SEMINAR ON
NONCOMPARTMENTAL PHARMACOKINETICS

Presented by:
Ch. Karthik Siva Chaitanya
M.Pharm (1st sem), Pharmaceutics
UCPSc, KU.
Contents:

- Introduction to noncompartmental pharmacokinetic approach
- Differences between compartment and noncompartment models
- Concepts of noncompartmental model
  Statistical moments theory-Mean residence time
- Different pharmacokinetic parameters in noncompartment model
• **Noncompartment pharmacokinetics** is a new approach devised to study the time course of drug in the body without assuming any compartment model. Based on the *statistical moment theory*.

• **Model independent method**
  Overcomes some of the drawbacks associated with classical compartment modeling. Basic assumption is that drug or metabolite follows first-order kinetics.
### Noncompartment and Compartment models - Comparison

<table>
<thead>
<tr>
<th>Compartment models</th>
<th>Noncompartment models</th>
</tr>
</thead>
<tbody>
<tr>
<td>These require elaborate assumptions to fit the data</td>
<td>Do not require assumptions to compartment model.</td>
</tr>
<tr>
<td>Curve fitting of experimental data using computers. It is a tedious method.</td>
<td>Simple algebraic equations. No curve fitting and no computers</td>
</tr>
<tr>
<td>Applicable to linear and nonlinear pharmacokinetics</td>
<td>Applicable to linear pharmacokinetics.</td>
</tr>
<tr>
<td>C₁ - time profile is regarded as expressions of exponents</td>
<td>C₁ – time profile is regarded as statistical distribution.</td>
</tr>
<tr>
<td>These are useful for most of the situations, though assumptions of modeling are involved.</td>
<td>Particularly useful for the applications of clinical pharmacokinetics, bioavailability, and bioequivalence studies.</td>
</tr>
</tbody>
</table>
Advantages:

- Derivation of PK parameters is easy, because of simple algebraic equations

- Mathematical treatment remains same, for drug or metabolite, provided elimination follows first order kinetics

- Drug disposition kinetics need not be described in detail
Disadvantages:

- Information regarding plasma drug concentration-time profile is expressed as an average.
- Generally not useful for describing the time course of drug in the blood.
- It is applicable only for linear pharmacokinetics.
Statistical Moment Theory

- **Statistical moment**: A mathematical description of a discrete distribution of data.
- Statistical moments calculated from a set of concentration-time data represent an estimate of the true moment (or the true probability density function (PDF) that describes the true relationship between concentration and time).
- Statistical moment theory provides a unique way to study time-related changes in macroscopic events.
- Assume the drug molecules are eliminated according to a kinetic function, \( f(t) = C_0 e^{-kt} \)
\[ \mu_m \text{ or } m\text{th moment} = \int_0^\infty t^m f(t) \, dt \]

where \( f(t) \) is the probability density function, \( t \) is time, and \( m \) is the \( m\)th moment.

For example, when \( m = 0 \), substituting for \( m = 0 \) yields Equation 2, called the zero moment, \( \mu_0 \):

\[ \mu_0 = \int_0^\infty f(t) \, dt \quad [\text{AUC}]_0^\infty = \int_0^\infty C \, dt \]

If the distribution is a true probability function, the area under the zero moment curve is 1.

Substituting into Equation 1 with \( m = 1 \), Equation 3 gives the first moment \( \mu_1 \):

\[ \mu_1 = \int_0^\infty t^1 f(t) \, dt \quad [\text{AUMC}]_0^\infty = \int_0^\infty t \times C \, dt \]

The area under the curve \( f(t) \) times \( t \) is called the AUMC, or the area under the first moment curve. The first moment, \( \mu_1 \), defines the mean of the distribution.
I.V. bolus injection – Calculation of AUC and AUMC

