PHARMACOKINETICS SMALL GROUP I:

Question 1
Absorption of the anti-fungal agent, itraconazole, is dependent on a low gastric pH. Calculate the relative concentrations of a weak acid (with a pKa of 5.4) in the plasma (pH 7.4) and in the stomach (pH 1.4). If the total steady state concentration of itraconazole in the stomach were 1 µg/ml, what concentration would be expected in the plasma? If a 55-year old male were taking large doses of antacids for heartburn, how would a change in the pH of the stomach alter absorption of this drug?

Answer:
This question relates to the effects of pH on drugs that are weak acids or bases: _drug absorption and distribution can be very sensitive to pH_.

Using the Henderson-Hasselbalch equation for acids, the students should calculate the relative concentration of A⁻ and use this to determine which form the medication will be in (ionized versus non-ionized) in both the stomach and the plasma. Then the students should be able to verbally explain the consequences if the gastric pH is altered.

pKa - pH = log   [AH]   or pKa – pH = Log [Non-ionized]
                          [A⁻]   [Ionized]

AH is non-ionized so it diffuses across the membrane more readily than A⁻.

Stomach

pKa - pH = log [AH]
                         [A⁻]

5.4 - 1.4 = log [AH]
                         [A⁻]

4 = log [AH]
            [A⁻]

1 x 10⁴ = [AH]
                    [A⁻]

10,000 = [AH]
                    [A⁻]

Total drug in plasma = 101   Total drug in stomach = 1.0001
A weak acid will be trapped in more alkaline compartments.

set [AH] to 1 and solve for [A⁻]

[AH] = 10,000   1 =10,000 x [A⁻]   [A⁻] = 0.0001
 [A⁻]

Total ₛₜₒₘₐ𝒸ₕ = [AH] + [A⁻] = 1.0001

In the stomach, almost all of the drug is in the non-ionized form [AH] which is more lipid soluble. This lipid soluble form favors permeation across the membrane.
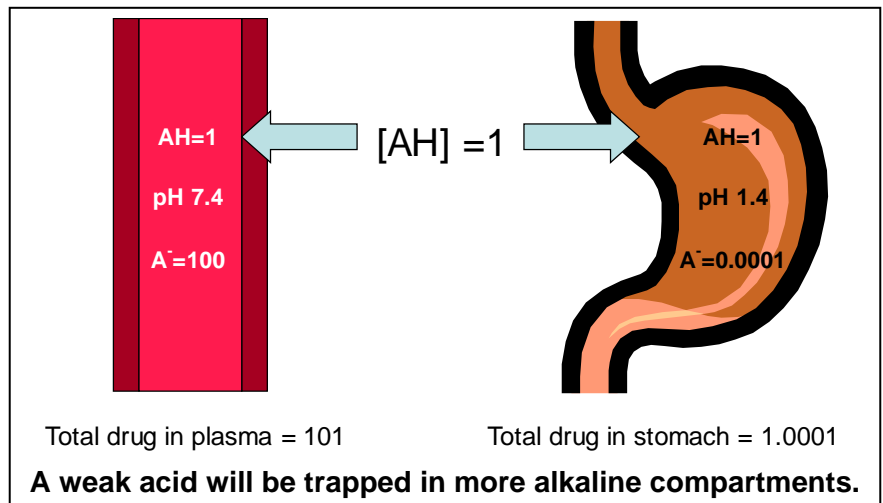
<u>PLASMA</u>

$5.4 - 7.4 = \log([AH]/[A^-])$

$-2 = \log([AH]/[A^-])$

$10^{-2} = \dfrac{[AH]}{[A^-]}$

$0.01 = \dfrac{[AH]}{[A^-]}$ Most of the drug in the plasma is in the ionized form [A-]

set [AH] to 1   and solve for [A⁻] to be able to compare the concentrations of the drug in the plasma and the stomach. The non-ionized form, AH, can diffuse across the membrane and equilibrate.

$\dfrac{[AH]}{[A^-]} = 0.01$ $1 = 0.01 \times [A^-]$ $[A^-] = 100$

Total $_{plasma}$ = [AH] + [A⁻] = 1 + 100 = 101

In the plasma, ~99% of the drug will be in the <u>ionized</u> form, which will not diffuse as easily across membranes. Thus, the drug is essentially trapped in the more alkaline compartment. If the <u>total</u> concentration in the stomach were 1 µg/ml, the <u>total</u> concentration in the plasma would be 101 µg/ml.

