The Influence of the Shape of the Plasma Drug Concentration Profile upon the Pharmacological Effect

Mark Knowles[1] and Stephen S. Hwang[2,3]

Received July 21, 1994; accepted August 5, 1994

KEY WORDS: drug concentration; plasma; concentration–effect relationship; constant infusion; bolus administration.

INTRODUCTION

This work examines the relationship between the shape of a plasma drug concentration profile and the time integrated drug effect (1). The results depend on the shape (linear, concave, convex or sigmoidal) of the concentration-effect curve. Motivation is provided by the observations of differences in the observed effect between the constant infusion and the bolus administration of the same dose of bumetanide (2), furosemide (3,4) ketorolac (5), cefazolin (6) and valproic acid (7). The constant infusion yields more effect than the bolus administration in most but not all the quoted examples. Thus, it is not possible to reach a general conclusion from these empirical observations.

THEORY

Assume that the effect of the drug is directly related to the plasma drug concentration C, and that $E(C)$ is the effect of the drug when the plasma drug concentration is equal to C. The objective of this analysis is to evaluate how the shape of the plasma drug concentration profile $\{C(t): 0 \leq t \leq \tau\}$, on the dosing interval $[0, \tau]$, influences the time integrated effect, E_{total}, when the area under the plasma drug concentration profile, AUC, is fixed at an arbitrary value.

$$E_{total} = \int_0^\tau E(C(t))\, dt \tag{1}$$

Case 1. Linear Concentration-Effect Relationship. In this case, the effect integrated over time is directly proportional to the integral of the plasma concentration curve (AUC). Therefore, E_{total} is the same for all plasma drug concentration profiles having the same AUC.

Case 2. Concave Concentration-Effect Relationship. A mathematical relationship known as Jensen's Inequality (8) states that if E is any concave function and $C(t)$ is a function defined on $[0, \tau]$, then

$$\int_0^\tau E(C(t))dt \leq \tau * E\left(\frac{1}{\tau}\int_0^\tau C(t)\, dt\right). \tag{2}$$

In other words, eq. 2 states that the integrated effect for any concentration profile is equal to or less than the integrated effect for the flat profile with $C = C_{avg}$. We are interested in the case where E represents the effect of a drug and $\{C(t): 0 \leq t \leq \tau\}$ is a plasma concentration profile over the dosing interval $[0, \tau]$. We wish to maximize the left-hand side of eq. 2, over all concentration profiles having a given AUC *value*. It is easy to see that if we take $C(t) \equiv AUC/\tau$ to be constant, then the upper bound given by the right-hand side of eq. 2 is achieved. Any other profile will produce a smaller integrated effect. For example, the E_{max} model defined by

$$E(C) = \frac{E_{max}C}{EC_{50} + C'}$$

is a concave function for $C \geq 0$ (see the curve labeled $s = 1$ in Figure 1), and it follows that the constant profile is optimal in the sense that it maximizes E_{total}.

Case 3. Convex Concentration-Effect Relationship. If $E(C)$ is convex (see the lower segment of the curve with $s = 10$ in Figure 1), then the inequality in eq. 1 is reversed and it follows that the constant profile minimizes E_{total} among all profiles having the same AUC.

Case 4. Sigmoidal Concentration-Effect Relationship. If $E(C)$ is sigmoidal, then there is a single inflection point C_0, such that $E(C)$ is convex for $C < C_0$ and concave for $C > C_0$, (see the curves with s>1 in Figure 1). It is shown in the appendix that the optimal profile is constant on the interval $[0, t_0]$, and 0 on the complimentary interval $(t_0, \tau]$, where t_0 depends on the functional form of $E(C)$ and on the AUC. It may happen that $t_0 = \tau$, in which case the optimal profile is constant over the entire dosing interval $[0, \tau]$.

