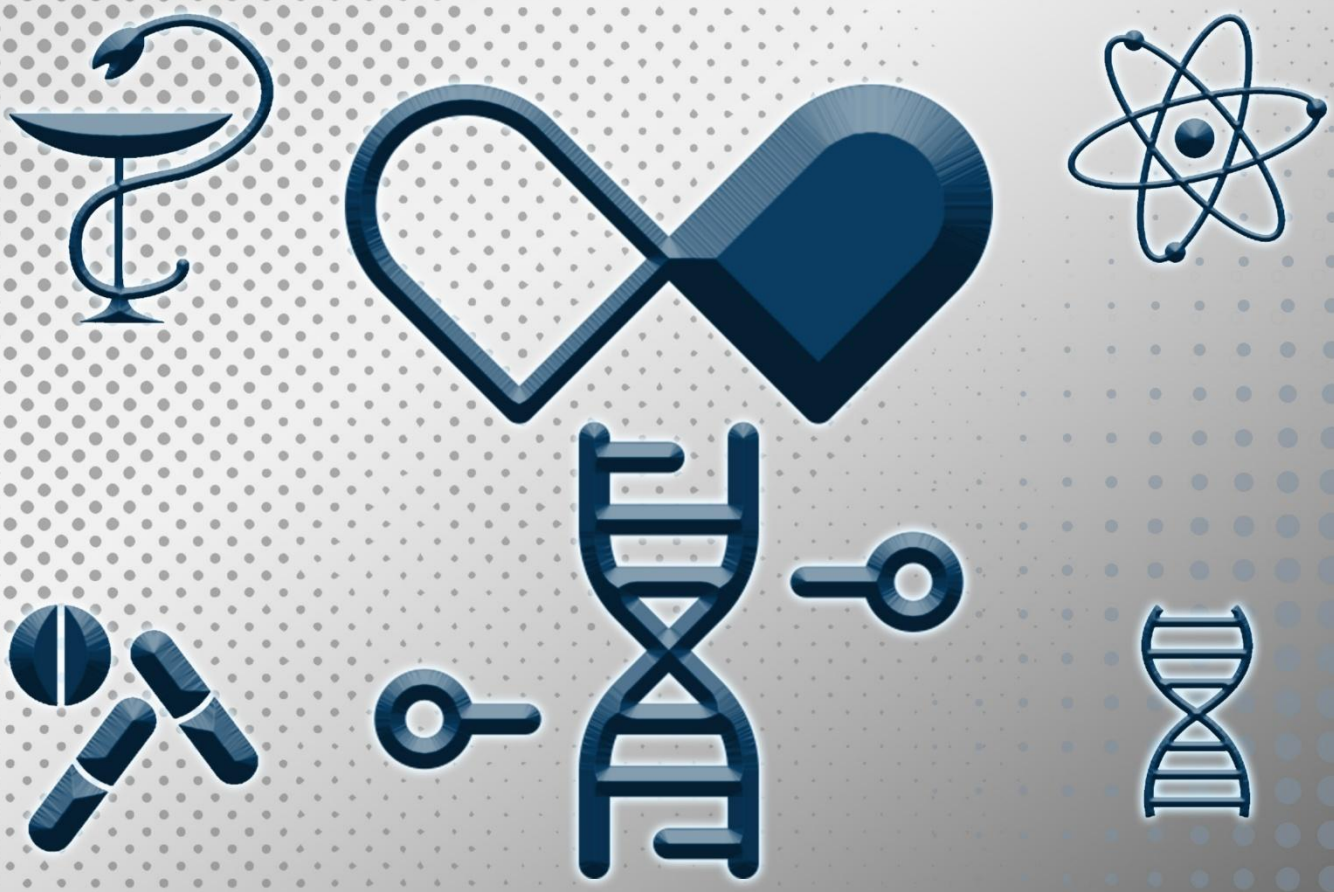
Pharmacology



Done By:

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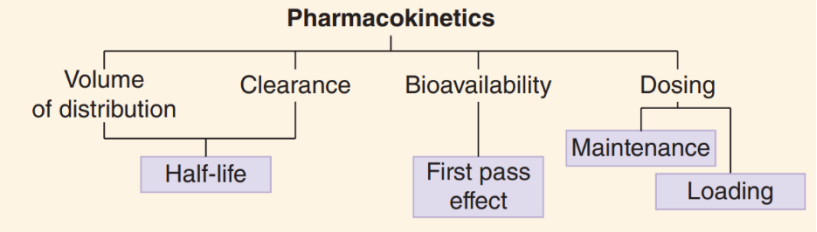
Pharmacokinetics:

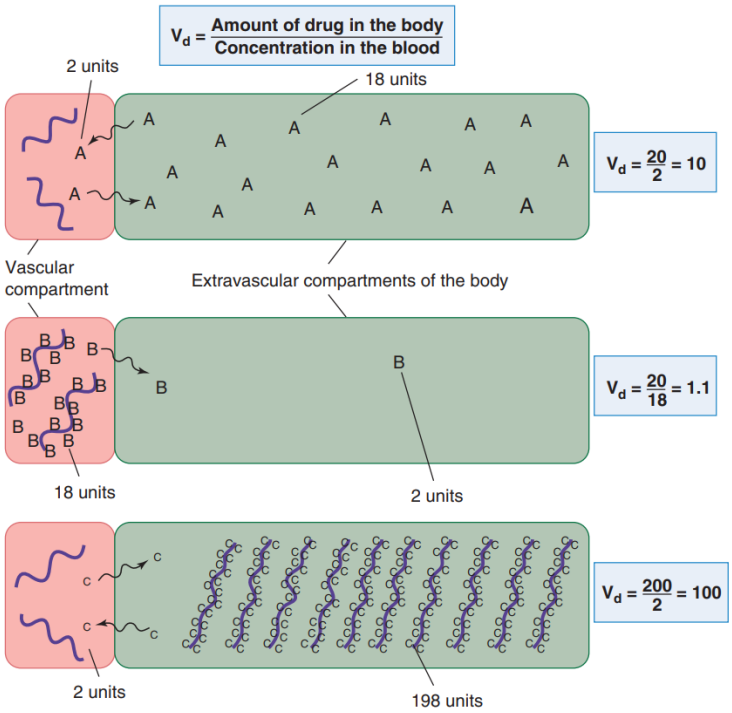
- The effects of the body on drugs.
- Deals with drug absorption, **distribution**, metabolism, and elimination (ADME).



- Apparent Volume of distribution (Vd): The ratio of drug amount in the body to its concentration in the plasma or blood & expressed as Vd per kilogram of body weight (Vd/kg).
- Clearance: The ratio of the rate of elimination of a drug to its concentration in the plasma or blood.
- Bioavailability: The fraction (or percentage) of administered drug that reaches systemic circulation.
- First-pass effect, (pre-systemic elimination): The elimination of drug that occurs before it enters the systemic circulation.
- Pharmacokinetics parameters:
  - Clearance: measures the ability of the body to eliminate the drug.
  - Volume of distribution: measures the apparent space in the body available to contain the drug.

Volume of distribution

- Relates the amount of drug in the body to the concentration of drug (C) in blood or plasma.

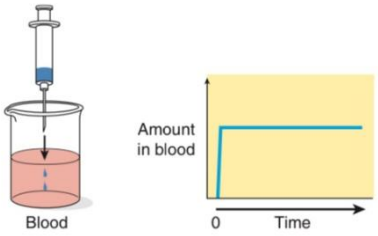


- Drugs with high Vd have higher concentrations in extravascular tissue than vascular compartment.
- Drugs with minimum Vd are those that retained within the vascular compartment.
  - Those that are completely retained in plasma will have a Vd = plasma volume (4% of B.W).

- Factors that affect Vd:
  - Inert binding sites in the blood (i.e., Albumin).
  - Inert binding sites in the tissue (i.e., tissue proteins).
    - ➔ The drug's concentration in plasma may drop to very low values even though the total amount in the body is large.
    - ➔ Vd may greatly exceed the total physical volume of the body.
  - What will happen to VD in?
    - ➔ Coadministration of drug that binds to albumin?
    - ➔ Water-soluble drugs?
    - ➔ Lipid-soluble drugs?
    - ➔ Dehydration?
    - ➔ Renal failure?
    - ➔ Liver failure?

Vd and the "Loading dose "

- The loading dose: The initial (first) dose to be administered before "maintenance dose" to reach a specific concentration in the blood (desired therapeutic concentration).
- We require Loading Dose if:
  - Therapeutic concentration must be achieved rapidly.
  - Large volume of distribution (Vd).
- LD is calculated as the following:



$$\text{Loading dose} = \frac{V_d \times \text{Desired plasma concentration}}{\text{Bioavailability}}$$

  - Note: in almost all cases we use parenteral injections; thus, Bioavailability =1.
  - If the loading dose is large (Vd much larger than blood volume), the dose should be given slowly to prevent toxicity due to excessively high plasma levels during the distribution phase.