If the pH of the stomach is less acidic (higher pH), more of the drug will be in the ionized form and less will be absorbed, resulting in possible clinical failure. Conversely, if the pH is more acidic (decreased pH), more of the drug would be in the non-ionized form resulting in increased absorption. This pharmacokinetic principle explains why an acidic environment is needed to enhance itraconazole absorption. Often, patients are asked to take itraconzole capsules with a can of Coca Cola® to help decrease stomach pH.

Note: H2 blockers (e.g., Ranitidine (Zantac®)) increase gastric pH 2-3 units, and proton pump blockers (e.g., Omeprazole (Prilosec®)) increase gastric pH 3-4 units. These agents are now available over the counter (OTC) and it is imperative to question patients regarding OTC medications to screen for drug interactions.

Question 2
2A. Define the term bioavailability and list at least four reasons why the bioavailability of a drug is often less than 100%?

Answer:
Bioavailability is the percentage or fraction of the administered dose of a drug that reaches the systemic circulation of the patient in its active form.

(i) **Inherent chemical and physical properties of the administered drug (e.g. lipophilicity, pKa, molecular size etc)- may reduce the efficiency with which the drug is absorbed. If the drug cannot be efficiently absorbed it is likely to be excreted or degraded before it can reach the systemic circulation.**

(ii) **The dosage form (e.g. tablet, capsule, elixir) prevents 100% of the administered drug from being absorbed into the systemic circulation (may relate to incomplete dissolution of the drug in the GI fluids).**

(iii) **Route of administration (oral, parenteral, topical, transdermal, rectal etc): oral or rectal doses of drug enter the portal circulation and may be subject to "first pass" metabolism in the liver. In contrast, i.v. administration of a drug by-passes the liver and reaches the systemic circulation without undergoing metabolism.**

(iv) **The stability of the active ingredient in the GI tract e.g. the drug can be partially destroyed in the stomach or maybe metabolized by enzymes present in the gut wall, or by enzymes produced by microorganisms present in the GI tract. For example, cyclosporin is metabolized by CYP3A4 present in the gut wall.**

(v) **Formation of insoluble complexes with materials within the GI tract that prevent absorption e.g. calcium containing-foods such as dairy products form insoluble complexes with tetracycline.**

2B. Digoxin is a digitalis glycoside that exerts positive inotropic effects on the heart. It is indicated in the treatment of atrial fibrillation or flutter and may be used as adjunctive therapy for congestive heart failure. The bioavailability (F) of digoxin varies depending on formulation.

Dosage Form	Bioavailability (%)
IV	100
Tablet	70
Elixir	80
Capsules	90-100
IM	90-100

Patient E.F. has been admitted for a closed head injury and has a nasogastric tube for the administration of medication and nutrition. Prior to admission, E.F. was on a therapeutic dose of digoxin 0.2 mg capsule once a day. With the nasogastric tube, E.F. will receive digoxin tablets crushed and administered via the tube. Determine the dose (mg) of digoxin tablets that should be prescribed.

Answer:
Bioavailability depends on formulation and route of administration: dose adjustment inversely proportional to bioavailability

0.2 mg $_{capsules}$ x 1 = X mg $_{tablets}$ x 0.7 $\boxed{Dose_1 \ x \ F_1 =}$

X = 0.29 mg

Give 0.25mg tablet (crushed) via NG tube daily

Question 3

a. How will the plasma protein binding of drugs be altered by the following conditions, and what are the expected effects of this on Volume of Distribution (V_d) and Clearance of Elimination (CL)?

- Burns
- Chronic Liver Disease
- Renal Failure
- Co-administration of Sulfadiazine (highly protein-bound antibiotic)

b. Daptomycin is an antibacterial drug that exhibits high plasma protein binding (protein binding 90–93%, 60% to albumin). How would daptomycin loading dose and maintenance dosing rate be adjusted in patients with thermal burn injury?

