The Use of Multiple Doses and Pharmacodynamic System Analysis to Distinguish Between Dispositional Delays and Time-Variant Pharmacodynamics

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Pharmacokinetic-pharmacodynamic modeling algorithms, in general, rely on hysteresis minimization techniques that assume time-invariant pharmacodynamics (constant biophase concentration-effect relationships). When time-variant pharmacodynamics are observed, a specific model for tolerance or sensitization is required. However, with single dosing, hysteresis that results from a time-variant biophase concentration-effect relationship cannot be distinguished from hysteresis caused by dispositional delays. This can lead to the inappropriate minimization of hysteresis. As an approach to this problem, simulated and real kinetic-dynamic data were analyzed with the pharmacodynamic system analysis program ATTRACT. The use of a multiple dosing regimen and this hysteresis minimization algorithm resulted in a simple diagnostic test to distinguish between dispositional effects of acute tolerance and sensitization.

KEY WORDS: pharmacodynamic system analysis; hysteresis; time-variant pharmacodynamics; dispositional delay.

INTRODUCTION

We have examined the application of the pharmacodynamic system analysis software, ATTRACT (1) to distinguish between hysteresis resulting from dispositional delays, and hysteresis resulting from time-variant pharmacodynamics. For the purpose of this discussion, dispositional delays include: 1) any delay in the distribution of active drug to the effect site, relative to the sampling site, 2) any delay in effect onset caused by the linear formation of an active metabolite, including any delay in the distribution of such a metabolite to its effect site. Time-variant pharmacodynamics refers to a biophase drug concentration-effect relationship that does not obey the principle of stationarity (is not constant over time). Most pharmacokinetic-pharmacodynamic modeling methods are based on hysteresis minimization techniques that assume time-invariant pharmacodynamics (no acute tolerance or sensitization), i.e., the hysteresis is due to dispositional factors (2). Otherwise, a parametric pharmacodynamic model would be needed to define the pharmacodynamic time-dependence (3). However, nonparametric hysteresis minimization algorithms that make the assumption of time-invariant pharmacodynamics could be useful diagnostic tools for the identification of time-variant pharmacodynamic systems if it can be shown that the hysteresis is not due to dispositional effects.

The theoretical framework underlying the pharmacodynamic system analysis software, ATTRACT, has already been described in detail (1). The system analysis approach is primarily aimed at the prediction of drug response and not at estimating model parameters, or structures. Basically, the model links a predictor variable to a response. The predictor variable (usually plasma concentration) is linearly related to the biophase drug concentration by the convolution of the plasma concentration-time function with an exponential function called the *conduction function*. When this is a monoexponential function, the first-order rate constant describing the lag to the biophase is equivalent to the rate constant describing elimination from the effect compartment in a classical effect-compartment model, i.e. k_{e0}. The resulting biophase concentration is directly related to the predicted response (or effect) by the second component of the system analysis model, known as the *transduction function*. The conduction and transduction functions can be thought of as the dispositional and effect components, respectively, of the system analysis model. In order to maintain consistency with the terminology in the ATTRACT software, the terms conduction function and transduction function have been used in this discussion.

Although it is not crucial for some system analysis models to assume time-invariant pharmacodynamics (4), the accurate minimization of hysteresis by the ATTRACT algorithm depends upon this assumption. As explained by Veng-Pedersen and Modi (1), sensitization or tolerance can result in the incomplete minimization of the hysteresis loop by ATTRACT because of the dependence of the transduction function on a prior drug concentration (or predictor variable). Alternatively, this situation can lead to a false collapse of the hysteresis. The ATTRACT algorithm generates an apparent biophase concentration-effect relationship (transduction data) by estimating a conduction function that would minimize the hysteresis in the plasma drug concentration-effect relationship. Therefore, acute sensitization of the pharmacological effector, for example, would be treated as a component of the conduction function and appear as a distribution lag. This is especially true for the hysteresis resulting from a single dose of drug.

Hysteresis loops are caused by either dispositional effects, time variant pharmacodynamics, or a combination of the two. Therefore, if it can be shown that hysteresis is not entirely due to dispositional effects, time-variant pharmacodynamics would be implicated. The analysis of concentration-effect data from a single dose experiment does not allow the separation of these two components. However, the analysis of data from a multiple dose scenario, exhibiting more than one hysteresis loop, should identify whether or not the hysteresis is caused by dispositional effects.

