GRADING SHEET – MODELLING PROJECTS

STUDENT NAME: IAN PROVEN S932507
PROJECT TITLE: ~~PHARMACOKINETICS~~ - THE MODELLING OF DRUG ADMINISTRATION

GRAMMAR SPELLING	5		4
DESCRIPTION OF PROBLEM	5	good – 4 cases considered	4
IDENTIFICATION OF VARIABLES AND PARAMETERS	5	basically good but with a little confusion concerning 'residuals'.	4
ASSUMPTIONS INCLUDING DESCRIPTION AND REASONS	10	– many assumptions listed out although justification for some a little weak – I do not like the assumption that residuals on gut can be ignored.	10
MATHEMATICAL ANALYSIS	20	good results although too much reliance on initial inspection is made. At least one assumption made for simplicity could be removed.	12
CONCLUSIONS AND SUGGESTIONS FOR IMPROVEMENT	5	4 cases considered, discussion & shortcomings made	5
EXAMPLE(S)	5	some experimental data shown but no attempt is made to use the model with this data	3
REFERENCES	5	good but many of these references were supplied by me or T.G. Vith	4
ADDITIONAL COMMENTS overall – very good first attempt		TOTAL (OUT OF 60)	46

Pharmacokinetics - The Modeling of Drug Administration

Ian Proven
5932507

Course: 6.337
Instructor: T.G. Berry
Date: March 30, 1990

TABLE OF CONTENTS

INTRODUCTION

In the prescription of drugs, Pharmacists often employ Mathematical Models that help formulate optimum dosages.

The problem is to determine the best possible PharmacoKinetic model for a given situation. The body has many "mechanisms" at work that constantly deplete an administered drug supply. The bodily function of excretion in the kidneys steadily removes much of the drug from the blood tissue. Body Metabolism can "burn" much of the drug in the digestive tract, if taken orally. As well, some drugs have an affinity for certain body tissues, other than the one that they were prescribed for. Thus, the drug may be "captured" by these tissues. Obviously, finding the correct model for a drug may be very challenging and requires much laboratory testing.

In determining an optimum dosage many considerations must be made. Many drugs have a "MINIMUM EFFECTIVE CONCENTRATION" (MEC), a level below which the drug concentration is too low to have the desired effect. Conversely, many drugs have a "MINIMUM TOXIC CONCENTRATION" (MTC) which represents the level above which the drug "barely" produces an observable toxic effect.

Two of the many methods of administration include Rapid Intravenous Injection (IV Bolus) and Oral Injection. These administration methods may be applied to models which involve a single dose or multiple doses of a drug.

Using C_1, C_2, C_3 and R_0, R_1, R_2, a conjecture for C_n & R_n respectively are:

$$C_n = C_0\left(1 + e^{-kT} + e^{-2kT} + \ldots + e^{-(n-1)kT}\right)$$

$$R_n = C_0\left(e^{-kT} + e^{-2kT} + \ldots + e^{-nkT}\right)$$

what about intermediate times?

no proof given

Proof by Induction.

Notice that C_n and R_n are geometrical series, and hence may be rewritten as:

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

which represents the residual Concentration for any dosage number n.

Now if $n \to \infty$, $e^{-nkT} \to 0$ yielding:

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

which is, in fact, the lower limit of the Residual Concentrations. Hence this multiple injection scheme seems to achieve a "steady-state" with lower bound R_∞.

Similarly for C_n:

C_n can be written in geometrical series form:

$$C_n = \frac{C_0\left(1 - e^{-nkT}\right)}{1 - e^{-kT}}$$

which represents the Concentration of the drug immediately after the administration of dose n.

Again as $n \to \infty$, $e^{-nKT} \to 0$:

$$C^\infty = \frac{C_0}{1-e^{-KT}}$$

And C^∞ is the upper bound of the concentration of the drug in the compartment. Hence in steady state the drug concentration effectively "oscillates" between R^∞ and C^∞

ANALYSIS OF C^∞, R^∞ :

Since it is known that C^∞ is an upper bound for the drug concentration, is there a period T that will allow $C(t)$ to stay below any upper bound, say U ?

Want:

$$C^\infty \leq U$$

$$\frac{C_0}{1-e^{-KT}} \leq U$$

$$\frac{C_0}{U} \leq 1-e^{-KT}$$

$$e^{-KT} \leq 1-\frac{C_0}{U}$$

$$\ln e^{-KT} \leq \ln\left(1-\frac{C_0}{U}\right)$$

$$-KT \leq \ln\left(1-\frac{C_0}{U}\right)$$

$$T \geq -\frac{1}{K}\ln\left(\frac{U-C_0}{U}\right)$$

or $T = -\frac{1}{K}\ln\left(\frac{U-C_0}{U}\right) \equiv \frac{1}{K}\ln\left(\frac{U}{U-C_0}\right)$

is a sufficiently long (minimum) period that C^∞ stays below U.

Similarly, since R^{∞} provides a lower bound for the drug concentration, a period T can be determined such that $R^{\infty} \geq L$, some lower bound:

want: $R^{\infty} \geq L$

$$\frac{C_0 e^{-KT}}{1-e^{KT}} \geq L$$

$$\frac{C_0}{L} \geq \frac{1-e^{-KT}}{e^{-KT}}$$

$$\frac{C_0}{L} \geq e^{KT} - 1$$

$$\frac{C_0}{L} + 1 \geq e^{KT}$$

$$\ln\left(\frac{C_0}{L}+1\right) \geq \ln e^{KT}$$

$$\ln\left(\frac{C_0+L}{L}\right) \geq KT$$

$$T \leq \frac{1}{K} \ln\left(\frac{C_0+L}{L}\right)$$

$$\therefore T = \frac{1}{K} \ln\left(\frac{C_0+L}{L}\right)$$

will provide a sufficiently short (actually = gives the maximum) time period such that the lower bound R^{∞} is not crossed. (ie from above)

Note that if T gets larger the maximum bound (upper) decreases, and if T decreases in size, the upper bound is raised.

See Fig 4.2 in CASE (4) for a basic example of this phenomenon of different time periods.

Also note if the dosage supply is cut-off the curve just follows the natural Malthusian elimination.

CONCLUSIONS – CASE (2)

This model, while it effectively demonstrates the result of a Multiple Rapid Intravenous Injection Scheme, has some practical shortcomings:

The assumption ~~that~~ K is constant may be somewhat suspect as metabolic rates and excretion rates may vary day-to-day or even during 1 day. This however is unavoidable, generally and at best, an average K should be considered.

Secondly, if the injections are given only in waking hours the residual concentration falls during the night, hence the Total Concentration may then fall below MEC. } presumably doses are missed.

Another shortcoming is the time required to reach MEC. For the first few injections the concentration of the drug may be below MEC. Solutions for this problem include decreasing the period between injections, or by using a LOADING DOSE, which may be double or triple the "usual" Co. This loading dose quickly builds up the Residual Concentration, and would also be effective for the case in the preceding paragraph.

Finally the drug may not conform to a single compartment model. A two (or more) compartment Scheme may have to be devised which accounts for slower tissue release of the drug (rather than being proportional to the blood conc.).

Therefore, while this model seems a little more robust than its single dose predecessor, it is not without fault.

