Pharmacodynamics and Drug Development
Perspectives in Clinical Pharmacology

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2 Simultaneous Pharmacokinetic/ Pharmacodynamic Modeling

WAYNE A. COLBURN AND MICHAEL A. ELDON

Simultaneous pharmacokinetic/pharmacodynamic modeling is the use of integrated pharmacokinetic and pharmacodynamic models to interpret and extrapolate the temporal relationship between some sampled drug concentration and observed drug effect. The basis for such modeling is the need to analyze and describe measurable concentration–effect data, as well as to make clinically relevant extrapolations from experimental conditions to therapeutic conditions. Investigation of drug action using pharmacokinetic or dose–response models is well established in clinical pharmacology; the linking of these tools through specific mathematical models is relatively new.

Pharmacokinetics contributes to clinical pharmacology by providing a means to characterize drug distribution and elimination. Its usefulness is predicated on the assumption that measurable drug concentrations are related to drug effect in some manner, thereby forming the basis for determining concentration–effect relationships (pharmacodynamics) and employing therapeutic drug monitoring. In recent years, significant advances have been made in technologies to measure drug and metabolite concentrations in biological matrices, further advancing the use of pharmacokinetics as an adjunct to optimizing drug therapy. Concurrent advances in the ability to quantitate and understand drug effects have similarly promoted the study and use of pharmacodynamics.

Pharmacokinetic/pharmacodynamic relationships have been investigated in two general approaches. The first approach involves the determination of drug effect and concentration over a series of doses administered to a relatively large patient population. Correlation of concentration and effect is performed retrospectively, usually resulting in the determination of target plasma drug concentration ranges which are thought to provide some level of drug effect while minimizing the risk of toxicity (1). Unfortunately, this approach is relatively imprecise due to its sensitivity to inter-subject variability in pharmacokinetic as well as pharmacological factors. It is the imprecision and non-specificity of this method which requires the study of large numbers of patients to determine a therapeutic dose range, and even then may lead to

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inappropriate conclusions that drug effect and blood or plasma drug concentrations are 'not correlated'.

The relevant question is not whether concentration and effect are related for a given drug, but rather how are they related and what is necessary to elucidate the relationship. Answering these questions is the goal of the second approach, which involves correlation of graded pharmacological responses with circulating drug concentration in a smaller number of patients. This more specific approach allows investigation of the nature of drug effect and its relationship to drug concentration, while minimizing the impact of pharmacokinetic and pharmacodynamic inter-subject variability.

This chapter is concerned with the latter approach and gives an overview of key developments during evolution of simultaneous pharmacokinetic/pharmacodynamic modeling, a review of contemporary methods, and goals for future refinement of the topic. Detailed discussion of pharmacokinetic theory and practice will not be given here. The reader is directed to excellent references on the topic (2,3) for further information.

EVOLUTION TO THE PRESENT

PHARMACOKINETIC APPROACHES

The evolution to simultaneous modeling was based on the desire to refine understanding of drug action. This was expressed in 1967 by Brodie (4) when he observed that fewer patients were required to determine antimalarial activity if drug effect was correlated to plasma concentration rather than dose. In retrospect, this observation could most likely be attributed to the reduction of inter-subject variability in the pharmacokinetic component of the dose–response relationship. During this stage of evolution, Levy (5) proposed that for many drugs, the intensity of effect was linearly related to log concentration over the range of 20–80% of the maximum possible effect (E_{max}). He suggested the following equation to describe the concentration–effect relationship after intravenous drug dosing:

$$E = m \cdot \log A + e \qquad (1)$$

where E is the effect intensity, A is the amount of drug present (which may be represented by concentration values), m is the slope of the linear plot of E versus log A, and e is the intercept of that plot. This equation is based on the assumption that effect is directly related to drug concentration at the site of action and is rapidly reversible. However, the log transformation is only pseudo-linear over the 20–80% effect range, owing to the underlying sigmoid nature of the dose–response relationship.

Assuming that the drug exhibited a one-compartment pharmacokinetic profile, Levy further proposed the following equation to describe the decline of effect after intravenous drug administration (5):

$$E = E_i - (K \cdot m)/2.3 \cdot t \tag{2}$$

where E_i is the initial effect intensity, K is the apparent first-order elimination rate constant, t is time, and all other parameters are as previously defined. These equations predict that the intensity of effect is linearly related to log concentration, and that effect declines linearly rather than exponentially following bolus drug administration. The practice of relating effect to log concentration data was a logical extension of analyzing dose–response relationships using the log transform. The log transform does compress the dose or concentration range and linearize the concentration–effect relationship over the inner 20–80% of the effect range. However, as discussed by Holford and Sheiner (6), this method of data analysis does not explain effect at the extremes of the concentration range (i.e., zero effect when no drug is present), provide a means to estimate E_{max}, or accommodate the existence of baseline effect. While the log transformation may be applicable for specific drugs, it is not a suitable substitute for characterizing the entire range of the dose or concentration–effect relationship as later described in the sections on parametric and semi-parametric methods.

Additionally, Equations 1 and 2 do not permit assessment of the delay in onset of drug effect following administration by routes requiring drug absorption or distribution before reaching the effector site, or the persistence of effect when drug is no longer present in plasma. This delay in drug equilibration between the sampled biofluid and the responding tissue gives rise to hysteresis in the effect versus concentration plot as shown in Figure 1.

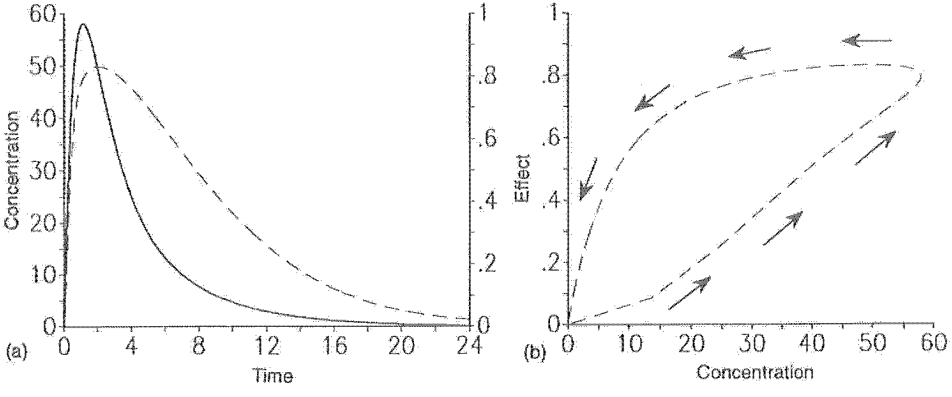

Figure 1. (a) Theoretical plasma concentration (solid line) and effect (dashed line) profiles versus time following extravascular drug administration. (b) Corresponding counterclockwise hysteresis plot of effect versus plasma concentration data from (a)

Levy *et al.* (7) addressed the problem of equilibration delay by extending the relationships described by Equations 1 and 2 to include multicompartment pharmacokinetic models and empirically comparing pharmacokinetic and drug effect profiles. This approach was used to investigate the relationship between mental performance test scores and predicted lysergic acid diethylamide (LSD) pharmacokinetics from work by Aghajanian and Bing (8). Figure 2 shows pharmacokinetic and effect profiles from this experiment. Based on a two-compartment pharmacokinetic model, effect (reduction in performance score) did not appear to be directly related to central compartment (plasma) concentrations, but rather to the time course of drug in the second or tissue compartment. However, counterclockwise hysteresis was still evident in the plot of performance score versus fraction of dose in the tissue compartment, as shown in Figure 3. Accordingly, a third compartment representing slowly equilibrating tissue was added to the pharmacokinetic model. This modification of the model resulted in a linear plot of performance score versus fraction of dose in the slowly equilibrating compartment, shown in Figure 4, indicating that the observed equilibration delay between plasma LSD concentration and effect could be explained by the effector compartment being pharmacokinetically distinct from the plasma compartment.

