Model in Pharmacokinetics (repeated use of dosage)

Name : Tina Tam
Student no. : 6600217
Course no. : 6.337
Instructor : Prof. T.G.Berry

Description of the problem

The problem of how much of a dosage to prescribe for a drug and how often the dosage should be administered is an important question in pharmacology. For most drugs, there is a concentration below which the drug is ineffective and the concentration above which the drug is dangerous. In this case, the repeatedly use of the drug will only be considered in this report.

Thus, the problem leads to what happens to the concentration of a drug in the body when the drug is introduced into the body repeatedly. Will repeated application of the drug cause the concentration to become larger eventually? How should the time interval between the application of the drugs be chosen in order to maintain a safe and effective concentration in the body? The above questions will be discussed in this report.

Identification of variables and parameters

Let **H** be the highest, safe level of the drug.

Let **L** be the lowest effective level of the drug.

Let **C(t)** be the concentration of the drug that depends on time (t).

Let **T** be the time interval which the drug is administered.

Let $\mathbf{C_0}$ be the initial concentration of the drug at time (t) = 0.

Let **R** be the residual concentration that depends upon the concentration of the drug and the time interval.

Let **k** be the elimination constant of the drug.

Assumptions

Assume that :

(1) The initial concentration (C_0) with time (T) is between the lowest effective level (L) and the highest safe level (H).

(2) The concentration is immediately increased throughout the body when the dose is administered.

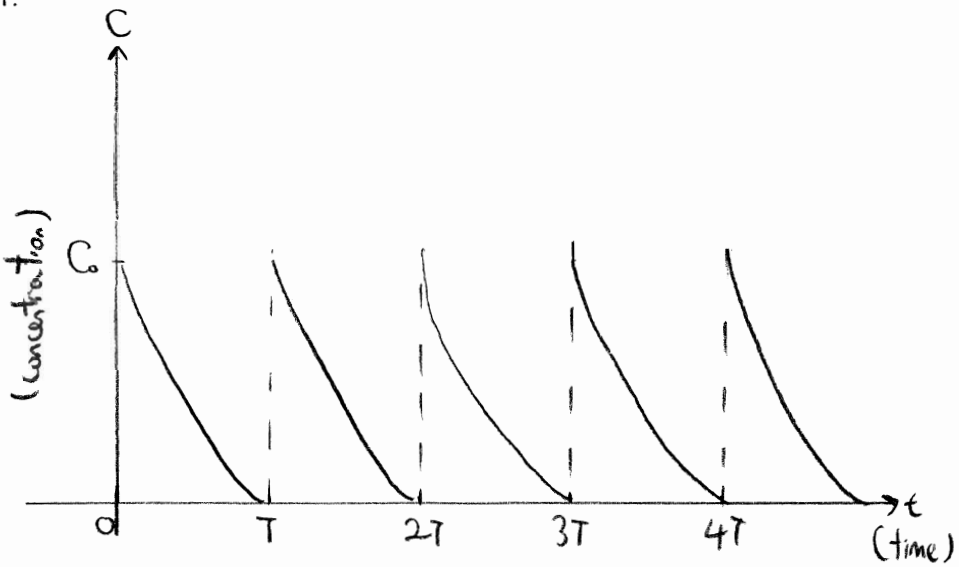
(3) The function C(t) is continuous, non positive, monotone decreasing function.

(4) There are several factors that determine the concentration C(t), for examples, dosage amount, dosage interval, decay rate, assimilation rate, body weight, blood volume and other various factor.
In order to simplify the assumptions, let the body weight and the blood volume are constants, that the concentration level is the critical factor in determining the effect of the drug.

(5) The decrease rate in the concentration of the drug in the bloodstream will be proportional to the concentration itself.

(6) The drug is directly injected into the blood.

The following 2 figures show the relationship between the concentration of the drug , the residual concentration and the time interval.



Can residual be zero? see page 10.

