

# PHAR 7632 Chapter 4

## One Compartment IV Bolus

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### IV Bolus One Compartment Model

#### Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- understand the separate assumptions associated with the one compartment model, rapid IV bolus dosing and linear elimination
- understand the properties of first order kinetics, linear models
- be able to write the differential equations for a simple pharmacokinetic model
- be able to define, use, and calculate the parameters:
  - $k_{el}$  (elimination rate constant)
  - $V$  (apparent volume of distribution)
  - $t_{1/2}$  (half-life)
  - AUC (area under the concentration *versus* time curve)
  - Cl (clearance)
 as they apply to a one compartment linear model
- be able to use the integrated equations for a one compartment linear model to perform various dose and dosing regimen calculations

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 movement into, within and exit from the body. It also includes the study of drug metabolism or biotransformation rates. The body is a very complex system and a drug undergoes many steps as it is being **absorbed**, **distributed** through the body, **metabolized** or **excreted** (ADME).

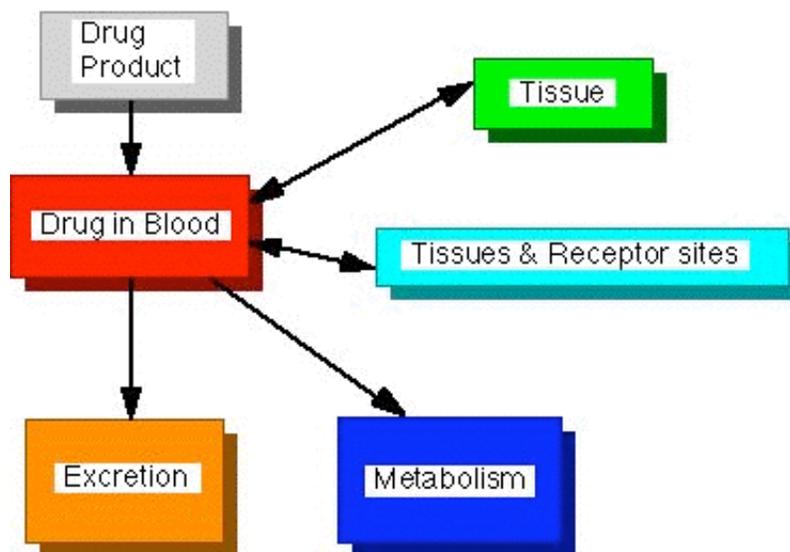


Figure 5.1.1 Drug Disposition

The drug also interacts with receptors and causes therapeutic and/or toxic responses. Although the details of drug kinetics are complicated it is fortunate that we can often approximate drug kinetic processes using "simple" mathematical models.

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### Assumptions

We will start the course with a one compartment - linear model. Also, we will first consider drug kinetics after a rapid intravenous injection, an IV bolus injection. According to this model we will consider the body to behave as a single well- mixed container. To use this model mathematically we need to make a number of assumptions.

#### 1. One compartment

The drug in the blood is in rapid equilibrium with drug in the extravascular tissues. The drug concentration may not be equal in each tissue or fluid however we will assume that they are proportional to the concentration of drug in the blood at all times. This is not an exact representation however it is useful for a number of drugs to a reasonable approximation.

#### 2. Rapid Mixing

We also need to assume that the drug is mixed instantaneously in blood or plasma. The actual time taken for mixing is usually very short, within a few of minutes, and in comparison with normal sampling times it is insignificant. We usually don't sample fast enough to see drug mixing in the blood.

#### 3. Linear Model

We will assume that drug elimination follows first order kinetics. First order kinetics means that the rate of change of drug concentration by any process is directly proportional to the drug concentration remaining to undertake that process. Remember first order kinetics is an assumption of a linear model not a one compartment model. If we have a linear if we double the dose, the concentration will double at each time point.

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### Linear Model - First Order Kinetics

#### First-order kinetics

To illustrate first order kinetics we might consider what would happen if we were to give a drug by iv bolus injection, collect blood samples at various times and measure the plasma concentrations of the drug. We might see a steady decrease in concentration as the drug is eliminated, as shown in Figure 4.3.1.

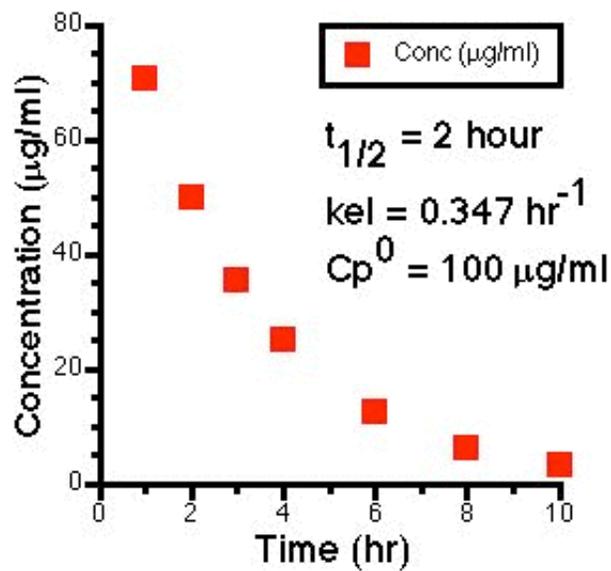


Figure 4.3.1. Concentration *versus* time

### Rate versus $C_p$

If we measure the slope of this curve at a number of times we are actually measuring the **rate of change of concentration at each time point**,  $\Delta C_p/\Delta t$ , represented by the straight line tangents in Figure 4.3.2.

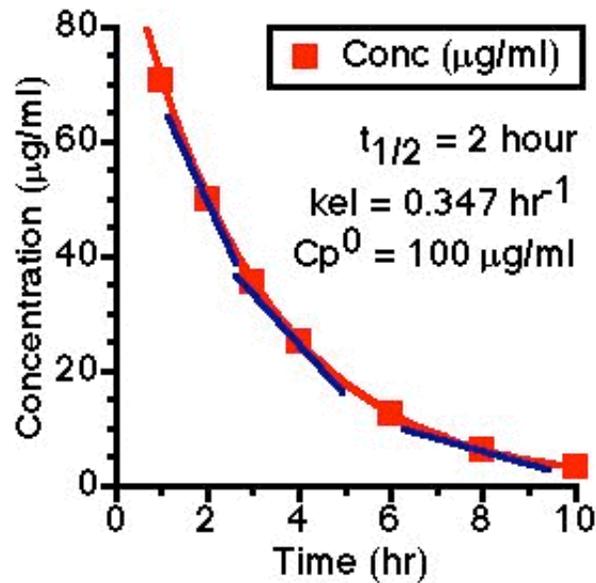


Figure 4.3.2 Same as Figure 4.3.1 with Tangents shown

Now if we plot this rate of change *versus* the plasma concentration, for each data point, we will get a straight line when first order kinetics are obeyed. This is shown in Figure 4.3.3.