Answer:
Emphasize that protein binding can affect drug distribution and clearance and hence changes in plasma protein may require adjustments of dosing.

a. **The first three conditions result in a <u>decrease</u> in serum albumin concentration (i.e. they induce hypoalbuminemia). In renal failure, the affinity of albumin for binding drugs may also be reduced. Other conditions that may lead to hypoalbuminemia (serum albumin < 3.5 g/dL) include pregnancy, cystic fibrosis, and malnutrition. Few therapeutic drugs affect the binding of other drugs to albumin because at therapeutic plasma concentrations they occupy only a tiny fraction of the available sites. Sulfonamides are an exception because they occupy about 50% of the binding sites at therapeutic concentrations and so can cause unexpected effects by displacing other drugs. For highly to moderately protein-bound drugs, hypoalbuminemia (or the presence of a competing sulfonamide drug) may increase the ratio of unbound to protein-bound drug in the plasma. This will tend to increase the V_d of drugs (in general, only unbound drug will distribute to tissues) and increase their clearance (only unbound drug is filtered by the kidney or extracted by the liver).**

b. **Studies comparing burns patients with healthy subjects have demonstrated that both initial peak daptomycin plasma concentrations (C_{max}) and Area Under the Curve (AUC) values in the burns patients were reduced to nearly half those observed in the healthy subjects. For a concentration-dependent antibacterial such as daptomycin, such pharmacokinetic outcomes can gravely compromise antibacterial efficacy. Both loading dose and maintenance dosing rate of daptomycin should be increased in burn patients because of the increased V_d and CL, respectively.**

Question 4

Aminoglycosides (e.g. gentamicin, tobramycin, amikacin) are antibiotics used in the treatment of aerobic gram-negative bacterial infections. Aminoglycosides are water-soluble medications that primarily distribute into extracellular fluid. In 'normal' individuals, the extracellular fluid compartment approximates 25% of total body weight, whereas in the adipose tissue of obese individuals the extracellular fluid is only about 10% of total body weight.

In a normal healthy individual the volume of distribution of gentamycin is 0.25 L/kg and the loading dose is 2 mg/kg. What effect would you anticipate each of the following conditions to have on the loading dose of gentamycin and other aminoglycosides in such patients?

    a) Dehydration
    b) Cystic Fibrosis
    c) Congestive Heart Failure (CHF)
    d) Gross obesity
    e) Neonates

Answer:
Emphasize that since loading dose is dependent on V_d, LD must be adjusted if Vd changes.

Loading Dose = V_d x TC

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a) Dehydration: Decreased volume of distribution (less extracellular fluid to distribute into): decrease loading dose proportional to decreased V_d.

b) Cystic Fibrosis (CF): Patients with cystic fibrosis have a markedly increased V_d of 0.35 L/kg due to increases in extracellular fluid brought about by the disease process. Because of increased V_d; the LD should also be increased.

c) Congestive Heart Failure (CHF): Due to increased fluid caused by the edema present in CHF there will be an increase in the V_d, therefore the loading dose should also be increased.

d) Grossly Obese: If a grossly obese patient's actual body weight were used to calculate loading dose there is a risk that the patient will be overdosed relative to a normal lean individual of comparative height. This is due to the fact that a significant proportion of the patient's body weight is comprised of adipose tissue into which aminoglycosides do not effectively partition (i.e. only 10% extracellular fluid). Hence, in obese individuals dosage is determined using "lean body weight" (LBW) rather than the patient's actual body weight (ABW):

> **To calculate lean body weight (LBW):**
>
> **Female: 45.5 kg + 2.3kg x**

An additional correction factor is included that takes into account the quantity of excess weight caused by adipose tissue.

**Dosing weight (DW) for a grossly obese patient:**

DW = LBW + 0.4(ABW - LBW)

e) **Neonates: Neonatal and infants tend to have a larger volume of distribution than adults. Increased volume of distribution due to increased total body water (premature infants exhibit body composition up to 90% water—'waterbags'), therefore increase loading dose accordingly. Over the time span from birth and first years of age, the volume of distribution continues to decline from an initial value of >0.5 L/kg to the adult value of 0.25 L/kg.**
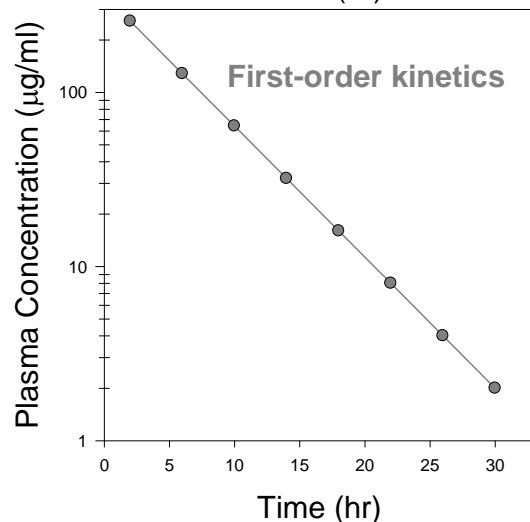
Question 5
Define first- and zero-order kinetics of elimination.