The pharmacokinetic compartment approach is limited in that it is dependent on identifying a potentially complex pharmacokinetic model with concentrations

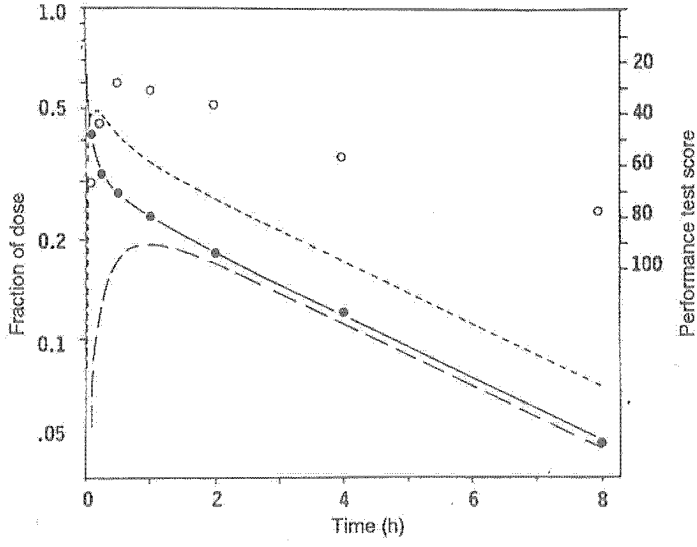

Figure 2. Observed (•) and predicted (upper curve) amounts of LSD in the central compartment, predicted amounts in the tissue compartment (lower curve) of a two-compartment model, and performance test scores (○) following intravenous administration of LSD to normal subjects (From reference 7, with permission)

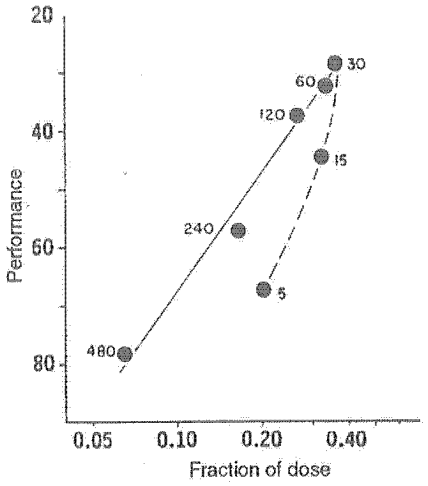

Figure 3. Relationship between performance scores and the fractional amount of LSD in the tissue compartment of the two-compartment pharmacokinetic model (From reference 7, with permission)

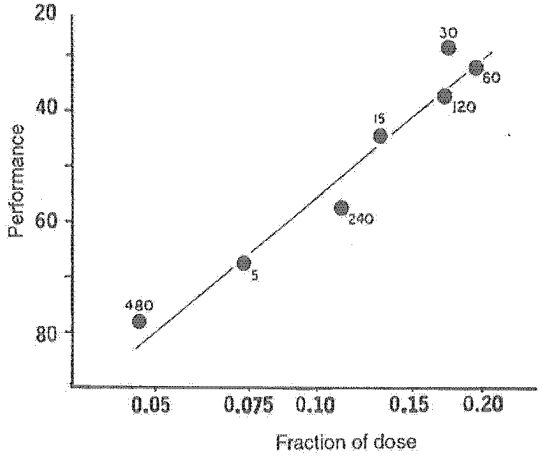

Figure 4. Relationship between performance scores and the fractional amount of LSD in the slowly equilibrating tissue compartment of a three-compartment pharmacokinetic model (From reference 7, with permission)

in at least one compartment correlatable with the effect profile. In many cases, pharmacokinetic compartments are not readily recognizable as distinct body tissues which may be of interest, and therefore may not contribute to any real understanding of the effector site. An extension of this concept will be addressed later in this chapter.

PHARMACODYNAMIC APPROACHES

In 1968, Wagner (9) proposed using the Hill equation to model the hyperbolic relationship between drug effect and dose or concentration. This proposal has been widely adopted and the model has been parameterized for analysis of *in vitro* and *in vivo* concentration–effect relationships as the sigmoid E_{max} model shown below:

$$E = \frac{E_{max} \cdot C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} \tag{3}$$

where E is intensity of effect, E_{max} is the maximum possible effect in the system being studied, C is the drug concentration, EC_{50} is the steady-state drug concentration evoking 50% of E_{max}, and γ is the sigmoidicity parameter indicating the slope and shape of the curve. Note that when the value of γ is 1, the concentration–effect curve is a simple hyperbola and the model is termed the E_{max} model. A typical sigmoid effect–concentration curve depicting parameters of this model is shown in Figure 5.

Hyperbolic models have been used to describe various binding phenomena such as Michaelis–Menten enzyme kinetics and protein binding, thereby linking the use of the E_{max} models to receptor binding theory (10). Clark (11) also proposed the use of a similar equation to model dose–response relationship as an application of mass action theory. The use of hyperbolic models to represent biological processes is empirically reasonable since they describe the widely observed phenomena that as the maximum response (effect) is approached, increasing levels of stimulation (concentration) are required to reach the maximum. The E_{max} models offer advantages over the logarithmic model suggested by Levy (5) in that they predict effect over the entire concentration range, including zero effect when concentration equals zero, and the maximum possible effect (E_{max}).

Wagner (9) also proposed inserting concentration–time data predicted from pharmacokinetic models into the Hill equation to predict the time course of *in vivo* response, based on its similarity to *in vitro* experiments where the concentration in the bath solution could be varied to study response. This approach has been expanded to simultaneously fitting pharmacokinetic and pharmacodynamic models to concentration–effect data as detailed in the Present methods section of this chapter.

Several other pharmacodynamic models and modifications of the E_{max} model have been used to describe concentration–effect relationships. Examples of these are as follows.

The linear model

$$E = S \cdot C + E_0 \tag{4}$$

where S is the slope of the linear effect versus concentration plot, E_0 is the effect

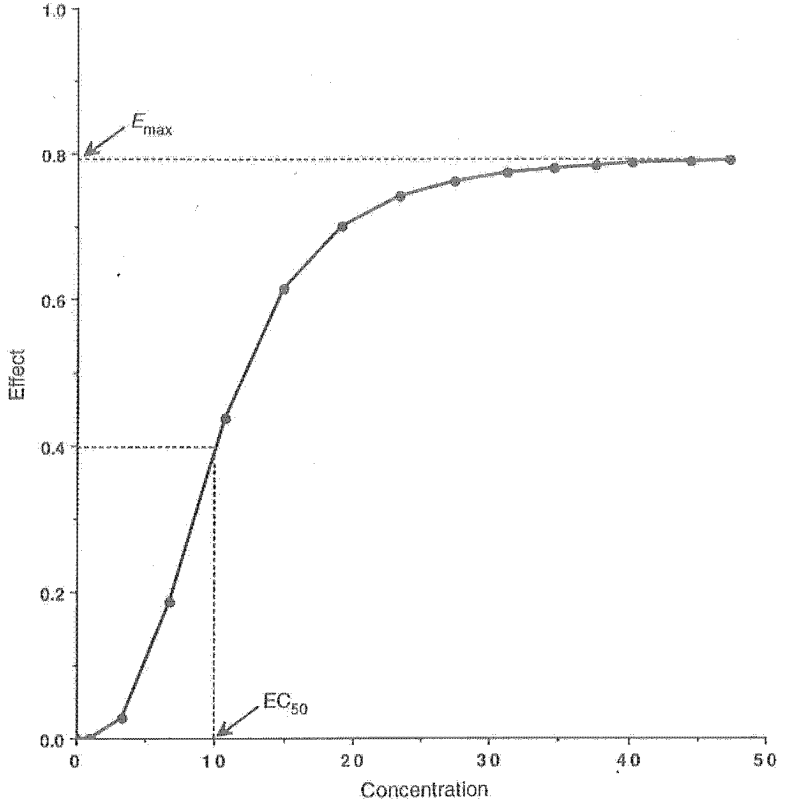

Figure 5. Plot of drug effect versus concentration simulated using the sigmoid E_{max} model given in Equation 3 (parameter values: $E_{max} = 0.79$, $EC_{50} = 10$, and $\gamma = 3$)

intensity when no drug is present, and E and C are as previously defined. The linear model has limited application, usually to defined segments of the true response curve, since it predicts that effect increases with increasing concentration without limit.

