Pharmacokinetics (PK)

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Pharmacokinetics

- Pharmacokinetics refers to what the body does to a drug, it consists of:
- **Absorption:** First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.

- **Distribution:** Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.

- **Metabolism:** Third, the drug may be biotransformed by metabolism by the liver or other tissues.

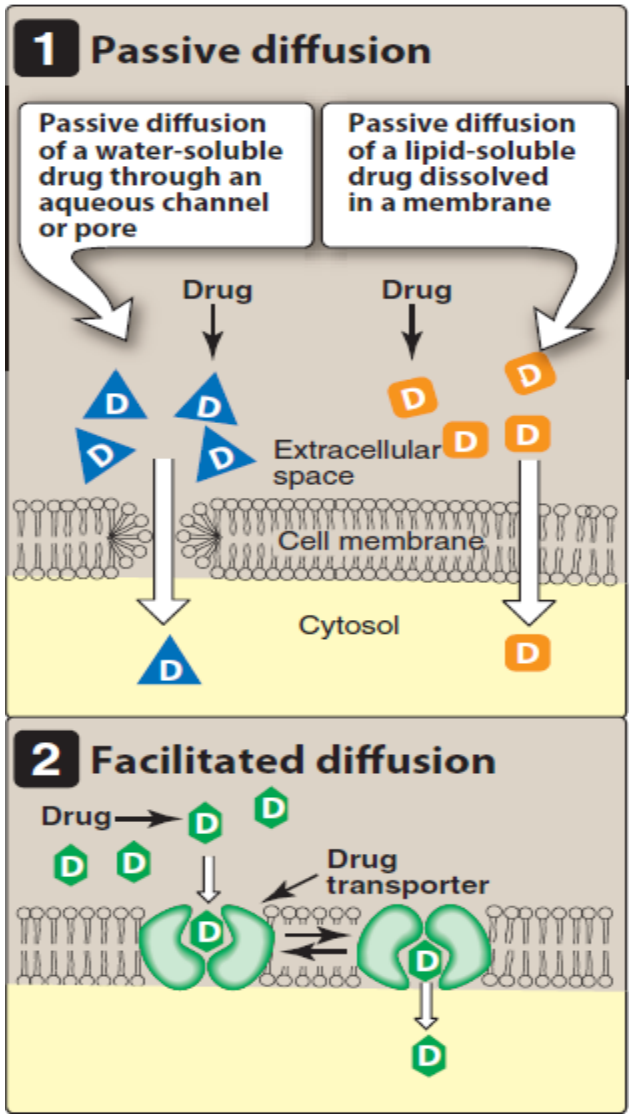
- **Elimination**: Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces

