One Compartment Model

One Compartment I.V. Bolus

- Objectives
  - Understand the assumptions used for this model
  - Understand the properties of first order processes
    - Linear processes
  - Use appropriate integrated equations
  - Use and calculate the parameters; kel, $t_{1/2}$, V and AUC

One Compartment I.V. Bolus

- Pharmacokinetics
- Assumptions
  - One Compartment, Rapid Mixing, Linear Model
- First-Order Kinetics
- Plasma Data
  - Elimination Rate Constant, Apparent Volume of Distribution, AUC, Half-Life

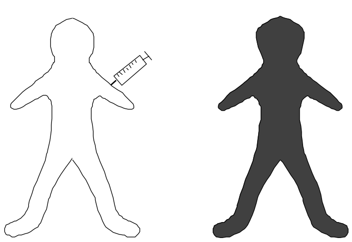
Pharmacokinetics

- Definition: Pharmacokinetics is the study of drug and/or metabolite kinetics in the body. It deals with a mathematical description of the rates of drug transfer through body tissues or fluids. The body is a very complex system and a drug undergoes many steps while it is being absorbed, distributed through the body, metabolised or excreted.

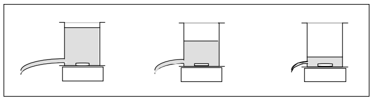
Assumptions

- One Compartment
  - Not necessarily equal concentrations but in equilibrium
- Rapid Mixing
  - Actual mixing time is very short
- Linear Model
  - First order processes (including elimination)

One Compartment - Rapid Mixing



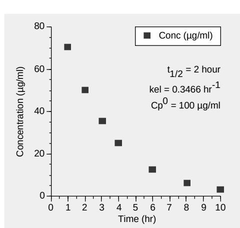
Linear Model - First Order Elimination



Linear Model - Beaker Exp

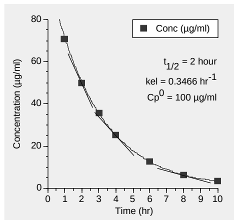
Rate versus Cp

- Cp versus Time



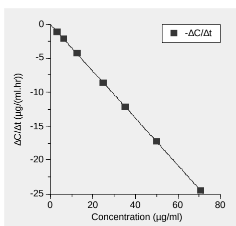
Rate versus Cp

- Cp versus Time with Tangents

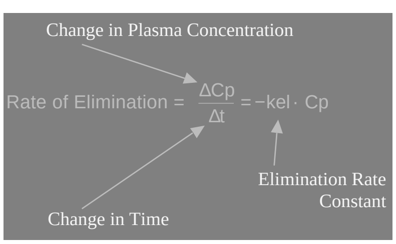


Rate versus Cp

- Rate versus Cp

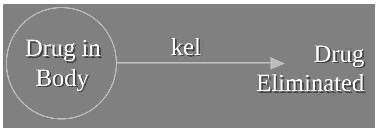


Rate versus Cp



Plasma Data

- Scheme - Diagram



$$\frac{dCp}{dt} = -kel \cdot Cp$$

Differential Equation

Elimination Rate Constant

- Symbol - kel
- Units $time^{-1}$
  - e.g. hr^{-1}, min^{-1}
- Independent of Concentration
- NOT Rate
  - Rate is dependent on Cp

Integrated Equation

Rearrange

$$\frac{dCp}{dt} = -kel \cdot Cp$$

$$\frac{dCp}{Cp} = -kel \cdot dt$$

Integrate

$$\int_{Cp(0)}^{Cp(t)} \frac{dCp}{Cp} = -kel \cdot \int_{t=0}^{t=t} dt$$

Integration Limits

$$[\ln Cp]_{Cp(0)}^{Cp(t)} = -kel \cdot [t]_0^t$$

$$\ln Cp^t - \ln Cp^0 = -kel \cdot t + \cancel{kel \cdot 0}$$

Integrated Equation

Rearrange

$$\ln Cp^t - \ln Cp^0 = -kel \cdot t + \cancel{kel \cdot 0}$$

$$\ln Cp^t = \ln Cp^0 - kel \cdot t$$

y = a - m • t

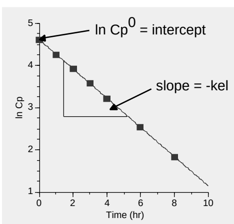
$$\ln\left[\frac{Cp^t}{Cp^0}\right] = -kel \cdot t$$

