Principles of Pharmacodynamics & Pharmacokinetics

Pharmacokinetics: Single & Multi-compartment models Part 2

Dr Robert Dickinson
Faculty of Medicine
Imperial College
Biophysics Group
Blackett Laboratory
South Kensington Campus
r.dickinson@imperial.ac.uk

Apparent volume of distribution, V

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

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

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

$$\therefore Cp^0 = \frac{dose}{V}$$

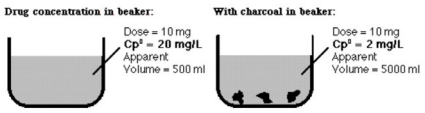
$$Cp = Cp^0 \bullet e^{-k_{el} \bullet t}$$

$$Cp = \frac{dose}{V} \bullet e^{-k_{el} \bullet t}$$

Apparent volume of distribution, V, is not a physiological volume (may be much larger than body volume!). It is a theoretical volume relating dose delivered to the concentration in the plasma, Cp.

Examples of apparent volumes of distribution

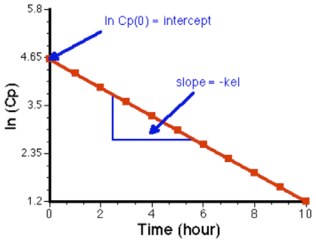
Drug	V (l/kg)	V (l) (70kg)
sulfisoxasole	0.16	11.2
phenytoin	0.63	44.1
phenobarbital	0.55	38.5
diazepam	2.4	168
digoxin	7	490



The one compartment model assumes rapid equilibrium in drug concentration throughout body, but does not assume that concentration is the same in all tissues.

In the theoretical experiment above, the same 10mg dose is put in each beaker (patient). On the left the measured concentration, Cp^0 = 20mg/ml, giving a value of V=500ml. On the right much of the drug is bound in the charcoal (tissue), and a much lower free concentration is measured Cp^0 = 2mg/ml, giving an apparent volume of 10 times greater, V=5 litres.

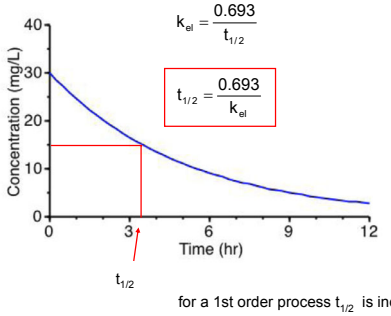
Calculating V



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

Apparent volume of distribution can be calculated from Cp^0 determined by extrapolating the ln (Cp) vs time plot back to t=0 (even if there is no actual measurement at t=0).

$t_{1/2}$ – half time of elimination



$$k_{el} = \frac{0.693}{t_{1/2}}$$

$$t_{1/2} = \frac{0.693}{k_{el}}$$

$$\ln(Cp) = \ln(Cp^0) - k_{el} \bullet t$$

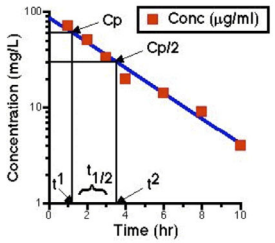
$$\ln\left(\frac{Cp}{Cp'}\right) = -k_{el} \bullet (t - t')$$

$$\text{if } \frac{Cp}{Cp'} = \frac{1}{2}$$

$$\ln(2) = k_{el} \bullet t_{1/2} = 0.693$$

for a 1st order process $t_{1/2}$ is independent of concentration

May be more practical to determine $t_{1/2}$ from a semi-log plot

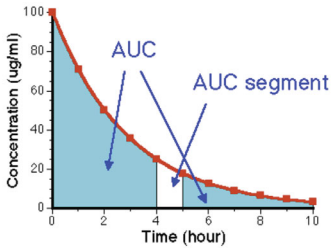


Any two points on the line can be used provided Cp'/Cp=1/2

Example values for elimination rate constants & half-times

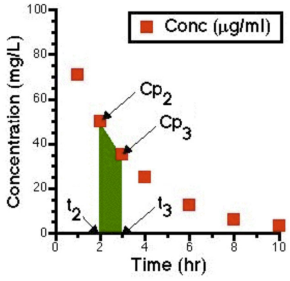
Drug	k_{el} (hr^{-1})	$t_{1/2}$ (hr^{-1})
paracetamol	0.277	2.5
diazepam	0.021	33
digoxin	0.016	43
gentamicin	0.347	2
lidocaine	0.390	1.8

Area under the plasma concentration time curve (AUC)



AUC may be calculated analytically as the integral of the function describing Cp or it can be determined *numerically* using the trapezoid rule

