Feasibility of Effect-Controlled Clinical Trials of Drugs with Pharmacodynamic Hysteresis Using Sparse Data

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Purpose. To explore, by simulation procedures, the feasibility of characterizing, from sparse data, the concentration-effect relationship of drugs with pharmacodynamic hysteresis.

Methods. For computer simulations, the concentration-effect relationship was assumed to be describable by the Sigmoid-E_{max} equation, the site of drug action was located in a distinct effect compartment (k_{eo} = 10 × k_{elim}), and the pharmacokinetics were those of either a linear one- or two-compartment system. In view of the poor estimability of the parameters of the Sigmoid-E_{max} model under the usual clinical conditions, central compartment post-distributive drug concentrations required to elicit various intensities of effect within the therapeutic range were used as data descriptors. Effect intensities of 5 and 25, or 25 and 50 units (with the "unknown" E_{max} = 100 units) were targeted in multiple-dose (steady state) trial designs. From these data, drug concentrations required to produce effect intensities of 15 and 50 units were estimated by both log-linear and linear interpolation and the actual effect intensities produced by these concentrations were calculated. These simulations were performed over a wide range of Hill coefficient values (0.5 to 4.0) and dosing intervals (0.1 to 1.5 × elimination $t_{1/2}$).

Results. Acceptable results could be obtained by measuring drug concentrations and effect intensities at or near the end of a dosing interval. The largest deviations of effective concentration estimates (in terms of effect intensity) occurred at a Hill coefficient value of 0.5 and the results were very little affected by changing the dosing interval.

Conclusions. Our results demonstrate that effect-controlled clinical trials, with sparse data, of drugs with pharmacodynamic hysteresis for determining concentration-effect relationship in the therapeutic range are feasible in principle.

KEY WORDS: effect-controlled clinical trials; pharmacodynamics; pharmacodynamic hysteresis; sparse data.

INTRODUCTION

The need to search for predictors of pharmacodynamic individuality (covariates) by studying large samples of diverse populations has led to proposals of various strategies to determine drug concentration-effect relationships in clinical trials involving sparse data collection (1–5). So far, studies have addressed the case of reversibly and direct acting drugs that equilibrate almost instantaneously between the biophase and what pharmacokineticists refer to as the central compartment of the body. Here we focus on a more difficult case, that of drugs which exhibit pharmacodynamic hysteresis, i.e. a temporal shift in the time course of the pharmacologic effect relative to the time course of drug concentrations in plasma, a phenomenon that can often be modeled by designating a distinct effect compartment within the body (6). Our purpose was to determine if effect-controlled clinical trials of such drugs, using sparse sampling (only two concentration and effect measurements per subject) are feasible in principle. By incorporating measurement and controller error estimates in the simulation strategies described here, feasibility assessments can be made for specific drugs.

Though not generally recognized, the parameters of the Sigmoid-E_{max} model are poorly estimable for most drugs (5), the exceptions being those whose effect can be safely increased to 95 percent or more of E_{max} (typically, general anesthetics and neuromuscular blockers (6,7). Consequently, other data descriptors have been used to describe concentration-effect relationships in the safely measurable or therapeutic range. For example, one can determine the drug concentrations required to obtain effect intensities at the upper and lower limits of the usual therapeutic effect range (2). With these data descriptors, one can calculate, by interpolation, the concentrations required to produce effect intensities within that range. However, since the location of the two descriptors on the Sigmoid-E_{max} curve is not known when E_{max} cannot be determined, one does not know if the interpolation should be linear or log-linear. Consequently, both methods must be employed and their results must be compared to determine the utility of the interpolation method (2).

We selected two pairs of effect intensities as effect targets; one pair encompassing the central (log-linear) region of the Sigmoid-E_{max} curve, the other being in the lower region where the concentration-effect relationship is approximately linear. The pharmacokinetics of the drug were assumed to exhibit the characteristics of either a one- or two-compartment model, and the hypothetical effect compartment was assumed to be very small and relatively deep (i.e., slow to equilibrate).

METHODS

The drug concentration-pharmacologic effect relationship was assumed to be describable by the Sigmoid-E_{max} equation (6) with E_{max} = 100 percent, EC_{50} = 5 concentration units and γ = 2. The rate constant k_{eo} for equilibration of the drug between the hypothetical central and effect compartment (6) was assumed to be 0.693 reciprocal time units. The amount of drug in the effect compartment was assumed to be very much smaller than the total amount of drug in the body. The pharmacokinetic constants for the one-compartment and two-compartment linear pharmacokinetic systems are shown in Figure 1.

