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Model-Independent Steady-State Plasma Level Predictions in Autonomic Nonlinear Pharmacokinetics I: Derivation and Theoretical Analysis

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Abstract □ Current drug level predictions in nonlinear pharmacokinetics are based on specific pharmacokinetic models in contrast to the model-independent (structureless), dose-linearity, and superposition principles used in linear pharmacokinetics. Such model-dependent methods may not provide reliable predictions due to their inherent nonuniqueness, computational complexity, and often unrealistic kinetic assumptions. Some novel model-independent methods for predicting the steady-state drug levels of extravascular, intravenous bolus, and intravenous infusion administrations are presented that should overcome such disadvantages. The methods only assume an autonomic nonlinear kinetic behavior, which implies that following an intravenous bolus administration the derivatives of the drug concentration–time profile at arbitrary drug levels are independent of the dose given. Such a kinetic behavior is found for any nonlinear pharmacokinetic system when the rate of change of the drug level following an intravenous bolus administrations depends only on the drug level, *i.e.*, $dC/dt = -q(C)$, where q can be any function dependent only on C and time-invariant kinetic parameters. The basic approach presented represents a novel alternative which avoids the very difficult and often impractical task of identifying and incorporating the numerous kinetic parameters and processes responsible for the observed drug concentration data into a useful pharmacokinetic model. The focus in the kinetic analysis is instead on two much simpler processes: (*a*) fitting empirical functions to estimate the mean drug disposition behavior of the subject or population and (*b*) testing the validity of the assumptions involved.

Keyphrases □ Pharmacokinetics—nonlinear, model independent, steady-state plasma drug-level predictions, theory and mathematical models □ Plasma drug levels—prediction at steady state, model-independent nonlinear pharmacokinetics, theory and mathematical models

Steady-state plasma level predictions in linear pharmacokinetics are done by extrapolations using the dose-linearity and superposition principles or by using the convolution property of linear pharmacokinetics. The plasma level profiles used for the predictions are most commonly determined by fitting suitable model-independent[1] equations, typically of an exponential type, to available plasma level data. Such model-independent methods cannot be used for drugs showing nonlinear pharmacokinetics because the superposition and dose-linearity principles do not apply. Consequently, drug level predictions in nonlinear pharmacokinetics have been based on model-dependent methods, which may not provide reliable predictions due to their inherent nonuniqueness, computational complexity, and often unrealistic model assumptions. A model-independent approach is presented which overcomes some of these disadvantages.

THEORETICAL

The proposed methodology applies to drugs showing what will be called *autonomic nonlinear pharmacokinetics; i.e.*, the drug-concentration profile resulting from an intravenous bolus dose adheres to the autonomic differential equation:

$$\frac{dC}{dt} = -q(C) \qquad \text{(Eq. 1)}$$

where q stands for any function only dependent on the drug concentration C and time-invariant kinetic parameters. It is assumed that q is such that the solution of Eq. 1, $C(t)$, is monotonically decreasing with time. Autonomic nonlinear pharmacokinetics is readily identified in a model-independent manner from "the horizontal superposition property" (Fig. 1). Different intravenous bolus doses result in drug-concentration profiles with identical slopes

[1] The terminology "model-independent" is used here to denote a general approach not based on a specific structured (model-dependent) kinetic analysis of the individual kinetic components of the pharmacokinetics.

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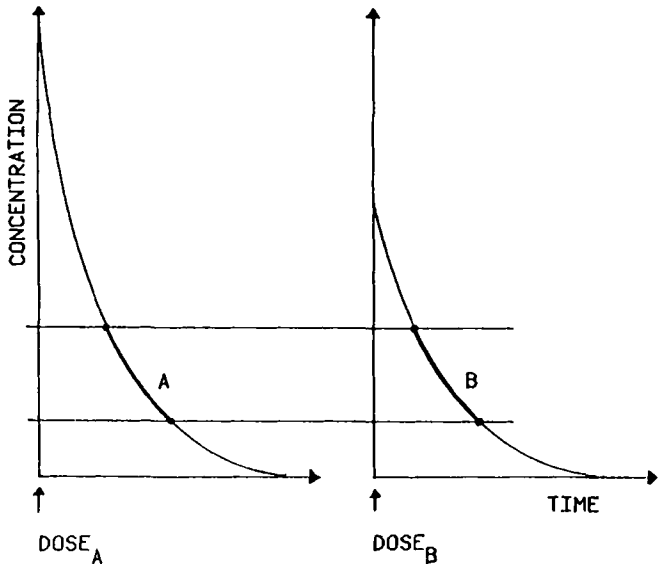