Antilog and rearrange

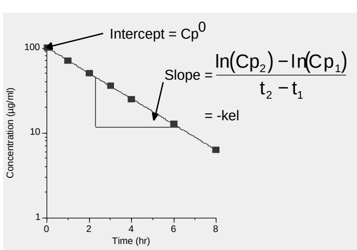
$$Cp^t = Cp^0 \cdot e^{-kel \cdot t}$$

Integrated Equation

Plot of ln Cp versus Time



Plot of Cp versus Time



Practice Calculation

- Calculate Cp at 6 hours given Cp^0 = 15 mg/L and kel = 0.25 hr^{-1}
- The equation: $Cp^t = Cp^0 \cdot e^{-kel \cdot t}$
- Cp = 15 x $e^{-0.25}$ x 6 = 15 x 0.223
  = 3.35 mg/L

Example kel Values

	kel, hr(-1)	t(1/2), hr
Acetaminophen	0.28	2.5
Diazepam	0.021	33
Digoxin	0.017	40
Gentamicin	0.35	2.1
Lidocaine	0.43	1.6
Theophylline	0.063	11

Apparent Volume of Distribution

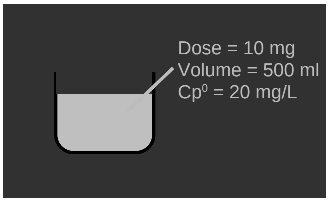
- Relates Dose (mg) to Concentration (mg/L)
- Mathematical 'fudge' factor

$$V = \frac{\text{amount of drug in body}}{\text{concentration measured in plasma}}$$

$$V = \frac{X}{Cp}$$

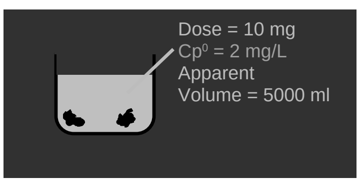
Apparent Volume of Distribution

- At time zero, X = Dose



Apparent Volume

- Distribution out of central compartment



Example V Values

Drug	V (L/kg)	V (L, 70 kg)
Sulfisoxazole	0.16	11.2
Phenytoin	0.63	44.1
Phenobarbital	0.55	38.5
Diazepam	2.4	168
Digoxin	7	490

Integrated Equation for Cp

Since $V = \frac{Dose}{Cp^0}$

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

$Cp = \frac{Dose}{V} \cdot e^{-kel \cdot t}$

Integrated Equation

1. Example Calculations

- Data: Dose = 500 mg, V = 30 L, kel = 0.2 hr^{-1}
- Question: Cp at 0, 2, and 4 hours?
- Equation: $Cp = \frac{Dose}{V} \cdot e^{-kel \cdot t}$
- Cp^0 = 500/30 = 16.7 mg/L
- Cp^{2hr} = 16.7 x $e^{-0.2x2}$ = 11.2 mg/L
- Cp^{4hr} = 16.7 x $e^{-0.2x4}$ = 7.5 mg/L

2. Example Calculations

- Data: Dose = 400 mg, Cp^{2hr} = 4.5 mg/L, Cp^{6hr} = 3.7 mg/L
- Question: kel and V?
- Equation: $kel = \frac{\ln(Cp^1) - \ln(Cp^2)}{t^2 - t^1}$
- kel = (ln(4.5) - ln(3.7))/(6-2) = 0.049 hr^{-1}
- ln Cp^0 = ln(4.5) + 0.049 x 2 = 1.602
- Cp^0 = 4.96
- V = Dose/Cp0 = 400/4.96 = 80.6 L

3. Example Calculation

- Data: kel = 0.17 hr[1], V = 25 L
- Question: Dose to achieve 2.4 mg/L at 6 hr?
- Equation: $Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$
- 2.4 = (Dose/25) x $e^{0.17}$ x 6
- Dose = 60/0.36 = 166.7 mg
- CHECK UNITS

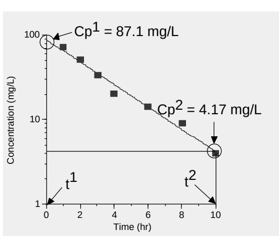
4. Example Calculations

- Data: Dose 500 mg

Time (hr)	1	2	3	4	6	8	10
Concentration (µg/ml)	72	51	33	20	14	9	4

- Question: Calculate kel and V

4. Example Calculation



4. Example Calculations

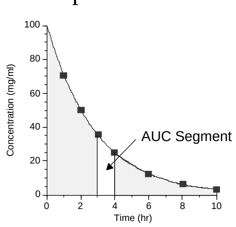
- Equation: $kel = \frac{\ln(Cp^1) - \ln(Cp^2)}{t^2 - t^1}$
- kel = (ln 87.1 - ln 4.17)/(10 - 0)
  = (4.467 - 1.428)/10
  = 3.04/10 = 0.304 hr^{-1}
- V = Dose/Cp^0 = 500/87.1 = 5.74 L

