Multicompartment Pharmacokinetic Models

Objectives

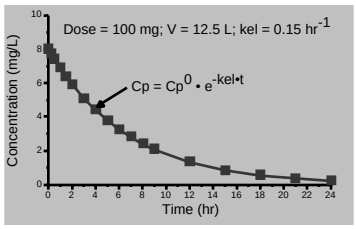
- To draw schemes and write differential equations for multicompartment models
- To recognize and use integrated equations to calculate dosage regimens
- To determine parameter values using the method of residuals
- To calculate various V values
- To use the non-compartmental method of parameter estimation

Multicompartment Models

- Rapid equilibration assumption not always true
- Distribution may take some finite time
- Body may be represented by two ‘equilibrated’ compartments with distribution between the two
- Semi-log figure will show a ‘distribution’ phase

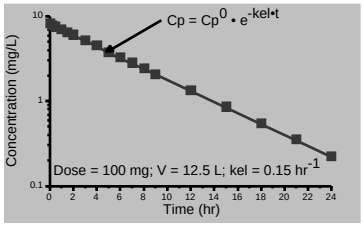
One Compartment Model

Linear Plot



One Compartment Model

Semi-log Plot



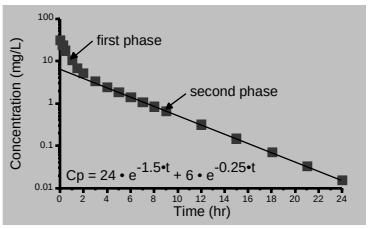
Drug Disposition

Distribution

- Commonly observed when early data are collected
- Deviation from a single exponential line
- A rapid drop followed by a slower terminal phase
- Body can be represented by two (or more) compartments

Two Compartment

Semi-log Plot

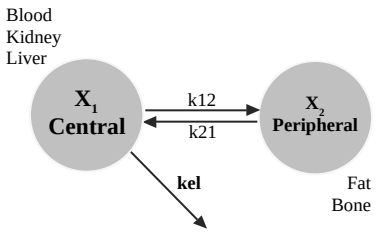


Two Compartments

- Central compartment
  - rapidly perfused tissues
- Peripheral compartment
  - slowly perfused tissues

Two Compartment

Scheme



Two Compartment

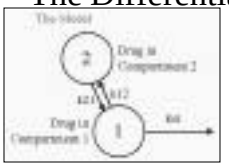
- Differential Equations
- Central Compartment

$$\frac{dX_1}{dt} = -kel \cdot X_1 - k12 \cdot X_1 + k21 \cdot X_2$$

- Peripheral Compartment

$$\frac{dX_2}{dt} = k12 \cdot X_1 - k21 \cdot X_2$$

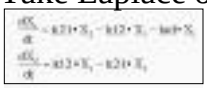
The Differential Equations



$$\frac{dX_1}{dt} = k21 \cdot X_2 - k12 \cdot X_1 - kel \cdot X_1$$

$$\frac{dX_2}{dt} = k12 \cdot X_1 - k21 \cdot X_2$$

Take Laplace of the Equations



$$s \cdot \bar{X}_1 - X_1(0) = k21 \cdot \bar{X}_2 - k12 \cdot \bar{X}_1 - kel \cdot \bar{X}_1$$

$$s \cdot \bar{X}_2 - X_2(0) = k12 \cdot \bar{X}_1 - k21 \cdot \bar{X}_2$$

Since $X_1(0)$ = Dose and $X_2(0) = 0$

$$\bar{X}_2 = \frac{k12 \cdot \bar{X}_1}{(s + k21)}$$

Substitute and Rearrange

$$s \cdot \bar{X}_1 - \text{Dose} = \frac{k21 \cdot k12 \cdot \bar{X}_1}{(s + k21)} - (k12 + kel) \cdot \bar{X}_1$$

$$s \cdot \bar{X}_1 + (k12 + kel) \cdot \bar{X}_1 - \frac{k21 \cdot k12 \cdot \bar{X}_1}{(s + k21)} = \text{Dose}$$

