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MEDICINE

Pharmacology

2021_2022

General principles one (1)

Introductory definitions

Medical pharmacology is a basic science. It the science dealing with small molecules used to prevent, diagnose or treat.

Clinical pharmacology is the science concerned with the rational, safe & effective use of drugs in humans. It combines elements of basic pharmacology with clinical medicine; in other words, it involves the complex interaction between the drug & the patient.

Drug → is any chemical molecule that can interact with body systems at the molecular level & produce effect.

The drug-body interactions

Pharmacodynamics ⇐ Drug-Body interactions. ⇒ Pharmacokinetics.

The effect of the drug on the body [the mechanism of drug action & pharmacological effects.]

The effect of the body on the drug. [Absorption, distribution, metabolism & excretion]. ADME

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part 1 Pharmacodynamics (Mechanism of drug action)

Pharmacodynamics is summarized as what a drug does to the body; a drug may produce effects through:-

- Interaction with body control systems (regulatory proteins):-
  a. Receptors b. ion channels c. enzymes d. carrier molecules.
- Direct chemical or physical mechanism.
- Interaction with certain metabolic pathways.

A. Receptors

Receptors:- they are protein macromolecules .when they combine with a drug, they may be activated or blocked.

Ligands:- is any molecule that can combine with the receptors,

- Full (agonist) → activate the receptor & result in maximal response
- Partial agonist → don't active the R throughly (efficacy between 0 & 100%) submaximal response
- Antagonist → block the receptor (zero efficacy)
- Inverse agonist → reduce the activity of receptor (negative efficacy)

Affinity:- it is the empathy of the receptor to the ligand.
It determines the number of receptor occupied by the drug.

Types of receptors (4) ↓

Ion channel-linked receptors (direct ligand-gated ion channels)

- The receptor is an ion channel consists of 5 transmembrane subunits (α_1, α_2, β, δ, σ).
- Binding of the agonist to the extracellular part of the receptor causes opening of of the channel for a specific ion.
- The response of these receptors is very fast & their duration is very short.

Examples

- Nicotinic Ach receptors in the motor-end plate: the ion channel opens for Na^+ ion in response to stimulation by Ach.
- The Gama aminobuteric acid (GABA) receptors in the brain: the ion channel opens for Cl^- ions in response to stimulation by GABA.

G-protein-linked receptors

- The receptor consists of 7 membrane subunits
- Binding of the agonist to the extracellular part of the receptor causes activation of intracellular G-protein.
- When the G-protein is activated, its α subunit binds to GTP to be phospholated & bring stimulatory or inhibitory response.
- Their response is slower than ion channel receptor but their duration is longer.

- Stimulatory G-protein (Gs)
  leads to increase adenyl cyclase enzyme → ↑ cAMP → activation of specific proteins (protein kinases)
  Ex. of Gs-coupled receptors ⇒ β_1 & β_2 adrenergic receptors.
- Inhibitory G-protein (Gi)
  leads to decrease adenyl cyclase enzyme → ↓ cAMP → inhibition of protein kinase.
  Ex. of Gi-coupled receptors ⇒ α_2 adrenergic receptors & M2 muscarinic receptors
- Gq-coupled receptors
  they increase inositol triphosphate (IP3) & diacylglycerol (DAG)
  IP3 ↑ free intracellular Ca^{2+}
  Ex. of Gq-coupled receptors ⇒ α_1-adrenergic receptors, & M_1 & M_3 muscarinic receptors

Tyrosine kinase (TK)-linked receptors

- The receptor consists of 2 large domains :- an extracellular hormone-binding domain & an intracellular TK-binding domain connected by transmembrane segment
- Binding of the agonist to the hormone-binding domain causes activation of the intracellular domain to active TK enzyme → activation of several proteins known as "signaling proteins".

Example
- Insuline receptor.

Intracellular receptors DNA-linked receptors / Nuclear receptors

- They are located inside the cell either in the cytoplasm or directly on the DNA
- They regulate transcription of genes in the nucleus or the mitochondria
- Their agonist must enter inside the cell to reach them.
- They have two important features :-
  - The response is slow (time is required for synthesis of new proteins)
  - The effects persist for long time after the agonist is removed.
    . cortico steroids / sex hormones

Types of drug receptor bonds ↓

The ionic bond
an electrical attraction between two opposing charges
It is stronger but reversible.

The hydrogen bond
It is an attraction between two hydrogen bonds
It is weak & reversible

The covalent bond.
very strong & irreversible
If occured between drug & receptor, the receptor becomes permanently blocked

Biological response to drug receptor binding

(Dose-response relationship studies)

When a drug combines with a receptor, this may lead to one of the following:-

Aggonist effect ⇒ means that the drug combines with the receptor & gives response

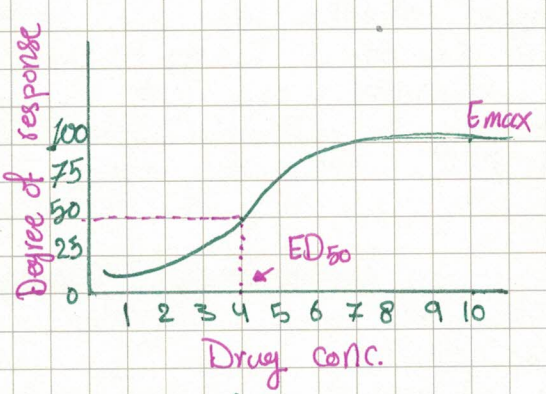
Antagonist effect ⇒ means ~~that~~ that the drug combines with the receptor but gives NO response, and prevents the receptor from binding to another drug

Agonist effect

There are 2 types of response to drugs:-

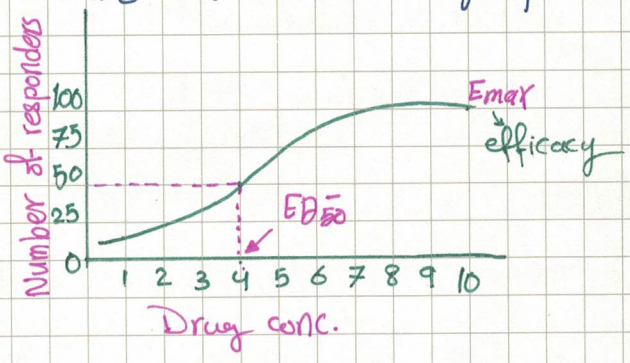
Graded response

- The response is increased proportionally to the dose of the agonist
  e.g. → the response of the heart to adrenalline
- It is the response to most drugs.
- The response could be tested in one or more animals.



