Multiple Oral Dose Administration

Objectives

- To recognize and use the integrated equations for multiple oral dose administration
- To calculate appropriate multiple dose regimen
- To define, calculate and use the parameter $\overline{Cp}$
- To use the superposition principle to calculate Cp after non uniform dosing regimen

Oral Dose Administration

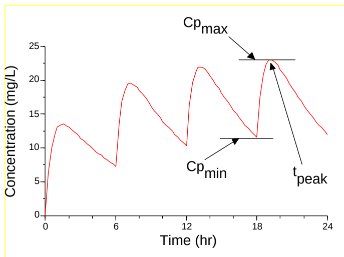
- Single Dose

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

- Multiple Dose

$$Cp = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[\frac{1 - e^{-n \cdot kel \cdot \tau}}{1 - e^{-kel \cdot \tau}} \cdot e^{-kel \cdot t} - \frac{1 - e^{-n \cdot ka \cdot \tau}}{1 - e^{-ka \cdot \tau}} \cdot e^{-ka \cdot t} \right]$$

Cp versus Time



Cp_{max} and Cp_{min}

– Cp_{max} could be calculated if t_{max} is known from 'full' equation
– Cp_{min} can be calculated at t = 0 or $t = \tau$

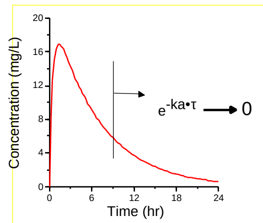
Cp_{min} Equation

at t = 0 and with n large -> ∞
$e^{-n \cdot kel \cdot \tau}$ and $e^{-n \cdot kel \cdot \tau}$ both -> 0

$$Cp_{min} = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[\frac{1}{1 - e^{-kel \cdot \tau}} - \frac{1}{1 - e^{-ka \cdot \tau}} \right]$$

Simplify Equation

if $e^{-ka \cdot \tau} >> 0$



Simplify Equation…

$$Cp_{min} = \frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[\frac{e^{-kel \cdot \tau}}{1 - e^{-kel \cdot \tau}}\right]$$

or

$$Cp_{min} = A \cdot \left[\frac{R}{1 - R}\right]$$

Accumulation

$$\frac{Cp_{min}}{Cp_1^{\tau}} = \frac{\frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[\frac{e^{-kel \cdot \tau}}{1 - e^{-kel \cdot \tau}}\right]}{\frac{F \cdot Dose \cdot ka}{V \cdot (ka - kel)} \cdot \left[e^{-kel \cdot \tau}\right]}$$

or

$$\frac{Cp_{min}}{Cp_1^{\tau}} = \frac{A \cdot \left[\frac{R}{1 - R}\right]}{A \cdot R} = \frac{1}{(1 - R)} = \frac{1}{1 - e^{-kel \cdot \tau}}$$

if $e^{-ka \cdot \tau} \approx 0$

Loading Dose =

$$\text{Loading Dose} = \frac{\text{Maintenance Dose}}{(1 - R)}$$

Further Simplification

– if ka >> kel

$$\frac{ka}{(ka - kel)} \approx 1$$

$$Cp_{min} = \frac{F \cdot Dose}{V} \cdot \left[\frac{e^{-kel \cdot \tau}}{1 - e^{-kel \cdot \tau}} \right]$$

– this is an even more extreme approximation

– if ka unknown but absorption fast it may be useful

The Three Equations

F	1	
Dose	250	mg
ka	2	hr -1
kel	0.15	hr -1
V	15	L
Tau	6	hr
	Cp min	
Full Equation	12.3444	
ka• tau >> ∞	12.3445	
ka >> kel	11.4186	

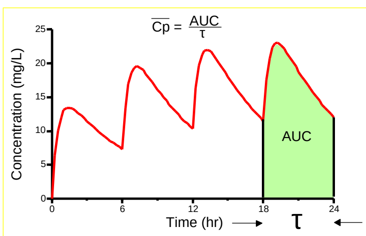
EXCEL

Average Concentration, $\overline{Cp}$

- Average plasma concentration during steady state can be useful
- Calculated as AUC/τ

$$\overline{Cp} = \frac{\int_0^{\tau} Cp \bullet dt}{\tau} = \frac{F \bullet Dose}{V \bullet kel \bullet \tau}$$

Graphical Representation



Average Concentration

$$\overline{Cp} = \frac{\int_0^{\tau} Cp \bullet dt}{\tau} = \frac{F \bullet Dose}{V \bullet kel \bullet \tau}$$

- Note Changing the Dose and the Dosing Interval by the Same Factor gives the SAME $\overline{Cp}$
- e.g. 300 mg q12h gives the same $\overline{Cp}$ as 100 mg q4h
  - however Cp_{min} and Cp_{max} would change

