CLINICAL PHARMACOKINETICS – TIME COURSE OF DRUG ACTION

6.1 CLINICAL PHARMACOKINETICS

- The underlying principle of clinical pharmacokinetics is that a relationship exists between the effects of a drug and the concentration of drug in the body.
- In clinical pharmacokinetics we try to provide:

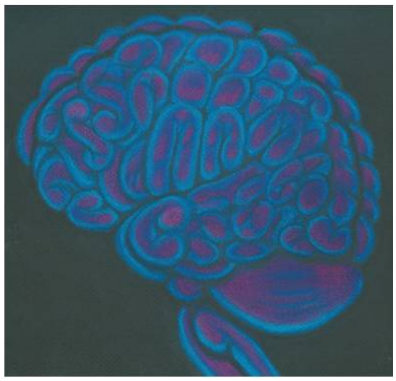
1) a quantitative relationship between drug dose and effect
2) a framework to interpret measurements of drug concentrations in biological fluids to benefit patient drug therapy.

- The most important parameters determining drug disposition in humans are:

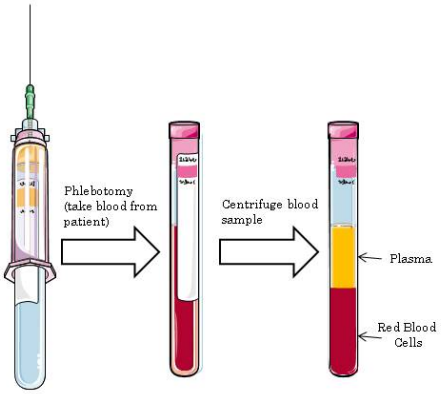
1) Clearance – the body's efficiency in drug elimination.
2) Volume of Distribution – the **apparent** space in the body available to contain the drug.
3) Elimination Half Life ($T_{1/2}$) – a measure of the rate of removal of the drug from the body.
4) Bioavailability – the fraction of drug that reaches the systemic circulation unchanged.

6.2 PLASMA DRUG CONCENTRATIONS

Measuring Drug Concentrations



- Ideally drug concentrations would be measured from the site of action.
- In reality, this is not feasible.
- Let's take the example of drugs used to treat schizophrenia. These drugs act in the brain.
- Clearly taking a sample from a patient's brain to measure drug concentrations is invasive and would likely do more harm than good.

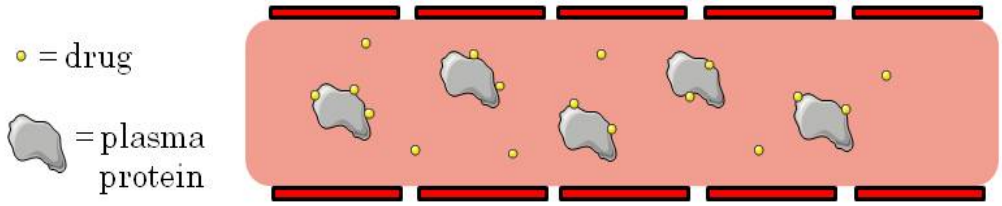


- In reality drug concentrations are usually measured in plasma.
- Plasma is a good site to measure drug concentrations because:

1) It is relatively non-invasive.
2) For most drugs there is a good correlation between plasma concentration and therapeutic and toxic drug effects.

Free vs. Total Plasma Drug Concentration

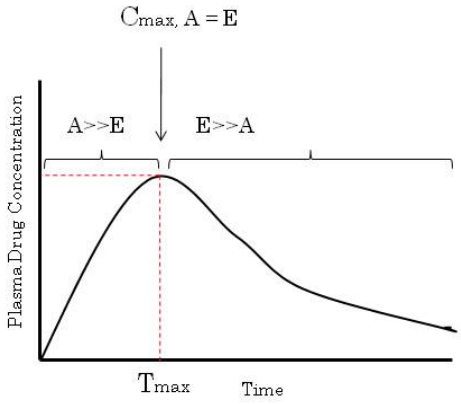
- Recall that drugs in plasma exist as bound to plasma proteins or free.
- It is only free drug that is able to elicit a pharmacological response.
- In theory, measuring free drug concentration would be ideal to guide drug dosing.
- In reality, measuring free drug concentration is difficult and tedious so total (free + protein bound) concentration is usually measured.
- For most drugs, measuring total plasma concentration provides enough information to guide drug dosing.