Quantal response.

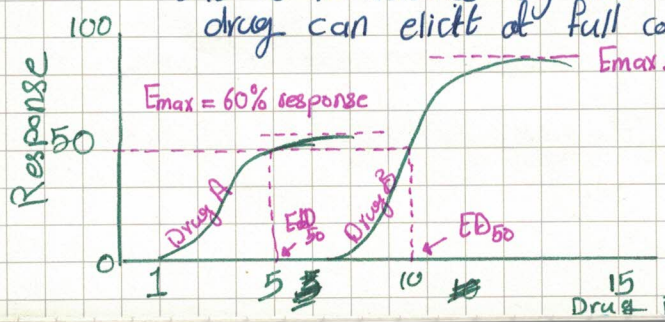
- The response does not increase proportionally to the agonist but it is all-or-none response.
  e.g.: prevention of convulsions by antiepileptic drugs.
- It is response to few drugs.
- The response could not be tested in one animal & must be tested in a group.



Effectiveness & Safety

Efficacy

- It is the ability of a drug to produce response (effect) after binding to the receptor
- It is measured by the Emax (the maximal response that a drug can elicit at full concentration)



A is more potent than B
B is more effective than A

A → Partial agonist
B → Full agonist

Potency

- ED50 (effective Dose) is the dose of the drug that gives 50% of the Emax, or it is the dose that gives the desired effect in 50% of a test population of subjects.
- A drug that gives ED50 by smaller doses is described as "potent" drug
- Potency of drugs is generally less clinically important than efficacy because you can increase the dose of a less potent drug to obtain the effect of a more potent one (provided that it is not toxic)

Safety

- TD50 (Toxic Dose) is the dose of the drug needed to cause a harmful effect in 50% of a test population of subjects.
- LD50 (Lethal Dose) is the dose needed to cause death in 50% of a test group of animals. It is experimental term that can be determined in animals.

Therapeutic index (TI) LD50/ED50

- It is the ratio between the LD50 & the ED50. It is a measure of safety, if there is a large difference between the dose of a drug that produces the desired effect & the dose that produces a toxic effect, it is said that the drug has a large TI
- Drugs with high TI are more safe for clinical use, and vice versa.
  eg → warfarin has a narrow TI & requires careful & therapeutic monitoring.

Antagonist effect

Antagonism:- is the ligand that combines with the receptor & does not active it.
It has no intrinsic activity, but may cause a pharmacological response by inhibiting the actions of endogenous substances or other drugs

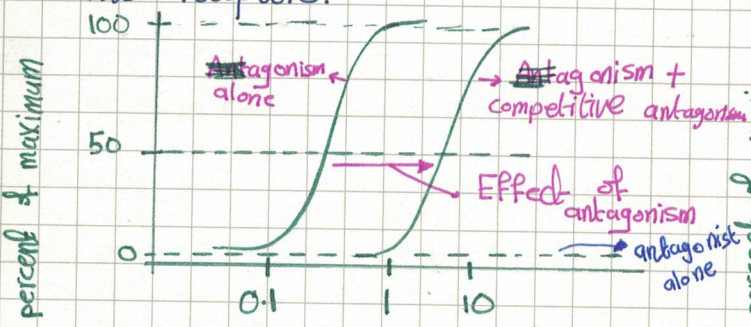
- If the antagonist binds to the same site of the agonist on the receptor, it is called competitive antagonist
- If the antagonist binds to another site on the receptor, & prevented the action of the agonist, it is called non-competitive antagonist

Competitive antagonism may be reversible or irreversible.

⇓

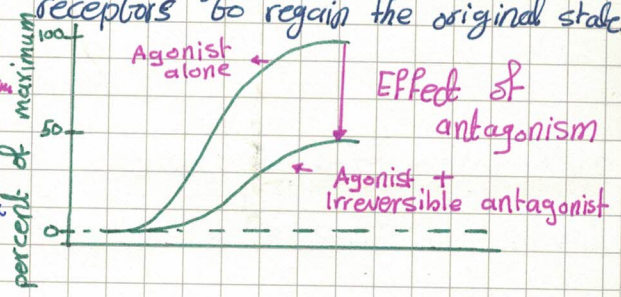
- Reversible antagonism

makes weak bond with the receptor so as you can overcome the block by giving high doses of the agonist, & even you get the maximal response in presence of the antagonist (i.e surmountable effect)
The duration block is short because the antagonist can be easily washed of the receptors.



- Irreversible antagonism

makes covalent bond with the receptor so as you can't overcome the block or get the maximal response by increasing the dose of the agonist (i.e non surmountable effect). The occupied receptors are permanently blocked, so the duration of block is long, & the body has to synthesize new receptors to regain the original state



Other types of drug antagonism ↓ It is not at the level of receptor

- Chemical antagonism

eg one acidic drug when added to a basic drug can cause percipitation of each other's.
E.X → the addition of gentamycin (basis) to carpenicillin (acidic) in the same syringe causes chemical complex.

- Physical antagonism

antagonism between two drugs carrying opposite charges.
E.X → protamine is used for treatment of heparin overdose because protamine carries +ve charge while heparine carries -ve charge.
1 mg = 100 units

- Physiological antagonism

antagonism between two drugs producing opposite effects by activation of different receptors.
E.X → adrenaline is the physiological antagonist of histamine because while histamine causes hypotension & bronchoconstriction through activation of histamine H_1 receptors, adrenalline causes hepertension & bronchodilation through activation of adrenergic α & β receptors respectively.

