Project 6.337

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Prescribing Drug Dosage

Abstract:

Pharmacokinetics is the study of the rate processes involved in the absorption; distribution & elimination of drugs in the human body. The rate at which a compound is eliminated from the body is an important factor in regulating pharmacological response. However, human being (animals) are complex & to treat events taking place in intact organisms, some simplification of reality is required, which is the basis of pharmaco-kinetic modelling. Pharamacokinetic models are developed to trace the elimination of the compound. The "proof" for such a model is generally considered to be accurate fit of the experimental results. Model parameters are evaluated & examined for their biological significance.

Pharamacokinetics describe the time-dependent changes of plasma drug concentration & the time dependent changes of the total amount of drug in the body following various routes of administration. The two most common routes of drug administration are intervenous infusion and a fixed-dose, fixed time interval regimen, for example: "two tablets every four hours." ~~Administ~~ Administration of a drug is often more convenient by fixed doses than by continous infusion, but fixed doses result in time dependent fluctuations in the circulating level of drug.

In this work the problem of how much of a desage to prescribe for a drug and how often the dosage should be administered is an important one in pharamacology.

For most drugs there is a concentration below which

the drug is ineffective & a concentration above which the drug is dangerous.

Problem Identification

How can the doses & the time between doses be adjusted to maintain a safe but effective concentration of the drug in the blood?

The concentration in the blood resulting from a single dose of a drug normally decreases with time as the drug is eliminated from the body.

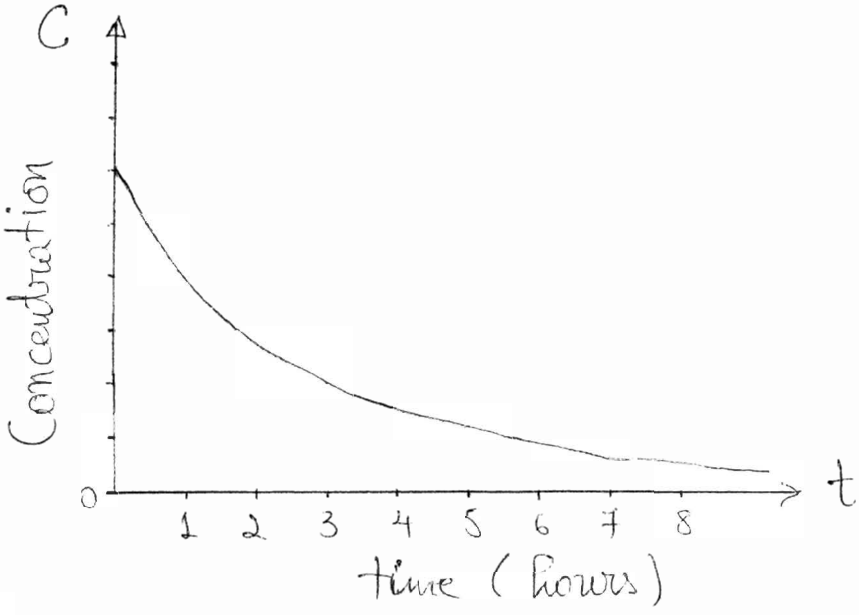


figure I

Figure (I) shows the concentration of a drug in the bloodstream decreases with time.

However, It is interesting to know what happens to the concentration of drug in the blood as doses are given at regular intervals. Will repeated application of the drug cause the concentration to become too large eventually?

Let:-
- H ~~be~~ denote the highest safe level of the drug.
- L its lowest effective level
- C_0 be a dosage that is desirable to prescribe
- T time between doses so that the concentration of the drug in the bloodstream remains between L & H over each dose period.

Let us consider several ways in which the drugs might be administered.

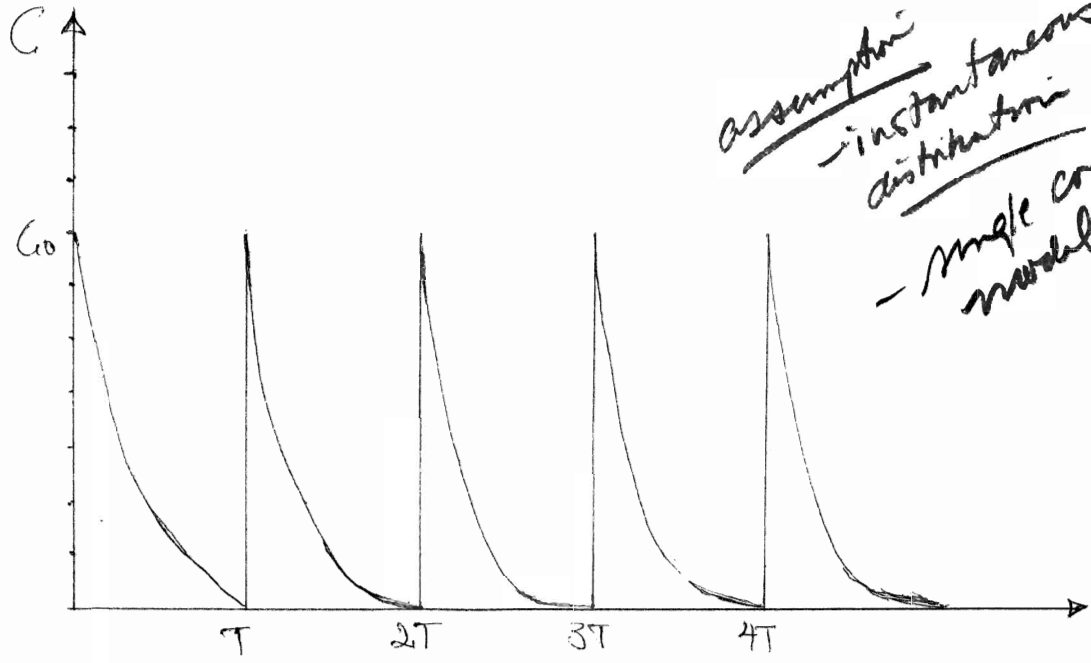


figure II(a)

