Noncompartment Model - Pharmacokinetics

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Noncompartment Model - Pharmacokinetics

Objectives of this session

The participant shall be able to:
- Explain the concepts of noncompartment model
- Explain the differences between compartment and noncompartment models
- Describe different pharmacokinetic parameters in noncompartment model
Noncompartment Model - Pharmacokinetics

Noncompartmental model pharmacokinetics is a new approach devised to study the time course of drug in the body based on the statistical moment theory.

Model independent method
Overcomes some of the drawbacks associated with classical compartment modeling.

Peak plasma drug concentration, $C_{max}$
Time of peak concentration, $t_{max}$
Area under the curve, AUC
Noncompartment Model - Pharmacokinetics

$C_{max}$

Graphic method

Equation: $C_{max}$ is a function of several factors

$$C_{max} = \frac{FK_aD}{V_1(k_a - k_{10})(e^{-k_{10}t_{max}} - e^{-k_{at_{max}}})}$$
Noncompartment Model - Pharmacokinetics

$C_{\text{max}}$ First point $C_{\text{max}}$

It raises a question about the measurement of true $C_{\text{max}}$ because of insufficient early sampling times.

It requires a carefully chosen pilot study.

Early time points between 3 to 15 minutes.

Followed by additional sample collection (two to five) in the first hour.
Eq: \( t_{\text{max}} \) is a function of several factors

\[
2.303 \log \left( \frac{k_a}{k_{10}} \right) = \frac{t_{\text{max}}}{(k_a - k_{10})}
\]
Area of one trapezoid = 
\[ \frac{1}{2}(C_{n-1} + C_n)(t_n - t_{n-1}) \]

Area under the curve, AUC = 
\[ \sum (\text{areas of the trapezoids}) \]
Noncompartment Model - Pharmacokinetics

AUC

![Graph showing concentration over time](image)

- Concentration (μg/ml)
- Time (hr)

GrCP
CVS
Noncompartment Model – AUC

\[ [\text{AUC}]_0^\infty = [\text{AUC}]_0^t + \frac{C_t^*}{\lambda_Z} \]

Where \( C_t^* \) = last measurable \( C_t \) \( \mu g/ml \)
\( \lambda_Z \) = termination elimination rate constant, \( h^{-1} \)

Elimination rate constant is calculated separately
Noncompartment Model - Pharmacokinetics

Applications

Useful for estimating certain pharmacokinetic parameters without specifically referring to any models

Estimating PK parameters

- Bioavailability
- Clearance
- Apparent volume of distribution
- Fraction of dose of drug absorbed
- Mean absorption time
- Mean resident time
- Average plasma steady state conc. of drug or its metabolite
Noncompartment Model - Pharmacokinetics

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.
Noncompartment Model - Pharmacokinetics

Disadvantages

a) Information regarding plasma drug concentration-time profile is expressed as an average

b) Generally not useful for describing the time course of drug in the blood

c) It is applicable only for linear pharmacokinetics
## 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>Time course changes in $C_1$ can be predicted precisely.</td>
<td>Time course changes in $C_1$ cannot be predicted precisely.</td>
</tr>
<tr>
<td>Applicable to linear and nonlinear pharmacokinetics</td>
<td>Applicable to linear pharmacokinetics.</td>
</tr>
<tr>
<td>$C_1$ - time profile is regarded as expressions of exponents.</td>
<td>$C_1$ – time profile is regarded as statistical distribution.</td>
</tr>
</tbody>
</table>
## Noncompartment and Compartment models – Comparison

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<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>
Noncompartment Model –

Statistical Moment Theory

Approach is based on the statistical moment theory

Categorisation of moments

Zero Moment

*Zero moment* of a drug concentration in plasma versus time curve is referred to as the total area under concentration from zero to infinity, or simply AUC

\[
[AUC]_{0}^{\infty} = \int C \, dt
\]
Noncompartment Model –

Statistical Moment Theory

Area of trapezoid = 

$$(1/2)(C_{n-1} + C_n)(t_n - t_{n-1})$$

Area under the curve, AUC =

$$\Sigma \text{(areas of the trapezoids)}$$

$$[AUC]_0^\infty = [AUC]_0^t + \frac{C_t^*}{\lambda_Z}$$

Where $C_t^* =$ last measurable $C_t$, $\mu g/ml$

$\lambda_Z =$ termination elimination rate constant, h$^{-1}$

Elimination rate constant is calculated separately
Noncompartment Model –

Statistical Moment Theory

Applications

Used for calculating bioavailability and drug clearance

First Moment

First moment of a plasma drug concentration
- time profile is referred to as mean residence time (MRT)

\[
\text{MRT} = \frac{[\text{AUMC}]_{0}^{\infty}}{[\text{AUC}]_{0}^{\infty}} = \frac{\int t \times C \, dt}{\int C \, dt}
\]
Noncompartment Model –

