PHARMACOKINETICS

L. McKnight

SUMMARY OF CONSTANTS, VARIABLES AND NOTATIONAL PECULIARITIES

In the discussion that follows, we will make use of the following symbols to identify constants and variables:

A - concentration of drug in the stomach (mg/mL)

B - concentration of drug in the bloodstream (mg/mL)

$\frac{dA}{dt}$ - change in concentration in the stomach (mg/(mL*hr))

$\frac{dB}{dt}$ - change in concentration in the bloodstream (mg/(mL*hr))

t - time (hrs)

Z - elimination constant from the the stomach (also the absorption constant for the bloodstream) (1/hr)

K - elimination constant from the bloodstream (1/hr)

C - concentration of drug for a single dose (mg/mL)

T - time interval between doses (hrs)

H - level of toxicity of the drug in the bloodstream (mg/mL)

L - minimum effective level of the drug in the bloodstream (mg/mL)

S - level of toxicity of the drug in the stomach (mg/mL)

R - residual concentration of the drug in the bloodstream (mg/mL)

V - residual concentration of the drug in the stomach (mg/mL)

We will also make use of the following notations:

<k> - following a variable will denote a subscript

Description of Problem

Given a two compartment model, with compartment A ~~being~~ representing the stomach, and compartment B ~~being~~ representing the bloodstream, we wish to determine how much of a dosage to prescribe for a drug, and how often the dosage should be administered, so that we are able to maintain a concentration in the therapeutic range of the bloodstream. We also wish to look at the problem of having a toxicity level in the stomach and prescribing a dosage at a time interval such that the concentration of the drug in the stomach will consistently be below this toxicity level.

drug orally administered

Initial Assumptions

Before we begin our discussion we will make several initial assumptions about the problem with which we are dealing (note: many more assumptions will be made throughout the course of the discussion).

We will first of all assume that the concentration level in a given compartment is the critical factor in determining the effect of the drug.

Secondly, we will assume that drug is eliminated from a particular compartment at a rate which is proportional to the amount of drug present, and that all of the drug is eliminated in the way (ie. we will not take into account any break-down of the drug which may occur due to enzymatic or other processes, processes which may or may not eliminate the drug at rate proportional to the amount of drug present). Indeed, clinical experiments have shown that there are grounds upon which to make this assumption.

In addition, for ease and simplicity, we will assume the rates of elimination and absorption, in either of the compartments, can be represented by a continuous function.

To conclude our list of initial assumptions, we will

assume that the absorption of the drug by the stomach is instantaneous.

Do you mean that the distribution of the drug throughout the stomach is instantaneous?

Part I: A One Compartment Model

In finding a solution to our problem, we shall begin with a brief discussion of a one-compartment model (representing the stomach).

Assuming that the absorption of the drug by the stomach is instantaneous, and assuming that the rate of elimination is proportional to the amount of drug present, we propose the following equation:

$$\frac{dA}{dt} = -Z * A,$$

where A denotes the concentration in the stomach and Z is the elimination constant of the drug in the stomach. (Note that $\frac{dA}{dt}$ is negative, as it should be, since the drug is being removed from the body).

Based on the assumption that the drug is instantaneously absorbed into the stomach, and assuming that the initial dose, C, occurs at time t = 0, we must solve the problem:

$$\frac{dA}{dt} = -Z * A, \quad A(0) = C.$$

Solving by separation of variables yields:

$$A(t) = X * \exp(-Z * t).$$

and the condition A(0) = C implies that

$$X = C.$$

Thus,

$$A(t) = C * \exp(-Z * t).$$

repeated doses

We will now consider what happens when the same dosage of the drug is administered again. Let V<1> denote the residual that remains after a time interval of length T has passed. According to our model, the residual is:

$$V<1> = C * \exp(-Z * T).$$

We then administer a second dose (at time t = T). The concentration jumps to:

$$\begin{aligned} A<1> &= V<1> + C \\ &= C + C * \exp(-Z * T) \\ &= C * (1 + \exp(-Z * T)). \end{aligned}$$