- Pharmacokinetics antagonism

  - One drug may prevent absorption of another drug e.g antacids → ↓ absorption of iron & aspirin.
  - One drug may increase metabolism of another drug e.g rifampicin induces hepatic enzymes & ↑ metabolism of oral contraceptive pills.
  - One drug may ↑ excretion of another drug. e.g $NaHCO_3$ cause alkalinization of urine & ↑ excretion of acidic drug like aspirin.

B Ion channels

How drugs could modulate ion channels?

- Physical block: e.g blocking of Na^+ channels by local anesthetics
- The ion channel may be part of the receptor e.g ion-channel-linked-receptors
- The ion channel may be modulated by G-protein linked receptors.
- Ion channels may be modulated by intracellular ATP e.g ATPase sensitive k^+ channels in the pancreatic β cells, rise of intracellular ATP causes closure of pancreatic k^+ channels.

C. Enzymes

How drugs could effect enzymes?

- The drug may act as a competitive (reversible) inhibitor of the enzyme e.g neostigmine on cholinesterase enzyme.
- The drug may act as irreversible inhibitor of the enzyme. e.g organophosphate on cholinesterase enzyme.
- The drug may act as false substrate for the enzyme e.g α-methyldopa is a false substrate for dopa decarboxylase. دوبا ديكربوكسيليز
- The drug may induce or inhibit hepatic microsomal enzymes activity.

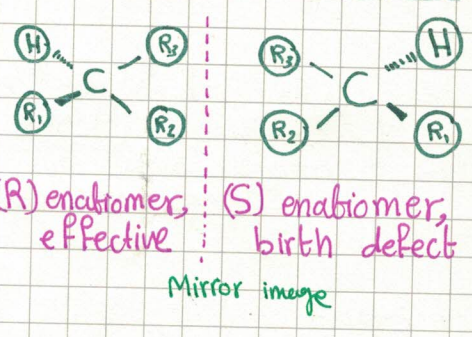
D Carrier molecules (transporter)

- These are small protein molecules that carry organic molecules across the cell membrane when they are too large or too polar
- Drugs could effect ~~effect~~ carrier molecules by blocking their ~~rego~~ recognition site.

Part 2 Factors affecting dose-response relationship

A Factors related to the drug

1. **Drug shape (stereoisomerism):**
   - Most drugs have multiple stereoisomers (enantiomers) (e.g. L-thyroxin & D thyroxin). The receptor is usually sensitive for one stereoisomer & not suitable for another, like the hand & the glove. This means that one isomer may be hundred times more potent than the other. In other instances one isomer is beneficial while the other is toxic.
   - This phenomenon may explain how a single drug could act as agonist and antagonist (i.e partial agonist) because many drugs are present in "racemic mixture" rather than as pure isomers; or how one isomer is effective & the other isomer is toxic.



2. **Molecular weight (MW) :-**
   - Most drugs have MW between 100-1000 Da. Drug particles larger than MW 1000 Da cannot be absorped or distributed. They should be given parenterally.
   - Drug particles larger than MW 1000 Da cannot cross placental barrier.

3. **Time of drug administration (chronopharmacology)** renal blood flow
   - Many body functions (e.g. liver metabolism, RBF, blood pressure, HR, gastric emptying time, etc.) have daily circadian rhythm. Some enzymes responsible for metabolism of drugs are active in the morning or evening.
   - Also many diseases (e.g. asthma attacks, myocardial infarction...) are circadian phase dependent.
   - Chronopharmacology is the science dealing with tailoring drug medication according to the circadin rhythm of the body to get better response and/or to avoid possible side effects.

Examples :-

- Episodes of acute bronchial asthma are common at night due to circadian variation of cortisol & other inflammatory mediators, so it is better to give the anti-asthmatic medication in the evening.
- Blood pressure is at its peak during afternoon, so it is better to give the antihypertensive medications at morning.

4. **Drug cumulation :-**

Cumulation occurs when the rate of drug administration exceeds the rate of its elimination (especially in patients with liver or renal disease). Some drugs are cumulative due to their slow rate of elimination e.g digoxin.

5. **Drug combination :-**

Drug combination is very common in clinical practice. When two or more drugs are combined together, one of the following many occur:

- **Summation or addition :-**

  Summation means that the combined effect of two drugs is equal to the sum of their individual effects (e.g → 1+1=2). It usually occurs between drugs having the same mechanism, for example → the use of two simple analgesics together.

- **Synergism & potentiation :-**

  Synergism means that the combined effect of two drugs is greater than the sum of their individual effects (i.e → 1+1=3). The two drugs usually have different mechanisms of action, for example → the use of penicillin with aminoglycosides to exert bactericidal effect. → They are complementary to each other

  Potentiation is similar to synergism but, in potentiation, the effect of one drug itself is greatly increased by intake of another drug without notable effect (i.e → 1+0=2), for example → Phenobarbitone has no analgesic action but it can potentiate the analgesic action of aspirin.

- **Antagonism :-**

  One drug abolishes the effect of the other (i.e → 1+1=0).

B Factors related to the patient.

1. **Age, sex and weight** → mg/kg

   Hyperthyroidism ↑↑ dose.

2. **Pathological status**

   Liver or kidney diseases significantly alter the response to drugs due to altered metabolism. Also the failing heart is more sensitive to digitalis than the normal heart.

3. **Pharmacogenetic factors (idiosyncrasy)**

   It is abnormal response to drugs due to genetic abnormality in drug metabolism.

These are some examples ↓

Examples of heritable condition causing EXAGGERATED drug response

a Pseudocholinestrase deficiency :- muscle paralysis

b Glucose-6-phosphate dehydrogenase (G6PD) deficiency.

c Thiopurine methyltransferase (TPMT) deficiency.
↓ metabolism → anticancer drug
(slow) → Neuropathy (rapid) → liver damage

d Acetylator phenotypes.