In this figure II(a) the time between doses is such that effectively there is no build up of drug in the system. In other words the "residual concentration" from previous doses is essentially approximately zero.

Assume that the elimination process began at the time of injection & continued throughout the distribution phase. Then the concentration of drug in the plasma, C, can be determine C_0, which is the concentration of drug that would have been achieved had the distribution phase

been achieved instantly.

For example: If 10 mg of drug is injected into a patient & the plasma concentration extrapolated to zero time concentration is $C_0 = 1.0$ mg/L (from graph shown in figure II(a)), then the circulating level of drug decreases exponentially with time & approximately zero.

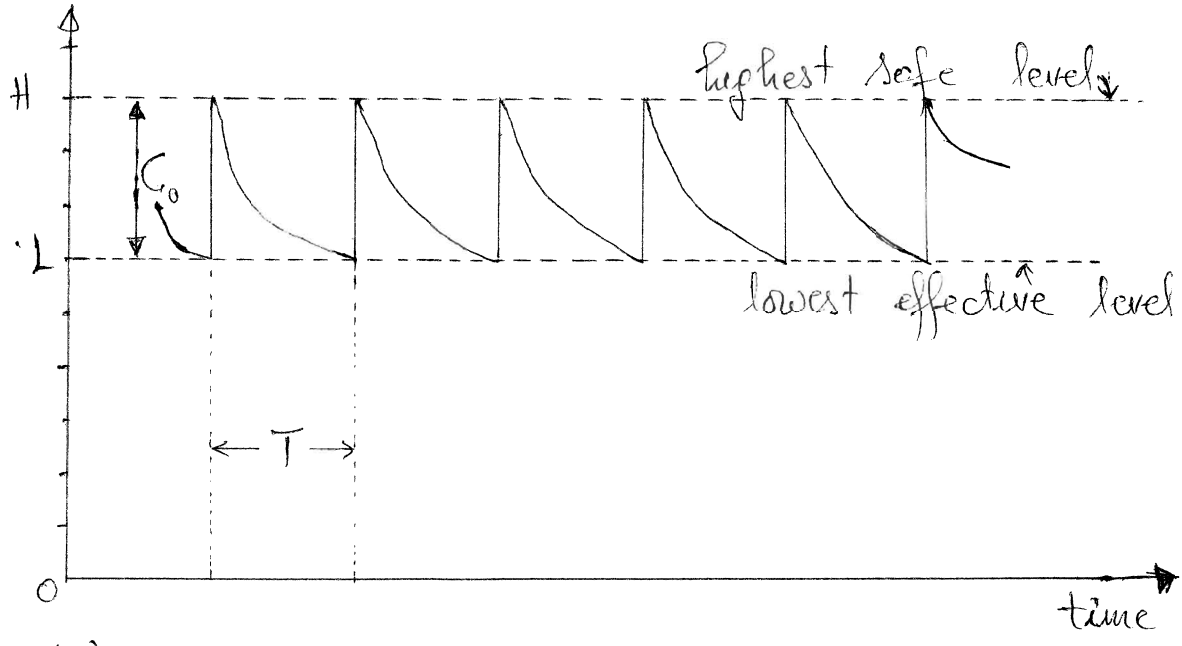


figure II(b)

- The interval between doses relative to the amount administered & the decay rate of the concentration is such that a residual concentration exists at each time the drug is taken (after the first dose). Furthermore, as depicted in the graph, this residual level seems to be approaching a limit. We will be concerned with determining if this situation is indeed the case & if so, what that limit must be. The ultimate goal in prescribing drugs is to determine doses such that the lowest effective level L & the highest safe level H, as showed below.