The baseline subtraction model

$$E - E_0 = \frac{E_{max} \cdot C^{\gamma}}{EC_{50}{}^{\gamma} + C^{\gamma}} \tag{5}$$

This model is based on the assumption that E_0 can be subtracted from the effect data, leaving the 0–100% response curve intact. This may not be the case when endogenous substances bind to the receptor or interact biochemically to maintain the baseline effect. In this situation, the baseline effect should be included in the model as given below in Equation 6.

The baseline inclusion model

$$E = \frac{E_{max} \cdot (C + C_0)^{\gamma}}{EC_{50}^{\gamma} + (C + C_0)^{\gamma}} \quad (6)$$

where C_0 is the concentration of drug which would be required to generate baseline effect such that E includes the baseline effect. The concepts and applications of the baseline subtraction and inclusion models have been previously described (12).

The inhibitory E_{max} model

$$E = E_0 - \frac{E_{max} \cdot C^{\gamma}}{IC_{50}^{\gamma} + C^{\gamma}} \quad (7)$$

where IC_{50} is the drug concentration causing 50% inhibition of E_{max}. This model is useful for investigating the effects of inhibitory drugs without transforming the data. Its use will result in an inverted effect versus concentration plot with the maximum and minimum effects occurring at zero and the maximum concentration value. Reviews of these and other pharmacodynamic models (6,12,13) and examples of their application (6,14,15) have recently been published. In addition, Colburn (12) has discussed many considerations of pharmacokinetic/pharmacodynamic study design, including selection of dosing routes and regimens and corresponding pharmacodynamic models. Alternative models including those for dealing with indirect effects and tolerance will be presented in the section on future developments.

PRESENT

The present state of simultaneous pharmacokinetic/pharmacodynamic modeling has drawn heavily on the foundations of relating effect to an accessible biofluid as described in the preceding section. This too has evolved, beginning with fully parameterized pharmacokinetic and pharmacodynamic models linked by a parametric model. Recent advances have been made where both pharmacokinetic and pharmacodynamic data are analyzed non-parametrically, that is, without assuming that the correct underlying model and its parameters are known and/or identifiable. This latter approach is perhaps better termed semi-parametric since the parameters of the linking model are still estimated. Although the term parametric was not originally applied to the first simultaneous pharmacokinetic/pharmacodynamic models, it has come into use since the advent of the semi-parametric methods.

PARAMETRIC APPROACH

Sheiner *et al.* (16) first proposed that the pharmacokinetic model parameters could be substituted into the Hill equation such that concentration and effect profiles could be simultaneously modeled using non-linear regression. The novel aspect of their compartment model-based approach was the inclusion of a theoretical effect compartment related to the central (plasma) compartment, but not influencing the overall pharmacokinetic profile due to its relatively small size. A schematic representation of the model is shown in Figure 6(a). Drug transfer into and loss from the effect compartment were controlled by first-order rate constants and drug effect was assumed to be directly related to the amount of drug in the effect compartment at any time. The plasma to effect compartment transfer rate constant, k_{1E} and amount of drug transferred to the effect compartment were assumed to be so small that the pharmacokinetic profile would not be altered and that the negligible amount of drug in the effect compartment did not need to be returned to the central compartment. Under these conditions, the rate constant for drug loss from the effect compartment, K_{E0}, would control the temporal relationship between effect and the concentration profile in the plasma compartment.

Sheiner *et al.* (16) evaluated the model using concentration–effect data obtained following *d*-tubocurarine administration as a two-stage intravenous infusion to healthy patients and to patients with end-stage renal failure. They concluded that the method was robust and could predict the equilibrium delay between appearance of drug in plasma and onset of effect, shown in Figure 7. One of the main advantages of this approach is that it allows the characterization

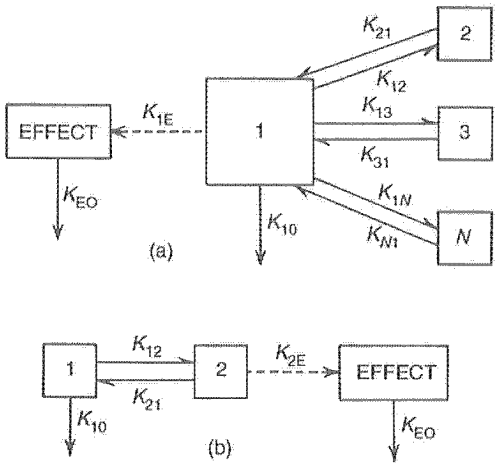

Figure 6. Schematic representation of central compartment (a) and peripheral compartment (b) effect models used in pharmacokinetic/pharmacodynamic modeling

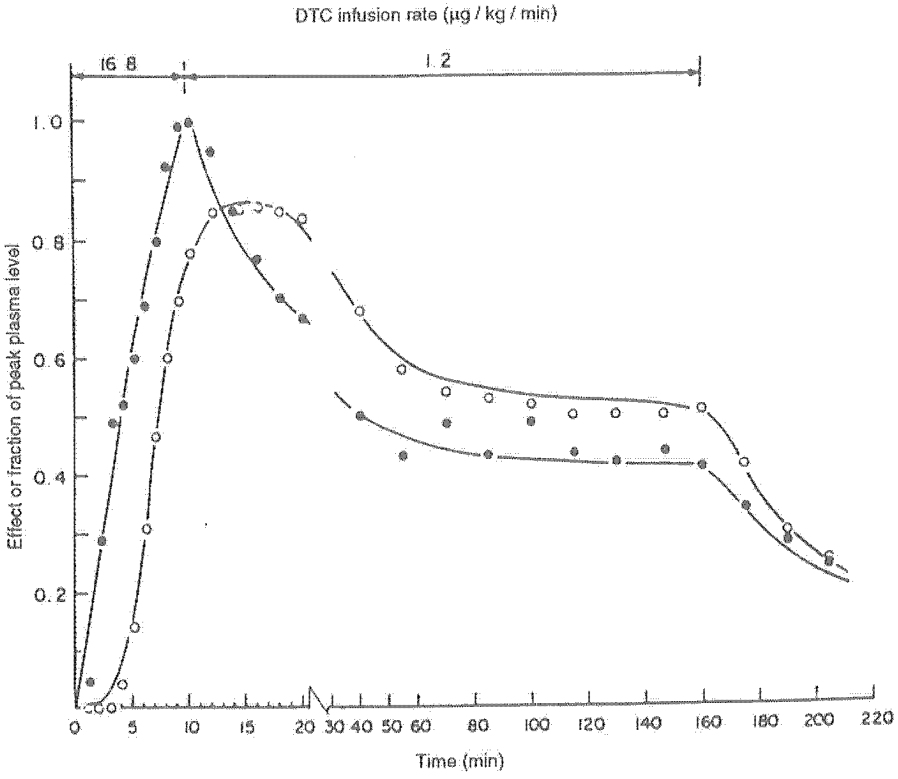

Figure 7. Observed *d*-tubocurarine plasma concentrations (•) and effect (○) during and following intravenous infusion of the drug. Solid line: best fit of the pharmacokinetic/pharmacodynamic model to the data (From reference 16, with permission)

of the concentration–effect relationship under non-steady-state conditions. Conversely, many factors of drug effect such as receptor binding and post-binding events are grouped and represented in the model by a single first-order rate constant.

