Clinical Pharmacokinetic Equations and Calculations

Part I

Dr. Muhannad R. M. Salih

B.Sc, M.Pharm (Clinical Pharmacy), Ph.D, RPH

Pharmacy Department, Al-Rasheed University College

muhanad_rmk@yahoo.com

One-compartment model equations

- When medications are administered to humans, the body acts as if it is a series of compartments.

- In many cases, the drug distributes from the blood into the tissues quickly, and a pseudoequilibrium of drug movement between blood and tissues is established rapidly.

- When this occurs, a *one-compartment model* can be used to describe the serum concentrations of a drug.

One-compartment model equations

- The simplest multicompartment model is a *two-compartment model* which represents;

1. the body as a *central compartment* into which drug is administered.

2. a *peripheral compartment* into which drug distributes.

Intravenous bolus equation

- When a drug is given as an intravenous bolus and the drug distributes from the blood into the tissues quickly, the serum concentrations often decline in a straight line.

- In this case, a one-compartment model intravenous bolus equation can be used:

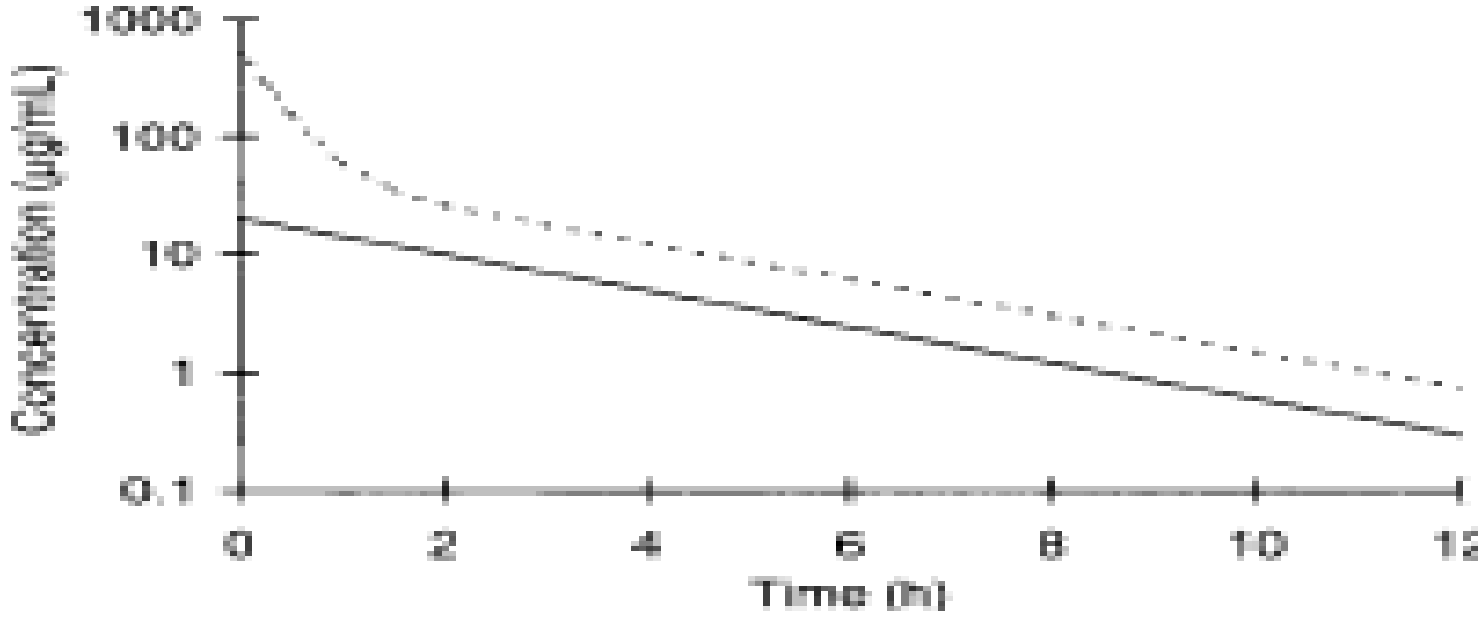
$$C = (D/V)e^{-ke\ t}$$

t: the time after the intravenous bolus was given (t = 0 at the time the dose was administered)

C: the concentration at time = t

V: the volume of distribution

k_e: the elimination rate constant



The solid line shows the serum concentration/time graph for a drug that follows one-compartment model pharmacokinetics after intravenous bolus administration. Drug distribution occurs instantaneously, and serum concentrations decline in a straight line on semilogarithmic axes. The dashed line represents the serum concentration/time plot for a drug that follows two-compartment model pharmacokinetics after an intravenous bolus is given. Immediately after the dose is given, serum concentrations decline rapidly. This portion of the curve is known as the **distribution phase**. **During the distribution phase, drug is distributing between blood and tissues and is removed from the body via hepatic metabolism and renal elimination**. Later, serum concentrations decline more slowly during the elimination phase. During the elimination phase, drug is primarily being removed from the body.