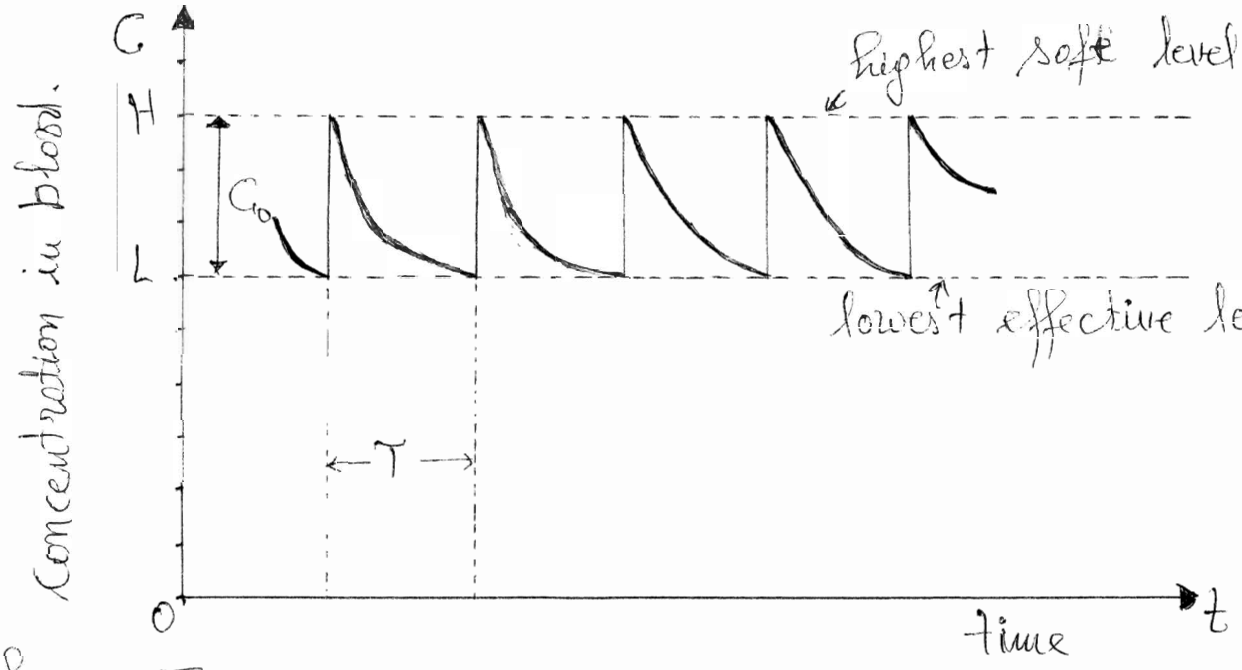


figure III

Safe but effective levels of the drug in the blood. C_0 is the change in concentration produced by one dose & T is the time interval between doses.

To determine the limiting residual level, which depends upon the assumptions for the rate of assimulation of the drug in the bloodstream & the rate of decay after assimulation.

Assumptions.

In order to solve the problem first we have identified, let us consider the factors that determine the concentration C(t) of the drug in the blood-stream at any time t.

Let :-

D - be decay rate
A - be assimilation rate
da - be dosage amount.
dI - be dosage interval
-Etc

$$C(t) = f(0, A, d_A, d_I, \ldots)$$

& various other factors including body weight & blood volume. To simplify the assumptions, let's assume that body weight & blood volume are constants (say an average over some specific age group), & that concentration level is the critical factor in determining the effect of a drug.

Next determine submodels for decay rate & assimilation rate.

Submodel for decay rate.

Consider the elimination of the drug from the bloodstream. Probably this is a discrete phenomenon, but let's approximate it by a continuous function. Clinical experiments have revealed that the decrease in the concentration of a drug in the bloodstream will be proportional to the concentration itself. Mathematically, this assumption means that if we assume the concentration of drug in the blood at time t is a differentiable function $C(t)$, then

$$C'(t) = -kC(t) \quad \text{----} \quad (1)$$

In this formula k is a positive constant, called the elimination constant of the drug. Notice $C'(t)$ is negative, as it should be if it is to describe a decreasing concentration. Usually the quantities in eq'n (1) are measured as follows. The time t is given in hours, $C(t)$ is milligrams per milliliter of blood (mg/ml), $C'(t)$ is mg ml^{-1} hr^{-1} & k is hr^{-1}

Assume now that the concentrations A & L can be determined experimentally for a given population, such

as an age group. Then set drug concentration for a single dose at the level.

But this will not work!

$$C_0 = H - L \qquad \text{---} \quad (2)$$

Assume that C_0 is the concentration at $t=0$, then the model

$$\frac{dC}{dt} = -kC \qquad C(0) = C_0 \qquad \text{---} \quad (3)$$

Where k is +ve constant but the (-) sign show a decreasing concentration.

Solving the model

First separate the variables & rewrite equation (3) by moving all terms involving C & dC to one side of the equation & all terms in dt & dt to the other side. This gives

This was done in class. Not now the typesetting

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

Seperable

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

Integrate both sides of this last equation

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

$$\ln|C| = -kt + C_1 \qquad \text{---} \quad (4)$$

for some constant C_1. Applying the condition $C(0) = C_0$ to equation (4) to find C_1 results in

$$\ln C_0 = -K t_0 + C_1$$

OR

$$C_1 = \ln C_0 - K t_0$$

Then substitution for C_1 into (4) gives

$$\ln C = -Kt + \ln C_0 - K t_0$$

OR

$$\ln \frac{C}{C_0} = -K(t + t_0)$$

Finally, by taking the exponential of both sides of the preceding equation & multiplying the result by C_0 then

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

OR

$$C = C_0 e^{-kt} \qquad \text{---------} \quad (5)$$

Equation (5), which is known as the Malthusian model

To obtain the concentration at time $t > 0$, multiply the initial concentration C_0 by e^{-kt}, the graph of $C(t)$ looks like this