Figure 1—*Illustration of the horizontal superposition property of autonomic nonlinear pharmacokinetics (A = B), which is characterized by an intravenous bolus disposition behavior that follows to the general autonomic differential equation (Eq. 1).*

at the same concentration levels. Thus, a horizontal shift of the curves will result in their exact superposition (Fig. 1). For example, a parallel first-order and Michaelis–Menten elimination:

$$\frac{dC}{dt} = -KC - \frac{V_m C}{K_m + C} \qquad \text{(Eq. 2)}$$

will result in this behavior; so will any pharmacokinetic system incorporating nonlinear binding, excretion, metabolism, *etc.*, as long as the kinetics can be described in the general form of Eq. 1. However, due to the model-independent nature of the method proposed, there is no need to postulate a specific kinetic relationship.

The most studied nonlinear drug, phenytoin, appears quite consistent to show autonomic disposition kinetics (1). The fall-off curves studied for 10 subjects for a period of 4 consecutive days after different daily doses of phenytoin were discontinued seem to agree well with Eq. 1 (1). Other examples of the horizontal shift and the superposition concept include the pharmacokinetics of alcohol (2).

Steady-State Prediction of Extravascular Dosing—In linear pharmacokinetics, steady-state predictions can be made solely from a single dose, without using the information about the basic disposition of the drug provided by an intravenous drug administration. For example, if data from a single extravascular dose is well approximated by a sum of exponentials:

$$C(t) = \sum_{i=1}^{m} A_i e^{-\alpha_i t} \qquad \text{(Eq. 3)}$$

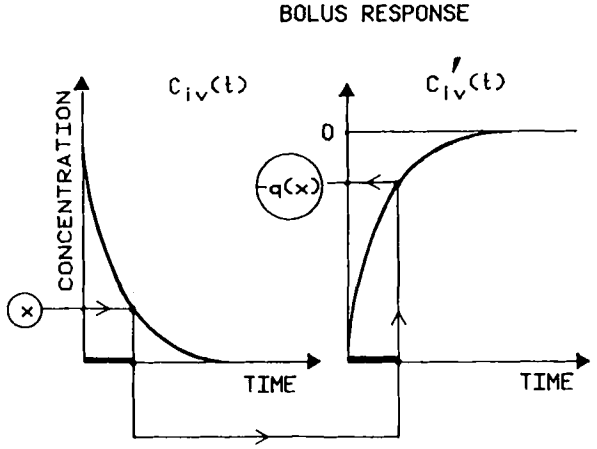

Figure 2—*Empirical evaluation of the disposition function* q *(Eq. 1) according to Eq. 9. The function* $C_{iv}(t)$ *denotes a suitable, monotonically decreasing function fitted to data from an intravenous bolus injection;* $C'_{iv} = dC_{iv}(t)/dt$.

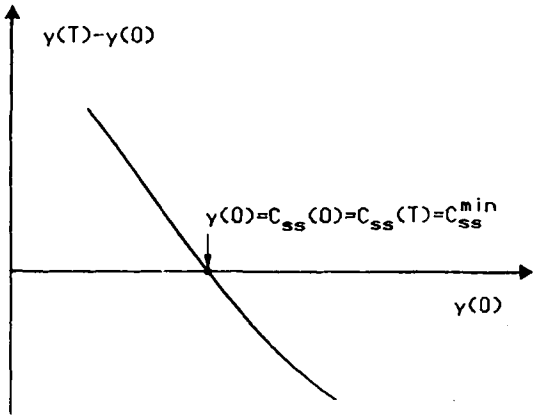

Figure 3—*Boundary value behavior of Eq. 14 (Eq. 13 simplified). An initial value for* y(0) *is chosen and improved by an iterative procedure until the corresponding* y(T) *value, obtained by numerical integration of Eq. 14, is the same as* y(0), *in which case the steady-state solution* $C_{ss}(t) = y(t)$ *is obtained.*

where $\Sigma A_i = 0$, then the steady state can be predicted by:

$$C_{ss}(t) = \sum_{i=1}^{n} \frac{A_i e^{-\alpha_i t}}{1 - e^{-\alpha_i T}} \qquad \text{(Eq. 4)}$$

where T is the dosing interval.