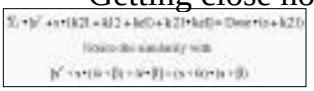
$$\bar{X}_1 \cdot [s \cdot (s + k21) + (k12 + kel) \cdot (s + k21) - k21 \cdot k12] = \text{Dose} \cdot (s + k21)$$

$$\bar{X}_1 \cdot [s^2 + s \cdot (k21 + k12 + kel) + k21 \cdot kel] = \text{Dose} \cdot (s + k21)$$

Notice the similarity with

$$[s^2 + s \cdot (\alpha + \beta) + \alpha \cdot \beta] = (s + \alpha) \cdot (s + \beta)$$

Getting close now



If $(\alpha + \beta) = k21 + k12 + kel$

and $\alpha \cdot \beta = k21 \cdot kel$

$$\bar{X}_1 \cdot [s^2 + s \cdot (\alpha + \beta) + \alpha \cdot \beta] = \text{Dose} \cdot (s + k21)$$

$$\bar{X}_1 \cdot (s + \alpha) \cdot (s + \beta) = \text{Dose} \cdot (s + k21)$$

$$\bar{X}_1 = \frac{\text{Dose} \cdot (s + k21)}{(s + \alpha) \cdot (s + \beta)}$$

Back Transforming

$$\bar{X}_1 = \frac{\text{Dose} \cdot (s + k21)}{(s + \alpha) \cdot (s + \beta)}$$

The denominator has a power of 2 in s and no repeat terms. Note the numerator has a power of 1 in s

Considering the denominator:

$$(s + \alpha) \cdot (s + \beta) = 0$$

Roots or solutions are $-\alpha$ and $-\beta$

Root 1

$$\overline{X}_1 = \frac{Dose \bullet (s + k21)}{(s + \alpha) \bullet (s + \beta)}$$

First root is -α

$$\frac{Dose \bullet (s + k21)}{(s + \alpha) \bullet (s + \beta)}$$

$$\frac{Dose \bullet (k21 - \alpha)}{(\beta - \alpha)} \bullet e^{-\alpha \bullet t}$$

Root 2

$$\overline{X}_1 = \frac{Dose \bullet (s + k21)}{(s + \alpha) \bullet (s + \beta)}$$

Second root is -β

$$\frac{Dose \bullet (s + k21)}{(s + \alpha) \bullet (s + \beta)}$$

$$\frac{Dose \bullet (k21 - \beta)}{(\alpha - \beta)} \bullet e^{-\beta \bullet t}$$

Putting It Together

$$\frac{Dose \bullet (\alpha - k21)}{(\alpha - \beta)} \bullet e^{-\alpha \bullet t} \qquad \frac{Dose \bullet (k21 - \beta)}{(\alpha - \beta)} \bullet e^{-\beta \bullet t}$$

$$\frac{Dose \bullet (\alpha - k21)}{(\alpha - \beta)} \bullet e^{-\alpha \bullet t} + \frac{Dose \bullet (k21 - \beta)}{(\alpha - \beta)} \bullet e^{-\beta \bullet t}$$

OR

$$\boxed{Cp = A \bullet e^{-\alpha \bullet t} + B \bullet e^{-\beta \bullet t}}$$

where $A = \frac{Dose \bullet (\alpha - k21)}{V_1 \bullet (\alpha - \beta)}$

and $B = \frac{Dose \bullet (k21 - \beta)}{V_1 \bullet (\alpha - \beta)}$

Integrated Equation

$$Cp = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$$

$\alpha + \beta = kel + k12 + k21$

$\alpha \cdot \beta = kel \cdot k21$

$$\alpha,\beta = \frac{(\alpha+\beta) \pm \sqrt{(\alpha+\beta)^2 - 4 \cdot \alpha \cdot \beta}}{2}$$

or

$$\alpha,\beta = \frac{(kel + k12 + k21) \pm \sqrt{(kel + k12 + k21)^2 - 4 \cdot kel \cdot k21}}{2}$$