One-compartment model equations

- In some clinical situations, it is possible to use a one-compartment model to compute doses for a drug even if drug distribution takes time to complete.

- In this case, drug serum concentrations are not obtained in a patient until after the *distribution phase is over.*

Intravenous bolus equation

- Most drugs given intravenously cannot be given as an actual intravenous bolus because of side effects related to rapid injection.

- A short infusion of 5–30 minutes can avoid these types of adverse effects.

- *If the intravenous infusion time is very short compared to the half-life* of the drug so that a large amount of drug is not eliminated during the infusion time, intravenous bolus equations can still be used.

Intravenous bolus equation

- For example, a patient is given a theophylline loading dose of 400 mg intravenously over 20 minutes.

- If it is assume that the

Vd =30 L

K_e = 0.116 h^{-1}

t 1/2 = 0.693/ke

= 0.693/0.115 h^{-1}= 6 h

Intravenous bolus equation

- To compute the expected theophylline concentration 4 hours after the dose was given, a one-compartment model intravenous bolus equation can be used:

$$C = (D/V)e^{-ke\ t}$$

$$=(400\ mg/30\ L)e^{-(0.115\ h^{-1})(4\ h)}$$

$$= 8.4\ mg/L$$

Intravenous bolus equation

- In general, it is still possible to use a one compartment model intravenous bolus equation *if the duration of the distribution phase and infusion time is small compared to the half-life of the drug and only a small amount of drug is eliminated during the infusion and distribution phases*.

- The strategy used in this situation is to infuse the medication and wait for the distribution phase to be over before obtaining serum concentrations in the patient.

Intravenous bolus equation

- For instance, vancomycin must be infused slowly over 1 hour in order to avoid hypotension and red flushing around the head and neck areas.

- Additionally, vancomycin distributes slowly to tissues with a 30 – 60 minutes distribution phase.