Figure 1 : No residual build up with the initial concentration at time interval T

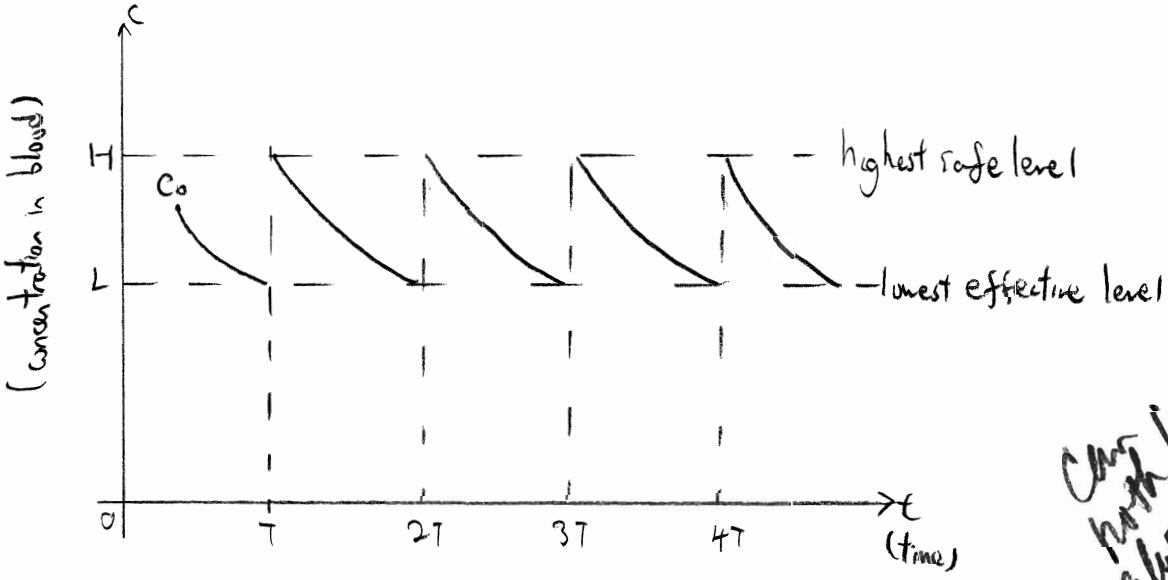


Figure 2 : the concentration of the drug and the residual build up at time interval T

Can levels both always be attended each time?

Mathematical Analysis

Under the above assumptions, mathematically, the assumption (5) implies the concentration of the drug in the bloodstream at time (t) is a differential function C(t), then

$$C'(t) = -kC(t)$$

where k is a positive constant.

