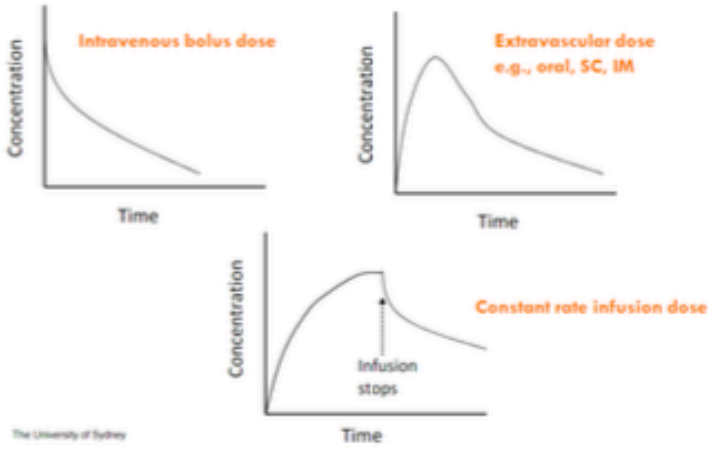
Introduction to Pharmacokinetics and Pharmacodynamics

Pharmacokinetics

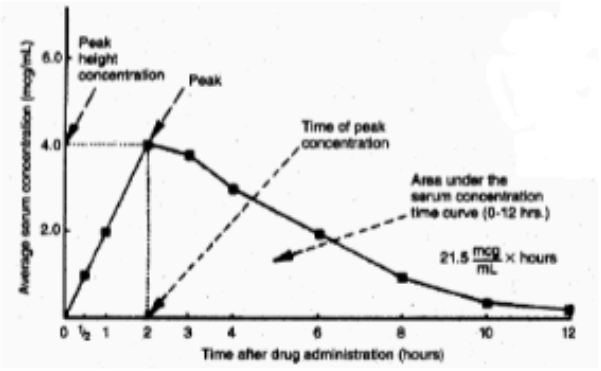
- What the body does to the drug, the disposition of a drug in the body
- How the body absorbs, distributes, metabolises and eliminates/excretes the drug
- Absorption
    - Different routes of administration lead to different rates of absorption and by extension, different concentration-time profiles
    - Choice of route of administration is dependent on
        - Time for effect to take place, is a rapid onset required?
        - Convenience
        - Physiochemical properties of the drug
        - Cost
        - Location of action, local vs. systemic
    - Bioavailability
        - Fraction of a dose absorbed
        - Determines the dose adjustment between different routes of administration
- Distribution
    - The drug in plasma and tissues
    - Volume of distribution, (volume e.g. L OR L/kg)
        - Extent of distribution
        - Determines the loading dose/initial dose
- Metabolism
    - The drug is made into metabolite (more water soluble), ready for elimination
- Elimination
    - Main routes of elimination are;
        - Renally cleared into the urine
        - Hepatic/biliary clearance into the stool
    - Clearance (volume/time e.g. L/H)
        - Efficiency of drug elimination
        - Determines the dose rate
        - Is cumulative, i.e. a drug can be cleared both renally and biliary, they add together to make total clearance
    - Half life ($t_{1/2}$) (time e.g. hours)
        - Determines how long a drug stays in the body, determines the frequency of dosing

Concentration- Time Relationship (PK)

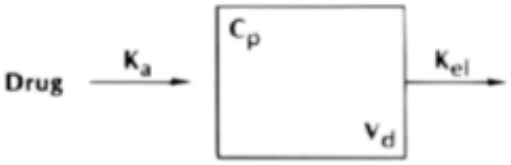


Mono-Exponential Pharmacokinetics

Relationship Between Drug Concentration and Time After Dose Administration



One Compartment Model (mono-exponential PK)

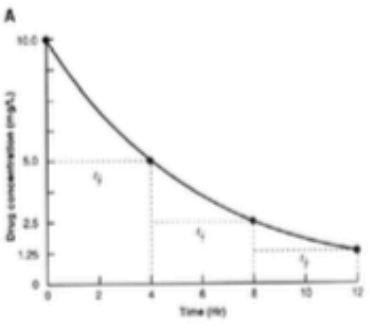


Cp is the drug concentration in plasma

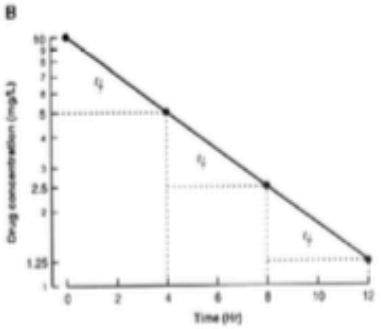
Vd is the volume of the compartment or volume of distribution