- **First-order kinetics of elimination:**
  The rate of drug elimination is proportional to the amount of drug present in the body. This is true for most drugs used clinically. With first-order kinetics, if the dosing rate is doubled, the steady-state concentration will double.
- **Zero-order kinetics of elimination:**
  Some drugs like phenytoin, aspirin and ethyl alcohol are exceptions to the rule in that they follow dose-dependent kinetics of elimination. At low doses and plasma concentrations, they follow apparent first-order kinetics, but at higher doses and plasma concentrations the metabolic pathways become saturated and the drugs exhibit <u>zero-order kinetics of elimination</u> (a constant amount of drug is eliminated per unit time; drug metabolism is capacity-limited and is not proportional to the amount of drug present in the body). Under these conditions, changes in the dosing rate may result in disproportionate, non-linear changes in drug concentrations, and toxicity may develop.
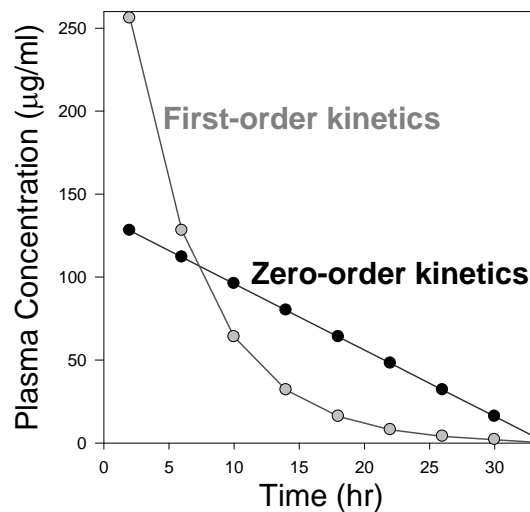
Plotted on a linear Y-axis scale, drug concentration decays

On a semi-log plot (logarithmic Y-axis scale), first-order

Question 6

Vancomycin is a glycopeptide antibiotic primarily used for the treatment of infections due to gram-positive aerobic bacteria. Vancomycin therapy is generally reserved for the treatment of resistant organisms or in patients with allergies to conventional therapy. Vancomycin is eliminated primarily by the kidneys, with 80-90% of an intravenously administered dose being recovered in the urine in patients with normal or moderately impaired renal function. The half-life of vancomycin is markedly prolonged in patients with renal failure. Vancomycin undergoes significant first pass metabolism and does not achieve systemic levels after oral administration, thus requiring intravenous administration for systemic infections.