Clearance

- Relates the rate of elimination to the plasma concentration:

$$CL = \frac{\text{Rate of elimination of drug}}{\text{Plasma drug concentration}}$$

$$(\text{Units} = \text{Volume per unit time})$$

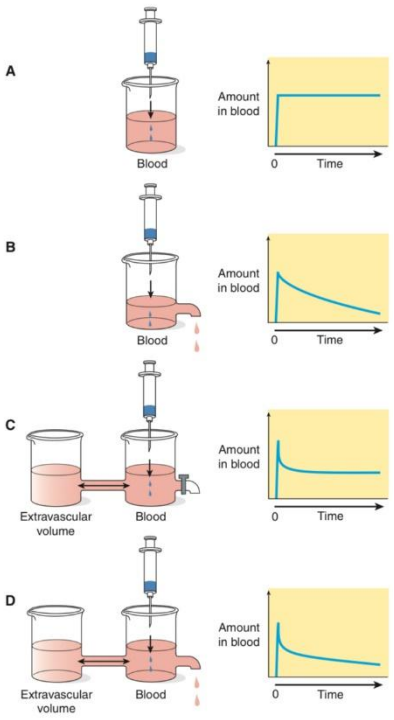
- Sometimes expressed as CL per kg of body weight
- Elimination of drug from the body have many routes:
  - Kidney, lung, liver, and other organs.
- Systemic clearance equals the separate clearances at each organ.

$$CL_{kidney} = \frac{\text{Rate of elimination}_{kidney}}{C} \quad (3a)$$

$$CL_{liver} = \frac{\text{Rate of elimination}_{liver}}{C} \quad (3b)$$

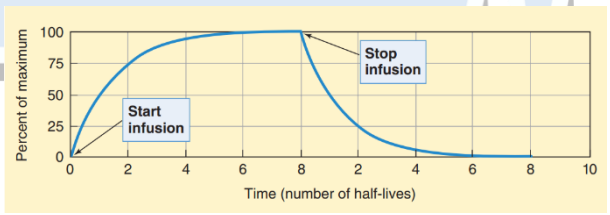
$$CL_{other} = \frac{\text{Rate of elimination}_{other}}{C} \quad (3c)$$

$$CL_{systemic} = CL_{kidney} + CL_{liver} + CL_{other} \quad (3d)$$



Half-life (t1/2):

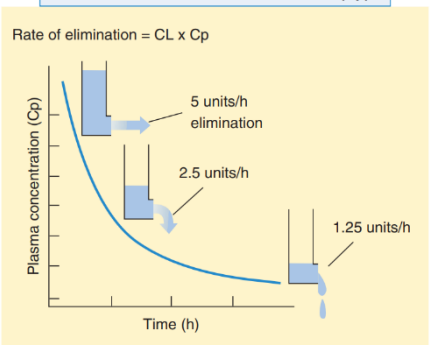
- The time required to eliminate 50% of the drug.
- Derived parameter, determined by Vd and CL.
  - Directly related to Vd.
  - Inversely related to CL.



- Determines the rate of drug concentration rises during infusion & falls after administration is stopped.
- Disease, age, and others usually alter the clearance of a drug much more than they alter its Vd.
  - The most important factor determining clearance is Half-life.

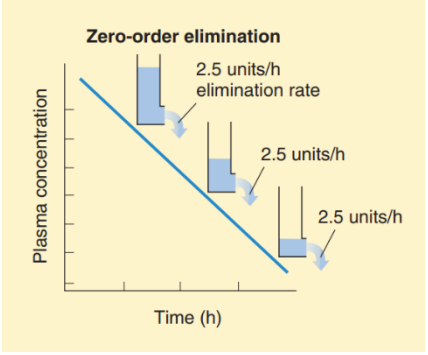
Rate of elimination:

$$\text{Clearance (CL)} = \frac{\text{Rate of elimination}}{\text{Plasma concentration (Cp)}}$$



- First-Order kinetics (elimination):
  - Applied to most drugs.
  - For those drugs we have:
    - ➔ **Constant half-life, thus constant clearance**.
    - ➔ **Inconstant rate of elimination**.
    - ➔ Whatever the amount of the drug we take.
    - ➔ Liver enzymes can keep metabolizing 50% of the medication.
      - Without being saturated.
      - The higher the concentration, the greater the amount of drug eliminated per unit time.
  - Affected by Blood flow:
    - ➔ Clearance of drug by organ is equivalent to organs' extraction capability for that drug times the rate of delivery of drug to the organ.
    - ➔ Thus, drug clearance that is very effectively extracted by an organ is often **flow-limited**.
      - Total clearance is related to blood flow through the eliminating organ.
        - ⇨ Thus, anything that affects blood flow may have more dramatic effects on clearance than disease of the organ of elimination.

