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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:

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot R \tag{1}$$

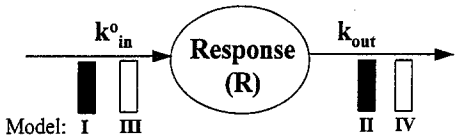
where k_{in} represents the apparent zero-order rate constant for production of the response, k_{out} defines the first-order rate constant for loss of the response, and R is assumed to be stationary with an initial value of R_0. The response variable, R, can be a directly measured entity or it may be 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 $SC_{50}\rightarrow 0$:

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

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

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

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

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

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

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

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

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

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

Area Between the Baseline and Effect Curve (ABEC):

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

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

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

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

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

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

capacity (I_{max} or S_{max}) of the drug. Since $k_{in} = k_{out} \cdot R_0$ at steady-state, solutions are possible using either k_{in} or k_{out}. Thus:

$$S_I = -k_{in} \cdot I_{max} = -k_{out} \cdot R_0 \cdot I_{max} \quad \text{(Model I)} \tag{23}$$

$$S_I = k_{in} \cdot I_{max} = k_{out} \cdot R_0 \cdot I_{max} \quad \text{(Model II)} \tag{24}$$

$$S_I = k_{in} \cdot S_{max} = k_{out} \cdot R_0 \cdot S_{max} \quad \text{(Model III)} \tag{25}$$

$$S_I = -k_{in} \cdot S_{max} = -k_{out} \cdot R_0 \cdot S_{max} \quad \text{(Model IV)} \tag{26}$$

METHODS

Pharmacokinetics

Methylprednisolone was selected as the model drug for simulation since its pharmacokinetics can be described using a linear, one-compartment model, and it has been found to produce several indirect pharmacodynamic responses. A volume of distribution (V) of 90 L and elimination rate constant (k_{el}) of 0.3 hr^{-1} were used to simulate monotonic plasma concentration-time profiles at various doses (D) using

$$C_p = \left(\frac{D \cdot 1000}{V}\right) \cdot e^{-k_{el} \cdot t} \tag{27}$$

where the factor 1000 converts the plasma concentrations to ng/ml for mg dose units.

Pharmacodynamics

The I_{max} or S_{max}, IC_{50} or SC_{50}, and dose were varied individually to define their effects on the pharmacodynamic response. A wide range for the I_{max} (0.2 to 1.0), S_{max} (0.2 to 1.5), IC_{50} (10 to 500 ng/ml), SC_{50} (10 to 500 ng/ml), and dose (10 to 10,000 mg) were used for simulations. The differential equations for Models I to IV were used in the PCNONLIN program (SCI Software Inc., Apex, NC) to simulate the response versus time profiles. The initial condition ($R_0 = 30$) and values of $k_{in} = 9$ unit/hr and $k_{out} = 0.3$ hr^{-1} were chosen to produce reasonable response patterns. The ABEC was generated over 0 to t_r where t_r is the time taken by the response to return to baseline (R_0) after drug administration. The Initial Slope (S_I) of the response versus time curve was calculated over 0 to 1 hr.

RESULTS

Model I

Figure 2 shows the effects of changes in either I_{max}, IC_{50}, or dose of a drug which produces its pharmacodynamic response by inhibition of the