6A. WC is a 82 year old male admitted from an outside hospital for management of enterococcal endocarditis. As he has a history of penicillin allergy (develops shortness of breath and wheezing), it has been decided that he will receive 6 weeks of vancomycin and gentamicin therapy. The serum concentration - time profile after a 1 gram dose of vancomycin for this patient is depicted in the following graph. Calculate the half-life of the drug using the graph.
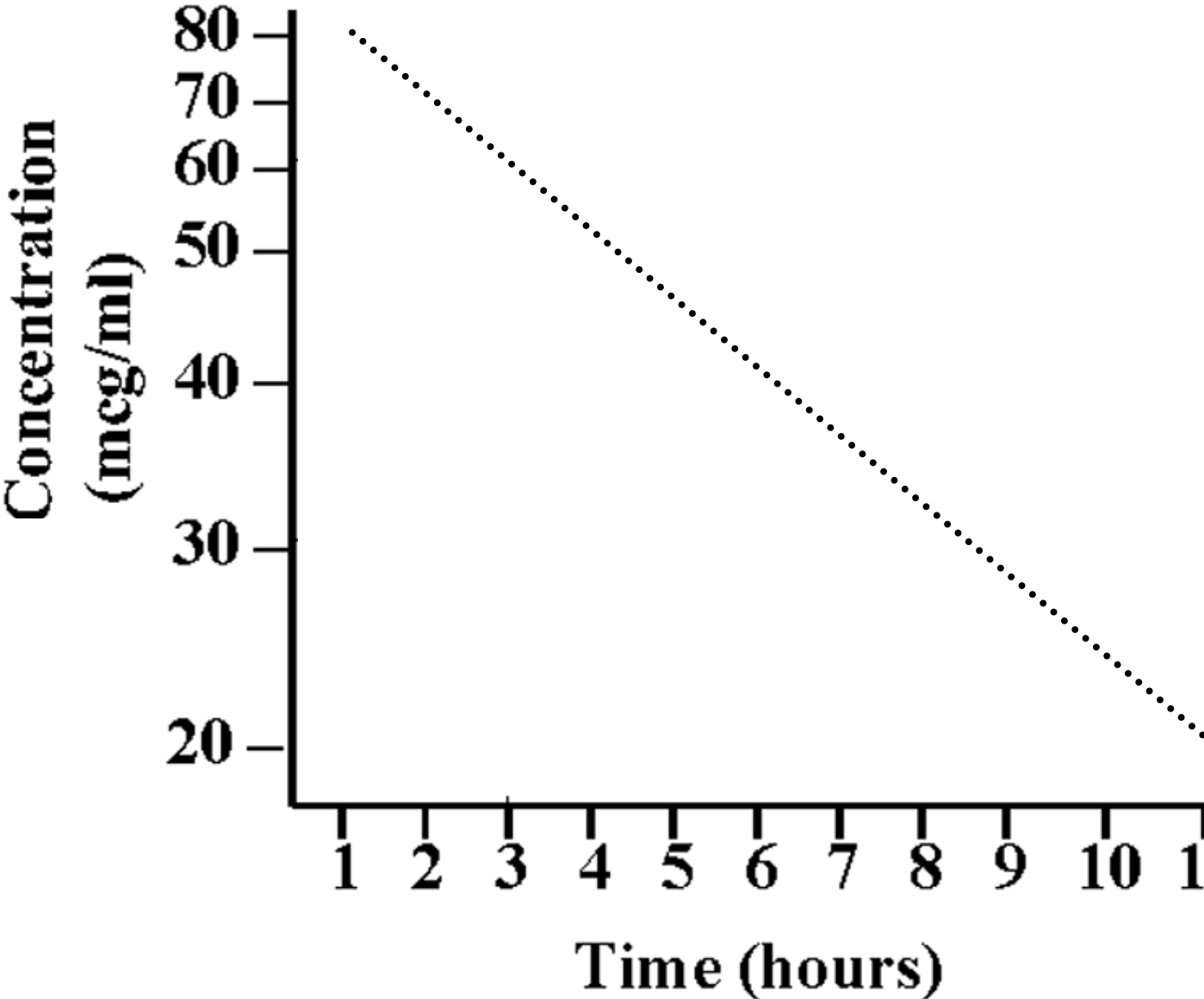
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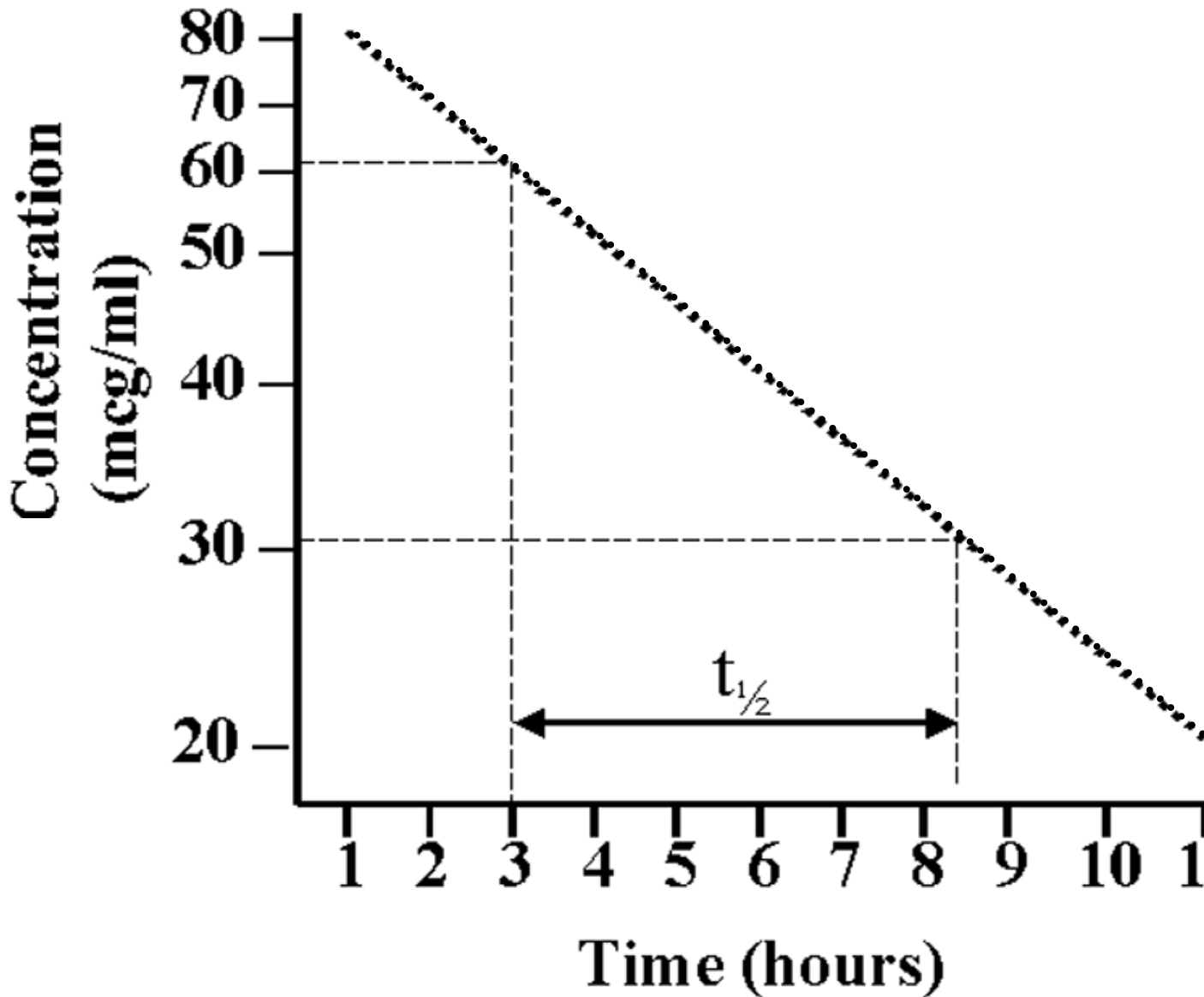
Emphasize that most drugs exhibit 1st order kinetics (exponential elimination—linear time course when plotted in semi-log format). $t_{1/2}$ is constant for drugs with 1st order kinetics.

