In this topic guide you will learn how to construct semi-log plots from data on drug concentration with regard to absorption and elimination. It will also introduce the use of semi-log plots to determine the rate of absorption and elimination and to determine when the total amount of a drug or a fraction of it has been absorbed. Finally, it will discuss how to calculate the half-life for drug elimination.

On successful completion of this topic you will:
• be able to analyse and calculate clinical data (LO1).

To achieve a Pass in this unit you need to show that you can:
• calculate rates of absorption and excretion, half-life, total amount absorbed and fraction absorbed (1.2).
1 Calculating the rate of absorption of drugs

Unless administered by IV, all drugs must diffuse across cell membranes before entering the bloodstream and so the rate of their absorption can be influenced by numerous factors (see Topic guide 8.3). It is difficult to sample drug concentrations in the tissues so measurements must be made from body fluids such as the blood/plasma, urine, saliva, etc.

The compartmental model is a simplified representation of the body whereby each compartment represents a group of similar tissues or fluids. The central compartment can include the heart, liver, lungs, kidneys and the blood while peripheral compartments may be adipose tissue, muscle tissue, cerebrospinal fluid, etc.

The plasma drug concentration (i.e. in the central compartment) will, due to kinetic homogeneity, reflect that in other tissues, including the receptor site where the drug is required to produce its therapeutic effect.

The drug concentration is defined as the amount of drug in a given volume, for example, mg/l.

As the receptor sites for drugs are usually inaccessible, it is difficult to take samples for the direct measurement of drug concentrations. For example, the receptor sites for digoxin, which is used in the treatment of various heart conditions, are thought to be within the myocardium (heart muscle). We can, however, measure drug concentration in body fluids such as the blood plasma, urine, etc.

The rate of absorption of a drug can be calculated by first measuring its concentration in the plasma at various intervals from immediately after it has been administered. A plot of the drug concentration (on the y axis) versus time (on the x axis) will show a positive curve that will normally level off and fall as the drug starts to be excreted (see Figure 8.2.1).

The steep part of the curve in Figure 8.2.1 indicates that the rate of absorption is higher immediately after administration but falls off as the drug is completely absorbed and begins to be eliminated. This means that the rate of absorption is proportional to the amount of drug at the absorption site.
Thus the rate of absorption can be represented by the change in concentration with (the change in) time:

\[
\text{Rate} = \frac{dC}{dt} \\
\rightarrow \text{Rate} = kC^o
\]

Where \( k \) = the rate constant, \( C \) = the drug concentration in the plasma at a given time, \( o \) = the order of absorption, \( d \) = the rate of change (increase).

**Semi-log plots**

A straight line gives a better picture of the relationship than a curve. However, if the concentration values are converted to their natural logarithms (\( \ln \) found using the \( \ln \) function on a scientific calculator), and these plotted against time, a more linear relationship can be obtained by drawing a line of best fit through the points – the steeper the line, the faster the rate of absorption.

![Semi-log plot](Figure 8.2.2): Semi-log plot.

**Key terms**

**Natural logarithms (\( \ln \)):** Obtained using the \( \ln \) function on a common scientific calculator.

**Line of best fit:** When the points do not all join up to give a complete straight line but a line can be drawn through the centre of gravity with as many of them as close to it as possible, it is referred to as a ‘line of best fit’.

![Semi-log plot](Figure 8.2.2): Semi-log plot.

Such a plot as that in Figure 8.2.2 is referred to as a semi-log plot as one of the axes has been converted into the logarithm. It is easier to predict plasma concentrations for any given period from a straight line rather than a curve and to determine both the rate constant (\( k \)), which is the slope of the line, and the order of the rate of absorption (\( o \)).

The semi-log plot in Figure 8.2.2 shows that the rate of absorption is first order as it is proportional to the amount of drug in the plasma. For a zero order rate of absorption, the rate would be constant for some defined period of time and the semi-log plot would not show a linear relationship. In fact, the plot of concentration versus time would be a straight line as the same amount would be absorbed after a given time interval regardless of the initial concentration, for example, as shown in Table 8.2.1.

**Table 8.2.1: Rate of absorption.**

<table>
<thead>
<tr>
<th>Time/hr</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>% absorbed</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
</tr>
</tbody>
</table>

Having obtained the rate constant (\( k \)) and the order (\( o \)), the rate of absorption for any given dosage of the drug can be calculated.
Activity
For the first five hours after drug A has been administered orally, the plasma samples for hourly intervals show the concentrations (mg/l) given in Table 8.2.2.

1. Plot the graph for concentration versus time.
2. Plot the graph for the natural logarithm of concentration versus time.
3. Calculate the rate constant $k$.
4. For drug B the rate constant has a value of 0.375. Which of the two drugs has the greater rate of absorption?