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METHODS

Simulation of Plasma Concentrations

An open one-compartment model with zero-order input was used to simulate the plasma concentration-time curves (Equation 1):

$$C_t = \frac{R_0}{V \cdot K} \cdot (1 - \exp^{-K \cdot \tau}) \qquad when\ t \leq \tau \qquad (1)$$

$$C_t = \frac{R_0}{V \cdot K} \cdot (1 - \exp^{-K \cdot \tau}) \cdot \exp^{-k \cdot (t-\tau)} \qquad when\ t > \tau$$

where C_t is the plasma concentration at time t, R_0 is the zero-order of infusion, V is the volume of distribution, K is the elimination rate constant and τ is the duration of the infusion (5). The same plasma concentration-time data were used for all pharmacokinetic-pharmacodynamic simulations; only the link model and pharmacodynamic model were changed. In both simulation studies (sensitization and dispositional hysteresis), the model was dosed twice: once at 0 minutes and once at 20 minutes. This was accomplished by applying the principle of superposition and summing the responses from each single dose. Plasma and effect samples were taken at 0, 2, 4, 5, 10, 15, 20, 22, 24, 25, 30, 35, 40, 45, and 50 minutes. Table I summarizes the pharmacokinetic and pharmacodynamic parameters used for all of the simulations.

Acute Sensitization of the Pharmacological Response

A multiple infusion experiment was simulated with a hypothetical pharmacokinetic-pharmacodynamic model that demonstrated acute sensitization of the pharmacological response. The pharmacokinetic model was described above. The pharmacodynamic component of the model described an effect that increased as a function of time (t) and plasma concentration (Cp) (Equation 2):

$$E_t = \left(\frac{E_{max} \cdot C_p}{EC_{50} + C_p}\right) \cdot q \qquad (2)$$

where E_t is the drug effect at time t, E_{max} is the maximal effect, EC_{50} is the plasma concentration at half-maximal effect and q is an arbitrary time-variant parameter (increasing over time to simulate sensitization) that was generated from $t/(a + t)$, where a is a function regulating the degree of sensitization over time (t).

This time-variant pharmacodynamic model is a simple, empirical representation of a time-dependent biophase concentration-effect relationship and was employed for the sole purpose of generating hysteresis due to time-variant pharmacodynamics. A more complex, physiologically-realistic model of sensitization could also have been employed. The model was dosed twice (at 0 and 20 minutes) with a five-minute zero-order infusion of 100 mass units of drug. The simulated data from 0 to 20 minutes (first infusion only) and 0 to 50 minutes (entire simulation) were analyzed with ATTRACT in order to illustrate the problem associated with a single dose experiment.

Acute Tolerance of the Pharmacological Response

It is well known that nicotine's effect on heart rate exhibits acute tolerance (6, 7). Data from a published pharmacokinetic-pharmacodynamic study of tolerance to nicotine's effect on heart rate (3) were modeled with ATTRACT. In these experiments, a time-variant pharmacodynamic profile (tolerance) was observed when two intravenous infusions of nicotine (2.5 μg/kg/minute for 30 minutes each, separated by 60 minutes) were administered to smokers. These experiments resulted in successive proteresis (clockwise hysteresis) loops between plasma nicotine concentration and effect. Published data from these experiments were obtained and analyzed with ATTRACT.

Dispositional Delay

Finally, a multiple infusion experiment was simulated with a hypothetical time-invariant pharmacokinetic-pharmacodynamic model. The same pharmacokinetic model as described above was used to simulate plasma concentration over time after the two infusions. A dispositional delay to the biophase was modeled with an effect compartment (Equation 3) (2):

$$C_{e_t} = \frac{R_0 \cdot K_{e0}}{V} \cdot \left\{\frac{(1 - \exp^{-K \cdot \tau})}{K \cdot (K_{e0} - K)} + \frac{(1 - \exp^{-K \cdot t})}{K \cdot (K_{e0} - K)}\right\} \qquad when\ t \leq \tau \qquad (3)$$