Area under the Curve, AUC

- Parameter used to measure Product Efficiency
- Can be used to calculate Cp^0, V and Clearance

Area under the Curve, AUC

- Area under the plasma concentration curve



AUC - Analytical Solution

$$AUC = \int_{t=0}^{t=\infty} Cp^t \cdot dt$$ Narrow, dt slices

$$AUC = \frac{Dose}{V} \cdot \int_{t=0}^{t=\infty} e^{-kel \cdot t} \cdot dt$$ since $Cp = \frac{Dose}{V} \cdot e^{-kel \cdot t}$

$$AUC = \frac{Dose}{V} \cdot \left[\frac{e^{-kel \cdot t}}{-kel}\right]_{t=0}^{t=\infty}$$

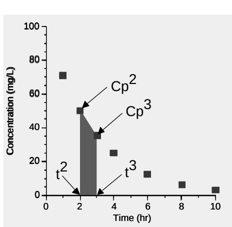
$$AUC = \frac{Dose}{V \bullet kel} = \frac{Cp^0}{kel}$$

AUC - Numerical Solution

- Trapezoidal Rule
  - Four sided figure with two parallel sides
  - Segment area:

$$AUC^{2-3} = \frac{Cp^2 + Cp^3}{2} \bullet \left(t^3 - t^2\right)$$

AUC - Numerical Solution

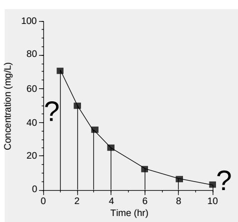


AUC - Numerical Solution

- Area from first to last data point

$$AUC^{1-n} = \sum \left\{ \frac{Cp^1 + Cp^2}{2} \bullet \left(t^2 - t^1\right) \right\}$$
$$+ \left\{ \frac{Cp^2 + Cp^3}{2} \bullet \left(t^3 - t^2\right) \right\} +$$

AUC - Numerical Solution



AUC - Numerical Solution

First Segment $AUC^{0-1} = \frac{Cp^0 + Cp^1}{2} \bullet t^1$

Last Segment $AUC = \frac{Cp^{last}}{kel}$

$$AUC^{0-\infty} = \frac{Cp^0 + Cp^1}{2} \bullet t^1 + \sum \left\{ \frac{Cp^1 + Cp^2}{2} \bullet \left(t^2 - t^1\right) \right\}$$
$$+ \left\{ \frac{Cp^2 + Cp^3}{2} \bullet \left(t^3 - t^2\right) \right\} + \quad + \frac{Cp^{last}}{kel}$$

AUC Example Calculation

- Using the trapezoidal rule

Time hr	Concentration mg/L	ΔAUC	AUC mg.hr/L
0	100 *		
1	71	85.5	85.5
2	50	60.5	146.0
3	35	42.5	188.5
4	25	30.0	218.5
6	12	37.0	255.5
8	6.2	18.2	273.7
10	3.1	9.3	283.0
Total		8.9	291.9

Half-life, $t_{1/2}$

- Time for concentration to fall to half the original value
- Property of First Order Kinetics
- Units of time, e.g. min, hr

Half-life, $t_{1/2}$

$$\frac{Cp}{2} = Cp \bullet e^{-kel \bullet t_{1/2}}$$

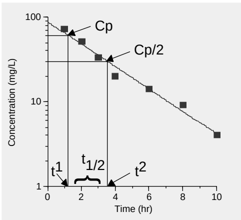
$$\frac{1}{2} = e^{-kel \bullet t_{1/2}}$$

$$\ln 2 = kel \bullet t_{1/2} = 0.693$$

$$t_{1/2} = \frac{\ln 2}{kel} = \frac{0.693}{kel}$$

NOTE: Independent of concentration

Half-life, $t_{1/2}$



Consider Cp/4 and Cp/8

Example $t_{1/2}$ Values

	in x half-lives	% left	% lost
Cp > Cp/2	1	50	50
Cp > Cp/4	2	25	75
Cp > Cp/8	3	12.5	87.5
Cp > Cp/16	4	6.25	93.75
Cp > Cp/32	5	3.125	96.875
Cp > Cp/64	6	1.563	98.438
Cp > Cp/128	7	0.781	99.219

HyperCard Practice Stack

- One Compartment - IV Bolus Dose