[4]

Examples of heritable conditions causing DECREASED drug response:-

- Resistance to coumarin (warafin) anticoagulants.
  → x vit k epoxide reductase
- Resistance to Vit D (Vit. D resistant rickets).
  x-chromosome linked disease
- Resistance to mydriatics.

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4. Hyporeactivity to drugs:-

(Tolerance; tachyphylaxis; drug resistance)

Tolerance → means progressive decrease in drug response with successive administration. The same response could be obtained by higher doses. It occurs over long period.

Tachyphylaxis → is an acute type of tolerance that occurs very rapidly.

Mechanism of tolerance:- ① Pharmacodynamic tolerance :-
occur due to:-

Receptor desensitization :- Prolonged exposure to the drug leads to slow conformational changes in the receptors by which the receptor shape becomes no longer fitted well with the drugs.

Receptor down-regulation :- Prolonged exposure to the drugs leads to decrease number of the functional receptors.

Exhaustion of mediators :- e.g → depletion of catecholamines by amphetamine.

② Pharmacokinetic tolerance :-
- Due to ↑ metabolic degeneration of a drug by induction of hepatic enzymes . e.g → with chronic administration of ethanol

③ Behavioral tolerance:-
- It occurs by a drug independent learning of the brain how to actively overcome a certain drug induced effect through practice e.g → with psychoactive drugs

5. Hyperreactivity to drugs :
Rebound & withdrawal effect

Rebound effect → is recurring of symptoms in exaggerated from when a drug is suddenly stopped after a long period of administration.

Mechanism:- Prolonged administration of the antagonist leads to up-regulation (↑number) of receptors. when the antagonist is suddenly stopped, severe reaction occurs e.g → severe tachychardia & arrhythmia occurs after sudden stopping of beta blockers

Withdrawal effect → (syndrome) is recurring of symptoms in exaggerated form addition of new symptoms. when a drug is suddenly stopped, e.g → withdrawal effects that occurs after sudden stopping of opioids in opioid addicts.

N.B. some examples of drugs should not be stopped suddenly.

Drug	Sudden withdrawal can lead to
Beta-blockers	Severe tachycardia, arrhythmia, & even myocardial infarction.
clonidine	Sever hypertension (hepertensive crisis)
Cimetidine, HCl	Severe hyperacidity & even peptic ulceration.
Corticosteroids	Acute Addisonian crisis.
Morphine	Withdrawal symptoms
Warafin	Thrombotic catastophes

Part 3 Clinical Pharmacokinetics

Pharmacokinetics is the journey of the drug inside the body.
It includes 4 processes ↓ADME

Absorption of drugs

It is the passage of drug from the site of administration to the plasma.
The main routes of administration :- [oral, sublingual, rectal, inhalation ...]
oral = GIT; topical; parenteral

Factors affecting drug absorption :-

A. Factors related to the drug

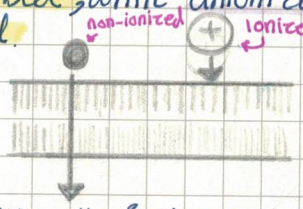
Molecular size :- small molecules are absorbed than large molecules.
Dose :- absorption increases with increasing the dose (up to limit)
Drug formulation e.g. → sustained-release tablets are slow in absorption.
Local effects of the drug :- e.g. → drugs producing VC↓ their own absorption
Drug combination :- e.g. → Vit C ↑ absorption of iron.
Lipid solubility :- drug ionization, & the pKa of the drug.

B Factors related to the absorbing surface :-

Route of administration :- I.V. route is the fastest while rectal is the slowest.
Integrity of the absorbing surface :- may ↑ or ↓ absorption.
Local blood flow :- ischemia ↓ absorption.
Specific factors :- e.g. → apoferritin system for iron.

The pKa & drug ionization

principles :- Ionized (polar; charged) → water-soluble drugs are poorly absorbed, while unionized (non-polar, non-charged) drugs are more absorbed.



- Most drugs are weak acids or bases.
  They become ionized or non-ionized according to the pH around them.
  - Acid drugs (eg. aspirin) are more ionized in alkaline pH & vice virsa.
  - Basic drugs (eg. amphetamine) are more ionized in acidic pH & vice virsa.

pKa of a drug :- is the pH at which 50% of the drug is ionized & 50% is non-ionized. where p = inverse log
Ka = association / dissociation constant.

Example of pH variation & drug kinetics with aspirin

Aspirin is an acidic drug; its pka = 3.5
The pH of the stomach is 1.5 The pH of the intestine is 8.5.

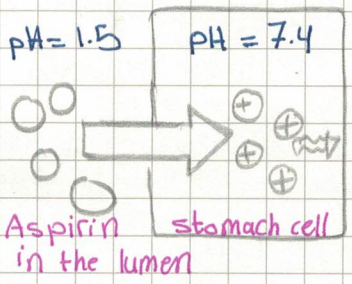
▶ When aspirin is put in the stomach :-

- Aspirin is acidic drug & becomes more absorbable in acidic pH.
- Log (unionized/ionized*) = pka - pH = 3.5 - 8.5 = -5 (10^{-5})
- This means that the ratio of unionized/ionized = 1/100000 (0.00001) parts are absorbed & 0.99999 parts are non-absorbed).

* The above rule applies only to acidic drugs like aspirin. For basic drugs, the ratio would be reserved.

▶ Ion trapping of aspirin :-

In the stomach, aspirin is more absorbable into stomach cells but once entered the cells, the pH changes from 1.5 outside to 7.4 inside the cell.
So, aspirin becomes ionized inside the cells & can't diffuse out-side them again → gastric ulcer القرحة الهضمية



Clinical significance of pka

- Knowing the site of drug absorption from the GIT
- Treatment of drug toxicity :-
  - Toxicity with acidic drugs (e.g. aspirin) could be treated by alkalinization of urine, which renders this drug more ionized in urine & less reabsorbable.
  - Toxicity with basic drugs (e.g. amphetamine) could be treated by acidification of urine, which renders this drug more ionized in urine & less reabsorbable.
- Ion trapping in breast milk :-
  The pH of the breast milk is 7, i.e it is considered acidic in relation to plasma (pH = 7.4)
- Basic drugs (with pka > 7.2) tend to be ionized & thus trapped, inside breast milk more than acidic drugs; hence, the milk/plasma ratio (M/P) would be high.

