A SEMINAR ON

METHODS OF DETERMINING ABSORPTION RATE CONSTANT

by

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INTRODUCTION

- Absorption can be defined as the process of movement of unchanged drug from site of administration to site of measurement i.e. plasma.
- The actual drug absorption process may be zero-order, first-order, or a combination of rate processes that is not easily quantitated.
For a drug that follows one-compartment kinetics and administered extra vascularly, the time course of drug concentration in plasma is expressed by a bi exponential equation 1.

\[ C_p = \frac{kaFX_0}{Vd(ka - kel)} (e^{-kelt} - e^{-kat}) \]

→ Equation-1
Equation 1 can be written as

$$C_p = A e^{-k_e t} - A e^{-k_a t} \quad \rightarrow \text{Equation-2}$$

where

$$A = \frac{kaFX_0}{Vd(ka - k_e)}$$

Figure 1. Semi-log plot of $C_p$ versus Time after Oral Administration
During the elimination phase, when absorption is almost over, \( K_a \gg K_{el} \) and the value of second exponential approaches zero \( (e^{-kat}) \) whereas the first exponential \( (e^{-ket}) \) retains some finite value.

At this time, the equation 2 reduced to

\[
\overleftarrow{C_p} = A.e^{-kel.t} \quad \rightarrow \text{equation -3}
\]

where \( \overleftarrow{c_p} \) represents the back extrapolated plasma concentration values.

A plot of log \( c_p \) verses \( t \) gives terminal linear phase having slope = \(-ket/2.303\).

Back extrapolation of this straight line to time zero yields \( y \)-intercept equals to=\( \log A \)
Figure 2. Semi-log Plot of Cp versus Time after oral administration of single dose

Intercept = \log\left(\frac{K_a F X_0}{V_d (K_a - K)} \right)

Slope = - \frac{k_e}{2.303}

Back extrapolation terminal portion of curve logCp
Subtracting of true plasma concentration values i.e. equation 2 from extrapolated plasma concentration values i.e. equation 3 yields a series of \textit{residual concentration} values.

\[ C_r = \bar{c}_p - c_p \]

\[ C_r = A.e^{-ka \cdot t} \quad \rightarrow \text{equation 4} \]

Plotting the \( C_r \) versus time should give another straight line graph with a slope equal to \(- \frac{k_a}{2.303}\) and the same intercept as before, i.e. \( \log A \).
Figure 3. Semi-log Plot of Cp versus Time
From the slope, the absorption rate constant $K_a$ can be estimated.

In this method of calculation it is important to remember that the following *assumptions* are made:

1. It is assumed that $k_a$ is at least five times larger than $k_{el}$, if not neither constant can be determined accurately.

2. It is assumed that the *absorption* and *elimination* processes both follow the *first order*, if not the residual line and, perhaps, the elimination line will not be straight.
LAG TIME

- The time delay prior to the commencement of the first order drug absorption is known as Lag time ($t_0$).
- In some instances absorption of drug a single oral dose not started immediately due to such physiological factors as stomach-emptying time and intestinal mobility or due to formulation itself.

\[
C_p = \frac{Fk_a D_0}{V_D (k_a - k)} \left( e^{-k(t-t_0)} - e^{-k_a(t-t_0)} \right)
\]

where $Fk_a D_0 / V D (k_a - k)$ is the y value at the point of intersection of the residual lines in.

\[
C_p = Be^{-kt} - Ae^{-k_a t}
\]

where $A$ and $B$ represents the intercepts after extrapolation of the residual lines for absorption and elimination, respectively.
Figure 4. Determination of lag time by graphically
Flip-Flop of $k_a$ and $k_{el}$

- The estimation of the rate constant for absorption and elimination by method of residuals is based on the assumption that $k_a \gg k_{el}$.
- If $k_{el} \gg k_a$, then the values of $k_a$ from the terminal phase and $k_{el}$ from the residual line are obtained.
- This phenomenon is called flip-flop of the absorption and elimination rate constant.
- The only way to be sure of estimates is to compare $k_{el}$ calculated from oral administration with $k_{el}$ from intravenous data.
METHOD OF RESIDUALS FOR TWO COMPARTMENT MODEL

There are three first order processes occurring simultaneously i.e. absorption, distribution and elimination.