References: 5, 6

CASE (3) ORAL INJECTION, SINGLE DOSE

In the oral administration of a drug (ie. by pill, capsule, or liquid) consideration must be made for the "entrance" of the drug into the compartment from the gastro-intestinal tract (ie. the gut). Similarly, as with previous cases, the elimination of the drug must also be taken into account.

ASSUMPTIONS:

① As before, for simplicity, the model will attempt to describe a one compartment model. (ie. one in which any change in concentration of the drug in the blood is proportional to the change of the concentration of the drug in the body tissues.

② That we shall analyze the amount of drug in the body, for simplicity, as the amount of drug is proportional to the concentration. (concentration = amount / volume) } ?

③ ~~That~~ The absorption of the drug by the gut follows a first order process, as before. And similarly the elimination of the drug from the blood follows a first order process, for simplicity

④ Assume that all of the drug intaken into the gut is eventually absorbed into the blood. This removes any consideration of only a fraction of the drug dose entering the blood.

⑤ For generality we shall assume that all forms of oral drugs act identically and do not interact with any contents in the gut or gastro-intestinal fluids.

⑥ All general assumptions still apply

Let:
t - represent time (hrs) and $t(0) = t_0$ (initial time)
$C_1(t)$ - be the amount of drug in the gut at any time $t \geq 0$
$C_2(t)$ - be the amount of drug in the blood at time t, $t \geq 0$
$C_3(t)$ - be the amount of drug eliminated (ie in Kidney) at time t, $t \geq 0$
K_e - the elimination constant (hour^{-1}), $K_e > 0$
K_a - the absorption constant of the drug into the compartment, $K_a > 0$
C_0 - is the initial amount of the drug issued at time t_0

The following system of linear first order equations is obtained:

① the equation representing the removal rate of the drug from the gut:

$$\frac{dC_1(t)}{dt} = -K_a C_1(t) \quad , \quad C_1(t_0) = C_0$$

② The change in amount of drug in the blood, which is the amount obtained from the gut, less the amount eliminated:

$$\frac{dC_2(t)}{dt} = K_a C_1(t) - K_e C_2(t) \quad , \quad C_2(t_0) = 0$$

③ The change in the amount of drug eliminated:

$$\frac{dC_3(t)}{dt} = K_e C_2(t) \quad , \quad C_3(t_0) = 0$$

Solving ①:

$$\frac{dC_1(t)}{dt} = -K_a C_1(t) \quad C_1(t_0) = C_0$$

$$\int \frac{dC_1}{C_1} = -K_a \int dt$$

$$\Rightarrow \ln|C_1| = -K_a t + A \quad , \; A \text{ - constant of integration}$$
$$\ln C_1 = -K_a t \quad \text{since } C_1(t) \geq 0$$

Exponentiating:

$$e^{\ln C_1} = e^{-K_a t + A}$$

$$C_1(t) = Be^{-K_a t}$$

but $C_1(t_0) = C_0$

$$\therefore C_1(t) = C_0 e^{-K_a t} \quad - (*)$$

The function (*) was previously analyzed in case (1).

Now, using (*) we can solve equation (2) of the system:

$$\frac{dC_2(t)}{dt} = K_a C_1(t) - K_e C_2(t) \quad , \quad C_2(t_0) = 0$$

Substituting for $C_1(t)$ by (*):

$$\frac{dC_2(t)}{dt} = K_a C_0 e^{-K_a t} - K_e C_2(t)$$

This is a linear first order differential equation, which can be written as:

$$\frac{dC_2(t)}{dt} + K_e C_2(t) = K_a C_0 e^{-K_a t}$$

Integrating factor:

$$e^{K_e t}$$

∴ the equation becomes:

$$e^{K_e t} C_2(t) = \int K_a C_0 e^{-K_a t} e^{K_e t} dt$$

$$= K_a C_0 \int e^{-K_a t + K_e t} dt$$

$$= \frac{K_a C_0}{-K_a + K_e} e^{-K_a t} e^{K_e t} + D \quad , \quad D \text{ an integration constant}$$

$\Rightarrow$ Solve for C_2:

$$C_2(t) = \frac{K_a C_0}{-K_a + K_e} \frac{e^{-K_a t}}{e^{K_e t}} \cdot e^{K_e t} + \frac{D}{e^{K_e t}}$$

$$C_2(t) = \frac{K_a C_0}{-K_a + K_e} e^{-K_a t} + \frac{D}{e^{K_e t}}$$

↓ initially

Now, at $C_2(0) = 0$ (No amount of drug is in the blood)

$$0 = \frac{K_a C_0}{-K_a + K_e} e^{-K_a(0)} + D e^{-K_e(0)}$$

$$\therefore D = -\frac{K_a C_0}{(-K_a + K_e)}$$

∴ The initial value form of $C_2(t)$:

$$C_2(t) = \frac{K_a C_0}{-K_a + K_e} e^{-K_a t} - \frac{K_a C_0}{(-K_a + K_e)} e^{-K_e t}$$

$$C_2(t) = \frac{K_a C_0}{-K_a + K_e} \left(e^{-K_a t} - e^{-K_e t}\right) \quad - (**)$$

Note now that the assumption must be made that $K_a \neq K_e$, or the model becomes undefined.

Solving for (3):

$$\frac{dC_3(t)}{dt} = K_e C_2(t) \quad , C_3(0) = 0$$

Substituting $(**)$ in (3) yields:

$$\frac{dC_3(t)}{dt} = K_e \frac{K_a C_0}{-K_a + K_e} \left(e^{-K_a t} - e^{-K_e t}\right)$$

which is a separable linear first order differential equation:

$$\int dC_3(t) = \int K_e \frac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a t} - e^{-K_e t}\right) dt$$

$$C_3(t) = \int \frac{K_e K_a C_0}{(-K_a + K_e)} e^{-K_a t}\,dt - \int \frac{K_e K_a C_0}{(-K_a + K_e)} e^{-K_e t}\,dt$$

$$= \frac{K_e K_a C_0}{(-K_a + K_e)} \cdot \frac{1}{(-K_a)} e^{-K_a t} - \frac{K_e K_a C_0}{(-K_a + K_e)} \cdot \frac{1}{(-K_e)} e^{-K_e t} + E$$

E a constant of integration

factoring a -1 from the denominator:

$$C_3(t) = \left(\frac{K_e K_a C_0}{(K_a - K_e)}\right)\left(\frac{e^{-K_a t}}{K_a} - \frac{e^{-K_e t}}{K_e}\right) + E$$