Graphically, measure the time it takes for the serum concentration to decrease by 50% (e.g. from 60 mcg/ml to 30 mcg/ml). This time is what is known as the half-life of a drug.

Answer: $t_{1/2}$ = 5.5 hours

6B. After one week of therapy, CW.'s renal function starts to deteriorate and then stabilizes, but he is continued on the same dose of vancomycin. After several days serum levels are checked

and are found to be elevated. The vancomycin therapy is then held with orders to restart therapy once the level is <15 mg/L. Using the following serum concentration - time data, estimate the drug's half-life and the time when the patient should receive another dose of vancomycin (in relation to when the last serum concentration was obtained).

Serum Concentration (mg/L)	Day and Time
Level 1: 55.2	Monday 8pm
Level 2: 27.3	Tuesday 8am

Answer:
Emphasize that the exponential 1st order rate equation can be used to predict future concentrations based on measured concentrations at a point in time.

The elimination rate and half-life could be estimated using the levels provided assuming linear pharmacokinetics or calculated using the elimination constant, provided the patient remains at steady state (no acute changes in renal function).

a) Because vancomycin exhibits 1st order pharmacokinetics, the half life can be estimated from the above information or plotted graphically. Upon review of the serum concentrations, the students should note that level 2 represents approximately 50% of level 1 and that it took approximately 12 hours to reach that level. Therefore the half-life approximates 12 hours. Using this data, the level should be <15 twelve hours after the time the second level was drawn or 8PM on Tuesday. The patient should be able to receive a dose then.

