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Characterization of Four Basic Models of Indirect Pharmacodynamic Responses[1]

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Four basic models of indirect pharmacodynamic responses were characterized in terms of changing dose, I_{max} or S_{max}, and IC_{50} or SC_{50} to examine the effects of these fundamental drug properties on response profiles. Standard pharmacokinetic parameters were used for generating plasma concentration, and response-time profiles using computer simulations. Comparisons to theoretical expectations were made. In all four models, the maximum response (R_{max}) (inhibition or stimulation) and the time of its occurrence ($T_{R_{max}}$) were dependent on the model, dose, I_{max} or S_{max}, and IC_{50} or SC_{50} values. An increase in dose or a decrease in IC_{50} or SC_{50} by the same factor produced, as theoretically expected, identical and superimposable pharmacodynamic response patterns in each of the models. Some parameters ($T_{R_{max}}$, ABEC) were nearly proportional to log dose, while others (R_{max}, $C_{R_{max}}$) were nonlinear. Assessment of expected response signature patterns as demonstrated in this report may be helpful in experimental designs and in assigning appropriate models to pharmacodynamic data.

KEY WORDS: pharmacodynamics; indirect response models.

INTRODUCTION

In the field of pharmacodynamics, there are various approaches to correlate the time course of pharmacological effects with plasma drug concentrations. However, the selection of the appropriate procedure for modeling of pharmacokinetic-pharmacodynamic data should, if possible, be based on the mechanism by which a drug produces its response. Previously, four

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basic models were proposed for describing the pharmacodynamic responses of drugs produced by indirect mechanisms such as by inhibition or stimulation of the production or dissipation of factors controlling the measured response (1). The classic example of an indirect mechanism is the inhibition of prothrombin complex activity by the anticoagulant warfarin (2). The applicability of these models to a diverse array of drugs has recently been demonstrated (3).

The pharmacokinetic/pharmacodynamic parameter(s) of a drug can be influenced by genetic, environmental, physiologic, or pathologic factors. Primary or secondary drugs given clinically can change pharmacokinetic and/or pharmacodynamic parameters or response profiles of the drug. For instance, gender affects both the kinetics (clearance) and dynamics (IC_{50}) of methylprednisolone (4). The IC_{50} values for T-helper and T-suppressor cell trafficking effects increased significantly after multiple dosing of methylprednisolone in asthma patients (5). In the drug discovery process, it is commonplace to develop a congeneric series of compounds with differences in physicochemical, pharmacokinetic, and intrinsic potency properties, and thereby alter the pharmacodynamic profiles (6). At present, the availability of suitable experimental data is limited for full understanding of the effects of changes in intrinsic pharmacodynamic parameters on the overall response patterns. Such data include the drug concentrations and pharmacological effects simultaneously measured after administration of drugs at different rates or dose levels.

In the present report, we have further examined response patterns (data signatures) expected from four basic indirect pharmacodynamic response models in terms of the dose, maximum inhibition or stimulation capacity (I_{max} or S_{max}), and drug concentration producing 50% inhibition or stimulation (IC_{50} or SC_{50}). These are fundamental properties or variables of a drug and biological system. Full understanding of mechanism-based physiological models requires varied doses and/or administration rates to generate various pharmacodynamic response patterns. It was sought to determine whether it is possible to generalize the data signatures of the dynamics of drugs that have indirect response mechanisms and to provide simulations that complement and extend theoretical relationships developed recently for these models (7,8).

THEORETICAL

The basic premise of this study is that the measured response (R) to a drug is produced by an indirect mechanism. The rate of change of the response over time with no drug present can be described as:

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot R \qquad (1)$$

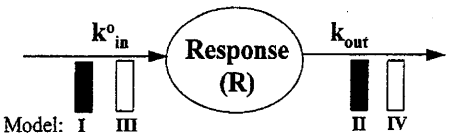
where k_{in} represents the apparent zero-order rate constant for production of the response, k_{out} defines the first-order rate constant for loss of the response, and R is assumed to be stationary with an initial value of R_0. The response variable, R, can be a directly measured entity or it may be an observed response which is directly and immediately proportional to the concentration of a mediator. It is assumed that k_{in} and k_{out} fully account for production and loss of the response.

For the four models shown in Fig. 1, the rate of change of the response over time in the presence of drug can be described as:

$$\frac{dR}{dt} = k_{in} \cdot \{1 + H_1(t)\} - k_{out} \cdot \{1 + H_2(t)\} \cdot R \tag{2}$$

Models I ($n=1$) and II ($n=2$) represent processes that inhibit the factors controlling drug response (Fig. 1) where inhibition processes operate according to:

$$H_n(t) = -\frac{I_{max} \cdot C_p}{IC_{50} + C_p} \tag{3}$$



$$\frac{dR}{dt} = k_{in} \cdot \{1+H_1(t)\} - k_{out} \cdot \{1+H_2(t)\} \cdot R$$

Model	$H_1(t)$	$H_2(t)$	Condition
I	$-\left(\frac{I_{max} \cdot C_p}{IC_{50} + C_p}\right)$	0	$0 < I_{max} \leq 1$
II	0	$-\left(\frac{I_{max} \cdot C_p}{IC_{50} + C_p}\right)$	$0 < I_{max} \leq 1$
III	$\left(\frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right)$	0	$0 < S_{max}$
IV	0	$\left(\frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right)$	$0 < S_{max}$

Key: IC_{50} Inhibition SC_{50} Stimulation

Fig. 1. Four basic indirect response models represent processes that inhibit or stimulate the factors controlling drug response.