To make predictions in nonlinear pharmacokinetics in a model-independent way, it is, contrary to the linear case above, always necessary to have data available from a known intravenous administration to evaluate and properly account for the basic disposition behavior[2]. In the present case, data from an intravenous administration are used to empirically determine the functional behavior of the disposition function q (Eq. 1) without knowing its functional (algebraic) form. This is done as follows. Let $C_{iv}(t)$ denote a suitable monotonically decreasing equation that fits the intravenous bolus data well (*e.g.*, by least-squares regression):

$$C = C_{iv}(t) \qquad \text{(Eq. 5)}$$

then:

$$\frac{dC}{dt} = dC_{iv}(t)/dt = C'_{iv}(t) \qquad \text{(Eq. 6)}$$

Since $C_{iv}(t)$ is monotonically decreasing its inverse $C_{iv}^{-1}(C)$ exists, and can be found algebraically or numerically:

$$t = C_{iv}^{-1}(C) \qquad \text{(Eq. 7)}$$

Substituting Eq. 7 into Eq. 6 gives:

$$\frac{dC}{dt} = C'_{iv}[C_{iv}^{-1}(C)] \qquad \text{(Eq. 8)}$$

Comparing Eqs. 8 and 1, it is seen that the disposition function q can be evaluated empirically from the function $C_{iv}(t)$ fitted to the intravenous bolus data:

$$q(x) = -C'_{iv}[C_{iv}^{-1}(x)] \qquad \text{(Eq. 9)}$$

The simple evaluation of $q(x)$ is illustrated graphically in Fig. 2.

Consider now a single extravascular dosing, which results in some arbitrary systemic drug input $f(t)$ (mass/time). The differential equation relating to this input is:

$$\frac{dC}{dt} = -q(C) + \frac{f(t)}{v} \qquad \text{(Eq. 10)}$$

where v is a constant of dimension volume. Let $C_f(t)$ denote a suitable arbitrary equation that fits the data from the extravascular dosing well, then $C_f(t)$ should satisfy Eq. 10 to give:

$$f(t) = v[q(C_f(t)) + C'_f(t)] \qquad \text{(Eq. 11)}$$

[2] This may seem as a disadvantage in comparison with the model-dependent methods, where such predictions can be made without this additional information. However, such predictions will be highly inaccurate and unreliable because the disposition parameters in such models are allowed to "float" in an unconstrained way in the curve fitting. There is only hope for reasonable predictions if additional data from an intravenous administration are available, so the disposition parameters can be estimated without the confounding interference from the absorption process.

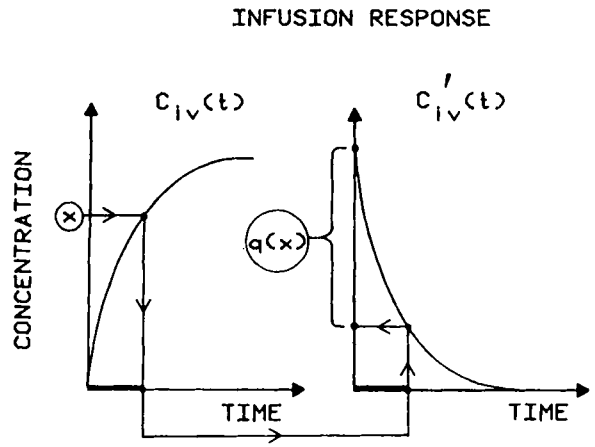

Figure 4—*Empirical evaluation of the disposition function* q *(Eq. 1) according to Eq. 17. The function* $C_{iv}(t)$ *denotes a suitable monotonically increasing function fitted to data from a constant-rate intravenous infusion;* $C'_{iv}(t) = dC_{iv}(t)/dt$.

Consider next the same extravascular dose given to the same subject at regular dosing intervals, T. Let the following assumptions be made:

1. The drug disposition kinetics do not change (kinetic parameters of q are time invariant).
2. The drug absorption $f(t)$ from each dose is reproducible.
3. The drug is absorbed quickly enough in comparison with the dosing interval T, so that the absorption is completed before a new dose is given.