After a second time interval of length T, the residual is:

$$\begin{aligned} V<2> &= A<1> * \exp(-Z * T) \\ &= C * \exp(-Z * T) * (1 + \exp(-Z * T)) \\ &= C * \exp(-Z * T) + (C * \exp(-2Z * T) \end{aligned}$$

At t = 2T, administering a third dose gives:

$$A<2> = C + V<2>$$

$$= C + C * \exp(-Z * T) + C * \exp(-2Z * T)$$

$$= C * [1 + \exp(-Z * T) + \exp(-2Z * T)]$$

By mathematical induction, we see that

$$V\langle n\rangle = C * \exp(-ZT) * [1 + \exp(-ZT) + \ldots + \exp(-(n-1)ZT))]$$

and

$$A\langle n\rangle = C * [1 + \exp(-ZT) + \ldots + \exp(-nZT)].$$

We know that $1 + r^{2} + \ldots + r^{n-1} = \frac{1-r^{n}}{1-r}$.

Substitution into this formula gives:

$$V\langle n\rangle = \frac{C * \exp(-ZT) * [1 - \exp(-nZT)]}{1 - \exp(-KaT)}$$

and

$$A\langle n\rangle = \frac{C * [1 - \exp(-(n+1)ZT)]}{1 - \exp(-ZT)}.$$

If we are to administer the dosage indefinitely, at time intervals of length T, the limiting value of the residuals can be found by taking the limit of V<n> as n --> oo:

$$V = \lim_{n \to \infty} V\langle n\rangle = \lim_{n \to \infty} \frac{C * \exp(-ZT) * [1 - \exp(-nZT)]}{1 - \exp(-ZT)}$$

$$= \frac{C * \exp(-ZT)}{1 - \exp(-ZT)},$$

or if you prefer:

$$V = \frac{C}{\exp(ZT) - 1}. \qquad (1)$$

If the desired dosage level is to approach the highest safe level in the stomach, S, then we want A<n-1> to approach S as n approaches oo.

$$S = \lim_{n \to \infty} A_{n-1}$$

$$= \lim_{n \to \infty} (C + V_{n-1})$$

$$= C + V$$

Could actually solve for T.

To examine the residual concentrations, V, for different intervals T between doses, let us look at V compared to C, the change in concentration due to each dose. To compare, write equation (1) as:

$$\frac{V}{C} = \frac{1}{\exp(ZT) - 1}.$$

Before we proceed, it should be noted that since V_n is obtained by adding a positive quantity $[C * \exp(-nZT)]$, and since V_1 is positive, V_n is also positive. It should also be noted that V_n is less than V.

Now, if T is large,

$$\frac{V}{C} = \frac{1}{\exp(ZT) - 1} \quad \text{--> } 0,$$

and so the residual concentration is almost zero. However, If T is small, so that exp(ZT) is not much larger than 1, $\frac{V}{C}$ is a good deal larger than 1.

As V_n becomes larger, there is no appreciable difference between the concentration in the blood and the rise in concentration C due to each dose. When we have this condition (loss = gain), the concentration will fluctuate between V + C (at the start of each period) and V (at the end of each period).

Some diagrams would be helpful.

Part II: A Two-Compartment Model

We shall now extend our discussion to a two-compartment model. In this model we continue to assume that the drug is instantaneously ~~absorbed into~~ distributed throughout the stomach (compartment 1). However, we do not make the assumption that the drug is absorbed instantaneously into the bloodstream. Hence, we incorporate a second, slow equilibrating compartment into our original model.

Let B denote the concentration of drug in the bloodstream, and, once again, let A denote the concentration of drug in the stomach. As in the one-compartment model, the rate of elimination of the drug in the stomach is proportional to the amount of drug present, and so the change in concentration of drug in the stomach is again given by:

$$\frac{dA}{dt} = -Z * A,$$

where Z again is the elimination constant for the drug in the stomach.

In the bloodstream, the change of drug concentration is dependent not only on the rate of elimination from the bloodstream, but also on the rate of absorption of drug from

the stomach. Assuming that the rate of elimination of the drug from the blood is proportional to the amount present, the equation for the change in the concentration in the stomach is given by:

$$\frac{dB}{dt} = (Z * A) - (K * B), \qquad (2)$$

where K is the elimination constant for the drug in the bloodstream.