Colburn (17) investigated the model proposed by Sheiner *et al.* (16) and found that it was able to represent a wide variety of pharmacokinetic and pharmacodynamic phenomena. He derived effect equations applicable to several classical compartment models and extended the approach to accommodate the effect compartment concentration being driven from a peripheral compartment as shown in Figure 6(b). In the interest of model identifiability, he recommended that central and peripheral compartment models be fit to each data set and that

drug be administered by several routes of administration before extrapolating the concentration–effect relationship beyond observed data. Additionally, a model selected from fitting to single-dose data should be tested for adequacy by studying the transition from single to multiple doses, since predicted and observed effects will systematically diverge when multiple doses are administered if an incorrect model has been chosen (17). Potential divergence due to inappropriate model selection is illustrated in Figure 8.

The peripheral compartment effect model (Figure 6(b)) can be used to explain apparent changes in pharmacokinetic/pharmacodynamic relationships as a function of route of administration, or other phenomena not explained by the central compartment effect model (Figure 6A) (14). The peripheral compartment effect model provides an additional tool for explaining non-parallelism between concentration and effect modeled using the central compartment effect model. Modeling the effect compartment as driven by a peripheral compartment may be more physiologically relevant if the effector tissue is believed to be a pharmacokinetically identifiable tissue. More representative models could result if the pharmacokinetic compartment model is replaced with a physiological flow model where the target organ thought to be the receptor/effector site can be isolated (14).

Further refinement of the pharmacokinetic/pharmacodynamic model is possible using specially designed studies to isolate and identify the rate-limiting components of the proposed model (12). By using a varying first-order rate of intravenous administration, rate-limiting and/or controlling steps such as receptor binding can be isolated from the model. Alternatively, one may find that diffusion to the receptor is the slowest step, and construct the model to reflect this. Elucidation of a robust model that can predict drug effect under a variety of conditions will aid in selecting dosage regimens and optimizing therapy.

SEMI-PARAMETRIC APPROACH

Parametric modeling requires thorough understanding of the intrinsic pharmacokinetic and pharmacodynamic models before combining them, as well as the ability to identify and reliably estimate each parameter of the combined model. This may often be difficult, depending on noise level of the pharmacokinetic and pharmacodynamic data sets and the characteristics of the underlying models for a given drug. In an attempt to minimize these factors, Fuseau and Sheiner (18) proposed that the pharmacodynamic component of the combined model could be modeled non-parametrically using the relationship between observed effect and the effect compartment drug concentration (Ce) predicted using a parametric pharmacokinetic model. To achieve this, it is necessary to assume that the relationship between Ce and effect is instantaneous and invariant with time, i.e., tolerance and sensitization do not occur. As in the parametric approach, the effect compartment is modeled as receiving negligible

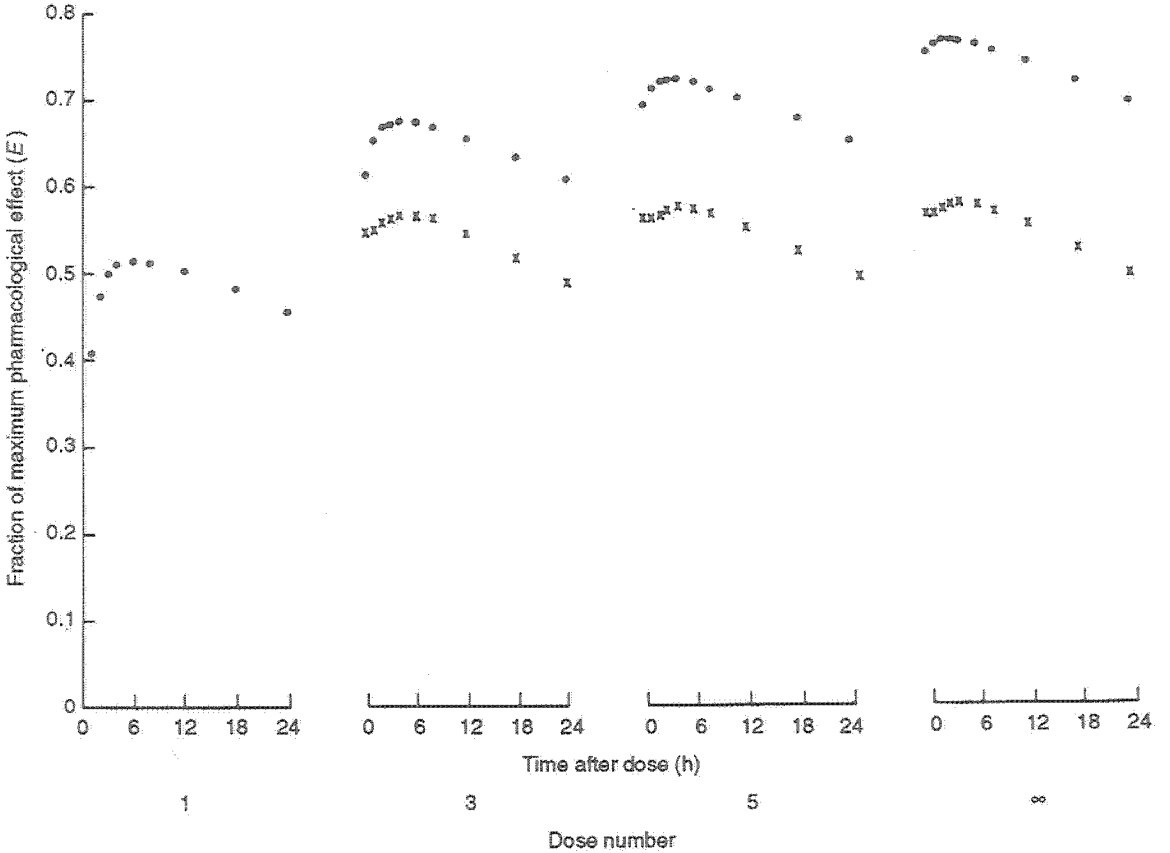

Figure 8. Predicted pharmacological effect during multiple-dose administration assuming central (x) or peripheral (•) effects when the effect is actually related to the peripheral compartment (From reference 17, with permission)

amounts of drug with the concentration profile determined by K_{E0} and the plasma drug concentration (Cp). In the non-parametric pharmacodynamic approach, hysteresis between effect and Ce is suppressed by choosing K_{E0} such that the ascending and descending arms of the effect–Ce plot are superimposable (18). The best estimate of K_{E0} is determined using a univariate search method which minimizes the average squared difference between observed and interpolated effect values from the hysteresis plot as shown in Figure 9.

Fuseau and Sheiner (18) tested the non-parametric pharmacodynamic method using simulations based on hyperbolic and sigmoid E_{max} models as well as models of the β-function (convex Ce–E relationship), tolerance, sensitization and non-equilibrium between Ce and the receptor, the latter three which violate the assumptions of the method. The proposed method was found to be acceptable for both E_{max} models and the β function model when adequate numbers of data having minimal error were used. However, the non-parametric method could not provide accurate or precise estimates of K_{E0} when applied to data from the tolerance, sensitization or non-equilibrium simulation models. Additionally, performance was reduced for all simulation models when too few data or noisy data were used.