The steady-state drug level profile will, under these assumptions, follow Eq. 10:

$$\frac{dC_{ss}}{dt} = -q(C_{ss}) + \frac{f(t)}{v} \qquad \text{(Eq. 12)}$$

The drug absorption is assumed reproducible; thus, $f(t)$ in Eq. 12 can be substituted with the expression in Eq. 11 to give:

$$\frac{dC_{ss}}{dt} = -q(C_{ss}) + q[C_f(t)] + C'_f(t) \qquad \text{(Eq. 13)}$$

Equation 13 is the final differential equation from which the steady-state drug level profile $C_{ss}(t)$ can be calculated, when data from a single extravascular dose are available in addition to data from an intravenous bolus administration. Mathematically $C_{ss}(t)$ is the solution, $y(t)$, to a boundary value problem, which can be stated in its most simplified form as follows. Find the particular solution $y(t)$ of the differential equation:

$$\frac{dy}{dt} = -q(y) + g(t) \qquad \text{(Eq. 14)}$$

which satisfies the boundary condition:

$$y(0) = y(T) \qquad \text{(Eq. 15)}$$

Equation 14, which is a simplified restatement of Eq. 13, is recognized as a simple first-order differential equation which can be integrated numerically using a suitable algorithm[3]. The initial value $y(0)$ of Eq. 14 is unknown. An initial estimate for $y(0)$ is therefore required as a tentative solution which can be improved in an iterative manner as follows. Integration of Eq. 14 (from $t = 0$ to tT) produces a $y(T)$ corresponding to the current $y(0)$. If $y(T) > y(0)$, then $y(0)$ is too small and must be increased in the next iteration. Similarly if $y(T) < y(0)$, then $y(0)$ should be decreased in the next iteration. The $y(0) - y(T)$ *versus* $y(0)$ relationship is sketched in Fig. 3. The above so-called "shooting method" is a standard approach to solve nonlinear boundary value problems and is easily implemented on a computer. When the process converges, *i.e.*, $y(0) = y(T)$, then the steady-state profile $C_{ss}(t) = y(t)$ is given by the integration of Eq. 14 in the last iteration. The steady-state minimum and maximum levels are simple "by-products" of the process; *i.e.*, $C_{ss}^{min} = y(0) = y(T)$ and C_{ss}^{max} is the maximum value of $y(t)$ reached in the last integration. The mean steady-state level can readily be calculated by integrating the $y(t)$ points (*e.g.*, using a trapezoidal or log-trapezoidal rule) and dividing the area by the dosing interval (4):

$$\bar{C}_{ss} = \int_0^T y(t)dt/T \qquad \text{(Eq. 16)}$$

[3] A Runge-Kutta method (3) appears to be a suitable first choice because of its simplicity and economical evaluation. However, it must be expected that in some cases Eq. 14 may be numerically unstable in the integration region (which varies during the boundary value iterations), in which case the Runge-Kutta method is inaccurate. This inaccuracy can readily be detected by comparing the integration results to those obtained using a substantially smaller (*e.g.*, 1/10) step size. In such cases, it is necessary to switch to a more elaborate and accurate multistep predictor-corrector type algorithm (3).

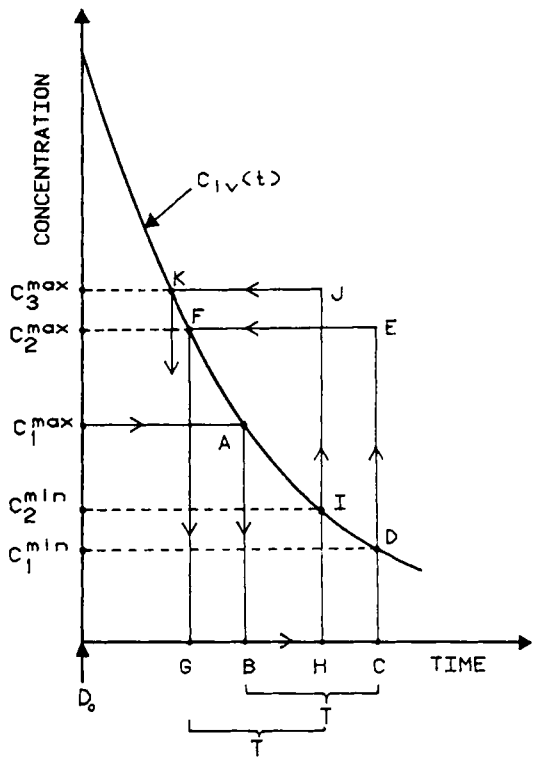

Figure 5—*Hysteresis iteration method (Eqs. 19–24) to predict peak and trough plasma levels in multiple intravenous bolus dosing. The steady-state drug level is reached at convergence when* $C_{n+1}^{max} \simeq C_n^{max}$ *and* $C_{n+1}^{min} \simeq C_n^{min}$. *The function* $C_{iv}(t)$ *denotes a suitable monotonically decreasing function fitted to data from an intravenous bolus administration, and* T *is the dosing period.*