Since $C_3(t) = 0$ when $t = 0$, we solve for E

$$C_3(0) = 0 = \frac{K_e K_a C_0}{(K_a - K_e)}\left(\frac{e^{-K_a(0)}}{K_a} - \frac{e^{-K_e(0)}}{K_e}\right) + E$$

$$0 = \frac{K_e K_a C_0}{K_a - K_e}\left(\frac{1}{K_a} - \frac{1}{K_e}\right) + E$$

$$E = \frac{K_e K_a C_0}{K_a - K_e}\left(\frac{1}{K_e} - \frac{1}{K_a}\right)$$

$$= \frac{K_e K_a C_0}{K_a - K_e}\left(\frac{K_a}{K_a K_e} - \frac{K_e}{K_a K_e}\right)$$

$$= C_0$$

∴ The initial value solution of $C_3(t)$:

$$C_3(t) = \frac{K_e K_a C_0}{(K_a - K_e)}\left(\frac{e^{-K_a t}}{K_a} - \frac{e^{-K_e t}}{K_e}\right) + C_0$$

can be written in other useful forms

ANALYSIS OF THE EXPLICIT SOLUTIONS $C_1(t)$, C_2

Recall:

$$C_1(t) = C_0 e^{-K_a t}$$

$$C_2(t) = \frac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a t} - e^{-K_e t}\right)$$

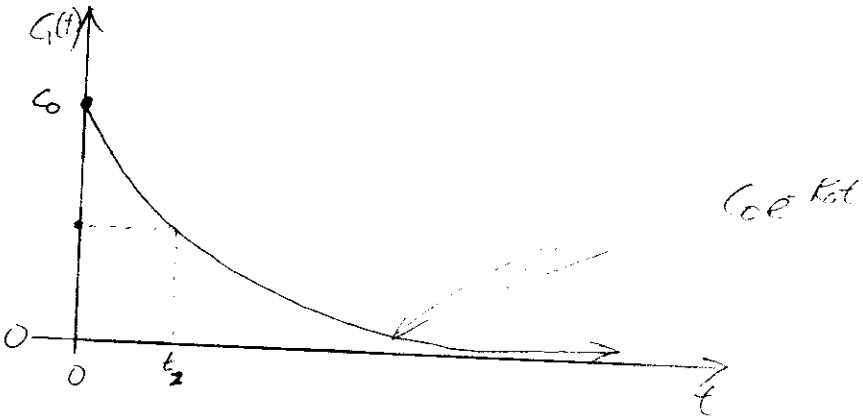
$$C_3(t) = \frac{K_e K_a C_0}{(K_a - K_e)} \left(\frac{e^{-K_a t}}{K_a} - \frac{e^{-K_e t}}{K_e}\right) + C_0$$

① ANALYSIS OF $C_1(t)$:

$$C_1(t) = C_0 e^{-K_a t}$$

For this function, FIGURE (3.1) is obtained:

FIGURE (3.1) $C_1(t)$ vs. t



This sketch is instantly recognizable as a Malthusian-type decay.

To find the time that any amount of drug C_1 is still in the gut, solve for t:

$$C_1(t) = C_0 e^{-K_a t}$$

$$\Rightarrow \frac{C_1}{C_0} = e^{-K_a t}$$

$$\Rightarrow \ln\left(\frac{C_1}{C_0}\right) = \ln e^{-K_a t}$$

$$\ln\left(\frac{C_1}{C_0}\right) = -K_a t$$

$$\therefore \quad t = \frac{1}{-K_a}\ln\left(\frac{C_1}{C_0}\right) \iff \frac{1}{K_a}\ln\left(\frac{C_0}{C_1}\right)$$

Again, This t gives the time any amount C_1 $(0 < C_1 \leq C_0)$ that is remaining in the gut.

Determining the half-life of the drug in the gut: $C_1 = \frac{1}{2}C_0$
(i.e. at what time is the drug half gone from the gut)

$$t_{\frac{1}{2}} = \frac{1}{-K_a}\left(\frac{\frac{1}{2}C_0}{C_0}\right)$$

$$= \frac{1}{-K_a}\ln\left(\frac{1}{2}\right) \cong \frac{.693}{K_a}$$

Notice that the half-life is independent of the initial dose amount.

(2) ANALYSIS OF $C_2(t)$:

$$C_2(t) = \frac{K_a C_0}{(-K_a + K_e)}\left(e^{-K_a t} - e^{-K_e t}\right), \quad C_2(t_0) = 0$$

Intuitively, as the equation for $C_2(t)$ is based on the d.e.

$$\frac{dC_2(t)}{dt} = K_a C_1(t) - K_e C_2(t)$$

which says that the change in amount of drug in the blood is equal to the amount absorbed from the gut, less the amount of drug eliminated, leads to the suspicion that the amount of drug may have a a maximum at some time.

Consider the plot of $C_2(t)$ vs t

FIGURE 3.2 $C(t)$ vs. t

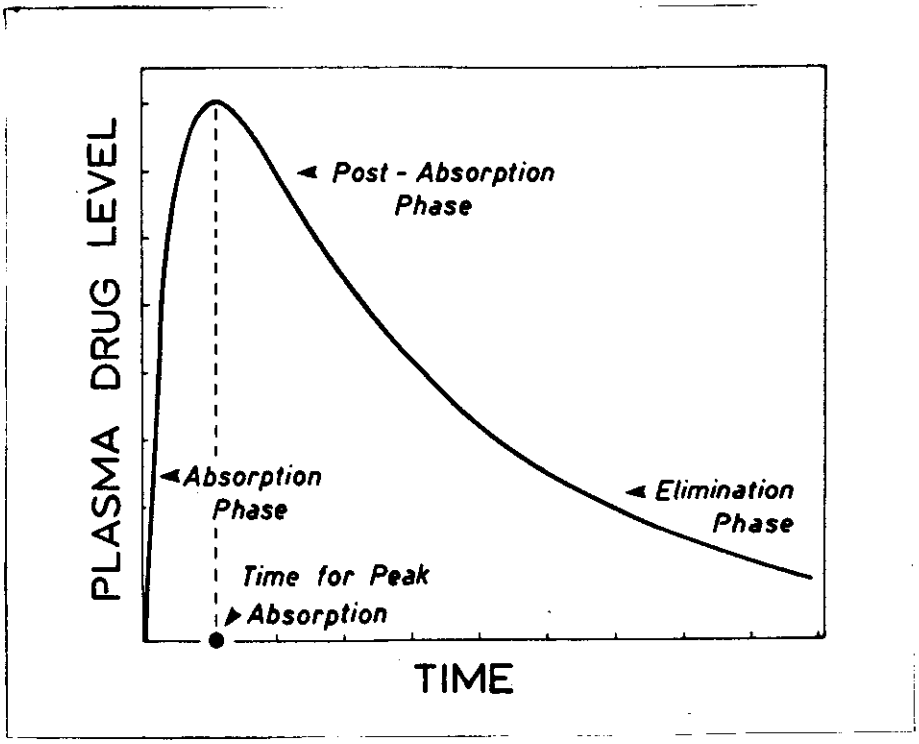


Figure 3.2 Plasma level – time curve for a drug given in a single oral dose. The drug absorption and elimination phases of the curve are shown.