Subsequently, Unadkat *et al.* (19) extended the non-parametric pharmacodynamic approach to include pharmacokinetic modeling such that pharmacokinetics and pharmacodynamics could be simultaneously modeled non-parametrically with the link model still used to estimate the parameter K_{E0}, thereby allowing 'semi-parametric' simultaneous pharmacokinetic/pharmacodynamic modelling. The advantages of this approach are that fewer assumptions about either the underlying pharmacokinetic or pharmacodynamic model are

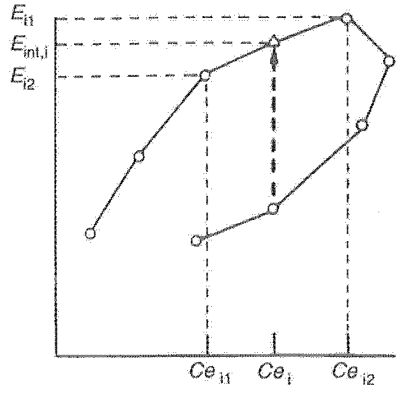

Figure 9. Application of the non-parametric pharmacodynamic method of Fuseau and Sheiner (18) to estimate K_{E0} by minimizing the average squared difference between observed (E_{i1} and E_{i2}) and interpolated ($E_{int,i}$) effect data. Ce values are corresponding effect compartment concentration values estimated using a parametric pharmacokinetic model (From reference 18, with permission)

required. Unadkat *et al.* (19) described this as a two-stage process where observed *Cp* values are used to model pharmacodynamics and determine the linking K_{E0} value. Simple linear interpolation is used to estimate *Cp*–time values if missing from the *Cp*–effect data set as shown in Figure 10. The resultant *Cp*–time data set is used to estimate *Ce* as a function of time by numerically integrating the following equation for a given value of K_{E0} (19):

$$dCe/dt = K_1 \cdot C_p - K_{E0} \cdot Ce \tag{8}$$

where K_1 is effect compartment input rate constant (assumed to be equal to K_{E0}) and all other parameters are as previously defined. A starting estimate of K_{E0} is selected and the parameter value is increased or decreased incrementally depending on the direction of hysteresis and area between the limbs of the effect–Ce plot corresponding to each K_{E0} value. The process is iterated until the K_{E0} value which minimizes the area within the hysteresis loop is found.

This approach assumes that *Ce* and hence effect is a function of observed (and interpolated) *Cp* as determined by the value of K_{E0}, independent of intrinsic pharmacokinetics. Based on a series of simulations, the authors (19) suggested that this approach is nearly as efficient as the parametric approach even when

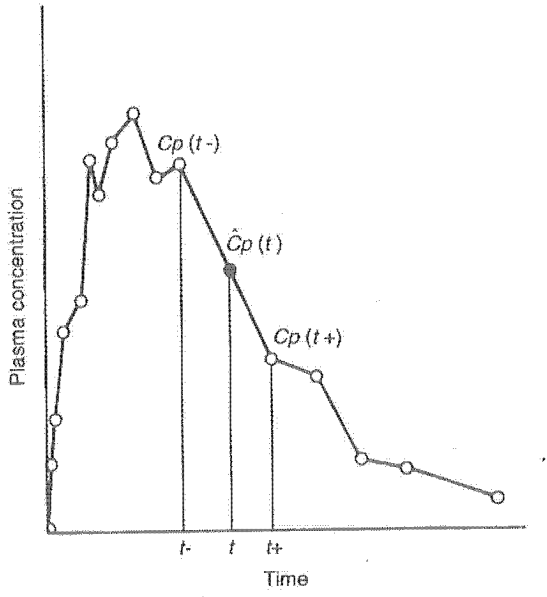

Figure 10. Example of non-parametric 'fit'of plasma concentration (*Cp*) versus time data (○). If *Cp* was not observed at a pharmacodynamic observation time, it is estimated using linear interpolation between the nearest bracketing observed values ($Cp(t-)$ and $Cp(t+)$) (From reference 19, with permission)

the underlying models were known, but considerably more robust when the underlying models were mis-specified.

Shafer *et al.* (20) reported a comparison of the above method with parametric pharmacokinetic/pharmacodynamic modeling in the evaluation of the neuromuscular blocking drug metocurine in laboratory animals. The semi-parametric method was found to give results in close agreement with the parametric method. When results differed between methods, visual examination of the data suggested that the semi-parametric method better described the data.

An advantage of the parametric approach is that it allows description of the concentration–effect relationship using a relatively small number of parameters, some of which may be physiologically relevant, derived from all data pairs. In contrast, EC_{50} estimated from concentration–effect data following non-parametric pharmacodynamic analysis must be obtained by interpolation of two observed data pairs, and no estimate of steepness of the *Ce–E* curve is available (20). Shafer *et al.* (20) proposed that when the underlying pharmacodynamic model was known with confidence, the non-parametric pharmacokinetic model is useful for determining the *Ce–E* relationship using a parametric pharmacodynamic model. The semi-parametric methods have also been recommended for examination of raw concentration–effect data before attempting parametric analysis of the pharmacodynamic model (18,20).

Grevel (15) has recommended that the non-parametric pharmacodynamic model be considered as a means to determine true therapeutic equivalence based on comparison of drug effect as an alternative to pharmacokinetic bioequivalence testing, since it is possible that different *Cp*–time profiles may yield comparable effect–time profiles. This recommendation is based on the ability of the model to filter random noise in the data and to interpolate between individual effect measurements.

Verotta *et al.* (21) proposed an additional semi-parametric model capable of describing both counterclockwise and clockwise *Ce–E* hysteresis arising from differences in rate of distribution between the venous, arterial and effect compartments. Counterclockwise hysteresis, the subject of previously discussed pharmacodynamic models, occurs when the venous drug concentration (*Cv*: previously termed *Cp* in this chapter) equilibrates faster with the arterial concentration (*Ca*) than with *Ce*, whereas clockwise hysteresis occurs when *Ce* equilibrates faster with *Ca* than with *Cv*. The relationships between these three compartments and the respective controlling first-order rate constants are shown in Figure 11.

In this semi-parametric approach, *Ce* is estimated using numerical convolution and deconvolution (21). It is assumed that arterial input is instantaneous with input from intravenous injection or inhalation, and that the arterial input rate, *In*, is known. The previously described non-parametric pharmacodynamic approach (18) is used to search for values of k_{0e} and k_{0v}, the equilibration rate constants corresponding to the effect and venous compartments, respectively, such that the *Ce–E* hysteresis plot is collapsed. An improved simultaneous

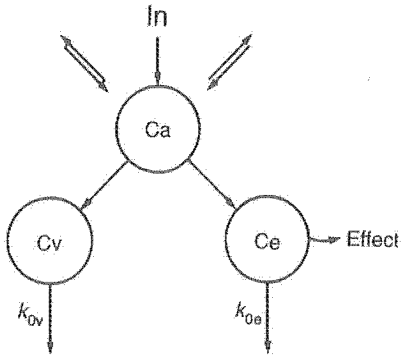

Figure 11. Semi-parametric pharmacokinetic–pharmacodynamic link model capable of describing both clockwise and counterclockwise concentration–effect hysteresis. *Ca*, *Cv* and *Ce* are concentrations in the arterial, venous and effect compartments, respectively; k_{0v} and k_{0e} are first-order rate constants for drug loss from the depicted compartments; and *In* represents the input function for the arterial compartment (From reference 22, by permission of Oxford University Press)

modeling algorithm with fewer restrictions on the profiles of the *E*-time and *Ce*-time data sets is used to collapse the hysteresis plot while performing a trial-and-error search for k_{0e} and k_{0v} (22). The improved algorithm does not require that the *Ce*–*E* response curve follow any particular functional form as did previous methods.

Verotta *et al.* (21) applied this method to concentration–effect data obtained following administration of nicotine as a stepped-rate intravenous infusion to healthy human subjects (23), and were able to model the clockwise hysteresis observed in the heart rate versus plasma concentration plot. Further application of this method to the investigation of nicotine pharmacodynamics following its administration in intravenous infusion, cigarette and chewing gum forms has been reported (24). In this later work, the semi-parametric approach was useful in discriminating between models of nicotine effect reflecting distributional hysteresis and true pharmacological tolerance and distributional hysteresis only.

This approach is subject to a series of intuitively satisfiable assumptions which mostly arise from constraints on the route of administration and convolution–deconvolution necessary to estimate *Ce* in the presence of 'noise' in the data (21). However, this approach now eliminates all constraints on the functional forms of the pharmacokinetic and pharmacodynamic model components, and can now explain *Ce*–*E* hysteresis in either direction.