Substituting our value for A (calculated in part I) into equation (2) gives:

$$\frac{dB}{dt} = Z * C * \exp(-Zt) - KB$$

or

$$\frac{dB}{dt} + KB = Z * C * \exp(-Zt)$$

This is simply a first order differential eqaution which can be solved by the use of integrating factors:

$$\frac{d}{dt}[\exp(Kt) * B(t)] = Z * C * \exp((K-Z)t)$$

$$\exp(Kt) * B(t) = Z * C \int \exp((K-Z)t)\, dt$$

$$= \frac{Z * C}{K - Z} * \exp((K-Z)t) + W$$

Thus,

$$B(t) = \frac{Z * C}{K - Z} * \exp(-Zt) + W * \exp(-Kt) \qquad (3)$$

We assume that when the initial dose is administered, at time t = 0, none of the drug is instantly absorbed into the bloodstream; ie. B(0) = 0. Applying this I.C. to equation (3):

$$B(0) = \frac{Z * C}{K - Z} + W = 0 \quad ==> W = \frac{-Z * C}{K - Z}$$

So, $$B(t) = \frac{Z * C}{K - Z} * \exp(-Zt) - \frac{Z * C}{K - Z} * \exp(-Kt)$$

or equivalently,

$$B(t) = \frac{Z * C}{Z - K} * [\exp(-Kt) - \exp(-Zt)]$$

We will assume that $Z > K$. To justify this assumption, we note that if the rate of absorption in the bloodstream is less than the rate of elimination, then there would never be an appreciable amount of drug in the bloodstream. As soon as some of the drug was absorbed, it would almost immediately be eliminated. In addition, there is sufficient experimental evidence to justify our claim.

Now, consider the residual of the drug in the bloodstream after a time interval of length T has passed after the initial dose of C (denote this residual R<1>). According to our model, the residual is:

$$R<1> = \frac{Z * C}{Z - K} * [\exp(-KT) - \exp(-ZT)]$$

If we administer a second dose of concentration C (at time t = T), the concentration in the bloodstream becomes:

$$B<1> = R<1> + C$$

$$= \frac{Z * C}{Z - K} * [\exp(-KT) - \exp(-ZT)] + C$$

$$= C * [1 + \frac{Z}{Z - K} * (\exp(-KT) - \exp(-ZT))]$$

For notational convenience, we shall, for the time being, let

$$Y = \frac{Z}{Z - K} * [\exp(-KT) - \exp(-ZT)]$$

After another time interval of length T has passed, the residual is:

$$R\langle 2\rangle = Y * R\langle 1\rangle$$
$$= Y * C * [1 + Y]$$

By mathematical induction, it can be shown that, indeed, the residual after time t = nT is given by:

$$R\langle n\rangle = C * Y * [1 + Y + \ldots + Y^{n-1}]$$
$$= C * Y * \frac{[1 - Y^{n}]}{[1 - Y]}$$

for n = 1, 2, 3, ...

That is,

$$R\langle n\rangle = C * \left[\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right] * \frac{\left[1 - \left(\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right)^{n}\right]}{1 - \left[\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right]}$$

Let us now examine this residual value:

$$R\langle n\rangle = C * \left[\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right] * \frac{\left[1 - \left(\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right)^{n}\right]}{1 - \left[\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right]}$$

Since Z > K, exp(-KT) > exp(-ZT), and so

$$\exp(-KT) - \exp(-ZT) > 0.$$

And since exp(m) $\geq$ 1 for any m $\geq$ 0, exp(-m) $\leq$ 1.

So, exp(-KT) < 1, and exp(-ZT) < 1.

Thus, $0 < \exp(-KT) - \exp(-ZT) < 1$, and since $Z > K$,

$\frac{Z}{Z - K} > 0$.

To find the limiting value of the residual, take the limit as $n \to \infty$ of $R\langle n \rangle$.

As $n \to \infty$, since $0 < \exp(-KT) - \exp(-ZT) < 1$,

$(\exp(-KT) - \exp(-ZT))^{n} \to 0$.

