Intravenous Infusion

Objectives

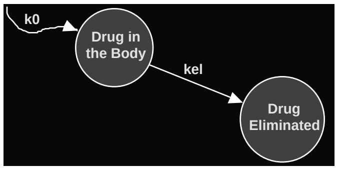
- To understand the diagrams, schemes, and graphs associated with single and multiple infusion regimens
- To recognize the differential and integrated equations associated with single or multiple infusion regimens
- To use the integrated equations to:
  - Determine kel and V parameter values
  - Develop safe dosage regimens

Intravenous Infusion

- Hospital Setting
- Maintenance therapy
- Stable and compatible drug
- Drugs too toxic for bolus administration
  - E.g. Phenytoin < 50 mg/min
    - Solvent the problem ?

Clinical Pharmacology: An Electronic Drug Reference

Scheme



Differential Equation

$$\frac{V \bullet dCp}{dt} = k0 - kel \bullet V \bullet Cp$$

Input +ve
From infusion

Output -ve
By Elimination

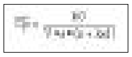
Integration

$$V \bullet s \bullet \overline{Cp} - Cp(0) = \frac{k0}{s} - kel \bullet V \bullet \overline{Cp}$$

$$V \bullet \overline{Cp} \bullet (s + kel) = \frac{k0}{s}$$

$$\overline{Cp} = \frac{k0}{V \bullet s \bullet (s + kel)}$$

Back-Transform



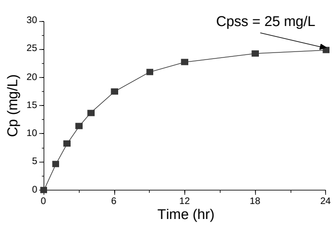
Two roots: 0 and -kel

$$Cp = \frac{k0}{V \cdot kel} + \frac{k0}{V \cdot -kel} \cdot e^{-kel \cdot t}$$

$$\boxed{Cp = \frac{k0}{V \cdot kel} \cdot \left[1 - e^{-kel \cdot t}\right]}$$

Similar to the Equation for Cumulative Amount Excreted Equation

Continuous Infusion



Approach to Steady State

$$Cp = \frac{k0}{kel \cdot V} \cdot \left[1 - e^{-kel \cdot t}\right]$$

When t = ∞ then $e^{-kel \cdot t} = 0$

$$\boxed{Cp^{ss} = \frac{k0}{kel \cdot V}}$$

$$\frac{V \cdot dCp}{dt} = k0 - kel \cdot V \cdot Cp = 0$$

Example Calculation

- Data: $t_{1/2}$ = 4 hr; V = 25 L; Cp^{ss} = 15 mg/L
- Question: What is the required k0
- kel = 0.693/4 = 0.17 hr^{-1}
- k0 = kel • V • Cp^{ss} = 0.17 x 25 x 15
  = 63.8 mg/hr
- Using 60 mg/hr
- Cp^{ss} = 60/(0.17 x 25) = 14.1 mg/L

Time to Reach Cp^{ss}

- Time to Reach Effective Cp - Cp^{ss}

$$Cp = \frac{Cp^{ss}}{2} = Cp^{ss} \bullet \left[1 - e^{-kel \bullet t_{half}}\right]$$

$$\frac{1}{2} = 1 - e^{-kel \bullet t_{half}}$$

$$\frac{1}{2} = e^{-kel \bullet t_{half}} \text{ or } 2 = e^{kel \bullet t_{half}}$$

$$\ln 2 = kel \bullet t_{half} = 0.693 = kel \bullet t_{1/2}$$

$$t_{half} = t_{1/2}$$

That is, the time it takes to get to half Cp^{ss} is the elimination half-life

Time to Reach Cp^{ss}

- Approach to Cp^{ss} is exponential in nature
- However, speed of approach is controlled by kel NOT k0
- And, the value of Cp^{ss} IS controlled or determined by k0

Time to Reach Cp^{ss}

- 50% to steady state in 1 half-life
- 75% to steady state in 2 half-lives
- 86% to steady state in 3 half-lives
- 94% to steady state in 4 half-lives
- If $t_{1/2}$ is 4 hours then it will take 16 hours to reach 94% of the desired Cp^{ss}

Example Calculation

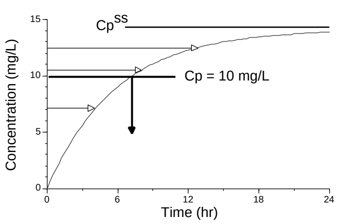
- Data: k0 = 60 mg/hr; kel = 0.17 hr^{-1}; Cp_{reqd} = 10 mg/L; Cp^{ss} = 14. mg/L
- Question: How long will it take to reach Cp_{reqd}

$$Cp = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet t}\right]$$

$$10 = \frac{60}{0.17x25} x\left[1 - e^{-0.17xt}\right]$$

$$0.292 = e^{-0.17xt} \quad OR \quad t = 7.24 \text{ hr}$$

Time to Reach Cp^{ss}



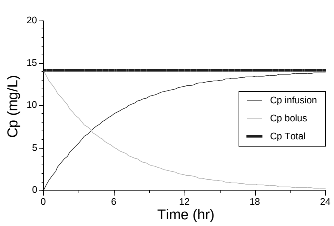
Strategies for Faster Approach to Cp^{ss}

- Combine Bolus and Infusion Administration
  - When a bolus dose is possible
- Fast then Slow Infusion Regimen