- Assumes the body is one compartment and all the drug is distributed instantaneously and uniformly throughout the entire compartment, there are no barriers within the environment
- Assumes the volume of each compartment remains constant
- Ka represents the rate that the drug is absorbed into the body (absorption rate constant)
- Kel represents the rate that the drug is eliminated from the body (elimination rate constant)
- Cp is plasma concentration of the drug, (Cp = A/V), amount/ volume, ($Cp = Cp^0 \times e^{-Kel \times t}$)
- Vd is volume of distribution, in a one-compartment model it is constant, Vd = dose/Cp^0
- Any decline in plasma drug concentration is only by elimination
- A one compartment model displays mono-exponential pharmacokinetics, first order output

Concentration-Time Profiles (First Order)



Linear Scale

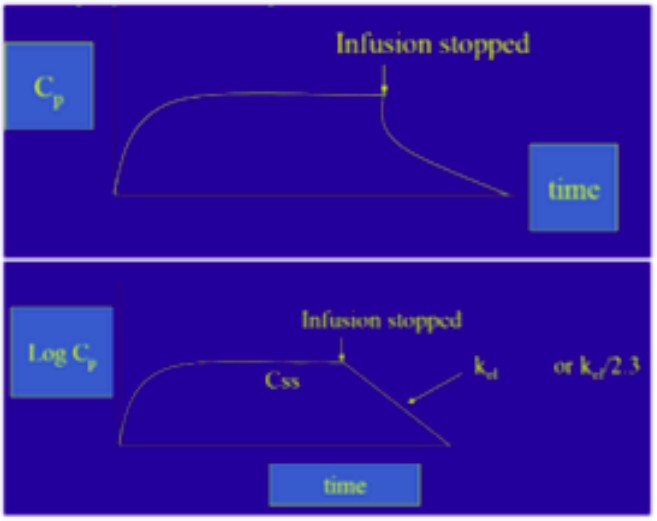


Semi-log Scale or Log-linear Scale

Intravenous Infusions

Intravenous Infusion

- Is a long term infusion
- Zero-order input and first-order output – both occurring at the same time
- There is a constant zero-order rate of input, this is good because
    - Drugs can be given with fluids, electrolytes or nutrients
    - The rate of infusion can be easily regulated to fit individual needs
    - A constant rate of input prevents fluctuations



Linear Scale

Semi-log Scale

Steady State Concentration

- When you first administer a drug,
    - The input rate is more than the elimination rate
    - As plasma concentration increases, the elimination rate also increases
    - Eventually, the elimination rate reaches a maximum equal to the infusion rate
    - Here, steady state concentration has been reached
    - Input rate = output rate
- You can not get to steady state concentration faster by increasing the input rate
- Steady state concentration is dependent on the half-life of the drug (4.3 half-lives)
- Input rate = steady state concentration x clearance
- Steady state concentration = input rate/ clearance

Plasma Concentration During Infusion

- Plasma Concentration = input rate/ (Vd x kel) x $(1-e^{-kelxt})$

Plasma Concentration After Infusion

- Plasma Concentration = plasma concentration (at end of infusion) x $e^{-kelxt'}$

Drug Metabolism - Hepatic Physiology

The Liver

- Maintains blood glucose
  - Glucagon causes the liver to release glucose
  - Insulin causes the liver to store glucose as glycogen
- Maintains/distributes cholesterol
  - Too much cholesterol may build up in blood vessels, the liver removes it via bile
  - If there is not enough cholesterol, the liver converts triglycerides to cholesterol
- Maintains pH levels
  - The liver accounts for 20% of the body's oxygen consumption and therefore produces bicarbonate – this is offset by urea synthesis which uses up bicarbonate
  - When the liver produces ketone bodies, it lowers blood pH
- Synthesis of amino acids
  - The liver synthesises most non-essential amino acids
  - Liver also breaks down amino acids and repackages it into urea
- Neutralisation of Neurotransmitters, Hormones and Drugs
  - The liver breaks down serotonin, oxytocin, oestrogen and testosterone etc.
- Produces ketone bodies, amino acids, albumin, transport proteins, coagulation factors etc.
- Distributes cholesterol and triglycerides
- Removes waste products
- Destruction of pathogens and old red blood cells
  - The liver destroys some bacteria and viruses
  - When the liver breaks down old reb blood cells, bilirubin is a byproduct
- Makes bile and synthesises bile salts
  - Produces 600mL to 1 L per day
  - Assists in the breakdown of fats in the gut
  - Bile is alkaline and helps to neutralise stomach acid
  - Biliary excretion – the removal of toxin/drug products from the blood into the bile and then removed from the body via the gut
- Hepatic Portal Vein
  - From the GI tract to the liver
  - Deoxygenated, nutrient rich and low pressure
- Hepatic Portal Artery
  - From the heart to the liver
  - Oxygenated and high pressure

Liver Failure

- Low blood sugar
- Bleeding easily
- Excess oestrogen
- Blood pressure changes
- Jaundice
- Infection
- Acidosis