Multiple IV Bolus Dose Administration

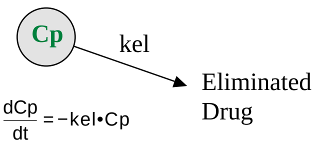
Objectives

- Understand drug accumulation after repeated dose administration
- Recognize and use integrated equations for Cp after multiple IV bolus doses
- Understand loading dose, maintenance dose, and dosing interval
- Calculate appropriate multiple dose regimen
  - to achieve desired Cp_{min}/Cp_{max} values

Single Dose Equations

- IV Bolus
- IV Infusion
- Oral Administration

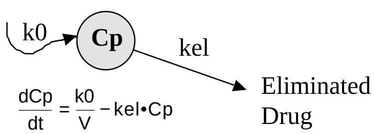
IV Bolus



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

$$Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

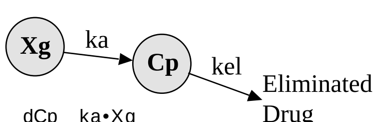
IV Infusion



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

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

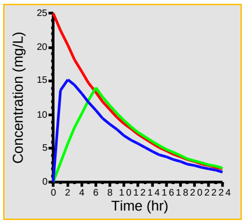
Oral Administration



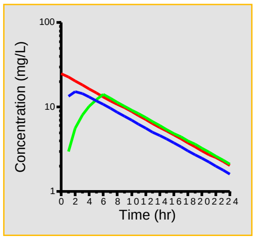
$$\frac{dCp}{dt} = \frac{ka \bullet Xg}{V} - kel \bullet Cp$$

$$Cp = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left[e^{-kel \bullet t} - e^{-ka \bullet t}\right]$$

Linear Plots



Semi-log Plots



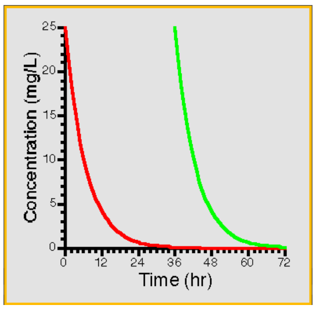
Multiple Dose

- Aspirin
  - Headache - single dose
  - Arthritis - multiple dose
- Antibiotics, anti-hypertensives, etc.
  - Multiple dose to maintain effective concentrations

Multiple I.V. Bolus

- Accumulation
  - Subsequent doses given before drug from previous dose(s) eliminated
- Plateau - Steady State
  - Amount of drug eliminated during dosing interval the same as the dose given every dosing interval

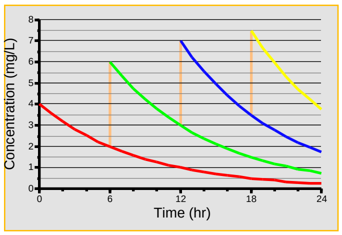
Independent Doses



Accumulating Dose

- Second and subsequent doses given before previous doses removed from patient
- Example: Give 100 mg dose every six hours
  - $t_{1/2}$ = 6 hr and V = 25 L
- Cp^0 = Dose/V = 100/25 = 4 mg/L
- After 6 hours Cp = 2 mg/L (after one half-life)

Accumulating Doses



As a table

Start		End	Cp lost
4	-->	2 mg/L	2 mg/L
6	-->	3 mg/L	3 mg/L
7	-->	3.5 mg/L	3.5 mg/L
7.5	-->	3.75 mg/L	3.75 mg/L
	......		
8	-->	4 mg/L	4 mg/L

Note: Cp lost = Cp gained by each dose

Development of a General Equation

– At the end of the first dosing interval, τ

$$Cp_1^{\tau} = Cp_1^{0} \bullet e^{-kel \bullet \tau}$$

where $Cp_{\text{dose number}}^{\text{time since last dose}}$

– At the start of the second interval

$$Cp_2^{0} = Cp_1^{\tau} + Cp_1^{0} = Cp_1^{0} \bullet e^{-kel \bullet \tau} + Cp_1^{0}$$

Redefine $e^{-kel \bullet \tau}$ as R

– At the start of the second interval

$$Cp_2^0 = Cp_1^\tau + Cp_1^0 = Cp_1^0 \bullet R + Cp_1^0$$

– At the end of the second interval

$$Cp_2^\tau = Cp_1^0 \bullet R + Cp_1^0 \bullet R^2$$

– At the start of the third interval

$$Cp_3^0 = Cp_1^0 + Cp_1^0 \bullet R + Cp_1^0 \bullet R^2$$

Geometric Series

– Start of Interval, n

$$Cp_n^0 = Cp_1^0 + Cp_1^0 \bullet R + Cp_1^0 \bullet R^2 + \cdots + Cp_1^0 \bullet R^{n-1}$$

– End of Interval, n

$$Cp_n^\tau = Cp_1^0 \bullet R + Cp_1^0 \bullet R^2 + Cp_1^0 \bullet R^3 + \cdots + Cp_1^0 \bullet R^n$$