Simulations were performed for repetitive oral dosings at intervals of 1.0 to 15 time units (equivalent to 0.1 to 1.5 times the elimination $t_{1/2}$), an absorption half-life of 0.250 time unit and an F value (oral bioavailability) of unity. This was done using the simulation module of the ADAPT II program (release 2) (8,9). The calculations were carried out in the following order (cited equations in Appendices I to III):

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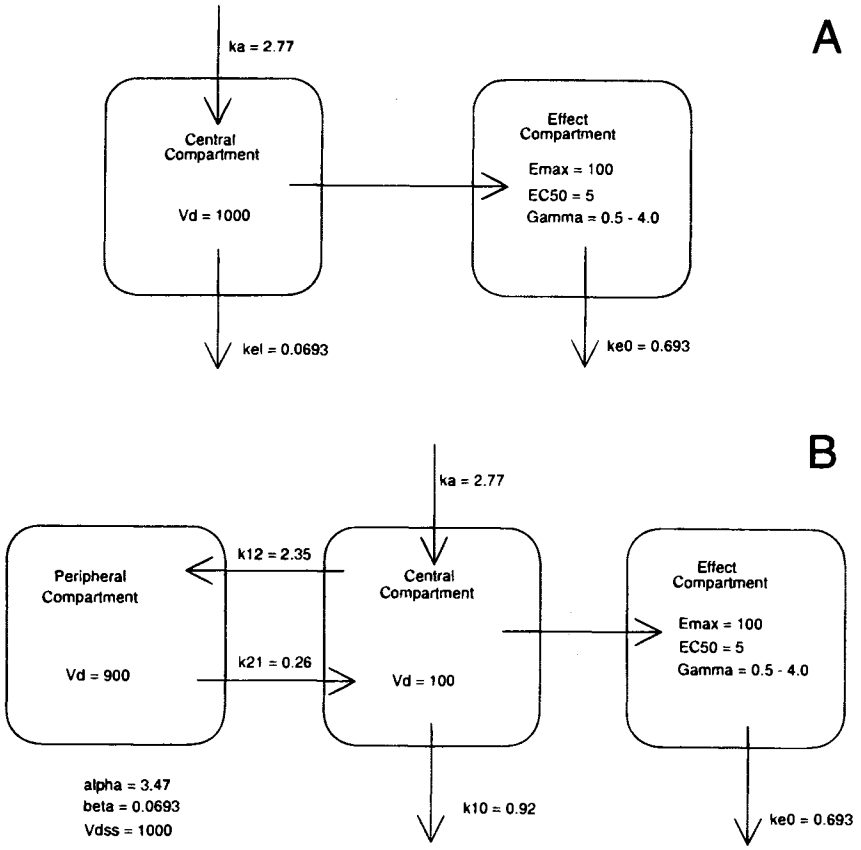

Fig. 1. Pharmacokinetic-pharmacodynamic models used for the simulations. Rate constants are in arbitrary, reciprocal units of time; E_{max} and EC_{50} are in arbitrary effect intensity and concentration units, respectively; the distribution volumes are in arbitrary units of volume. The upper model is referred to in the text as the one-compartment model and the lower one is referred to as the two-compartment model.

a. The concentration of drug in the effect compartment at the end of a steady state dosing interval required to achieve an intensity of effect of either 5, 25 or 75 percent of E_{max} at the end of the dosing interval was calculated (Eq. 3AII).

b. The dosing rate required to produce the above concentration was determined for the one- and two-compartment systems (Eq. 4AII).

c. The drug concentrations in the effect compartment throughout the dosing interval, at the dosing rate of (b), were calculated for the one- and two-compartment systems (Eq. 3AI).

d. The intensities of effect throughout the dosing interval, at the dosing rate of (b), were calculated by using the concentrations of (c) in Eq. 5AI).

e. The concentrations of drug in plasma corresponding to the effect compartment concentrations in (c) were then determined for the one- and two-compartment systems (Eq. 2AI).

f. Using the effect intensities in (d) and the plasma concentrations in (e) for the lower and higher dosing rates, the slope of the effect intensity—Ln plasma concentration relationship (Eq. 2AIII) as well as the slope of the effect intensity-plasma concentration relationship (Eq. 6AIII) can be calculated. Interpolations can then be performed in the usual manner, using the slope value and the coordinates of one of the two measured concentration-effect or ln concentration-effect points.

RESULTS AND DISCUSSION

The time courses of drug concentrations in the plasma and hypothetical effect compartment of the standard one-compartment pharmacokinetic model (Fig. 1) during a dosing interval at steady state (oral doses every $0.667 \cdot t_{1/2}$) are shown in Figure 2. Also shown in Figure 2 is the time-dependent relationship between drug concentration in plasma and intensity of effect during the dosing interval. Corresponding curves for the standard two-compartment model are shown in Figure 3. Significant pharmacodynamic hysteresis is evident in both cases. Of interest is the earlier onset and greater maximum effect exhibited by the two-compartment simulation. This is due to the higher plasma concentrations of the two-compartment system during the distribution phase.

