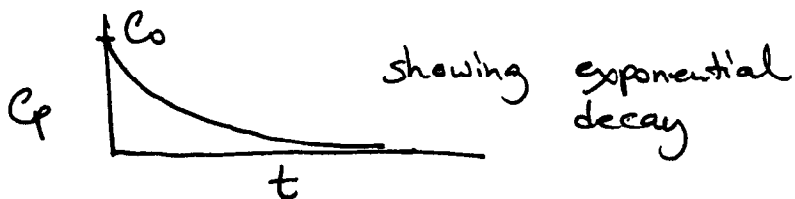


Problem Set 1 - Fall 1998

$$1) C_p = C_0 \cdot e^{-kt}$$



2) This equation shows 1st order elimination. Actually, the "order" is more obvious from the rate expression,

$$\frac{dC}{dt} = -kC$$

where the elimination rate is dependent on concentration to the 1st power, C^1 . The rate expression for a zero-order elimination process is

$$\frac{dC}{dt} = -k \cdot C^0 = -k \cdot 1 = -k.$$

These rate expressions are integrated to give the $C_p(t)$ ~~exp~~ equations you have already seen:

zero order $\frac{dC}{dt} = -k$ $\xrightarrow[\text{to give}]{\text{Integrated}}$ $C = C_0 - kt$

1st order $\frac{dC}{dt} = -k \cdot C$ \longrightarrow $C = C_0 \cdot e^{-kt}$

3) By definition, half-life is the time required for the concentration to drop to $\frac{1}{2}$ the initial amount (duh-----). So

$$C_p(t) = C_0 \quad \text{at } t=0$$

$$\text{and } C_p(t) = \frac{C_0}{2} \quad \text{at } t = t_{1/2}.$$

(Here I have written the concentration explicitly as a function of time, $C_p(t)$. This is not common notation in most pharmacokinetic texts). To find the half-life, $t_{1/2}$, we need to solve the $C_p(t)$ equation for the time when $C_p(t) = C_0/2$:

$$C_p(t) = C_0 \cdot e^{-kt} \quad \text{in general}$$

$$\text{At } t_{1/2}, \quad C_p(t) = \frac{C_0}{2} = C_0 \cdot e^{-kt_{1/2}}$$

This rearranges to give

$$\frac{\cancel{C_0}}{2 \cdot \cancel{C_0}} = e^{-kt_{1/2}}$$

$$\frac{1}{2} = e^{-kt_{1/2}}$$

Taking the natural log of both sides,

$$\ln\left(\frac{1}{2}\right) = -kt_{1/2}$$

$$\ln(1) - \ln(2) = -kt_{1/2}$$

$$\ln(2) = kt_{1/2}$$

or

$$t_{1/2} = \ln(2)/k$$

If $t_{1/2} = 4 \text{ hr}$, what is k ?

$$t_{1/2} = \ln 2 / k$$

$$\text{or } k = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{4 \text{ hr}} = \boxed{0.173 \text{ hr}^{-1}}$$

4) $C_0 = 70 \mu\text{g/ml}$, $t_{1/2} = 6 \text{ hr}$.

In order to calculate the concentrations at the given time points, we need to find k .

$$k = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{6 \text{ hr}} = \underline{0.116 \text{ hr}^{-1}}$$

Now, at $t = 6 \text{ hr}$,

$$\begin{aligned} C_p(t) &= C_0 \cdot e^{-kt} \\ &= (70 \mu\text{g/ml}) \cdot e^{-(0.116 \text{ hr}^{-1})(6 \text{ hr})} \\ &= \boxed{35.0 \mu\text{g/ml}} \end{aligned}$$

Was this calculation necessary?

- No; If $t_{1/2} = 6 \text{ hr}$, then every 6 hours, the concentration will drop by one-half the amount (for first-order elimination). So,

t (hr)	C_p ($\mu\text{g/ml}$)
0	70
6	35
12	17.5
18	8.75

and so on.

If $C_{p0} = 70 \mu\text{g/ml}$, $t_{1/2} = 6 \text{ hr}$, and elimination is zero-order, it is understood that every 6 hrs, the concentration will drop by $\frac{70}{2} = 35 \mu\text{g/ml}$. Half-life is concentration-dependent for zero-order elimination. Thus, a reference concentration must be known. For zero-order elimination, it would be more appropriate to state that the rate of elimination is $35 \mu\text{g/ml}$ every 6 hours.

t (hr)	C_p ($\mu\text{g/ml}$)
0	70
6	35
12	0

5) As stated above, $t_{1/2}$ is concentration-dependent for zero-order elimination. For 1st order elimination, half-life is independent of concentration: If $t_{1/2} = 12 \text{ hrs}$, then every 12 hours, the concentration will drop by one-half regardless of how large or small the concentration is.

6) If a drug has a large degree of plasma protein binding, any change in the amount of plasma proteins can have a profound effect on the volume of distribution of the drug and the resulting plasma concentrations. Patient 1 has albumine levels lower than

normal. Thus, there are fewer sites for binding to take place in the plasma. With less drug bound in the plasma, more drug is free to distribute into the tissues. So, we expect to see a larger volume of distribution for Patient 1 (providing the drug is able to cross membranes) which will result in lower plasma concentrations. To reach the plasma concentrations observed with the normal patient (patient 2), patient 1 should receive a larger dose.

7) Given: $D = 750\text{mg}$, $C_p = 105\ \mu\text{g/ml}$

Recall the equation for the initial plasma concentration following an iv bolus dose,

$$C_p = \frac{D}{V_d}$$

Solving this for V_d gives

$$V_d = \frac{D}{C_p}$$

$$= \frac{750\text{mg}}{105\ \mu\text{g/ml}} \cdot \frac{1000\ \mu\text{g}}{1\text{mg}} \cdot \frac{1\text{L}}{1000\text{ml}}$$

$$V_d = 7.14\text{L}$$

$V_d = 3\text{L}$ theoretical lower limit

$V_d = 7\text{L}$ practical lower limit

Very low V_d . This drug is either completely bound to plasma proteins or is unable to cross membranes.