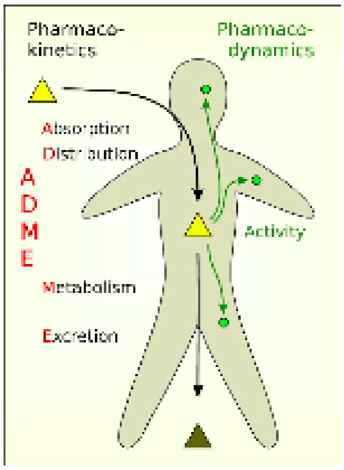
Introduction to Pharmacokinetics (PK) and Pharmacodynamics (PD)



Pharmacokinetics

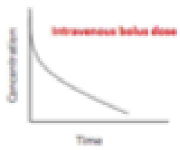
- What the body does to the drug, the study of drug absorption, distribution, metabolism and excretion

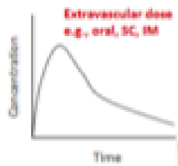
Pharmacodynamics

- What the drug does to the body, biochemical and physiological effects of drugs, relationship between drug concentration and drug effect
- Drug action

Impact of Different Routes of Administration on Drug Disposition and Action

- Different routes of administration and dosage form lead to different
    - Concentration- time profiles
    - Onset of action
    - Duration of therapy
    - Location of effect
    - Ease of administration
    - Cost
- Is dependent on
    - Solubility
    - Stability
    - Availability
- Action
    - Both biochemical and physiological effects
    - Dependent on drug reaching drug receptors





Role of Pharmacokinetics and Pharmacodynamics in Drug Development and Medicines Regulation

- Pharmacodynamics and pharmacodynamics are the main considerations in drug development
- A drug must be safe (PK), effective (PD), non-toxic, be soluble etc.
- Pharmacokinetics are the biggest reason why drugs do not make it to the market

Affecting Drug Response

- Pregnancy
- Obesity
- Age
- Environmental factors
- Genetics
- Disease
- Drug interactions
- Drug adherence

Absorption, Distribution, Metabolism and Elimination (Pharmacokinetics)

Absorption

- The process where a drug enters the bloodstream
- Bioavailability is the measure of absorption, how much of the given drug makes it to the bloodstream, (a fraction)
- Drug formulation, route of administration etc. can impact absorption
- Incomplete or erratic absorption can lead to variability in drug effects

Distribution

- The process where a drug is spread across the body
- The drug may go to certain organs, or bind to proteins in the blood serum
- The volume of distribution (Vd), is a parameter used to measure the extent of distribution
- Variations in tissue distribution, blood flow etc. can lead to a different pharmacological effect

Metabolism

- The process where a drug is chemically altered to make it more water soluble, facilitating elimination
- Primarily done in the liver where enzymes like cytochrome P450 play a big role
- Genetic variance in such drug metabolising enzymes can alter how an individual metabolises drugs
- Can convert an active drug to an inactive form or produce active metabolites, which may have good or bad effects
- A drug's half life plays a part in metabolism

Elimination

- The process where a drug or its metabolites are removed from the body
- Done mainly through the kidney (urine) or liver (bile and ultimately stool)
- People with liver/kidney impairment fail to effectively eliminate drugs, meaning they may have drug accumulation, leading to an increased risk of toxicity
- The rate of elimination is described by the drug's half life
- Clearance (Cl); volume/time

How Pharmacokinetics Informs the Use of Different Brands of a Medicine

- If two drugs achieve the same drug concentration in the body they are considered bioequivalent
- Absorption rate (Cmax) and the extent of drug absorption (AUC) are the main contributors to bioequivalence

Pharmacokinetics

Pharmacokinetics

- Examines how drug concentration in different body parts is affected by route of administration, dosage form
- Important in drug development, accumulation, toxicity, distribution, etc.
- Has drug safety applications, therapeutic index; toxic dose/ effective dose.