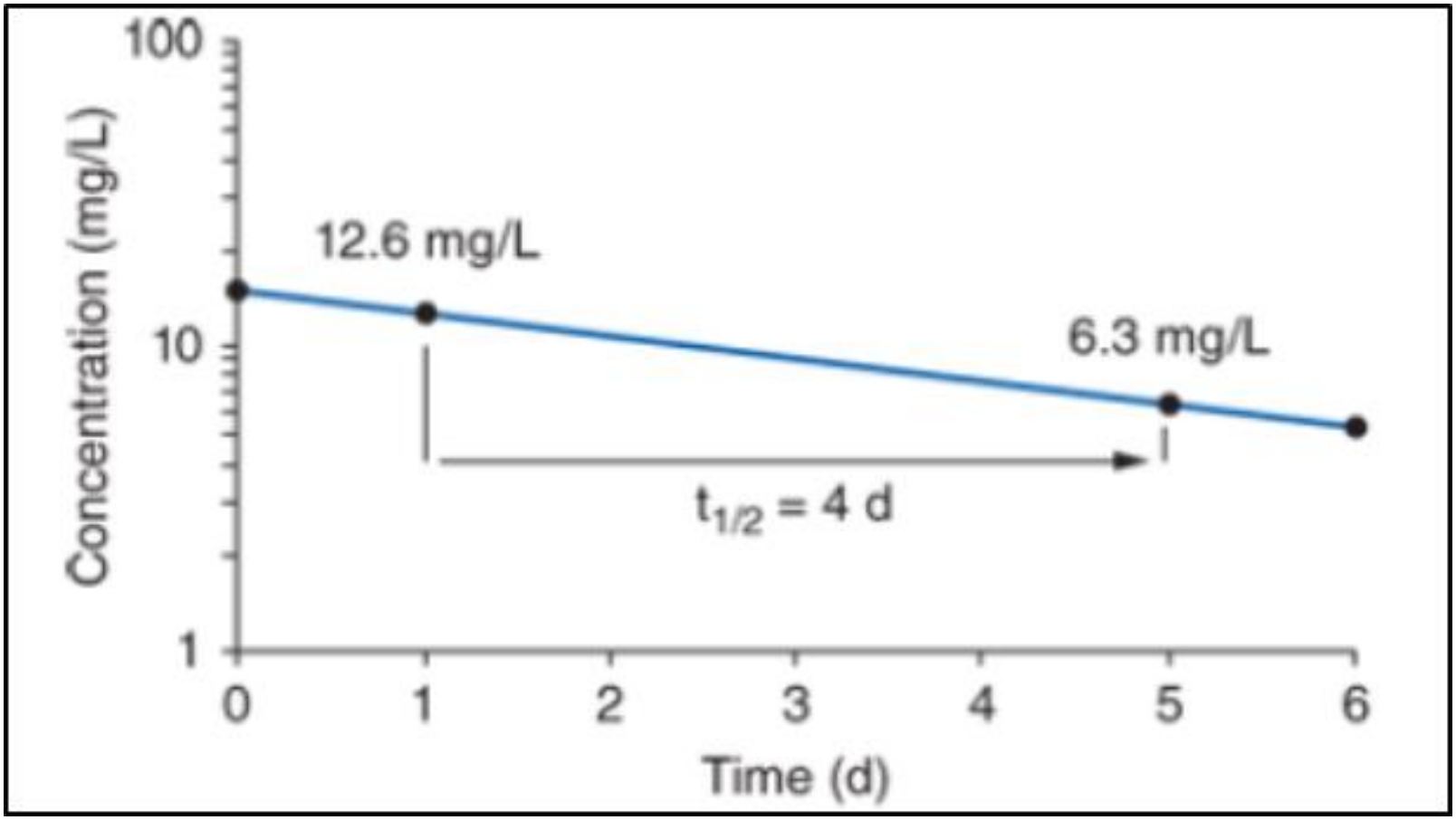
- Because the half-life of vancomycin in patients with normal renal function is approximately 8 hours, *a one compartment model intravenous bolus equation* can be used to compute concentrations in the postinfusion, postdistribution phase without a large amount of error.

Intravenous bolus equation

- Pharmacokinetic parameters for patients can also be computed for use in the equations.

- For example, a patient was given an intravenous loading dose of phenobarbital 600 mg over a period of about an hour.

- ***One day*** and ***four days*** after the dose was administered phenobarbital serum concentrations were ***12.6 mg/L*** and ***7.5 mg/L***, respectively.


100
10
1
Concentration (mg/L)
12.6 mg/L
6.3 mg/L
$t_{1/2}$ = 4 d
0
1
2
3
4
5
6
Time (d)

Intravenous bolus equation

- The elimination rate constant can be computed using the following equation:

$$k_e = -(\ln C1 - \ln C2)/(t1 - t2)$$

k_e = -[ln (12.6 mg/L) - ln (7.5 mg/L)]/(1 d - 4 d)