Sum of Geometric Series

– At Start of Interval n

$$Cp_n^0 = Cp_1^0 \bullet \left[\frac{1-R^n}{1-R}\right] = \frac{Dose}{V} \bullet \left[\frac{1-e^{-n \bullet kel \bullet \tau}}{1-e^{-kel \bullet \tau}}\right]$$

– At the End of Interval n

$$Cp_n^\tau = Cp_1^0 \bullet \left[\frac{1-R^n}{1-R}\right] \bullet R = \frac{Dose}{V} \bullet \left[\frac{1-e^{-n \bullet kel \bullet \tau}}{1-e^{-kel \bullet \tau}}\right] \bullet e^{-kel \bullet \tau}$$

General Equation

$$Cp_n^t = \frac{Dose}{V} \bullet \left[\frac{1 - e^{-n \bullet kel \bullet \tau}}{1 - e^{-kel \bullet \tau}} \right] \bullet e^{-kel \bullet t}$$

Cp_{max} and Cp_{min}

– After ‘many’ doses, as n approaches ∞ $e^{-n \bullet kel \bullet t} = R^n$ approaches 0

$$Cp_\infty^0 = Cp_{max} = \frac{Cp_1^0}{(1-R)} = \frac{Dose}{V \bullet (1-R)}$$

AND

$$Cp_\infty^\tau = Cp_{min} = \frac{Cp_1^0 \bullet R}{(1-R)} = \frac{Dose \bullet R}{V \bullet (1-R)}$$

Example

– Data: Dose 100 mg q6h; $t_{1/2}$ = 4 hr; kel = 0.17 hr^{-1}; V = 10 L; R = $e^{-0.17 \times 6}$ = 0.35

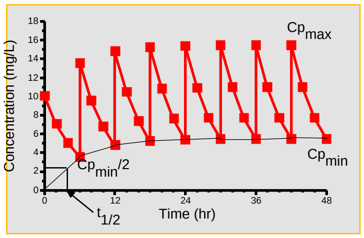
– Question: What are Cpmax and Cpmin

– Results:

$$Cp_{max} = \frac{Dose}{V \bullet (1-R)} = \frac{100}{10 \bullet (1-0.35)} = 15.5 \text{ mg/L}$$

$$Cp_{min} = \frac{Dose \bullet R}{V \bullet (1-R)} = Cp_{max} \bullet R = 15.5 \times 0.35 = 5.4 \text{ mg/L}$$

The Approach to Cp_{max}



Approach to Cp_{max}

- Loading Dose = Cp_{max} • V = 15.5 x 10 = 155 mg
- Dosing Regimen: 155 mg IV loading dose followed by 100 mg q6h
- Maintenance Dose = (1 - R) • Loading Dose

Another Example

- Data: Cp_{max} = 35 mg/L (MTC); Cp_{min} = 10 mg/L (MEC); V = 25 L; kel = 0.15 hr^{-1}
- Question: Calculate Dosage Regimen
- Equation:

$$\frac{Cp_{max}}{Cp_{min}} = \frac{Dose}{V \bullet (1-R)} \bullet \frac{V \bullet (1-R)}{Dose \bullet R} = \frac{1}{R}$$

The Calculations

$$R = \frac{Cp_{min}}{Cp_{max}} = \frac{10}{35} = 0.2857 = e^{-kel \bullet \tau}$$

$$-kel \bullet \tau = -1.2528$$

or

$$\tau = 8.35 \text{ hr}$$

The Calculations cont.

– Using a dosing interval of 8 hours

$$\text{Thus } R = e^{-kel \bullet \tau} = e^{-8 \times 0.15} = 0.3012$$

$$Cp_{max} = \frac{Dose}{V \bullet (1 - R)}$$

$$\begin{aligned} Dose &= Cp_{max} \bullet V \bullet (1 - R) \\ &= 35 \times 25 \times (1 - 0.3012) \\ &= 611 \text{ mg} \end{aligned}$$

The Dosing Regimen

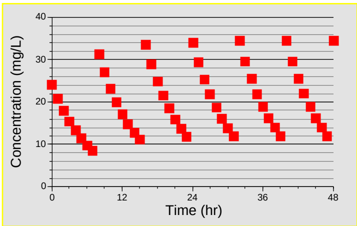
– Loading Dose = Cp_{max} • V = 35 x 25 = 875 mg
– Loading Dose: 875 or 850 mg
– Maintenance Dose: 600 mg q8h

Checking the Approximation

$$Cp_{max} = \frac{Dose}{V \bullet (1-R)} = \frac{600}{25 \times (1-0.3012)} = 34.3 \text{ mg/L}$$

$$Cp_{min} = Cp_{max} \bullet R = 10.3 \text{ mg/L}$$

A Graphical Answer



Computer Simulation

- On-Line Applets
  - Linear
  - Semi-log
- SAAM II

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