Plasma concentration of the drug depends initially on three process (three exponents), then on two processes of distribution and elimination (two exponentials) and finally on elimination process only (mono exponential).

\[ C = C_0 e^{-kat} + A e^{-\alpha t} + B e^{-\beta t} \]
Figure 5

\[ A = \frac{x_0}{V_0} \frac{(\alpha - K_{12})}{(\alpha - \beta)} \]

\[ B = \frac{x_0}{V_c} \frac{(K_{12} - \beta)}{(\alpha - \beta)} \]
APPLICATIONS

➢ To calculate absorption rate constant for a drug administered orally, absorbed by first order kinetics and confer the characteristics of one and two compartment open model.
➢ For a drug following intravenous administration and confer multy compartmental characteristics.

LIMITATIONS

When the absorption is complex rather than a simple first order process.
WAGNER-NELSON METHOD

The Wagner-Nelson method of calculation does not require a model assumption concerning the absorption process.

The assumptions are

(1) The body behaves as a single homogeneous compartment,

(2) Drug elimination obeys the first order kinetics.

For any e.v administration,

The amount administered = The amount absorbed (A) + The Amount unabsorbed (U)
The amount absorbed (A) to any time \( t \) = the amount of the drug in the body (\( X \)) + the amount of the drug eliminated from the body to any time, \( t \) (\( X_e \))

\[
A = X + X_e
\]

6

Taking the derivative with respective time

\[
dA/dt = dX/dt + dXe/dt
\]

7

but \( X = V_d \cdot C \), hence

\[
dX/dt = V_d \cdot dC/dt
\]

and \( dXe/dt = KX \) therefore,

\[
dXe/dt = K \cdot V_d \cdot C
\]

therefore,
\[ \frac{dA}{dt} = Vd \cdot \frac{dC}{dt} + K \cdot Vd \cdot C \]

\[ dA = Vd \cdot dC + K \cdot Vd \cdot C \cdot dt \]

Integrating equation 8 between limits of \( t = 0 \) to \( t = t \) gives,

\[ \int_{0}^{t} dA = Vd \int_{0}^{t} dC + K \cdot Vd \int_{0}^{t} C \cdot dt \]

\[ A_{t} - A_{0} = Vd \left| Ct - C_{0} \right| + K \cdot Vd \int_{0}^{t} C \cdot dt \]

\( A_{0} = \) amount of drug absorbed at \( t = 0 \) is zero, \& \( C_{0} = 0 \). So,

\[ A_{t} = Vd \cdot Ct + K \cdot Vd \int_{0}^{t} C \cdot dt \]

Rearranging the above equation

\[ \frac{At}{Vd} = Ct + K \int_{0}^{t} C \cdot dt \]
Where $At/Vd$ is the amount of drug absorbed up to time $t$ divided by the volume of distribution

$C_t = $ plasma concentration at time $t$

\[
\int_0^t C \cdot dt = \text{AUC up to time } t.
\]

Integrating equation 8 between the limits of $t = 0$ to $t = \infty$

And rearranging the equation, give the following

\[
\int_0^\infty dA = Vd\int_0^\infty dC + K.Vd.\int_0^\infty C \cdot dt
\]

\[
A_{\infty} = Vd.(C_{\infty} - C0) + K.Vd.\int_0^\infty C \cdot dt \quad \text{but } C_{\infty} = 0, \ C_0 = 0
\]

\[
\frac{A_{\infty}}{Vd} = K\int_0^\infty C \cdot dt
\]
Where, $\frac{A}{Vd} = \text{the total amount of drug absorbed from the dosage form up to infinity time divided by the volume of the distribution of the drug.}$

$$\int_{0}^{\infty} C.dt = \text{AUC up to } \infty$$

The fraction of absorbed at any time is obtained when equation 9 is divided by equation 10

$$\frac{At}{A_{\infty}} = \frac{\left( Ct + K \int_{0}^{t} C.dt \right)}{K \int_{0}^{\infty} Cdt}$$ \hspace{1cm} 11

the fraction of unabsorbed at any time t is

$$1 - \frac{At}{A_{\infty}} = 1 - \frac{\left( Ct + K \int_{0}^{t} C.dt \right)}{K \int_{0}^{\infty} Cdt}$$ \hspace{1cm} 12
Percent of unabsorbed drug versus time plot - Zero order

