fundamentals of clinical pharmacokinetics

by JOHN G WAGNER
Phm.B., B.S.P., B.A., Ph.D

Professor of Pharmacy, College of Pharmacy, and Staff Member of the Upjohn Center for Clinical Pharmacology, Medical School, The University of Michigan, Ann Arbor, Michigan 48104, U.S.A.

FIRST EDITION 1975

Library of Congress Catalog Number 75-5443
ISBN 0-914678-20-4

$37.50

Printed in the United States of America by The Hamilton Press, Inc., Hamilton, Illinois 62341

a single dose the concentration initially would be equal to C_0. The value of ϵ in column 2 is the ratio of the dosage interval to the half-life. When ϵ is small, the doses are given close together, and when ϵ is large, the doses are given far apart. Since, even when $\epsilon = 5$, $C_\infty^{max} = 1.032\, C_0$, then for all dosage regimens listed in table 3-1, drug accumulation exists according to the concentration build-up concept. However, in the last column of table 3-1, are listed the drug accumulation indices calculated by means of equation 3-2. Only when $\epsilon > 1$ is $R_A > 1$. Hence, by the "amount criterion" drug accumulation only occurs for this model when the dosage interval is less than 1.443 times the half-life of elimination. Dosage regimen calculations can also be made then based on: (1) prediction of average amounts of drug in the "body" or a particular compartment (such as the central compartment of the two compartment open model), or (2) prediction that, say, a patient with poor renal function will have the same average steady state amount of drug in the body as a patient with normal renal function. Both approaches are considered in later sections.

There is a considerable difference in the levels of sophistication which can be applied to dosage regimen calculations. The levels vary all the way from calculations which can be performed quickly by the human brain, to those which can be performed readily with a pencil and paper, to those which can be performed readily with an electronic calculator, and finally to those which require the use of a large digital computer. All of these types will be considered in subsequent sections.

According to Krüger-Thiemer,[3] a dosage regimen consists of the following quantities: (a) a dosage interval (τ); (b) a dose ratio = initial (loading) dose/maintenance dose; and (c) the maintenance dose. One criterion of acceptance of a dosage regimen is the ratio of the maximum to the minimum concentration of drug in plasma or the maximum and minimum amounts of drug in the "body" at steady state compared with the average amount.

3.2 SIMPLE DOSAGE REGIMEN CALCULATIONS

3.2.1 Based on the Elimination Half-Life. The half-life of elimination of a drug (or the corresponding first order rate constant) is the most important pharmacokinetic parameter for dosage regimen evaluation. This is the half-life estimated from *terminal* blood (serum or plasma) concentration

If nothing else is known about a drug except its half-life of elimination, then the following dosage regimen "rule" is useful: Make the dosage interval equal to the half-life of elimination, make the loading or initial dose equal to twice the maintenance dose, and make the maintenance dose equal to the minimum amount of drug in the "body" necessary for effective therapy.[6] This "rule" is based

condition that $\tau = t_{1/2}$ and $\epsilon = 1$, the ratio $C_\infty^{max}/C_\infty^{min} = 2$, and the drug accumulation index, R_A, is equal to 1.443 (or $1/\ln 2$) = 1/0.693). Interestingly enough, clinical experience and practical reasons have lead physicians in the past to use this rule without knowing its theoretical foundation.[6]

3.2.2 Based on *Average* Steady-State Blood Levels. The equation of Wagner *et al.*,[12] shown as equation 3-4, is most useful in dosage regimen calculations.

$$\bar{C}_\infty = \frac{FD}{VK\tau} = \frac{FD}{\bar{V}_{Cl}\,\tau} \qquad \text{Eq. (3-4)}$$

In equation 3-4, $\bar{C}_\infty$ is the *average* (*not* the minimum) steady-state whole blood, plasma or serum concentration, F is the fraction of the dose which is absorbed, D is the dose, V is the volume of distribution, K is the elimination rate constant, τ is the dosage interval, and $\bar{V}_{Cl}$ is the blood (serum or plasma) clearance (sometimes called the "body" clearance). The middle term of equation 3-4 indicates how the equation was originally written,[12] but the term on the far right is a more generalized way of writing the equation. Note that $\bar{C}_\infty$ is defined by equation 3-5, and is an application of the central limit theorem of calculus. As a result of the equivalency of areas shown in figure 3-1, and

$$\bar{C}_\infty = \frac{A_0^\tau}{\tau} = \frac{\int_{t_1}^{t_2} C_\infty(t)dt}{\tau}$$

$$\text{where } \tau = t_2 - t_1 \qquad \text{Eq. (3-5)}$$

equations 3-4 and 3-5, we may also write equation 3-6. If concentrations

$$A_0^\infty = A_0^\tau = \frac{FD}{\bar{V}_{Cl}} \qquad \text{Eq. (3-6)}$$

are measured at a sufficient number of different times following oral or intramuscular administration of a single dose of drug to define A_0^∞, or a sufficient number of different times after a given dose at steady-state to define A_0^τ, (*i.e.* $F/\bar{V}_{Cl} = A_0^\infty/D = A_0^\tau/D$). After single doses the area A_0^∞ may be estimated by means of equations 10-2 through 10-6 given in chapter 10.

