Area Under Blood Level versus *Time Curves at Steady State for Daily Dosing at Unequal Dosing Intervals*

Most problems that deal with steady-state drug blood levels for multiple dosing assume that doses are administered at equal intervals during a 24-h period, *e.g.*, four tablets every 6 h or three tablets every 8 h. For the one-compartment model, for example, under these circumstances, it is well known that at steady state, the area under the blood level *versus* time curve (AUC) during a 24-h period is (Total Daily Dose)/k_e, where k_e is the first-order elimination rate constant. A question of interest is the value of the AUC at steady state when the doses are not given at equal intervals but where the dosage regimen is regular over some period, in particular, 24 h. This is the more realistic situation, *e.g.*, one tablet at 8 a.m., noon, 4 p.m. and 8 p.m. The following simple proof shows that for the above conditions, at a constant total daily dosage, the AUC at steady state is independent of the dosage time intervals for any input function. The following differential equation describes a one-compartment model, in general:

$$dX_c/dt = f[X(t)] - k_e X_c \qquad \text{(Eq. 1)}$$

where $f[X(t)]$ is in the input function (absorption) and $k_e X_c$ represents first-order elimination.

If $X(t)$ is periodic, so is $f[X(t)]$. (Note that the 24-h dosing schedule does not change.) At steady state, X_c will be periodic with the same period. Here, the period is 24 h for a regular 24-h dosing regimen. Integrating Eq. 1 from t_0 to $t_0 + T$:

$$\int_{t_0}^{t_0+T} (dX_c/dt)dt = \int_{t_0}^{t_0+T} f[X(t)]dt - k_e \int_{t_0}^{t_0+T} X_c dt \qquad \text{(Eq. 2)}$$

$X_c(t_0 + T) - X_c(t_0)$ = (Total dose from t_0 to $t_0 + T$) $- k_e$(AUC) from t_0 to $t_0 + T$. If T is the period (24 h in this example): $X_c(t_0 + T) = X_c(t_0)$, and (Total 24-h dose) = $X_{24} = k_e(\text{AUC})_{24}$, or AUC = $(X_{24})/k_e$. Therefore, the AUC over a 24-h period is dependent on the total dose given during the 24 h, and independent of how it is administered providing that the regimen is periodic.

Using a similar argument, it can be shown that this conclusion holds also for higher-compartment models with any input function, if dosing is periodic during a specific interval.

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Secret Formulations from the Industry's Perspective

As an individual who has worked in industry some 10 years now, I was most disturbed at some of the comments and implications in Dr. Feldmann's editorial[1] "Putting an End to Secret Formulations." First of all, I take strong exception to his assertion that the reason for industry's reluctance to disclose our formulations is simply to create an illusion of mystery. Those of us in the formulation development end of the business feel very strongly that protection of our formulations is indeed an important issue with respect to competition. While it may be true that another firm could "crack" our formulas if they were willing to invest enough analytical effort (although I question whether it is only a "moderate challenge" for the analyst to completely quantitate any given formula), the very fact that such an effort would have to be made presents a significant barrier to our competition. We have no obligation or desire to give away the substantial investment we have made in developing our formulas without compelling justification. To do otherwise makes no more sense than for GM to provide blueprints of their latest design innovations to Ford and Chrysler on request.

Dr. Feldmann alludes several times to the possibility that (perish the thought!) industry's primary motivation might be to make a profit. Obviously, it *is* the goal of industry as well as the rest of the drug distribution system to make a profit (without which there would be no industry as we know it in the free world, no viable private sector, no pharmaceutical research, and, very likely, no funding for APhA, APS, or this Journal) and we have nothing to apologize for this. A profit is not at all necessarily inconsistent with high ethical standards and a genuine concern for mankind, both of which the U.S. pharmaceutical industry has repeatedly demonstrated. Dr. Feldmann provides no basis for his emotional accusation that somehow industry has been trading "human lives" for profits by not labeling our products with the entire listing of ingredients. Although I am personally unaware of any documented evidence that formulation excipients are causing significant medical problems, there may indeed be a persuasive justification for this information being made available due to substantive safety issues. However, such arguments should be factually presented and weighed against legitimate commercial concerns, not couched in emotional tirades based on highly questionable assumptions.

Beyond these specific concerns, I am disturbed at the hostile tone of this editorial towards industry. I would hope that the Association has matured beyond the simplistic big-business-always-wears-black-hats mentality that was so prevalent in our society in the late 60's and early 70's. The pharmaceutical industry is certainly not above criticism, but the consistently negative portrayals of industry practices and ethics in such editorials are not only inaccurate in my opinion but can hardly be called objective. Such apparent bias and the inevitable polarization it encourages seems highly inappropriate for an organization which claims to represent all of pharmacy.

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[1] E. G. Feldmann, *J. Pharm. Sci.*, **73**, 577 (1984).

Author's Response

I wish to assure Dr. Mendenhall, as well as all our readers, that no "hostile tone" toward industry was intended in my editorial that he cited. Certainly, we can disagree regarding specific policies and still maintain cordial working relationships and feelings of mutual respect.

In fact, the matter of maintaining secrecy regarding drug product ingredients has been an issue of considerable difference of opinion *within* the pharmaceutical industry. In my discussions with industry colleagues over the past several years, many of them have favored full ingredient disclosure for precisely the reasons mentioned in the editorial. And, at the same time, many other industry colleagues felt contrary-minded.

Indeed, it is my understanding that such differences in viewpoint existed not only among industry scientists, but also between various firms. This had prevented PMA as an organization from supporting the concept of complete ingredient disclosure. However, we were happy to learn that 2 months following our editorial, at its meeting on July 9, the PMA Board of Directors voted that its member companies will voluntarily list inactive ingredients in product labeling. According to the PMA announcement, this action "is intended to provide added safety for persons sensitive to an inactive ingredient."

As to the two "specific concerns" voiced by Dr. Mendenhall: (*a*) our readers can make their own judgments as to the relative difficulty that a qualified analytical laboratory would currently encounter in determining the qualitative composition of a typical drug product, and (*b*) each of us in his or her own conscience needs to reconcile the degree that our profit motives will be balanced against our humanitarian and societal concerns.

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