Table 8.2.2: Plasma samples at hourly intervals.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma concentration for drug A (mg)</td>
<td>0</td>
<td>44</td>
<td>68</td>
<td>74</td>
<td>78</td>
<td>80</td>
</tr>
</tbody>
</table>

2. Calculating the rate of excretion of drugs

The clearance of a drug is the measure of the removal of the drug from the body. Expressed as volume/time, it describes the removal of the drug from a volume of plasma in a given unit of time. Drugs can be cleared from the body by different routes and mechanisms which include hepatic, renal and biliary excretion. The total body clearance of the drug is thus the sum of all the clearances by the various pathways:

$$\text{Cl}_t = \text{Cl}_r + \text{Cl}_m + \text{Cl}_b + \text{Cl}_{\text{other}}$$

Where:

- $\text{Cl}_t$ = total body clearance
- $\text{Cl}_r$ = renal clearance
- $\text{Cl}_m$ = clearance by liver metabolism etc.
- $\text{Cl}_b$ = biliary clearance
- $\text{Cl}_{\text{other}}$ = clearance by other routes including gastrointestinal tract, pulmonary etc.

An organ’s ability to remove a drug can be measured by relating the drug concentration in the blood entering the organ ($C_{in}$) and that in the blood exiting ($C_{out}$). This extraction ratio ($E$) is given by:

$$E = \frac{C_{in} - C_{out}}{C_{in}}$$

The drug clearance is determined by the blood flow and the extraction ratio:

$$\text{organ clearance (Cl}_{\text{other}}) = \text{blood flow (Q)} \times \text{extraction ratio (E)}$$

However, the simplest method of determining the rate of drug elimination from the body is by measuring the plasma drug concentration after administration on a continuous basis and again plotting it against time. This time the plot of the drug concentration (on the y axis) versus time (on the x axis) will show a negative curve that levels off as the drug has been completely excreted (see Figure 8.2.3).
The semi-log plot (natural log of the drug concentration versus time) produces a straight line, the slope of which can be used to determine the rate constant and the order. From this, the rate can be calculated using the equation:

\[
\text{Rate} = -\frac{dC}{dt}
\]

\[\rightarrow \text{Rate} = -kC^o\]

\[k = \text{the rate constant}\]

\[C = \text{the drug concentration in the plasma at a given time}\]

\[o = \text{the order of absorption}\]

\[d = \text{the rate of change (decrease)}\]

Figure 8.2.4: Semi-log plot.

Again, such semi-log plots can be used to determine whether the excretion of a drug from the blood plasma is first order or zero order. Most drugs are eliminated by a first order process (as represented by the semi-log plot shown in Figure 8.2.4) whereby the amount of drug eliminated in a given period of time is directly proportional to the amount of drug in the body. The amount of drug eliminated over a certain time period increases as the amount of drug in the body increases, and vice versa.

When the drug is eliminated by a zero order process, the amount of drug eliminated for each interval is constant, regardless of the amount of drug in the body, for example, from 100% to 80%, 60%, 40%, etc. Thus, when the concentration is plotted against time, a straight line results while the semi-log plot will give a curve.

**Half-life**

The half-life \((t_{1/2})\) is the time it takes for half the initial amount of drug to be removed from the blood plasma. It often relates to the duration of the drug’s action and is used to determine when another dose should be administered. One way to measure the half-life is to examine the semi-log plot of the drug concentration versus time and observe the time required for the plasma drug concentration to decrease by one half. For example, in the semi-log plot shown in Figure 8.2.5, the decrease from 10 to 5 mg/l takes approximately 2 hours. It takes the same time to decrease from 5 to 2.5 mg/l, from 7 to 3.5 mg/l, etc.
The half-life can also be calculated mathematically using the following equation:

\[
t_{1/2} = \frac{0.693}{k}
\]

where \( k \) is the elimination rate constant (calculated from the slope of the straight line in the semi-log plot).

Consequently, if the half-life is known, the elimination rate constant can be determined by rearranging the above equation:

\[
k = \frac{0.693}{t_{1/2}}
\]

**Activity**

1000 mg of a drug has been administered with the plasma samples for hourly intervals showing the concentrations given in Table 8.2.3.

1. Plot the graph for concentration versus time.
2. Plot the graph for the natural logarithm of concentration versus time and draw a line of best fit.
3. Calculate the rate constant \( k \) for elimination.
4. Calculate the half-life for the drug elimination using the mathematical formula.
5. Check how the answer obtained for step 4 compares with an examination of the semi-log plot (i.e. observe the time taken between the log of 1000 and that of 500).

**Table 8.2.3**

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Plasma concentration (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1000</td>
</tr>
<tr>
<td>1</td>
<td>880</td>
</tr>
<tr>
<td>2</td>
<td>774</td>
</tr>
<tr>
<td>3</td>
<td>681</td>
</tr>
<tr>
<td>4</td>
<td>599</td>
</tr>
<tr>
<td>5</td>
<td>527</td>
</tr>
<tr>
<td>6</td>
<td>464</td>
</tr>
<tr>
<td>7</td>
<td>408</td>
</tr>
</tbody>
</table>

**Case study**

The average half-lives (hr) of some common drugs are:

- Digoxin: 39
- Enoxaparin: 3.8
- Gentamicin: 2.5
- Lithium: 22
- Vancomycin: 5.6

**Further reading**


**Acknowledgements**

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