It is really more desirable to estimate the value of $F/\bar{V}_{Cl}$ by measuring plasma concentrations after several different doses of the drug and plotting A_0^∞ *versus* D. It is also more desirable to express the dose, D, in mg/kg body weight so that the abscissa scale constitutes a distribution for each fixed D value. In this case, least squares regression techniques applicable to a bivariate normal distribution may be used to calculate the regression line. The slope of the regresion line for such a plot

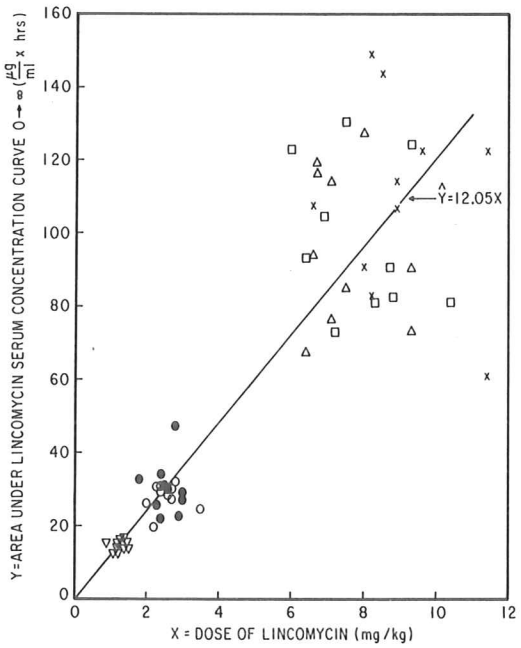

Fig. 3-2. Plot of A_0^∞ under single dose serum concentration curve *versus* mg/kg dose of lincomycin hydrochloride following intramuscular administration. Each point corresponds to a different subject. The three arrays correspond to doses of 100, 200 and 600 mg. of the antibiotic. The slope of 12.05 represents a suitable value of F/V_{cl} to use for future predictions. From Wagner, J. G.: Use of Computers in Pharmacokinetics. *Clin. Pharmacol. Ther. 8:*201–218 (1967). (Reprinted with the permission of the publisher.)

is a sort of mean value of $F/\bar{V}_{Cl}$ for the population and can be used to make predictions as indicated below. An example of such a plot is shown in figure 3-2 where the area under the serum concentration curve following intramuscular administration of lincomycin hydrochloride is plotted against the mg/kg dose of the antibiotic.[14] The regression is highly significant ($P < .001$). The $100r^2$ value is 74 percent, indicating that 74 percent of the variability of the area is accounted for by differences in the mg/kg doses. Since the intercept was not significantly different from zero the least squares line forced through the origin was calculated (*i.e.*, $\hat{y} = 12.05x$ where $\hat{y}$ is the estimated value of A_0^∞ and x is the mg/kg dose) and is the line drawn in the figure. The "zero intercept" is indicated by the theory embodied in equation 3-6. Thus, in this case, $F/\bar{V}_{Cl} = 12.05$ kg/L. (The units were obtained as follows: $\frac{\mu g/ml}{mg/kg} = \frac{\mu g}{ml} \times \frac{kg}{10^3\,\mu g} = kg/L$). A typical dosage regimen question which may be answered with such information is indicated below.

Question: What would be the expected average steady state serum concentration if a 60 kg person were administered 200 mg of lincomycin hydrochloride every 8 hours?

Answer:
$$\bar{C}_\infty = \left(\frac{F}{\bar{V}_{Cl}}\right)\left(\frac{D}{\tau}\right)$$
$$= \left(12.05\right)\left(\frac{200/60}{8}\right) = 5\,\mu g/ml$$

It should be noted that the answer was obtained by simply separating the factors in the right hand side of equation 3-4, and remembering that when $F/\bar{V}_{Cl}$ has units of kg/L, D must be in mg/kg, and $\bar{C}_\infty$ will have dimensions of $\mu g/ml$. It must also be remembered that this answer was obtained using a least squares slope value of 12.05 and because of the scatter of points about the line in figure 3-2 the answer of 5 $\mu g/ml$ is a type of "average" or reasonable estimates of the range of expected $\bar{C}_\infty$ values. The slope of the least squares line not forced through the origin was 11.42 with the 95 percent confidence interval of 9.64 to 13.4. If the latter values are substituted for $F/\bar{V}_{Cl}$ in the above equation instead of 12.05, one obtains 4.0 and 5.6 $\mu g/ml$, respectively.

It should be noted that application of equations 3-4 through 3-6 above are independent of whether the one or two compartment open model applies to the data being evaluated since the mean clearance is used. In terms of the one compartment open model, the mean clearance is equal to VK, but for the two compartment open model, the mean clearance is equal to V_1k_{el} or $V_{d\ area}\beta$.

Another type of question which may be answered with the above information is indicated below.

Question: What dosage could be employed for a 50 kg woman to provide an average steady state level of lincomycin hydrochloride of 3 $\mu g/ml$ if the drug is administered intramuscularly?

Answer: First rearrange equation 3-4 and substitute the known values as follows:

$$\frac{D}{\tau} = (\bar{C}_\infty)(1/\bar{V}_{Cl}) = (3)(1/12.05) \simeq 1/4$$

Hence, any combination of D and τ which will give a ratio of D/τ equal to 1/4 will be an answer. You have to remember, again, that since the clearance has units of L/kg, and its reciprocal, kg/L, that D must be in units of mg/kg. One answer is $D = 100$ mg/50 kg $= 2$ mg/kg and $\tau = 8$ hours since $D/\tau = 3/12 = 1/4$. Such answers are "ball-park" answers and very useful in the clinical situation.

Orr *et al.*[13] published a method for estimating individual drug-dosage regimens, but what they call "occupancy/ml" is exactly equivalent to $F/\bar{V}_{Cl} = A_0^\infty/D = A_0^7/D$ and really does not require a new name. Their method is equivalent to that discussed above

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.