In summary, the steps required to predict the steady-state plasma levels are:

1. Suitable arbitrary equations $C_{iv}(t)$ and $C_f(t)$ are fitted to data from a single intravenous bolus and extravascular (*e.g.*, oral) administration, respectively.
2. The intravenous bolus response approximation, $C_{iv}(t)$, and the absorption response approximation, $C_f(t)$, are differentiated algebraically to define $C'_{iv}(t)$ and $C'_f(t)$.
3. An initial estimate for $y(0)$ is chosen (*e.g.*, zero) and Eq. 14 (*i.e.*, Eq. 13) is integrated repeatedly in an iterative manner that improves the $y(0)$ value until it closely agrees with its corresponding $y(T)$ value. When converged the steady-state drug level is given by the integrated equation, $C_{ss}(t) = y(t)$.

Not all drugs can be given by an intravenous bolus administration due to excessive side effects resulting from a too rapid systemic input. However, Eq. 13 can still be applied if the drug in question can be administered by a constant-rate intravenous infusion. In this case it can be shown (Appendix I) that the disposition function q in Eq. 13 can be evaluated empirically according to:

$$q(x) = C'_{iv}(0) - C'_{iv}[C_{iv}^{-1}(x)] \qquad \text{(Eq. 17)}$$

where C_{iv} (contrary to C_{iv} in Eq. 8) is an arbitrary monotonically increasing function which provides a good fit to the data from the constant-rate drug infusion. The evaluation of $q(x)$ in this case is illustrated graphically in Fig. 4.

A simple precaution must be taken in the initial ($t = 0$) evaluation of q during the numerical integration of Eq. 14 (Eq. 13). An evaluation of $q(0)$ according to Eq. 9 may cause floating point overflow. For example, if a monotonically decreasing function $C_{iv}(t)$ which asymptotically approaches zero for $t \to \infty$ has been chosen for the intravenous bolus approximation, then $C_{iv}^{-1}(x) \to \infty$ for $x \to 0$ and $C_{iv}^{-1}(0)$ is not defined. Thus, $q(0)$ cannot be evaluated according to Eq. 9 in this case. However, by setting $q(0) = 0$ (see Appendix I) the problem is readily solved. Subsequent evaluations of $q(x)$ for $x > 0$ should not cause any numerical problems.

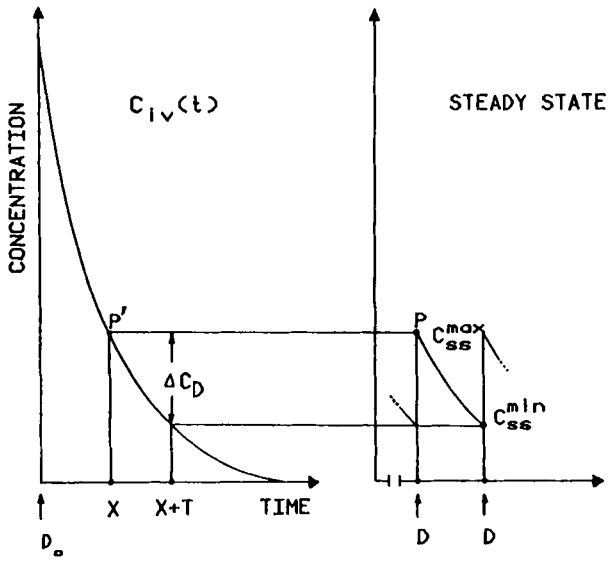

Figure 6—*Solution configuration of the root-solving method (Eq. 30) to determine the steady-state peak and trough drug levels in intravenous bolus administration. The function $C_{iv}(t)$ denotes a suitable, monotonically decreasing function fitted to data from an intravenous bolus administration, and T is the dosing period.*

The evaluation of the inverse $C_{iv}(t)$ function (Eq. 7) is done in a straightforward manner by numerically finding the root, t, of the expression:

$$C - C_{iv}(t) = 0 \qquad \text{(Eq. 18)}$$

for given values of C, where $C_{iv}(t)$ is the function previously fitted to the data from the intravenous drug administration. Most scientific computer program libraries (5-7) and many books dealing with numerical analysis (3, 8) have general programs for finding the root of an arbitrary nonlinear equation, suitable for solving Eq. 18 in a routine manner. The same root-finding algorithm used to solve Eq. 18 can also be used in the "shooting method" to find the root of the boundary value function (Fig. 3).

