

Mathematics in Pharmacokinetics

What and Why (A second attempt to make it clearer)

We have used equations for concentration (C) as a function of time (t). We will continue to use these equations since the plasma concentrations of drugs will be important in determining amount of dose, frequency of dose, etc. From these concentration/time equations we can determine the elimination rate constant (k_e), the half-life of the drug ($t_{1/2}$), and the area under the curve (AUC), and predict concentrations at given time points.

The rate of decrease in concentration (C) with time can be described by the equation

$$\frac{dC}{dt} = -kC^n ,$$

where n is the “order” of the rate process. We will consider two cases: zero-order (n=0) and first-order (n=1).

Zero-order

If $n = 0$, the rate expression is (from above)

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

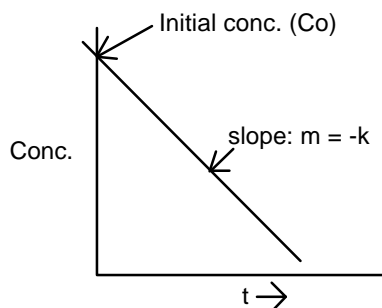
or

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

We can then say that the rate of decrease in concentration is independent of concentration and depends only on the rate constant k. So, in a zero-order process, the same amount of drug will disappear in a given amount of time regardless of how much drug is present.

e.g. If $k = 2 \text{ mg/l/hr}$, my concentration will decrease by 2mg/l every hour whether the starting concentration is 10 mg/l or 100 mg/l.

This process of constant change will show a linear plot when graphing C vs t.



Since equations for straight lines have the same form ($y = mx + b$), we can easily write down an equation for C in terms of t from the information in this graph. We can also obtain an equation for C(t) by solving the zero-order rate equation given earlier (i.e. “solve the differential equation”).

Recall the equation

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

Rearranging $dC = -kdt$

We now need to integrate (to remove the differential and obtain an equation for C). The limits of integration are typically

C:	$C_0 \rightarrow C$
and t:	$0 \rightarrow t$

This will give us an equation where the concentration is C_0 at $t=0$ and C at time t.

Integrating

$$\int dC = \int -kdt$$

$$= -k \int dt$$

$$C]_{C_0}^C = -kt]_0^t$$

$$C - C_0 = -k(t - 0)$$

$$= -kt$$

solving for C gives

$$C = C_0 - kt$$

$\begin{array}{c} \downarrow \\ y \end{array}$
 $\begin{array}{c} \downarrow \\ b \end{array}$
 $\begin{array}{c} \downarrow \\ + \end{array}$
 $\begin{array}{c} \downarrow \\ m \end{array}$
 $\begin{array}{c} \downarrow \\ x \end{array}$

From this we see that the y-intercept is C_0 (the initial concentration) and the slope is $-k$ (the negative of the rate constant). This is a rather straight-forward way of obtaining k ($m = -k$).

Note: The “rate of change” can be found by taking the derivative (d/dt).

$$\frac{dC}{dt} = \frac{d}{dt}(C_0 - kt) = -k, \text{ which is what we started with.}$$

What about the half-life $t_{1/2}$? The half-life gives us an idea of how long the drug will stay in the body. Would we expect the $t_{1/2}$ to be dependent or independent of the drug concentration?

Recall that $t_{1/2}$ of a drug is the time required for half of the drug to go away. Since the rate of decrease ($-dC/dt$) for a zero-order process is independent of concentration, we see that the more drug we start off with, the more time is required for half to be removed.

e.g. Say that the rate of decrease is 2 mg/l/hr as before. If our initial concentration is $C_0 = 100$ mg/l, it will take a long time for half of this to go away (and have a concentration $C = 50$ mg/l). However, if $C_0 = 10$ mg/l, it will take a much shorter time to reach $C = 5$ mg/l. Thus, $t_{1/2}$ is concentration-dependent for a zero-order process.

We can prove this by solving our equation $C(t)$ for $t_{1/2}$.