To determine if the maximum indicated by the sketch occurs, the first derivative test is applied to $C_2(t)$

$$C_2(t) = \frac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a t} - e^{-K_e t}\right)$$

$$\frac{dC_2(t)}{dt} = \frac{K_a C_0}{(-K_a + K_e)} \left(-K_a e^{-K_a t} + K_e e^{-K_e t}\right)$$

has critical points if $C_2'(t) = 0$ or is undefined:
(cannot be undefined as $-K_a \neq -K_e$ by assumption previously)

$$\therefore \frac{d}{dt}(C_2(t)) = 0 \text{ occurs if } -K_a e^{-K_a t} + K_e e^{-K_e t} = 0$$

$$\Rightarrow K_a e^{-K_a t} = K_e e^{-K_e t}$$
$$\Rightarrow \ln(K_a e^{-K_a t}) = \ln(K_e e^{-K_e t})$$
$$\Rightarrow \ln K_a + \ln e^{-K_a t} = \ln K_e + \ln e^{-K_e t}$$

$$\Rightarrow \ln K_a - K_a t = \ln K_e - K_e t$$

$$K_e t - K_a t = \ln K_e - \ln K_a$$

$$t_2 = \ln\left(\frac{K_e}{K_a}\right)\frac{1}{(K_e - K_a)}$$

Hence a maximum amount of drug is absorbed at t_2. Notice that this time is independent of the amount of drug initially injected.

The amount of drug in the blood at t_2 can be determined:

$$C_2(t_2) = \frac{K_a C_0}{(-K_a + K_e)}\left(e^{-K_a \ln\left(\frac{K_e}{K_a}\right)\frac{1}{K_e - K_a}} - e^{-K_e \ln\left(\frac{K_e}{K_a}\right)\frac{1}{K_e - K_a}}\right)$$

$$= \frac{K_a C_0}{(-K_a + K_e)}\left(\left(\frac{K_e}{K_a}\right)^{\frac{-K_a}{K_e - K_a}} - \left(\frac{K_e}{K_a}\right)^{\frac{-K_e}{K_e - K_a}}\right)$$

$$= \frac{K_a C_0}{(-K_a + K_e)}\left(\frac{K_e}{K_a}\right)^{\frac{-K_a + K_e}{K_e - K_a}}$$

$$C_2(t_2) = \frac{K_e C_0}{-K_a + K_e}$$

naturally! — ∴ the MAXIMUM amount of drug in the compartment is directly proportional to the initial dosage amount and is independent of time.

Determining the time t, for a given amount of drug in the blood (C_2)
Solve for t:

$$C_2(t) = \frac{K_a C_0}{(-K_a + K_e)}\left(e^{-K_a t} - e^{-K_e t}\right)$$

$$\frac{(-K_a + K_e)}{K_a C_0} C_2 = e^{-K_a t} - e^{-K_e t}$$

$$\ln\left(\frac{(-K_a + K_e)}{K_a C_0} C_2\right) = \ln\left(e^{-K_a t} - e^{-K_e t}\right)$$

$$\Rightarrow \ln\left(\frac{(-K_a+K_e)C_2}{K_aC_0}\right) = \ln\left(\frac{e^{-K_at}}{e^{-K_et}}\right)$$

$$\ln\left(\frac{K_a+K_e}{K_aC_0}\cdot C_2\right) = \ln\left(e^{-K_at+K_et}\right)$$

$$(-K_a+K_e)t = \ln\left(\frac{-K_a+K_e}{K_aC_0}\cdot C_2\right)$$

$$t = \frac{1}{(-K_a+K_e)}\ln\left(\frac{-K_a+K_e}{K_aC_0}C_2\right)$$

which finds the time for an amount of drug such that $C_2 > 0$.

(3) ANALYSIS OF $C_3(t)$

$$C_3(t) = \frac{K_eK_aC_0}{(K_a-K_e)}\left(\frac{e^{-K_at}}{K_a} - \frac{e^{-K_et}}{K_e}\right) + C_0$$

Here, intuitively, the expectation is that "eventually" all of the drug will be eliminated from the system. Further, it does not seem unlikely that this model "part" may behave inversely proportional to the absorption part of the model. } ?

The following sketch of $C_3(t)$ vs t (bottom one) tends to show agreement with the above assessment:

FIGURE 3.3 $C_2(t)$ vs t and $C_{\infty}(t)$ vs t

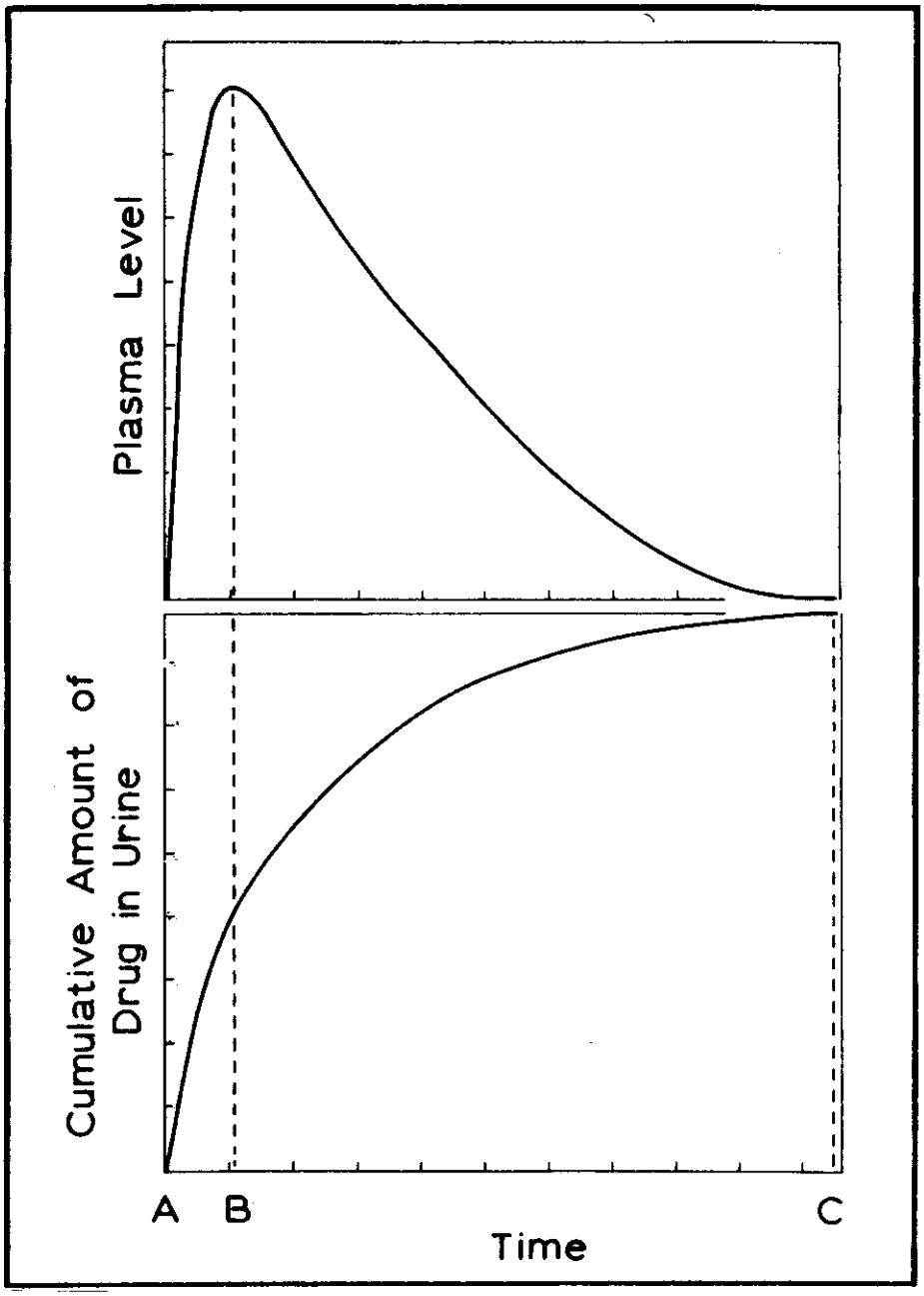


Figure 3.3 Corresponding plots relating the plasma level–time curve and the cumulative urinary drug excretion.