It is evident from Eq. 13 that in order to calculate the steady-state drug levels, the single-dose response function $C_f(t)$ only needs to be evaluated in the time interval $t = 0$ to $t = T$. This is a definite advantage, since the difficult problem of evaluating or extrapolating $C_f(t)$ beyond $t = T$ is avoided. This would not be the case for a method that makes use of area under the curve (AUC) or total clearance.

Steady-State Prediction of Intravenous Bolus Dosing—The following derivation shows how the plasma level profile in any drug interval in multiple dosing can be predicted from data from a single intravenous bolus dosing. Let $C_{iv}(t)$ denote an arbitrary monotonically decreasing function that provides a good fit to data from an intravenous bolus dose D_0. If after the drug is eliminated the same subject is given an intravenous bolus dose D every T hours,

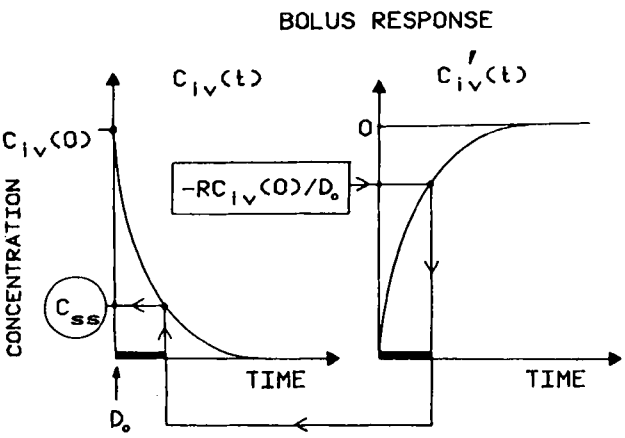

Figure 7—*Method to predict the steady-state drug level, C_{ss}, resulting from a constant rate, R, drug infusion. The prediction is done according to Eq. 36 on the basis of data from an intravenous bolus (D_0) administration. The function $C_{iv}(t)$ denotes a suitable monotonically decreasing function fitted to the intravenous bolus data; $C'_{iv}(t) = dC_{iv}(t)/dt$.*

then the predicted initial concentration C^{max} will be $DC_{iv}(0)/D_0$ if it is assumed that the autonomic nonlinear pharmacokinetics show a dose-linear initial behavior. This appears a reasonable assumption, since the nonlinearity is more likely to be due to secretion and metabolic processes than to the initial distribution.

The decline in the drug level from C_1^{max} will, due to the horizontal superposition property (Fig. 1), follow the $C_{iv}(t)$ curve. Thus, if point A in Fig. 5 is the point on the $C_{iv}(t)$ curve at the C_1^{max} level, then the first dosing profile is predicted by the curve segment AD which stretches over T hours (BC, Fig. 5). When the second dose is given at point D, then the drug level rises to point E where ED = AB = C_1^{max} (Fig. 5). Point E (C_2^{max}) is projected to point F on the $C_{iv}(t)$ curve. Point F now becomes the new point replacing the original point A and the same procedure is iterated, *i.e.*, GH = T hours, I = C_2^{min}, J = C_3^{max}, *etc.*

The peak and trough levels C_n^{max} and C_n^{min} ($n = 1, 2, \ldots$) can quickly be predicted graphically according to this hysteresis iteration method. However, it is more accurate to evaluate these quantities on a computer according to the corresponding algorithm, specified by Eqs. 19-24:

$$C_1^{max} = DC_{iv}(0)/D_0 \qquad \text{(Eq. 19)}$$

$$n = 1 \qquad \text{(Eq. 20)}$$

$$t = C_{iv}^{-1}(C_n^{max}) + T \qquad \text{(Eq. 21)}$$

$$C_n^{min} = C_{iv}(t) \qquad \text{(Eq. 22)}$$

$$n = n + 1 \qquad \text{(Eq. 23)}$$

$$C_n^{max} = C_{n-1}^{min} + C_1^{max} \qquad \text{(Eq. 24)}$$

The peak and trough levels are obtained sequentially when iterating Eqs. 21-24 as indicated. The iterations will eventually converge such that $C_{n+1}^{max} \simeq C_n^{max}$ and $C_{n+1}^{min} \simeq C_n^{min}$, in which case, by definition, the steady-state drug level profile has been reached. The mean steady-state drug level can subsequently be calculated from:

$$\bar{C}_{ss} = \int_{t-T}^{t} C_{iv}(u)du/T \qquad \text{(Eq. 25)}$$

where t in Eq. 25 is the t value calculated in Eq. 21 at convergence.