At $t_{1/2}$, $C = C_0/2$ (by definition of half-life)

The general equation $C = C_0 - kt$ becomes

$$\frac{C_0}{2} = C_0 - kt_{1/2} \quad \text{at } t_{1/2}$$

Solving for $t_{1/2}$,

$$\begin{aligned}\frac{C_0}{2} &= C_0 - kt_{1/2} \\ \frac{C_0}{2} - C_0 &= -kt_{1/2} \\ -\frac{C_0}{2} &= -kt_{1/2} \\ \frac{C_0}{2k} &= t_{1/2}\end{aligned}$$

First Order

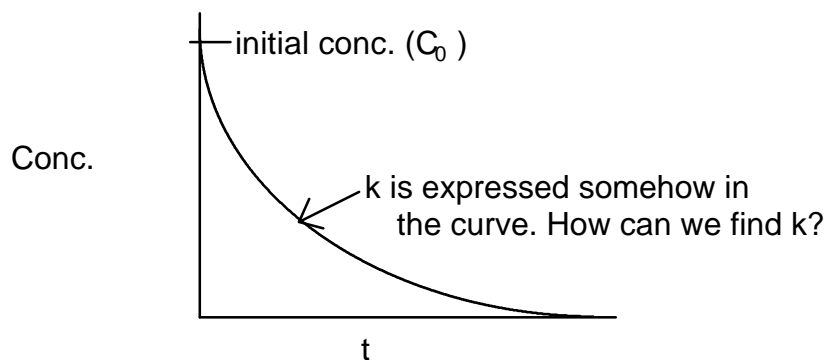
$$\frac{dC}{dt} = -kC^n$$

If $n = 1$, we have

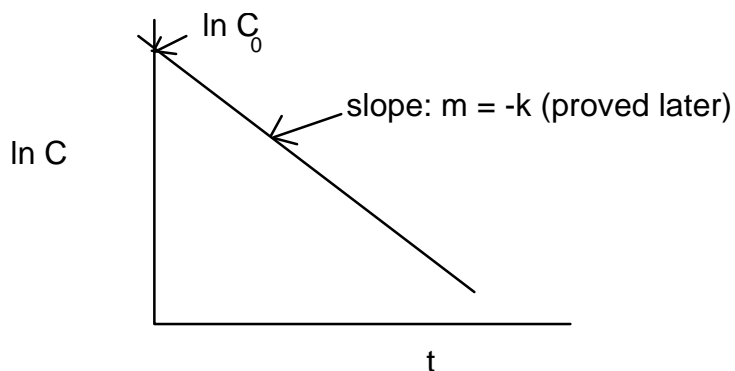
$$\frac{dC}{dt} = -kC$$

Thus, the rate of change depends on both the rate constant and concentration. So, the amount of drug that goes away in a given time period depends on how much drug we start with.

A typical 1st order plot is



This curve can be transformed to a linear plot by using $\ln C$ instead of C (i.e. taking the natural logarithm of our concentrations and graphing this value vs t).



Here again we see a straight line which should have an equation of the form $y = mx + b$.

We need to solve the differential equation to obtain an equation for c in terms of t .

Starting with the rate expression,

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

$$dC = -kCdt$$

We need to divide through by C (to get the C 's and t 's on opposite sides of the equation),

$$dC/C = -kdt$$

Integrating (again with $C:C_0 \rightarrow t$ and $t: 0 \rightarrow t$)

$$\int \frac{dC}{C} = \int -kdt$$

$$\ln C \Big|_{C_0}^C = -kt \Big|_0^t$$

$$\ln C - \ln C_0 = -kt$$

$$\ln C = \ln C_0 - kt \quad (\text{this is the equation for the straight line seen when plotting } \ln C \text{ vs } t)$$

We can transform this equation to obtain C rather than $\ln C$ by:

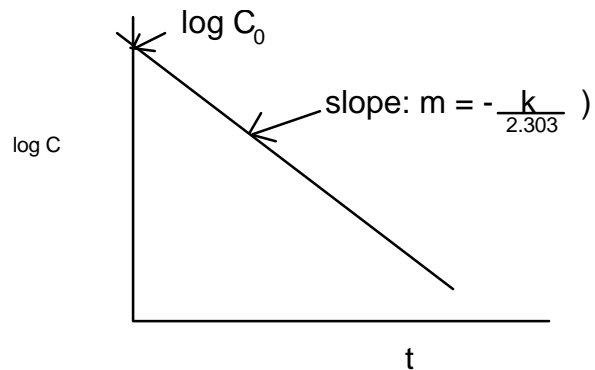
$$C^{\ln C} = e^{\ln C_0 - kt}$$

$$C = e^{\ln C_0} \cdot e^{-kt}$$

$$C = C_0 e^{-kt}$$

So, a first-order process shows an exponential decay.