Our design strategy for effect-controlled clinical trials with sparse data has been to target two effect intensities at the end of a dosing interval at steady state, one at the upper and the other at the lower limit of the usual clinical range of a drug's effect intensity, and then to interpolate between these points to determine the drug concentration required to produce an effect intensity within that range at steady state (2). Figure 4 shows estimates of the plasma concentration required to obtain an effect intensity of 50 units (CE_{50}) based on the "measured"

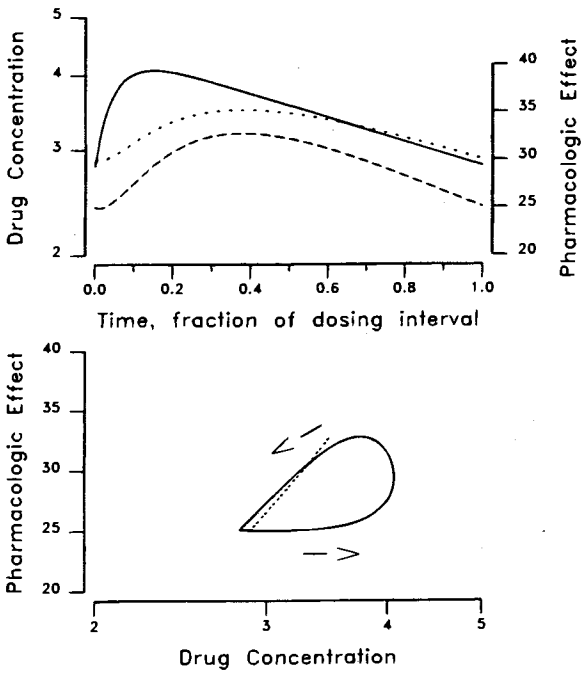

Fig. 2. Upper panel: Time course of concentrations and effect intensities at steady state of a drug administered every 0.667 $t_{1/2}$ ($t_{1/2}$ is 0.693/k_{el}) at a dosing rate that produces an effect intensity of 25 units at the end of the dosing interval. One-compartment model. The continuous line represents the plasma concentrations whereas the stippled line (---) represents the drug concentrations in the effect compartment. The broken line (— — —) shows the time course of the pharmacologic effect. Lower panel: Relationship between effect intensity and plasma concentration (continuous line) or effect compartment concentration (stippled line) during the dosing interval. The arrows indicate the progression of time.

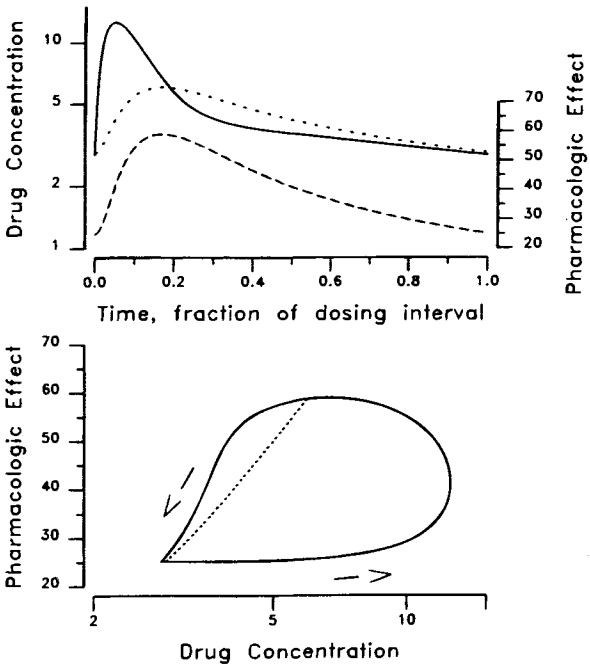

Fig. 3. As in Figure 2 except that the pharmacokinetic model is a two-compartment system.