6.3 DRUG CONCENTRATION TIME CURVES

Oral Administration

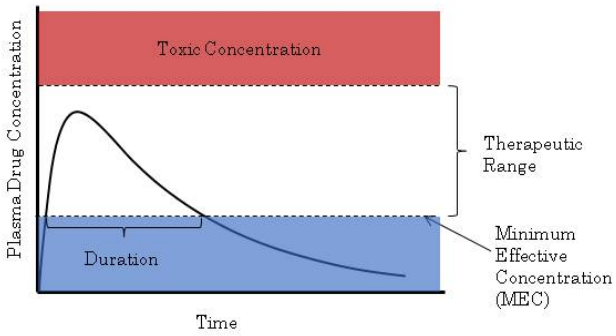
- When a drug is administered orally it must be absorbed into the blood.
- At the beginning, the rate of drug absorption is greater than the rate of drug elimination so plasma drug concentrations increase.
- At a later time, the rate of absorption equals the rate of elimination. This is the peak of the concentration time curve and is called the Cmax.
- After the Cmax, the rate of elimination is greater than the rate of absorption so the concentration begins to decline.



A = Absorption
E = Elimination

Characteristics of Plasma Concentration Time Curves

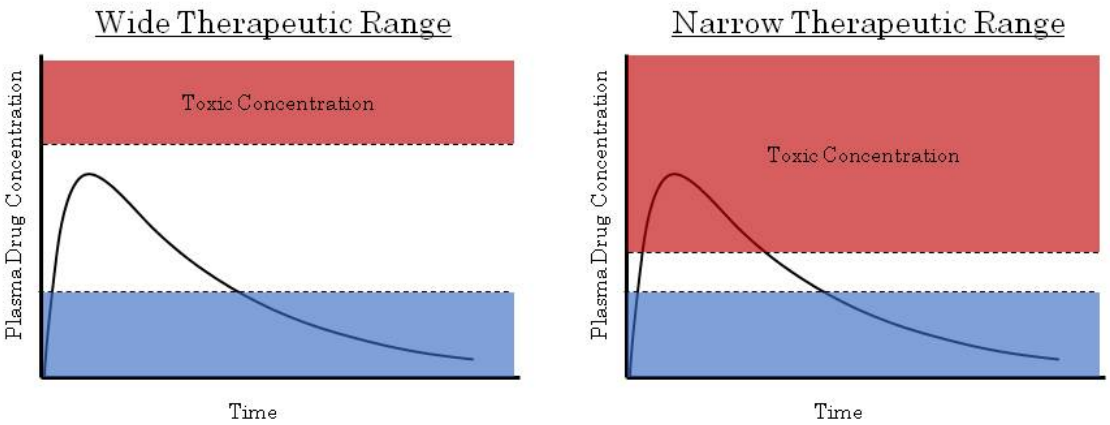
- Plasma drug concentrations must be high enough to have a therapeutic effect but not so high as to induce toxicity.
- **Minimum Effective Concentration (MEC)**
  - The minimum concentration required to have a therapeutic effect. Drug concentrations below this level do not have a therapeutic effect.
- **Duration**
  - Length of time the drug concentration is above the MEC.
- **Toxic Concentration**
  - If plasma concentrations are too high, toxic side effects will occur.



- **Therapeutic Range**
  - Drug concentrations above the MEC but below toxic concentrations. The goal of pharmacotherapy is to attain plasma concentrations in the therapeutic range.