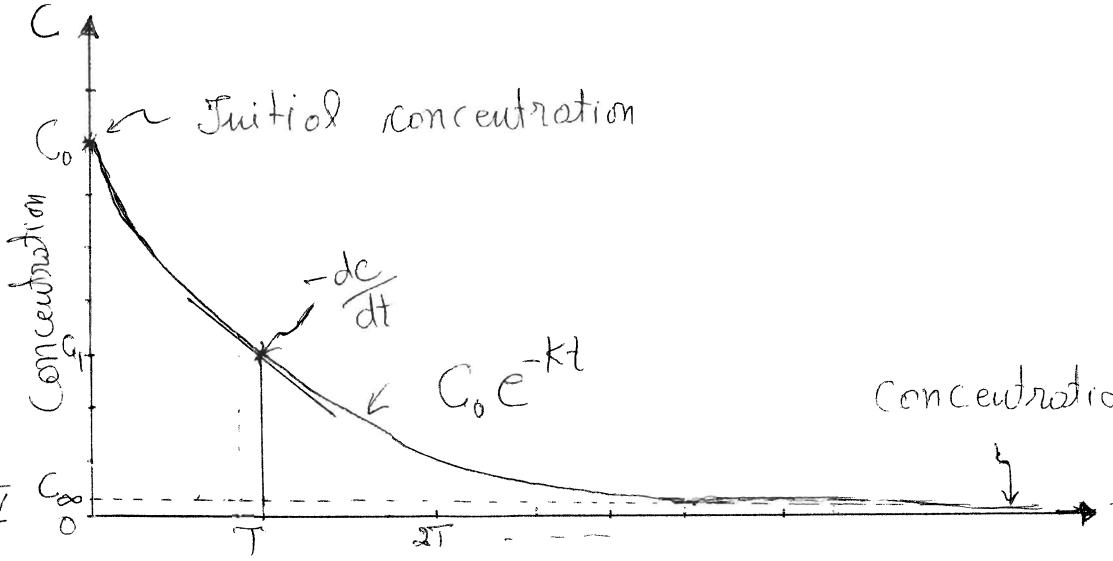


Figure IV

⇒ Exponential model for decay of drug concentration with t

Discussion how the elimination constant k in equation (1) could be obtained experimentally for a given drug.
In 1918, Harned showed that the decomposition rate of hydrogen peroxide, catalysed by 0.02 M KI, was proportional to the concentration of hydrogen peroxide remaining in the reaction mixture at any time. The reaction

$$2H_2O_2 = 2H_2O + O_2$$

The data for the reaction are.

t (minutes)	C	K (min^{-1})
0	57.90	—
5	50.40	0.0278
10	43.90	0.0277
25	29.10	0.0275
45	16.70	0.0276
65	9.60	0.0276
∞	0	—

how are these determined? $k = -\frac{1}{t}\ln\left(\frac{C}{C_0}\right)$ (see next page)

Table 1. Decomposition of hydrogen peroxide at 25°C in Aqueous solution containing 0.02 M KI [H.S Harned. J. Am. Chem. Soc. 40, 1462, 1918]

Although two molecules of hydrogen peroxide appear in the stoichiometric equation as first written, the reaction was found to be first-order. The rate equation is written

$$\frac{-dc}{dt} = kC \quad \text{----- (*)}$$

Is this terminology used before?

in which C is the concentration of hydrogen peroxide remaining undecomposed at time t, & k is the first-order velocity constant. Integrating equation (*) between concentration C_0 at time $t = 0$ & concentration

C at some later time t.

$$\int_{C_0}^{C} \frac{dc}{C} = -k \int_0^t dt$$

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

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

mult (-1)

$$kt = \ln\left(\frac{C_0}{C}\right)$$

$$k = \left[\ln\left(\frac{C_0}{C}\right)\right] / t \quad --- \quad (6)$$

Equation (5) expresses the fact that, in first-order (d.e reaction) the concentration decreases exponentially with time. As shown in figure IV, the concentration begins at C_0 & decreases as the reaction becomes progressively slower. The concentration asymptotically approaches a final value (C_∞) as time proceeds toward infinity.

purely $C_\infty = 0$

Example 1:- The catalytic decomposition of hydrogen peroxide may be followed by measuring the volume of oxygen liberated in a gas burette. From such an experiment, it was found that the concentration of hydrogen peroxide remaining after 65 minutes, expressed as the volume in milliliters of gas evolved, was 9.60 from an initial concentration of 57.90. Calculate k using (6) equation

Solution:

$$K = \frac{\ln\left(\frac{C_0}{C}\right)}{t} = \frac{\ln\left(\frac{57.90}{9.60}\right)}{65} = \frac{1.796954286}{65}$$

$$\therefore K = 0.02765 \text{ min}^{-1}$$

Is that all?

Submodel for Assimilation Rate.

Having made an assumption about how drug concentrations decrease with time, let's consider how they increase again when drugs are administered. Our initial assumption is that when a drug is taken, it is diffused so rapidly throughout the blood that the graph of the concentration for the absorption period is, for all practical purposes, vertical. That is, we assume an instantaneous rise in concentration whenever a drug is administered. This assumption may not be as reasonable for a drug accumulates in the bloodstream with repeated doses.

Drug Accumulation with Repeated Doses.

Consider what happens to the concentration $C(t)$ when a dose that is capable of raising the concentration by C_0 mg/ml each time it is given is administered regularly at fixed time intervals of length T.

Suppose at time $t = 0$ the first dose is administered. According to the model (5), after T hours have elapsed, the residual $R_1 = C_0 e^{-KT}$ remains in the blood, & then the second dose is administered. Because of the assumption concerning the increase in drug concentration as previously discussed, the level of concentration instaneously 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 blood. This possibility of accumulation of the drug in the blood is depicted in the graph below.