= 0.173 d^{-1}

$$t_{1/2} = 0.693/k_e$$

= 0.693/0.173 d-1

= 4 d

Intravenous bolus equation

$V = D/C_0$

$C_0 = C/e^{-ke\ t}$

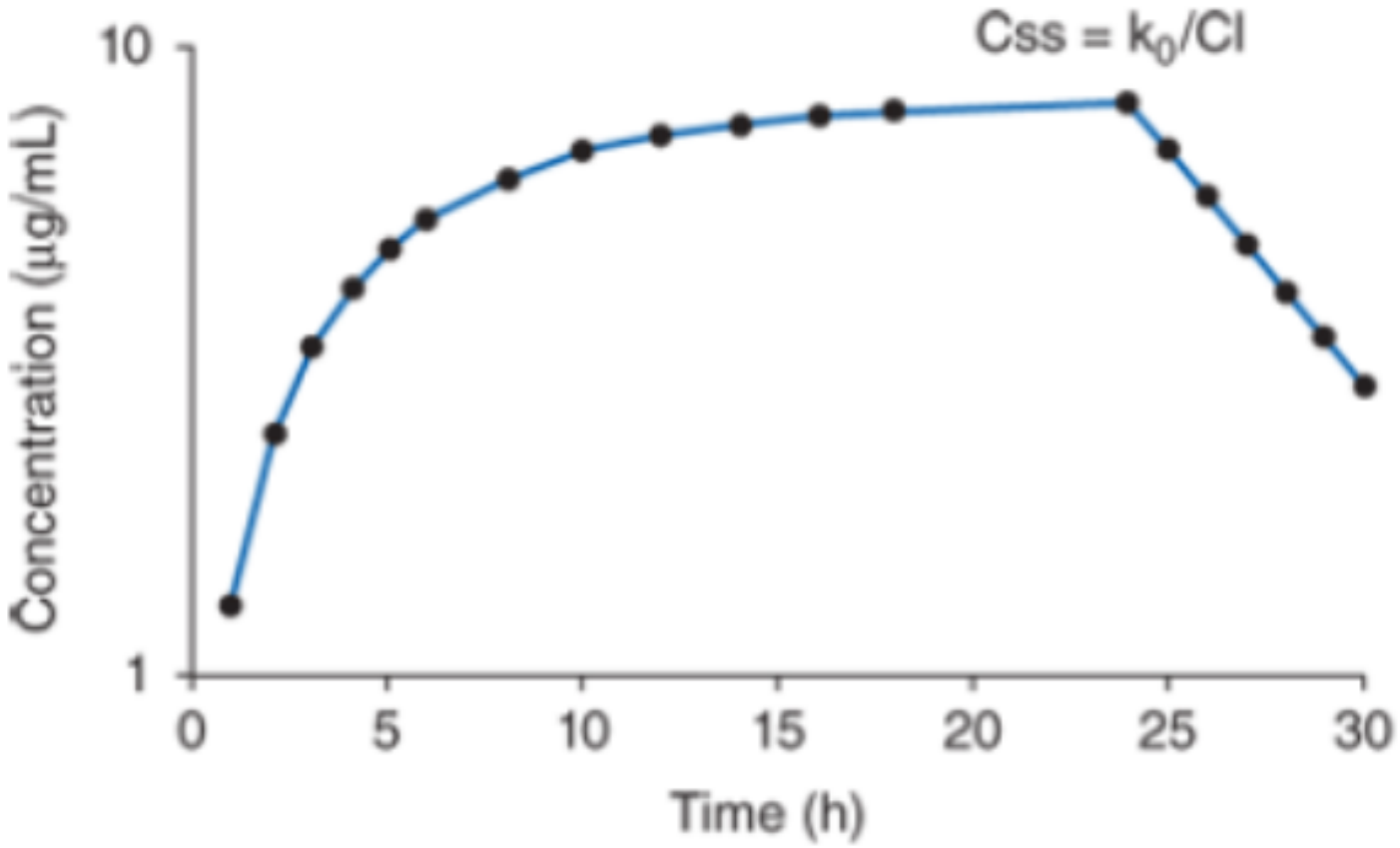
$= (12.6\ mg / L) / e^{-(0.173\ d-1)(1\ d)}$

$= 15.0\ mg/L$

$V = D/C_0$

$= 600\ mg / (15\ mg/L) = 40\ L$

Continuous and Intermittent Intravenous Infusion Equations



If a drug is given as a continuous intravenous infusion, serum concentrations increase until a steady-state concentration (Css) is achieved in 3–5 half-lives. The steady-state concentration is determined by the quotient of the infusion rate (k_0) and drug clearance (Cl): $C_{ss} = k_0/Cl$. When the infusion is discontinued, serum concentrations decline in a straight line.

Continuous and Intermittent Intravenous Infusion Equations

- In this case, a one compartment model intravenous infusion equation can be used to compute concentrations (C) while the infusion is running:

$$C = (k_0/Cl)(1 - e^{-ke\,t})$$

$$C = [k_0/(k_e\,V)](1 - e^{-ke\,t})$$

k_0 :the drug infusion rate (amount per unit time, such as mg/h or µg/min)
Cl :the drug clearance
K_e: elimination rate constant
t: the time that the infusion has been running

Continuous and Intermittent Intravenous Infusion Equations

- If the infusion is allowed to continue until steady state is achieved, the steady-state concentration (Css) can be calculated easily:

$$Css = k_0/Cl$$

$$Css = k_0/(k_e\ V)$$

Continuous and Intermittent Intravenous Infusion Equations

- If the infusion is stopped, postinfusion serum concentrations ($C_{postinfusion}$) can be computed by the following equation:

$$C_{postinfusion} = C_{end}\, e^{-k_e\, t_{postinfusion}}$$

k_e: elimination rate constant
$t_{postinfusion}$: postinfusion time
($t_{postinfusion}$ = 0 at end of infusion and increases from that point)

Continuous and Intermittent Intravenous Infusion Equations

- For example, a patient is administered 60 mg/h of theophylline, **V = 40 L** and **k_e = 0.139 h^{-1}**.