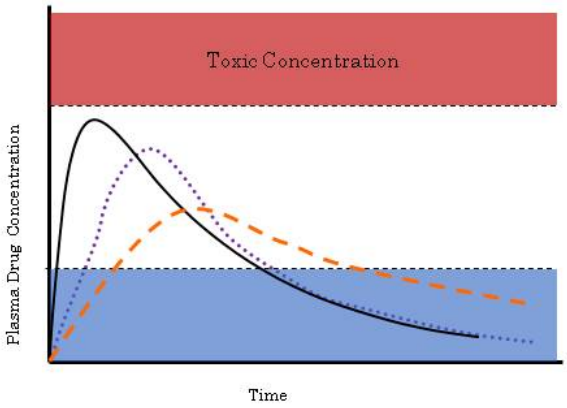
Therapeutic Range

- The width of the therapeutic range is an index for how safely a drug can be used.
- Drugs with a narrow therapeutic range are difficult to administer safely since there is only a narrow window where the drug will be effective and not toxic.
- Drugs with a narrow therapeutic range often undergo therapeutic monitoring to ensure that drug concentrations are within the target range.
- **NOTE** Therapeutic Range may also be referred to as the therapeutic window.



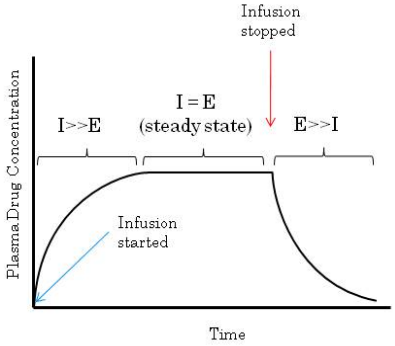
Onset of Action

- Drugs given orally are subject to a lag time before they reach the MEC.
- The lag time varies between different drugs.
- The rate and extent of absorption affect the onset of action.
- The onset of action determines how soon a drug's effect will occur.



Continuous Intravenous Infusion

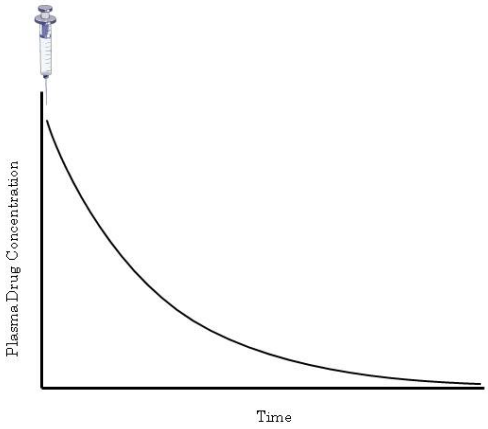
- In continuous intravenous infusion, the rate of drug entry into the body is constant.
- Using intravenous administration there is no drug absorption as the drug directly enters the systemic circulation.
- After initiation of the infusion, the plasma concentration rises until the rate of elimination equals the infusion rate.
- When the rate of elimination equals the infusion rate, the plasma drug levels do not change over time. This is referred to as steady state.
- When the infusion is stopped, plasma drug concentrations decrease.