Statistical Moment Theory

Area of one trapezoid

Area under the curve, AUC

\[ [\text{AUC}]_0^\infty = [\text{AUC}]_0^t + \frac{t^*C_t^*}{\lambda_Z} + \frac{C^*}{\lambda_Z^2} \]

Where \( C_t^* = \) last measurable \( C_t \) \( \mu g / ml \)

\( \lambda_Z = \) termination elimination rate constant, h\(^{-1}\)

Elimination rate constant is calculated separately
Noncompartment Models – Analysis

<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>
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**I.v. bolus injection – Calculation of AUC and AUMC**
Noncompartment Models – Analysis

I.v. bolus injection - AUC

CVS

Grnp
Noncompartment Models – Analysis

**I.v. bolus injection - AUMC**
### Noncompartment Models – Analysis

<table>
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<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.hr²/L)</th>
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<tr>
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**Oral product - Calculation of AUC and AUMC**
Noncompartment Models – PK Parameters

Oral product - AUC

Grcp

CVS
Noncompartment Models – PK Parameters

![Graph showing oral product AUMC](image)

- **Oral product - AUMC**
Noncompartment Model –

Second Moment

*Second moment* is referred to as variance of the mean residence time (VRT) of the drug in the body.

\[
VRT = \frac{\int t^2 C \, dt}{\int C \, dt} = \frac{(1-\text{MRT})^2 \int C \, dt}{\text{AUC}}
\]

Higher moments are prone to unacceptable level of errors.
Noncompartment Models – PK Parameters

Mean Residence Time – Half Life

Mean residence time (MRT) defined as the average amount of time spent by the drug in the body before being eliminated

\[
MRT = \frac{AUMC}{AUC} = \frac{\int t \times C. \, dt}{\int C. \, dt}
\]

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
Noncompartment Models – PK Parameters
Mean Residence Time – Half Life
Like half life, MRT is a function of both distribution and elimination

\[ \text{MRT} = \frac{1}{k_{10}} \]

Plasma elimination half life, \( t_{1/2} = \frac{0.693}{k_{10}} \)

Plasma elimination half life, \( t_{1/2} = 0.693 \times \text{MRT} \)

In two compartment model, concept of MRT would be still useful, because of non compartment model
Noncompartment Models – PK Parameters

Mean Residence Time – Half Life

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

\[
MRT_{iv} = MRT_{inst} - \frac{T}{2}
\]

Where \( T = \) duration of infusion, h
Noncompartment Models – PK Parameters

Apparent Volume of Distribution at Steady State

Apparent volume of distribution \( V_{1ss} \) is independent of drug elimination

\[
V_{1ss} = \frac{\text{AUMC}}{\text{dose}_{iv}} (\text{AUC})^2
\]

This equation is applicable to i.v. bolus administration.

It solely reflects the anatomic space occupied by the drug and the relative degree of drug binding in blood and extravascular space.
Noncompartment Models – PK Parameters

Apparent Volume of Distribution at Steady State

If drug is given by short term constant rate i.v. infusion

\[ V_{1ss} = \frac{\text{Infused dose (AUMC)}}{(AUC)^2} \]

\[ V_{1ss} = \frac{\text{Infused dose} \times \tau}{2(AUC)} \]

Since infused dose is equal to \( R_0 \)

\[ V_{1ss} = \frac{R_0 \times \tau (AUMC)}{2(AUC)^2} = \frac{R_0 \tau^2}{2(AUC)} \]
Noncompartment Models – PK Parameters

Drug Clearance ($Cl$)

*Clearance* is defined as the ratio of the dose after a single *i.v.* injection to the total area under the drug concentration – time curve.