Log Percent of unabsorbed drug versus time plot - First order

Slope = absorption rate constant

Slope = $-k_a/2.303$
Wagner Nelson Method Procedure

1. Plot log concentration of drug versus time.
2. Find K from the terminal part of slope when the slope is \(-\frac{K}{2.303}\).
3. Find \(AUC_t^0\) by plotting Cp versus time.
4. Find \(K.AUC_t^0\) by multiplying each \(AUC_t^0\) by K.
5. Find \(AUC_{\infty}^0\) by adding up all the AUC pieces, from \(t = 0\) to \(t = \infty\).
6. Determine the 1-(Ab/Ab\(\infty\)) value corresponding to each time point using by the table.
7. Plot 1-(Ab/Ab\(\infty\)) versus time on semi log paper, with 1-(Ab/Ab\(\infty\))on the logarithmic axis.
For Example

<table>
<thead>
<tr>
<th>Time $t_n$ (hr)</th>
<th>Concentration $C_p$ ($\mu g/mL$)</th>
<th>$[AUC]^t_{n,t}$</th>
<th>$[AUC]^t_0$</th>
<th>$k[AUC]^t_0$</th>
<th>$C_p + k[AUC]^t_0$</th>
<th>$\frac{Ab}{Ab^\infty}$</th>
<th>$\left(1 - \frac{Ab}{Ab^\infty}\right)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.</td>
<td>0.</td>
<td>0.</td>
<td>0.</td>
<td>0.287</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.13</td>
<td>1.57</td>
<td>1.57</td>
<td>0.157</td>
<td>3.287</td>
<td>0.328</td>
<td>0.672</td>
</tr>
<tr>
<td>2</td>
<td>4.93</td>
<td>4.03</td>
<td>5.60</td>
<td>0.560</td>
<td>5.490</td>
<td>0.548</td>
<td>0.452</td>
</tr>
<tr>
<td>3</td>
<td>5.86</td>
<td>5.40</td>
<td>10.99</td>
<td>1.099</td>
<td>6.959</td>
<td>0.695</td>
<td>0.305</td>
</tr>
<tr>
<td>4</td>
<td>6.25</td>
<td>6.06</td>
<td>17.05</td>
<td>1.705</td>
<td>7.955</td>
<td>0.794</td>
<td>0.205</td>
</tr>
<tr>
<td>5</td>
<td>6.28</td>
<td>6.26</td>
<td>23.31</td>
<td>2.331</td>
<td>8.610</td>
<td>0.856</td>
<td>0.140</td>
</tr>
</tbody>
</table>

$k = 0.1 \text{ hr}^{-1}$
APPLICATIONS

- To understand the absorption kinetics without prior assumption.
- Two formulations of a drug that differ substantially in terms of how much of drug is eventually absorbed which is reflected in

\[ Ct + K \int_{0}^{t} C \cdot dt \]

Vs time plots

LIMITATIONS

- It applies rigorously only to the drugs with one compartmental characteristics.
- However, when conc vs time curve after oral administration shows multi compartmental characteristics and on IV administration shows one compartmental model, analysis by this method gives incorrect result
LOO-RIEGELMAN METHOD

➢ Loo-Riegelman method is useful in determining the absorption rate constant for a drug follows a *two compartment* model.

➢ It requires the plasma concentration time data after i.v. bolus and oral administration to obtain all necessary kinetic constants.

➢ This method can be applied to drug that can distributed by any number of compartments.
Ab = Xc + Xt + X₃  \rightarrow  \text{Equation 3.1}

\begin{align*}
Xc &= Vc \cdot C_p \\
Xt &= Vt \cdot C_t \\
X₃ &= Vc \cdot k_{13} \int C \cdot dt = Vc \cdot k_{13} \cdot \text{[AUC]}_0^t
\end{align*}

Substituting Xc and X₃ into equation 3.1

\begin{align*}
Ab &= Vc \cdot C_p + Xt + Vc \cdot k_{13} \cdot \text{[AUC]}_0^t  \rightarrow \text{Equation 3.2}
\end{align*}
• Dividing the equation 3.2 by \( V_c \), we get
\[
\frac{A_b}{V_c} = C_p + \frac{X_t}{V_c} + K_{13} \ [AUC]_0^t \quad \rightarrow \text{Equation 3.3}
\]