I = Infusion rate
E = Elimination rate

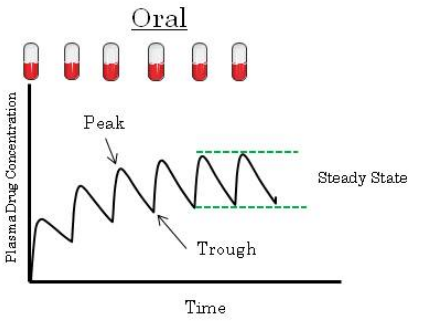
IV Bolus

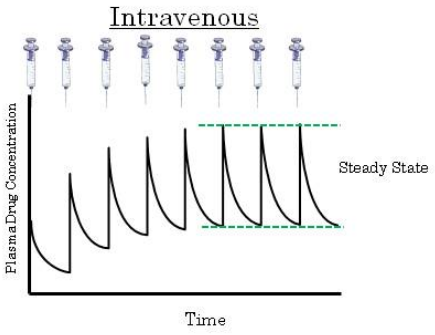
- For IV bolus, the drug is rapidly injected directly into the blood.
- After the drug is injected it quickly distributes.
- Once distributed the drug is eliminated over time.
- The elimination of a drug usually follows first order kinetics, a concept introduced in Module 4. This means that the rate of elimination is dependent on the blood concentration. The higher the blood concentration, the greater the rate of elimination.



Repeated Dosing

- When patients take repeated dosing of drugs, accumulation occurs.
- Repeated dosing of drugs results in accumulation in the body until a plateau is reached. This plateau is called steady state.
- When drugs are repeatedly administered orally or as an IV bolus, drug concentrations fluctuate. The high level is referred to as the peak, and the low level referred to as the trough. The goal of drug therapy is for the fluctuations at steady state to be within the therapeutic range.
- Steady state is reached when the peak and trough concentrations are the same between doses.
- For drugs with a narrow therapeutic range, therapeutic drug monitoring is performed by taking a trough blood sample and measuring the drug concentration.

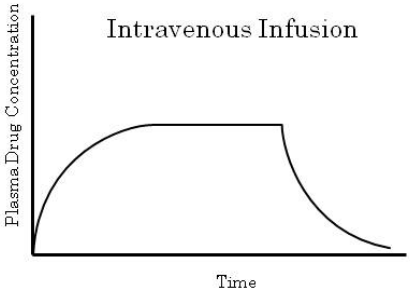


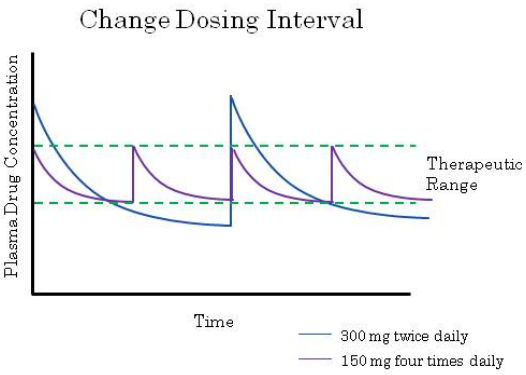


Reducing Fluctuations in Plasma Drug Concentration

- There are 3 ways to reduce fluctuations in plasma drug concentrations:

1) **Use continuous IV infusion**
   This method allows constant drug levels (no peaks and troughs). Unfortunately this is usually not feasible.
2) **Use depot preparations**
   Depot preparations (*see module 2*) release drug at a slow and constant rate. This minimizes peaks and troughs.
3) **Change the dosing interval**
   Giving the same total daily dose multiple times per day reduces the size of peaks and troughs.





6.4 PHARMACOKINETIC PARAMETERS

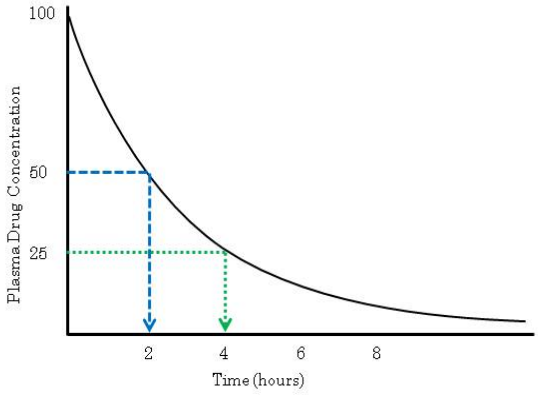
Clearance (Cl)