Parameter Determination

Method of Residuals

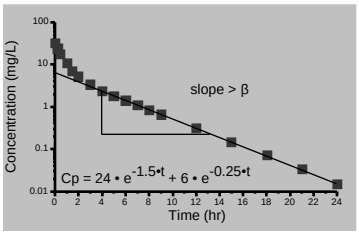
- Parameters A, B, α and β can be determined using the method of residuals
- Since $\alpha > \beta$ (if $\alpha/\beta > 5$)
  - $e^{-\alpha \cdot t}$ approaches 0 quickly
- Terminal data points will be on a line

Method of Residuals

$$Cp^{late} = B \cdot e^{-\beta \cdot t}$$

- Plotted on semi-log graph paper should give a straight line
- Calculate β from the terminal slope

Terminal Slope

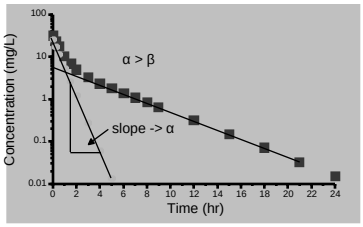


Terminal Half-life

- $t_{1/2} = \ln(2)/\beta$
- Biological or terminal half-life
- [= equivalent to ln(2)/kel with one compartment model]

Residual

Residual = $Cp - Cp^{late} = A \bullet e^{-\alpha \bullet t}$



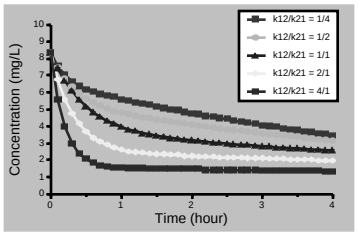
Now Calculate k21, kel, k12

$$k21 = \frac{A \cdot \beta + B \cdot \alpha}{A + B}$$

$$kel = \frac{\alpha \cdot \beta}{k21}$$

$$k12 = \alpha + \beta - k21 - kel$$

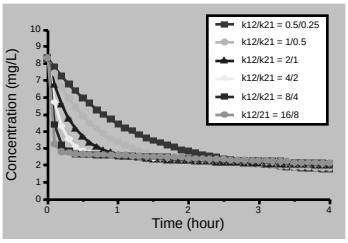
Effect of k12 and k21 Ratio



Effect of k12 and k21 Ratio

- Effect of k12/k21 ratio
- The higher the ratio greater the distribution into the peripheral compartment
- At the extremes
  - low ratio - less distribution into second compartment
  - high ratio and no early data - looks like one compartment model

Magnitude of k12 and k21



Magnitude of k21 and k12

- Larger values approach one compartment assumption

Volume of Distribution

V_1

- V_1 Apparent volume of central compartment

$$V_1 = \frac{\text{Dose}}{A+B} = \frac{\text{Dose}}{Cp^0} \left(\text{since } A+B=Cp^0\right)$$

- Use to calculate Cp^0 after an IV bolus administration

Volume of Distribution

V_{area}

- V_{area} (= V_{β})

$$V_{area} = \frac{Dose}{\beta \cdot AUC} = \frac{V_1 \cdot kel}{\beta} = \frac{Clearance}{\beta}$$

- Useful for dosing calculations, easy to calculate from Dose and AUC

Volume of Distribution

V_{extrap}

- V_{extrap} Volume extrapolated

$$V_{extrap} = \frac{Dose}{B}$$

- Ignores distribution phase

Volume of Distribution

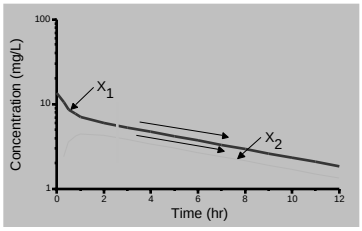
V_{ss}

- V_{ss} Steady state volume

$$V_{ss} = V_1 \cdot \frac{k12 + k21}{k21}$$

- Relates total amount in the body (at steady state) with drug concentrations in plasma or blood