Setting the value of \( t = \infty \), this equation becomes
\[
A_b^\infty / V_c = 0 + 0 + K_{13} \ [AUC]_0^\infty
\]
\[
A_b^\infty / V_c = K_{13} \ [AUC]_0^\infty \quad \rightarrow \text{Equation 3.4}
\]

• Where, \( A_b^\infty \) is the amount of the drug that will be ultimately absorbed from the dosage form.
\[
F = A_b^\infty / X_0 \quad \rightarrow \text{Equation 3.5}
\]
The fraction of the dose absorbed at any time in comparison with $Ab^\infty$ can be obtained by dividing the equation 3.3 by equation 3.4.

\[
\frac{Ab}{Ab^\alpha} = \frac{C + \frac{Xt}{Vc} + K_{13}(AUC)^t_0}{K_{13}(AUC)^\infty_0}
\]

→ equation 3.6

Where, $\frac{Xt}{Vc} = C_t = \text{tissue concentration}$

figure 8

Absorption rate constant by Loo- Riegelman method
\[(C_t)_{t_n} = \frac{k_{12} \Delta C_p \Delta t}{2} + \frac{k_{12}}{k_{21}} (C_p)_{t_{n-1}} (1 - e^{-k_{21} \Delta t}) + (C_t)_{t_{n-1}} e^{-k_{21} \Delta t}\]  

→ Equation 3.7

Where

- \(C_t\) = Apparent tissue concentration
- \(t_n\) = time of sampling for sample \(n\)
- \(t_{n-1}\) = time of sampling for the sampling point preceding sample \(n\)
- \((C_p)_{t_{n-1}}\) = concentration of drug at central compartment for sample \(n-1\)
- \(C_p\) = concentration difference at central compartment between two sampling times.
- \(\Delta t\) = Time difference between two sampling times.
Example To Calculate \( C_t \) values

\[
(C_t)_{t_n} = \frac{k_{12} \Delta C_p \Delta t}{2} + \frac{k_{12}}{k_{21}} (C_p)_{t_{n-1}} (1 - e^{-k_{21} \Delta t}) + (C_t)_{t_{n-1}} e^{-k_{21} \Delta t}
\]

<table>
<thead>
<tr>
<th>( (C_p)_{t_n} )</th>
<th>( (t) )</th>
<th>( \Delta C_p )</th>
<th>( \Delta t )</th>
<th>( \frac{(k_{12} \Delta C_p \Delta t)}{2} )</th>
<th>( (C_p)_{t_n} )</th>
<th>( \frac{(k_{12}/k_{21}) \times (1 - e^{-k_{21} \Delta t})}{(1 - e^{-k_{21} \Delta t})} )</th>
<th>( (C_p)<em>{t</em>{n-1}} \times k_{12}/k_{21} e^{-k_{21} \Delta t} )</th>
<th>( (C_t)<em>{t</em>{n-1}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.00</td>
<td>0.5</td>
<td>3.0</td>
<td>0.5</td>
<td>0.218</td>
<td>0.134</td>
<td>0</td>
<td>0</td>
<td>0.218</td>
</tr>
<tr>
<td>5.20</td>
<td>1.0</td>
<td>2.2</td>
<td>0.5</td>
<td>0.160</td>
<td>3.00</td>
<td>0.402</td>
<td>0.187</td>
<td>0.749</td>
</tr>
<tr>
<td>6.50</td>
<td>1.5</td>
<td>1.3</td>
<td>0.5</td>
<td>0.094</td>
<td>5.20</td>
<td>0.697</td>
<td>0.642</td>
<td>1.433</td>
</tr>
<tr>
<td>7.30</td>
<td>2.0</td>
<td>0.8</td>
<td>0.5</td>
<td>0.058</td>
<td>6.50</td>
<td>0.871</td>
<td>1.228</td>
<td>2.157</td>
</tr>
<tr>
<td>7.60</td>
<td>2.5</td>
<td>0.3</td>
<td>0.5</td>
<td>0.022</td>
<td>7.30</td>
<td>0.978</td>
<td>1.849</td>
<td>2.849</td>
</tr>
</tbody>
</table>

\( K = 0.16 \text{ hr}^{-1}, k_{12} = 0.29 \text{ hr}^{-1}, k_{21} = 0.31 \text{ hr}^{-1}. \)
APPLICATIONS