The sigmoidal E_{max} model (9) is defined by

$$E(C) = \frac{E_{max}C^s}{EC_{50}^s + C^s}. \tag{3}$$

For $s > 1$, this function has a single inflection point at C_0,

$$C_0 = EC_{50}\left(\frac{s-1}{s+1}\right)^{\frac{1}{s}}.$$

For $C < C_0$, $E(C)$ is convex and for $C > C_0$, $E(C)$ is concave. Figure 1 displays the sigmoidal E_{max} model for $s = 2$, 5 and 10.

We consider a series of step-function concentration profiles with the concentration equal to AUC/t_1 over an interval $[0, t_1]$, and equal to 0 on the complimentary interval $(t_1, \tau]$ with t_1 ranging from 0 to τ. For these profiles the integrated effect is given by

$$\int_0^\tau E\, dt = t_1\, E\left(\frac{AUC}{t_1}\right) \tag{4}$$

The profile with the maximal integrated effect is when t_1 equals t_0 as defined below:

$$t_0 = \begin{cases} \dfrac{AUC}{EC_{50}(s-1)^{1/s}}, & AUC < \tau\, EC_{50}(s-1)^{1/s} \\ \tau, & AUC \geq \tau\, EC_{50}(s-1)^{1/s}. \end{cases} \tag{5}$$

Kaojarern et al (3) have shown that the quantity $EC_{50}(s-1)^{1/s}$, appearing in eq. 5, is the concentration that produces max-

[1] Gensia Inc., 9360 Towne Centre Drive, San Diego, California, 92121.

[2] ALZA Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, California, 94303-0802.

[3] To whom correspondence shold be addressed.

0724-8741/95/0100-0168$07.50/0

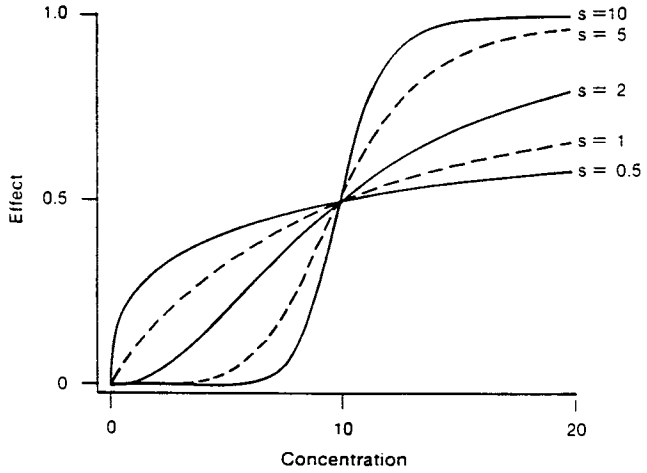

Figure 1. Sigmoid E_{max} (eq. 3) for 5 values of the parameter s, with $EC_{50} = 10$ and $E_{max} = 1$.

imum efficiency, where efficiency is defined as the effect divided by the concentration. Thus, when AUC/τ is greater than or equal to the most efficient concentration, the constant profile is optimal (ie $t_0 = \tau$); otherwise a step function is optimal (ie, $t_0 < \tau$).

Table I compares E_{total} for the constant profile and for the steady-state, monoexponential profiles,

$$C(t) = \frac{k\,AUC}{1 - e^{-k\tau}}\, e^{-kt}, \qquad (6)$$

with four different values of the dosing interval τ. For $s = ½$ and $s = 1$, the concentration-effect relationship is concave and the constant profile is optimal for all values of AUC. For $s > 1$ the concentration-effect relationship is sigmoidal and the constant profile may or may not be optimal depending on the value of AUC/τ. In fact, eq. 5 states that the constant profile is optimal only when $AUC/\tau \geq EC_{50}(s-1)^{1/s}$. For $s = 2$, this equals EC_{50}, and we see from Table I that for $C_{avg} = EC_{20}$, E_{total} for the constant profile is 80% of the optimal value, while for $C_{avg} = EC_{50}$ or EC_{80}, the constant profile is optimal. The notation EC_p ($p = 20$, 50, 80) is used for the concentration at which the effect is p percent of its maximum value.