$$TI = \frac{TD_{50}}{ED_{50}}$$

Key Pharmacokinetic Parameters

- Clearance (L/h)
  - Efficiency of elimination of a drug
  - The irreversible elimination from circulation
  - Volume of blood cleared per unit time
  - Cl (L/h) = dose (mg) / AUC (mg*h/L)
  - Elimination rate (mg/h) = Cl total (L/h) * [Drug] (mg/L)

$$\text{Cl (L/h)} = \frac{\text{Dose (mg)/}}{\text{AUC (mg.h/L)}}$$

- Volume of distribution (L,L/kg)
  - The extent of distribution, not real
  - The amount of drug in the body to the plasma concentration
  - Back calculated from initial drug concentration $_{plasma}C_0$ following given IV dose
  - V = dose (mg) / C_0 (mg/L)
  - Lipophilic drugs can traverse membranes
    - Apparent V_d greater than 3L
  - Hydrophilic drugs are trapped in the plasma
    - Apparent V_d approximately 3L

$$V = \frac{Dose(mg)}{C_0\left(\frac{mg}{L}\right)}$$

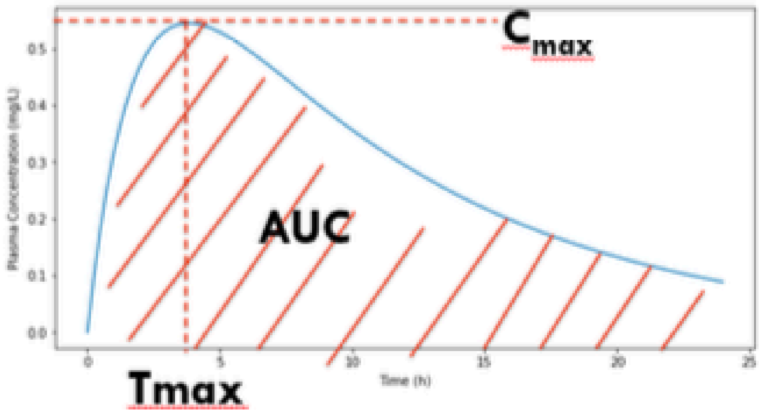
- Half-Life
  - Time to halve the amount of drug in the body
  - Determines by clearance and volume of distribution
  - K = Cl/ V_d

$$k = \frac{Cl}{Vd}$$

- Bioavailability
  - Fraction of drug that gets absorbed
  - Compared against IV infusion which is 100% bioavailable
  - F= AUC/100

- C max (concentration max), T max (time at concentration max), AUC (area under curve)
    - Calculate AUC using trapezoidal rule, Area = $(t_2 - t_1) \times c_2 - c_1 / 2$

Single Oral Dose Plasma-Time Curve

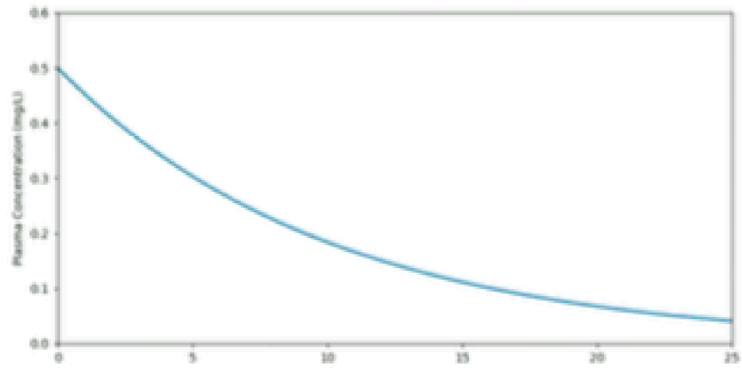


Rises when absorption is higher than elimination

Cmax when they are equal

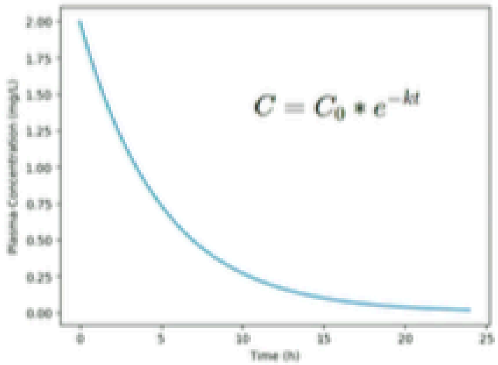
Falls when elimination is higher than absorption

Single IV Dose Plasma-Time Curve



First Order Kinetics

When a constant proportion of the drug is eliminated



Zero Order Kinetics

When a constant amount of the drug is eliminated