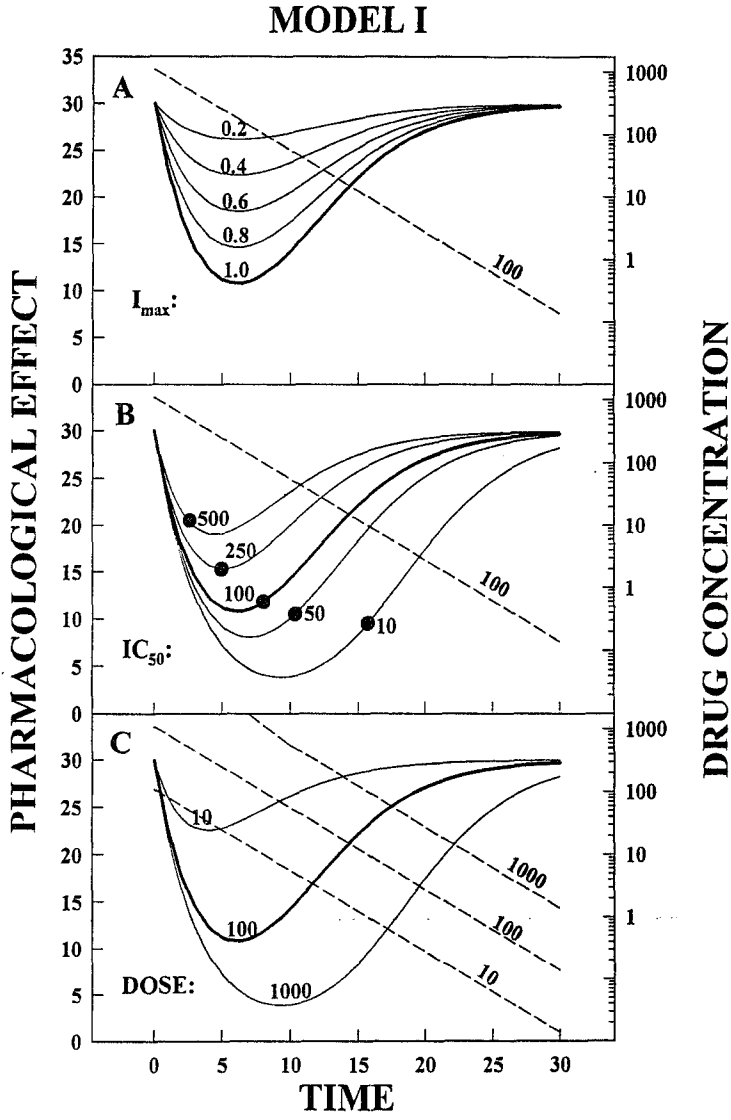


Fig. 2. Model I simulations of the pharmacodynamic response variables (solid lines) with respect to time after a single iv bolus dose. Simulated pharmacokinetic profiles at the corresponding doses are shown by dashed lines. The indicated values of I_{max} (0.2 to 1.0) (A); IC_{50} (10 to 500) (B); and doses (10 to 1000) (C); were used to study their effects on pharmacodynamic response and pharmacokinetic profiles. The heavy curves show the identical standard condition for all simulations ($I_{max} = 1.0$, $IC_{50} = 100$ ng/ml, Dose = 100). The dots in Panel B indicate the response and time when $C_p = IC_{50}$.

Table I. Effect of I_{max} or S_{max} on Properties of the Response Profiles

I_{max} or S_{max}	Model I	Model II	Model III	Model IV
		R_{max} (%R_{max})[a]		
0.2	26.2 (−13)	34.4 (15)	33.8 (13)	26.6 (−11)
0.4	22.4 (−25)	39.7 (33)	37.6 (25)	23.8 (−21)
0.6	18.6 (−38)	45.9 (53)	41.4 (38)	21.4 (−29)
0.8	14.8 (−51)	54.5 (82)	45.2 (51)	19.4 (−35)
1.0	11.0 (−63)	65.1 (117)	49.0 (63)	17.7 (−41)
1.5	NA[c]	NA[c]	58.5 (95)	14.5 (−52)
		Initial Slope[b] (S_I)		
0.2	−1.4	1.4	1.4	−1.4
0.4	−2.8	3.0	2.8	−2.7
0.6	−4.2	4.6	4.2	−3.9
0.8	−5.6	6.3	5.6	−5.1
1.0	−7.0	8.0	7.0	−6.2
1.5	NA[c]	NA[c]	10.6	−8.8
		ABEC		
0.2	50	55	50	45
0.4	99	121	99	84
0.6	149	204	149	116
0.8	198	309	198	144
1.0	248	444	248	169
1.5	NA[c]	NA[c]	372	219
		$T_{R_{max}}$		
0.2	6.2	6.2	6.2	6.2
0.4	6.2	6.5	6.2	6.0
0.6	6.2	7.0	6.2	5.7
0.8	6.2	7.2	6.2	5.5
1.0	6.2	7.5	6.2	5.2
1.5	NA[c]	NA[c]	6.2	5.0
		$C_{R_{max}}$		
0.2	173	173	173	173
0.4	173	158	173	184
0.6	173	136	173	201
0.8	173	128	173	213
1.0	173	117	173	234
1.5	NA[c]	NA[c]	173	247

[a] $\%R_{max} = [(R_{max} - R_0)/R_0] \cdot 100$
[b] Initial slope $= (\Delta R/\Delta t)_{\Delta t = 1}$
[c] NA: Not Applicable.

factors controlling k_{in} (Fig. 1: Model I). The numerical values of the properties such as R_{max}, S_I, ABEC, $T_{R_{max}}$, and $C_{R_{max}}$ resulting from the simulations are provided in Tables I–III for the three parameters varied. The increase in I_{max} resulted in a proportional increase in the maximum inhibitory response (R_{max}) up to the expected limit of 0. The initial slope (S_I) of response vs. time curves behaved similarly (Fig. 2A). A five-fold increase in I_{max} (from 0.2 to 1.0) produced an increase in the maximum percent R_{max} and S_I by nearly the same magnitude (R_{max} increased from 12.7 to 63.3%,

Table II. Effect of IC_{50} or SC_{50} on Properties of the Response Profiles[a]