FUTURE

The future of pharmacokinetic/pharmacodynamic modeling, as we see it, lies

in the following general areas:

1. Tolerance and sensitization models.
2. More sophisticated models for hysteresis, indirect effects and the link.
3. The influence of endogenous ligands on drug binding to receptors.
4. General application to individual patients.

We will develop each of these concepts in the following section.

TOLERANCE AND SENSITIZATION

In our view, these two processes can be mirror images of each other or tolerance can reflect a metabolic inhibition process. In a receptor-based model, the receptor becomes tolerant or sensitive to the drug or class of drugs during a course of therapy. In that receptors and enzymes act through a common binding phenomenon (25), enzyme induction and inhibition models that have been successfully applied to pharmacokinetic modeling should also be applicable to receptor theory. For receptor tolerance, enzyme–metabolite product inhibition could be applicable (26) or receptor sensitization and tolerance could be viewed as analogous to enzyme induction (27), wherein the drug molecule of interest can influence the receptor directly to increase or decrease response in a mirror image fashion. We have chosen to use the second option for the purposes of our simulations.

The values for the pharmacodynamic parameters EC_{50}, K_{E0}, γ and E_{max}, can change during sensitization or tolerance. For the purpose of simulation, we will use the following monoexponential decline in plasma drug concentration (Cp) after an intravenous dose:

$$C_p = C_0 \exp(-\lambda t) \tag{9}$$

The concentration in the effect compartment is described as follows:

$$C_e = \frac{K_{E0} \cdot C_0}{(\gamma - K_{E0})} [\exp(-\lambda t) - \exp(-K_{E0} t)] \tag{10}$$

C_e is then used to determine the fractional pharmacological effect (E/E_{max}), where E is the measured effect and E_{max} is the maximal possible effect using the following sigmoid E_{max} model:

$$E/E_{max} = \frac{C_e^{\gamma}}{EC_{50}^{\gamma} + C_e^{\gamma}} \tag{11}$$

Tolerance can be described as an increase in EC_{50} or a decrease in γ, K_{E0} or E_{max}. Sensitization can be described as a decrease in EC_{50} or an increase in γ,

K_{E0} or E_{max}. Since tolerance and sensitization are time-dependent phenomena, the following simplified equations can be used to model them:

Increase

$$P = P[1 + Q(1 - \exp^{-KT})] \tag{12}$$

where P is the parameter of interest, Q is a multiplication factor which can range from 0 to ∞ to determine the extent of the possible increase, K is the rate constant for the increase and T is the time during which the parameter value increases before once again becoming constant. This equation can be used to calculate changes in EC_{50}, K_{E0}, E_{max} and γ which result in tolerance, sensitization, sensitization and sensitization, respectively.

Decrease

$$P = P[(1 - R) + R \cdot \exp^{-KT}] \tag{13}$$

where P is the parameter of interest and R is a multiplication factor that ranges from 0 to unity and establishes the fractional decrease that can occur. (For example, if $R = 0.75$, P can only decline to 0.25 of its original value, and if $R = 0.90$, P can only decline to 0.10 of its original value.) K is the rate constant for the decrease and T is the time during which the parameter decreases before once again becoming constant. This equation can be used to calculate changes in EC_{50}, K_{E0}, E_{max} and γ which result in sensitization, tolerance, tolerance and tolerance, respectively.

Examples of these eight concepts are presented in Figures 12–15.

Figure 12: The steady-state conditions clearly show an increase in E/E_{max} when sensitization has occurred and a decrease in E/E_{max} when tolerance has occurred as a result of changes in EC_{50}. The transition phases are more complex. Relative E/E_{max} values decrease during the time course of tolerance, whereas the E/E_{max} differences during the time course are not as obvious for sensitization due to its proximity to the E_{max} value.

Figure 13: The steady-state conditions show an increase in E/E_{max} with steeper slopes when sensitization has occurred and a decrease in E/E_{max} with a more shallow slope when tolerance has occurred. Although the γ transition phases are not as uniform as the steady-state conditions, they appear to be more predictable than the EC_{50} transition phases. E/E_{max} and slope changes are gradual and more intuitively simple. Curves show anticipated identical intercepts at the EC_{50} both in the up and down portions of the curves due to identical EC_{50} values and identical K_{E0} values during the γ changes. However, because of the transition from baseline, the extent of the E/E_{max} differences are less pronounced than with the steady-state conditions.

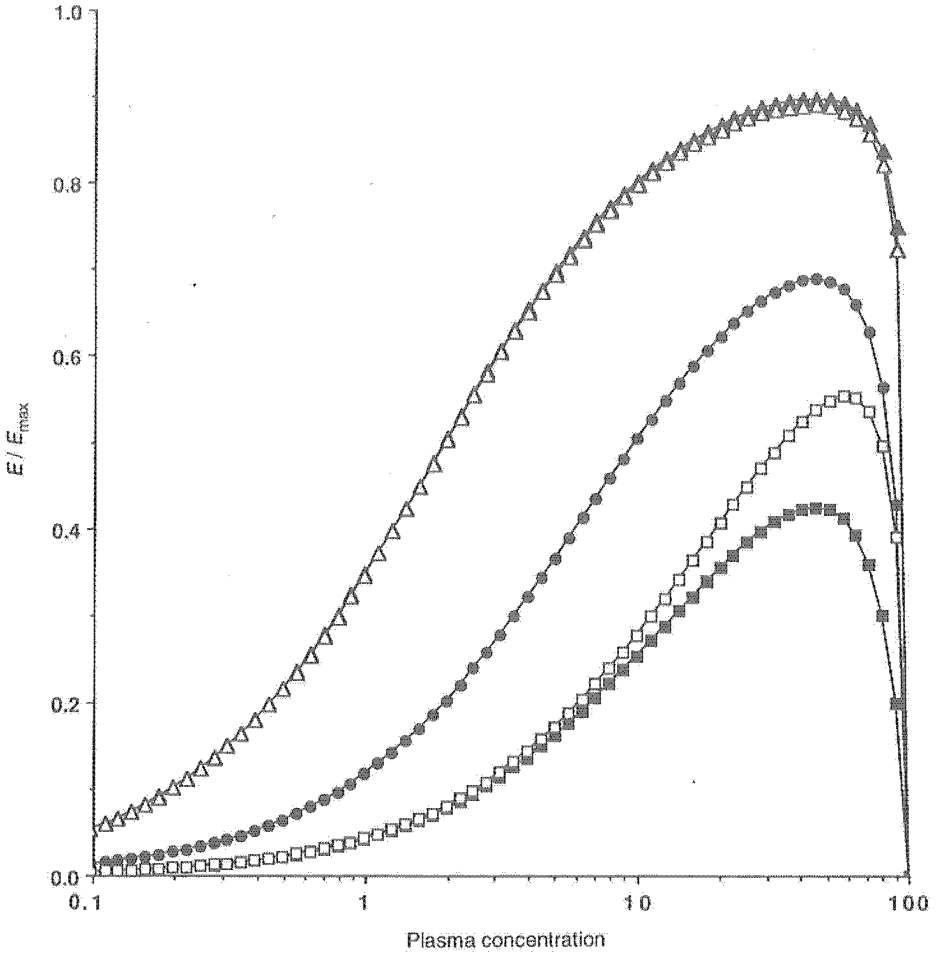

Figure 12. Tolerance or sensitization associated with increased or decreased EC_{50} values, respectively. Curves show the baseline (•), tolerance (■) and sensitized (▲) steady-state conditions as well as the transition from baseline to tolerance (□) and sensitization (△) during the time course of the study

Figure 14: Steady-state conditions show an increase in E/E_{max} with an earlier time for maximum effect when sensitization has occurred and a decrease in E/E_{max} associated with a later time for maximum effect when tolerance has occurred. Again, the transition process exhibits attenuated E/E_{max} effects as well as attenuated differences in time to maximum effect.