- Zero-order kinetics (elimination):
  - A small number of medications follow zero order kinetics.
    ➔ Ethanol and phenytoin and aspirin at therapeutic or toxic dose.
  - There will be saturation in the liver metabolizing enzymes, and thus they are able to only metabolize a fixed amount of the drug.
  - For those drugs we have:
    ➔ A constant amount of drug is eliminated per unit time (**Constant rate of elimination**).
    ➔ **Inconstant half-life, thus Inconstant clearance**.



Factors affect clearance

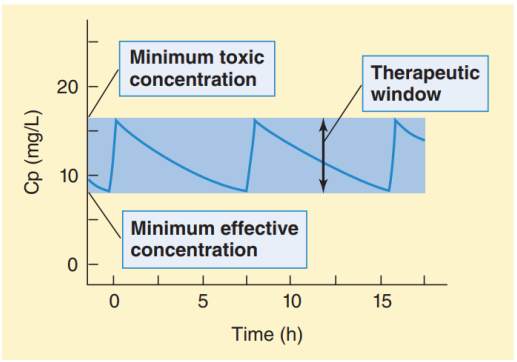
- Polarity of the drug? More polar ↓ clearance.
- Renal function? Impaired ↓ clearance.
- Half-life? Low half-life faster clearance.
- PH? According to Henderson-Hasselbalch equation.
- Vd? Not related.

Clearance and the Maintenance Dosage:

- The maintenance dosage is a function of clearance:

$$\text{Dosing rate} = \frac{\text{CL} \times \text{Desired plasma concentratition}}{\text{Bioavailability}}$$

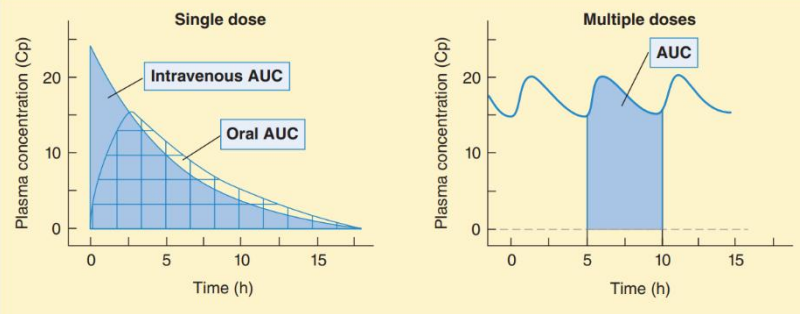
- Notes:
  - We may use parenteral injections (Bioavailability =1) or oral (Bioavailability <1).
  - Vd is not involved in the calculation of maintenance dosing rate.
  - The number of doses to be given per day:
    ➔ Determined by:
      - Half-life of the drug
      - Therapeutic Window
    ➔ Given as:
      - Large dose given at long intervals.
        ⇨ If the difference between the toxic and therapeutic concentrations is large.
          ↳ Low risk of toxicity.
      - Smaller doses at more frequent intervals.
        ⇨ If the difference between the toxic and therapeutic concentrations is small.
          ↳ To prevent toxicity.



BIOAVAILABILITY

- The fraction (F) of the administered dose that reaches the systemic circulation.
- Defined as unity (100%) in case of IV administration; all the dose reach the systemic circulation.
- Is it less than 100%?
  - Yes, if administrated by other routes,

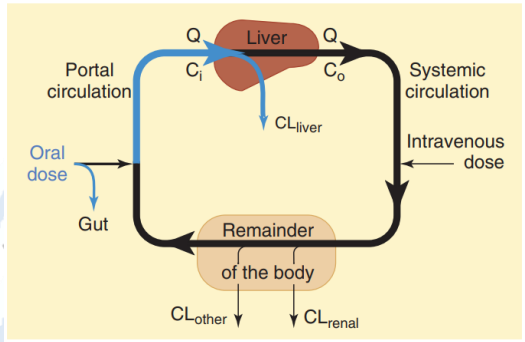
- Bioavailability is generally reduced by:
  - ➔ Drug Distribution into other tissues that occurs before systemic circulation.
  - ➔ Incomplete absorption (expulsion of drug by intestinal transporters),
  - ➔ First-pass metabolism.
- Even for drugs with equal bioavailabilities:
  - ➔ Entry into systemic circulation occurs over varying periods of time, depending on the drug formulation and other factors.
- To account for such factors, the concentration appearing in the plasma is integrated over time to obtain an **integrated total area under the plasma concentration curve (AUC).**



- AUC: is used to calculate the bioavailability of a drug.
- Bioavailability = $AUC_{(route)}/AUC_{(IV)}$.