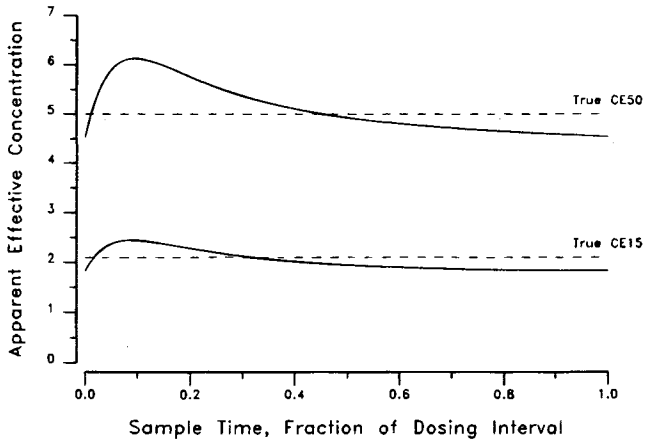

Fig. 4. Estimated drug concentrations in plasma required to produce effect intensities of 15 and 50 units, respectively (CE_{15} and CE_{50}). One compartment, standard model, dosing interval = 0.667 $t_{1/2}$. CE_{50} was estimated by log-linear interpolation of drug concentrations at effect intensities of 25 and 75 units whereas CE_{15} was estimated by linear interpolation of drug concentrations at effect intensities of 5 and 25 units.

concentrations at effect intensities of 25 and 75 units as well as estimates of CE_{15} based on "measured" concentrations at effect intensities of 5 and 25 units, for the one-compartment model. The true CE_{50} and CE_{15} values were calculated directly from the model parameters, without interpolation, assuming true steady state as during a constant rate i.v. infusion. Similar information for the two-compartment system is presented in Figure 5. It is evident that the pronounced distribution disequilibrium during the early part of the dosing interval causes substantial overestimates of CE values, particularly for the two-compartment system. The eventual (though minor) underestimates of CE values when measurements are made toward the end of the dosing interval are caused mainly by a reversal of the concentration gradient between the effect compartment and the plasma after drug absorption and distribution, i.e. in the elimination phase. It is well appreciated that plasma concentration-effect data on the descending limb of a hysteresis curve do not yield exact estimates of pharmacodynamic parameter values (10).

In further simulations we explored the utility of the interpolation method as a function of the Hill exponent value when concentrations and effects are measured at the end of a dosing interval. Since E_{max} would ordinarily be unknown, interpolations to determine CE_{15} and CE_{50} were made both linearly and log-linearly. To appreciate the clinical implications, the effect intensities corresponding to the estimated CE values were also determined. Results for the one-compartment system, presented in Figure 6, show good estimation of CE_{15} and CE_{50} values by log-linear interpolation over a wide range of Hill coefficient values. On the other hand, linear interpolation caused overestimation of CE_{50} values when the Hill coefficient was 1 or less, and therefore resulted in greater than intended effect intensities. However, due to the nonlinear relationship between concentration and effect, the magnitude of error in the concentration far exceeded that of the effect intensity (Fig. 6). Similar results were obtained for the two-compartment system (Fig. 7). It should be noted that the CE_{50} is independent of the Hill coeffi-

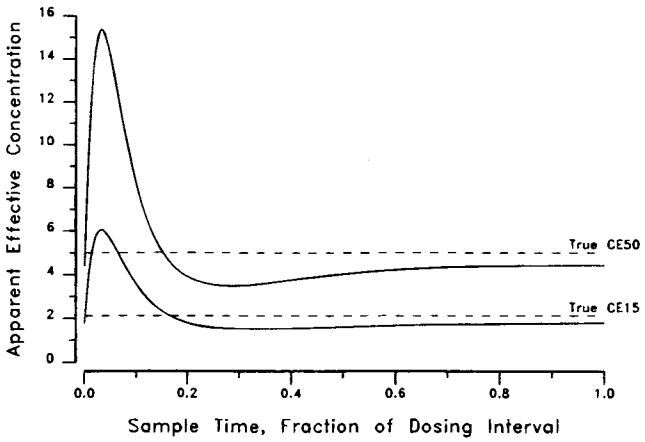

Fig. 5. As in figure 4 except that the pharmacokinetic model is a two-compartment system.

cient value because in this specific case it is equal to the parameter EC_{50} of the pharmacodynamic model used for the simulations. As the Hill coefficient is changed, the concentration-effect curve swivels around a point with the coordinates EC_{50} and 50 units effect intensity. This is not the case for CE_{15} which is sensitive to changes of the Hill coefficient, particularly in the low range of Hill coefficient values.