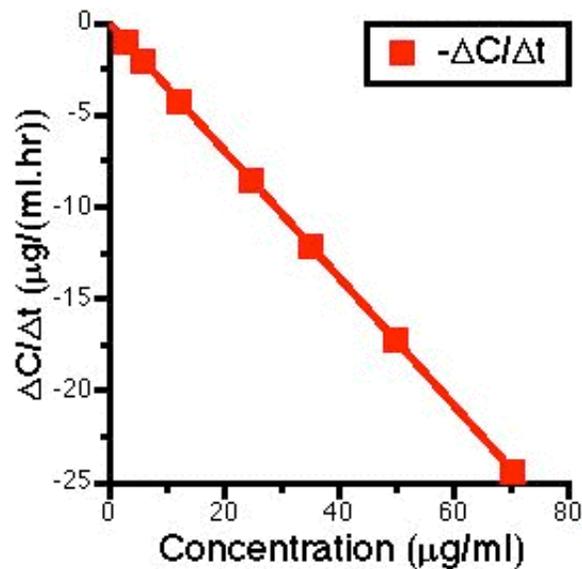


Figure 4.3.3 Plot of  $\Delta C_p/\Delta t$  *versus*  $C_p$  for first order process

This behavior can be expressed mathematically as:-

$$\text{Rate of Change of } C_p \text{ versus time} = -\frac{\Delta C_p}{\Delta t} = k_{el} \cdot C_p$$

Change in Cp

Change in time

Proportionality constant called the elimination rate constant,  $k_{el}$

Equation 4.3.1

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### One Compartment Model

#### Scheme or Diagram describing the Model

The one compartment pharmacokinetic model can be represented schematically as:-

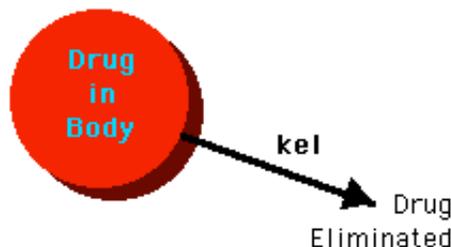


Figure 4.4.1 Scheme for a One Compartment Model, Intravenous (IV) Bolus Administration

#### Developing the Differential Equation

From the previous page on Figure 4.3.2 we estimated the slope of the  $C_p$  versus time line at various times. Plotting  $\Delta C_p / \Delta t$  (the slope) versus  $C_p$  produced a straight line plot (Figure 4.3.3). Thus the rate of change of  $C_p$  versus time is proportional to the concentration remaining to be eliminated,  $C_p$ . The slope of this line. The proportionality constant can be defined as **kel**, the elimination rate constant. If we measure the slope over very small time intervals we are calculating the tangent to the line. We can now say that the rate of change of  $C_p$  versus time is the differential of the concentration with respect to time as  $\Delta t$  approaches 0;  $\Delta C_p / \Delta t$  approaches  $dC_p / dt$  which gives:

$$\frac{dC_p}{dt} = -k_{el} \cdot C_p$$

Equation 4.4.1 Rate of Change of Concentration versus Concentration

Equation 4.4.1 is a **differential equation** for the one-compartment model after an IV bolus administration. By taking very small time steps we are going from the gross or large time interval term  $\Delta C_p / \Delta t$  to the continuously varying  $dC_p / dt$  term. Note, the negative sign in front of the  $k_{el}$  term. The slope or tangent is decreasing or negative for positive concentration values.

Equation 4.4.1 relates the rate of change of  $C_p$  versus time. We can also relate the rate of elimination to the concentration remaining. [Previously](#), we developed the required differential equations by looking at the arrows leaving or entering a component of the model. In Figure 4.4.1 there is one arrow leaving one component. Thus we could write the differential equation for the model shown above as Equation 4.4.1.

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### Integrated Equations

The differential equations developed on the previous page provide concise descriptions of the rate of change of drug concentration ( $dC_p/dt$ ) or the elimination rate ( $dX/dt$ ). However, they can be difficult to use when trying to determine  $k_{el}$  or  $Cl$ . Measuring the tangent of the  $C_p$  *versus* time plot can not be determined accurately. Later in the Chapter dealing with the [Analysis of Urine Data](#) we will describe measuring the rate of excretion directly from the data. However, integrated forms of Equation 4.4.1 and 4.5.1 are generally more useful.

[Laplace transforms](#) can be used to integrate Equation 4.5.1.

$$\frac{dC_p}{dt} = -k_{el} \cdot C_p$$

**Equation 4.5.1 Rate of Change of Concentration *versus* Concentration**

to give

$$C_p = C_p^0 \cdot e^{-k_{el} \cdot t}$$

**Equation 4.5.2 Integrated Equation for  $C_p$  *versus* Time**

This equation describes the **single exponential** decline in drug concentration as a function of time. This fall in plasma concentration is called **mono-exponential** decay. If we know  $k_{el}$  and  $C_{p0}$  we could calculate  $C_p$  at any time after a single IV bolus dose. However, it still isn't very convenient for estimating a value of  $k_{el}$  from concentration *versus* time data. We could use a non linear regression program such as [Boomer](#) however for estimation purposes using graph paper we would prefer a straight line equation. A straight line equation can be achieved by taking the natural logarithm of both side of Equation 4.5.2

$$\ln(C_p) = \ln(C_{p_0}) - k_{el} \cdot t$$

**Equation 4.5.3  $\ln(C_p)$  *versus* Time**

This integrated (logarithmic) form of the equation for  $C_p$  represents a **straight line equation**, that is an equation of the form:  $y = a - m \cdot t$  with  $a$  = intercept and  $m$  = slope.

Plotting  $\ln(C_p)$  versus  $t$  should give a straight line with a slope of  $-k_{el}$  and an intercept of  $\ln(C_p^0)$ .