Since Co is the concentration at t = 0, then

$$\frac{dC}{dt} = -kC, \quad C(0) = C_0, \qquad \ldots (1)$$

then, solving the above equation by separate the variables, this gives

$$\frac{1}{C}\, dC = -k\, dt$$

Integration of both sides of this last equation yields

$$\ln |C| = -kt + D \qquad \text{for some constant } D$$

then,

$$C = e^{(-kt+D)}$$

$$C = Be^{-kT} \qquad \text{where } B = e^{D}$$

Apply the initial condition, $C(0) = C_0$, gives

$$C(t) = C_0 e^{-kT} \qquad \ldots(2)$$

The graph of C(t) looks like the following figure

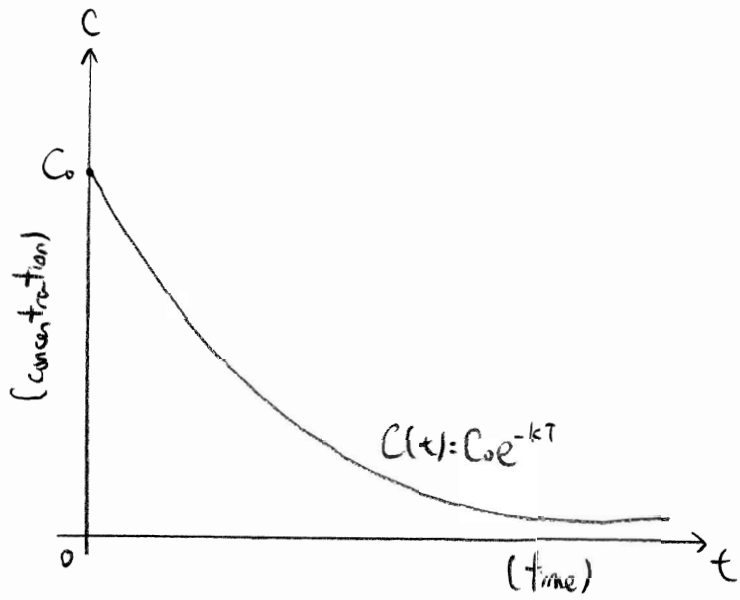


Figure 3 : Exponential model for decay of drug concentration with time t

Suppose at time t = 0 the first dose is administered.. According to the equation (2), after T hours have elapsed, the residual $R_1 = C_0 e^{(-kT)}$ remains in the blood , and then the second dose is administered. Since, from the assumptions concerning the drug concentration as before, the level of concentration instantaneously jumps to $C_1 = C_0 + C_0 e^{-kT}$. Then after T hours elapse again, the residual $R_2 = C_1 e^{-kT} = C_0 e^{-kT} + C_0 e^{-2kT}$ remains

in the bloodstream. Therefore, the possibilities of the drug in the bloodstream is depicted in the following graph.

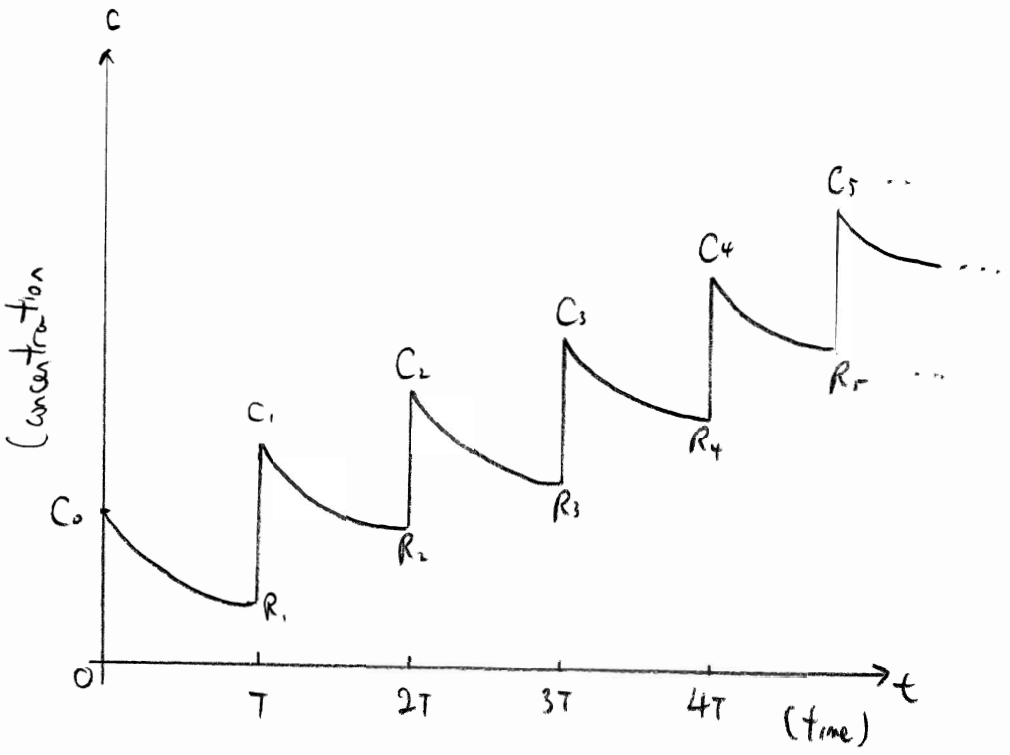


Figure 4 : possible effect of repeating equal doses

Since, residual (R) is depends on the concentration of the drug at time t. It is not difficult to find a formula for n th residual Rn. Suppose, C_{i-1} is the concentration of the drug at the beginning of the i th interval and R_i the residual concentration at the end of it, the relationship between C_{i-1} and Ri is obtained by the following table

i	C_{i-1}	R_i
1	C_0 (multiply by e^{-kt}) ---> C_0e^{-kT}	
2	(add Co and R1) $Co + Coe^{-kT}$	$Coe^{-kT} + Coe^{-2kT}$
3	$Co + Coe^{-kT} + Coe^{-2kT}$	$Coe^{-kT} + Coe^{-2kT} + Coe^{-3kT}$
.	.	.
.	.	.
.	.	.
n		$Coe^{-kT} + \ldots + Coe^{-nkT}$