$$C_{e_t} = \frac{R_0 \cdot K_{e0}}{V} \cdot \left\{\frac{(1 - \exp^{-K \cdot \tau})}{K \cdot (K_{e0} - K)} \cdot \exp^{-K \cdot (t-\tau)} + \frac{(1 - \exp^{-K_{e0} \cdot t})}{K_{e0} \cdot (K - K_{e0})} \cdot \exp_{-K_{e0}(t-\tau)}\right\} \qquad when\ t > \tau$$

where C_{et} is the effect compartment drug concentration at time t and K_{e0} is the first-order rate constant governing the disappearance of effect. The pharmacodynamic model linked the concentration of drug in the effect compartment to effect via a standard E_{max} model (Hill coefficient of 1, see Table I for parameter values). Therefore, both hysteresis loops were caused solely by a delay in distribution of drug to the biophase, relative to the plasma. Data from the entire simulation were modeled with the ATTRACT algorithm.

RESULTS AND DISCUSSION

The plasma concentration-effect relationship resulting from the sensitization simulation is shown in Figure 1. The pharmacodynamic system analysis resulted in a complete

Table I. Pharmacokinetic and Pharmacodynamic Model Parameters Used in the Simulation of Concentration-Effect Data[a]

Dose	Rate (R_0)	Duration (τ)	V	K	K_{e0}	E_{max}	EC_{50}	a
100	20	5	10	0.08	0.1	1	10	50

[a]All parameter values are expressed in arbitrary units of mass and volume. Time is in minutes; dosing rate (amount/minute), dosing interval (minutes), and rate constants (minutes^{-1}).

collapse of the first hysteresis loop (0 to 20 minutes) (Figure 2). However, when the entire data set, including both hysteresis loops, was analyzed with the ATTRACT algorithm, the resulting biophase concentration-effect relationship was not completely collapsed (Figure 3). In fact, some proteresis (clockwise hysteresis) is evident in the second loop. This is due to the under-estimation of the conduction function rate constant when the first loop is collapsed. Sensitization is hidden as a component of the conduction function, so the rate of conduction (distribution to and from the biophase) appears to be slower than it actually is (appears as greater time lag to the biophase). Since the model is a linear system and follows superposition, the model biophase concentration lingers longer than the actual biophase concentration does. Thus the model over-estimates the biophase concentration at the late time points, leading to proteresis. A time-variant transduction function cannot be hidden by the conduction function in a multiple dose experiment because the changing transduction function would necessitate a different conduction function for each hysteresis loop.

The model used for this simulation is a simplistic representation of sensitization. A complex sensitization model, such as a positive feedback model, is probably more physiologically realistic, and might result in data that would make the distinction between dispositional effects and time-variant pharmacodynamics more difficult. However, even the simple empirical model used here provides the most important component; a transduction function that is not constant with time.

Acute tolerance also prevents the complete collapse of proteresis loops by the pharmacodynamic system analysis algorithm. The nicotine plasma concentration-effect relationship after successive intravenous infusions exhibits two proteresis loops. When these data were analyzed with ATTRACT, the result was the inability to collapse the proteresis (Figure 4). In the absence of any dispositional delays, acute tolerance results in an effect-time curve that reaches a maximum before the plasma concentration-time curve does. It is impossible by a convolution type operation to arrive at a biophase concentration-time curve that peaks earlier than the plasma concentration-time curve when plasma concentration is the predictor variable. Thus, tolerance cannot be accounted for by a linear convolution type of conduction function.

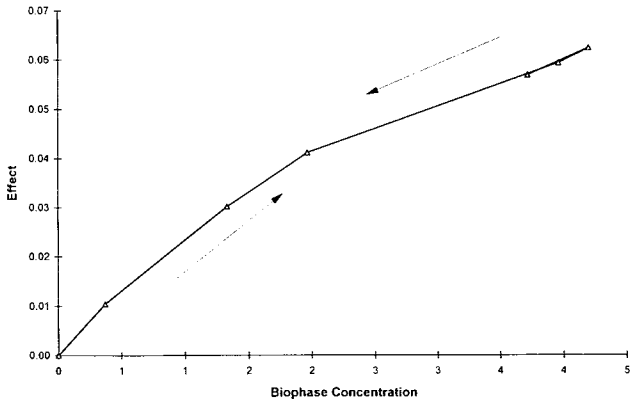

Figure 2: Pharmacodynamic system analysis of one dose from the model-simulated multiple infusion experiment with sensitization. Data from the first loop (0 to 20 minutes) of the multiple hysteresis shown in Figure 1 were analyzed with ATTRACT. The resulting biophase concentration-effect relationship is shown. Effect and concentration are expressed in arbitrary units. Arrows indicate the sequence of events over time.