When $C_{avg} = EC_{50}$ or EC_{80}, the constant profile is always better than the monoexponential profiles, even when it is not optimal, though the differences may be small. As the dosing interval τ decreases, the monoexponential profile becomes flatter and E_{total} for the monoexponential profile approaches that for the constant profile.

Table I. E_{avg} for Monoexponential Profiles with Dosing Interval τ (eq. 6), and the Contant Profile, Expressed as a Percent of the Optimal E_{avg}. $EC_{50} = 10$, $E_{max} = 1$, and s is the Power Appearing in the E_{max} Model (eq. 3)

C_{avg}	τ	s = ½	s = 1	s = 2	s = 5	s = 10
EC_{20}	4 HL	92.2	91.7	83.0	63.6	54.2
	2 HL	97.8	97.6	81.6	58.1	54.7
	1 HL	99.4	99.4	80.5	49.3	46.2
	½ HL	99.9	99.8	80.1	45.2	37.2
	Constant	100.0	100.0	80.0	43.5	31.8
EC_{50}	4 HL	92.8	87.0	80.9	64.6	54.1
	2 HL	98.0	96.2	93.2	73.7	61.4
	1 HL	99.5	99.0	98.1	79.2	65.5
	½ HL	99.9	99.8	99.5	81.5	67.8
	Constant	100.0	100.0	100.00	82.5	69.2
EC_{80}	4 HL	95.9	90.1	77.9	61.4	53.1
	2 HL	99.0	97.4	93.2	79.1	65.4
	1 HL	99.7	99.4	98.3	92.8	79.4
	½ HL	99.9	99.8	99.6	98.0	90.4
	Constant	100.0	100.0	100.0	100.0	96.4

DISCUSSION

Wagner (1) evaluated the impact of dosing regimen on the integrated effect using a one-compartment disposition pharmacokinetic model and a sigmoidal concentration-effect equation with the s value ranging from 1 to 2. A second pharmacokinetic model with a first-order absorption and one-compartment disposition was also evaluated. The general observation was that the integrated effect tended to increase as the same total dose was divided and given more frequently. It was not demonstrated that the maximal effect was achieved with a constant concentration profile. The previous work did not consider a convex concentration-effect relationship nor reach the correct conclusions for the sigmoidal concentration-effect relationship where a constant plasma concentration profile does not necessarily give the maximal effect as discussed in this report.

When the concentration-effect relationship is concave (convex), a constant plasma drug concentration profile gives the maximum (minimum) integrated drug effect. When this relationship is sigmoidal, the concentration profile that gives the maximum integrated effect is constant over all or part of the dosing interval and 0 over the remaining part. The exact form depends on AUC/τ and on the particular concentration-effect relationship.

We considered the case of a single therapeutic effect integrated over time. Measures of overall effect other than the time integrated effect could be considered. Also, a drug may have multiple effects, some beneficial and some harmful, in which case the objective would be to enhance the beneficial effects and limit the harmful ones. These considerations increase the complexity of the calculations and require further work.

APPENDIX

When the concentration-effect relationship is sigmoidal, the concentration profile that maximizes the time integrated effect is 0 on some interval and is a positive constant on the complementary interval.

Suppose that $C(t)$ is a step function, meaning that $C(t)$ is constant, equal to C_i, on each interval $(t_{i-1}, t_i]$, with $0 = t_0 < t_1 < \cdots < t_n = \tau$. Let C_0 be the inflection point of the sigmoidal concentration-effect curve and let $\Delta_i = t_i - t_{i-1}$. If some C_i is positive and less than C_0, then define $C^*(t)$ to equal $C(t)$ everywhere except on the interval $(t_{i-1}, t_i]$, where it is defined by

$$C^*(t) = \begin{cases} 0, & t_{i-1} \leq t < t_i - \Delta_i \dfrac{C_i}{C_0} \\ C_0, & t_i - \Delta_i \dfrac{C_i}{C_0} \leq t \leq t_i \end{cases}$$