Distribution of drugs

Sites of drug distribution :-

- Plasma → 3 Liters
- Extracellular water → 9 liters
- Intracellular water → 29 Liters

→ total = 41 L

Volume of distribution (Vd)

→ theoretical

↳ The apparent volume of water into which the drug is distributed in the body after distribution equilibrium.

calculation

$$Vd = \frac{\text{Total amount of the drug in the body}}{\text{Plasma conc. of the drug (after distribution equilibrium)}} \quad L$$

clinical significance

- Determination of the site of drug distribution eg :-
  - A total Vd < 5 L → means that the drug is confined to the vascular compartment & can be removed by dialysis
  - A total Vd 5-15 L → means that the drug is restricted to the ECF
  - A total Vd > 41 L → means that the drug is highly bound to tissue proteins ~~that~~ & cannot be removed by dialysis
- Calculation of the total amount of drug in the body by single measurement of plasma concentration (From the equation)
- Calculation of the loading dose (LD) needed to attain a desired plasma concentration (C_p) $LD = Vd \times C_p$
- Calculation of drug clearance

$$\text{clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Binding of drugs to plasma proteins

- Most drugs when introduced into the body are bounded to plasma protein
- Albumin :- the most important plasma protein & it can bind -ve or +ve charged drugs.

clinical significance:-

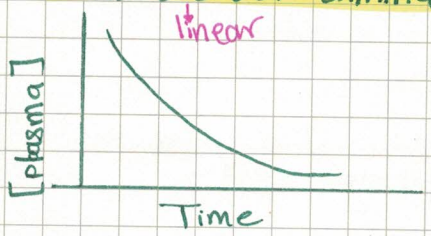
- The pharmacological effect of the drug is related only to its free part not to its bound part (the bound part acts only as a ~~reversible~~ reservoir from which the drug is slowly released)
- Binding of drugs to plasma proteins prolongs their effects.
- When the drug has high plasma protein binding (e.g. 99% for warafin), the free part that exerts the pharmacologic effect is 1%. Any small displacement of the bound part by another drug (say for example another 1% is displaced) can lead dramatic toxicity (doubles the amount of the free part in plasma)
- Many diseases states (e.g. chronic liver disease, pregnancy, renal failure) can affect the level of albumin & the nature of plasma proteins, thus causing serious problems with some drugs.

Excretion & Elimination of drugs

excretion metabolism

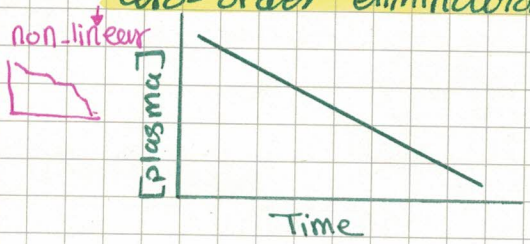
Elimination of drugs may follow one of 2 processes (orders):-

First-order elimination



- occurs to most drugs
- Constant ratio (%) of the drugs is eliminated per unit time i.e. the rate of elimination is proportional to plasma concentration.
- The higher the concentration, the greater the rate of elimination
- Elimination does not depend on saturable enzyme system.
- The $t_{1/2}$ of the drug is constant
- Drug cumulation is not common.

Zero-order elimination.



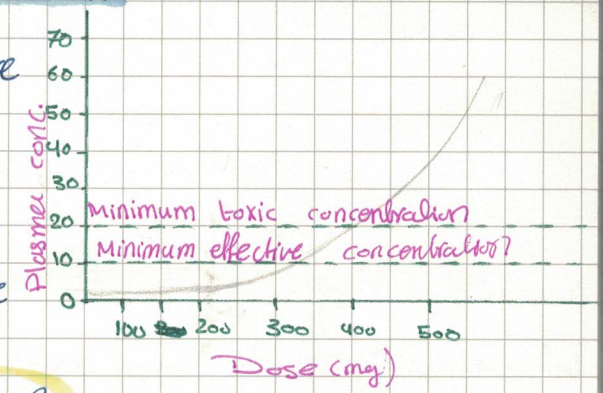
- Occurs to limited number of drugs.
- Constan amount of the drug is eliminated per unit i.e. the rate of elimination is not proportional to plasma concentration. A familiar example is ethanol, concentrations of which decline at a constant rate of approximately 15mg/100mL/h.
- Elimination depends on saturable enzyme system.
- The $t_{1/2}$ of the drug is not constant.
- Drug cumulation is common.

Examples of drugs eliminated by zero-order : prednisolone / theophyline

N.B Some drugs are eliminated by first-order elimination in low doses & by zero-order elimination in high doses e.g → aspirin & phenytoin

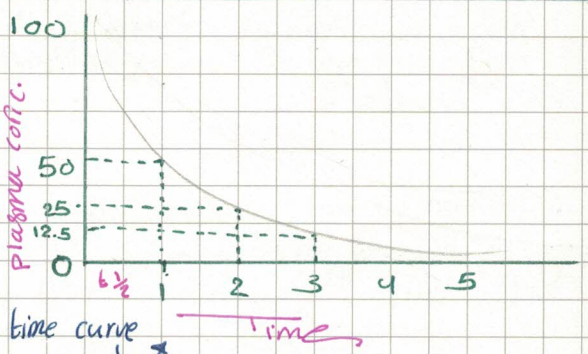
Clinical significance of zero-order elimination:-

- Modest change in drug dose may produce unexpected toxicity.
- Elimination of drugs or attainment of Cpss takes long time.
- Changes in drug formulation may produce adverse effects.
- Drug cumulation & interactions are common.



Elimination half-life ($t_{1/2}$)

Definition → It is the time taken for the concentration of a drug in blood to fall half to its original value.