When the targeted effect intensities are at the end of a dosing interval, usually the nadir of drug concentrations, considerably higher and potentially toxic concentrations and effect intensities occur earlier in the dosing interval. A decrease in the dosing interval of a drug administered orally in rapidly absorbed form will reduce peak concentrations and effect inten-

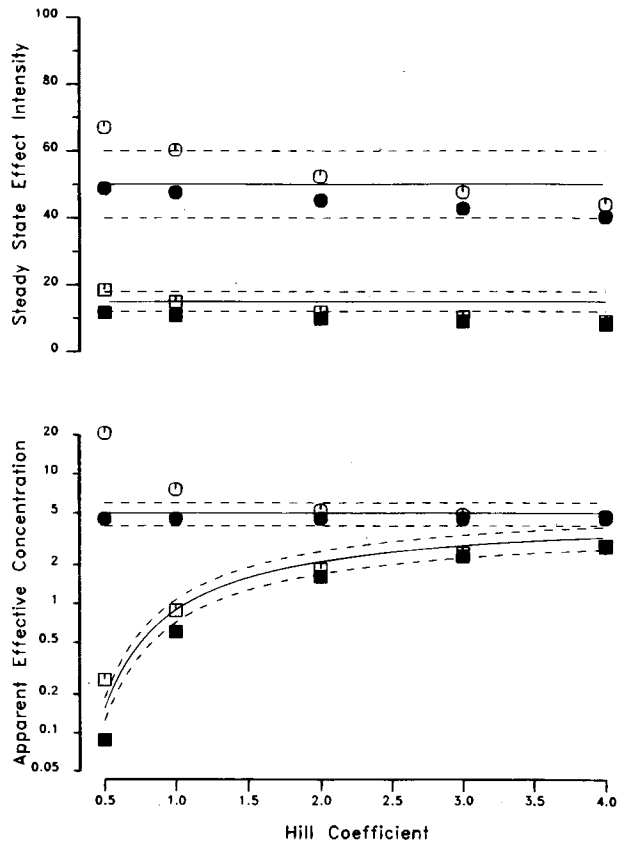

Fig. 6. Estimated CE_{15} (squares in lower panel) and CE_{50} (circles in lower panel) and corresponding predicted effect intensities as a function of gamma value (Hill Coefficient) at steady state for a drug administered every 0.667 $t_{1/2}$. Solid symbols, log-linear interpolation; open symbols, linear interpolation. Continuous line, true values; stippled lines, ±20 percent of true value. One-compartment model. Measurements of effective concentrations at end of dosing interval.

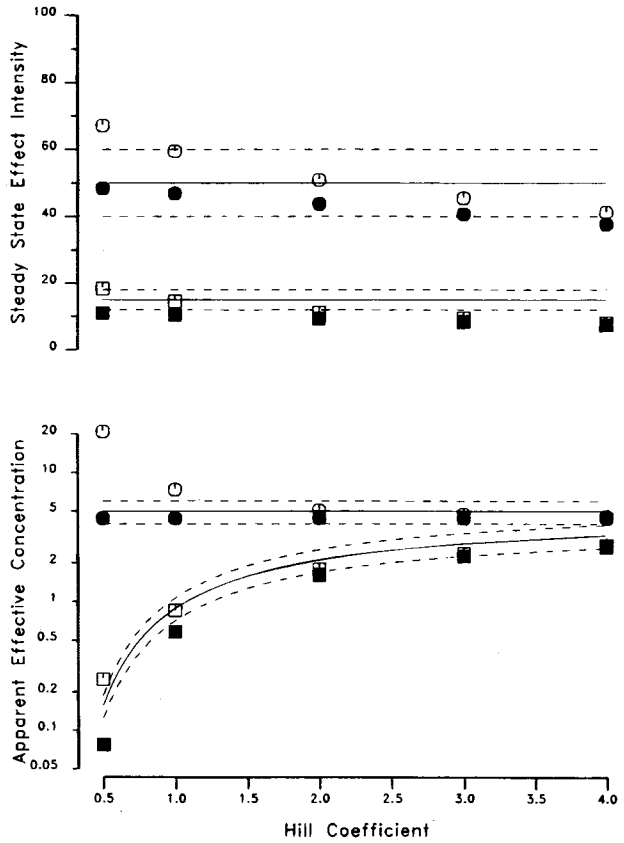

Fig. 7. As in figure 6 except that the pharmacokinetic system is a two-compartment model.

Table I. Peak Effect Intensity as a Function of Dosing Interval and Target Effect Intensity at the End of a Dosing Interval at Steady State[a]

Dosing Interval	Target Effect Intensity:	One-Compartment 5	25	75	Two-Compartment 5	25	75
1.0		5.0	25	75	5.2	26	76
3.0		5.3	26	76	8.2	36	83
6.7		7.1	33	81	18	59	93
10.0		10	42	87	31	74	96
15.0		18	57	92	53	88	98

[a] Calculations are based on the parameter values of the standard model described in Figure 1.

sities (Table I) and also lower the daily drug dosing rate (Table II). A change in the dosing interval has very little effect on estimates of CE_{15} and CE_{50} and their corresponding actual effect intensities. This is shown for different Hill coefficient values and the one-compartment model in Figure 8. As noted previously, the linear interpolation method produces substantial overestimates of CE values at Hill coefficients of 0.5 and 1 (though the corresponding effect intensities are much less affected). When the coefficient has a value of 4, even a very small error in the estimated CE has a pronounced influence on the corresponding effect intensity due to the steepness of the concentration-effect relationship (Figure 8, lower right panel). Results obtained with the two-compartment system (not shown) are almost identical.