Table 1 : calculation of residual concentration drug

From the table 1 :

$$R_n = Coe^{-kT} + Coe^{-2kT} + \ldots + Coe^{-nkT}$$

$$= Coe^{-kT}(1 + r^2 + r + \ldots + r^{n-1}) \qquad \ldots (3)$$

where $r = e^{-kT}$

By the definition of Geometric series:

$$1 + r + r^2 + \ldots + r^{n-1} = \frac{1-r^n}{1-r}$$

so, substitute the above result of r to equation (3):

$$R_n = \frac{C_0\, e^{-kT}\,(1 - e^{-nkT})}{1 - e^{-kT}}$$

It is obvious that the number e^{-nkT} is close to 0 when n is large.

Thus, take the limits to R_n, yields :

$$R = \lim_{n \to \infty} R_n = \frac{C_0\, e^{-kT}}{1 - e^{-kT}}$$

or,

$$R = \frac{C_0}{e^{kT} - 1} \qquad \ldots (4)$$

After obtaining the equation for the residual, then examine the residual concentration R in different time interval.

From Table 1 , the concentration C_{n-1} at the beginning of the n th time interval is given by

$$C_{n-1} = C_0 + R_{n-1}$$

If the desired dosage level is required to approach the highest safe level (H) as in figure 2, then, C_{n-1} approaches to H when n becomes larger. That is,

$$H = \lim_{n \to \infty} C_{n-1} = \lim (C_0 + R_{n-1}) = C_0 + R$$

Thus, $C_0 = H - L$ yields

$$R = L$$

In order to compare the residual concentration (R) for different time intervals (T) between the administered of the drug. Let the ratio be

$$\frac{R}{C_0} = \frac{1}{e^{kT} - 1} \qquad \ldots (5)$$

From the above equation, it is obvious that R/C_0 will be close to 0 whenever the time (T) between the doses is long enough to make $e^{kT}-1$ sufficiently large. From the table (1), when R_n is obtained from the previous R_{n-1} by adding a positive quantity $C_0 e^{-nkT}$. It shows that all R_n's are positive, since, R_1 is positive. That is,

$$0 < R_n < R$$

for all n .

This implies that whenever R is small, Rn's is even smaller. Thus, if T is long enough to make $e^{kT} - 1$ sufficiently large, the residual concentration R from each dose is almost zero. Then, the various administrations of the drug are independent, and the graph of C(t) is same as figure 1.

On the other hand, as R_n becomes larger, the concentration C_n after each doses becomes larger. The loss during the time period after each doses increases with larger Cn is given by equation (1).

Consequently, the drop in concentration after each dose becomes close to the rise in concentration C_0 due to each dose. When the loss in concentration equalling the gain, the concentration will oscillate between R at the end of period and $(R + C_0)$ at the start of each period. This situation is shown in the following figure.