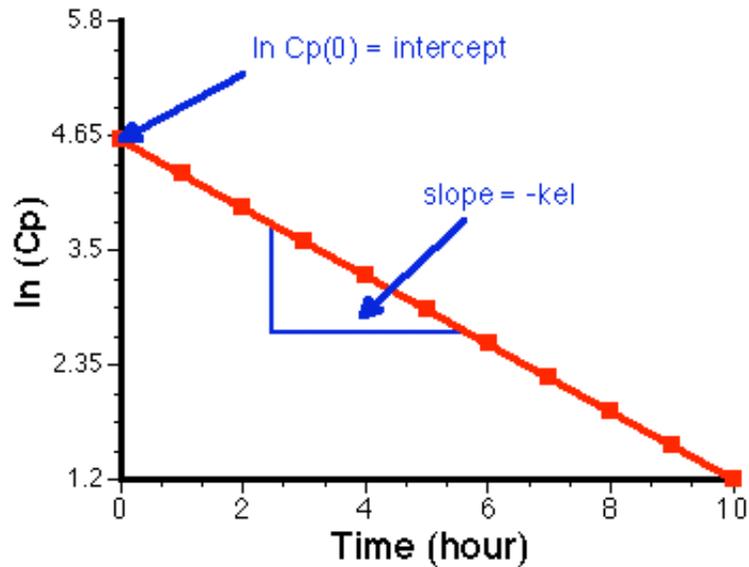


Figure 4.5.1 Linear plot of  $\ln(C_p)$  versus time

NOTICE, there are no UNITS for  $\ln(C_p)$  in Figure 4.5.1. There units of hour for time (X axis) so slope has units of **time<sup>-1</sup>** e.g.  $\text{min}^{-1}$ ,  $\text{hr}^{-1}$ .

Now we can measure  $k_{el}$  by determining  $C_p$  versus time and plotting  $\ln(C_p)$  versus time.

Alternately we could use semi-log graph paper. As mentioned [earlier](#) the scale on the y-axis are proportional to the log of the number, not the number itself. This plot allows us to calculate the slope and thus  $k_{el}$  given  $C_p$  versus time data.

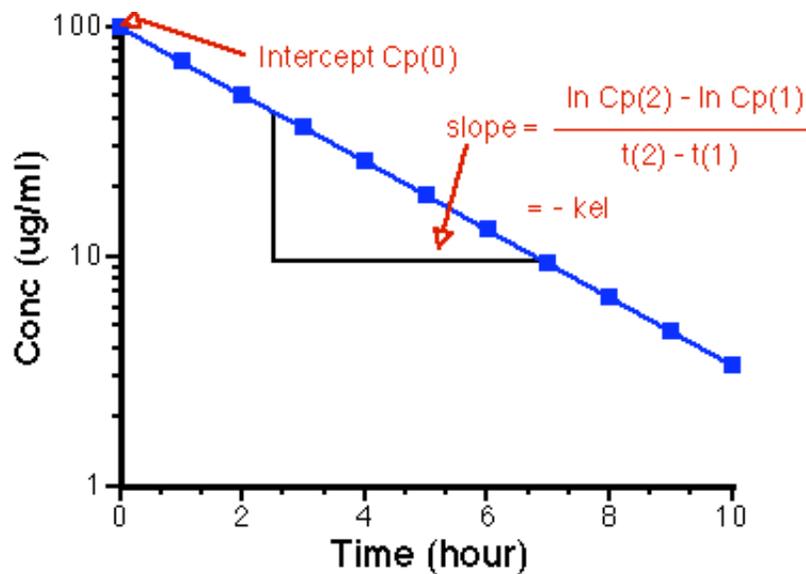


Figure 4.5.2. Semi-log plot of  $C_p$  versus time

Click on the figure to view the Java Applet window

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### Elimination Rate Constant, kel

The elimination rate constant (abbreviated as kel, k10, and sometimes ke) is the first order rate constant describing drug elimination from the body. This is an overall elimination rate constant describing removal of the drug by all elimination processes including excretion and metabolism. Metabolites are different chemical entities and have their own elimination rate constant.

The elimination rate constant is the proportionality constant relating the rate of change drug concentration and concentration OR the rate of elimination of the drug and the amount of drug remaining to be eliminated.

### Defining Equations:

Table 4.6.1 Equations Defining kel

$\frac{dC_p}{dt} = -k_{el} \cdot C_p$	$\frac{dX}{dt} = -k_{el} \cdot X$
Equation 4.6.1 Rate of Change of $C_p$ versus $C_p$	Equation 4.6.2 Elimination Rate versus Amount Remaining, $X$

### Units:

By inspection of Equations 4.6.1. or 4.6.2 it can be seen that the units for kel are  $\text{time}^{-1}$ , for example  $\text{hr}^{-1}$ ,  $\text{min}^{-1}$ , or  $\text{day}^{-1}$ . In both equations the rate expression is divided by  $C_p$  or  $X$ , respectively to provide units for kel. Thus:

Table 4.6.2 Units for kel

$\frac{\text{mass/volume}}{\text{time}} \div \text{mass/volume} = \frac{1}{\text{time}}$	$\frac{\text{mass}}{\text{time}} \div \text{mass} = \frac{1}{\text{time}}$
Units for kel from Equation 4.6.1	Units for kel from Equation 4.6.2

### Determining Values of kel:

From the integrated equation presented on the previous page:

$$\ln(C_p) = \ln(C_{p_0}) - k_{el} \cdot t$$

Equation 4.6.3 Ln( $C_p$ ) versus time

Plotting  $\ln(C_p)$  values *versus*  $t$ , time should result in a straight line with a slope equal to  $-k_{el}$ , thus  $k_{el}$  can be calculated as:

$$k_{el} = \frac{\ln(C_{p_1}) - \ln(C_{p_2})}{t_2 - t_1}$$

**Equation 4.6.4  $k_{el}$  from -slope**

Thus with two value for  $C_p$  and time data a value for  $k_{el}$  can be determined. With more than two  $C_p$  - time data points it is possible to plot the data on semi-log graph paper and draw a 'best-fit' line through the data points. This plot is shown on the previous page. The best answer for  $k_{el}$  can be calculated by taking points at either end of the 'best-fit' line. This approach has been covered in more detail [earlier in Chapter 2](#).

**Note:** It is important to distinguish between the elimination rate and the elimination rate constant. The rate (tangent or slope,  $dC_p/dt$ ) changes as the concentration changes, however, for a linear model the rate constant ( $k_{el}$ ) is constant, it does not change.