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Cp (mg/L)</th>
<th>Cp*t (mg.hr/L)</th>
<th>AUC (mg.hr/L)</th>
<th>AUMC (mg.hr^2/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>7.09</td>
<td>7.09</td>
<td>7.54</td>
<td>3.54</td>
</tr>
<tr>
<td>2</td>
<td>6.29</td>
<td>12.6</td>
<td>14.2</td>
<td>13.4</td>
</tr>
<tr>
<td>3</td>
<td>5.58</td>
<td>16.7</td>
<td>20.2</td>
<td>28.1</td>
</tr>
<tr>
<td>4</td>
<td>4.95</td>
<td>19.8</td>
<td>25.4</td>
<td>46.3</td>
</tr>
<tr>
<td>6</td>
<td>3.89</td>
<td>23.4</td>
<td>34.3</td>
<td>89.5</td>
</tr>
<tr>
<td>9</td>
<td>2.71</td>
<td>24.5</td>
<td>44.2</td>
<td>161.2</td>
</tr>
<tr>
<td>12</td>
<td>1.89</td>
<td>22.7</td>
<td>51.1</td>
<td>232</td>
</tr>
<tr>
<td>18</td>
<td>0.92</td>
<td>16.6</td>
<td>59.6</td>
<td>350</td>
</tr>
<tr>
<td>24</td>
<td>0.44</td>
<td>10.8</td>
<td>63.7</td>
<td>432</td>
</tr>
<tr>
<td>∞</td>
<td></td>
<td></td>
<td>67.4</td>
<td>553</td>
</tr>
</tbody>
</table>

\[
[AUC]_t = [AUC]_0 + \frac{C_t^*}{\lambda_z} \\
[AUC]_\infty = [AUC]_0 + \frac{t^*C_t^* + C^*}{\lambda_z + \lambda_z^2} \\
\text{Where } C_t^* \text{ is last measurable } C_t \text{ mg/ml, } \lambda_z \text{ is termination elimination rate constant, } h^{-1}
\]
Mean residence time (MRT):

- The term mean residence time (MRT) describes the average time for all the drug molecules to reside in the body.

\[
MRT = \frac{\text{total residence time for all drug molecules in body}}{\text{total number of drug molecules}}
\]

\[
MRT = \frac{\sum_{i=1}^{m} n_i t_i}{N}
\]

Ch. Karthik SivaChaitanya, M.Pharm 1st Sem, UCPSc, KU
MRT represents the time for 63.2% of drug eliminated when given i.v. bolus injection.

It is analogous to plasma elimination half life, $t_{1/2}$, i.e., 50% elimination.

Like half life, MRT is a function of both distribution and elimination.

For i.v bolus dose

$$MRT = \frac{1}{k_{10}}$$
In noncompartmental terms, $MRT = \frac{1}{k}$

$k$ is constant equal to ratio of clearance to Vss

Vss is volume of distribution at steady state

Plasma elimination half life: $t_{1/2} = \frac{0.693}{k_{10}}$

$t_{1/2} = 0.693MRT$

MRT_{iv} is used for comparison. For eg: following constant rate of infusion

$MRT_{iv} = MRT_{inst} - \frac{T}{2}$

Where $T =$ duration of infusion
DRUG ABSORPTION:

- MAT (Mean absorption time) is defined as the differences in mean residence time (MRT) after different modes of administration.

\[ MAT = MRT_{ni} - MRT_{iv} \]

- \( MRT_{ni} \) = mean residence time of drug by non-instantaneous route, h
- \( MRT_{iv} \) = mean residence time of drug by i.v. bolus injection

Same equation is used for i.m. injection
MAT = \frac{1}{k_a} \\

Absorption half life, \( t_{1/2} = \frac{0.693}{k_a} \)

Absorption half life, \( t_{1/2} = 0.693 \text{MAT} \)

When absorption follows zero order

\[
\text{MAT} = \frac{T}{2}
\]

T = time over which absorption takes place, h

MAT can be used for comparison of dosage forms
OTHER APPLICATIONS OF MRT

- Mean Dissolution Time (MDT)
  \[ MDT = \text{MRT}_{\text{test}} - \text{MRT}_{\text{soln}} \]

- In oral administration,
  \[ \text{MRT}_{\text{oral}} = \text{MRT}_{\text{iv}} + \frac{1}{K_a} \]

- For evaluation of absorption data,
  \[ \text{MAT} = \text{MRT}_{\text{test}} - \text{MRT}_{\text{iv}} \]
  \[ \text{MAT} = \frac{1}{K_a} \]
  Ka is first order absorption rate constant
Drug Clearance:

• After iv bolus administration, \( Cl = \frac{Dose_{iv}}{AUC} \)

• At steady state after constant rate iv infusion
  \[ Cl = \frac{k_0}{C^{ss}} \]

  \( k_0 \) is rate of infusion ; \( C^{ss} \) is steady state concentration

• By using extraction ratio \( Cl = Q(ER) \)
APPARENT VOLUME OF DISTRIBUTION:

- $V_{ss}$ is volume of distribution at steady state independent of elimination
- $V_{ss} = \text{i.v dose}(\text{AUMC})/(\text{AUC})$
- If drug is given by constant rate i.v infusion
  Where $k_0$ is infusion rate; $\tau$ is duration of infusion

$$V_{ss} = \frac{\text{Infused dose} \times (\text{AUMC})}{(\text{AUC})^2}$$

$$V_{ss} = \frac{k_0 \times \tau \times (\text{AUMC})}{2(\text{AUC})^2} - \frac{k_0 \tau^2}{2(\text{AUC})}$$
Steady State Plasma Drug Concentration:

- The CSS is a function of the effective rate of dosing and total body clearance of the drug in a patient.

In continuous infusion

\[ C_{ss} = \frac{k_o}{Cl} \]

In multiple dosage regimen

\[ C = \frac{AUC^{ss}}{\tau} \]

Average plasma drug concentration at steady state, \( C \)
AUC_{ss} \text{ is AUC from } t=0 \text{ to } t=\tau \text{ during a dosing interval at steady state}

\[ C = \frac{F \times \text{dosing rate}}{C_l} \]

F is fraction bioavailable

If a drug is given in a dose of 400 mg every 8 hours, dosing rate is 400/8, i.e., 50 mg/hour

• **Method of superposition** is used for predicting steady state concentration on repetitive dosing from data obtained after a single dose.
Predicting the Time to Steady State:

- Time required for the drug to reach steady state, i.e., 99%, takes 6.65 half lives.

- In extravascular route (or prolonged release drug products), the time required to attain ss takes longer than predicted by biological half life.

- In multicompartment disposition, time required to attain to ss is shorter than that predicted by terminal half life.
In noncompartment models, when the drug is administered repetitive dosing, fss

\[ f_{ss} = \frac{AUC_0^t}{AUC} \]

\( AUC = \text{area under the curve in single dose} \)
Bioavailability:

- **Bioavailability** refers to the fractional dose of a dosage form that reaches systemic circulation.
  - For i.v. bolus injection, bioavailability is referred to as unity (=1)
- Bioavailability (F) of a dosage form

\[
Absolute\ bioavailability, \ F = \frac{AUC_{oral} \cdot D_{iv}}{AUC_{iv} \cdot D_{oral}}
\]

Relative bioavailability, \( F_r \), may be expressed by comparing the zeromoments of a product with a standard product.
Fraction metabolised:

\[
\text{Fraction metabolized, } Fm = \frac{\text{AUC}_x^1}{\text{AUC}_1}
\]

- \(\text{AUC}_x^1\) is area under the curve of metabolite concentration in plasma versus time from zero to infinity

- \(\text{AUC}_1\) is the total area under the metabolite concentration – time curve after a equimolar intravenous dose of a metabolite
CONCLUSION:

- The noncompartmental pharmacokinetic methods permit a comprehensive pharmacokinetic analysis without resort to curve fitting, sophisticated computers or tedious mathematical equations.

- Although these methods cannot be applied to all pharmacokinetic problems, they are useful for most problems and are particularly useful for the clinical application of pharmacokinetics.
References:

- Milo Gibaldi, Biopharmaceutics and clinical pharmacokinetics, 4th edition, pg no 17-26
- D.Perrier, M.Gibaldi Pharmacokinetics, 2nd edition, pg no 409-417
- Leon Shargel, Applied biopharmaceutics and pharmacokinetics, 5th edition, pg no 717-753
- V.Venkateshwarlu, Biopharmaceutics and pharmacokinetics, pg no 309-330
- www.pharainfo.net
THANK YOU