The AUC is the same for C^* and C, but

$$\int_{t_{i-1}}^{t_i} E(C^*(t))dt = E(C_0) \cdot \frac{\Delta_i C_i}{C_0} > \Delta_i E(C_i) = \int_{t_{i-1}}^{t_i} E(C(t))dt$$

and so the total effect has increased. The inequality follows from the convexity of $E(C)$ for $C \leq C_0$. This shows that if $C(t)$ is to be optimal, it must take values that are either 0 or greater than or equal to the inflection point C_0. On the other hand, it follows from the concavity of $E(C)$ for $C > C_0$ that if all the C_i greater than C_0 are replaced by their average value, $(\Sigma\, \Delta_i\, C_i)/(\Sigma\, \Delta_i)$, then the total effect will be increased while the AUC remains constant.

This demonstrates that among all step function profiles, the optimal profile must be either constant everywhere, or 0 on some interval and a positive constant on the complimentary interval. Since any concentration profile can be approximated, with arbitrary precision, by step functions, the same result holds among all concentration profiles.

If $C(t)$ is optimal for a given AUC, so that $C(t) = AUC/t_0$ on $[0, t_0]$ and $C(t) = 0$ on $(t_0, \tau]$, then

$$\int_0^{\tau} E(C(t))\, dt = t_0 E\left(\frac{AUC}{t_0}\right)$$

and t_0 can be found to make this maximal, as in Case 4 above. Note that this solution is not unique. Any profile that is equal to AUC/t_0 for a total amount of time t_0 (not necessarily on the interval $[0, t_0]$), and equal to 0 for a total amount of time τ-t_0, will give the same E_{avg}.

REFERENCES

1. J. G. Wagner. Kinetics of Pharmacologic Response. I. Proposed Relationships between Responses and Drug Concentration in the Intact Animal and Man. J Theoret. Biol. 20:173–201 (1968).
2. D. W. Rudy, J. R. Voelker, P. K. Greene, F. A. Esparza, D. C. Brater. Loop diuretics for chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. Ann Intern. Med. 115:360–366 (1991).
3. M. Lahav, A. Regev, P. Ra'anani, and E. Theodor. Intermittent administration of furosemide vs continuous infusion preceded by by a loading dose for congestive heart failure. Chest **102**:725–731 (1992).
4. S. Kaojarern, B. Day and D. C. Brater. The time course of delivery of furosemide into urine: an independent determinant of overall response. Kidney Int **22**:69–74 (1982).
5. J. W. Burns, H. A. Aitken, R. E. S. Bullingham, C. S. McArdle, and G. N. C. Kenny. Double-blind comparison of the morphine sparing effect of continuous and intermittent i.m. administration of ketorolac. British Journal of Anaesthesia **67**:235–238 (1991).
6. D. H. Livingston, and M. T. Wang, Continuous infusion of cefazolin is superior to intermittent dosing in decreasing infection after hemorrhagic shock. The American Journal of Surgery. **165**:203–207 (1993).
7. H. Nau, H.-J. Merker, K. Brendel, Ch. Gansau, I. Hauser, and W. Wittfoht. Disposition, embryotoxicity, and teratogenicity of valproic acid in the mouse as related to man. In R. H. Levy, W. H. Pitlick, M. Eichelbaum and J. Meijer (eds.) Metabolism of antiepileptic drugs, Raven Press, New York, 1984, pp. 85–96.
8. G. G. Hardy, J. E. Littlewood, and G. Polya. Inequalities. Cambridge University Press, Cambridge, 1952, pp. 150–151.
9. N. H. G. Holford and L. B. Sheiner. Kinetics of pharmacologic response. Pharmacol. Ther. **16**:143–166 (1982).