IC_{50} or SC_{50}	Model I	Model II	Model III	Model IV
		R_{max} (%R_{max})		
0	$\{R_0 \cdot (1 - I_{max})\}$	$\{R_0/(1 - I_{max})\}$	$\{R_0 \cdot (1 + S_{max})\}$	$\{R_0/(1 + S_{max})\}$
10	4.0 (−87)	108.4 (261)	56.0 (87)	15.6 (−48)
50	8.1 (−73)	74.8 (149)	51.9 (73)	16.8 (−44)
100	11.0 (−63)	65.1 (117)	49.0 (63)	17.7 (−41)
250	15.5 (−48)	52.0 (74)	44.5 (48)	19.5 (−35)
500	18.4 (−39)	44.9 (50)	41.6 (39)	21.6 (−28)
		Initial Slope (S_I)		
0	$-k_{in} \cdot I_{max}$	$k_{in} \cdot I_{max}$	$k_{in} \cdot S_{max}$	$-k_{in} \cdot S_{max}$
10	−7.7	8.9	7.7	−6.7
50	−7.4	8.5	7.4	−6.5
100	−7.0	8.0	7.0	−6.2
250	−6.2	6.9	6.2	−5.5
500	−5.1	5.6	5.1	−4.6
		ABEC		
0	∞	∞	∞	∞
10	464	1259	464	279
50	312	638	312	203
100	248	444	248	169
250	169	254	169	125
500	116	155	116	92
		$T_{R_{max}}$		
0	∞	∞	∞	∞
10	9.5	12.5	9.5	7.5
50	7.0	9.0	7.0	6.0
100	6.2	7.5	6.2	5.2
250	5.2	6.0	5.2	4.5
500	4.2	5.0	4.2	4.2
		$C_{R_{max}}$		
0	0	0	0	0
10	64	26	64	117
50	136	75	136	184
100	173	117	173	234
250	234	184	234	288
500	315	248	315	315

[a] Symbols are defined in Glossary.

and S_I increased from 1.4 to 7.0) (Table I). The area between the baseline and the effect curve (ABEC) was calculated to characterize the overall effect of the drug. The ABEC increased proportionally with the increase in I_{max} (Table I) as expected [Eq. (19)]. The time of occurrence of the maximum response $T_{R_{max}}$ was independent of I_{max} and, therefore, plasma drug concentrations at the time of maximal response $C_{R_{max}}$ remained constant with the change in I_{max}. This is a general expectation for these models (note Remark 4: Ref. 7).

The effect of IC_{50} on the dynamic response profile is shown in Fig. 2B. Lower IC_{50} values yield more pronounced effects. The percent maximum

Table III. Effect of Dose on Properties of the Response Profiles[a]

Dose	Model I	Model II	Model III	Model IV
		R_{max} (%R_{max})		
10	22.5 (−25)	39.5 (32)	37.2 (24)	24.0 (−20)
100	11.0 (−63)	65.1 (117)	49.0 (63)	17.7 (−41)
1000	4.0 (−87)	108.4 (261)	56.0 (87)	15.6 (−48)
10000	1.3 (−96)	180.6 (502)	58.7 (96)	15.1 (−50)
∞	$\{R_0 \cdot (1-I_{max})\}$	$\{R_0/(1-I_{max})\}$	$\{R_0 \cdot (1+S_{max})\}$	$\{R_0/(1+S_{max})\}$
		Initial Slope (S_I)		
10	−3.8	4.1	3.8	−3.5
100	−7.0	8.0	7.0	−6.2
1000	−7.7	8.9	7.7	−6.7
10000	−7.8	9.0	7.8	−6.8
∞	$-k_{in} \cdot I_{max}$	$k_{in} \cdot I_{max}$	$k_{in} \cdot S_{max}$	$-k_{in} \cdot S_{max}$
		ABEC		
10	74	89	74	63
100	248	444	248	169
1000	464	1259	464	279
10000	659	2493	659	369
∞	∞	∞	∞	∞
		$T_{R_{max}}$		
10	4.0	4.2	4.0	4.0
100	6.2	7.5	6.2	5.2
1000	9.5	12.5	9.5	7.0
10000	13.0	18.0	13.0	10.0
∞	∞	∞	∞	∞
		$C_{R_{max}}$		
10	33	32	33	33
100	173	117	173	234
1000	643	261	643	1360
10000	2249	502	2249	5532
∞	∞	∞	∞	∞

[a] Symbols are defined in Glossary.

inhibitory response (%R_{max}), S_I, and ABEC increased with the decrease in IC_{50}. The $T_{R_{max}}$ shifted to later times and, therefore, $C_{R_{max}}$ decreased with the decrease in IC_{50} (Table II). The limiting value of R_{max} as $IC_{50} \rightarrow 0$ is $R_0 \cdot (1 - I_{max})$ [Table II and Eq. (10)].