Since $\frac{Z}{Z - K} > 1$, $\left\{\frac{Z}{Z - K}\right\}^{n} \to \infty$

However, $[\exp(-KT) - \exp(-ZT)]^{n} \to 0$ faster than

$\left\{\frac{Z}{Z - K}\right\}^{n} \to \infty$, so the product

$$\left[\frac{Z}{Z - K}(\exp(-KT) - \exp(-ZT))\right]^{n} \to 0 \quad \text{as} \quad n \to \infty.$$

Hence,

$$R = \lim_{n \to \infty} R\langle n \rangle$$

$$= C * \left[\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right] * \frac{\left[1 - \left(\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right)^{n}\right]}{1 - \left[\frac{Z}{Z-K}(e^{-KT} - e^{-ZT})\right]}$$

or if you prefer,

$$R = \frac{C}{\frac{Z - K}{Z * (\exp(-KT) - \exp(-ZT)} - 1}.$$

DETERMINING DOSE SCHEDULE IN THE TWO-COMPARTMENT MODEL

We would like to know what happens to residual concentrations, R, for different intervals T between doses. We shall hence look at the change in concentration due to each dose; ie. look at R compared with C.

Rewrite our equation for R as

$$\frac{R}{C} = \frac{Z}{Z - K} * \frac{[\exp(-KT) - \exp(-ZT)]}{[1 - \frac{Z}{Z - K}(\exp(-KT) - \exp(-ZT))]}$$

As T --> oo, exp(-KT) --> 0

exp(-ZT) --> 0, and so

exp(-KT) - exp(-ZT) --> 0

(since Z > K),

so, $\frac{R}{C}$ --> 0.

Therefore, for large T, $\frac{R}{C} \simeq 0$

Since R<1> is a positive number and since each subsequent R<n> is obtained by adding a positive quantity to the preceeding residual value, we know that R<n> > 0. It can also clearly be seen that R<n> < R.

If the time interval T is long enough to make exp(-KT) - exp(-ZT) --> 0, then the residual is almost 0.

However, if T is short, we can see that:

$$\frac{R}{C} = \frac{Z}{Z - K} * \frac{[\exp(-KT) - \exp(-ZT)]}{[1 - \frac{Z}{Z - K}(\exp(-KT) - \exp(-ZT))]} > 1.$$

As R<n> becomes larger, the concentration in the blood,

B<n-1>, after each dose, becomes larger. [Note: The loss after each dose increases with larger B<n> (since elimination is proportional to the amount of drug in the blood)].

Ultimately, the drop in concentration becomes very close to the rise in concentration C due to each dose. When we have this condition of loss = gain, the concentration will oscillate between R + C, and R.

Let us look at the therapeutic range of the drug. Let L denote the minimum effective level of the drug in the bloodstream, and H denote the toxicity level. We should note here that in practice, the levels H and L given for a particular drug are generally "safe" levels. That is to say, if the concentration rises slightly above H, it will not be toxic, and if it falls slightly below L it will still be effective.

Ignoring, for the time being, the possibility of a toxicity level in the stomach, we wish to maximize the time between doses. In our attempt to do this, we set

$$C = H - L$$

OK

and

$$R = L.$$

It would have been more useful to set $\lim_{n \to \infty} (B_n)_{max} = H$

Substituting these values into the equation for R gives:

$$L = \frac{H - L}{\frac{Z - K}{Z * [\exp(-KT) - \exp(-ZT)]} - 1}$$

We shall attempt to solve for T:

$$\left[\left(\frac{Z - K}{Z}\right)\left(\exp(-KT) - \exp(-ZT)\right)^{-1} - 1\right] * L = H - L$$

$$\left(\frac{Z - K}{Z}\right)\left(\exp(-KT) - \exp(-ZT)\right)^{-1} = \frac{H}{L}$$

$$\left[\exp(-KT) - \exp(-ZT)\right]^{-1} = \frac{Z}{Z - K} * \frac{H}{L}$$

$$\exp(-KT) - \exp(-ZT) = \frac{Z - K}{Z} * \frac{L}{H} \qquad (4)$$

It is plain to see that we cannot solve this equation for T. (analytically)

As one option of finding T, if the parameters for a particular drug are known, the equation can be solved by one of numerous numerical techniques.