Clinically observed interindividual differences in the EC_{50} of drugs are often more than ten-fold and sometimes more than 100-fold (1,11,12). In that context, the estimates provided by effect-controlled clinical trials with two targeted effect intensities, as reflected by our simulations, provide a reasonable representation of individual drug concentration-pharmacologic effect relationships. It is encouraging that this applies even to drugs that exhibit pharmacodynamic hysteresis. The quality of the pharmacodynamic descriptor estimates will depend on the magnitude of effect and concentration measurement errors, the pharmacokinetic and pharmacodynamic characteristics of the drug, and aspects of clinical trial design. It is essential therefore to assess the feasibility and utility of various trial designs for a specific drug by simulations which include consideration of controller imprecision and measurement error estimates for that drug obtained from a preceding, measurement-intensive pilot study (3).

Table II. Daily Dosing Rates Required to Produce Various Effect Intensities at the End of a Dosing Interval at Steady State: Role of Dosing Interval[a]

Dosing Interval	Target Effect Intensity:	One-Compartment 5	25	75	Two-Compartment 5	25	75
1.0		1.9	4.8	14	2.6	6.4	19
3.0		1.9	4.9	15	2.9	7.4	22
6.7		2.1	5.4	16	3.7	9.3	28
10.0		2.4	6.1	18	4.2	11	32
15.0		2.9	7.4	22	5.2	13	39

[a] Calculations are based on the parameters of the standard model described in Figure 1.

APPENDIX I

Calculation of the Time Course of Drug Concentrations in the Central and Effect Site Compartments and the Pharmacologic Effect Intensity

Outlined here are the equations for calculating the time course of drug concentration in the central and effect site compartments as well as the time course of pharmacologic effect intensity as a function of time during a steady state oral dosing regimen with equally spaced dosing intervals. These equations are applicable for any N compartment mammillary model with first-order pharmacokinetic characteristics.

The time course of drug concentrations in the plasma or central compartment (C_p) can be described by the multiple dose function (13,14):

$$C_p(t') = \frac{\text{Dose}}{V_c} \sum_{i=1}^{N+1} A_i \frac{1 - e^{-\Psi T\lambda_i}}{1 - e^{-T\lambda_i}} e^{-\lambda_i t'} \qquad (1AI)$$

where V_c is the volume of the central compartment, Dose is the administered dose, Σ is the continued summation, N is the number of driving force compartments in the disposition model, A_i and λ_i are the hybrid preexponential and exponential coefficients of the i^{th} exponential term, Ψ represents the dose number, T is the dosing interval and t' is the time since the last dose. For steady dosing regimens Ψ approaches infinity and the first exponential term in the numerator vanishes. Thus Equation 1AI collapses to

$$C_pss(t') = \frac{\text{Dose}}{V_c} \sum_{i=1}^{N+1} A_i \frac{e^{-\lambda_i t'}}{1 - e^{-T\lambda_i}} \qquad (2AI)$$

where C_pss refers to concentrations in the central compartment *at any time during a steady state dosing interval.*

Equations for the time course of drug concentrations in the hypothetical effect compartment of several mammillary pharmacokinetic models have been presented by Holford and Sheiner [15]. Applying the multiple dose function to these polyexponential equations yields the corresponding time course of steady state drug concentrations (Ce) in the hypothetical effect compartment which is described by the equation:

$$C_ess(t') = \frac{\text{Dose}}{V_c} \sum_{i=1}^{N+2} B_i \frac{e^{-\lambda_i t'}}{1 - e^{-T\lambda_i}} \qquad (3AI)$$

where B_i is the hybrid preexponential coefficient of the i^{th} exponential term and C_ess refers to concentrations in the effect site compartment at *any time during a steady state dosing interval.*

The concentration-effect relationship is described by the Sigmoid E_{max} model presented in Equation 4AI. In this equation Effect is the intensity of effect, C_e is the drug concentration in the effect compartment, E_{max} is the maximum effect intensity achievable, EC_{50} is the drug concentration that produces one-half the maximum effect, and γ is a constant reflecting the steepness of the concentration-effect relationship.

$$\text{Effect} = \frac{C_e^{\gamma} E_{max}}{C_e^{\gamma} + EC_{50}^{\gamma}} \qquad (4AI)$$