Figure 2C shows the effect of dose on the dynamic response and pharmacokinetic profiles. The curves show a typical declining response with a delayed nadir, later return to baseline, and greater effects with larger doses. This is expected to occur for any monotonic drug concentration profile (see Remark 1, Ref. 7). The %R_{max}, S_I, ABEC, $T_{R_{max}}$ and $C_{R_{max}}$ values increased with the increase in dose (Table III), but R_{max} and S_I have limiting values of 0 [$=R_0 \cdot (1 - I_{max})$] and −9 ($= -k_{in} \cdot I_{max}$) at larger doses (Dose$\rightarrow\infty$). The ABEC and $T_{R_{max}}$ continue increasing in proportion to log dose. This was demonstrated previously for ABEC (9). Note the corresponding relationship

for R_{max} in Eq. (10) (7). However, both $C_{R_{max}}$ and $T_{R_{max}}$ increase to infinity as Dose$\rightarrow\infty$ [Eqs. (22) and (32), Ref. 7]. This is also seen for $C_{R_{max}}$ in Eq. (15) when $R_{max}\rightarrow 0$ and $I_{max}=1$.

It is interesting to note that an increase in dose or decrease in IC_{50} by the same factor (i.e., constant Dose/IC_{50} ratio) results in identical and superimposable pharmacodynamic response patterns for this and subsequent models (see Appendix). For instance, the dose of 1000 at $IC_{50}=100$ produced the same response as that produced at the dose of 100 at $IC_{50}=10$ (Fig. 2B, C). This property allows use of the ratio $(IC_{50}\cdot V)/D$ as a nondimensional parameter in seeking generalized solutions for these types of models (7).

Model II

Figure 3 characterizes Model II with respect to changes in either I_{max}, IC_{50}, or dose. The drug described by Model II produces its pharmacodynamic response by inhibition of k_{out} (Fig. 1: Model II). The effect of I_{max} on the pharmacodynamic response variable is shown in Fig. 3A. The maximum stimulatory response (R_{max}), initial slope, and ABEC values increased with the increase in I_{max} (Table I). The $T_{R_{max}}$ shifted to later times and, therefore, $C_{R_{max}}$ decreased with the increase in I_{max} (Table I). The R_{max} will have a specific limiting value when $0<I_{max}<1$. However, if $I_{max}=1$, $R_{max}\rightarrow\infty$ with large doses or low IC_{50} values [see Table III, Eqs. (11) and (12)]. This is a unique characteristic for Model II (7).

The effect of IC_{50} on the dynamic response is shown in Fig. 3B. Lower IC_{50} values produce larger effect profiles. The R_{max}, S_I, and ABEC values increased with the decrease in IC_{50} (Table II). The limiting value of R_{max} as $IC_{50}\rightarrow 0$ is $R_0/(1-I_{max})$ [Table II, Eqs. (11) and (12)]. The $T_{R_{max}}$ shifted to later times and, therefore, $C_{R_{max}}$ decreased with the decrease in IC_{50} (Table II). The value of $C_{R_{max}}$ is proportional to IC_{50} [Eq. (16)].

The effect of dose on the dynamic response and pharmacokinetic profiles are shown in Fig. 3C. The curves show increasing observed effects with a delayed maximum and slow return to baseline; these effects increase in relation to dose. These type of patterns are expected to occur for any monotonic drug concentration profile (note Remark 1, Ref. 7). The R_{max}, S_I, ABEC, $T_{R_{max}}$ and $C_{R_{max}}$ values increased with the increase in dose (Table III). The S_I has a limiting value of 9 ($=k_{in}\cdot I_{max}$) at larger doses (Dose$\rightarrow\infty$), while ABEC, $T_{R_{max}}$ and $C_{R_{max}}$ values continue increasing in proportion to log dose. The value of R_{max} increases in proportion to dose only when $I_{max}=1$, otherwise large doses produce a limiting value of $R_0/\mathrm{Cl}-I_{max})$ [Table III and Eq. (64), Ref. 7]. Both $T_{R_{max}}$ and $C_{R_{max}}$ increase to infinity as Dose$\rightarrow\infty$ [Eqs. (22) and (32) of Ref. 7].