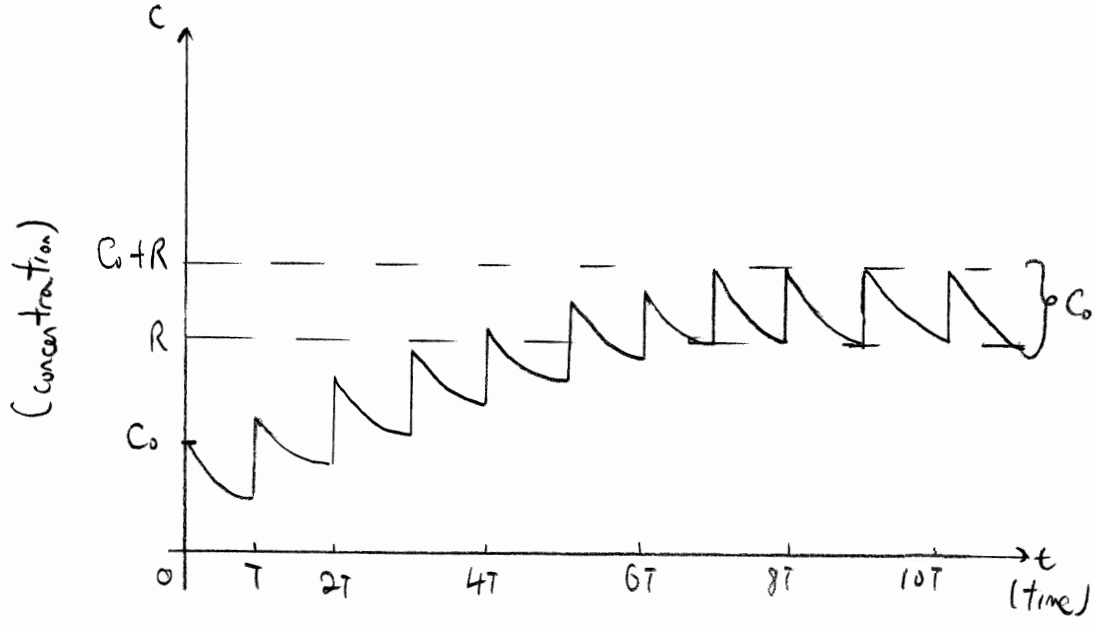


Figure 5 : Build up of drug concentration when the time interval between the doses is small

In order to maximize the efficiency of the drug in a time interval, so that, the concentration of the drug will not rise above the highest safe level (H) or will not fall below the lowest efficient level (L). By setting $R = L$ and $C_0 = H - L$, then substitute to the equation (4) gives

$$L = \frac{H - L}{e^{kT} - 1}$$

By solving the above equation to obtain

$$e^{kT} = \frac{H}{L}$$

taking the logarithm of both sides gives

$$T = \frac{1}{k} \ln \frac{H}{L}$$

To reach the effective level rapidly, administration of a dose will instantaneously produce a blood concentration of H , therefore, the medication can be followed $T = (1/k) \ln (H/k)$ hours by a dose that raises the concentration by $C_0 = H - L$ (units)

Example:

Consider the case where the destruction of the drug is due to enzymatic action. By the Michaelis-Menton equation which is derived in most texts on biological chemistry, it is appropriate under some conditions to let $C(t) = -(at)/(b + t)$, where $a,b > 0$. When the concentration of the drug is very small, the enzymatic case reduces to the case of random action. Under the random action, the rate at which the drug is destroyed is proportional to the amount of the drug present. But when the concentration of the drug is large, as with repeated doses of an alcoholic beverage, the Michaelis-Menton equation provides a reasonable model. By putting $C(t) = -(at)/(b + t)$ into equation (5), and solving for R yields

$$\frac{R}{C_0} = \frac{1}{e^{(aT-Co)/b} - 1}$$

since, $R = L$, therefore,

$$L = \frac{C_0}{e^{(aT-Co)/b} - 1} \qquad \text{for } aT - C_0 > 0$$

and

$$Co + L = \frac{C_0}{e^{(aT-Co)/b} - 1} \qquad \text{for } aT - C_0 > 0$$

Notice that the solution exists in this case only if $C_0 < aT$. If $C_0 > aT$, then either the dosage is too large or the time interval is too short (or both) for the concentration to be reduced sufficiently between applications of the drug for a limit to be established. Thus, the lowest level of the drug concentration (L) increase if the initial drug concentration (C_0) increases and decreases if T increases.

Conclusion

If a dose that is capable of raising the concentration by C_0 is repeatedly administered at time interval of T hours, then the limiting value (R) of the residual concentrations is given by the equation (4). Also, the residual concentration buildup depends upon the time interval between the administered of the drug. According to this model, in order to obtain the efficient strength of the drug, the time interval between each dosage should be

$$T = (1/k) \ln (H/L)$$

where k is the elimination of the drug, H is the highest safe level of the drug, and L is the lowest efficient level of the drug.

According to the clinical experiments, the model provides a reliable and quantitatively for the prediction of concentration levels under varying conditions for dose rates. Moreover, the drug may be tested to determine experimentally the lowest effective level (L) and the highest safe level (H) , with appropriate safety factors to allow for inaccuracies in the modelling process.