Calculation → • From the plasma conc. versus time curve
• From equation ↓

$$\text{Clearance} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

plasma $t_{1/2}$ → the time needed to eliminate 50% of the drug from plasma

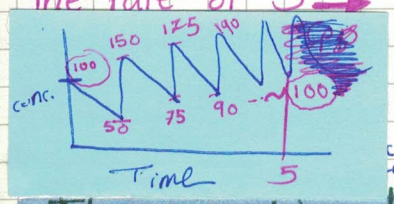
Clinical significance:-

- Determination of inter-dosage interval : drugs are given every $t_{1/2}$ to avoid wide fluctuations of the peak level (the highest plasma concentration of the drug) & trough level (the lowest plasma concentration)
- Time course of drug accumulation : if drug is started as a constant infusion the Cp will accumulate to approach steady-state after 4-5 $t_{1/2}$.
- Time course of drug elimination : If a drug is stopped after an infusion, the Cp will decline to reach complete elimination after 4-5 $t_{1/2}$
- Drugs having long $t_{1/2}$ could be given once daily to improve patient compliance.

Steady-state plasma concentration Cpss

Definition → the steady level of drug in plasma achieved when the rate of administration equals the rate of elimination.

The rule of 5 →



- The Cpss is reached after 4-5 $t_{1/2}$
- If we changed the dose, the new Cpss is reached after 4-5 $t_{1/2}$
- If dosing stops, complete elimination of drug from plasma occurs after 4-5 $t_{1/2}$

Therapeutic drug monitoring TDM

Definition → Monitoring of serum drug concentration to optimize drug therapy.

- Serum drug samples are usually taken when the drug has reached th Cpss (e.g. at the trough level, just before the next dose)
- TDM can be done by monitoring drug effect rather than conc. e.g. in warafin therapy, TDM is done via monitoring the INR (International norm)

Clinical significance:-

- To avoid toxicity in the following situations:-
  - Drugs with a low 'therapeutic index' e.g. lithium (1-2 mg/ml), digoxin & warafin
  - Presence of disease states e.g. liver or renal dysfunction, that can affect the drug's pharmacokinetics.
- To improve efficacy of drugs having pharmacokinetic problems e.g. phenytoin & other drugs with non-linear kinetics.
- Differentiation between drug resistance & patient non-compliance.

Clearance as a channel of elimination

Definition → Plasma clearance of a substance means the volume of plasma cleared from this substance per minute

calculation →

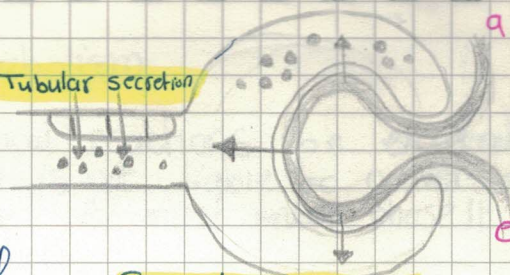
$$\text{clearance (Cl)} = \frac{0.693 \times Vd}{\text{Half-life } (t_{1/2})}$$

Clinical significance of renal clearance:-

If the drug is cleared by the kidney, clearance can help to determine whether this drug is eliminated by renal filtration or secretion: a drug that is eliminated only by filtration cannot exceed 127 ml/min
If clearance > 127 ml/min → drug is eliminated also by tubular secretion

Routes of elimination :-

- Kidney (the major route)
- Bile & liver.
- Lungs, intestine, milk, saliva & sweat



Clinical importance of knowing the route of elimination :-

Glumular filtration never exceeds 127 ml/min

- Help to adjust the dose to avoid cumulation.
- Avoid drugs eliminated by a diseased organ.
- Targeting therapy :- e.g → drugs eliminated by the lung could be used as expectorants.

Metabolism of drugs (biotransformation)

7

- The liver is the major site of drug metabolism but other organs can also metabolize e.g → kidneys, lungs, & adrenal glands.
- Many lipids soluble drugs must be converted into a water-soluble form (polar) to be excreted
- Some drugs are not metabolized at all & excreted uncharged (hard drugs)

water-soluble

Metabolism of drugs ~~may~~ lead to :-

- Conversion of active drug into inactive metabolites → termination of drug effect.
- Conversion of active drug into active metabolites → prolongation of drug effect.
  e.g → codeine (active drug) —metabolized to→ morphine (active product)
  opioids
- Conversion of inactive drug into active metabolites (prodrugs)
  e.g → enalapril (inactive drug) is metabolized to enalaprilat (active metabolites)
  *trigger tension
- Conversion of non-toxic drug into toxic metabolites
  e.g → paracetamol is converted into the toxic product N-acetylbenzo-quinone.

Biochemical reactions involved in drug metabolism

The drug must enter phase I of chemical reactions be excreted as water-soluble compound. If the drug is not liable to conversion into water-soluble compound by phase I, it must enter phase II to increase solubility & enhance elimination.

Phase I reactions

- Phase I reactions include oxidation, reduction & hydrolysis.
- Enzymes catalyzing phase I reactions include cytochrome P450, aldehyde & alcohol dehydrogenase, deminases, esterases, amidases & epoxide hydratases.
- The majority of phase I reactions is done by the cytochrome P450 (CYP450) enzyme system located primarily inside membranous vesicles (microsomes) on the surface of the smooth endoplasmic reticulum of parenchymal liver cells. CYP450 activity is also present in other tissue. e.g. kidney, testis, ovaries & GIT
- Although this class has more than 50 enzymes, six of them metabolize 90% of drugs. The most important subfamily is CYP3A4 which is responsible for metabolism of over 50% of drugs.
- Genetic polymorphism of several clinically important CYP450 enzymes is a source of drug metabolism in humans.
- Drugs may be metabolized by only one CYP450 enzyme (e.g. metoprolol by CYP2D6) or by multiple enzymes (e.g. warfarin)
- Some drugs & environmental substances can induce (↑ activity) or inhibit certain CYP450 enzymes leading to significant drug interactions.
- Other examples of non-microsomal oxidation include xanthine oxidase (converts xanthine to uric acid) & monoamine oxidase MAO (oxidizes catecholamines & sertonin). Only the microsomal enzymes are subjected to induction or inhibition by drugs.