Finally, a time-invariant pharmacokinetic-pharmacodynamic relationship was analyzed with the pharmacodynamic system analysis. The multiple infusion experiment simulated with the distribution lag model resulted in successive hysteresis loops (Figure 5). The hysteresis loops were completely collapsed with the ATTRACT algorithm (Figure 6). This is to be expected, since both the transduction and conduction functions are constant over time.

Although it is difficult to distinguish between dispositional hysteresis and hysteresis due to time-variant pharmacodynamics with data from a single dose study, pharmacodynamic system analysis of a multiple dose experiment allows for such a distinction, providing a semi-diagnostic tool.

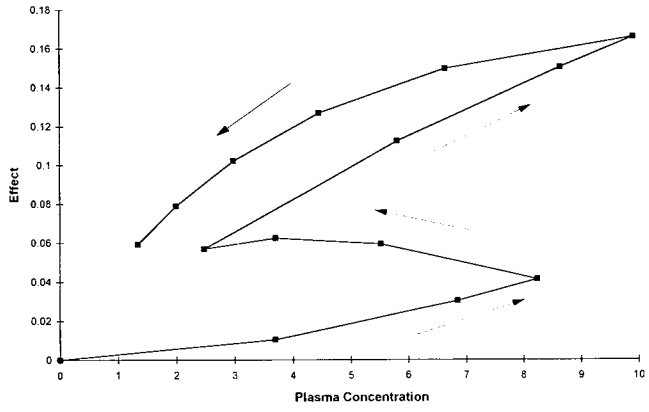

Figure 1: Model-simulated plasma concentration-effect relationship of a multiple infusion experiment showing sensitization. The pharmacodynamic model in this simulation generated an effect which was proportional to plasma drug concentration and sensitized with time. Effect and concentration are expressed in arbitrary units. Arrows indicate the sequence of events over time.

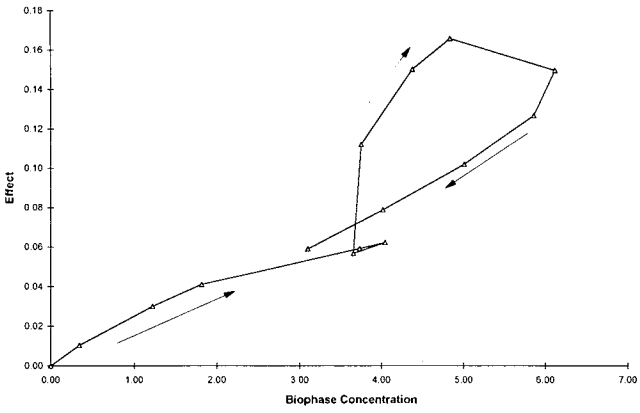

Figure 3: Pharmacodynamic system analysis of the model-simulated multiple infusion experiment with sensitization. The entire data set (0 to 50 minutes) from the multiple hysteresis simulation shown in Figure 1 was analyzed with ATTRACT. The resulting biophase concentration-effect relationship is shown. Effect and concentration are expressed in arbitrary units. Arrows indicate the sequence of events over time.