Here, the sketch suggests that a limit occurs at C_0 as $t \to \infty$

By taking the limit as $t \to \infty$ on $C_3(t)$, the supposition is proved:

$$\lim_{t\to\infty} C_3(t) = \lim_{t\to\infty} \frac{K_e K_a C_0}{K_a - K_e}\left(\frac{e^{-K_a t}}{K_a} - \frac{e^{-K_e t}}{K_e}\right) + C_0$$

$$\downarrow \qquad \downarrow$$

$$0 \qquad 0$$

$$\lim_{t\to\infty} C_3(t) = C_0$$

Determining the time t_1 that an amount of drug C_3 has been removed from the compartment

$$C_3(t) = \frac{K_e K_a C_0}{K_a - K_e}\left(\frac{e^{-K_a t}}{K_a} - \frac{e^{-K_e t}}{K_e}\right) + C_0$$

$$\frac{(C_3 - C_0)}{K_e K_a C_0} \cdot (K_a - K_e) = \frac{e^{-K_a t}}{K_a} - \frac{e^{-K_e t}}{K_e}$$

$$\ln\left(\frac{(C_3 - C_0)}{K_e K_a C_0}(K_a - K_e)\right) = \ln\left(\frac{e^{-K_a t}}{K_a} - \frac{e^{-K_e t}}{K_e}\right)$$

$$= \ln\left(\frac{\frac{e^{-K_a t}}{K_a}}{\frac{e^{-K_e t}}{K_e}}\right)$$

$$= \ln\left(\frac{K_e}{K_a} \cdot e^{-K_a t + K_e t}\right)$$

$$= \ln\left(\frac{K_e}{K_a}\right) + \ln\left(e^{-K_a t + K_e t}\right)$$

$$= \ln\left(\frac{K_e}{K_a}\right) + (-K_a t + K_e t)$$

$$\Rightarrow \ln\left(\frac{(C_3-C_0)(K_a-K_e)}{K_e K_a C_0 (-K_a+K_e)}\right) - \ln\left(\frac{K_e}{K_a}\right) = t$$

$$\therefore\ t = \frac{1}{(-K_a+K_e)} \cdot \ln\left(\frac{(C_3-C_0)}{K_e K_a C_0} K_a (K_a-K_e)\right)$$

for any amount of C_3 such that $0 < C_3 \leq C_0$

CONCLUSIONS - CASE (3)

As in the single dose, rapid intravenous injection case, this model only provides a reasonable drug regimen if K_e, the elimination constant, is quite small and/or if K_a, the drug absorption constant is large enough to "allows" enough drug into the compartment. This would allow the concentration of the drug in the blood to remain above Minimum Effective Concentration.

To prolong the time that the concentration is above MEC, a multiple Oral Dosage scheme could be considered.

DISADVANTAGES:

A major disadvantage of this model is that it assumes that all of the drug enters the compartment. A minor revision of the model could involve examining the problem of only a fraction of the drug entering the blood, while the remainder simply passes through the gastro-intestinal tract unabsorbed.

References: 8

CASE ④ - ORAL INJECTION, MULTIPLE DOSES

Finally, consideration is made of the Multiple Oral Dosage Regimen. Again, a fixed (oral) dose is administered over equally spaced time periods.

ASSUMPTIONS:

① All the general assumptions apply

② All the assumptions from case ③ apply

③ Similarly from Case ②, "The principle of superposition assumes that early doses of drug do not affect the pharmacokinetics of subsequent doses. Therefore, the blood levels after the second, third, or n^{th} dose will overlay or superimpose the blood level attained after the $(n-1)$th dose." [3]

④ To avoid complications, assume that there is "no" drug left in the gut when a new dose is taken. (i.e. "insignificant residual concentration") } ?

Note that there is no need to consider the drug levels in the gut or the amount of drug eliminated. This multiple dosage case will only consider the effect of the amount of drug in the blood.

Let:

K_e - be the drug elimination constant, $K_e > 0$
K_a - the drug absorption constant, $K_a > 0$
C_0 - the initial dosage amount, $C_0 > 0$
n - be the dosage number $n \geq 1$
T - be the period of time between doses.
t - be time, $t_0 = 0$
$C_n(t)$ - be the total amount of drug in the compartment at time t, after dose n
$R_n(t)$ - be the residual dosage after dose number $n+1$, $R(t_0) = 0$.

The rate of change of the amount of drug in the blood, as given in case (3) is:

$$\frac{dC(t)}{dt} = K_a C_1(t) - K_e C(t) \quad , \quad C(0) = C_0$$

where $C_1(t)$ is the amount of drug being absorbed.

The solution of $C_3(t)$: (again from (3))

$$C(t) = \frac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a t} - e^{-K_e t} \right)$$

Now at $t_0 = 0$ the initial dose is taken (i.e. $n=1$) and and $R(t_0) = 0$, by assumption

$$C_1 = C(0) = C(T_1) = 0 \,, \quad R_0 = 0$$

at $1T$: $R_1 = \dfrac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a T} - e^{-K_e t} \right)$

$$C_2 = \underbrace{C(T_1)}_{\downarrow 0} + R_1 = 0 + \frac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a T} - e^{-K_e T} \right)$$

at $2T$: $R_2 = \dfrac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a T} - e^{-K_e T} \right) + \dfrac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a 2T} - e^{-K_e 2T} \right)$

$$= \frac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a T} + e^{-2K_a T} - e^{-K_e T} - e^{-2K_e T} \right)$$

There is no medication at this time one obtained.

$$C_3 = \underbrace{C_2(T_2)}_{\Downarrow} + R_2$$

Notice that the amount of drug in the blood at dose j equals the residual amount of drug after dose $j-1$.

