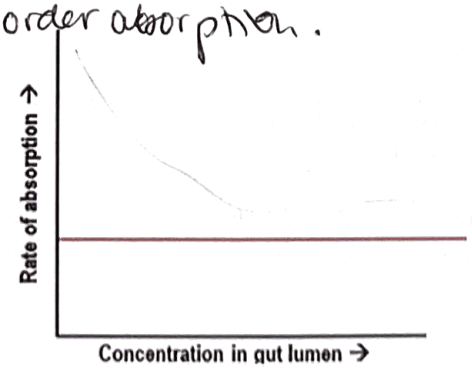
First order elimination kinetics – a constant proportion (i.e. percentage) of drug is eliminated per unit time. Concentration dependant process i.e. the higher the concentration, the faster the clearance. Logarithmic. Example Gentamicin.

Michaelis-Menten kinetics – enzymatic reactions where maximal rate of reaction is reached when drug concentration achieves 100% enzyme saturation.

Non-linear elimination kinetics is the term used to describe drug clearance when a drug at low concentration is cleared by first order and at high concentration by zero order kinetics.

zero order absorption.





zero order = capacity limited (saturatable)

first order = flow limited.

4. **Give examples of drugs with high/low extraction ratios**

Hepatic extraction ratio is the fraction of the drug entering the liver in the blood which is irreversibly removed during one pass of blood through the liver. Extraction ratio is determined by the free/unbound fraction of the drug and the intrinsic clearance rate.
Drugs with high extraction ratio – hepatic clearance depends on hepatic blood flow
Low extraction ratio- limited by uselessness of hepatic enzymes and metabolism unchanged in low flow states. Usually low extraction ratio is zero order elimination.

High hepatic extraction ratio	Low hepatic extraction ratio
• GTN • Verapamil • Propranolol • Lignocaine • Morphine • Ketamine • Metoprolol • Propofol	• Diazepam • Lorazepam • Warfarin • Phenytoin • Carbamazepine • Theophylline • Methadone • Rocuronium

5. **First pass elimination**
    - Following absorption across the gut wall, drug goes through portal system before entry in systemic circulation. A drug can be metabolised in the gut wall or portal blood but also in the liver itself/ It can also be excreted in the bile.
6. **Discuss the influence of protein binding on bioavailability**

The less protein bound a drug is, the more efficiently it can pass between fluid compartments. The usual binding proteins are:

- Albumin – basic so acidic and neutral drugs will bind to it
- Lipoprotein
- Glycoprotein
- Alpha, beta and gamma globulins
- Alpha1-acid glycoprotein – acidic so basic drugs will preferentially bind to it, increases in acute inflammation, alters quinidine, lignocaine, propranolol concentrations
- Famously highly bound drugs include phenytoin (95%) and warfarin (97%)

7. **Outline the pharmacokinetic considerations and changes in obese patients**

ABSORPTION
Gastric emptying may be ↑ or ↓ and this is unpredictable
Absorption from subcut route is slower due to poor blood flow to subcut fat
IM difficult due to poor access

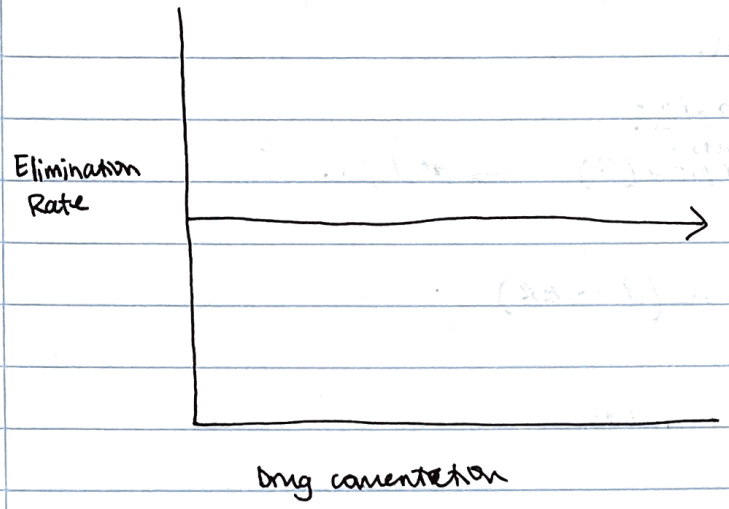
DISTRIBUTION
Increased volume of distribution for lipid soluble drugs
Increased accumulation of drugs in fat compartment – slow to fill up but linger
Blood flow to fat is slow