**Table 4.6.3. Example Values for Elimination Rate Constant (Ritschel, 1992)**

Drug	$k_{el}$ , hr <sup>-1</sup>
Acetaminophen	0.277
Diazepam	0.021
Digoxin	0.0161
Gentamicin	0.347
Lidocaine	0.39
Theophylline	0.126

## References

- Ritschel, W.A. 1992 **Handbook of Basic Pharmacokinetics**, 4th ed., Drug Intelligence Publications, p 533-549
- Elimination rate constant has been discussed on [the PharmPK listserv](#).

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### Apparent volume of distribution, V

$$C_p = C_p^0 \cdot e^{-k_{el} \cdot t}$$

Figure 4.7.1 Concentration as a function of Time

We can use Equation 4.7.1 to calculate the plasma concentration at any time when we know  $k_{el}$  and  $C_p^0$ . However, usually we don't know  $C_p^0$  ahead of time, but we do know the **dose**. A dose in **mass units**, maybe in mg. To calculate  $C_p^0$  we need to know the **volume** that the drug is distributed into. That is, the **apparent volume** of the mixing container, the body. This apparent volume of distribution is not a physiological volume. It won't be lower than blood or plasma volume but for some drugs it can be much larger than body volume. It is a mathematical 'fudge' factor relating the amount of drug in the body and the concentration of drug in the measured compartment, usually plasma.

### Defining Equations:

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

Equation 4.7.2 Definition for Apparent Volume of Distribution

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

Equation 4.7.3 Relationship between Amount and Concentration

Immediately after the intravenous dose is administered the amount of drug in the body is the IV dose. Thus:

$$V = \frac{\text{Dose}}{C_p^0}$$

Equation 4.7.4 Volume calculated from Dose and  $C_p^0$

or

$$C_p^0 = \frac{\text{Dose}}{V}$$

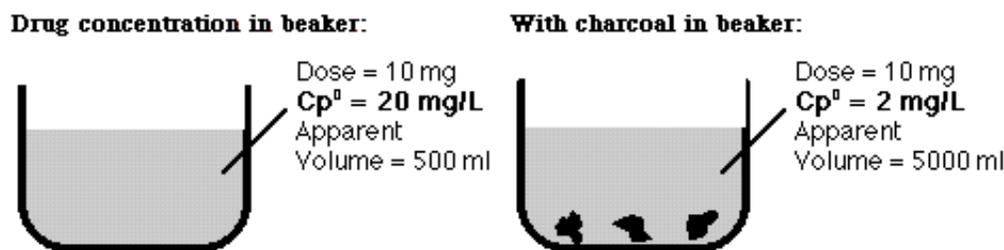
Equation 4.7.5 Initial Concentration calculated from Dose and V

Combining Equation 4.7.4 and Equation 4.7.1 we are able to derive an equation for drug concentration as a function of time given values of Dose, V, and  $k_{el}$ .

$$C_p = \frac{\text{Dose}}{V} \cdot e^{-k_{el} \cdot t}$$

**Equation 4.7.6 Concentration as a function of Time**

The one compartment model assumption is that there is a rapid equilibration in drug concentrations throughout the body, however, this does not mean that the concentration is the same throughout the body. This is illustrated in Figure 4.7.1. In the first beaker the concentration throughout the beaker is the same and the apparent volume of distribution is the same as the size of the beaker. In the second beaker after a rapid equilibrium, distribution between the solution (representing plasma) and the charcoal (representing various tissues of the body) may be complete. However, drug concentrations within the beaker (representing the patient) are not uniform. Much of the drug is held with the charcoal leaving much smaller concentrations in the solution. After measuring the drug concentration in the solution the apparent volume of the patient is much larger, the apparent volume of distribution is much larger.



**Figure 4.7.1 Apparent Volume of Distribution**

## Units:

The units for the apparent volume of distribution are volume units. Most commonly V is expressed in liters, L. On occasion the value for the apparent volume of distribution will be normalized for the weight of the subject and expressed as a percentage or more usually in liters/kilogram, L/Kg.

## Determining Values of V:

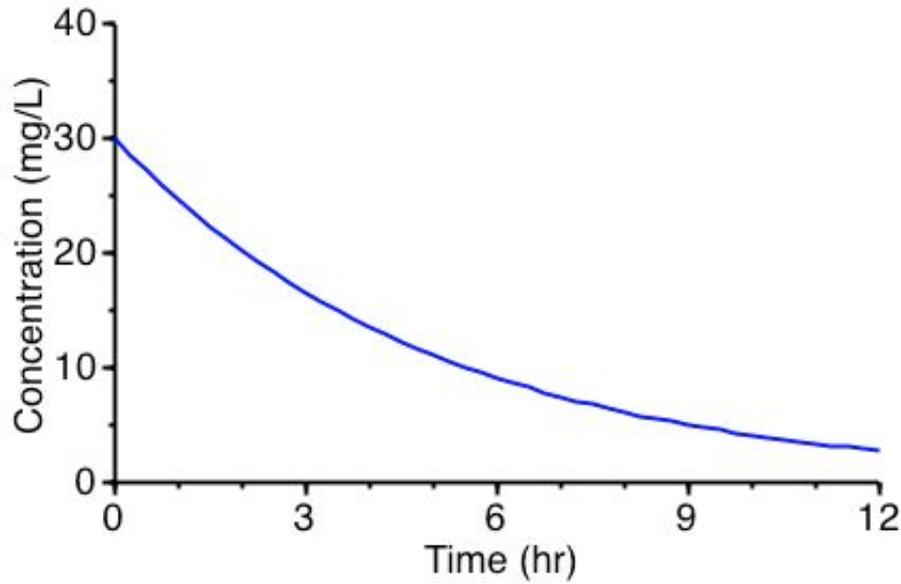
The usual method of calculating the apparent volume of distribution of the one compartment model is to extrapolate concentration *versus* time data back to the y-axis origin. See [Figure 4.5.1](#) for an example. This gives an estimate of  $C_p^0$ . When the IV bolus dose is known the apparent volume of distribution can be calculated from Equation 4.7.3, above.

**Table 4.7.1 Example values for apparent volume of distribution (Gibaldi, 1984)**

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

Note, the last figure in this table, for digoxin, is much larger than body volume. This drug must be extensively distributed into tissues, leaving low concentrations in the plasma, thus the body as a whole **appears** to have a very large volume, of distribution. Remember, this is not a physiological volume.

