Pharmacokinetics of Oral Administration

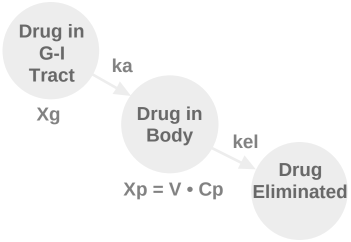
Objectives

- Understand the diagrams, schemes, and graphs associated with Oral Administration
- Write the associated Differential Equations
- Derive the associated Integrated Equation
- Understand the relationship between t_{max} and Cp_{max}
- Understand the Influence of ka and F on Cp for a given dose

Extravascular Administration

- Not IV
- All other Routes of Administration involve an Absorption Step including Oral, IM, SC, etc.
- Absorption Defined by Rate and Extent

Scheme



Equations for Drug in GI Tract

Differential Equation

$$\frac{dXg}{dt} = -ka \bullet Xg$$

$$s \bullet \overline{Xg} - Xg^0 = -ka \bullet \overline{Xg}$$

$$\overline{Xg} \bullet (s + ka) = Xg^0$$

$$\overline{Xg} = \frac{Xg^0}{(s + ka)}$$

$$Xg = Xg^0 \bullet e^{-ka \bullet t}$$

Integrated Equation

Equation for Amount in the Body

Differential Equation

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

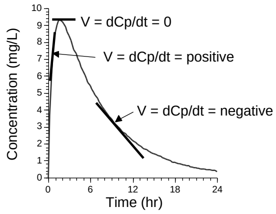
Absorption

Elimination

Rate at Selected Times

- Early: Xg >> V•Cp thus $\frac{V \bullet dCp}{dt}$ is positive
- Middle: Xg = V•Cp thus $\frac{V \bullet dCp}{dt}$ is zero
- Late: Xg << V•Cp thus $\frac{V \bullet dCp}{dt}$ is negative

Concentration versus Time



Integrated Equation

Differential Equation: $\frac{dXp}{dt} = \frac{V \bullet dCp}{dt} = ka \bullet Xg - kel \bullet V \bullet Cp$

$$s \bullet V \bullet \overline{Cp} - Cp^0 = ka \bullet \overline{Xg} - kel \bullet V \bullet \overline{Cp}$$

using $\overline{Xg} = \frac{Xg^0}{(s + ka)}$ from before

$$V \bullet \overline{Cp} \bullet (s + kel) = \frac{ka \bullet Xg^0}{(s + ka)}$$

$$\overline{Cp} = \frac{ka \bullet Xg^0}{V \bullet (s + kel) \bullet (s + ka)}$$

Integrated Equation

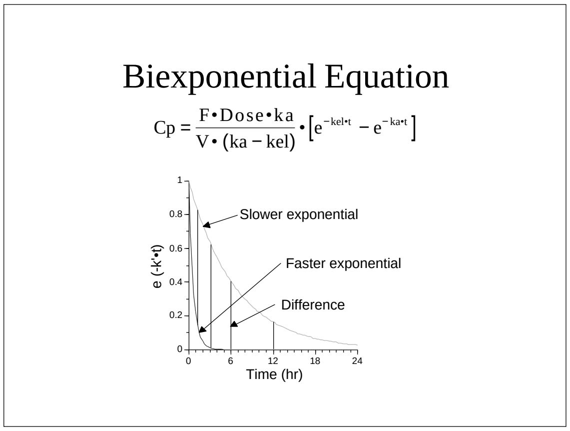
$$\overline{Cp} = \frac{ka \bullet Xg^0}{V \bullet (s + kel) \bullet (s + ka)}$$