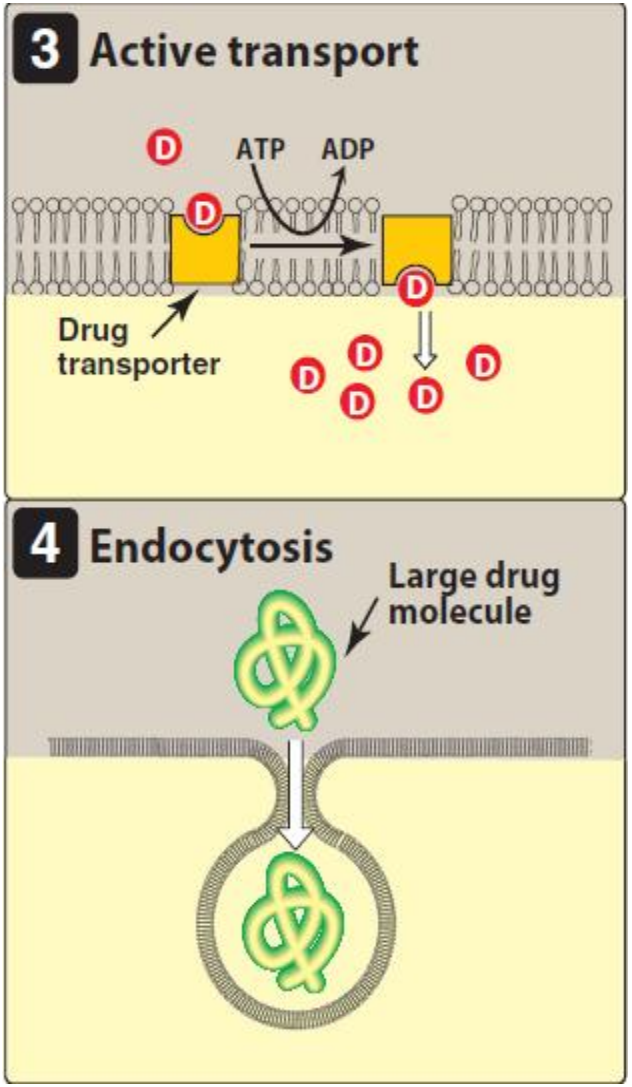
ABSORPTION OF DRUGS

- Absorption is the transfer of a drug from the site of administration to the bloodstream.

- The rate and extent of absorption depend on:
  - The environment where the drug is absorbed
  - Chemical characteristics of the drug
  - Route of administration

Mechanisms of absorption of drugs from the GI tract



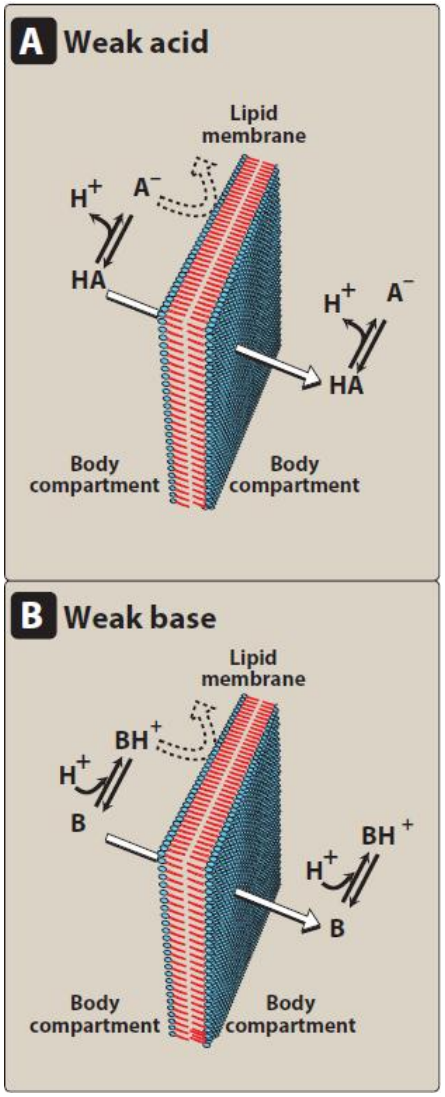


Factors influencing absorption

1. **Effect of pH on drug absorption:**

   Most drugs are either weak acids or weak bases.

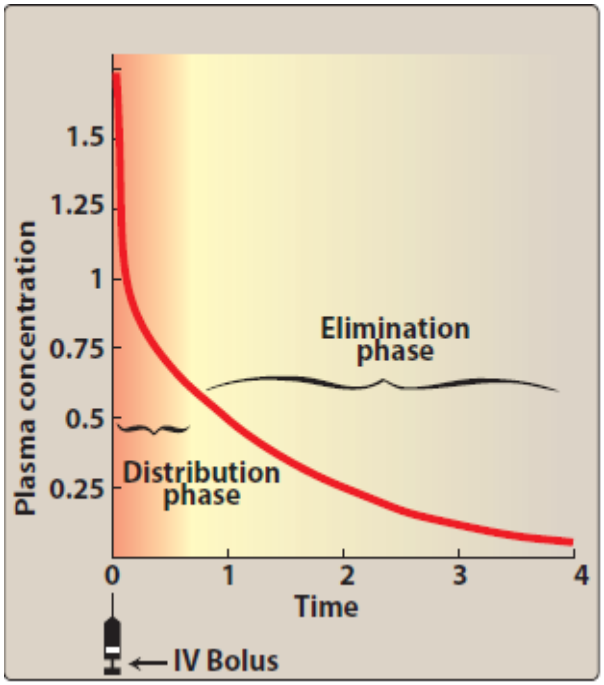
2. **Blood flow to the absorption site**
3. **Total surface area available for absorption**
4. **Contact time at the absorption surface**
5. **Expression of P-glycoprotein**



2. DRUG DISTRIBUTION

- It is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and the tissues.