Steady State Volume



Volumes of Distribution

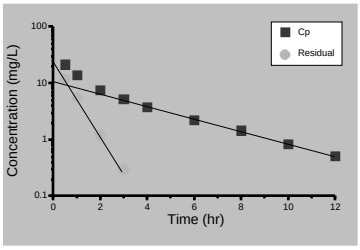
$V_{extrap} > V_{area} > V_{ss} > V_1$

Example Calculation

Time (hr)	Cp (mg/L)	Cp^{late} (mg/L)	Residual (mg/L)
0.5	20.6	8.8	11.8
1	13.4	7.8	5.6
2	7.3	6.1	1.2
3	5.0	4.7	0.3
4	3.7		
6	2.2		
8	1.4		
10	0.82		
12	0.50		

I.V. Bolus 500 mg

The Plots



Calculations

- B = 10 mg/L, β = (ln 10 - ln 0.5)/12 = 2.996/12 = 0.25 hr^{-1}
- A = 25 mg/L, α = (ln 25 - ln 0.27)/3 = 4.528/3 = 1.51 hr^{-1}
- $Cp = 25 \cdot e^{-1.51 \times t} + 10 \cdot e^{-0.25 \times t}$

Microconstants

$$k21 = \frac{A \cdot \beta + B \cdot \alpha}{A + B} = \frac{25 \times 0.25 + 10 \times 1.51}{25 + 10} = 0.61\ hr^{-1}$$

$$kel = \frac{\alpha \cdot \beta}{k21} = \frac{1.51 \times 0.25}{0.61} = 0.62\ hr^{-1}$$

$$k12 = \alpha + \beta - k21 - kel = 1.51 + 0.25 - 0.61 - 0.62 = 0.53\ hr^{-1}$$

Volumes of Distribution

$$V_1 = \frac{Dose}{A+B} = \frac{500}{25+10} = 14.3\ L$$

$$V_{area} = \frac{Dose}{\beta \cdot AUC} = \frac{500}{0.25 \times 58.3} = 34.3\ L$$

$$V_{extrap} = \frac{Dose}{B} = \frac{500}{10} = 50\ L$$

$$V_{ss} = V_1 \cdot \frac{k21 + k12}{k21} = 14.3 \times \frac{0.61 + 0.53}{0.61} = 26.7\ L$$

Note: $V_{extrap} > V_{area} > V_{ss} > V_1$

[50 > 34.3 > 26.7 > 14.3]

AUC = 56.3 + 2.0 = 58.3 mg.hr.L^{-1}

Dosage Calculations

Initial Concentration, Cp^0

$$V_1 = \frac{Dose}{Cp^0}$$

$$Dose = V_1 \cdot Cp^0_{required}$$

- To achieve a Cp^0 of 20 mg/L give 600 mg with V_1 = 30 L
- If V_1 = 16 L an IV Bolus Dose of 500 mg would result in a Cp^0 of 31.3 mg/L (=500/16)

Dosage Calculation

- Continuous Infusion

$$Cp^{ss} = \frac{k0}{kel \cdot V_1} = \frac{k0}{Clearance} = \frac{k0}{V_{area} \cdot \beta}$$

$$k0 = Cp^{ss} \cdot kel \cdot V_1$$

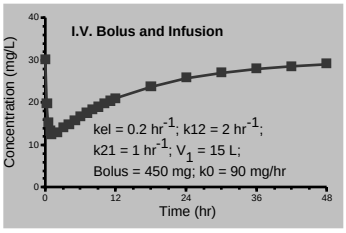
- If V_1 = 15 L and kel = 0.2 hr^{-1} a k0 of 90 mg/hr is required to produce a Cp^{ss} of 30 mg/L

Plasma Concentration

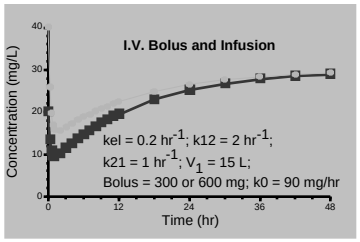
Time to Steady State

- Cp can be calculated after an IV bolus dose from A, B, α and β
- Cp after an IV infusion somewhat more involved
- Time to steady state controlled by β value
- Can be slow with long biological half-life