b) The elimination half-life and elimination constant can also be calculated mathematically. From the serum concentration data, the elimination rate constant k should be calculated using the following equations:

$$\frac{-k}{2.3} = \frac{\log C_1 - \log C_2}{t_1 - t_2} \qquad OR \qquad -k = \frac{\ln(C_1/C_2)}{(t_1 - t_2)}$$

$$k = \frac{-2.3(\log 55.2 - \log 27.3)}{10 - 22} \qquad\qquad = \frac{\ln(55.2/27.3)}{(22-10)}$$

$$k = 0.059 \text{ hr}^{-1}$$

Then calculate the half-life:
$$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.059 \text{hr}^{-1}} = 11.7\text{hrs}$$

The patient should be re-dosed when the serum concentration of vancomycin is <15 mg/L. It is optional for the student to calculate the exact time as to when the serum concentration will reach 15 mg/L. The equation below should be utilized.

$$C = C_o e^{-kt}$$

$$15 = 27.3 e^{-(0.059)(t)}$$

$$\ln 15 = \ln 27.3 - 0.059(t)$$

$$t = (3.3 - 2.7) \div 0.059$$

$$t = 10\text{hr}$$

Therefore, the patient should receive another dose of vancomycin approximately 10 hours after the last serum concentration was obtained (or 6pm on Tuesday).
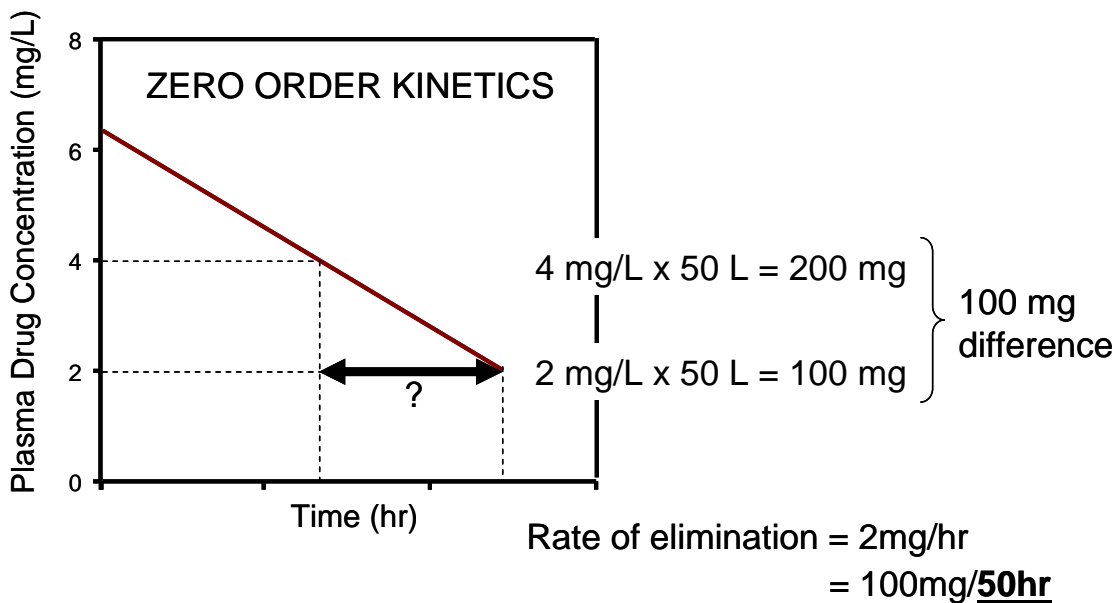
Question 7

A drug has a volume of distribution of 50 L and undergoes zero order elimination at a rate of 2 mg/hr at a plasma concentration greater than 2 mg/L. If a patient is brought to the emergency room with a plasma concentration of 4 mg/L of the drug, how long will it take (in hours) for the plasma concentration to decrease by 50%?

Answer:
50 hrs

If initial plasma concentration = 4 mg/L the total amount of drug "onboard" equals Vd x plasma concentration = 50L x 4 mg/L= 200 mg.

When the plasma concentration of drug falls by 50% to 2mg/L that will be equal to 100 mg (i.e. 50 L x 2 mg/L). Since the rate of elimination of the drug is 2 mg/hr, it will take 50 h for the plasma concentration to be reduced by 50% (i.e. 100 mg= 50 h x 2 mg/h).