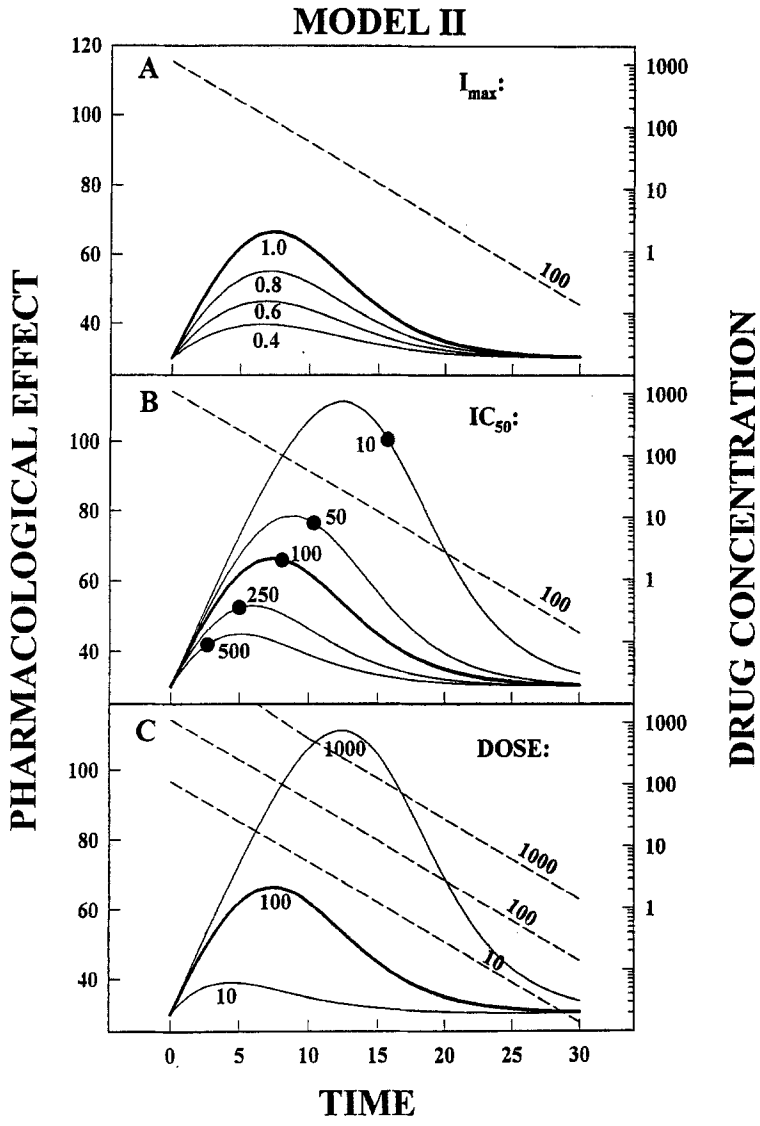


Fig. 3. Model II simulations of the pharmacodynamic response variables (solid lines) with respect to time after a single iv bolus dose. Simulated pharmacokinetic profiles at the corresponding doses are shown by dashed lines. The indicated values of I_{max} (0.2 to 1.0) (A); IC_{50} (10 to 500) (B); and doses (10 to 1000) (C); were used to study their effects on pharmacodynamic response and pharmacokinetic profiles. The heavy curves show the identical standard condition for all simulations ($I_{max} = 1.0$, $IC_{50} = 100$ ng/ml, Dose = 100). The dots in Panel B indicate the response and time when $C_p = IC_{50}$.

An increase in dose or decrease in IC_{50} by the same factor results in superimposable pharmacodynamic response patterns (Fig. 3B, C, and Appendix).

Model III

Figure 4 shows the effects of changes in either S_{max}, SC_{50}, or dose for a drug which produces its dynamic response by stimulation of k_{in} (Fig. 1: Model III). The effect of S_{max} on the dynamic response variable is shown in Fig. 4A. The maximum stimulatory response (R_{max}) and initial slope increased proportionally with an increase in S_{max}. The 7.5-fold increase in S_{max} (from 0.2 to 1.5) resulted in an increase in the maximum percent R_{max} and initial slope by nearly the same magnitude (R_{max} increased from 12.7 to 95.3% and initial slope increased from 1.41 to 10.55) (Table I). The former occurs because R_{max} is proportional to $R_0(1 + S_{max})$ at large doses [Eq. (13)]. The ABEC also increased proportionally with an increase in S_{max} (Table I) as expected according to Eq. (21). $T_{R_{max}}$ remained constant with the increase in S_{max} and, therefore, so did the $C_{R_{max}}$. This is expected for any monotonic drug disposition profile (see Remark 4, Ref. 7).

The effect of SC_{50} on the response variable is shown in Fig. 4B. Lower SC_{50} values produce pharmacologic effects with greater magnitudes and duration. The R_{max}, S_I, and ABEC values increased with the decrease in SC_{50} (Table II). The $T_{R_{max}}$ shifted to later times and, therefore, $C_{R_{max}}$ decreased with the decrease in SC_{50} (Table II).

Figure 4C shows the effect of dose on the response variable and pharmacokinetic profiles. The profiles show greater observed effects with a delayed maximum and slow return to baseline as dose is increased. These types of curves are expected to occur for any monotonic drug concentration pattern (note Remark 1, Ref. 7). The R_{max}, S_I, ABEC, $T_{R_{max}}$ and $C_{R_{max}}$ values increased with the increase in dose (Table III). The R_{max} and S_I have limiting values of 60 [$=R_0 \cdot (1 + S_{max})$] and 9 ($=k_{in} \cdot S_{max}$) at larger doses (Dose$\rightarrow\infty$) [Eq. (13); also see Eq. (65) of Ref. 7]. ABEC increases nearly proportional to log dose as expected from Eq. (21). However, both $C_{R_{max}}$ and $T_{R_{max}}$ increase to infinity as Dose$\rightarrow\infty$ [Eq. (22) and (32) of Ref. 7].