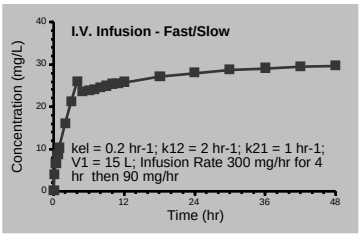
I.V. Bolus and Infusion



I.V. Bolus and Infusion

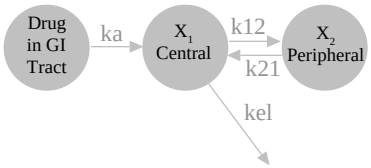


Fast and Slow I.V. Infusion



Oral Administration

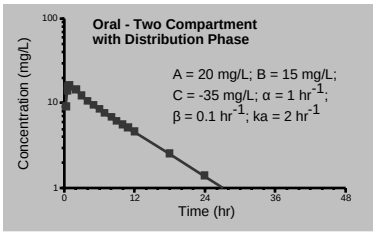
Scheme



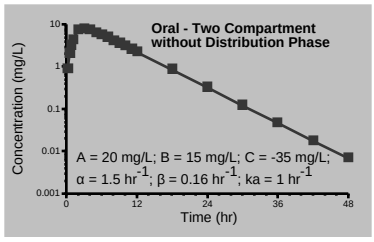
Differential Equation

$$\frac{dX_1}{dt} = ka \cdot Xg + k21 \cdot X_2 - (k12 + kel) \cdot X_1$$

Semi-log Plot



Semi-log Plot



Oral Dose

Two Compartment Model

- Bioavailability calculations the same as for a one compartment model
  - Use AUC comparison or
  - Use U∞ comparison
- These method work for any linear system (first order disposition)
- Method of residuals could be used to calculate α, β, and ka (if sufficiently different)

$\overline{Cp}$ Calculations

- Average Cp of 20 mg/L required with V_1 = 15 L, kel = 0.15 hr^{-1}, F = 0.9, and τ = 12 hr

$$\overline{Cp} = \frac{F \cdot Dose}{Clearance \cdot \tau} = \frac{F \cdot Dose}{kel \cdot V \cdot \tau} = \frac{F \cdot Dose}{\beta \cdot V_\beta \cdot \tau}$$

$$Dose = \frac{20 \times 15 \times 0.15 \times 12}{0.9} = 600 \text{ mg q12h}$$

MacKinetics

- Two compartment Demo

Example Data - 100 mg IV Bolus Dose

Time (hr)	Concentration (mg/L)
0.25	1.7
0.5	1.4
1	1.1
2	0.95
4	0.75
6	0.60
8	0.50
10	0.40
12	0.34

Clinical Example

- Lidocaine - Rapidly attain and maintain effective concentrations (2 - 6 mg/L)
  - Multiple bolus over 15 or 30 min + infusion
  - Exponentially declining infusion
  - Stepwise, tapering infusion
- k10 = 0.035 min^{-1} $t_{1/2}$ = 20 min
- k12 = 0.058 min^{-1} $t_{1/2}$ = 12 min
- k21 = 0.023 min^{-1} $t_{1/2}$ = 30 min
- V_1 = 0.49 L/kg = 34 L (70 kg patient)

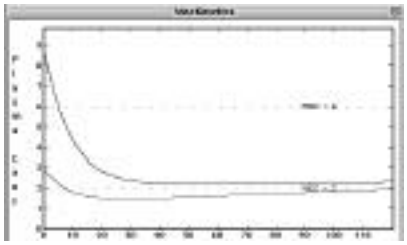
Evans, Schentag, and Jusko **Applied Pharmacokinetics**, 3rd ed., Applied Therapeutics, Vancouver, WA 1992

Lidocaine - Loading Dose

- Usual Dose - 50 to 100 mg followed by an infusion of 1 - 4 mg/min
  - Dip in concentration below therapeutic range
  - Increasing the loading dose to 200 - 300 mg may cause toxic doses
- Multiple Loading dose approach
  - Initial 75 mg followed by up to six 50 mg bolus doses to effect
    - Ectopic ventricular beats to less than 5 per minute **and** no complex ventricular arrhymias