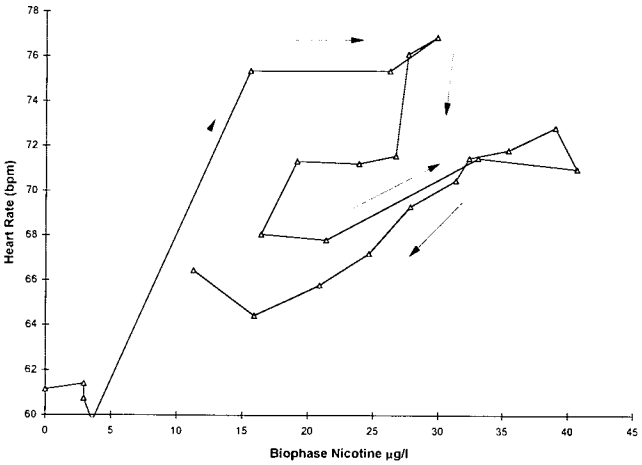

Figure 4: Pharmacodynamic system analysis of a multiple infusion experiment demonstrating acute tolerance to nicotine's effect on heart rate. The biophase concentration-effect relationship resulting from the attempted hysteresis minimization of published nicotine plasma concentration-effect data is shown. Arrows indicate the sequence of events over time.

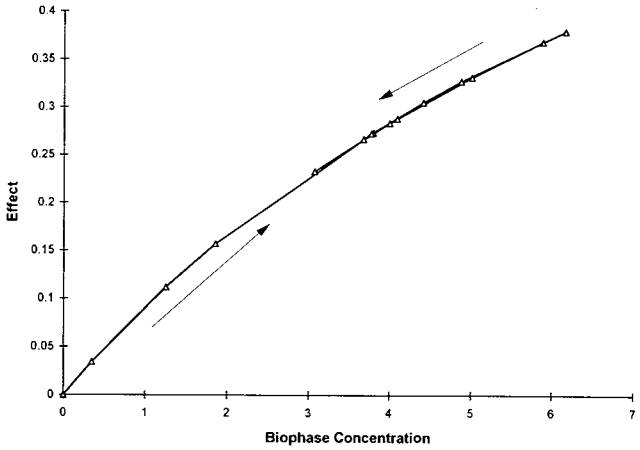

Figure 6: Pharmacodynamic system analysis of a model-simulated multiple infusion experiment demonstrating hysteresis due to a dispositional delay. The simulated data from Figure 5 were analyzed with ATTRACT and the resulting biophase concentration-effect relationship is shown. Effect and concentrations are expressed in arbitrary units. Arrows indicate the sequence of events over time.

Two of the examples described above do not incorporate experimental error and it is important to note that small time-variant effects could be difficult to identify with "noisy" data. Pronounced time-variant pharmacodynamics however, should easily be distinguished from pre-steady state distribution (dispositional) effects with this multiple-dose technique. It is also important to remember that these conclusions are only valid if basic assumptions (time-invariant linear drug distribution from the sampling site to the biophase and immediate, reversible transduction of the biophase drug concentration to a response) of the pharmacodynamic system analysis algorithm are met.

While the minimization of a single-dose hysteresis loop allows the simulation of observed effect after one dose, it does not accurately describe the hysteresis and will not predict the effect observed after multiple dose. The pharmacodynamic system analysis of multiple-dose experiments provides a means of extending the hysteresis minimization approach and the information gained.

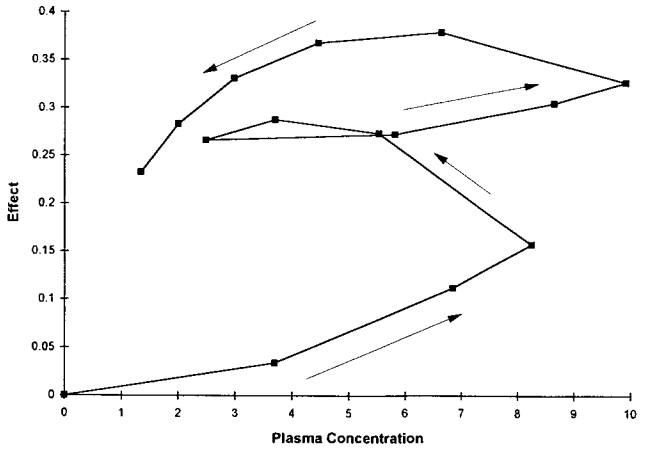

Figure 5: Simulation of hysteresis resulting from a multiple dose experiment with a time-invariant pharmacodynamic model and a biophase distribution delay. Effect and concentration are expressed in arbitrary units. Arrows indicate the sequence of events over time.

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