- Describes the efficiency of irreversible drug elimination from the body.
- Clearance is the volume of blood cleared per unit of time and is usually expressed as mL/min or L/hr.
- Clearance can be discussed by route of elimination (i.e. renal clearance, hepatic clearance etc).
- Total clearance is the sum of the clearance by all routes.
- Total drug clearance is important because it determines the dosage rate required to maintain a certain blood concentration of a drug.
- The relationship between drug concentration and clearance is:

$$\text{Dosing rate} = \text{Plasma Concentration} * \text{Clearance}$$

Half Life ($T_{1/2}$)

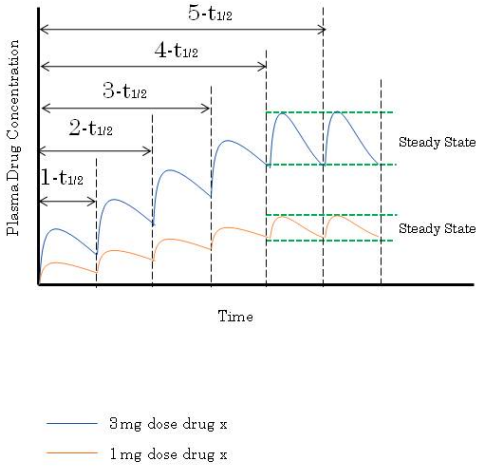
- Half life is the time it takes for the plasma drug concentration to decrease to 50%.
- Half life is related to the volume of distribution (Vd) and clearance (Cl) by the following equation:
  - $T_{1/2} = \frac{0.693 * Vd}{Cl}$
- Knowing a drug's half life is important in determining how long it takes to get to steady state and how long it will take for drug levels to decline once we stop administering the drug.



6.5 STEADY STATE PLASMA CONCENTRATION

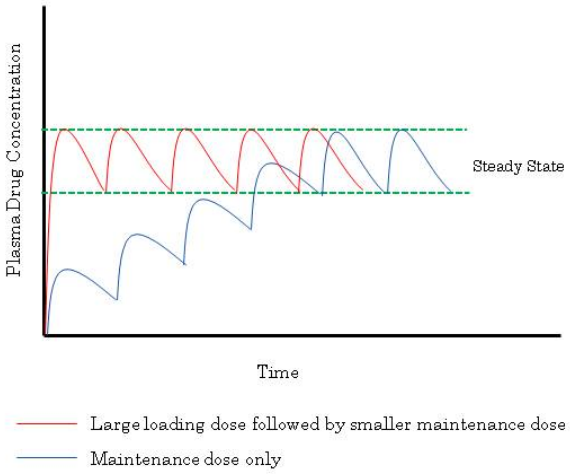
Time to Steady State

- When the same dose of a drug is administered repeatedly, it takes approximately 5-half lives to reach steady state.
- If the dose of drug remains constant, the time to reach steady state is independent of the size of the dose.
- This means that it will take the same time for a 3 mg dose of drug X and a 1 mg dose of drug X to reach steady state.
- However, the 3 mg dose of drug x will have higher steady state concentration than the 1 mg dose.



Loading Dose

- If a drug has a long half life, it can take a long time for a patient to reach steady state.
- For example, a drug with a half life of 24 hours (1 day) will take 120 hours (5 days) to reach steady state concentrations.
- To avoid this delay, large loading doses may be given to get patients to steady state quickly.
- Smaller maintenance doses are then administered to keep plasma drug concentrations at steady state.
- The loading dose may be calculated as:



Loading dose = target drug plasma concentration * Vd

**NOTE: this assumes 100% bioavailability

Decline from Steady State

- The time it takes for plasma concentrations to decline from steady state is dependent on a drug's half life.
- The time it takes for a drug to decline from steady state is independent of the dose.
- It takes 5 half lives for most of a drug (97%) to be eliminated from the body.
- It takes 9 half lives to eliminate every molecule of drug from the body. This is especially important when a patient is experiencing an allergic reaction.