The value of I_{max} is always less than or equal to unity, i.e., $0 < I_{max} \leq 1$. The plasma concentration of drug (C_p) can be defined as a function of time and IC_{50} is the drug concentration which produces 50% of the maximum inhibition achieved at the effect site.

A more specific form of Model I is:

$$\frac{dR}{dt} = k_{in} \cdot \{1 + H_1(t)\} - k_{out} \cdot R \tag{4}$$

while Model II is:

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot \{1 + H_2(t)\} \cdot R \tag{5}$$

Models III ($n = 1$) and IV ($n = 2$) represent processes that stimulate the factors controlling drug response (Fig. 1) where stimulation processes operate according to:

$$H_n(t) = \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \tag{6}$$

The SC_{50} represents drug concentration producing 50% of the maximum stimulation achieved at the effect side. The value of S_{max} can be any number greater than zero.

The more specific form of Model III is:

$$\frac{dR}{dt} = k_{in} \cdot \{1 + H_1(t)\} - k_{out} \cdot R \tag{7}$$

and Model IV is:

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot \{1 + H_2(t)\} \cdot R \tag{8}$$

A summary parameter used to characterize the overall effect of drug is the area between the baseline and the effect curve (ABEC) which is defined as

$$ABEC = |R_0 \cdot t_r - AUEC_{0-tr}| \tag{9}$$

where R_0 is the baseline value and AUEC is the area under or over the response vs. time curve over the time interval of 0 to t_r. The value of t_r is assumed $\rightarrow \infty$.

Some of the characteristics of the four basic indirect response models that have explicit solutions include the following (7,8):

Maximum Response (R_{max}) as Dose$\rightarrow\infty$ or IC_{50} or $SC_{50}\rightarrow 0$:

$$R_{max} \searrow R_0(1-I_{max}) \quad \text{Model I} \tag{10}$$

$$R_{max} \nearrow R_0/(1-I_{max}) \quad \text{if } I_{max}<1 \quad \text{Model II} \tag{11}$$

$$R_{max} \nearrow \infty \quad \text{if } I_{max}=1 \quad \text{Model II} \tag{12}$$

$$R_{max} \nearrow R_0(1+S_{max}) \quad \text{Model III} \tag{13}$$

$$R_{max} \searrow R_0/(1+S_{max}) \quad \text{Model IV} \tag{14}$$

Drug Concentrations occurring at R_{max} ($C_{R_{max}}$):

$$C_{R_{max}}=\frac{IC_{50}\cdot(R_0-R_{max})}{R_{max}-(1-I_{max})R_0} \quad \text{Model I} \tag{15}$$

$$C_{R_{max}}=\frac{IC_{50}\cdot(R_{max}-R_0)}{R_0-(1-I_{max})R_{max}} \quad \text{Model II} \tag{16}$$

$$C_{R_{max}}=\frac{SC_{50}\cdot(R_{max}-R_0)}{R_0(1+S_{max})-R_{max}} \quad \text{Model III} \tag{17}$$

$$C_{R_{max}}=\frac{SC_{50}\cdot(R_0-R_{max})}{R_{max}(1+S_{max})-R_0} \quad \text{Model IV} \tag{18}$$

Area Between the Baseline and Effect Curve (ABEC):

$$ABEC=R_0\frac{I_{max}}{k_{el}}\ln\left(1+\frac{D/V}{IC_{50}}\right) \quad \text{Model I} \tag{19}$$

$$ABEC(D\rightarrow\infty)=R_0\frac{I_{max}}{k_{el}}\frac{1}{1-I_{max}}\ln\left(1+\frac{D/V}{IC_{50}}\right) \quad \text{if } I_{max}\neq 1 \quad \text{Model II} \tag{20}$$

$$=R_0\frac{k_{out}}{2(k_{el})^2}\ln^2\left(1+\frac{D/V}{IC_{50}}\right) \quad \text{if } I_{max}=1 \quad \text{Model II}$$

$$ABEC=R_0\frac{S_{max}}{k_{el}}\ln\left(1+\frac{D/V}{SC_{50}}\right) \quad \text{Model III} \tag{21}$$

$$ABEC(D\rightarrow\infty)=R_0\frac{S_{max}}{k_{el}}\frac{1}{1+S_{max}}\ln\left(1+\frac{D/V}{SC_{50}}\right) \quad \text{Model IV} \tag{22}$$

Equations (20) and (22) are solutions which can be obtained only at high doses of drug.

Initial Slopes (S_I):

The limiting values of the initial slope (S_I) of the four models can be identified by setting Eqs. (4), (5), (7), and (8) equal to zero when $C_p\rightarrow\infty$. The limiting S_I value will also depend on the maximum inhibition or stimulation

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