- Loo Riegelman method is applicable for the drugs that confers multi compartmental characteristics.

\[
\frac{Ab}{Ab^a} = \frac{C + \frac{X_l}{V_c} + K_{13} (AUC)^l_0}{K_{13} (AUC)^\infty_0}
\]

LIMITATIONS

- It requires the concentration vs time data of both oral and IV administration of drug to same subject.
- An inherent limitation of this method is intra subject variability between oral and IV administration studies. The assumption be made that kinetics of drug distribution and elimination remain unchanged in interval between doses.
DECONVOLUTION METHOD

➢ It is a model independent method for determining the absorption rate and its use has been limited.

➢ It requires no assumptions regarding the no of compartments or kinetics of absorption.

➢ Linear distribution and elimination are assumed.

➢ It require both the data after oral and IV administration in same subject.
ESTIMATION $K_a$ FROM URINARY DATA

Using a plot of percent of drug unabsorbed versus time.

For a one-compartment model

\[ Ab = \text{total amount of drug absorbed} = D_B + D_E \]

5.1

\[ \frac{dAb}{dt} = \frac{dD_B}{dt} + \frac{dD_E}{dt} \]

5.2
Assuming first-order elimination kinetics with renal elimination constant $k_e$

\[
\frac{dD_u}{dt} = k_e D_B = k_e V_D C_p
\]  \hspace{1cm} 5.3

Rearranging Equation 5.3

\[
\frac{dC_p}{dt} = \frac{1}{k_e V_D} \left( \frac{dD_u}{dt} \right)
\]  \hspace{1cm} 5.4

Assuming a one-compartment model,

\[
V_D C_p = D_B
\]

Substituting $V_D C_p$ into Equation 5.2

\[
\frac{dA_b}{dt} = V_D \frac{dC_p}{dt} + \frac{dD_E}{dt}
\]  \hspace{1cm} 5.5

Substituting for $dC_p/dt$ into Equation 5.5 and $kD_u/k_e$ for $D_E$,

\[
\frac{dA_b}{dt} = \frac{d(D_u/dt)}{k_e dt} + \frac{k}{k_e} \left( \frac{dD_u}{dt} \right)
\]  \hspace{1cm} 5.6
When the above expression is integrated from zero to time $t$,

$$\text{Ab}_t = \frac{1}{k_c} \left( \frac{dD_u}{dt} \right)_t + \frac{k}{k_c} (D_u)_t$$

At $t = \infty$, the total amount of drug absorbed is $\text{Ab}^\infty$ and $dD_u/dt = 0$

$$\text{Ab}^\infty = \frac{k}{k_c} D_u^\infty$$

$D_u^\infty$ - total amount of unchanged drug excreted in the urine.

The fraction of drug absorbed at any time $t$

$$\frac{\text{Ab}_t}{\text{Ab}^\infty} = \frac{(dD_u/dt)_t + k(D_u)_t}{kD_u^\infty}$$

Slope = $-K_a/2.303$

figure 9
LIMITATIONS

- If the drug is rapidly absorbed, it may be difficult to obtain multiple early urine samples to describe the absorption phase accurately.

- Drugs with very slow absorption will have low concentrations.
SIGNIFICANCE OF ABSORPTION RATE CONSTANT

- The calculation of $k_a$ is useful in designing a *multiple-dosage regimen*. Knowledge of the $k_a$ and $k$ allows for the prediction of peak and trough plasma drug concentrations following multiple dosing.
- The peak time ($t_{\text{max}}$) in the plasma conc. versus time curve provides a convenient measure of absorption rate.
- With the increase in absorption rate constant, $C_{\text{max}}$ also increases.
Effect of a change in the absorption rate constant, $k_a$, on the plasma drug concentration-versus-time curve.
CONCLUSION

➢ To compare different formulations of same drug.
➢ The method of residual is used for the drugs which follow one or multi compartmental characteristics but the absorption process should not be complex.
➢ Wagner nelson method is used for the drug confers one compartmental characteristics by orally.
➢ Loo Riegelman method is applicable for the drug that confers multi compartmental characteristics.
➢ Deconvolution method has limited use due to its complexity.
➢ When there is lack of sufficiently sensitive analytic techniques to measure concentration of drugs in plasma, urinary excretion data is used.
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