After a single *i.v.* bolus injection:

$$ Cl = \frac{Dose_{iv}}{AUC} $$

Since infused dose is equal to $R_0$

$$ Cl = \frac{R_0}{C_1^{ss}} $$
Noncompartment Models – PK Parameters

Mean Absorption Time (MAT) - Drug Absorption

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

\[ \text{MAT} = \text{MRT}_{ni} - \text{MRT}_{iv} \]

\( \text{MRT}_{ni} \) = mean residence time of drug by non-instantaneous route, h

\( \text{MRT}_{iv} \) = mean residence time of drug by i.v. bolus injection, h

Same equation is used for i.m. injection

Absorption follows first order kinetics
Noncompartment Models – PK Parameters

Mean Absorption Time (MAT)

\[
\text{MAT} = \frac{1}{k_a}
\]

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

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

When absorption follows zero order

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

\( T = \text{time over which absorption takes place, h} \)
Noncompartment Models – PK Parameters

MAT - Applications

Used for the comparison of dosage forms

Eg: comparison of furosemide dosage forms
Noncompartment Models – PK Parameters

\[ \text{MRT(PO)} = \frac{\text{AUMC}}{\text{AUC}} = \frac{1361}{150} = 9.08 \text{ hr} \]

\[ \text{MAT} = \text{MRT(PO)} - \text{MRT(IV)} = 9.08 - 8.20 = 0.88 \text{ hr} \]

\[ \overline{ka} = \frac{1}{\text{MAT}} = \frac{1}{0.88} = 1.14 \text{ hr}^{-1} \]

\[ F = \frac{\text{AUC}_{\text{PO}} \cdot \text{Dose}_{\text{IV}}}{\text{AUC}_{\text{IV}} \cdot \text{Dose}_{\text{PO}}} = \frac{150 \times 100}{67.4 \times 250} = 0.89 \]
Noncompartment Models – PK Parameters

Steady State Plasma Drug Concentration

The $C_1^{ss}$ is a function of the effective rate of dosing and total body clearance of the drug in a patient.

In continuous infusion

$$C_1^{ss} = \frac{R_o}{Cl}$$

In multiple dosage regimen

$$C_{av}^{ss} = \frac{AUC^{ss}}{\tau}$$

When absorption follows zero order.
Noncompartment Models – PK Parameters

Steady State Plasma Drug Concentration

Average plasma drug concentration at steady state, $C_{av}^{ss}$

$$C_{av}^{ss} = \frac{F \times \text{dosing rate}}{Cl}$$

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

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
Noncompartment Models – PK Parameters
Predicting the Time to Steady State

In noncompartment models, when the drug is administered repetitive dosing, $f_{ss}$

$$f_{ss} = \frac{\text{AUC}_0^\prime}{\text{AUC}}$$

AUC = area under the curve in single dose

Bioavailability

*Bioavailability* refers to the fractional dose of a dosage form reaches systemic circulation

For *i.v.* bolus injection, bioavailability is referred as unity ($=1$)
Noncompartment Models – PK Parameters

Bioavailability

Bioavailability ($F$) of a dosage form

\[
F = \frac{AUC_{\text{oral}}}{AUC_{\text{iv}}} \div \frac{D_{\text{iv}}}{D_{\text{oral}}}
\]

Absolute bioavailability, $F = \frac{AUC_{\text{oral}}}{AUC_{\text{iv}}} \div \frac{D_{\text{iv}}}{D_{\text{oral}}}$

Equation assumes equal clearances in oral and $i.v.$ doses

Relative bioavailability, $F_r$ may be expressed by comparing the zero moments of a product with a standard product
Noncompartment Models – PK Parameters

Fraction of Drug Metabolised, $f_m$

Fraction of a drug metabolized, $f_m$, is equal to ratio of zero moments of the metabolite, administered the drug to the metabolite directly

Fraction metabolized, $f_m = \frac{\text{AUC}_x^1}{\text{AUC}^1}$

$\text{AUC}_x^1 = \text{AUC of metabolite, when drug is administered by i.v. bolus injection, zero to infinity time, } \mu g \cdot h/\text{ml}$

$\text{AUC}^1 = \text{AUC of metabolite, when metabolite is administered by i.v. bolus injection,}$
Noncompartment Models – PK Parameters
Fraction of Drug Metabolised, $f_m$
Metabolite is administered in equimolar i.v. dose
Thank you
Thank you