METABOLISM
Hepatic clearance slowed by fatty infiltration and and ↓CO
CYP450 can be increased

CLEARANCE
Diabetes can damage kidneys slowing renal clearance
Biliary clearance slowed by bile stasis

Difficult to estimate underlying muscle tissue for LBW
More likely to under and overdose obese individuals so need to monitor closely

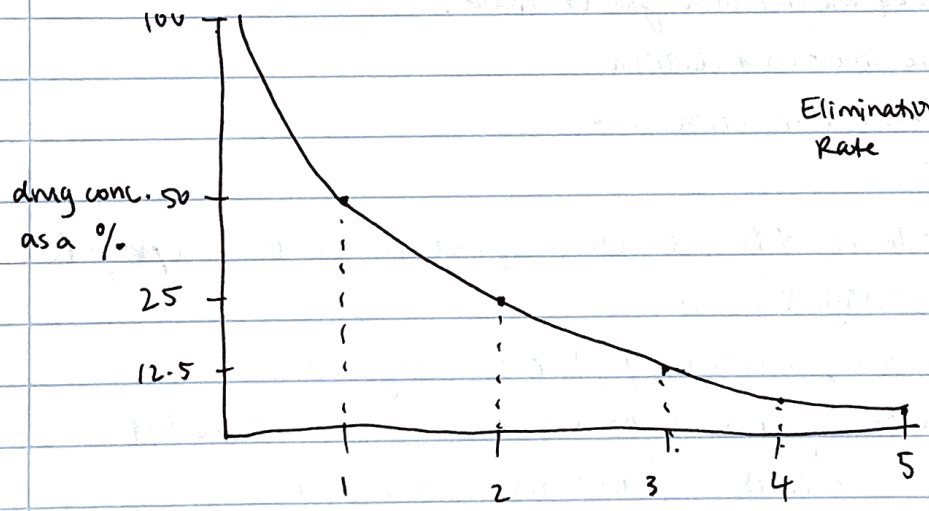
Zero order elimination kinetics: constant AMOUNT per unit time

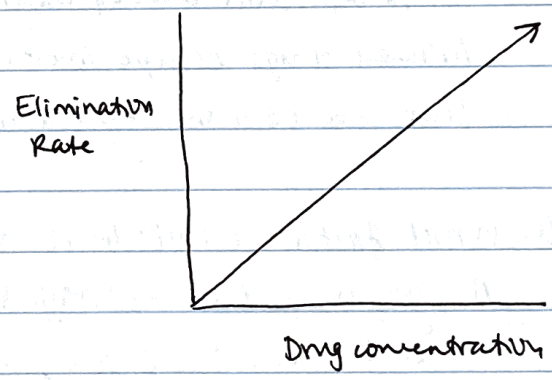


i.e ethanol

First order: constan PROPORTION / PERCENTAGE eliminated per unit time

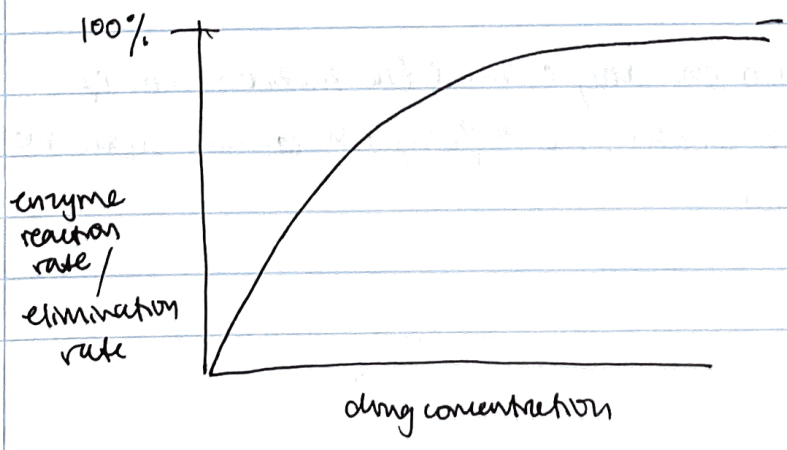
occurs when all enzymes + clearance mechanisms work well below max capacity.