The line in the figure below, Figure 4.7.2, was calculated with a dose of 450 mg, apparent volume of distribution of 15 L and elimination rate constant of  $0.20 \text{ hr}^{-1}$ . Calculate the curve with other parameter values using the Apple window.



**Figure 4.7.2. Concentration versus time**

Click on the figure to view the Java Applet window  
Java Applet as a [Semi-log Plot](#)

## References

- Gibaldi, M. 1984 "Biopharmaceutics and Clinical Pharmacokinetics", 3rd ed., Lea & Febiger, Chapter 12, page 214
- Volume has been discussed on [the PharmPK listserv](#)

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### Half-life of Elimination, $t_{1/2}$

Another important property of first order kinetics is the half-life of elimination,  $t_{1/2}$ .

### Defining Equation

The half-life is the time taken for the plasma concentration to fall to half its original value. Units for this parameter are units of time such as hour, minute, or day. Thus if  $C_p$  is the concentration at time one and  $C_p/2$  is the concentration at time one half-life later:-

$$\ln \frac{C_p}{2} = \ln C_p - k_{el} \cdot t_{1/2}$$

Equation 4.8.1

$$\ln \left[ \frac{C_p}{2} \cdot \frac{1}{C_p} \right] = -k_{el} \cdot t_{1/2}$$

Equation 4.8.2

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

Equation 4.8.3

$t_{1/2} = \frac{0.693}{k_{el}}$ <p>Equation 4.8.4</p>	OR	$k_{el} = \frac{0.693}{t_{1/2}}$ <p>Equation 4.8.5</p>
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Note: Independent of concentration. This a property of first order processes

These equations can be used as an approximate method of calculating  $k_{el}$ . If we look at a plot of  $C_p$  versus time on semi-log graph paper.

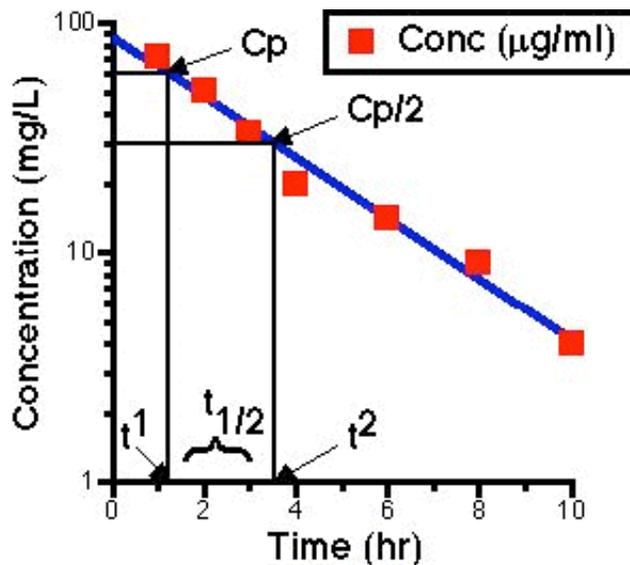


Figure 4.8.1 Semi-log Plot of  $C_p$  versus Time Illustrating  $t_{1/2}$  Calculation

The steps to take are:

1. Draw a line through the points (this tends to average the data)
2. Pick any  $C_p$  and  $t_1$  on the line
3. Determine  $C_p/2$  and  $t_2$  using the line
4. Calculate  $t_{1/2}$  as  $(t_2 - t_1)$

And finally  $k_{el} = 0.693/t_{1/2}$  (Equation 4.8.5)

You might also consider determining  $C_p/4$  or  $C_p/8$  after two half-lives or three half-lives, respectively. This should provide a more accurate answer as the differences in  $C_p$  and  $t$  will be larger.

The line smooths out the bumps. There may be less accurate data points, so by putting in a line you average the data. The half-life is the same whether going from 40 to 20 or from 10 to 5 mg/L. This is a property of the first order process.

**Note:**

Go from:

- $C_p \rightarrow C_p/2$  in 1 half-life i.e. 50.0 % lost 50.0 %
- $C_p \rightarrow C_p/4$  in 2 half-lives i.e. 25.0 % lost 75.0 %
- $C_p \rightarrow C_p/8$  in 3 half-lives i.e. 12.5 % lost 87.5 %
- $C_p \rightarrow C_p/16$  in 4 half-lives i.e. 6.25 % lost 93.75 %
- $C_p \rightarrow C_p/32$  in 5 half-lives i.e. 3.125 % lost 96.875 %
- $C_p \rightarrow C_p/64$  in 6 half-lives i.e. 1.563 % lost 98.438 %
- $C_p \rightarrow C_p/128$  in 7 half-lives i.e. 0.781 % lost 99.219 %

Thus over 95 % is lost or eliminated after 5 half-lives. Typically, with pharmacokinetic processes, this is considered the completion (my definition unless told otherwise) of the process [Although in theory it takes an infinite time]. Others may wish to wait 7 half-lives where over 99% of the process is complete. Others have suggested that three half-lives are sufficient.

**Table 4.8.1. Example Values for Elimination Half-life (Ritschel, 1980)**

Drug	t <sub>1/2</sub> , hr
Acetaminophen	2.5
Diazepam	33
Digoxin	40
Gentamicin	2.1
Lidocaine	1.6
Theophylline	11

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The half-life is a model independent term in that it describes the time it takes for a drug concentration (or other process) to fall to half the original value. For first order processes (as described and derived as above) this time is independent of concentration. When the kinetics are described by non-linear (non first order) kinetics, for example Michaelis-Menten kinetics, the half-life at one concentration may be quite different from the half-life at another concentration.

In the pharmacokinetic area of study the half-life of a drug usually refers to the biological or terminal half-life. These terms have different meaning for different people. I tend to view them both as referring to half-life measured for the terminal or slowest slope on the semi-log drug concentration *versus* time plot. At low concentration more processes tend to follow first order kinetics. However, at later times with lower concentrations assay sensitivity can be a serious problem. Also, if absorption is very slow the slowest slope may refer to the absorption process instead of drug disposition.

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#### References

- Ritschel, W.A. 1980 **Handbook of Basic Pharmacokinetics**, 2nd ed., Drug Intelligence Publications, p 413-426
- Half-life has been discussed on [the PharmPK listserv](#).
- Other [Pharmacokinetic textbooks](#)

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### Area under the plasma concentration time curve (AUC)

The area under the plasma (serum, or blood) concentration *versus* time curve (AUC) has an number of important uses in toxicology, biopharmaceutics and pharmacokinetics.