Figure 15: Steady-state conditions show an increase in E/E_{max} with a delay in the time to maximum effect when sensitization has occurred and a decrease in E/E_{max} with an earlier time to maximum effect when tolerance has

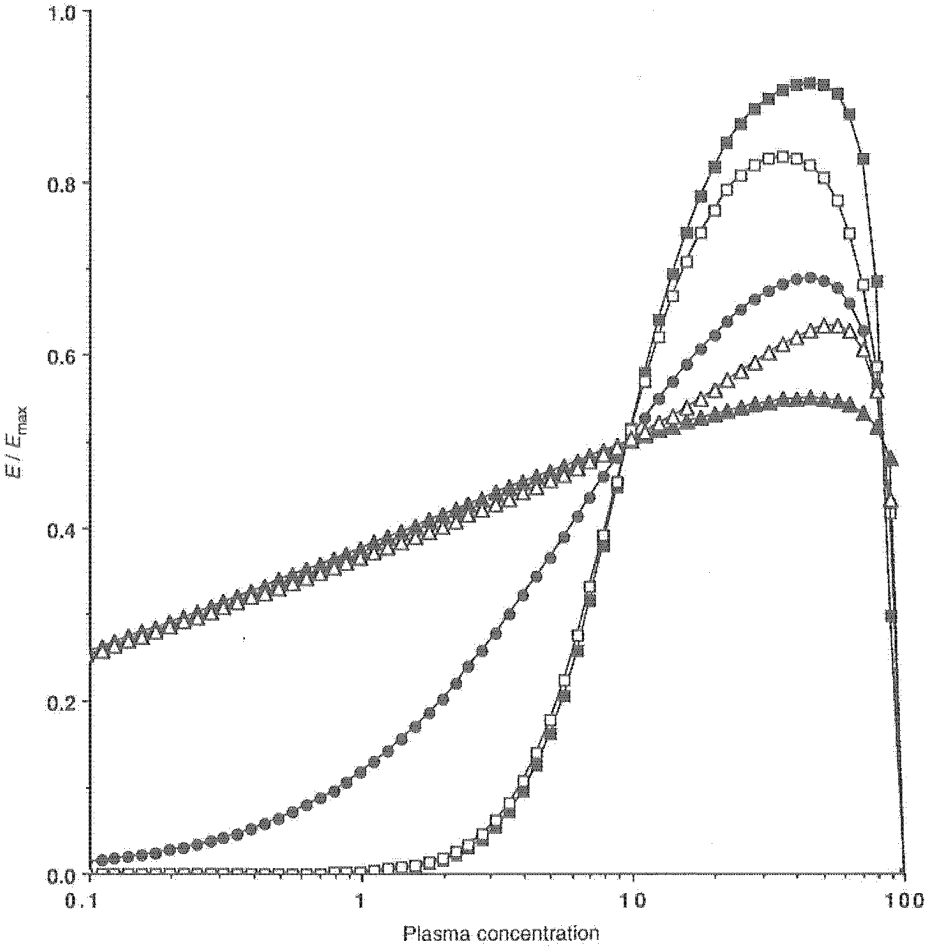

Figure 13. Tolerance or sensitization associated with decreased or increased γ values, respectively. Curves show the baseline (•), tolerance (▲) and sensitized (■) steady-state conditions as well as the transition from baseline to tolerance (△) and sensitization (□) during the time course of the study

occurred. During transition, changes in E/E_{max} are not as great, but the changes in times of maximum effect show greater delays during transition to the sensitized state and earlier time of maximum effect during transition to tolerance.

Although these examples may not encompass all possibilities for sensitization and tolerance, they do create a conceptual base on which to develop additional models.

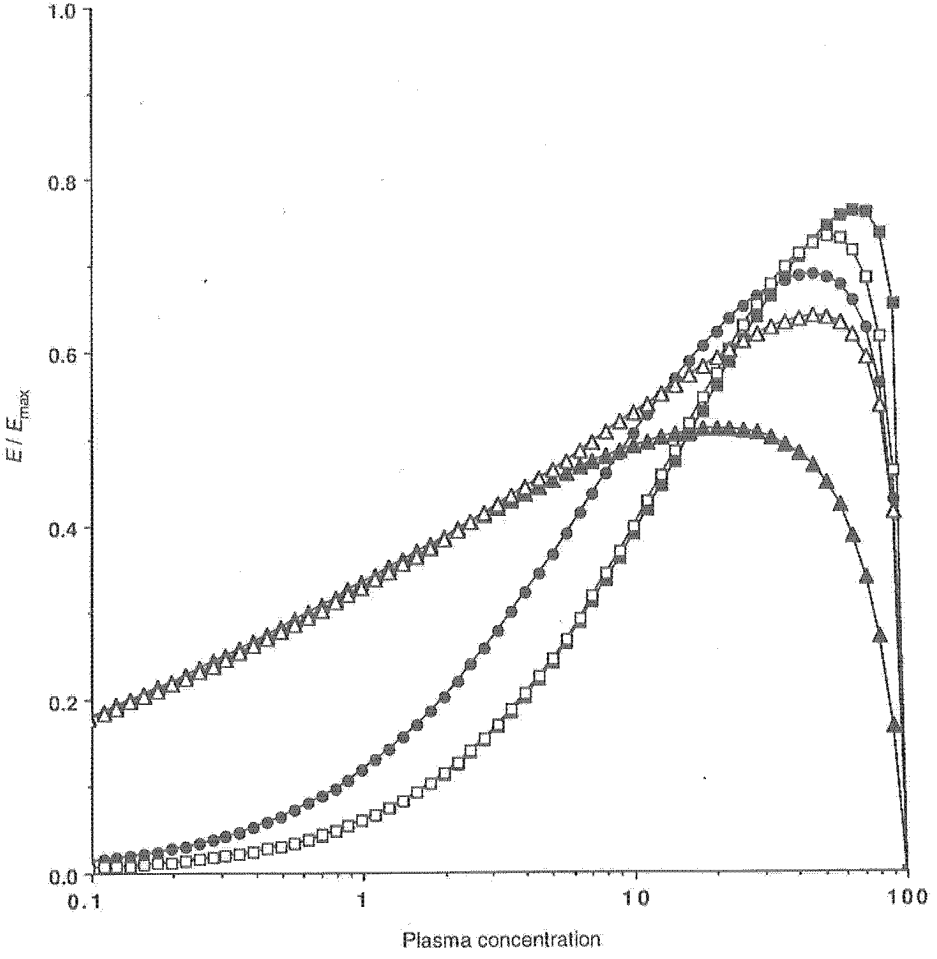

Figure 14. Tolerance or sensitization associated with decreased or increased K_{E0} values, respectively. Curves show the baseline (•), tolerance (▲) and sensitized (■) steady-state conditions as well as the transition from baseline to tolerance (△) and sensitization (□) during the time course of the study

The results that we obtained with the altered K_{E0} model suggest that this effector-link model may not be the most appropriate since K_{E0} acts as a single modulator for distribution from the pharmacokinetic compartment or exponential as well as the on-rate and off-rate for the receptor, with no drug return to the driving pharmacokinetic compartment or exponential. This representation clearly is an oversimplification of the true situation. A more realistic, yet complex, representation will be presented in the next section.