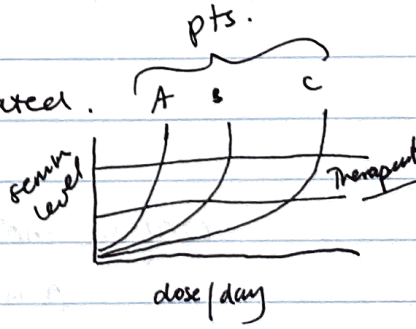




i.e. gentamicin

Michaelis-Menten elimination → system becomes saturated.





i.e phenytoin

→ needs very small dose adjustments.

First Pass Metabolism

Concentration of a drug is greatly reduced before it reaches the systemic circulation.

Generally related to liver + gut wall.

Extraction ratio (ER) = $\frac{\text{CL in Liver}}{\text{Hepatic blood flow (Q)}}$ → 90 L/h.

Bioavailability = Absorption × (1 − ER)

Completely removed by first pass metabolism

- Isoprenaline
- Lignocaine
- Testosterone
- Hydrocortisone.

50% of rectal dose of medication goes to liver.

Inhaled drugs escape liver metabolism

Lung can be a site of elimination for

VIVA Q: What factors contribute to differences in drug metabolism between people?

A: genetic factors → enzyme levels

diet + environmental, → induces/inhibits enzymes

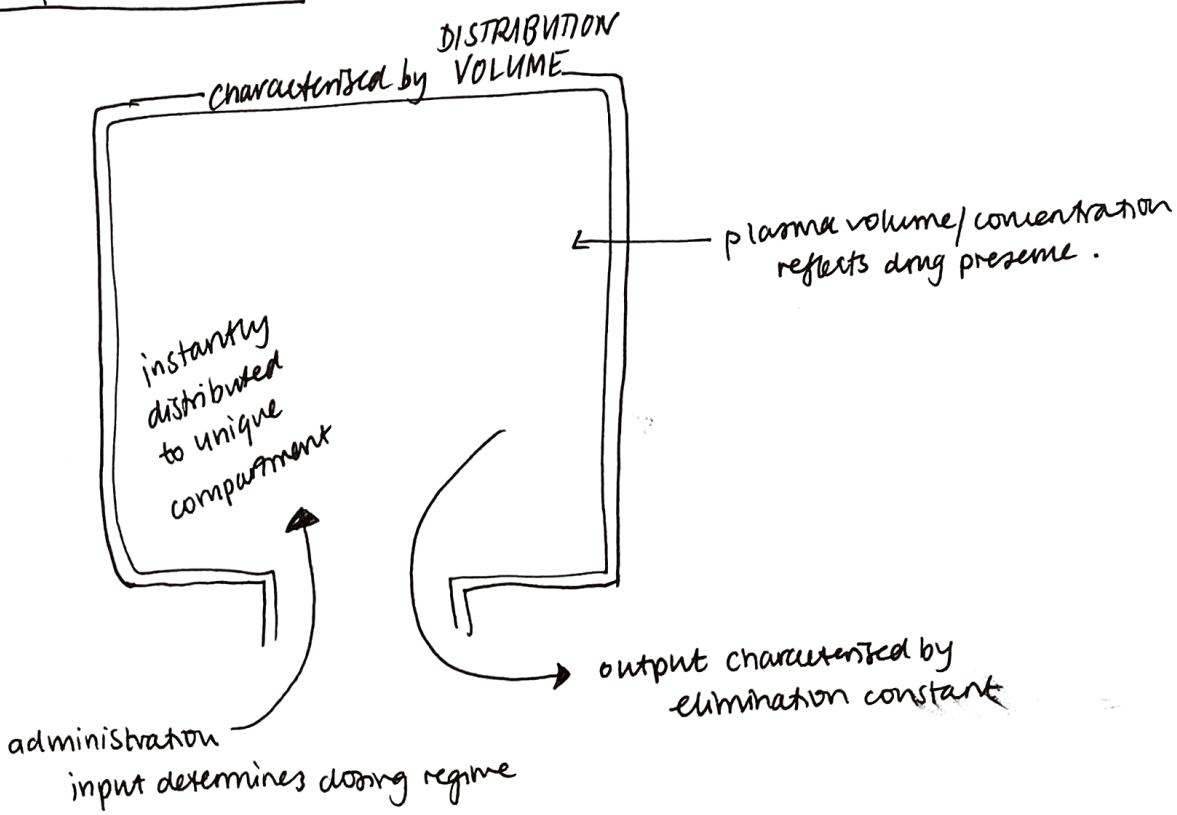
age + gender, → old + young ↓ metabolism, males ↑ metab.

