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 $t_{\text{max}}$ and $C_{\text{p, max}}$
- Understand the Influence of $k_a$ and $F$ on $C_p$ 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
\[
\frac{dX_g}{dt} = -ka \cdot X_g \\
\frac{dX_p}{dt} = -ka \cdot X_g \\
X_g \cdot s \cdot X_g = X_g^a \\
X_g = \frac{X_g^a}{s + ka} \\
X_g = X_g^a \cdot e^{-ka \cdot t}
\]

Integrated Equation

Equation for Amount in the Body

Differential Equation
\[
\frac{dX_p}{dt} = V \cdot \frac{dC_p}{dt} = ka \cdot X_g - kel \cdot V \cdot C_p
\]

Absorption

Elimination
Rate at Selected Times

- Early: \( X_g \gg V \cdot C_p \) thus \( \frac{V \cdot dC_p}{dt} \) is positive
- Middle: \( X_g = V \cdot C_p \) thus \( \frac{V \cdot dC_p}{dt} \) is zero
- Late: \( X_g \ll V \cdot C_p \) thus \( \frac{V \cdot dC_p}{dt} \) is negative

Concentration versus Time

Integrated Equation

Differential Equation:
\[
\frac{dX_g}{dt} = \frac{V \cdot dC_p}{dt} = k_a \cdot X_g - k_e_l \cdot V \cdot C_p
\]

\[
s \cdot V \cdot C_p - C_p = k_a \cdot X_g - k_e_l \cdot V \cdot C_p
\]

Using \( X_g = \frac{X_g^0}{s + k_a} \) from before

\[
V \cdot C_p \cdot (s + k_e_l) = \frac{k_a \cdot X_g^0}{s + k_a}
\]

\[
C_p = \frac{k_a \cdot X_g^0}{V \cdot (s + k_e_l) \cdot (s + k_a)}
\]
Integrated Equation

\[
C_p = \frac{ka \cdot X_g^0}{V \cdot (s + kel) \cdot (s + ka)}
\]

Two roots: \(-kel\) and \(-ka\)

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

Constant \(X\) Difference between Two Exponential Terms

Note: \(X_g^0 = F \cdot \text{Dose}\)

Biexponential Equation

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

Plasma Concentration

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

0 6 12 18 24

\(e^{-k' \cdot t}\)

0 6 12 18 24

Concentration (mg/L)

Time (hr)

0 6 12 18 24

Plasma Concentration

0 6 12 18 24

Concentration (mg/L)

Time (hr)
The Equation

\[ C_p = \frac{F \cdot \text{Dose} \cdot k_a}{V \cdot (k_a - k_e)} \left[ e^{-k_e t} - e^{-k_a t} \right] \]

\[ F \quad \text{Dose} \] 
\[ k_a \quad \text{Form Parameters} \]

\[ k_e \quad \text{Drug and Patient Parameters} \]

Time to Peak Concentration

\[ t_{\text{peak}} = \frac{1}{(k_a - k_e)} \ln \left( \frac{k_a}{k_e} \right) \]

Derived from differentiating \( \frac{dC_p}{dt} \) with respect to time and setting 2nd derivative to zero

Example: \( F = 0.9, \text{Dose} = 600 \text{ mg}, k_a = 1 \text{ hr}^{-1}, \) \( k_e = 0.15 \text{ hr}^{-1}, \) and \( V = 30 \text{ L} \)

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

\[ C_p = \frac{0.9 \times 600 \times 1}{30 \times (1 - 0.15)} \left[ e^{\left(0.15 \times 2.23\right)} - e^{\left(-0.15 \times 2.23\right)} \right] = 12.9 \text{ mg/L} \]

Time to Peak Concentration

\[ t_{\text{peak}} = \frac{1}{(k_a - k_e)} \ln \left( \frac{k_a}{k_e} \right) \]

Example: \( F = 0.9, \text{Dose} = 600 \text{ mg}, k_a = 0.2 \text{ hr}^{-1}, \) \( k_e = 0.15 \text{ hr}^{-1}, \) and \( V = 30 \text{ L} \)

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

\[ C_p = \frac{0.9 \times 600 \times 0.2}{30 \times (0.2 - 0.15)} \left[ e^{\left(-0.2 \times 5.75\right)} - e^{\left(0.15 \times 5.75\right)} \right] = 7.6 \text{ mg/L} \]
Absorption Rate Constant, $ka$

- $ka = 3 \text{ hr}^{-1}$; $t_{peak} = 1 \text{ hr}$
- $ka = 0.6 \text{ hr}^{-1}$; $t_{peak} = 2.75 \text{ hr}$
- $ka = 0.125 \text{ hr}^{-1}$; $t_{peak} = 6.25 \text{ hr}$

Extent of Absorption
Bioavailability, $F$

- $F = 1.0$
- $F = 0.66$
- $F = 0.33$

Plotting with Java

Screen Capture > Print
A Semi-log Plot

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 $t_{\text{max}}$ and $C_{\text{pmax}}$
• Understand the Influence of $k_a$ and $F$ on $C_p$ for a given dose