Microsomal enzyme induction

- Microsomal inducers ↑ rate of metabolism of some drugs leading to ↓ their serum levels & therapeutic failure
- Induction usually requires prolonged exposure to the inducing drug.
- Examples of inducing agents:- phenytoin (epilepsy), phenobarbitone (epilepsy), carbamazepine, rifampicin (TB), smoking, chronic alcohol intake, St john's wort.
- Clinical examples:-
  - Rifampicin accelerates metabolism of contraceptive pills leading to failure of contraception.
  - Phenytoin (epilepsy) accelerates metabolism of cyclosporine-A leading to graft rejection.

Microsomal enzyme inhibition

- Microsomal inhibitors ↓ rate of metabolism of some drugs leading to ↑ their serum levels & toxicity.
- Enzyme inhibition can occur after short period of exposure to the inhibiting drug.
- Examples of inhibiting agents:- macrolides antibiotics (eg. erythromycin), ciprofloxacin, cimetidine, ketoconazole, ritonavir, grapefruit juice.
- Clinical examples:-
  - Ciprofloxacin inhibits metabolism of warfarin (anticoagulant) leading to accumulation of warfarin & bleeding.
  - Erythromycin inhibits metabolism of theophylline leading to toxicity of theophylline (cardiac arrhythmia).

Phase II reactions (conjugation)

- It involves coupling of a drug or its metabolite to water-soluble substrate (usually glucuronic acid) to form water-soluble conjugate.
- Glucuronyl transferase → is a set of enzymes that responsible for the majority of phase II reactions. This set of enzymes is also located inside liver microsomes & is the only phase II reaction that is inducible by drugs & is a possible site of drug interactions e.g. phenobarbital includes glucuronidation of thyroid hormone & reduces their plasma level.
- Some glucurnoide conjugates secreted in bile can be hydrolyzed by intestinal bacteria & the free drug can be reabsorbed again (enterohepatic circulation), this can extend the action of some drugs.

- other examples of non-glucuronide conjugation reactions include sulphate conjugation (steroids), glycin conjugation (salicylic acid) & glutathione conjugation (ethacrynic acid).

First-pass metabolism (pre-systemic elimination)

Definition → metabolism of drugs at the site of administration before reaching systemic circulation

e.g →
- the liver after oral administration
- the lung after inhalation.
- the skin after topical administration ....

Hepatic first-pass metabolism:-

- Complete → lidocaine
- partial → propranolol, morphine, nitroglycerine.
- None → atenolol & mononitrates.

How to avoid ? * By increasing the dose of the drug.
* By giving through other routes e.g → sublingual, inhalation, IV...

Bioavailability

Definitions → It is the fraction of the drug become available for systemic effect after administration
- The bioavailability of drug given i.v is 100 %

Factors affecting bioavailability:-
* Factors affecting absorption
* Factors affecting metabolism.
* First-pass metabolism.

Part 4 Adverse drug reaction (ADR)

An ADR is any response to a drug which is noxious, unintended, & occurs at doses used in man for prophylaxis, diagnosis or therapy.

Predisposing factors :-

- Multiple drug therapy.
- Associated disease :- eg→ impaired renal or hepatic function
- Genetics :- can affect the pharmacokinetics.
- Extreme of age : due to age related changes in pharmacokinetics & dynamics.

Classification :-

Type A (Augmented)

These reactions are predictable from the known pharmacology of the drug. They may result from an exaggerated response (eg→ hypotention from an antihypertensive) or non-specificity (eg→ anticholinergic effects with tricyclic antidepressants)

prevention :-

- Take a careful history for predisposing factors.
- Use the smallest dose of the drug adequate for the desired effect.
- Adjust dosage to therapeutic end-points eg→ blood presure or INR.
- Adjust dosage to optimum plasma concentrations. eg→ digoxin
- Adjust dosage in relation to renal function, hepatic function, or other drugs.

Type B (Bizarre)

These are less common, less predictable, & may be severe. Examples are :-

- Immunologic → penicillin allergy.
- Genetic → haemolysis in G6PD deficiency.
- Disease → amoxycillin rash in glandular fever.
- Idiosyncratic → malignant hyperpyrexia in anesthesia.

Prevention :-

- Take a careful drug history, especially of allergies.
- Family history : allergies or genetic disease.
- Avoid drugs susceptible to ADRs in particular disease states eg→ clozapine in bone marrow depression.

	Type A	Type B
→	predictable	unpredictable
→	Dose-dependent	Dose-independent.
→	Hight incidence	Low incidence
→	May respond to dose adjustment	Generally need to stop the drug.

Drug-induced liver injury (DILI)

DILI accounts for up to 10% of all ADRs & may be fetal.
It may be classified into:-
According to time course: acute or chronic
According to mechanism: dose dependent, idiosynchralic or immune mediated
According to histological finding:- hepatocellular, cholestatic or mixed picture.

Hepatocellular (cytotoxic) DILI

- the drug or its metabolites affects parenchymal liver cells leading to cell necrosis & initiation of inflammatory process
- It may be ~~stoppy~~ spotty, zonal or diffuse
- Clinically it resembles viral hepatitis with ↑ALT & AST.

Comonon drugs:-
paracetamol - methyldopa - ~~amio~~
amiodarone - isoniazid - valproic acid.

Cholestatic DILI

- The drug or its metabolites affect the biliary canaliculi leading to narrowing or destruction of biliary passages.
- Clinically it resembles obstructive jaundice with pruritus & ↑ALP.

common drugs:-
Chloropromazine - sulfonylureas - oral contraceptive pills - anabolic steroids - macrolides - co-amoxiclav.