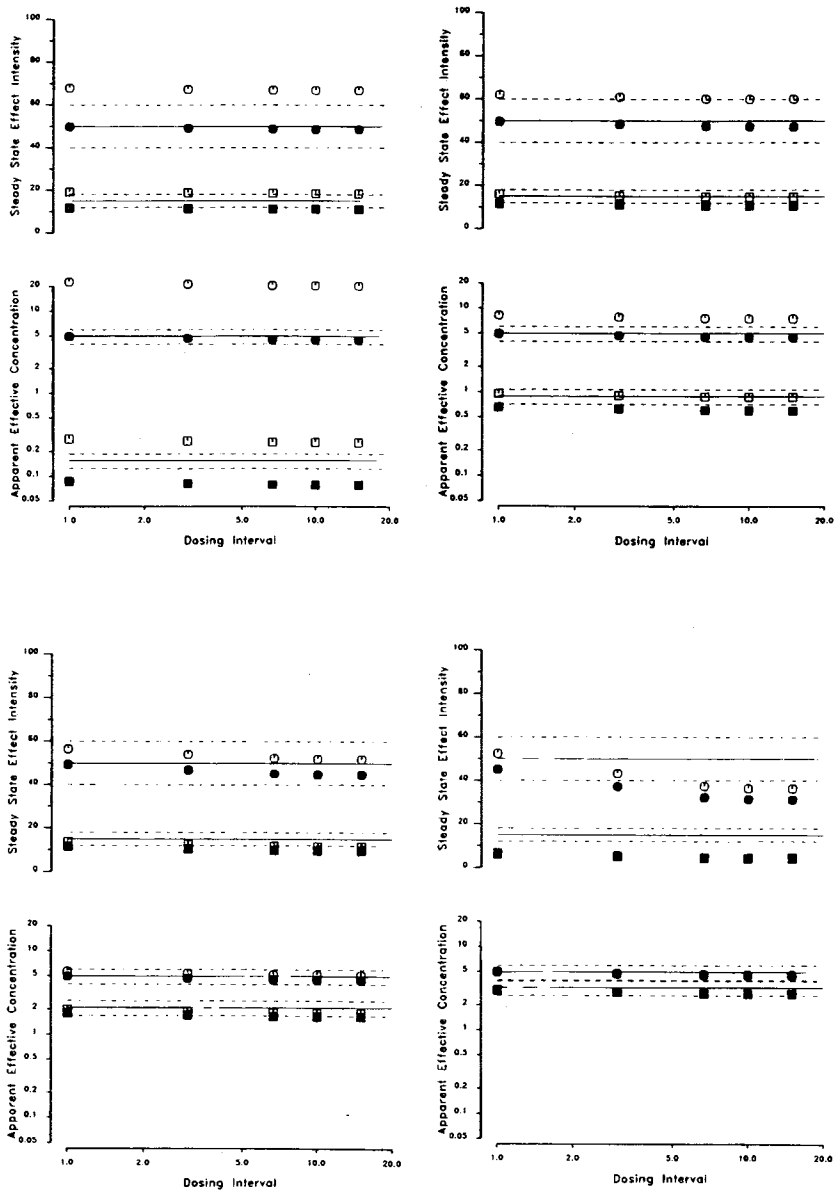

Fig. 8. Estimated CE_{15} (squares in lower panel) and CE_{50} (circles in lower panel) and corresponding predicted effect intensities as a function of dosing interval at steady state for a one-compartment drug, standard model except that gamma is 0.5 (upper left panel), 1 (upper right panel), 2 (lower left panel), or 4 (lower right panel). Solid symbols, log-linear interpolation; open symbols, linear interpolation. Continuous and stippled lines are true value and ±20 percent of true value, respectively. Measurement of effective concentrations at end of dosing interval.

The time course of pharmacologic effect intensity under steady state dosing conditions can be calculated at any time by substituting the right hand side of Equation 3AI for C_e in Equation 4AI. Thus:

$$\text{Effect}(t') = \frac{\left[\frac{\text{Dose}}{V_c}\sum_{i=1}^{N+2} B_i \frac{e^{-\lambda_i t'}}{1-e^{-T\lambda_i}}\right]^{\gamma} E_{\max}}{\left[\frac{\text{Dose}}{V_c}\sum_{i=1}^{N+2} B_i \frac{e^{-\lambda_i t'}}{1-e^{-T\lambda_i}}\right]^{\gamma} + EC_{50}^{\gamma}} \quad (5AI)$$

APPENDIX II

Calculation of the Dosing Rate Required to Produce a Given Intensity of Effect at the End of a Dosing Interval During Steady-state Oral Dosing