Two roots: -kel and -ka

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

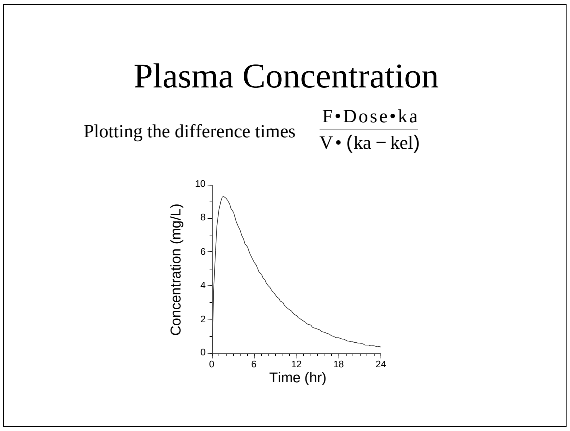
Constant **X** **Difference between Two Exponential Terms**

Note: Xg^0 = F • Dose



Biexponential Equation

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



Plasma Concentration

Plotting the difference times $\frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)}$

The Equation

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

$$\left.\begin{array}{r}\textbf{F}\\ \textbf{Dose}\\ \textbf{ka}\end{array}\right\} \begin{array}{l}\textbf{Dose and Dosage}\\ \textbf{Form Parameters}\end{array}$$

$$\left.\begin{array}{r}\textbf{kel}\\ \textbf{V}\end{array}\right\} \begin{array}{l}\textbf{Drug and Patient}\\ \textbf{Parameters}\end{array}$$

Time to Peak Concentration

$$t_{peak} = \frac{1}{(ka - kel)} \bullet \ln \left(\frac{ka}{kel} \right)$$

Derived from differentiating dCp/dt with respect to time and setting 2nd derivative to zero

Example: F = 0.9, Dose = 600 mg, ka = 1 hr^{-1}, kel = 0.15 hr^{-1}, and V = 30 L

$$t_{peak} = \frac{1}{(1 - 0.15)} x \ln \left(\frac{1}{0.15} \right) = 2.23 \text{ hr}$$

$$Cp = \frac{0.9x600x1}{30x(1 - 0.15)} x \left[e^{-0.15x2.23} - e^{-1x2.23} \right] = 12.9 \text{ mg/L}$$

Time to Peak Concentration

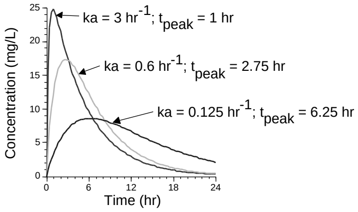
$$t_{peak} = \frac{1}{(ka - kel)} \bullet \ln \left(\frac{ka}{kel} \right)$$

Example: F = 0.9, Dose = 600 mg, ka = 0.2 hr^{-1}, kel = 0.15 hr^{-1}, and V = 30 L

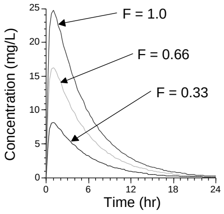
$$t_{peak} = \frac{1}{(0.2 - 0.15)} x \ln \left(\frac{0.2}{0.15} \right) = 5.75 \text{ hr}$$

$$Cp = \frac{0.9x600x0.2}{30x(0.2 - 0.15)} x \left[e^{-0.15x5.75} - e^{-0.2x5.75} \right] = 7.6 \text{ mg/L}$$

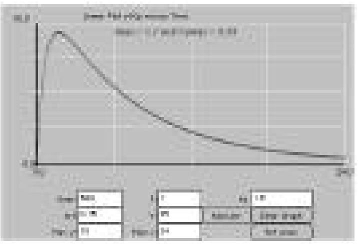
Absorption Rate Constant, ka



Extent of Absorption Bioavailability, F

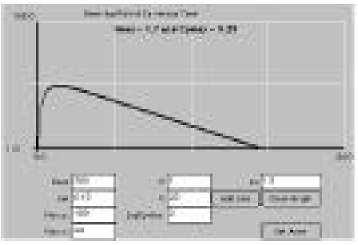


Plotting with Java



Screen Capture > Print

A Semi-log Plot



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