The preceding situation is represented by Figure (4.1):

FIGURE (4.1) - Multiple Oral Dosage Sketch

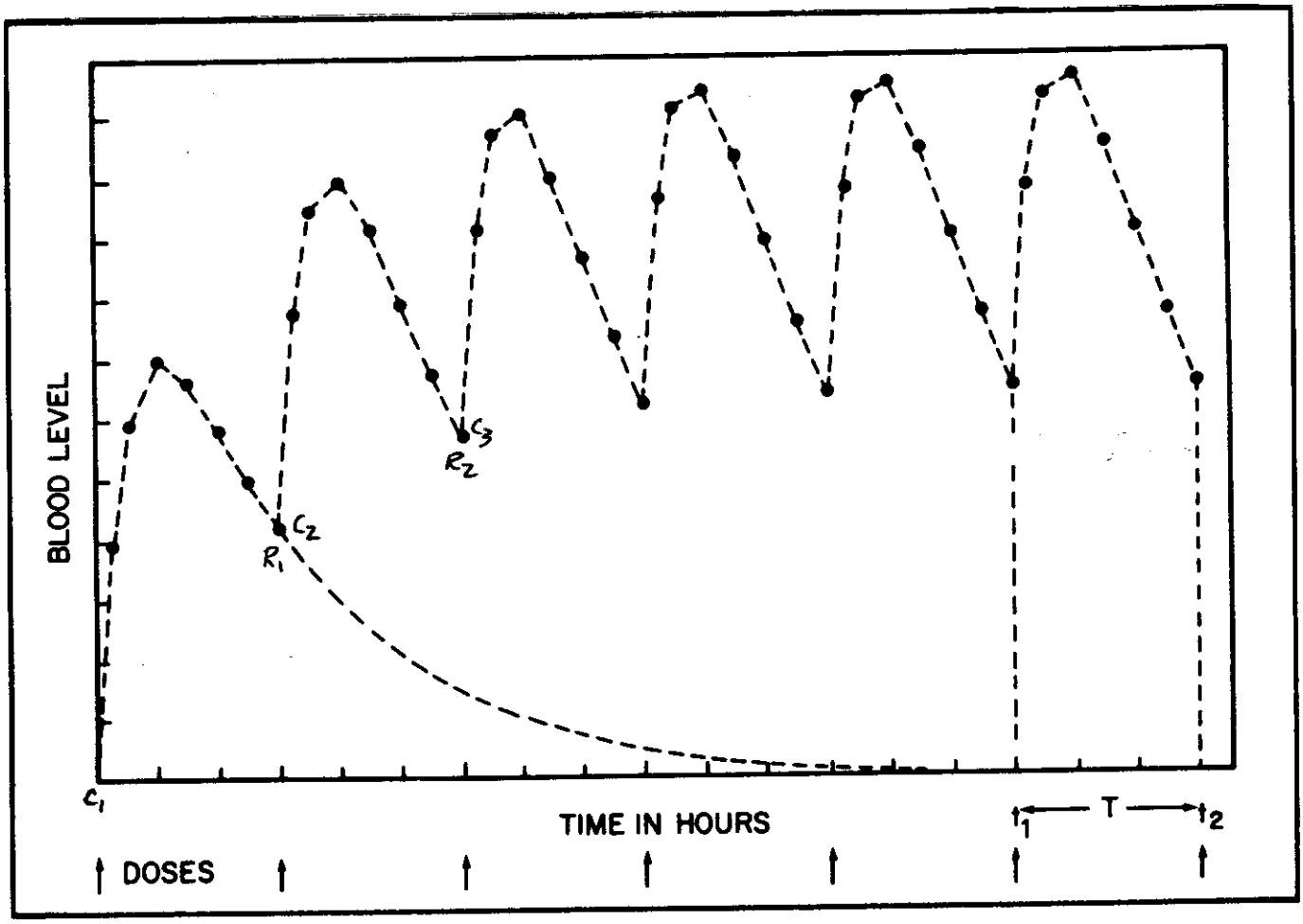


Figure 4.1. Simulated data showing blood levels after administration of multiple doses and accumulation of blood levels when equal doses are given at equal time intervals.

Thus a conjecture for R_j or C_{jH} is:

$$R_j = C_{jH} = \frac{K_a C_0}{(-K_a + K_e)} \left(e^{-K_a T} + e^{-2K_a T} + \dots + e^{-jK_a T} - e^{-K_e T} - e^{-2K_e T} - \dots - e^{-jK_e T} \right)$$

Notice that two geometrical series are formed, which can be solved analytically by the formula:

how?

$1 + r + r^2 + \cdots + r^{n-1} = \frac{1-r^n}{1-r}$, where $r = e^{-KaT}, e^{-KeT}$

$$\therefore R_n = C_{n+1} = \frac{KaCo}{(-Ka+Ke)}\left(e^{-KaT}\left(\frac{1-e^{-nKaT}}{1-e^{-KaT}}\right) - e^{-KeT}\left(\frac{1-e^{-nKeT}}{1-e^{-KeT}}\right)\right)$$

which gives the Residual amount of drug for the end of the n^{th} period, or equivalently, gives the total amount of drug at the beginning of the $(n+1)^{th}$ period.

Similarly for any time t, such that $pT < t > (p+1)T$ (ie a time between the p^{th} and $(p+1)^{th}$ intervals)

$$C_p(t_p) = \frac{KaCo}{-Ka+Ke}\left(e^{-Ka\,t_p}\left(\frac{1-e^{-nKaT}}{1-e^{-KaT}}\right) - e^{-KeT}\left(\frac{1-e^{-nKeT}}{1-e^{-KeT}}\right)\right)$$

Notice that this gives the amount of drug for any time t, and dosage number n.

Now consider, when n gets very large (ie $n \to \infty$) From previous experience, a "steady-state" will result:

Apply limit:

$$\lim_{t\to\infty} C_p = \lim_{n\to\infty} \frac{KaCo}{(-Ke+Ka)}\left(e^{-Ka}\left(\frac{1-e^{-nKaT}}{1-e^{-KaT}}\right) - e^{-KeT}\left(\frac{1-e^{-nKeT}}{1-e^{-KeT}}\right)\right)$$

which gives the "steady-state" drug amount for any time t, and period T:

$$C^{ss} = \frac{KaCo}{(-Ka+Ke)}\left(\frac{e^{-Kat}}{1-e^{-KaT}} - \frac{e^{-Ket}}{1-e^{-KeT}}\right)$$

Since this limit C^{∞} "fluctuates" as absorption and elimination occur as t increases, there is a Maximum C and a Minimum C which represent the upper & lower bounds that C^{∞} approaches in "steady-state."

C^{∞} doesn't fluctuate

Determining C^{∞}_{min}

At the start of a period, $t=T$, by assumption there is no absorption occurring. Hence the absorption part of the equation is effectively eliminated:

$$C^{\infty} = \frac{K_a C_0}{(-K_a + K_e)}\left(\frac{e^{-K_a T}}{1-e^{-K_a T}} - \frac{e^{-K_e T}}{1-e^{-K_e T}}\right)$$

$\downarrow 0$

$$\therefore C^{\infty}_{MIN} = \frac{K_a C_0}{-K_a + K_e}\left(\frac{-e^{-K_e T}}{1-e^{-K_e T}}\right)$$

Determining C^{∞}_{MAX}

To determine the upperbound for the "steady-state" Oral Regimen, recall from CASE (3) that the maximum amount present occurred at time:

$$t_{max} = \frac{1}{(-K_a + K_e)} \cdot \ln\left(\frac{K_e}{K_a}\right)$$

this is only an approximation based on the I.V. bolus model.

and $nT < t_{max} < (n+1)T$.

