• **References:**

• Basic & clinical pharmacology by Katzung
• Lippincott’s illustrated reviews by Finkel, Cubeddu & Clark
• Clinical pharmacology by Laurence
Learning Objectives
At the end of pharmacokinetic lectures you should be able to

1. Describe the terms ‘therapeutic window’ and ‘therapeutic range.’
2. Describe the relationship between plasma level and therapeutic response.
3. List three reasons why there may be no simple relationship between plasma level of parent drug and magnitude of the therapeutic response.
4. Define the terms ‘clearance’ (CL), half-life’ (t½), volume of distribution’ (V), and ‘area under the curve’ (AUC) as they relate to drug kinetic.
5. State that: \( CL = Cl_{renal} + Cl_{hepatic} \), and be able to predict the consequence of change in either component on the plasma drug concentrations.

6. Predict the concentration of a drug immediately after i.v. administration, given an apparent \( V \) in litres from a text.

7. Draw a graph to depict the plasma level profile of a drug given by i.v. infusion, and identify the factors that determine the shape of this graph.

8. State that at steady state: Administration Rate = Elimination Rate
9. Define the term ‘bioavailability’ (F), state the use of AUC values to calculate F.

10. Explain the basis underlying zero-order and first-order kinetics of drug elimination from plasma. Give examples of drugs which are metabolized according to these kinetics.

11. Describe the relationship between pH, pKa, and degree of ionisation of acidic and basic drugs, and use this relationship to predict movements of drugs across membranes at various sites of the body.

12. List the factors that influence drug absorption from the skin, lungs, and muscle.
13. List the factors that determine the rate and extent of distribution of a drug.

14. Predict the distribution of a drug, given its volume of distribution.

15. Describe the 1- and 2-compartment models of drug distribution.

16. Describe the processes involved in reversible and irreversible binding of drugs to lipids, tissue proteins, and plasma proteins. Describe the effect of plasma and tissue binding of drugs on their distribution in the body.

17. Describe the mechanisms underlying placental transfer of drugs.

18. Describe the mechanisms underlying transfer of drugs across the blood-brain barrier.
19. Outline, with examples, the principal routes by which drugs may be metabolized.

20. Describe the physico-chemical consequences of drug metabolism.

21. Describe the pharmacological consequences of drug metabolism.

22. List, with examples, the factors that may modify the level of metabolism of a drug.

23. Describe the processes involved in biliary excretion of drugs, and give examples of drugs excreted principally by this route.

24. Define the term ‘enterohepatic recirculation’ of drugs, and indicate its possible consequences on pharmacological action.

Give examples of drugs eliminated in the expired air and milk.
25. Describe the processes involved in the excretion of drugs in the urine.
26. Indicate how knowledge of the renal clearance of a drug may help in elucidating the renal handling of that drug.
27. Indicate the basis for determining modification of drug dosage in renal failure.

List the possible causes for inter-individual variation in drug response.

28. Describe, with examples, the pharmacokinetic and pharmacodynamic bases underlying drug-drug interactions.
30. Describe the phenomenon of genetic polymorphism as it relates to drug treatment.

31. Describe the mechanisms underlying the genetic polymorphism in the metabolism and effects of suxamethonium, isoniazid, and CYP2D6 substrates.

32. Describe the mechanism underlying the genetic polymorphism in erythrocyte glucose-6-phosphate dehydrogenase activity as it relates to oxidant drugs.

33. Describe the phenomenon of drug-induced malignant hyperthermia.
• **PHARMACOKINETIC INTERACTIONS:**

• Means the way in which the body handles the drug(s) by means of

• (Absorption → Distribution → Metabolism → Elimination) (Abb. ADME)
ORDERS OF REACTIONS CAN BE DIVIDED INTO:

1) 1ST ORDER REACTIONS (PROCESSES OR KINETICS):

- Drugs taken into the body are subjected to absorption, distribution, metabolism and elimination.
- In most instances, the rate at which the above processes (ADME) occur are PROPORTIONAL TO THE CONCENTRATION OF THE DRUG (high at high concentration of drug and falls in proportion at low concentration).

So, processes for which rate is proportional to concentration are called "FIRST ORDER".
2) **ZERO ORDER KINETICS:**

- As the amount of drug in the body rises, any metabolic processes that have limited capacity become "saturated", (I.e. the rate of the process reaches a maximum amount at which these processes remain constant).