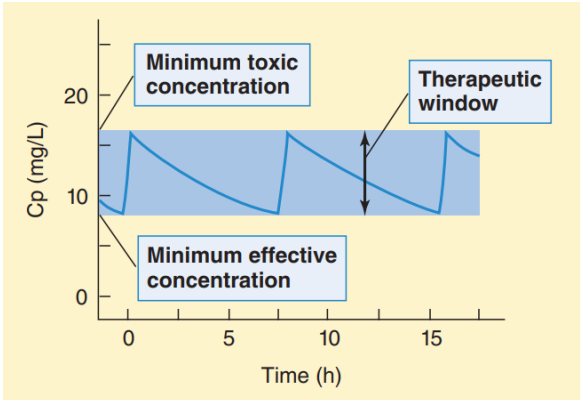
First-pass metabolism (Effect):

- Drugs that pass through the GIT (Oral, Anal) will be affected.
- After absorption across the gut wall, the portal blood delivers the drug to the liver prior systemic circulation.
- A drug can be metabolized in:
  - Gut wall.
  - The portal blood.
  - Liver (most commonly).
    - ➔ Can excrete the drug into the bile.
- This metabolism occurs before reaching systemic circulation.
  - By CYP3A4 enzyme systems.
  - Thus, reduction in bioavailability.



DOSAGE REGIMENS:

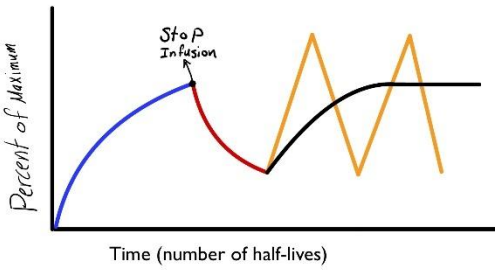
- It is a plan for drug administration over a period of time.
- It results in [1]achievement of therapeutic levels of the drug in the blood [2]over a period of time [3]without exceeding the minimum toxic concentration.
- To maintain the plasma concentration range over long periods of therapy, we need:
  - Schedule of maintenance doses.
  - If it is necessary to achieve the target plasma level rapidly, a loading dose may be used.



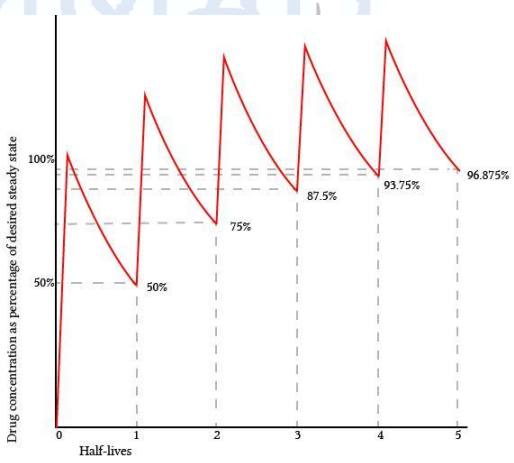
- Ideally, the dosing plan is based on knowledge of [1]minimum therapeutic & minimum toxic concentrations for the drug, as well as its [2]clearance and Vd.

Maintenance & Loading doses & steady state:

- Steady state: the condition in which the average total amount of drug in the body does not change over multiple dosing cycles (ie, the condition in which the rate of drug elimination equals the rate of administration).
- To really understand it focus:
  - We're putting somebody on a cardipin infusion.
  - We need the drug concentration of (100mg/ml).
  - We give it and everything is fine.
  - Due to normal physiological properties of this drug (i.e., $t_{1/2}$) its plasma levels will be decreased.
- This is the problem:
  - The reduction of the drug dose after its administration will affect the body response.
  - Thus, we maintain it by maintenance dose that is given many times over different time intervals.
    - ➔ The goal is to make the dosage rate = elimination rate.
      - Amount of drug that's coming in is equal to the amount of drug that's being eliminated from the body.
    - ➔ Thus, at this point [Steady state]; we have an average amount of drug relatively constant.
- At curves:
  - Start infusion: increase in the drug concentration.
  - Stop infusion: decrease in the drug concentration.
  - Because of steady state:
    - ➔ We notice the plateau that the concentration of the drug remains about the same.