- The distribution of a drug depends on:
  - Cardiac output and local blood flow
  - Capillary permeability
  - Tissue volume
  - The degree of binding of the drug to plasma and tissue proteins
  - Relative lipophilicity of the drug



Vd

- The apparent volume of distribution, Vd, is the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma.

$$V_d = \frac{\text{Amount of drug in the body}}{C_0}$$

- Vd is a useful pharmacokinetic parameter for calculating the loading dose of a drug

- Any factor that increases Vd can increase the half-life and extend the duration of action of the drug

Apparent Volume of Distribution (Vd)

- $Vd = \frac{\text{amount of drug in body}}{\text{plasma concentration}}$

- Loading dose = Vd x desired plasma concentration

- Plasma half-life: Time it takes for plasma concentration of a drug to drop to 50% of initial level.

3. **DRUG CLEARANCE THROUGH METABOLISM**

- Once a drug enters the body, the process of elimination begins.

- The three major routes of elimination are:
  - Hepatic metabolism
  - Biliary elimination
  - Urinary elimination

- Together, these elimination processes decrease the plasma concentration exponentially.
- A constant fraction of the drug present is eliminated in a given unit of time

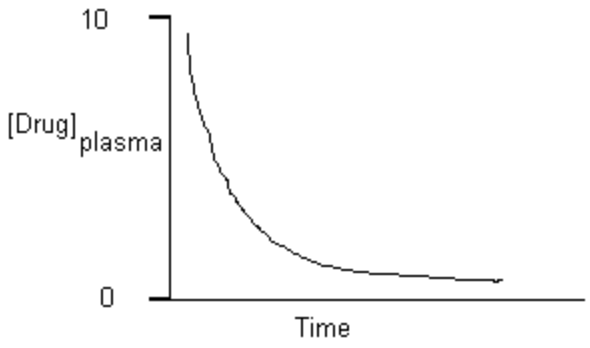
3. **DRUG CLEARANCE THROUGH METABOLISM**

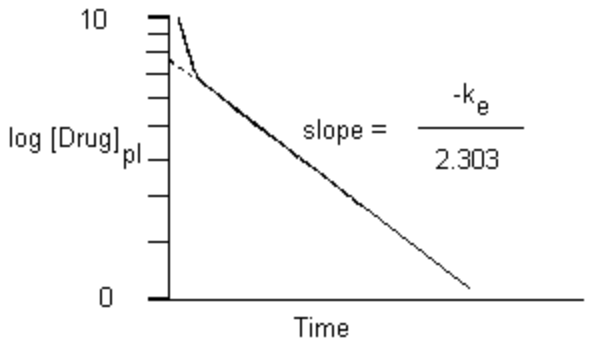
- Clearance: (CL) estimates the amount of drug cleared from the body per unit of time.
- Most drugs are eliminated according to first-order kinetics, although some, such as *aspirin in high doses, are eliminated according to zero-order* or nonlinear kinetics

First order kinetics

A constant ***fraction*** of drug is eliminated per unit of time.

When drug concentration is high, rate of disappearance is high.





Zero order kinetics

Rate of elimination is constant.

Rate of elimination is independent of drug concentration.