An increase in SC_{50} or a decrease in dose by the same factor produced identical responses (Fig. 4B, C, and Appendix).

Model IV

The effects of changes in either S_{max}, SC_{50}, or dose for a drug whose pharmacodynamic response can be described by Model IV are shown in Fig. 5. This model represents a drug that stimulates k_{out}. The effect of S_{max} on the response variable is shown in Fig. 5A. The maximum inhibitory

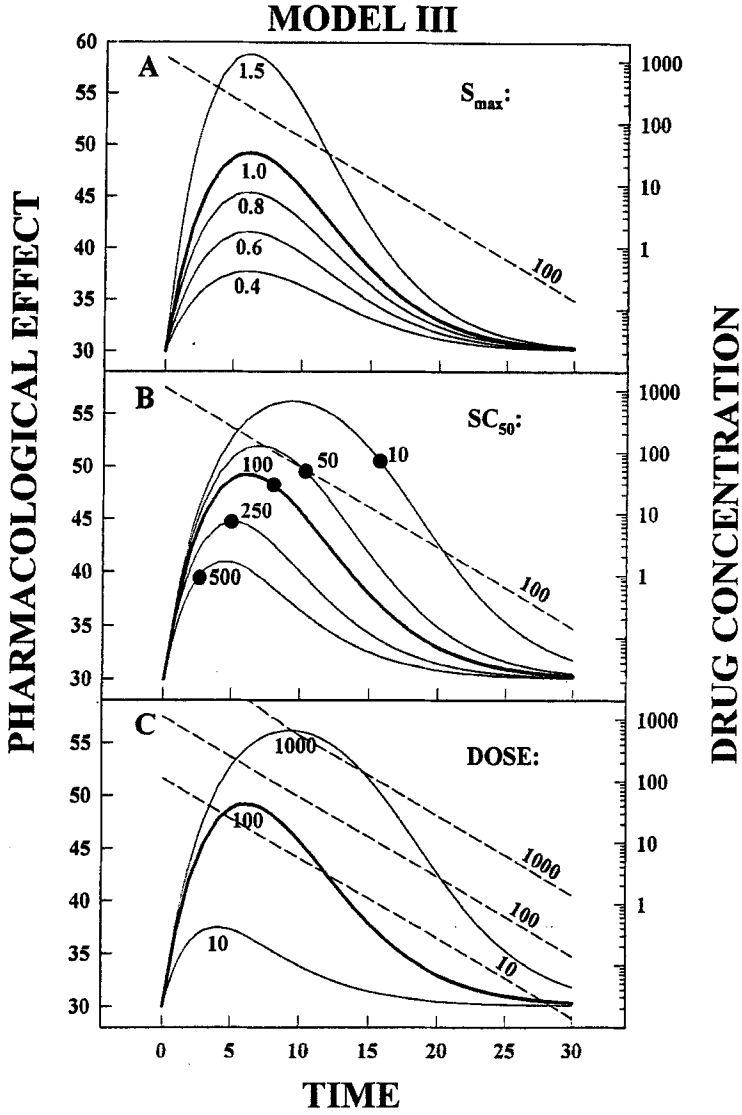


Fig. 4. Model III simulations of the pharmacodynamic response variables (solid lines) with respect to time after a single iv bolus dose. Simulated pharmacokinetic profiles at the corresponding doses are shown by dashed lines. The indicated values of S_{max} (0.2 to 1.0) (A); SC_{50} (10 to 500) (B); and doses (10 to 1000) (C); were used to study their effects on pharmacodynamic response and pharmacokinetic profiles. The heavy curves show the identical standard condition for all simulations ($S_{max} = 1.0$, $SC_{50} = 100$ ng/ml, Dose = 100). The dots in Panel B indicate the response and time when $C_p = SC_{50}$.