- Of most drugs how long we need to reach this steady state?
  - It takes about 4-5 half-lives.
  - Why? Because
    - ➔ It needs 4-5 half-lives to eliminate 97% of the drug.
    - ➔ 1st $t_{1/2}$: we eliminate 50%
    - ➔ 2nd $t_{1/2}$: we eliminate 75%
    - ➔ 3rd $t_{1/2}$: we eliminate 87.5%
    - ➔ 4th $t_{1/2}$: we eliminate 93.75%
    - ➔ 5th $t_{1/2}$: we eliminate ≈97%



- The **minimum effective concentration** determines **trough levels** of a drug given intermittently,
- The **minimum toxic concentration** determines the **permissible peak** plasma concentration.

ADJUSTMENT OF DOSAGE WHEN ELIMINATION IS ALTERED BY DISEASE

- Clearance of drugs that depend on renal elimination, reduced by:
  - Renal disease or reduced cardiac output.
- Impairment of hepatic clearance occurs (for high extraction drugs) when:

- Liver blood flow is reduced, as in heart failure,
- Severe cirrhosis and other forms of liver failure.

- Renal route of elimination is important thus, assessing renal function is important in estimating dosage in patients.
  - The most important renal variable is GFR, which equals creatinine clearance.
- The dosage in a patient with renal impairment may be corrected by:

$$\text{Corrected dosage} = \text{Average dosage} \times \frac{\text{Patient's } CL_{cr}}{100 \text{ mL/min}} \qquad (6)$$

- This way ignores nonrenal routes of clearance that may be significant.
  - If a drug is cleared partly by the kidney and partly by other routes,
  - Equation 6 should be applied to the part of the dose that is eliminated **only** by the kidney.
    - ➔ For example:
      - If a drug is 50% cleared by the kidney and 50% by the liver
      - Normal dosage is 200 mg/d, the hepatic & renal elimination rates are each 100 mg/d.
      - What the corrected dosage in a patient with a creatinine clearance of 20 mL/min will be:
        - ⇨ Dosage = $CL_{Liver} + CL_{Renal} = 100 + (100 * 0.20) = 120$mg.

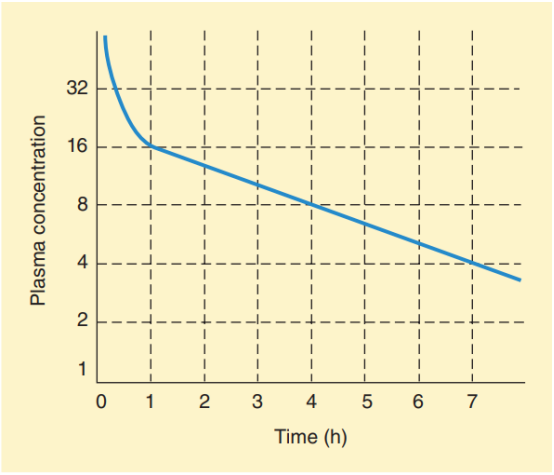
Questions:

1. The pharmacokinetic process or property that distinguishes the elimination of ethanol and high doses of phenytoin and aspirin from the elimination of most other drugs is called:
   (A) Distribution
   (B) Excretion
   (C) First-pass effect
   (D) First-order elimination
   (E) Zero-order elimination

   Answer:E
2. Ampicillin is eliminated by first-order kinetics. Which of the following statements best describes the process by which the plasma concentration of this drug declines?
   (A) There is only 1 metabolic path for drug elimination
   (B) The half-life is the same regardless of the plasma concentration
   (C) The drug is largely metabolized in the liver after oral administration and has low bioavailability
   (D) The rate of elimination is proportional to the rate of administration at all times.
   (E) The drug is distributed to only 1 compartment outside the vascular system

   Answer: B

3. A new drug was administered intravenously, and its plasma levels were measured for several hours. A graph was prepared as shown below, with the plasma levels plotted on a logarithmic ordinate and time on a linear abscissa. It was concluded that the drug has first-order kinetics. From this graph, what is the best estimate of the half-life?
   (A) 0.5 h
   (B) 1 h
   (C) 3 h
   (D) 4 h
   (E) 7 h



Answer: C

THE END OF CHAPTER 3