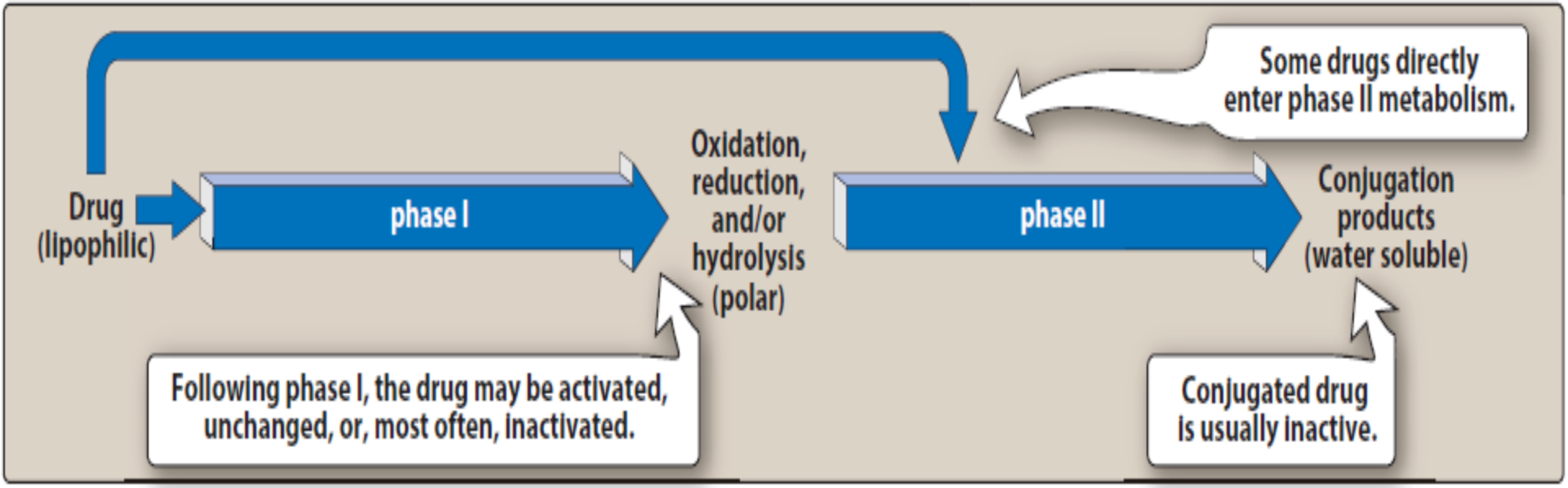
Constant *amount* eliminated per unit of time.

Example: Alcohol

Comparison

- First Order Elimination
  - [drug] decreases exponentially with time
  - Rate of elimination is proportional to [drug]
  - Plot of log [drug] or ln[drug] vs. time are linear
  - $t_{1/2}$ is constant regardless of [drug]
- Zero Order Elimination
  - [drug] decreases linearly with time
  - Rate of elimination is constant
  - Rate of elimination is independent of [drug]
  - No true $t_{1/2}$