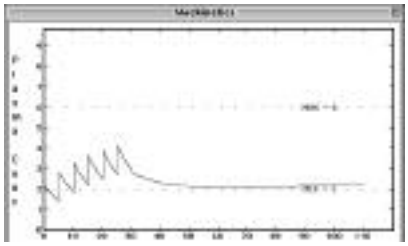
Lidocaine - Usual Dose

Usual Dose - Simulation



Minutes

Multiple Bolus Doses



Minutes

Non Compartmental Analysis

Linear Disposition

- First order elimination and distribution
- No assumptions about number of compartments
- Use t_{max}, Cp_{max}, AUC, AUMC
- New parameters:
  - AUMC (area under moment curve)
  - MRT (mean residence time)
  - MAT (mean absorption time)

AUMC

Area under the Moment Curve

- Use trapezoidal rule with t versus Cp•t data
- Last segment from

$$\frac{Cp^{last} \bullet t^{last}}{k} + \frac{Cp^{last}}{k^2}$$

- where k is slowest (last) exponential

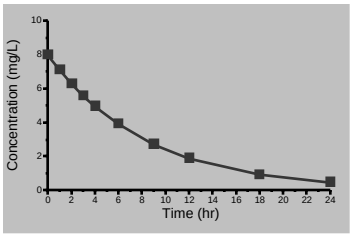
Non Compartmental Analysis

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

Linear System - 100 mg IV

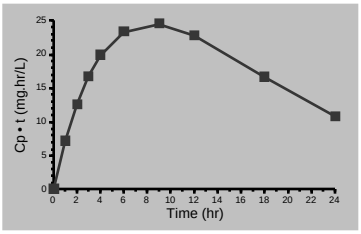
Plot of Cp versus t

IV Data



Plot of Cp•t versus t

IV Data



Parameter Calculations

$$MRT = \frac{AUMC}{AUC} = \frac{553}{67.4} = 8.2 \text{ hr}$$

$$\bar{k} = \frac{1}{MRT} = \frac{1}{8.2} = 0.122 \text{ hr}^{-1}$$

$$Cl = \frac{Dose}{AUC} = \frac{100}{67.4} = 1.48 \text{ L/hr}$$

$$V_{ss} = Cl \bullet MRT = 1.48 \times 8.2 = 12.2 \text{ L}$$

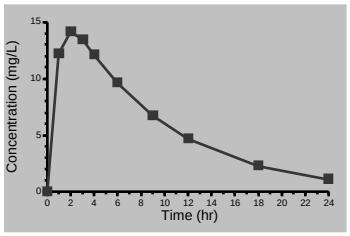
Non Compartmental Analysis

Time (hr)	Cp (mg/L)	Cp•t (mg.hr/L)	AUC (mg.hr/L)	AUMC ($mg.hr^2/L$)
0	0	0	0	0
1	12.2	12.2	6.09	6.09
2	14.1	28.3	19.2	26.3
3	13.4	40.3	33.0	60.6
4	12.2	48.6	45.8	105
6	9.64	57.9	67.6	212
9	6.73	60.6	92.2	389
12	4.69	56.4	109	565
18	2.28	41.2	130	857
24	1.11	26.7	141	1061
∞			150	1361

Linear System - 250 mg PO

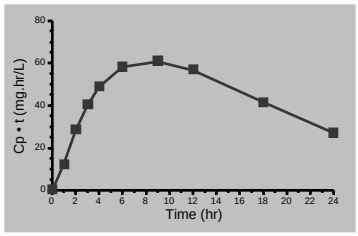
Plot of Cp versus t

PO Data



Plot of Cp•t versus t

PO Data



Parameter Calculations

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

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

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

$$F = \frac{AUC_{PO} \bullet Dose_{IV}}{AUC_{IV} \bullet Dose_{PO}} = \frac{150 \times 100}{67.4 \times 250} = 0.89$$

Objectives

- To draw schemes and write differential equations for multicompartment models
- To recognize and use integrated equations to calculate dosage regimens
- To determine parameter values using the method of residuals
- To calculate various V values
- To use the non-compartmental method of parameter estimation