drug − drug interactions (induces inhibitors, protein binding, renal clearance pharmacodynamic interactions)

disease states.

Enzyme induction → when one drug induces the metabolism of another, causing ↓ action. i.e Rifampicin causes induction of P450 enzymes

Single Compartment Model



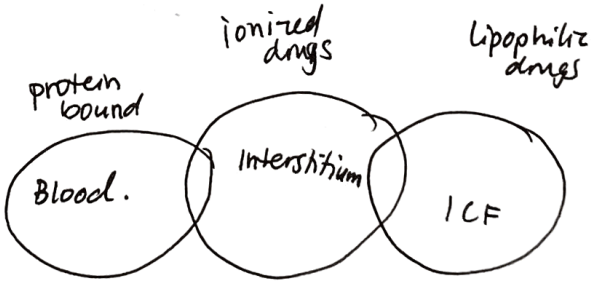
Accumulation occurs if drug is given < every 4 half lives.

The accumulation factor = $\frac{1}{\text{fraction lost each dose interval}}$

So if $t_{1/2}$ 1 hour & drug given every hour acc. factor = $\frac{1}{0.5} = 2$

Q. What determines where a drug is distributed?

- Vd
- Lipophilicity
- Blood flow
- capillary permeability (BBB)
- Plasma protein binding



Week 3 Notes- Pharmacology – Biotransformation → metabolism of drugs to make them inactive or to ↑ excretion via making them more hydrophyllic, or metabolising to a less active agent.

1. **Describe biotransformation reactions in the liver, using paracetamol as an example**
   Paracetamol is conjugated to harmless glucuronide and sulfate metabolites when it is taken in normal doses. If large overdose is taken, the metabolic pathway gets overwhelmed and a P450 dependent system converts some of the drug to a reactive intermediate NAPQI. If the gluthathione stores are exhausted (in an overdose), NAPQI binds with proteins in the hepatocytes inducing liver damage.

2. **What are the sites of drug biotransformation?**
   - Liver – primary site
   - GIT- clonazepam, chlorpromazine
   - Lung – angiotensin
   - Skin – Vit D.
   - Kidneys
   - Gastric acid- penicillin

   Phase I doesnt always preceed phase II. (isoniazid goes backwards)

3. **List phase 1, and 2 reactions** HOR
   Phase I reactions: **HYDROLYSIS, OXIDATION AND REDUCTION**. Parent drug to **MORE POLAR** metabolite by introducing or unmasking a **FUNCTIONAL GROUP** (-OH, -NH2, -SH)

   These can be excreted if polar enough or undergo a second reaction (**Phase II reaction**) where a new substrate (glucoronic acid, sulphuric acid, acetic acid) combines with the functional group to make it even more polar. These can occur together, singularly and in either direction. Enzymes responsible = transferases.