3. DRUG CLEARANCE THROUGH METABOLISM

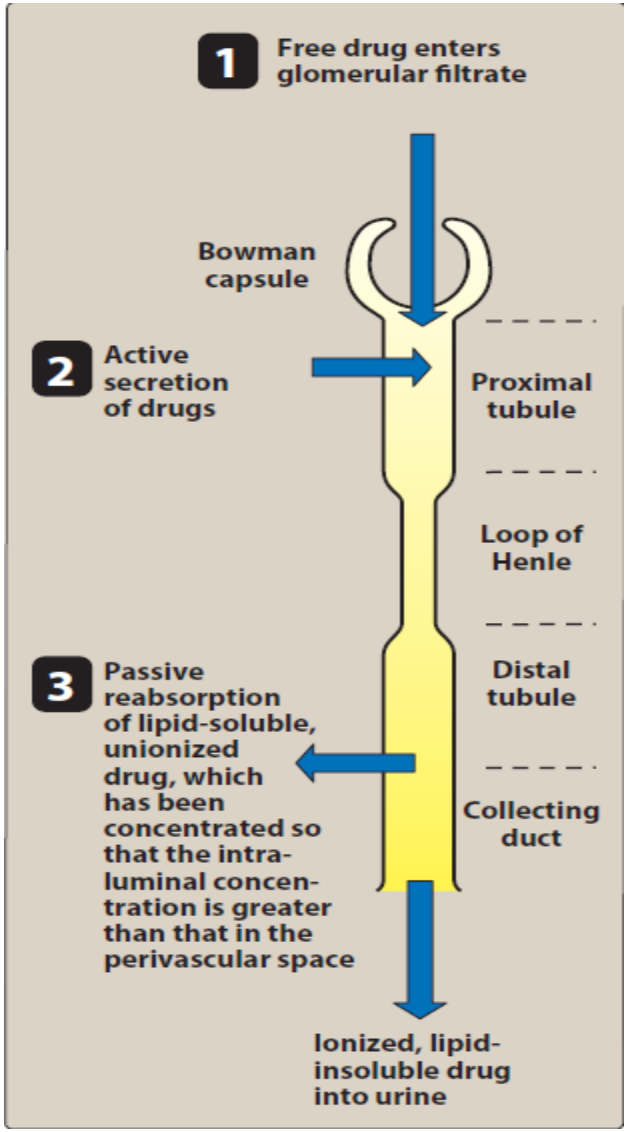


CYP450

- The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (xenobiotics)

4. **DRUG CLEARANCE BY THE KIDNEY**

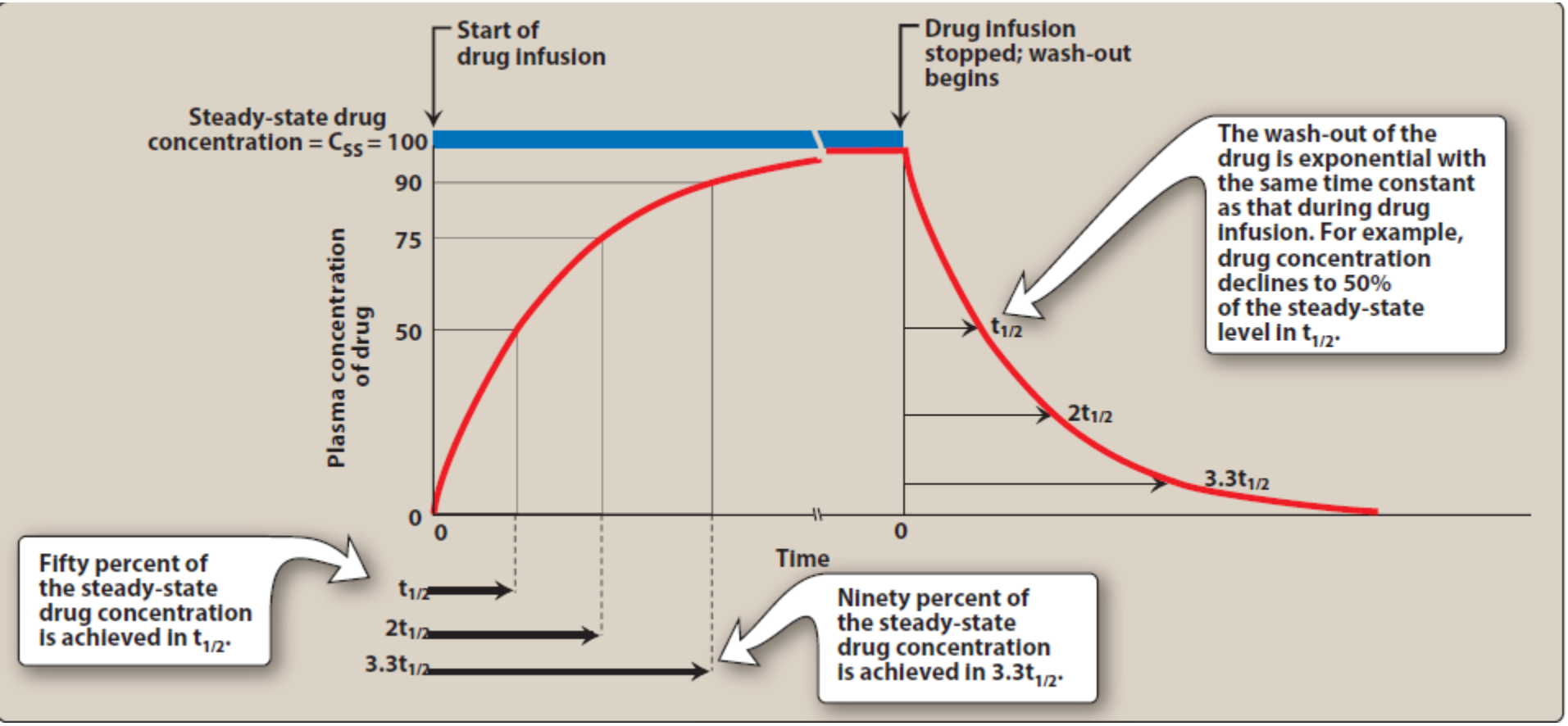
- Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes, the most important being elimination through the kidney into the urine