Suggestions for improvement

The model that introduced on the above, it appears to prescribing a safe and effective dosage of drug concentration.. According to the assumptions, the concentration is immediately increased throughout the body when the dose is administered. However a drug, such as aspirin, taken orally requires a finite time to diffuse into the bloodstream, therefore, the assumption is not realistic for such a drug. Thus, the graph of concentration versus time for a single dose might be different from figure (3), it is shown in figure (6).

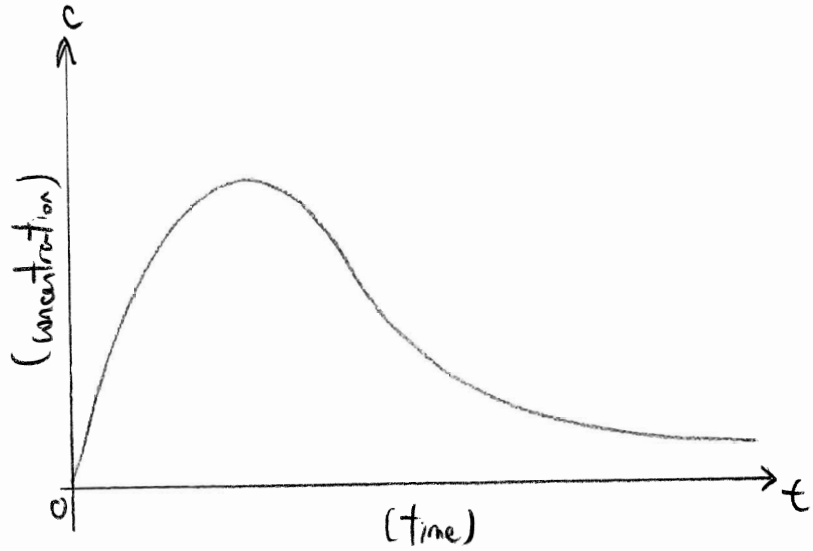


figure 6 : The concentration of a drug in the bloodstream for a single dose taken orally

Moreover, if the drug is taken by mouth, the concentration of the drug will decompose to several compartments, which is the application compartment, the dispersal compartment and the effect compartment. The change in the quantity of the drug is only depends on the reaction between each compartments. The relationship between those compartments is given in figure (7)

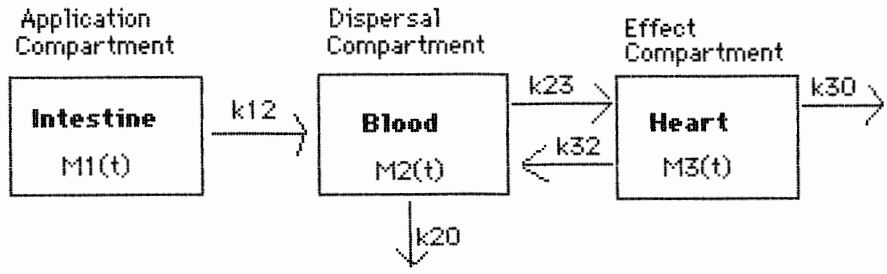


figure 7 : Basic model of the three compartments

Thus, the differential equations follow from the above figure gives :

$$\frac{dM_1}{dt} = -K_{12}A$$

$$\frac{dM_2}{dt} = -(K_{23} + K_{20})B + K_{12}A + K_{32}C$$

$$\frac{dM_3}{dt} = -(K_{32} + K_{30})C + K_{23}B$$

where K_{12}, K_{20}, K_{23}, K_{30} and $K_{32} > 0$

Therefore , for a general n- compartment system which describes kinetic reactions of the first order can be represented by the differential equation system :

$$\frac{dM_i}{dt} = -\sum_{\substack{j=0 \\ j\neq i}}^{n} K_{ij}\, M_i(t) + \sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ji}\, M_j(t)$$

Thus, solving the above system is more difficult then the one before.

REFERENCES

[1] S.Levin, Mathematical Models in Medicine, Workshop, Mainz, March 1976

[2] Murray S. Klamkin, Mathematical Modelling : Classroom Notes in Applied Mathematics, SIAM, 1987

[3] Frank R. Giodano, A First Course in Mathematical Modelling, Brooks Cole, 1985

[4] John Gurland, Stochastic Models in Medicine and Biology, Wisconsin Press, 1964