Drug concentrations in the effect compartment of the one-compartment model at the end of a steady-state dosing interval can be calculated in the following manner. Replacing t' with T in Equation 1AI yields:

$$C_e ss(T) = \frac{\text{Dose}}{V_c} \sum_{i=1}^{N+2} B_i \frac{e^{-\lambda_i T}}{1 - e^{-\lambda_i T}} \qquad (1AII)$$

where $C_e ss(T)$ is the drug concentration in the effect compartment at the end of a steady state dosing regimen. This equation can be solved for dose to yield Equation 2AII:

$$\text{Dose} = \frac{C_e ss(T) V_c}{\sum_{i=1}^{N+2} B_i \frac{e^{-\lambda_i T}}{1 - e^{-\lambda_i T}}} \qquad (2AII)$$

To calculate dosing rate it is necessary to specify the $C_e ss(T)$ which will produce a desired intensity of effect at the end of the dosing interval. The Sigmoid E_{max} model presented in Equation 4AI must be solved for C_e given the desired effect intensity. This solution is presented in Equation 3AII

$$C_e = \frac{EC_{50}\text{Effect}^{1/\gamma}}{(E_{max} - \text{Effect})^{1/\gamma}} \qquad (3AII)$$

Substituting the right-hand side of Eq. 3AII for $C_e ss(T)$ in the right-hand side of Equation 2AII yields the dose required to produce the desired effect intensity:

$$\text{Dose} = \frac{\frac{EC_{50}\text{Effect}^{1/\gamma}}{(E_{max} - \text{Effect})^{1/\gamma}} V_c}{\sum_{i=1}^{N+2} B_i \frac{e^{-\lambda_i T}}{1 - e^{-\lambda_i T}}} \qquad (4AII)$$

APPENDIX III

Calculation of the Slope and EC Parameters from Two-Point Effect-Controlled Data

Using the two-point effect-controlled trial design, effects are targeted to two different effect intensities representing the upper and lower limits of the usual therapeutic effect range. Within this effect range the concentration-effect relationship may be approximated by the following log-linear relationship:

$$\text{Effect} = \text{Slope} \cdot \text{Ln}(C_p ss) + \text{Intercept} \qquad (1AIII)$$

where Slope is the slope of the concentration-effect relationship based on the natural logarithm of the steady-state drug concentrations in the central compartment, and Intercept is the intercept of the Effect-Ln(Concentration) regression line on the Effect axis. Given two concentration-effect intensity pairs the slope of the natural log-linear concentration-effect relationship can be calculated as:

$$\text{Slope} = \frac{\text{Effect}_1 - \text{Effect}_2}{\text{Ln}(C_p ss_1) - \text{Ln}(C_p ss_2)} \qquad (2AIII)$$

where the subscripts 1 and 2 identify the first and second steady-state concentration-effect intensity pairs. The intercept of the log-linear concentration-effect relationship can be calculated with Equation 3AIII:

$$\text{Intercept} = \text{Effect}_1 - \frac{\text{Effect}_1 - \text{Effect}_2}{\text{Ln}(C_p ss_1) - \text{Ln}(C_p ss_2)} \cdot \text{Ln}(C_p ss_1) \qquad (3AIII)$$

An effective concentration producing an effect intensity of X within the therapeutic effect range, EC_x, can now be estimated by substituting the right-hand side of Equations 2AIII and 3AIII into Equation 1AIII and solving for $C_p ss$ after setting effect intensity to Effect_X

$$EC_X = e^{(\text{Effect}_X - \text{Intercept})/\text{Slope}} \qquad (4AIII)$$

If the relationship between drug concentration and effect intensity is assumed to be linear, then:

$$\text{Effect} = \text{Slope} \cdot Cp_{ss} + \text{Intercept} \qquad (5AIII)$$

where Slope is the slope of the linear concentration-effect relationship based on the steady state concentrations in the central compartment, and Intercept is the intercept of the effect-concentration regression line on the Effect axis. Given two concentration-effect intensity pairs the slope of the linear concentration-effect relationship can be calculated as:

$$\text{Slope} = \frac{\text{Effect}_1 - \text{Effect}_2}{Cp_{ss1} - Cp_{ss2}} \qquad (6AIII)$$

where the subscripts 1 and 2 identify the first and second steady-state concentration-effect intensity pairs. The intercept of the linear concentration-effect relationship can be calculated with Equation 7AIII:

$$\text{Intercept} = \text{Effect}_1 - \frac{\text{Effect}_1 - \text{Effect}_2}{C_p ss_1 - C_p ss_2} \cdot C_p ss_1 \qquad (7AIII)$$

An effective concentration producing an desired effect intensity of X within the therapeutic effect range, EC_x, can now be estimated by:

$$EC_x = \frac{\text{Effect}_X - \text{Intercept}}{\text{Slope}} \qquad (8AIII)$$

where Effect_X is the desired effect intensity.

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