Since this t_{max} represents the peak of the drug amount level, it occurs with respect to the first derivative of C^{∞}:

at 1T ?

$$\frac{dC_2}{dt} = \frac{d}{dt}\left(\frac{K_a C_0}{(-K_a+K_e)}\left(e^{-K_aT}-e^{-K_eT}\right)\right)$$

$$= \frac{K_a C_0}{(-K_a+K_e)}\left(-K_a e^{-K_aT} - (-K_e)e^{-K_eT}\right)$$

which is our single dose case, thus

$$t_1 = \frac{1}{-K_a+K_e}\ln\left(\frac{K_e}{K_a}\right)$$

at 2T

$$\frac{dC_2}{dt} = \frac{d}{dt}\left(\frac{K_a C_0}{K_a+K_e}\left(e^{-K_aT}+e^{-2K_aT}-e^{-K_eT}-e^{-2K_eT}\right)\right)$$

1 ?

$$= \frac{d}{dt}\left(\frac{K_a C_0}{-K_a+K_e}\left(e^{-K_aT}\left(1+e^{-K_aT}\right)-e^{-K_eT}\left(1+e^{-K_eT}\right)\right)\right)$$

$$= \frac{K_a C_0}{-K_a+K_e}\left(-K_a e^{-K_aT} - 2K_a e^{-2K_aT} + K_e e^{-K_eT} + 2K_e e^{-2K_eT}\right)$$

t is max when $\frac{dC_2}{dt}$ has a critical point (ie $\frac{dC_2}{dt}=0$ or Undefined)

Hence:

$$-K_a e^{-K_aT} - 2K_a e^{-2K_aT} + K_e e^{-K_eT} + 2K_e e^{-2K_eT} = 0$$

$$K_e e^{-K_eT} + 2K_e e^{-2K_eT} = K_a e^{-K_aT} + 2K_a e^{-2K_aT}$$

$$K_e e^{-K_eT}\left(1+e^{-K_eT}\right) = K_a e^{-K_aT}\left(1+e^{-K_aT}\right)$$

$$\frac{K_e}{K_a}\frac{\left(1+e^{-K_eT}\right)}{\left(1+e^{-K_aT}\right)} = \frac{e^{-K_aT}}{e^{-K_eT}}$$

$$\ln\left(\frac{K_e}{K_a}\cdot\frac{1+e^{-K_eT}}{1+e^{-K_aT}}\right) = \ln\left(e^{-K_aT+K_eT}\right)$$

$$\ln\left(\frac{K_e}{K_a}\cdot\frac{1+e^{-K_eT}}{1+e^{-K_aT}}\right) = (-K_a+K_e)t$$

$$t_2 = \frac{1}{-K_a+K_e}\ln\left(\frac{K_e}{K_a}\cdot\frac{1+e^{-K_eT}}{1+e^{-K_aT}}\right)$$

based on the above analysis, a conjecture for t_{max} at dosage number n:

$$= t^{n}_{max} \quad \frac{1}{-K_a+K_e} \ln\left(\frac{K_e}{K_a} \cdot \frac{1+e^{-K_eT}+e^{-2K_eT}+\ldots+e^{-(n-1)K_eT}}{1+e^{-K_aT}+e^{-2K_aT}+\ldots+e^{-(n-1)K_aT}}\right) \leftarrow \text{GEOMETRIC SERIES}$$

$$= \frac{1}{-K_a+K_e} \ln\left(\frac{K_e}{K_a} \cdot \left(\frac{\frac{1-e^{-nK_eT}}{1-e^{-K_eT}}}{\frac{1-e^{-nK_aT}}{1-e^{-K_aT}}}\right)\right) \Rightarrow$$

now as $n \to \infty$, which represents the maximum drug amount during "steady-state"

$$t^{\infty}_{max} = \frac{1}{-K_a+K_e} \ln\left(\frac{K_e}{K_a} \cdot \frac{1-e^{-K_aT}}{1-e^{-K_eT}}\right)$$ — agrees with my result.

Plugging this value into the equation for C^{∞} to find C^{∞}_{max}:

$$C^{\infty}(t^{\infty}_{max}) = \frac{K_aC_0}{-K_a+K_e}\left(\frac{e^{-K_at^{\infty}_{max}}}{1-e^{-K_aT}} - \frac{e^{-K_et^{\infty}_{max}}}{1-e^{-K_eT}}\right)$$

$$= \frac{K_aC_0}{-K_a+K_e}\left(\frac{e^{-K_a\left(\frac{1}{-K_a+K_e}\right)\ln\left(\frac{K_e}{K_a}\cdot\frac{1-e^{-K_aT}}{1-e^{-K_eT}}\right)}}{1-e^{-K_aT}} - \frac{e^{-K_e\frac{1}{-K_a+K_e}\ln\left(\frac{K_e}{K_a}\frac{1-e^{-K_aT}}{1-e^{-K_eT}}\right)}}{1-e^{-K_eT}}\right)$$

$$= \frac{K_aC_0}{-K_a+K_e}\left(\frac{\left(\frac{K_e}{K_a}\cdot\frac{1-e^{-K_aT}}{1-e^{-K_eT}}\right)^{\frac{K_a}{-K_a+K_e}}}{1-e^{-K_aT}} - \frac{\left(\frac{K_e}{K_a}\cdot\frac{1-e^{-K_aT}}{1-e^{-K_eT}}\right)^{\frac{-K_e}{K_a+K_e}}}{1-e^{-K_eT}}\right)$$

$$= \frac{K_aC_0}{-K_a+K_e}\left(\frac{\left(\frac{K_e}{K_a}\cdot\frac{1-e^{-K_aT}}{1-e^{-K_eT}}\right)^{\frac{K_a+K_e}{-K_a+K_e}}\left(\left(1-e^{-K_eT}\right)-\left(1-e^{-K_aT}\right)\right)}{\left(1-e^{-K_aT}\right)\left(1-e^{-K_eT}\right)}\right)$$

$$= \frac{K_a C_0}{(-K_e + K_a)} \left(\frac{1}{(1-e^{-K_e T})(1-e^{-K_a T})} \right) \left(\frac{K_e}{K_a} \cdot \frac{K_e e^{-K_a t}}{1-e^{-K_e T}} \right) \left((1-e^{-K_e t}) - (1-e^{-K_a t}) \right)$$

$$\therefore \quad C_{max}^{\infty} = \frac{C_0}{-K_a + K_e} \left[\frac{(1-e^{-K_e T}) - (1-e^{-K_a T})}{(1-e^{-K_e T})^2} \right]$$

* NOTE: Shargel, P. 238 obtains:

$$C_{max}^{\infty} = C_0 \left(\frac{1}{1-e^{-K_e T}} \right) e^{-K t_{MAX}^{\infty}}$$

Somehow !?!

This C_{MAX}^{∞} is the upper limit that multiple Oral dose regimen reaches, for a constant dosage amount over a constant time period.

Observations:

① Like the Multiple Rapid Intravenous Injection case, This model, in time, reaches a "steady-state". where limits exist for the upper & lower bounds of the drug amount in the blood.

② That when the drug supply terminates, the model follows a natural Malthusian decay.