(next page)

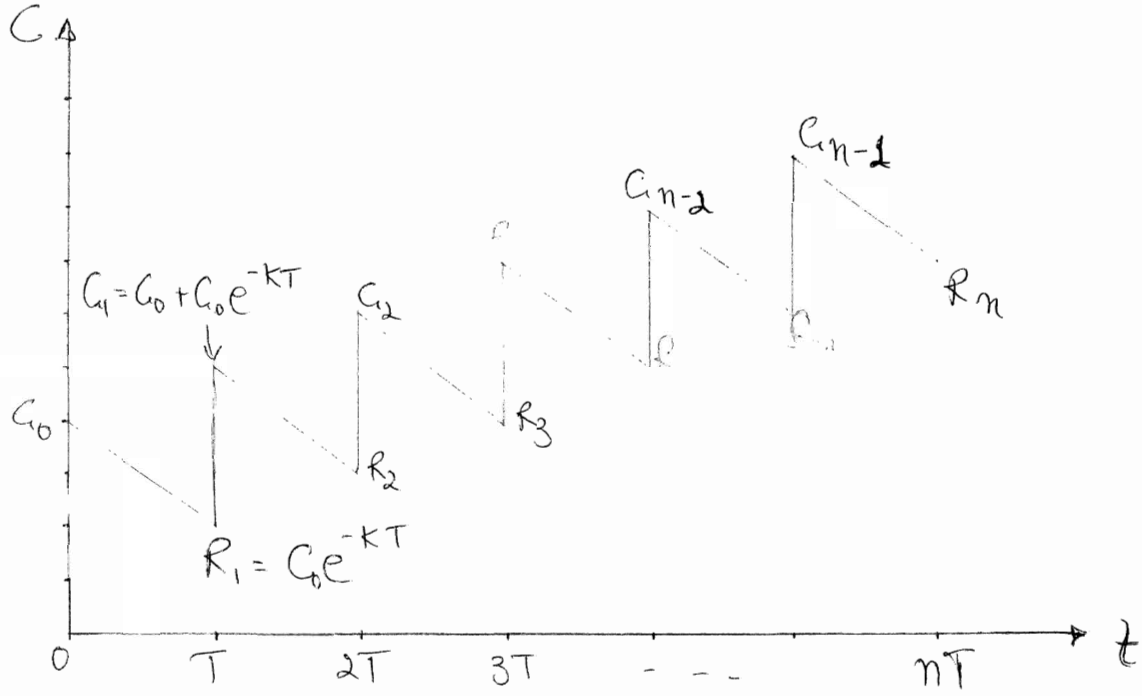


figure V. One possible effect of repeating equal doses.

Next, to determine a formula for the n^{th} residual R_n. If we let C_{i-1} be the concentration at the beginning of the i^{th} interval & R_i the residual concentration at the end of it, easily obtain the following table.

Table 2.

i	C_{i-1}	R_i
1	C_0 ← mult by e^{-KT}	$C_0 e^{-KT}$
	Add C_0	
2	$C_0 + C_0 e^{-KT}$	$C_0 e^{-KT} + C_0 e^{-2KT}$
3	$C_0 + C_0 e^{-KT} + C_0 e^{-2KT}$	$C_0 e^{-KT} + C_0 e^{-2KT} + C_0 e^{-3KT}$
⋮	⋮	⋮
n		$C_0 e^{-KT} + C_0 e^{-2KT} + \cdots + C_0 e^{-nKT}$

Table 2: Calculation of residual concentration of drug.

From the table:-

$$R_n = C_0 e^{-kT} + C_0 e^{-2kT} + \cdots + C_0 e^{-nkT} \quad \text{---- (7)}$$

Let $r = e^{-kT}$ then

$$R_n = C_0 e^{-kT}(1 + r + r^2 + \cdots r^{n-1}) \quad \text{---- (*)}$$

Since $1 + r + r^2 + \cdots + r^{n-1} = \dfrac{1 - r^n}{1 - r}$

& substitution for r into (*) gives

$$R_n = \frac{C_0 e^{-kT}(1 - e^{-nkT})}{1 - e^{-kT}} \quad \text{---- (8)}$$

Notice that the number e^{-nkT} is close to 0 when n is large. In fact, the larger n becomes, the closer e^{-nkT} gets to 0. As a result, the sequence of R_n's has a limiting value, which is called up R:

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

$$R = \frac{C_0 e^{-kT}}{1 - e^{-kT}}$$

OR

$$R = \frac{C_0}{e^{kT} - 1} \quad \text{---- (9)}$$

In summary if a dose that is capable of raising the concentration by C_0 mg/ml is repeated at intervals of T hours, then the limiting value R of residual concentrations is given by the formula (9). The number k in the formula is the elimination constant of the drug.

Determining the Dose Schedule.

From table 2. the concentration C_{n-1} at the beginning of the n^{th} interval is given by

$$C_{n-1} = C_0 + R_{n-1} \qquad \text{- - - - - (10)}$$

If the desired dosage level is required to approach the highest safe level H as depicted in figure III then we want C_{n-1} to approach H as n becomes large. That is

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

I still don't like this!