Bolus Dose plus Infusion

- Data: Cp^{ss} = 14.1 mg/L; V = 25 L; and kel = 0.17 hr^{-1}
- Loading Dose
  Dose = V • Cp^{ss} = 25 x 14.1 = 353 mg
- Maintenance Dose from before
  k0 = 60 mg/hr

Bolus Dose plus Infusion



Fast and Slow Infusion

- Data: Cp^{ss} = 14.1 mg/L; k0 = 60 mg/hr; V = 25 L; and kel = 0.17 hr^{-1}
- Required Fast Infusion over 30 minutes

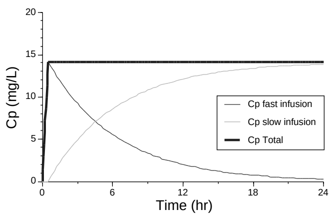
$$Cp = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet t}\right]$$

$$14.1 = \frac{k0}{0.17x25} x\left[1 - e^{-0.17x0.5}\right]$$

$$k0 = 735 \text{ mg/hr}$$

- Slow Infusion from before
  k0 = 60 mg/hr

Fast and Slow Infusion



Fast and Slow Infusion

- Dosage Regimen
  k0 = 735 mg/hr for 30 minutes
  k0 = 60 mg/hr
- NOTE: Cp^{ss} when k0 = 735 mg/hr

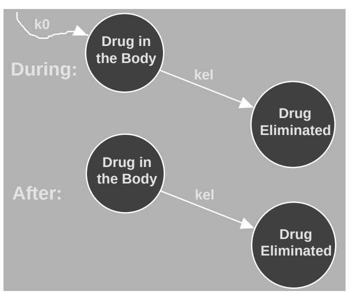
$$Cp^{ss} = \frac{k0}{kel \bullet V} = \frac{735}{0.17x25} = 173 \text{ mg/L}$$

Toxic Overdose

Once the Infusion Stops

- Schemes
- Equations
- Figures

Schemes



Equations

- Differential Equation

$$\frac{dCp}{dt} = -kel \bullet Cp$$

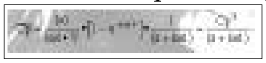
- Laplace Transform

Concentration at the End of the Infusion

$$s \bullet \overline{Cp} - \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet T}\right] = -kel \bullet \overline{Cp}$$

$$\overline{Cp} = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet T}\right] \bullet \frac{1}{(s + kel)} = \frac{Cp^{T}}{(s + kel)}$$

Equation (continued)

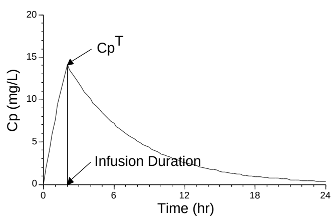


Take the Back Transform

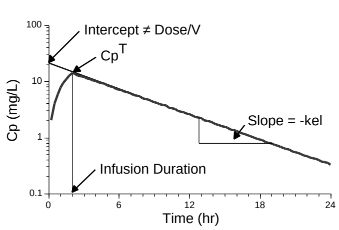
$$Cp = Cp^{T} \bullet e^{-kel \bullet (t-T)} = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet T}\right] \bullet e^{-kel \bullet (t-T)}$$

For t < T then T = t
For t > T then T = T

Linear Plot



Semi-log Plot

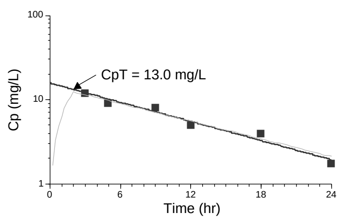


Example Calculation

Infusion Rate = 100 mg/hr for 2 hours

Time (hr)	Cp (mg/L)
3	12
5	9
9	8
12	5
18	3.9
24	1.7

Example Calculation



Elimination Rate Constant

$$kel = \frac{\ln Cp_1 - \ln Cp_2}{t_2 - t_1}$$

$$kel = \frac{\ln 13 - \ln 1.9}{24 - 2} = 0.087\ hr^{-1}$$

Apparent Volume of Distribution

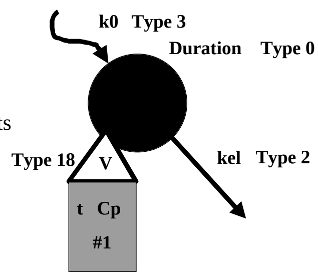
$$Cp^{T} = \frac{k0}{kel \bullet V} \bullet \left[1 - e^{-kel \bullet T}\right]$$

$$13 = \frac{100}{0.087xV} \bullet \left[1 - e^{-0.087x2}\right]$$

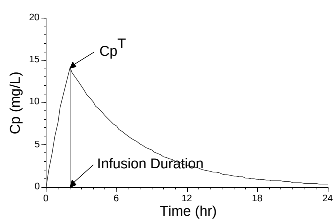
$$V = 88.4x\left[1 - 0.840\right] = 14.1\ L$$

Data Analysis

- Using Boomer
  - – Define Model
  - – Enter Data
  - – Review Results



Time Interrupts



Data Analysis

- Using Boomer
  - Define Model
  - Enter Data
  - Review Results

Data Analysis

- Using Boomer
  - Define Model
  - Enter Data
  - Review Results

Data Analysis

- Using SAAM II
  - Define Model
  - Enter Data
  - Review Results

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- Using SAAM II
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- Using SAAM II
  - Define Model
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HyperCard Stack

- One Compartment IV Infusion

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