③ As in case ② a change in the Time period T causes a "shift" in the limits of the "steady-state" as shown:

FIGURE 4.2

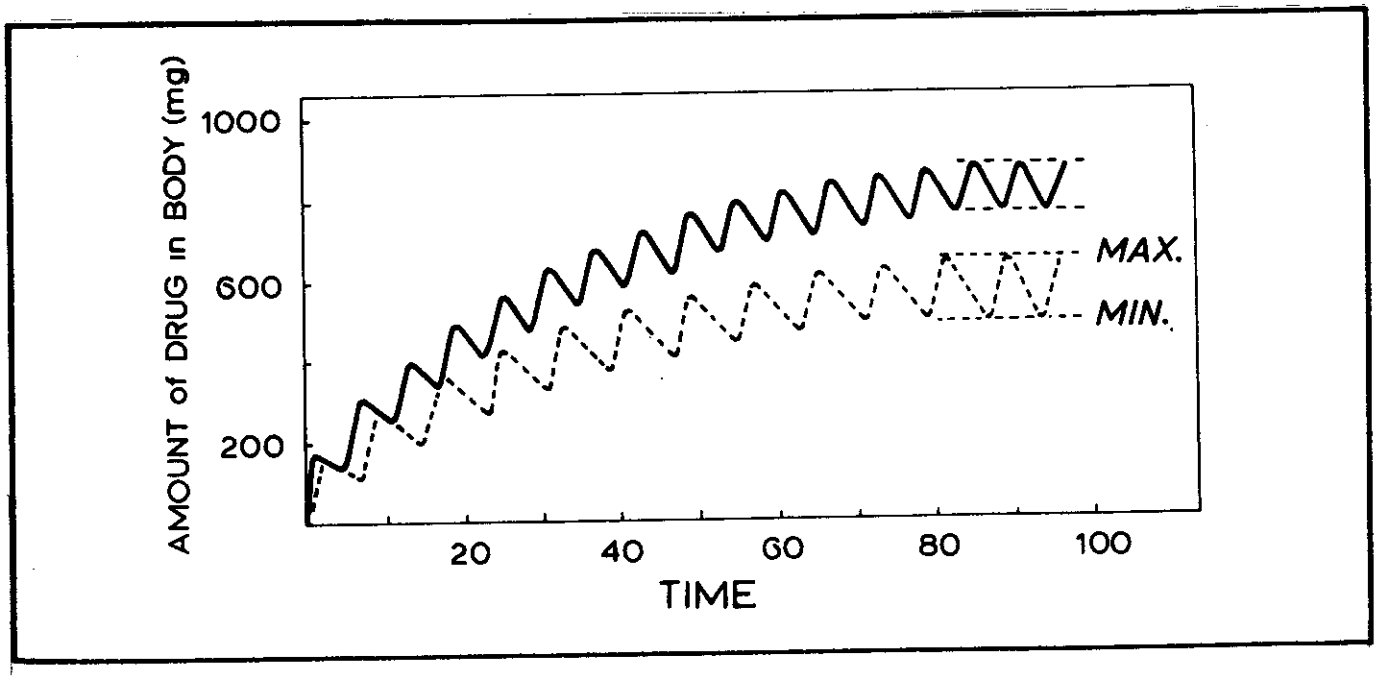


Figure 4.2 Amount of drug in the body as a function of time. Equal doses of drug were given every 6 hr (upper curve) and every 8 hr (lower curve). K_a and K remain constant.

CONCLUSIONS - CASE (4)

The multiple Oral Drug dosage Model provides good Theoretical results of the Drug supply in the body. However upon application of the Model attention must be given to dosage amount and period between dosages to provide the safest and most effective drug regimen. (i.e. MTC can never be exactly known) Therefore leeway must be given so as to not cause an overdose.

Shortcomings of this model are much the same as Case (2). Loading Doses or an effective "Waking Hour" regimen may be necessary to provide sufficient Residual Concentration. Therefore Model revision may be necessary. As well, the shortcomings of case (3) are magnified here, as multiple dosages are considered.

Reference: 12

EXAMPLE:

2. This problem deals with simple *compartment* models in physiology. See D. S. Riggs (1963) for further discussion, especially his Sec. 6-14 which treats problems of fitting curves to such models.

   (*a*) Treat the blood as a compartment containing a substance being removed by a physiological mechanism. What sort of equations could describe the concentration of the substance as a function of time? We need *simple* models. How can they be tested?

   (*b*) Let's be specific and assume that the removal is being done by the kidneys. In this case the rate of removal is usually proportional to the amount of the substance passing through a kidney per unit time. Construct a simple model based on concentrations.

   (*c*) The substance in (*b*) is a drug whose concentration should lie between 2 and 5 milligrams per 100 cubic centimeters. If the drug is taken internally, about 60% is quickly absorbed and most of the remainder is lost. In about 8 hours the body of an average person eliminates about 50% of the drug. A normal adult has about 5 liters of blood. Design a dosage program for the drug.

   (*d*) Most drugs are taken orally and require time to be absorbed by the blood. At the same time the drug is being removed by the kidneys. Model the situation. Here is some data on drugs taken from J. V. Swintosky (1956). The first drug is sulfapyridine, and the second is sodium salicylate. An O indicates oral administration. and an I indicates intravenous administration [to which (*a*) should apply]. The column headed "grams" gives the initial dosage, and the other columns indicate the concentration in the blood at various times after administration. How well does your model fit? Could you explain any discrepancies?

		Concentration (milligrams/cubic centimeters)							
Administration	Grams	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	24 hours
O	4.0	2.3	2.7	3.6	3.0	—	2.0	—	—
O	4.0	1.8	2.8	3.9	3.5	2.6	2.2	—	—
I	1.8	3.8	3.4	2.6	2.1	—	—	—	—
I	1.8	3.7	3.3	2.7	2.3	—	—	—	—
O	10	5.0	—	—	14.4	—	—	15.7	12.5
I	10	39.4	—	—	31.4	—	—	24.2	16.2
I	20	56.7	—	—	43.0	—	—	35.2	26.6

Unfortunately, here No explicitly given Ka or Ke is provided. Here, in (C) the elimination constants are to be calculated, but they assume that only part of the drug is absorbed, which is a complication of my simpler models

FOOTNOTES

[1] Leon Shargel and Andrew B.C. Yu, *Applied Biopharmaceutics and Pharmacokinetics* (Norwalk: Appleton-Century-Crofts, 1985), pp. 37-39.

[2] Frank R. Giordano and Maurice D. Weir, *A First Course In Mathematical Modeling* (Monterey: Brooks/Cole, 1985), pp. 316-318.

[3] Shargel, p. 229.

[4] Giordano, p. 319.

[5] T.G. Berry, "Test Solutions," 6:337, February 22, 1990, p. 6, 7.

[6] Giordano, pp. 319-322.

[7] Shargel, p. 106.

[8] Shargel, pp. 107-109.

[9] Shargel, p. 230.

[10] Shargel, p. 232.

[11] Shargel, pp. 237-240

[12] Edward A. Bender, An Introduction To Mathematical Modeling (Toronto: John Wiley and Sons, 1978), p. 156

BIBLIOGRAPHY

Bender, Edward A., An Introduction To Mathematical Modeling. Toronto: John Wiley and Sons, 1978.

Berry, T. G., "Test Solutions", 6.337, February 22, 1990.

Giordano, Frank R., and Maurice D. Weir, A First Course in Mathematical Modeling. Monterey: Brooks/Cole, 1985.

Shargel, Leon, and Andrew B. C. Yu, Applied Biopharmaceutics and Pharmacokinetics. Norwalk: Appleton-Century-Crofts, 1985.