Example Calculation

- Data: F = 1; V = 30 L; $t_{1/2}$ = 6 hr; kel = 0.116 hr^{-1}
- Question: Dose every 12 hours to achieve 15 mg/L
- Equation:

$$\overline{Cp} = \frac{F \bullet Dose}{V \bullet kel \bullet \tau}$$

$$Dose = \frac{\overline{Cp} \bullet V \bullet kel \bullet \tau}{F}$$

$$Dose = \frac{15x30x0.116x12}{1} = 624 \text{ mg}$$

Loading Dose

$$R = e^{-kel \bullet \tau} = e^{-0.116x12} = 0.25$$

$$\text{Loading Dose} = \frac{\text{Maintenance Dose}}{1-R}$$

$$\text{Loading Dose} = \frac{624}{1-0.25} = 832 \text{ mg}$$

- Dosing Regimen 800 - 850 mg to start then 600 - 650 mg every 12 hours

Estimate Cp_{min} and Cp_{max}

- Assuming ka >> kel and $e^{-ka \bullet \tau}$ -> 0

$$Cp_{min} = \frac{1 \times 624}{30} \times \left[\frac{0.25}{1-0.25}\right] = 6.93 \text{ mg/L}$$

$Cp_{max} \approx 15 + (15 - 7) = 23$ mg/L

$\overline{Cp} = 15$ mg/L

$Cp_{min} = 7$ mg/L

Alternative Regimen

312 mg q 6 h

$$Cp_{min} = \frac{1 \times 312}{30} \times \left[\frac{0.5}{1 - 0.5}\right] = 10.4 \text{ mg/L}$$

$Cp_{max} \approx 15 + (15 - 10) = 20$ mg/L

$\overline{Cp} = 15$ mg/L

$Cp_{min} = 10$ mg/L

Non-Uniform Dosing

Superposition Principle

- Applies when all disposition processes are linear
  - disposition = DME
  - linear = first order
- Allows addition of concentrations from separate doses = multiple dose
- Double the dose = double the concentration

Equations

$$Cp_1 = \frac{200}{15} \times e^{-0.15 \times t}$$

$$Cp_2 = \frac{300}{15} \times e^{-0.15 \times (t-6)}$$

$$Cp_3 = \frac{100}{15} \times e^{-0.15 \times (t-18)}$$

$Cp = Cp_1 + Cp_2 + Cp_3$

AL (24 hr)

Equations

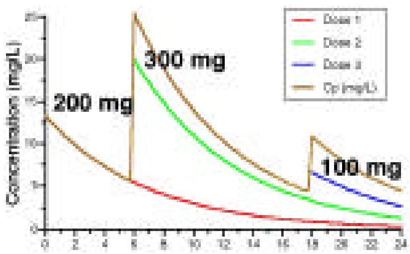
$$Cp_1 = \frac{200}{15} \times e^{-0.15 \times t} = 0.36 mg/L$$

$$Cp_2 = \frac{300}{15} \times e^{-0.15 \times (t-6)} = 1.34 mg/L$$

$$Cp_3 = \frac{100}{15} \times e^{-0.15 \times (t-18)} = 2.71 mg/L$$

$Cp = Cp_1 + Cp_2 + Cp_3 = 4.41$ mg/L

Graphical Representation



Another Approach

$$Cp_1^0 = \frac{200}{15} = 13.33 \text{ mg/L}$$

$$Cp_1^6 = 13.33xe^{-0.15x6} = 5.42 \text{ mg/L}$$

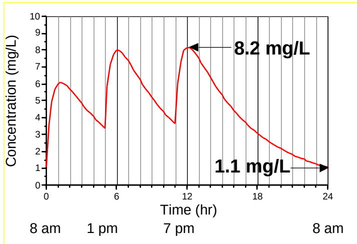
$$Cp_2^0 = 5.42 + \frac{300}{15} = 25.42 \text{ mg/L}$$

$$Cp_2^{12} = 25.42xe^{-0.15x12} = 4.20 \text{ mg/L}$$

$$Cp_3^0 = 4.20 + \frac{100}{15} = 10.87 \text{ mg/L}$$

$$Cp_3^6 = 10.87xe^{-0.15x6} = 4.42 \text{ mg/L}$$

Multiple Oral Doses at steady state



Oral Doses: 200 mg at 8 am, 1 pm, and 7 pm:
kel = 0.18 hr^{-1}; ka = 2 hr^{-1}; V = 30 L

Non-Uniform Dosing

May be acceptable if

- Drug has wide therapeutic index
- No therapeutic disadvantage to low overnight plasma concentration
  - e.g. analgesic if patient asleep

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