- The serum concentration of theophylline after receiving the drug for **8 hours** and **at steady state** can be calculated:

$$C = [k_0/(k_e V)](1 - e^{-ke\,t})$$

$$= [(60 \text{ mg/h})/(0.139 \text{ h}^{-1} \cdot 40 \text{ L})](1 - e^{-(0.139 \text{ h}^{-1})(8 \text{ h})})$$

$$= 7.2 \text{ mg/L}$$

Continuous and Intermittent Intravenous Infusion Equations

$$Css = k_0/(k_e\ V)$$
$$= (60\ mg/h)/(0.139\ h\text{-}1 \cdot 40\ L)$$
$$= 10.8\ mg/L$$

- If the infusion only ran for **8 hours**, the serum concentration **6 hours** after the infusion stopped would be:

$$C_{postinfusion} = C_{end}\ e^{-k_e\ t_{postinfusion}}$$
$$= (7.2\ mg/L)e^{-(0.139\ h\ -1)(6\ h)}$$
$$= 3.1\ mg/L$$

Continuous and Intermittent Intravenous Infusion Equations

- If the infusion ran until steady state was achieved, the serum concentration 6 hours after the infusion ended would be:

$$C_{postinfusion} = C_{end}\, e^{-k_e\, t_{postinfusion}}$$

$$= (10.8 \text{ mg/L}) e^{-(0.139 \text{ h}^{-1})(6 \text{ h})}$$

$$= 4.7 \text{ mg/L}$$

Continuous and Intermittent Intravenous Infusion Equations

- Even if serum concentrations exhibit a distribution phase after the drug infusion has ended, it is still possible to use one compartment model intravenous infusion equations for the drug without a large amount of error.

- The strategy used in this instance is to infuse the medication and wait for the distribution phase to be over before measuring serum drug concentrations in the patient.

Continuous and Intermittent Intravenous Infusion Equations

- For example, gentamicin, tobramycin, and amikacin are usually infused over **one-half hour**.

- When administered this way, these aminoglycoside antibiotics have distribution phases that last about **one-half hour**.

- Using this strategy, aminoglycoside serum concentrations are obtained no sooner than **one-half hour after a 30-minute** infusion in order to avoid the distribution phase.

Continuous and Intermittent Intravenous Infusion Equations

- If aminoglycosides are infused over **1 hour**, the distribution phase is **very short** and serum concentrations can be obtained

immediately

Continuous and Intermittent Intravenous Infusion Equations

- Pharmacokinetic constants can also be calculated for use in the equations.

- If a steady-state concentration is obtained after a continuous intravenous infusion has been running uninterrupted for 3–5 half-lives, the drug clearance (Cl) can be calculated by rearranging the steady-state infusion formula:

$$Cl = k_0/Css$$

Continuous and Intermittent Intravenous Infusion Equations

- For example, a patient receiving procainamide via intravenous infusion **(k_0 = 5 mg/min)** has a steady-state procainamide concentration measured as **8 mg/L**.

- Procainamide clearance can be computed using the following expression:

$Cl = k_0/Css$

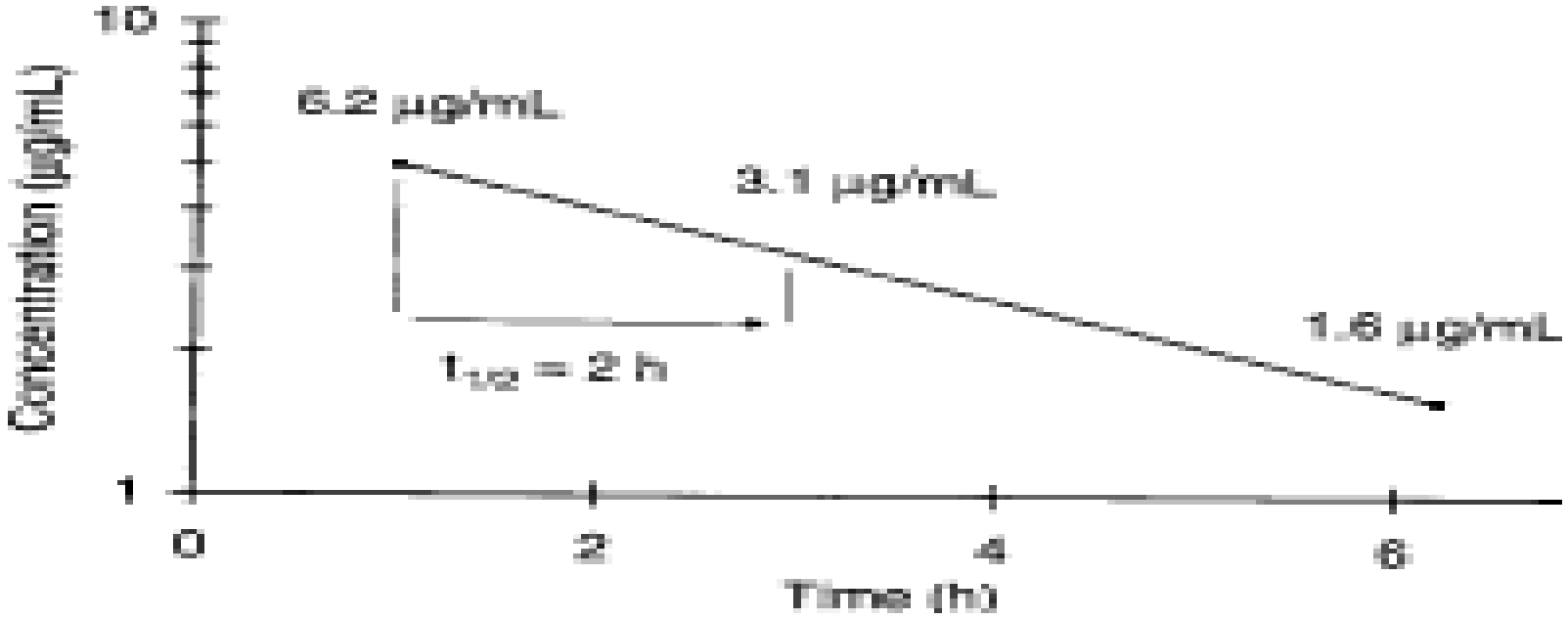
$= (5\ mg/min) / (8\ mg/L)$

$= 0.625\ L/min$

Continuous and Intermittent Intravenous Infusion Equations

- If the infusion did not run until steady state was achieved, it is still possible to compute pharmacokinetic parameters from postinfusion concentrations.

- Example, a patient was given a single 120-mg dose of tobramycin as a 60-minute infusion, and concentrations at the end of infusion (6.2 mg/L) and 4 hours after the infusion ended (1.6 mg/L) were obtained.



Tobramycin concentrations are plotted on semilogarithmic axes, and a straight line is drawn connecting the concentrations. Half-life ($t_{1/2}$) is determined by measuring the time needed for serum concentrations to decline by 1/2 (i.e., from 6.2 mg/L to 3.1 mg/L), and is converted to the elimination rate constant (k_e = 0.693/$t_{1/2}$ = 0.693/2 h = 0.347 h^{-1}).

Continuous and Intermittent Intravenous Infusion Equations

- Alternatively, the elimination rate constant can be calculated without plotting the concentrations using the following equation:

$$\mathbf{k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)}$$

$k_e = -[\ln (6.2\ mg/L) - \ln (1.6\ mg/L)] / (1\ h - 5\ h)$

$= 0.339\ h^{-1}$ (note the slight difference is due to rounding errors)

$$\mathbf{t_{1/2} = 0.693/k_e}$$

$= 0.693/0.339\ h^{-1}$

$= 2\ h$

Continuous and Intermittent Intravenous Infusion Equations

- The volume of distribution (V) can be computed using the following equation:

$$V = \frac{K_0 (1 - e^{- k_e t'})}{K_e [C_{max} - (C_{predose}\, e^{- k_e t'})]}$$

k_0: infusion rate

k_e: elimination rate constant

t': infusion time

C_{max}: maximum concentration at the end of infusion

$C_{predose}$: predose concentration

Continuous and Intermittent Intravenous Infusion Equations

$$V = \frac{(120\text{mg}/1\text{h})\,(1 - e^{-(0.339\ \text{h}^{-1})\,(1\text{h})})}{0.339\ \text{h}^{-1}\,[(6.2\text{mg/L}) - (0\ \text{mg/L} \cdot e^{-(0.339\ \text{h}^{-1})\,(1\text{h})})]}$$

$$= 16.4\ \text{L}$$