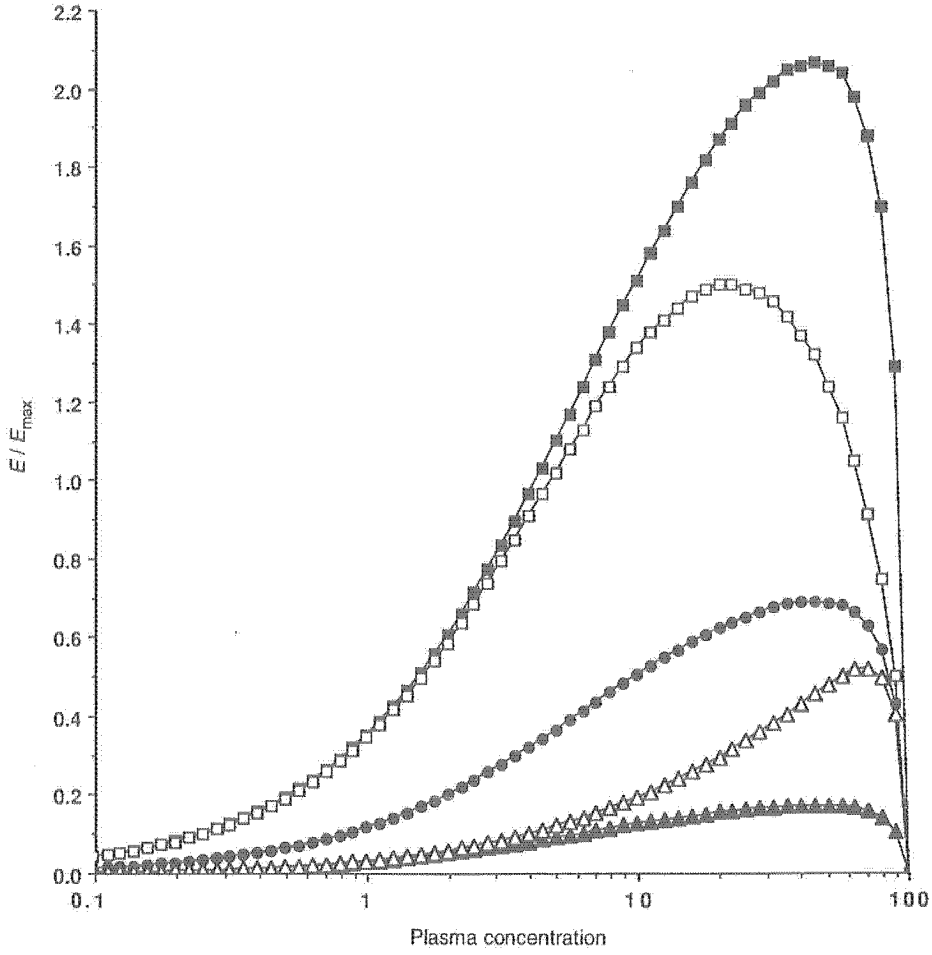

Figure 15. Tolerance or sensitization associated with decreased or increased E_{max}, respectively. Curves show the baseline (•), tolerance (▲) and sensitized (■) steady-state conditions as well as the transition from baseline to tolerance (△) and sensitization (□) during the time course of the study

HYSTERESIS, INDIRECT EFFECTS—THE LINK: THE BLACK BOX

The counterclockwise hysteresis often seen between drug effect and concentration during the course of study has been attributed to a delay in equilibration between plasma drug concentration and the drug concentration at the effect site (28). However, hysteresis can be the result of a multitude of factors, including delayed equilibration, number of steps between receptor binding and measured

effect and/or on/off rates at the receptor itself. In the past, these phenomena have been obscured within the link model—a black box that absorbs the events that occur between the pharmacokinetic profile and the observed pharmacological effect.

In the future, we will need to begin to break down and isolate the individual events that are currently combined in this effector link compartment. For example, disequilibration can be studied in animals using autoradiography and in humans using scintigraphy. The specific site of action, if known, can be isolated and the relationship between plasma drug concentrations and drug concentration at the site of action can be determined. In so doing, the investigator can determine whether disequilibration accounts for the difference between plasma pharmacokinetics of the drug and the observed pharmacodynamics.

Better, more sophisticated, models will need to be developed to incorporate all of the individual processes that are obscured within the K_{E0} segment of the current modeling approach. In the current models K_{E0} reflects distribution to the site of receptor binding as well as receptor on- and off-rates without allowing the redistribution process to influence the pharmacokinetic profile. The more comprehensive models of the future will need to provide for distribution to the site of receptor binding, receptor on-rate, receptor off-rate and redistribution back to the identifiable pharmacokinetic compartment as individual processes. Examples where this may be important from a pharmacokinetic perspective are the angiotensin-converting enzyme (ACE) inhibitors (29) and certain benzodiazepines (30) where persistent low plasma drug concentrations may reflect dissociation from the receptor. This situation cannot be accurately modeled with the current models. Also, when K_{E0} represents both on- and off-rates for the receptor, the individual processes cannot be separated to distinguish them during tolerance, sensitization or other pharmacodynamic changes.

Active metabolites can confound the modeling process because they can also account for non-parallelism in plasma drug concentration and effect. If active metabolites are present, they should also be measured along with the parent compound. The pharmacodynamic model must account for drug as well as metabolites to be identifiable. Even if it is possible to model the combined drug/metabolite(s), it would be advantageous to administer the metabolite(s) alone so that their contribution to effect can be isolated from that of the drug substance. Even with this information in hand, caution must be exercised against applying simple additivity principles. The time course of drug and active metabolite(s) will be different even if the metabolite(s) are formation rate limited and will be distinctly different if metabolite is eliminated more slowly than the administered drug. Also, the drug/metabolite(s) ratio will vary over time and as a function of route of administration. The influence of route of administration, independent of rate of administration, can be evaluated using first-order intravenous and intestinal infusions. Methods to model combined drug/metabolite pharmacokinetics and pharmacodynamics have been described previously (31).

In vitro and *ex vivo* methods for drugs and metabolites can also be used to assess receptor on- and off-rates. Although the absolute magnitude of the rate processes will depend on the experimental conditions, their general application to the *in vivo* situation have been shown to be predictive (30).

Even if active metabolites are not present, first-order intravenous infusions alluded to earlier can be used to isolate rate-limiting processes *in vivo*. By adjusting first-order infusion rates, an investigator can control various rate-limiting processes such as absorption, distribution and elimination as well as on-/off-rates for the receptor. Using three or four infusion rates allows the investigator to identify various individual rate processes that may be obscured during intravenous bolus or zero-order infusion, oral dosing or non-intravenous parenteral dosing.

ENDOGENOUS LIGANDS

Endogenous substances compete with drugs for receptor binding (32,33). This competition influences the validity of current pharmacokinetic/pharmacodynamic models if this competition is not addressed in the effect equations. The traditional baseline subtraction methods are not appropriate if the observed baseline effect is a function of receptor occupancy by endogenous or dietary substances. Effect equations can be derived (32) which account for this competition. Ignoring this competition leads to errant parameter estimation and, therefore, non-predictive models.

APPLICATION TO PATIENTS

One of the major shortcomings of current pharmacokinetic/pharmacodynamic modeling is that quite often the pharmacodynamic measure is not the therapeutic endpoint. For example, in antihypertensive therapy, the measured blood pressure response may not predict greater life expectancy for the hypertensive patient. Even more critical is the fact that quite often the measured effect may only be a surrogate for the desired endpoint due to a lack of understanding of the cause and effect relationships in the disease process. Unfortunately, we are relatively naive about many of the diseases we are attempting to treat.

Even when we know the therapeutic endpoints that are relevant to treating a disease, pharmacokinetic/pharmacodynamic modeling is a complex process and we have not focused on the individual patient. Rather, we have focused our attention on the population because of the complexity of the process and the cost that it entails.

For pharmacokinetic/pharmacodynamic modeling to be of direct value to therapy, simplified models will be needed that can be applied in an office setting to individualize therapy. A patient population database will need to be created and validated, then used to establish simplistic models such as a nomogram and

non-invasive effect measures that the clinician can use to calculate and adjust dosing regimens.

CONCLUSION/SUMMARY

Pharmacokinetic/pharmacodynamic modeling has provided a powerful tool for basic drug research and the drug development process. Now we are in a position to develop more sophisticated models and to apply them to individual patient therapies. The future cannot be brighter, but we must apply ourselves to the tasks at hand to develop more applicable and understandable models which increase their usefulness to drug development and improved drug therapy.

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