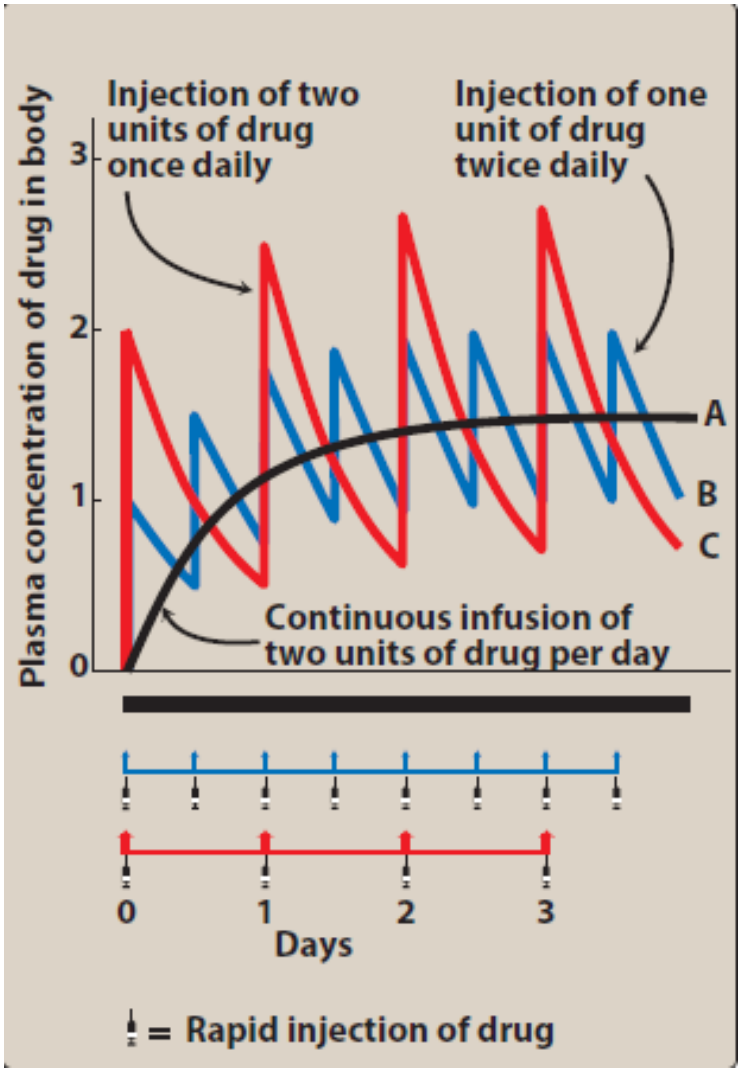


Dose Adjustment

- When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required.
- Patients who may have an increase in drug half-life include those with:
  - 1) Diminished renal or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage
  - 2) Decreased ability to extract drug from plasma, for example, in renal disease
  - 3) Decreased metabolism, for example, when a concomitant drug inhibits metabolism or in hepatic insufficiency, as with cirrhosis.