The steady-state drug levels can be calculated more directly without having to evaluate the inverse $C_{iv}(t)$ function (Eq. 21) according to the following alternative method. The peak level at steady state is equal to the trough level plus the concentration increment ΔC_D resulting from the dose injected at the end of the dosing interval:

$$C_{ss}^{max} = C_{ss}^{min} + \Delta C_D \qquad \text{(Eq. 26)}$$

As previously discussed, it is assumed that the pharmacokinetics show a dose-linear initial value behavior, so that ΔC_D is proportional to the dose:

$$\Delta C_D = D/V \qquad \text{(Eq. 27)}$$

Equation 26 can, as illustrated in Fig. 6, be transformed into an equivalent expression involving C_{iv}:

$$C_{iv}(X) = C_{iv}(X + T) + \Delta C_D \qquad \text{(Eq. 28)}$$

The proportionality term V in Eq. 27 is given by:

$$V = D_0/C_{iv}(0) \qquad \text{(Eq. 29)}$$

Combining Eqs. 27-29 yields the expression:

$$C_{iv}(X + T) + \frac{D}{D_0} C_{iv}(0) - C_{iv}(X) = 0 \qquad \text{(Eq. 30)}$$

Solving Eq. 30 for X numerically using any suitable general purpose root-finding program will subsequently give the steady-state peak, trough, and mean drug levels:

$$C_{ss}^{max} = C_{iv}(X) \qquad \text{(Eq. 31)}$$

$$C_{ss}^{min} = C_{iv}(X + T) \qquad \text{(Eq. 32)}$$

$$\bar{C}_{ss} = \int_{X}^{X+T} C_{iv}(u)du/T \qquad \text{(Eq. 33)}$$

The root-solving method (Eq. 30) is the most suitable because of its simplicity when the primary interest is to predict the steady-state quantities $\bar{C}_{ss}$, C_{ss}^{max}, and C_{ss}^{min}. However, if additionally it is desirable to evaluate how long (nT) it will take to reach 90% of steady state, then the hysteresis iteration method (Eqs. 19-24) must be used.

Steady-State Prediction of Constant-Rate Infusion—The differential

equation describing the drug level profile resulting from a constant-rate (R) intravenous infusion is given by Eq. 1A (see Appendix I). At steady state, $dC/dt = 0$, in which case Eqs. 1A and 29 give:

$$q(C_{ss}) = RC_{iv}(0)/D_0 \qquad \text{(Eq. 34)}$$

Let $q^{-1}(x)$ denote the inverse of the disposition function; then, the steady-state level is obtained by inversion of Eq. 34:

$$C_{ss} = q^{-1}(RC_{iv}(0)/D_0) \qquad \text{(Eq. 35)}$$

The problem is now to evaluate the $q^{-1}(x)$ function, which is best illustrated graphically as "q evaluated in reverse." If $-q(x)$ in Fig. 2 is set equal to $-RC_{iv}(0)/D_0$, then x will be $q^{-1}(RC_{iv}(0)/D_0)$, *i.e.*, x will be C_{ss} (Eq. 35). From this it is seen (Fig. 2) that:

$$C_{ss} = C_{iv}\,[C_{iv}^{-1}(-RC_{iv}(0)/D_0)] \qquad \text{(Eq. 36)}$$

where $C_{iv}^{-1}(\ )$ denotes the inverse of the $C_{iv}'(\ )$ function. Equation 36 enables the steady-state drug level resulting from a constant-rate (R) drug infusion to be predicted in a model-independent manner when data from an intravenous bolus dose (D_0) are available. The procedure is simply:

1. A suitable monotonically decreasing function $C_{iv}(t)$ is fitted (*e.g.*, by least-squares technique) to the intravenous bolus data to appropriately approximate the bolus response.
2. The function is differentiated to give $C_{iv}'(t)$.
3. The predicted steady-state drug level is calculated according to Eq. 36.

The evaluation procedure is graphically illustrated in Fig. 7. The evaluation of the inverse of $C_{iv}'(t)$ (Fig. 7) can be done readily in the same way as the inverse of $C_{iv}(t)$, as previously discussed (Eq. 18).