Trapezoid Rule

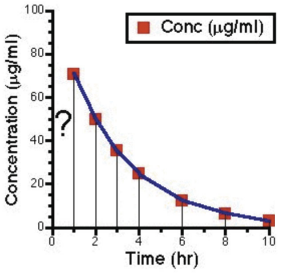


$$AUC_{1-n} = \sum \left\{ \frac{Cp_1 + Cp_2}{2} \bullet (t_2 - t_1) \right\} + \left\{ \frac{Cp_2 + Cp_3}{2} \bullet (t_3 - t_2) \right\} + \ldots$$

Trapezoid rule

1st segment - calculate Cp^0 by extrapolation of semi-log plot to t=0

$$\text{area} = \frac{Cp^0 - Cp^1}{2} \bullet (t_1 - 0)$$



- AUC has units of concentration x time
- used in *pharmacokinetics* to determine other parameters e.g. clearance CL
-
- used in *toxicology* as a measure of exposure to drug
- used in *biopharmaceutics* to assess different formulations of drug products

Definition of total clearance CL

$$\frac{\partial X}{\partial t} = CL \bullet Cp$$

rate of elimination = CL x concentration

$$\therefore CL = \frac{\frac{\partial X}{\partial t}}{Cp}$$

$$CL = \frac{dose}{AUC}$$

$$CL = \frac{\int_0^t \frac{\partial X}{\partial t} dt}{\int_0^t Cp\ dt} = \frac{dose}{AUC}$$

For a one compartment IV bolus

$$\left|\frac{\partial X}{\partial t}\right| = \left|V \bullet \frac{\partial Cp}{\partial t}\right| = CL \bullet Cp$$

but $$\frac{\partial Cp}{\partial t} = -k_{el} \bullet Cp$$

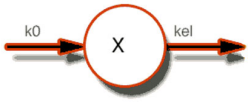
$\therefore$ $$CL = k_{el} \bullet V$$

or $$k_{el} = \frac{CL}{V}$$

Intravenous Infusion

- A variety of drugs are given by intravenous infusion
- Total Intravenous Anaesthesia (TIVA) is becoming common (*eg* with propofol)

Single compartment steady state continuous IV infusion



The drug infusion alters the plasma concentration versus time curve.

Model incorporates an infusion rate constant k_0.

Rate equation becomes:

$$\frac{\partial X}{\partial t} = k_0 - k_{el} X$$

Solution

$$X = \frac{k_0}{k_{el}}\left(1 - e^{-k_{el} \bullet t}\right)$$

$$\frac{\partial X}{\partial t} = k_0 - k_{el} X$$

$$\frac{\partial X}{k_0 - k_{el} X} = \partial t$$

integrating

$$\int \frac{\partial X}{k_0 - k_{el} X} = \int \partial t$$

$$\frac{-1}{k_{el}} \bullet \ln\left|k_0 - k_{el} X\right| + \ln A = t$$

$$\ln\left|k_0 - k_{el} X\right| + \ln A = -k_{el} \bullet t$$

$$A\left|k_0 - k_{el} X\right| = e^{-k_{el} \bullet t}$$

$$A\left|k_0 - k_{el} X\right| = e^{-k_{el} \bullet t}$$

solve for A using $X = 0$ at $t = 0$

$$A \bullet k_0 = 1 \quad \therefore A = \frac{1}{k_0}$$

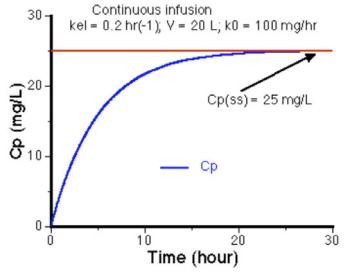
$$k_0 - k_{el} X = k_0 e^{-k_{el} \bullet t}$$

$$X = \frac{k_0}{k_{el}}\left(1 - e^{-k_{el} \bullet t}\right)$$

Steady state concentration, Cp^{ss}

$$X = \frac{k_0}{k_{el}}\left(1 - e^{-k_{el} \bullet t}\right)$$

$$Cp = \frac{k_0}{k_{el} V}\left(1 - e^{-k_{el} \bullet t}\right)$$



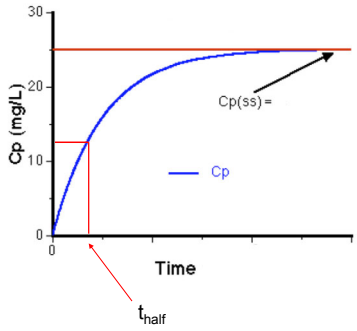
as $t \to \infty$ $e^{-k_{el} \bullet t} \to 0$

$$\therefore Cp^{ss} = \frac{k_0}{k_{el} V} = \frac{k_0}{CL}$$

Worked Example

- The average elimination half-time of a drug is 4hrs. If the apparent volume of distribution is 25 litres, what infusion rate is necessary to achieve a steady state plasma concentration of 15mg/litre?
- Answer
- $k_{el}=0.693 / t_{1/2}=0.17\ hr^{-1}$
- $k_0=k_{el} \times V \times Cp = 0.17\ hr^{-1} \times 25\ litres \times 15\ mg/litre = 63.8\ mg / hr$