Combining this last result with $C_0 = H - L$ yields

$$R = L \qquad \text{- - - - - - - - (11)}$$

A meaningful way to examine what happens to the residual concentration R for different intervals T between doses is to look at R in comparsion with C_0, the change in concentration due to each dose. To make this comparsion, we form the dimensionless ratio:

$$\frac{R}{C_0} = \frac{1}{e^{KT} - 1} \qquad \text{- - - - - - (12)}$$

see diagram

Equation (12) says that R/C_0 will be close to 0 whenever the time T between doses is long enough to make $e^{KT} - 1$ sufficiently large. As for the intermediate values of R_n; from table 2 that each R_n is obtained from the previous R_{n-1} by adding a positive quantity $C_0 e^{-nKT}$. This means that that all the R_n's are positive because R_1 is positive. It also means that R is larger than each of the R_n's.

$$0 < R_n < R_1 \qquad \text{for all } n.$$

The implication of this for drug dosage is that whenever R is small, the R_n's are even smaller. In particular, whenever T is long enough to make $e^{KT} - 1$ significantly larger, the residual concentration from each dose is almost nil. The various administrations of drug are then essentially independent, & the graph of C(t) looks like the one depicted in figure below.

good

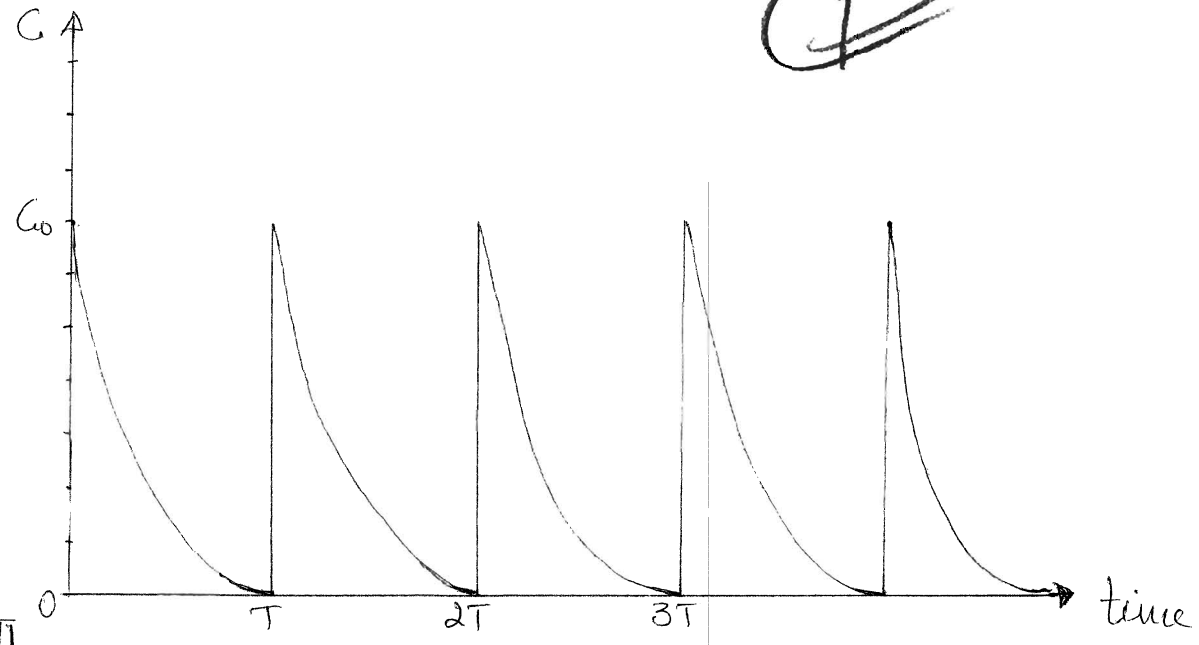
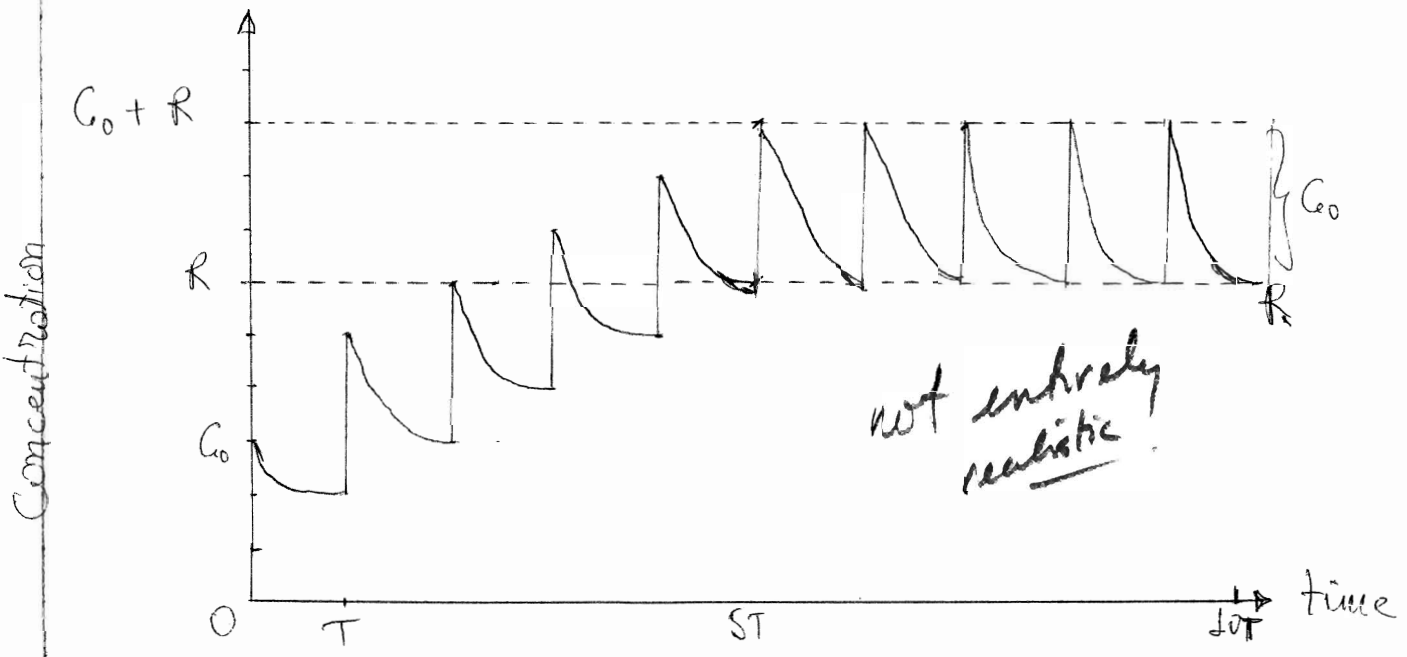