ZERO ORDER KINETICS

4 mg/L x 50 L = 200 mg ⎫
                        ⎬ 100 mg difference
2 mg/L x 50 L = 100 mg ⎭

Rate of elimination = 2mg/hr
                    = 100mg/**50hr**

Question 8

For a drug exhibiting one-compartment distribution and first-order kinetics of elimination, calculate the following:

8A. The fraction of an i.v. dose remaining in the body at 3hr, when the half-life is 6 hr.

> **Answer:**
> $C = C_o e^{-kt}$
>
> $k = \dfrac{0.693}{t_{1/2}} = \dfrac{0.693}{6hr} = 0.1155 \text{ hr}^{-1}$
>
> **Hence after 3hr the fraction left $(C/C_0) = e^{-0.1155 \text{ hr-1 x 3hr}} = \underline{0.71}$**

8B. The half-life of a drug, when 18% of the dose remains in the body 4 hr after an i.v. bolus dose.

> **Answer:**
> **Fraction of a drug remaining (C/C_0) after 4 hr $= 0.18 = e^{-k \text{ x 4hr}}$**
>
> **ln (0.18) = -1.715 = -k x 4**
>
> **k = 1.715/4 = 0.43 hr^{-1}**
>
> **$t_{1/2}$ = 0.693/k = 0.693/0.43 hr^{-1}**
>
> **$= \underline{1.6 \text{ hr}}$**

Question 9

Valproic acid is an anti-epileptic drug that is also used in the treatment of bipolar disorder. If the values of clearance and volume of distribution for valproic acid for an individual patient are 0.5 L/hr and 9L, respectively.

9A. Calculate the half-life of valproic acid.

> **Answer:**
> $t_{1/2} = \dfrac{0.693 \times V_d}{CL} = \dfrac{0.693 \times 9L}{0.5 \text{ L/hr}} = \underline{12.5 \text{ hr}}$

9B. What is the total amount of valproic acid in the body at distribution equilibrium when the plasma concentration is 60 mg/L?

> **Answer:**
> **Amount in body = V_d x C = 9 L x 60 mg/L = <u>540 mg</u>**

9C. What is the expected plasma concentration of valproic acid 12 hr after i.v. administration of a 700 mg dose?

> **Answer:**
>
> **C = C_0e^{-kt}**
> **V_d = Dose/C_0**
>
> **Plasma concentration C = <u>Dose</u> e^{-kt}**
> ** V_d**
>
> **k= <u>0.693</u> = <u>0.693</u> = 0.05544 hr^{-1}**
> ** $t_{1/2}$ 12.5 hr**
>
> **Therefore Plasma concentration = <u>Dose</u> e^{-kt}**
> ** V_d**
>
> > **= <u>700 mg</u> $e^{-(0.05544\ hr-1\ x\ 12\ hr)}$**
> > **   9L**
> >
> > **$\cong$ <u>40 mg/L</u>**

Question 10.
A 10 mg dose of diazepam is injected i.v. into a patient with status epilepticus. The half-life of the drug is 48 hrs and the volume of distribution is 80 L in this patient. Based upon these data calculate each of the following?

10A. The elimination rate constant.

$$k= \frac{0.693}{t_{1/2}} = 0.693/48 \text{ hr} = 0.0144 \text{ hr}^{-1}$$

10B. The plasma diazepam concentration 12 hr after giving the dose.

$$C = \frac{Dose}{V_d} e^{-kt}$$

$$= \frac{10 \text{ mg}}{80L} e^{-(0.0144 \text{ hr-1x 12 hr})}$$

$$= 0.105 \text{ mg/L}$$

10C. The fraction of the dose remaining in the body 48hr after the dose is given.

Since the half-life of the drug is 48 hr. 50% of the drug will remain in the body after one half-life

10D. The clearance of diazepam.

$$CL = k \times V_d = 0.0144 \text{ hr}^{-1} \times 80 \text{ L} = 1.15 \text{ L/hr}$$

10E. The amount of drug in the body (in mg) 1 week after giving the dose.

$$C = \frac{Dose}{V_d} e^{-kt}$$

$$C = \frac{10 \text{ mg}}{80L} e^{-(0.0144 \text{ hr-1 x 168 hr})} \qquad \textbf{Note 1 week = 7 x 24 = 168 hr}$$
$$= 0.011 \text{ mg/L (Drug concentration)}$$

To convert to amount of drug multiply by the V_d

i.e. V_d x C = 80L x 0.011 = 0.89 mg