**Toxicology** AUC can be used as a measure of drug exposure. It is derived from drug concentration and time so it gives a measure how much - how long a drug stays in a body. A long, low concentration exposure may be as important as shorter but higher concentration. Some drugs are dosed using AUC to quantitate the maximum tolerated exposure (AUC Dosing).

**Biopharmaceutics** The AUC measured after administration of a drug product is an important parameter in the comparison of drug products. Studies can be performed whereby different drug products may be given to a panel of subject on separate equations. These [bioequivalency or bioavailability studies](#) can be analysed by comparing AUC values.

**Pharmacokinetics** Drug AUC values can be used to determine other pharmacokinetic parameters, such as clearance or bioavailability, F. Similar techniques can be used to calculate area under the [first moment curve \(AUMC\) and thus mean resident times \(MRT\)](#).

The area under the plasma concentration *versus* time curve (AUC) has units of concentration times time. For example, mg.hr/L or mg.hr.L<sup>-1</sup>. AUC is used extensively in the calculation drug product performance, that is dosage form bioavailability. This is covered more extensively in [Chapter 18](#). AUC has also been used to quantitate drug exposure (concentration times time) to limit drug exposure or toxicology assessment. AUC and other area calculations are also used in non-compartmental pharmacokinetic parameter estimation as described in Chapter 19 and Clearance described on [the next page](#).

The calculation of AUC using the trapezoidal rule was previously described in [Chapter 2](#).

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#### References

- AUC has been discussed on [the PharmPK listserv](#).

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# PHAR 7632 Chapter 4

## One Compartment IV Bolus

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### Total Body Clearance (Cl)

Clearance is an important pharmacokinetic parameter that describes how quickly drugs are eliminated, metabolized or distributed throughout the body. It can be viewed as the proportionality constant relating the rate of these processes and drug concentration. For example the rate of elimination of a drug can be described by Equation 4.10.1.

$$\frac{dX}{dt} = -Cl \cdot C_p$$

**Equation 4.10.1 Rate of Elimination versus Concentration**

In Equation 4.10.1 the elimination rate constant,  $dX/dt$ , is related to the concentration of drug remaining. The proportionality constant for this relationship is Clearance, **Cl**. The symbol for clearance is Cl and the units are volume per time or ml/min, L/hr.

Equation 4.10.1 can be rearranged to give Equation 5.10.2 for clearance.

$$CL = \frac{-\frac{dX}{dt}}{C_p}$$

**Equation 4.10.2 Clearance calculated from Rate and Concentration**

Clearance can be calculated from this equation by measuring the amount of drug eliminated during some time interval and the drug concentration at the midpoint of this collection interval. The clearance of the endogenous material, creatinine, is measured by this method as described in [Chapter 16](#) to provide a measure of renal function.

Clearance can also be calculated from the integral of Equation 4.10.2. Integrating  $dX/dt$  and  $C_p$  with respect to time give Dose and AUC, respectively. The total amount that can be eliminated is the total amount administered, that is, the dose. Thus, clearance can be calculated as:

$$CL = \frac{\int \frac{dX}{dt} \cdot dt}{\int C_p \cdot dt} = \frac{\text{Dose}}{\text{AUC}}$$

**Equation 4.10.3 Clearance calculated from Dose and AUC**

In case of the one compartment model with an IV bolus dose the rate of elimination can be expressed as:

$$\frac{dX}{dt} = k_{el} \cdot X = -k_{el} \cdot V \cdot C_p = -CL \cdot C_p$$

thus a value for Total Body Clearance, CL, can be estimated from  $k_{el}$  and V for the one compartment model.

$$CL = k_{el} \cdot V$$

**Equation 4.10.4 Clearance calculated from  $k_{el}$  and V**

The clearance of a drug can be used to understand the processes involved in drug elimination, distribution and metabolism. Relating clearance to a patient renal or hepatic function can be used in the determination of suitable drug dosage regimens.

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**References**

- Clearance has been discussed on [the PharmPK listserv](#).

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# PHAR 7632 Chapter 4

## One Compartment IV Bolus

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### IV Bolus - Example 1

Question: What is the concentration of drug 0, 2 and 4 hours after a dose of 500 mg. Known pharmacokinetic parameters are apparent volume of distribution, V is 30 liter and the elimination rate constant, kel is 0.2 hr<sup>-1</sup>

Answer: Use Equation 4.11.1 to calculate the required concentrations

$$C_p = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

Equation 4.11.1 Concentration as a Function of Time

Thus:

$$C_p^{0 \text{ hours}} = \frac{Dose}{V} \bullet e^{-kel \bullet t} = \frac{500}{30} \bullet e^{-0.2 \times 0} = 16.7 \text{ mg/Liter}$$

$$C_p^{2 \text{ hours}} = \frac{Dose}{V} \bullet e^{-kel \bullet t} = \frac{500}{30} \bullet e^{-0.2 \times 2} = 11.2 \text{ mg/Liter}$$

$$C_p^{4 \text{ hours}} = \frac{Dose}{V} \bullet e^{-kel \bullet t} = \frac{500}{30} \bullet e^{-0.2 \times 4} = 7.49 \text{ mg/Liter}$$

### Try your own calculation

Calculator 4.11.1 Calculate Cp<sup>t</sup> after an IV Bolus

IV Bolus Dose:	<input type="text" value="500"/>	
Apparent Volume of Distribution:	<input type="text" value="30"/>	Cannot be zero
Elimination Rate Constant:	<input type="text" value="0.2"/>	
Time since IV Dose:	<input type="text" value="2"/>	
<input type="button" value="Calculate (using JavaScript)"/>		
The answer Cp <sup>t</sup> is:	<input type="text"/>	

If you get the **Error Message** Value is not a numeric literal or *NaN* this probably means that one of the required parameter fields is empty or a value is inappropriate.