- And this may happen due to the "limiting amount of enzymes" (i.e. no more enzymes are available to react).

- Further increase in the rate is impossible after saturation despite the increase in dose of the drug.
• So, THE RATE OF REACTION IS NOT PROPORTIONAL TO DOSE OR CONCENTRATION (A RATE-LIMITED OR DOSE-DEPENDENT OR ZERO-ORDER PROCESS) DUE TO "SATURATION".

• It takes place with certain drugs especially these used at high doses for example: "Aspirin" and "Ethanol".

• Enzyme-mediated metabolic reactions are the most likely to show rate limitation (enzyme saturation).
Example on 1st and 2nd order: Alcohol (Ethanol):
- Rate of Metabolism = 10 ml/hr. or 8 gm. /hr. for a 70 kg person.
- Half-life = 1 hr. at plasma concentration below 10 mg/dl = (2/3 glass of wine)
- If a 70 kg man drinks 1/2 bottle of Scotch whiskey = 375 ml (40% alcohol) = 150 ml pure alcohol
- Then, alcohol concentration in blood = 250 mg/dl
- If metabolism is 1st order (t_{1/2} = 1 hr.)
- Next morning (8:00 am) he would've less than 1 mg/dl
- But alcohol is subjected to zero-order kinetics due to enzyme saturation, so metabolizing 10 ml/hr.
- After 8 hours leaving 70 ml alcohol in blood = 120 mg/dl
- Legal limit = 80 mg/dl
- The figure below shows plasma concentration-time curve for a drug given IV and orally.
• **STEADY STATE:**
  • A state of equilibrium reached when drug doses are given repeatedly over a period of time (when the amount of drug absorbed equals that eliminated from the body).
  
  • The time taken to reach steady-state is $4-5 \ t_{1/2}$
  • If a drug given IV (single dose), plasma concentration will rise quickly as the drug enters blood to reach a peak.
  • Then, there will be a sharp drop in concentration (**drug distribution phase**).
  • Then, followed by steady decline as the drug is removed from blood by liver
  • and kidney (**drug elimination phase**).
The figure below shows plasma concentration after repetitive administration of equal doses at equal time intervals.
In case of multiple dosing (each half life) as in above figure, so with the passage of each half life period of time, the plasma concentration rises by half the difference between the current concentration and the ultimate steady-state (100%) concentration.
• In 1Xt₁/₂ concentration will reach 100/2 = 50%
• In 2Xt₁/₂ {50+50/2} = 75%
• In 3Xt₁/₂ {75+25/2} = 87%
• In 4Xt₁/₂ {87+12.5/2} = 93%
• In 5Xt₁/₂ {93+6.5/2} = 96.87% of the ultimate steady-state.

• When dosing stopped,
• Starting at 100%:
• In 1Xt₁/2 plasma concentration falls to 50% {100/2}
• In 2Xtl/2 50/2 = 25%
• In 3Xtl/2 25/2= 12.5%
• In 4Xtl/2 12.5/2= 6.25%
• In 5Xt₁/₂ 6.25/2= 3.125% of the original steady-state.
• If the elimination process is 1st order, then the time taken for any concentration point \{value\} in the elimination phase to fall to half its value is always the same.

• i.e. the half life or half time \( t_{1/2} \) is the time taken for the plasma concentration to fall by half is "constant".
Changes in plasma conc. following an IV bolus injection of a drug in the elimination phase.
• **HALF-LIFE (T_{1/2}):**
  • It represents the time required to attain 50% of the steady-state or to decay 50% from the steady-state condition after a change (starting or stopping) in a particular rate of a drug administration.

• **FACTORS AFFECTING HALF-LIFE:**
  • Rate of drug metabolism (inversely).
  • Rate of drug excretion (inversely).
  • Storage in tissues (directly).
  • Protein binding (inversely).
• **CLINICAL IMPORTANCE (APPLICATIONS) OF $T_{1/2}$:**

  • $T_{1/2}$ is only important when drug concentration is closely related to pharmacological effect.

  • So, $t_{1/2}$ is useful for drugs such as Morphine, Theophylline and Phenytoin in which drug concentration is closely related to the pharmacological effect. [i.e. it can be used to predict the maximal effect both on initiation of therapy and on changing dose regimes.

  • Similarly, when a drug is discontinued the decay in response can be estimated.

  • But half-life may be of less value in drugs like: Prednisolone and Diazepam in which the effect is poorly related to the drug concentration.
Thank you