figure VI
This figure shows drug concentration for long intervals between doses.

On the other hand, suppose the length of time T between doses is so short the e^{KT} is not very much larger than 1, so that R/C_0 is significantly greater than 1. As R_n becomes large, the concentration C_n after each dose become large. The loss during the time period after each dose increase with larger C_n from equation (3). Finally the drop in concentration after each dose becomes imperceptibly close to the rise in concentration C_0 due to each dose. When this condition perivails (the dose in

concentration equalling the drug), the concentration will oscillate between R at the end of each period & $R+C_0$ at the start of each period. This situation is depicted in figure (F)(VII)



This figure VII shows buildup of drug concentration when the interval between doses is short.

Suppose a drug is ineffective below the concentration L & harmful above some higher concentration H, as discussed previously. Assume now that L & H are "safe" guidelines so that a person would not suffer a sever overdose if the drug concentration rises some-what above H, & that it is not necessary to begin the buildup process all over again if the concentration falls slightly below L. Then for patient convenience we might opt for the strategy of maximizing the time between drug doses by setting $R=L$ and $C_0 = H-L$, as indicated previously. Then substitution of $R=L$ & $C_0 = H-L$ in equation (8) yields.

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

Where $R = L$ & $C_0 = H - L$

$$L = \lim_{n \to \infty} L_n = \frac{(H-L)\, e^{-KT}}{1 - e^{-KT}}$$

$$\therefore \quad L = \frac{H-L}{e^{KT} - 1}$$

To solve the preceding equation for e^{KT} to obtain from

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

$$L(e^{KT} - 1) = H - L$$

$$L(e^{KT} - 1) + L = H$$

$$Le^{KT} - L + L = H$$

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

Taking the logarithm of both sides of the last equation and dividing the result by K gives the desired close schedule.

Taking logarithm $\Rightarrow$ $KT = \ln(H/L)$

then

$$T = \frac{\ln(H/L)}{K}$$

$$\therefore \quad T = \frac{1}{K} \ln(H/L) \qquad \text{---------- (13)}$$

good

To reach an effective level rapidly, administer a dose, after a loading dose, that will immediately produce a blood concentration of H mg/ml. [For example, this loading dose might equal $2C_0$.] This medication can be followed every $T = \frac{1}{k} \ln \frac{H}{L}$ hours by a dose that raises the concentration by $C_0 = H - L$ mg/ml.

Examples.

1) If $k = 0.05\ hr^{-1}$ and the highest safe concentration is e times the lowest effective concentration, find the length of time between repeated doses that will ensure safe but effective concentrations. Does this give enough information to determine the size of each dose?

Solution: Given $k = 0.05\ hr^{-1}$

$H = e(L) \Rightarrow eL$

Find the time take?

Good example!

$$T = \frac{1}{k} \ln \frac{H}{L} \quad \text{---} \quad \text{eq. (13)}$$

$$T = \frac{1}{0.05\ hr^{-1}} \ln \left(\frac{eK}{K} \right) mg/ml$$

$$= 20\ hr \times (1)$$

$$= \underline{20\ hr}$$

Yes, this gives enough information to determine the size of each dose, because whenever T is long enough to make $e^{KT} - 1$ large but meaning, the residual concentration from each dose is almost nil

2) Given $H = 2$ mg/ml, $L = 0.5$ mg/ml, & $k = 0.02\ hr^{-1}$, Suppose that concentrations below 2 are not only ineffective but also harmful. Determine a scheme for administering this drug (in terms of concentration & time of dosage).