Note: We could have plotted $\log C$ vs t and still had a linear plot. We can convert from $\ln X$ to $\log X$ by

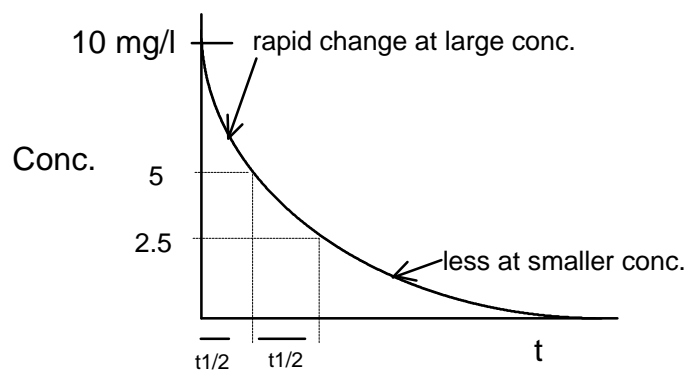


the equation is

$$\log C = \log C_0 - \frac{k}{2.303} t$$

AUC can be estimated as before: $AUC_{t \rightarrow \infty} = \frac{C_t}{t}$

Half-life: Is $t_{1/2}$ dependent or independent of concentration? Consider the plot of C vs t :



It seems that no matter where we start in the concentration curve, it takes the same amount of time for half the drug to disappear. Let's prove this.

Recall at $t_{1/2}$, $C = C_0/2$

Putting this into our equation gives

$$C_0/2 = C_0 e^{-kt_{1/2}}$$

Dividing through by C_0 and solving for $t_{1/2}$

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

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

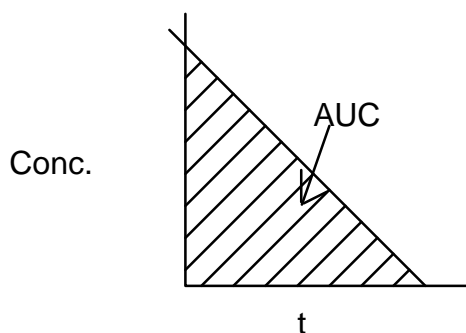
$$t_{1/2} = -\frac{\ln 1/2}{k}$$

$$t_{1/2} = 0.693/k$$

Thus, $t_{1/2}$ is independent of concentration for a first-order process.

AUC

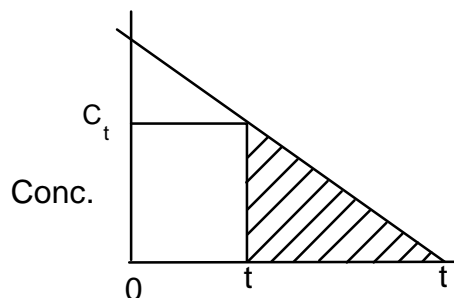
What about area under the curve (AUC)?



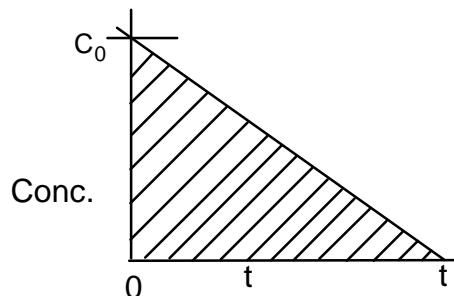
This is an important parameter since it combines information on concentrations achieved and the length of time the drug stays around.

To determine AUC, we integrate our equation for C over some time interval. Often $t: 0 \rightarrow \infty$. We can use two methods to determine AUC: the trapezoidal rule and integration. $AUC_{t \rightarrow \infty}$ (that is, the area under the curve from some time t to infinity) is estimated by integration.

$$AUC_{t \rightarrow \infty} = C_t/k$$



If $t = 0$, $AUC_{0 \rightarrow \infty} = C_0/k$



Summary.

Zero-order

rate expression: $dC/dt = -k$

solve the differential equation

equation for C $C = C_0 - kt$

to find k, plot: C vs t
slope: $m = -k$

$t_{1/2}$: $t_{1/2} = C_0/2k$

First-order

$dC/dt = -k \cdot C$

$C = C_0 e^{-kt}$

$\ln C$ vs t
slope: $m = -k$

$t_{1/2} = 0.693/k$