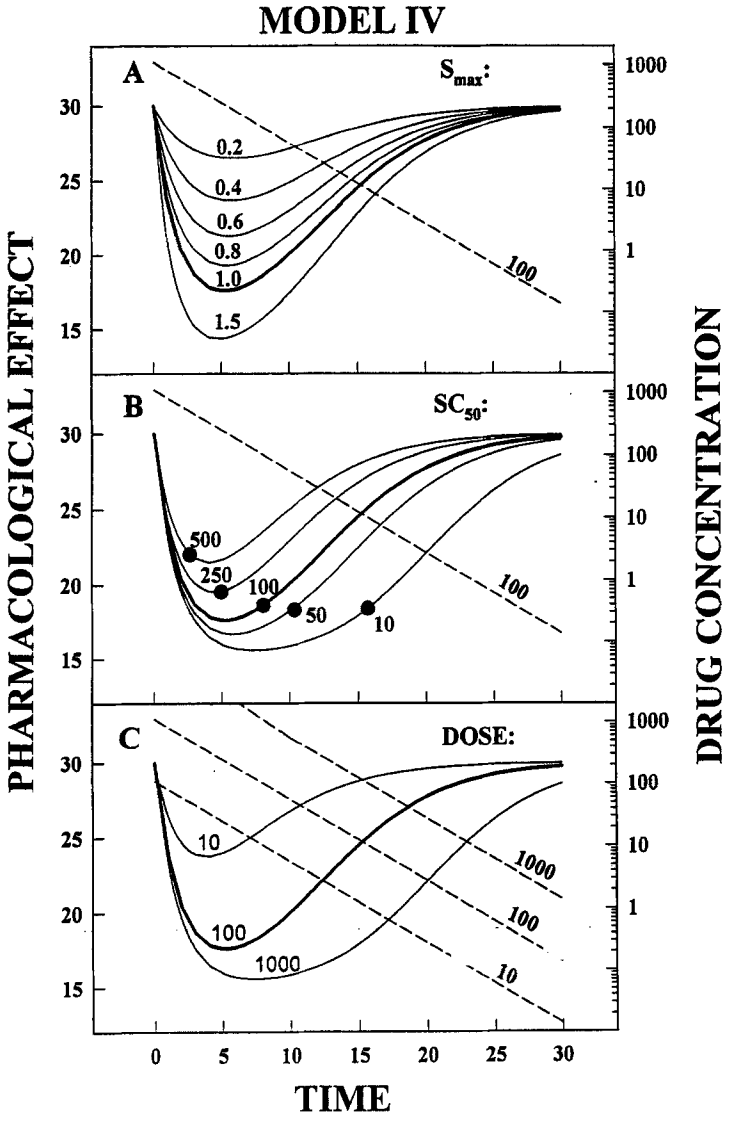


Fig. 5. Model IV simulations of the pharmacodynamic response variables (solid lines) with respect to time after a single iv bolus dose. Simulated pharmacokinetic profiles at the corresponding doses are shown by dashed lines. The indicated values of S_{max} (0.2 to 1.0) (A); SC_{50} (10 to 500) (B); and doses (10 to 1000); (C) were used to study their effects on pharmacodynamic response and pharmacokinetic profiles. The heavy curves show the identical standard condition for all simulations ($S_{max} = 1.0$, $SC_{50} = 100$ ng/ml, Dose = 100). The dots in Panel B indicate the response and time when $C_p = SC_{50}$.

response (R_{max}), initial slope and ABEC values increased with the increase in S_{max} (Table I). The limiting value of R_{max} is $R_0/(1+S_{max})$; see Eq. (14). The $T_{R_{max}}$ shifted to earlier times and, therefore, $C_{R_{max}}$ increased with the increase in S_{max} (Table I). Proportionality between $C_{R_{max}}$ and S_{max} is expected at higher doses [Eq. (18)]. ABEC is proportional to $S_{max}/(1+S_{max})$; see Eq. (22).

Figure 5B shows the effect of SC_{50} on the dynamic responses. Lower SC_{50} values produce response patterns with greater nadirs and duration. The percent maximum inhibitory response ($\%R_{max}$), S_I, and ABEC increased with the decrease in SC_{50} (Table II). $T_{R_{max}}$ shifted to later times and, therefore, $C_{R_{max}}$ decreased with the decrease in SC_{50} (Table II). These behaviors of ABEC and $C_{R_{max}}$ are in accordance with Eqs. (18) and (22).

The effect of an increase in dose on the dynamic response is shown in Fig. 5C. The curves show increasing observed effects with a delayed maximum and slow return to baseline; such effects increase with dose. The R_{max}, S_I, ABEC, $T_{R_{max}}$, and $C_{R_{max}}$ values increased with the increase in dose (Table III). The R_{max} and S_I have limiting values of 15 $[=R_0/(1+S_{max})]$ and -9 $(=-k_{in}\cdot S_{max})$ at larger doses (Dose$\rightarrow\infty$) [Eq. (26), Table III, and Eq. (27) of Ref. 7]. ABEC and $T_{R_{max}}$ continue increasing in proportion to log dose. However, both $C_{R_{max}}$ and $T_{R_{max}}$ increase to infinity as Dose$\rightarrow\infty$ (Eqs. (22) and (32) of Ref. 7). Again, these patterns are predicted by Eqs. (18) and (22).

An increase in dose or decrease in SC_{50} by the same factor results in the identical pharmacodynamic response patterns (Fig. 5B, C, and Appendix).