Steady State Concentration (Css)

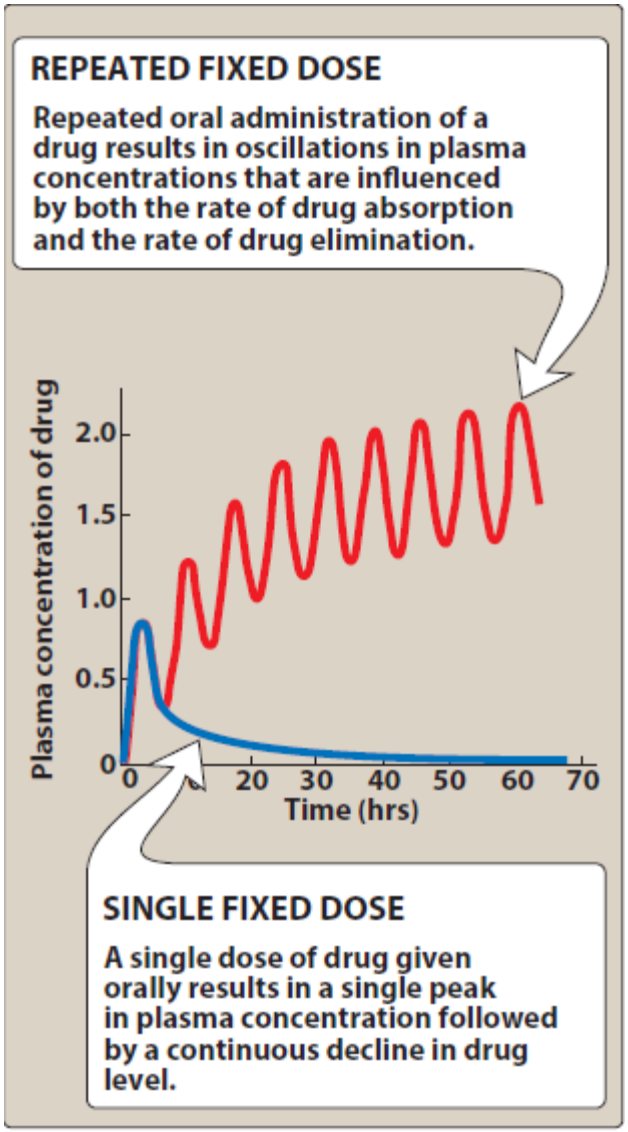


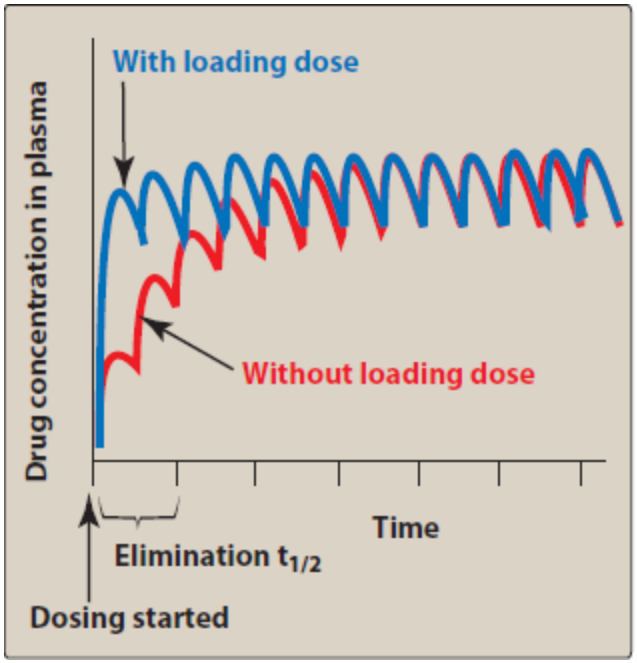


- Predicted plasma concentrations of a drug given by infusion **(A), twice-daily** injection **(B), or once-daily injection (C).**

Loading Dose

Loading dose = $(V_d) \times$ (desired steady-state plasma concentration)/F





$$\text{Dosing rate} = \frac{(\text{Target } C_{plasma})(CL)}{F}$$

Summery

- PK consists of 1.2.3.4
- For each of these elements there factors affecting them
- PK understanding is crucial for clinicians to design and adjust the dose regimen

Thank You