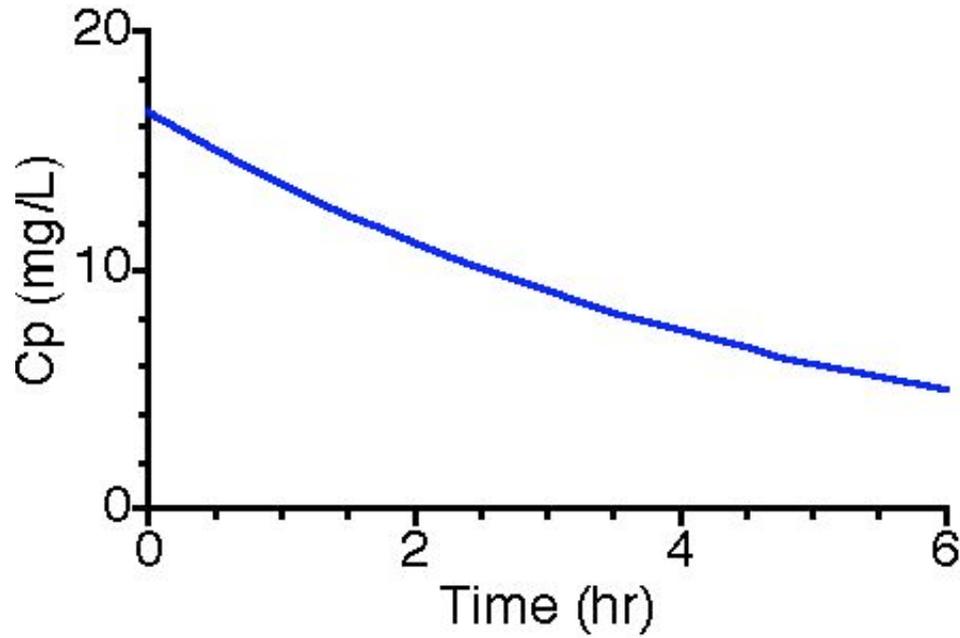


Figure 4.11.1. Concentration *versus* time

Click on the figure to view the Java Applet in a new window  
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# PHAR 7632 Chapter 4

## One Compartment IV Bolus

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### IV Bolus - Example 2

We can also calculate the pharmacokinetic parameters  $k_{el}$  and  $V$  if we know the dose given and the plasma concentrations at two (or more) times after an IV bolus administration. This time we will use Equation 4.12.1

$$k_{el} = \frac{\ln C_{p1} - \ln C_{p2}}{t_2 - t_1}$$

**Equation 4.12.1 Kel calculated from Two Concentration Values**

Question: If  $C_p^{2 \text{ hours}}$  is 4.5 mg/liter and  $C_p^{6 \text{ hours}}$  is 3.7 mg/liter after a 400 mg IV bolus dose what are the values of  $k_{el}$  and  $V$ .

$$\begin{aligned} k_{el} &= \frac{\ln C_{p1} - \ln C_{p2}}{t_2 - t_1} = \frac{\ln 4.5 - \ln 3.7}{6 - 2} \\ &= \frac{1.5041 - 1.3083}{4} = \frac{0.1958}{4} = 0.0489 \text{ hr}^{-1} \end{aligned}$$

Now using either the 2 hour or the 6 hour data point calculate the concentration at time zero.

$$\begin{aligned} C_p^{2 \text{ hour}} &= C_p^0 \bullet e^{-k_{el} \bullet t} \\ C_p^0 &= \frac{C_p^{2 \text{ hour}}}{e^{-k_{el} \bullet t}} = \frac{4.5}{e^{-0.0489 \times 2}} \\ &= \frac{4.5}{0.9068} = 4.96 \text{ mg/L} \end{aligned}$$

And now

$$V = \frac{\text{Dose}}{C_p^0} = \frac{400}{4.96} = 80.6 \text{ liter}$$

**Equation 4.12.2 V from Dose and  $C_p^0$**

and

$$CL = kel \bullet V = 0.0489 \times 80.6 = 3.94 \text{ L}$$

Equation 4.12.3 Clearance from kel and V

---

**Try your own calculation**

**Calculator 4.12.1 Calculate Parameter Values from Two Data Points Collected after an IV Bolus**

IV Bolus Dose:	400
First concentration:	4.5
Time of first Cp value:	2
Second concentration:	3.7
Time of second Cp value:	6
Calculate (using JavaScript)	
<b>kel</b> is:	
<b>t<sub>1/2</sub></b> is:	
<b>Cp<sup>0</sup></b> is:	
<b>V</b> is:	
<b>and Clearance</b> is:	

If you get the **Error Message** Value is not a numeric literal or *NaN* this probably means that one of the required parameter fields is empty or a value is inappropriate.

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Another example. A 45 yr, 74 kg male patient with severe nafcillin-resistant *Staph. aureus* infection is started on a new drug. He is given 1000 mg as a loading dose over 60 minutes (however, we will assume this is an IV bolus). This has poor renal function so we sample his blood at 2 and 12 hours to determine the pharmacokinetics of **this drug in this patient**. The concentrations were 18.6 and 13.1 mg/L, respectively. If the minimum effective concentration is 10 mg/L calculate the when the next dose should be given AND the dose required to increase the concentration back close to the maximum therapeutic concentration or 25 mg/L. HINT: Calculate kel, Cp<sup>0</sup>, t(10mg/L), V, and next dose. [Answers in a new window](#)

---

**References**

- Winter, M.E. 1988 **Basic Clinical Pharmacokinetics**, 2nd. ed., Applied Therapeutics, Vancouver, WA ISBN 0915486083

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# PHAR 7632 Chapter 4

## One Compartment IV Bolus

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### IV Bolus - Example 3

Question: What IV bolus dose is required to achieve a plasma concentration of 2.4  $\mu\text{g/ml}$  (= 2.4 mg/L) at 6 hours after the dose is administered. The elimination rate constant,  $k_{el}$ , is  $0.17 \text{ hr}^{-1}$ ) and the apparent volume of distribution,  $V$ , is 25 L.