As another option, could we assume that $\exp(-ZT) \simeq 0$? Let us try.

Since $Z > K$, $\exp(-ZT) < \exp(-KT)$. In addition, since the absorption of the drug by the bloodstream will end before the elimination of it, at some point $\exp(-ZT) \simeq 0$, while $\exp(-KT)$ will still have a value. So perhaps our assumption is not quite as unreasonable as it may originally have seemed.

Taking $\exp(-ZT) = 0$, equation (4) becomes

$$\frac{L}{H}\left[\frac{Z - K}{Z}\right] = \exp(-KT)$$

$$\ln\left[\frac{L}{H}\left(\frac{Z - K}{Z}\right)\right] = -KT$$

So, $$T = \ln \left\{ \frac{H}{L} \left(\frac{Z}{Z - K} \right) \right\}^{(1/K)}$$

We now consider the problem of prescribing dosage such that the concentration in the stomach remains below the toxicity level, and the concentration in the blood remains in the therapeutic range.

Supposed first that the level of toxicity in the stomach is greater than the level of toxicity in the bloodstream. ie. $L < H < S$.

It is clear that for this problem, we may simply adopt the preceeding discussion, in which $C = H - L$ and

$$T = \ln \left\{ \frac{H}{L} \left(\frac{Z}{Z - K} \right) \right\}^{(1/K)}.$$

This is due to the fact that we have assumed that $Z > K$. Since the stomach eliminates the drug more quickly than the blood, if we stay below the toxicity level H in the blood, we will naturally remain below level H in the stomach, and hence we will remain below the stomach's toxicity level S as well.

We will consider the cases in which $L < S < H$ and $S < L < H$ together. In order to maximize the time interval, we want to push the concentration A up to the highest level possible, in attempt to keep B above L. We want the drug to be administered at such time intervals and at such a dosage level that the concentration A in the stomach reaches its maximum value smaller than S and then oscillates between S and the residual value in the stomach, V, and such that the concentration B in the blood will reach its maximum level smaller than H and remain above L while it essentially fluctuates between H and its residual level R (where $R > L$).

Before we begin, we will make the assumption that all of the drug goes into the bloodstream from the stomach, and none of it is broken down by enzymatic or other processes before it is absorbed into the bloodstream. (This assumption is made because, depending on the drug, the enzymatic or other processes may break down the drug at rates which are not directly proportional to the amount of drug present).

OK

If the desired drug dosage level is to approach the highest safe level in the stomach, then we want

$$A\langle n-1\rangle \dashrightarrow S \quad \text{as} \quad n \dashrightarrow \infty.$$

actually want $\lim_{n\to\infty} A\langle n-1\rangle \leq S$

From our discussion of the one-compartment model,

$$V = \frac{C}{\exp(ZT) - 1} \qquad (5)$$

We want the residual in the stomach to be $V = S - C$.

Substitution into equation (5) gives

$$S - C = \frac{C}{\exp(ZT) - 1}$$

In the bloodstream, (from earlier discussion),

$$R = \frac{C}{\frac{Z - K}{Z(\exp(-KT) - \exp(-ZT))} - 1} \qquad (6)$$

erroneous!

We want $R = H - C$.

Substituting this value into equation (6) gives:

$$H - C = \frac{C}{\frac{Z - K}{Z(\exp(-KT) - \exp(-ZT))} - 1}.$$

We now have two equations in two unknowns. Theoretically, we can solve. Really, we cannot.

Rewriting equation (5) for C:

$$S - C = \frac{C}{\exp(ZT) - 1}$$

$$0 = S * \exp(ZT) - S - C * \exp(ZT)$$

$$C = S * (1 - \exp(-ZT)) \qquad (7)$$

Rewriting equation (6) for C:

$$C = (H - C) * \left[\frac{Z - K}{Z * (\exp(-KT) - \exp(-ZT))} - 1\right]$$

$$C = H - \frac{Z * [\exp(-KT) - \exp(-ZT)]}{Z - K} * H$$

Setting these equal to one another, we get

$$H - \frac{Z * [\exp(-KT) - \exp(-ZT)]}{Z - K} * H = S * (1 - \exp(-ZT)) \qquad (8)$$

Again, the difficulty in solving for T is evident.