time to reach half steady state, t_{half}



time to reach half steady state, t_{half}

$$Cp = \frac{k_0}{k_{el} V}\left(1 - e^{-k_{el} \bullet t}\right)$$

$$Cp = Cp^{ss}\left(1 - e^{-k_{el} \bullet t}\right)$$

$$\therefore \text{ if } Cp = \frac{Cp^{ss}}{2}$$

$$\frac{Cp^{ss}}{2} = Cp^{ss}\left(1 - e^{-k_{el} \bullet t_{half}}\right)$$

$$\frac{1}{2} = \left(1 - e^{-k_{el} \bullet t_{half}}\right)$$

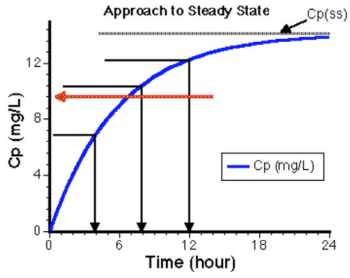
$$e^{-k_{el} \bullet t_{half}} = \frac{1}{2}$$

$$e^{k_{el} \bullet t_{half}} = 2$$

$$k_{el} \bullet t_{half} = \ln(2) = 0.693$$

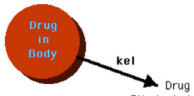
$$t_{half} = \frac{0.693}{k_{el}} = t_{1/2} \text{ (elimination)}$$

The approach to Cp^{ss} depends on the elimination process NOT the infusion rate

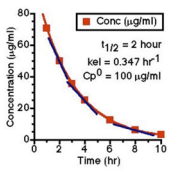


50 % C^{ss}	1 x t_{half}
75 % C^{ss}	2 x t_{half}
87.5 % C^{ss}	3 x t_{half}
94 % C^{ss}	4 x t_{half}

One-compartment summary



Estimating k_{el} and Cp^0 from data

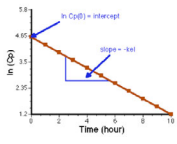


$Cp = Cp^0 \bullet e^{-k_{el} \bullet t}$ mono-exponential decay

taking natural logs

$\ln(Cp) = \ln(Cp^0) - k_{el} \bullet t$

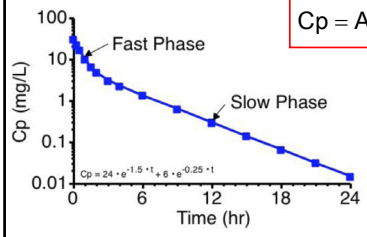
straight line y = mx + c



Real life is often complicated

Where do we go from here?

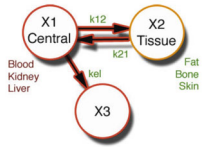
Sometimes one compartment is not enough



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

biexponential decay

two-compartment model



rate equation

$$\frac{\partial X_1}{\partial t} = -k_{el}X_1 - k_{12}X_1 + k_{21}X_2$$

solution

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

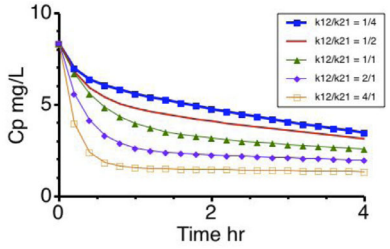
where

$$\alpha + \beta = k_{el} + k_{12} + k_{21}$$

and

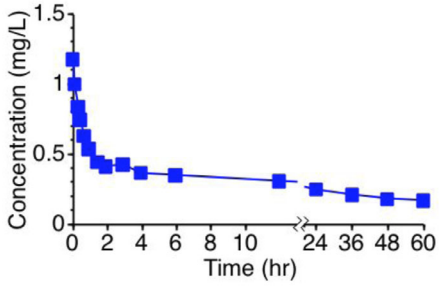
$$\alpha \bullet \beta = k_{el} \bullet k_{21}$$

Effect of k_{12} and k_{21} on drug concentration versus time



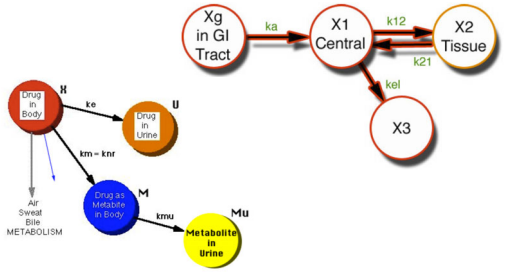
As k_{12}/k_{21} increases the more drug partitions into the peripheral compartment and the more "biexponential" the graph becomes

Pentobarbital distribution



Most general anaesthetics are very lipid-soluble. The first part of the concentration – time curve represents distribution in body fat stores.

More complex models may be necessary



Sometimes three or more compartments are required. This is not quite so easy to analyse manually, but these days technology is at hand to assist us……

Pharmacokinetic computer simulations!