   Examples:
   Phase I lignocaine – hydrolysis
   - Propranolol (P450)
   - Ethanol
   - Morphine
   - Warfarin

   Phase II TRANSFERASES.
   - Glucoronidation – morphine, diazepam, paracetamol, digoxin
   - Acetylation – clonazepam, isoniazid
   - Glutathione conjugation – paracetamol
   - Glycine conjugation- nicotinic acid
   - Sulfation- methyldopa, paracetamol
   - Methylation – dopamine, histamine
   - Water conjugation – benzopyrene

4. **Outline the CP450 metabolism pathway, what is the role of this system?** CYP3A4 = 30% of activity.
   Part of the biotransformation system to detoxify drugs/substrates
   Acts by oxidation (Phase 1 reaction) – one molecule of oxygen consumed per molecule of substrate
   Makes substrates more polar and thus easier to excrete or conjugate
   Acts on a large number of substances
   Microsomal drug oxidation in the liver
   Involves cytochrome P450, P450 reductase, NADPH and O2
   CP450 is a haemoproteins and active in the oxidised/ferric state.

5. **What is meant by enzyme induction, in liver biotransformation.**
   Repeated administration of a substrate brings about either **enhanced enzyme synthesis** or **reduced enzyme CP45-degradation** causing **increased metabolism** of the substrate

6. **List drugs that induce Cytochrome P450 pathways**
   On repeated administration, drugs induce P450 expression by ↑synthesis or ↓degradation
   - tobacco smoke
   - char grilled meat
   - cruciferous vegetables
   - omeprazole
   - St Johns wort
   - Ethanol via ↓degradation (substrate stabilisation)
   - Carbamazepine

   CYP/CP 450 2B1 – barbituates

CP 450 3A – steroids, macrolides, anticonvulsants
CP 450 2E1 – Chronic ethanol
CP 450 1A1- tobacco smoke

7. **List drugs that inhibit Cytochrome P450 pathways**
Macrolide antibiotics (erythromycin) are metabolised to components that then bind to P450 and inhibit it.
Chloramphenicol and steroids (spironolactone) are suicide inhibitors i.e. substrate inactivates the enzyme
- fluconazole, grapefruit juice
- Amiodarone
- Clopidogrel

Enzyme Inhibitors: SICKFACES.COM + Grapefruit
Sodium valproate; Isoniazid, Cimetidine; Ketoconazole; Fluconazole; Alcohol (binge); Chloramphenicol; Erythromycin; Sulphonamides; Ciproflox; Omeprazole; Metronidazole.
Enzyme inducers: CRAP GPs
Carbamazepine; Rifampicin; Alcohol (chronic); Phenytoin; Griseofulvin; Phenobarbitone; Sulphonylureas

8. **Outline the difference in metabolism between different opiates**
Codeine, oxycodone and hydrocodone undergo metabolism in the liver by P450 isoenzyme CYP2D6, resulting in the production of metabolites of greater potency. Fentanyl is metabolised by CYP3A4 isoenzyme

9. **How might new drugs be discovered or produced**

Chemical modification, random screening, rational design, gene methods, new drug target identification

10. **Describe process of clinical trials**
- New drug determined to be safe for human studies (after animal studies)
- Notice of Claimed Investigational Exemption for New Drug (IND)
- 4-6 years of testing on humans
- Phase 1: effects of drug doses established in small # of healthy volunteers 20 ish. Or diseased if ↑SE
- Phase 2: Studied in group with the target disease (proof of concept) 100people
- Phase 3: Studied in larger population – target group (>1000)
- Phase 4: the drug has been approved for marketing. The drug is monitored under actual conditions of use in a large number of patients

11. **During a clinical trial, what might confound the results?**
- Variable natural history of most diseases
- Presence of other diseases and risk factors
- Subject and observer bias

12. **What can be done to minimise confounders?**
- Large populations over sufficient time; cross-over trials
- Exclusion criteria; randomisation; cross-overs
- Placebo controls; blinding; cross-overs