Adopting the same reasoning as earlier, we let $\exp(-ZT) = 0$.

Then equation (8) becomes

$$S = H - \frac{H * Z * \exp(-KT)}{Z - K}$$

$$\exp(-KT) = \frac{HZ - HK - SZ + SK}{HZ}$$

$$-KT = \ln\left\{\frac{Z - K}{Z} + \frac{S * (K - Z)}{HZ}\right\}$$

$$T = \ln\left\{\frac{(Z - K)}{Z} + \frac{S * (K - Z)}{HZ}\right\}^{(-1/K)}$$

Substitution into equation (7) yields

$$C = S * \left[1 - \exp\left(-Z * \left\{\frac{Z - K}{Z} + \frac{S * (K - Z)}{HZ}\right\}^{(-1/K)}\right)\right]$$

Hence we would say to prescribe a dosage of

$$C = S * \left[1 - \exp\left(-Z * \left\{\frac{Z - K}{Z} + \frac{S * (K - Z)}{HZ}\right\}^{(-1/K)}\right)\right]$$

every

$$T = \ln\left\{\frac{Z - K}{Z} + \frac{S * (K - Z)}{HZ}\right\}^{(-1/K)}$$

hours.

There are several concerns to be had with this particular model.

To begin with, if Z is not very much larger than K, it may be fairly unreasonable to assume that exp(-ZT) = 0.

We have also assumed that all of the drug goes directly into the bloodstream, and none of it is broken down by enzymatic or other processes, or absorbed by the lymphatic system. Depending on how a particular drug reacts in the body, we may have to increase the levels of drug in the first compartment in order to compensate for the loss of drug going into the bloodstream. In addition, these reactions may or may not break down the drug at rates proportional to the amount of drug present. If not, other functions describing the action may have to be introduced into the model.

Thirdly, we have not dealt at all with the effects of body weight or blood volume. Fluctuations of these factors are certain to discredit our model to some extent.

Also, we have made the assumption that the concentration level of the drug is the critical factor in determining the effect of a drug. It is indeed possible that drugs exist for which concentration is not the determining factor of effectiveness. In studying the action of these drugs, our model will certainly fail.

Lastly, while our model will keep concentration levels in the bloodstream and in the stomach below toxicity levels, it fails to ensure that the concentration level in the bloodstream remains above the minimum effective level.

To improve upon our model, we might wish to consider incorporating a term which deals with the relationship between the weight of a patient and his/her blood volume (affecting the concentration of the drug in the bloodstream).

good

Also, it would likely be a good idea to think of a way to modify our model in such a way that we are able to ensure that the concentration of a drug in the bloodstream stays above the minimum effective level, while continuing to remain below the toxicity levels in the stomach and in the bloodstream. However, as of yet, I, personally, have not discovered a way in which that can be done.

good

Lastly, we may wish to look at functions which describe the rates at which different processes in the body break down a drug, and incorporate these functions into our model.

Bibliography

Blanck, J. Kinetics of Drug Action. Berlin; New York: Springer-Verlag, 1977.

Bourne, David W. Mathematical Modelling of Pharmaceutical Data with Examples from Pharmacokinetics. Oklahoma City, OK: University of Oklahoma, College of Pharmacy, 1991.

Burghes, David. Applying Mathematics: A Course in Mathematical Modelling. Chichester, West sussex: E. Horwood; New York: Distributor, North and South America, Halsted Press, 1982.

Giordano, Frank R. A First Course in Mathematical Modelling. Monterey, CA: Brooks/Cole Publishing Company, c1985.

Shargel, Leon. Applied Biopharmaceutics and Pharmacokinetics. Norwalk, Connecticut: Appleton Century Crofts.

Winter, Michael E. Basic Clinical Pharmacokinetics. San Francisco, CA: Applied Therapeutics, Inc.