DISCUSSION

The above derivations and theoretical analysis have shown how steady-state predictions can be made for extravascular, intravenous bolus, and intravenous infusion administrations for drugs showing autonomic nonlinear pharmacokinetics. The methodology is certainly not a general solution to the very difficult prediction problems in nonlinear pharmacokinetics. However, the methodology does seem appealing because it is model independent and requires few assumptions, which can be tested readily (*e.g.*, the horizontal superposition property, Fig. 1). It represents a novel alternative that appears less academic and more practical than the model-dependent methods with their often unrealistic kinetic assumptions and computational complexity. The methodology avoids the very difficult and often impractical task of identifying and incorporating the numerous kinetic parameters and processes responsible for the observed drug concentration data into a useful mathematical model. The focus in the kinetic analysis is instead on two much simpler processes: (*a*) fitting empirical functions to drug concentration data to estimate the mean drug disposition behavior of the subject or population (*i.e.*, the disposition function q) and (*b*) testing the validity of the assumptions involved.

The empirical sum of exponentials, which are fitted quite successfully in linear pharmacokinetics, apparently do not fit nonlinear pharmacokinetic data properly. Preliminary investigations were therefore carried out to identify a suitable type of function that could be used. It was found that the following function:

$$C_{iv}(t) = \frac{p_1 e^{-p_2 t}}{1 + e^{(p_3 - p_4 t)}} \qquad p_i > 0 \qquad \text{(Eq. 37)}$$

produced very excellent fits to all typical Michaelis-Menten type intravenous bolus data investigated. Extensions of the numerator and denominator in Eq. 37 to include more exponential terms seem to hold some promise for other types of administrations and other types of nonlinearities. Alternatively, the use of least-squares splines may provide a more general and flexible approximation approach (9). Work is in progress to experimentally investigate the methodology proposed.

APPENDIX I

The differential equation describing the drug level profile resulting from a constant-rate (R) intravenous infusion is:

$$\frac{dC}{dt} = -q(C) + \frac{R}{V} \qquad \text{(Eq. 1A)}$$

Let $C_{iv}(t)$ denote an arbitrary monotonically increasing function which fit the data from a constant-rate infusion well; then, dC/dt can be determined according to Eq. 8 as previously described. By comparing Eqs. 1A and 8, it is seen that the disposition function q can be estimated empirically from the function $C_{iv}(t)$ fitted to the intravenous infusion data according to:

$$q(x) = \frac{R}{V} - C_{iv}'(C_{iv}^{-1}(x)) \qquad \text{(Eq. 2a)}$$

It is evident from Eq. 1 that $q(0) = 0$ since $dC/dt = 0$ for $C = 0$ following an intravenous bolus administration. Thus, the volume term in Eq. 2A can be evaluated from the initial condition of Eq. 1A to give:

$$V = R/C_{iv}'(0) \qquad \text{(Eq. 3A)}$$

Inserting this expression for V into Eq. 2A gives Eq. 17.

APPENDIX II: GLOSSARY

A_i, α_i = Constants (parameters) of an empirical equation (Eq. 3)
C = Drug concentration
$C_f(t)$ = Drug concentration-time profile resulting from an arbitrary rate of systemic input $f(t)$
$C_f'(t)$ = $dC_f(t)/dt$
$C_{iv}(t)$ = Drug concentration-time profile resulting from an intravenous bolus dose or a constant-rate drug infusion (as indicated)
$C_{iv}^{-1}(\ )$ = Inverse function of $C_{iv}(t)$
$C_{iv}'(t)$ = $dC_{iv}(t)/dt$
$C_{iv}^{-1}(\ )$ = Inverse function of $C_{iv}'(t)$
C_n^{max}, C_n^{min} ($n = 1, 2, \ldots$) = Peak and trough drug concentrations, respectively, in the nth dosing period in an intravenous bolus dosing regimen
C_{ss} = Steady-state drug concentration
$\bar{C}_{ss}$ = Mean steady-state drug concentration
D = Intravenous bolus dose in multiple administration
D_0 = Intravenous bolus dose in a single administration
$f(t)$ = Arbitrary rate of systemic drug input (mass/time) resulting from an extravascular dose
$g(t)$ = $q[C_f(t)] + C_f'(t)$ (Eq. 14)
K = Constant kinetic parameter (Eq. 2)
K_m = Michaelis-Menten parameter (Eq. 2)
p_i = Constants (parameters) of an empirical equation (Eq. 37)
$q(\ )$ = Disposition function (Eq. 1)
$q^{-1}(\ )$ = Inverse of the disposition function q
R = Constant rate of intravenous drug infusion
t = Time
T = Dosing interval
v = Constant of dimension volume
V_m = Michaelis-Menten parameter (Eq. 2)
y = Variable defined by Eqs. 13 and 14

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