Answer: Rearrange Equation 4.11.1 to give Equation 4.13.1

$$Dose = \frac{C_p^t \bullet V}{e^{-k_{el} \bullet t}}$$

Equation 4.13.1 Dose For  $C_p$  at time  $t$

Substituting in the values we know

$$Dose = \frac{2.4 \times 25}{e^{-0.17 \times 6}} = \frac{60}{0.3606} = 166.4 \text{ mg}$$

Also note:

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

Equation 4.13.2 Concentration *versus* time

thus

$$C_p^0 = \frac{C_p}{e^{-k_{el} \bullet t}} = C_p \bullet e^{+k_{el} \bullet t}$$

Equation 4.13.3  $C_p^0$  from  $C_p$  and time

and

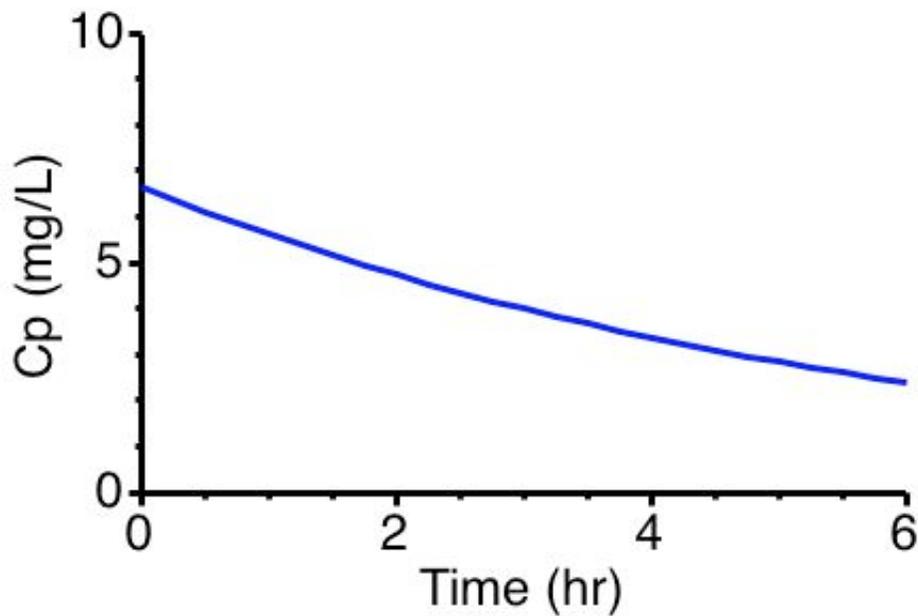
$$Dose = C_p^0 \bullet V$$

Equation 4.13.4 Dose from  $C_p^0$  and  $V$

**CHECK the UNITS****Try your own calculation****Calculator 4.13.1 Calculate the Required IV Bolus Dose**

Elimination rate constant:	<input type="text" value="0.17"/>	
Apparent Volume of Distribution:	<input type="text" value="25"/>	Cannot be zero
Keep $C_p$ above:	<input type="text" value="2.4"/>	
for how long:	<input type="text" value="6"/>	
<input type="button" value="Calculate (using JavaScript)"/>		
$C_p^0$ is:	<input type="text"/>	
and the required <b>Dose</b> is:	<input type="text"/>	

If you get the **Error Message** Value is not a numeric literal or *NaN* this probably means that one of the required parameter fields is empty or a value is inappropriate.



**Figure 4.13.1. Concentration versus time**

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# PHAR 7632 Chapter 4

## One Compartment IV Bolus

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### IV Bolus - Example 4

Question: After an I.V. bolus dose of 500 mg the data collected in Table 4.14.1 were collected. Calculate  $k_{el}$  and  $V$ .

Table 4.14.1 Concentration *versus* Time Data

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

Plot the data on semi-log graph paper (Figure 4.14.1) and determine  $C_p^1$ ,  $C_p^2$ ,  $t^1$  and  $t^2$ .

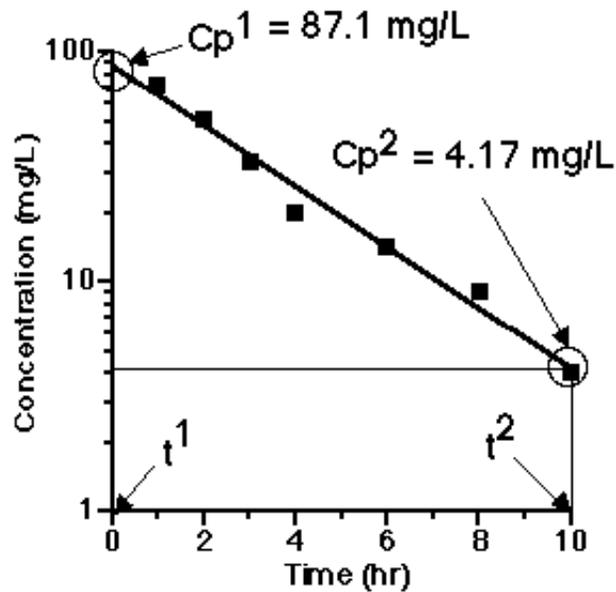


Figure 4.14.1 Plot of  $C_p$  *versus* Time on Semi-log Graph Paper After an I.V. Bolus Dose of 500 mg.

$$\begin{aligned}
 k_{el} &= \frac{\ln C_p^1 - \ln C_p^2}{t^2 - t^1} \\
 &= \frac{\ln 87.1 - \ln 4.17}{10 - 0} \\
 &= \frac{3.04}{10} = 0.304 \text{ hr}^{-1}
 \end{aligned}$$

and

$$V = \frac{\text{Dose}}{C_p^0} = \frac{500}{87.1} = 5.74 \text{ L}$$

Figure 4.14.2 V from dose and  $C_p^0$ 

and

$$Cl = k_{el} \bullet V = 0.304 \times 5.74 = 1.74 \text{ L/hr}$$

Equation 4.12.3 Clearance from  $k_{el}$  and V

## Try your own calculation

## Calculator 4.14.1 Calculate Parameter Values from Two Data Points from a Line drawn through Data Collected after an IV Bolus

IV Bolus Dose:	<input type="text" value="500"/>
First concentration:	<input type="text" value="87.1"/>
Time of first Cp value:	<input type="text" value="0"/>
Second concentration:	<input type="text" value="4.17"/>
Time of second Cp value:	<input type="text" value="10"/>
<input type="button" value="Calculate"/>	
<b>k<sub>el</sub></b> is:	<input type="text"/>
<b>t<sub>1/2</sub></b> is:	<input type="text"/>
<b>C<sub>p</sub><sup>0</sup></b> is:	<input type="text"/>
<b>V</b> is:	<input type="text"/>
<b>and Total Body Clearance</b> is:	<input type="text"/>

If you get the **Error Message** Value is not a numeric literal or *NaN* this probably means that one of the required parameter fields is empty or a value is inappropriate.

**For practice** you can plot these data collected after an IV bolus dose and [estimate pharmacokinetic parameters](#).

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