ADR on pregnancy

Key facts:-

- Fetal birth defects represent 2-3% of all births, the majority of which are related to drugs.
- Some fetal defects may be impossible to identify, or can be delayed.
  e.g. the use of diethylstilbesterol (estrogenic compound) during pregnancy is associated with development of adrenocarcinoma of girl's vagina at teen age.
- Three factors determine the risk of ~~teto~~ teratogenicity: dose of the drug, duration of administration, & stage of pregnancy.
- Most drugs with a MW > 1000 can cross the placental barrier.
- All drugs should be considered harmful until proven otherwise.

Mechanism of terabogenicity according to pregnancy stage:-

Before implantation (0-17 day), the defect is all-or-none
i.e → either death of embryo (abortion) or ~~none~~ no effect.

Early pregnancy (3-10 weeks), the most dangerous period
- the period of organogenesis.
- Selective interference can produce characteristic anatomical abnormality.
  e.g. aminoglycosides cause damage to 8th cranial nerve.

Late pregnancy
- Gross anatomical abnormalities are less liable to occur.
- Functional defects rather than anatomical abnormalities can occur especially in organs having delayed formation e.g. brain, testes, & bone.

Examples of terabogenic drugs.

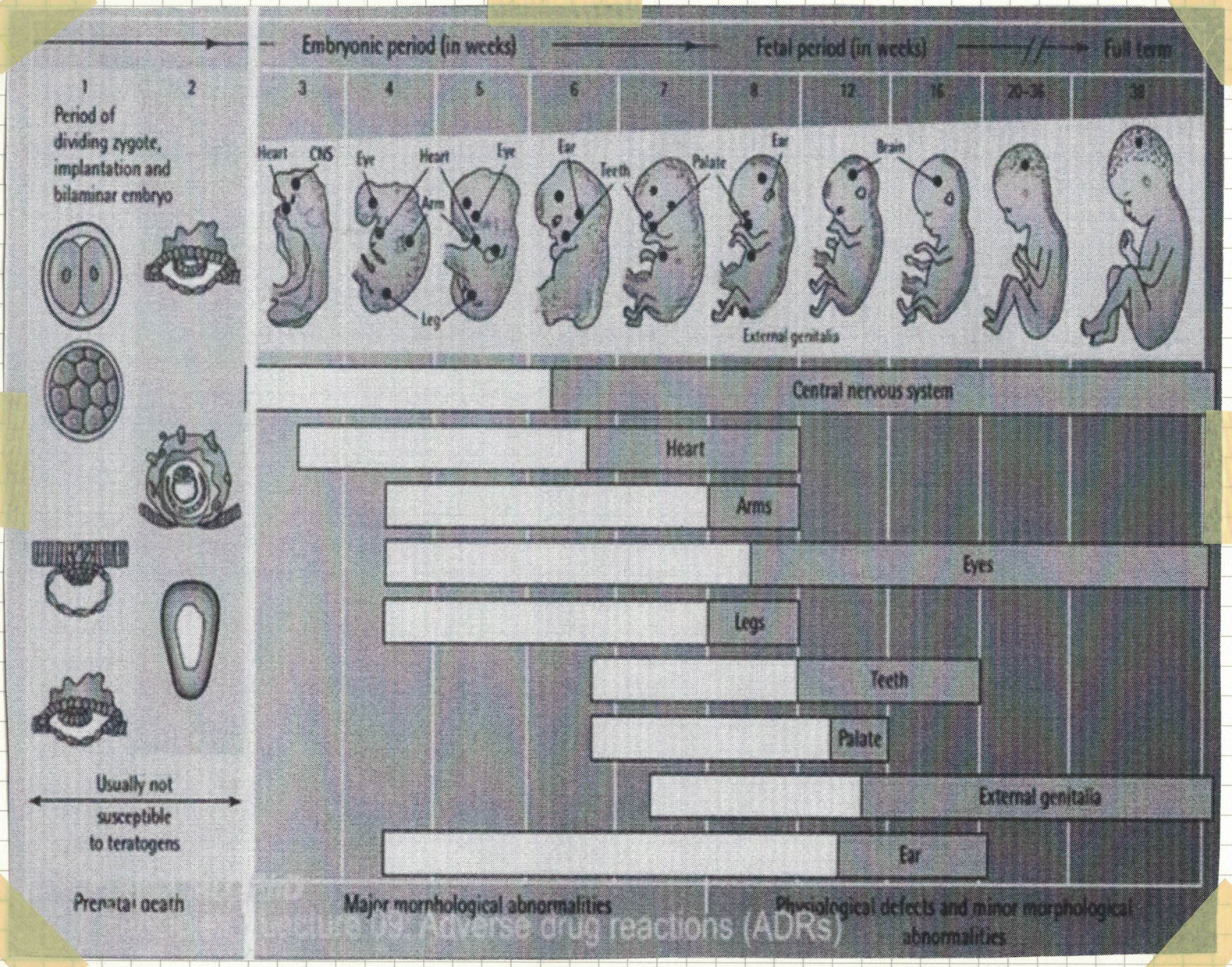
- **ACE inhibitors** → fetal pulmonary & renal dysfusion.
- **warfarin** → fetal intracerebral bleeding
- **Antiepileptic drugs** → neural tube defect (spina bifida).

The FDA pregnancy categories:

Category	Definition	Animal	Human
A	Adequate studies in animal and human did not show a risk to the fetus either in the first or in the late trimesters.	✓	✓
B	Animal studies did not show risk to the fetus but there are no adequate studies in human. or: Animal studies showed a fetal risk, but adequate studies in human did not show a risk to the fetus.	✓ ×	? ✓
C	Animal studies showed a risk to the fetus but there are no adequate studies in humans; the benefits from the use of the drug in pregnant women may by acceptable despite its potential risks.	×	?
		Benefit > Risk	
D	There is evidence of human fetal risk, but the potential benefit of the drug may outweigh its potential risk.	×	×
		Benefit > Risk	
X	Studies in animals and humans showed evidence of fetal risk. The potential risk of use in pregnant women clearly outweighs any potential benefit.	×	×
		Risk > Benefit	

→ cancer drug during pregnancy

→ Vit A



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