Solution

$$T = \frac{1}{k} \ln\left(\frac{H}{L}\right)$$

$$= \frac{1}{0.02} \ln\left(\frac{2\ \text{mg/ml}}{0.5\ \text{mg/ml}}\right)$$

$$= \frac{1}{0.02}(1.386294361)$$

$$= 69.3147506$$

$$\simeq \underline{69}\ \text{hrs}.$$

$C_0 = H - L \Rightarrow \quad C_0 = 2.0 - 0.5 = \underline{1.95}$ mg/ml

∴ This medication can be followed every 69 hrs by a dose that raises the concentration by 1.95 mg/ml. is administered.

3) Suppose that $k = 0.2\ hr^{-1}$ & that the smallest effective concentration is 0.03 mg/ml. A single dose that produces a concentration 0.1 mg/ml is administered. Approximately how many hours will the drug remain effective?

Solution (Given ⇒ $k = 0.2\ hr^{-1}$, $L = 0.03$ mg/ml, $C_0 = 0.1$ mg/ml)

$\Rightarrow C_0 = H - L$

$H = 0.1 + 0.03$

$= 0.13$ mg/ml

$$T = \frac{1}{k} \ln\left(\frac{H}{L}\right)$$

$$= \frac{1}{0.2\ hr^{-1}} \ln\left(\frac{0.13\ mg/ml}{0.03\ mg/ml}\right)$$

$$= 5\ hrs \ln(4.3333333)$$

$$= 5(1.466337069)\ hrs.$$

$$= 7.331685344$$

$\approx$ 7 hrs $\Rightarrow$ the drug remains effective.

Verifying the model

Our model for prescribing a safe & effective dosage of drug concentration appears to be a good one. It is in accord with the common medical practice of prescribing an initial dose several times larger than the succeeding periodic dose. Also the model is based on the assumption that the decreases in the concentration of the drug in the bloodstream is proportional to the concentration itself which has been verified clinically. Moreover, the elimination constant k, which is the positive constant of proportionality in that relationship, is an easily measured parameter, as discussed previously (Example 1). The model also provides quantitively for the prediction of concentration levels under varying conditions for dose rates, using Equation (9). Thus, the drug may be tested to determine experimentally the lowest effective level L & the highest safe level H, with appropriate safety factors to allow for inaccuracies in the modeling process. Then process. Then formulas

formula (2) & (3) can be used to prescribe a safe & effective dosage of the drug [Assuming the loading dose is several times larger than C_0.] So the model is useful

One deficiency in the model is the assumption of an instantaneous rise in concentration when ever a drug is administered. A drug, such as aspirin taking orally requires a finite time to diffuse into the bloodstream; the assumption, therefore, is not realistic for such a drug. For such cases the graph of concentration versus time for a single dose might resemble the graph shown below.

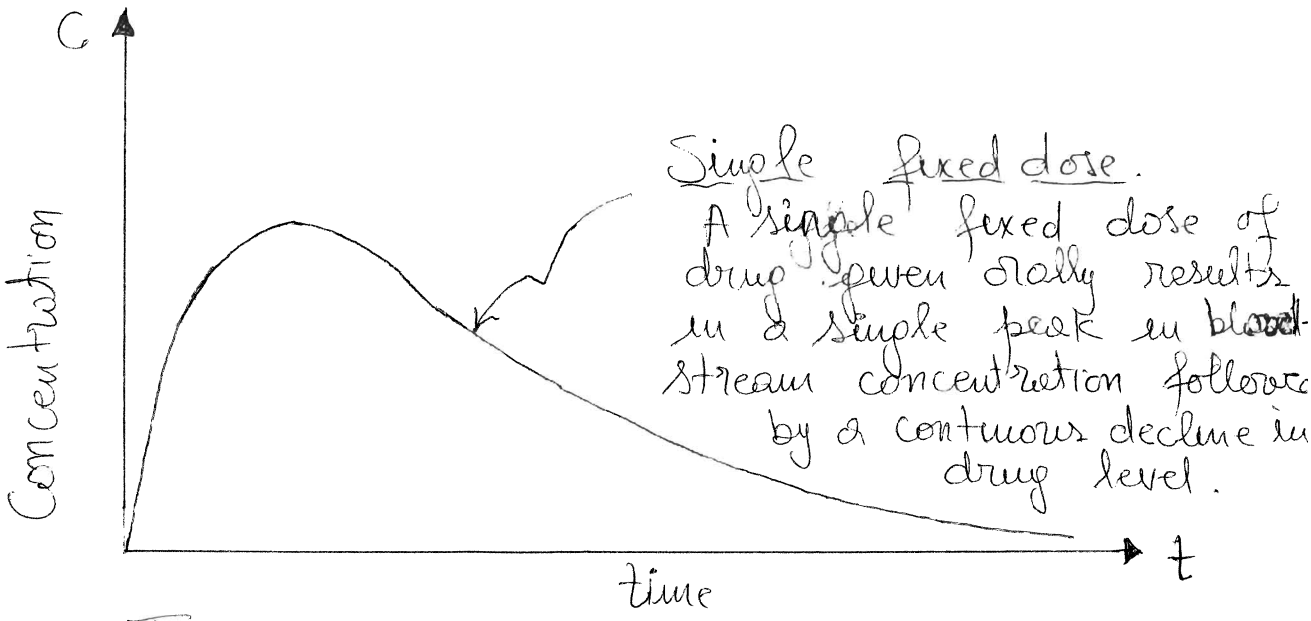


figure VIII

The concentration of a drug in the bloodstream for a single dose taken orally.

so what? could be considered further.

References

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