Effects of Dose

Since dose is the most readily manipulated variable in a pharmacodynamic study, it is of interest to assess how selected parameters relate to a wide range of doses of drug for each of the models. Figure 6 shows that $T_{R_{max}}$ is nearly linear with log dose over a wide range of doses for all models (see Eq. (62) of Ref. 7). Similar behavior occurs with ABEC. This is the theoretical expectation for all models except Model II when $I_{max}=1$, ABEC will be proportional to $\ln^2 D$ (8). Thus, curvature is seen in Fig. 6 (Model II).

As shown in Fig. 7, R_{max} shows a lower limit with log dose for Models I and IV (also see Eqs. (63) and (66) of Ref. 7), and an upper limit with log dose for Model III (also see Eq. (65) of Ref. 7). R_{max} continues increasing nonlinearly with log dose for Model II when $I_{max}=1$. However, if $I_{max}<1$, R_{max} has an upper limit of $R_0/(1-I_{max})$ with dose for Model II (see Eq. (64) of Ref. 7). These relationships are in accordance with Eqs. (10)–(14). It can also be seen in Fig. 7 that $C_{R_{max}}$ shows hyperbolic behavior with log dose for all four models. These patterns may be inferred from Eqs. (15)–(18).

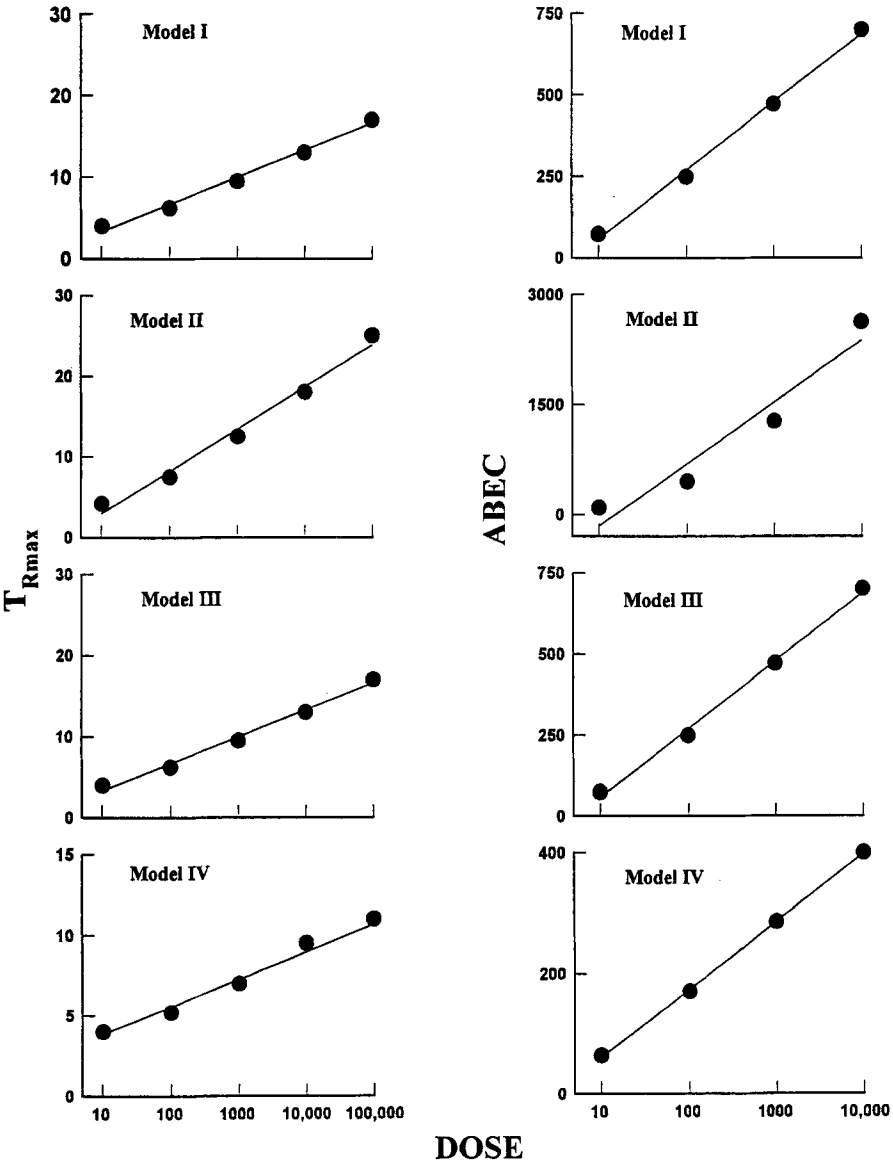


Fig. 6. The time to reach maximum effect ($T_{R_{max}}$) and the area between the baseline and effect curve (ABEC) vs. the log of drug dose for Models I to IV. Values of $I_{max} = 1.0$, $S_{max} = 1.0$, $IC_{50} = 100$ ng/ml, and $SC_{50} = 100$ ng/ml were used.

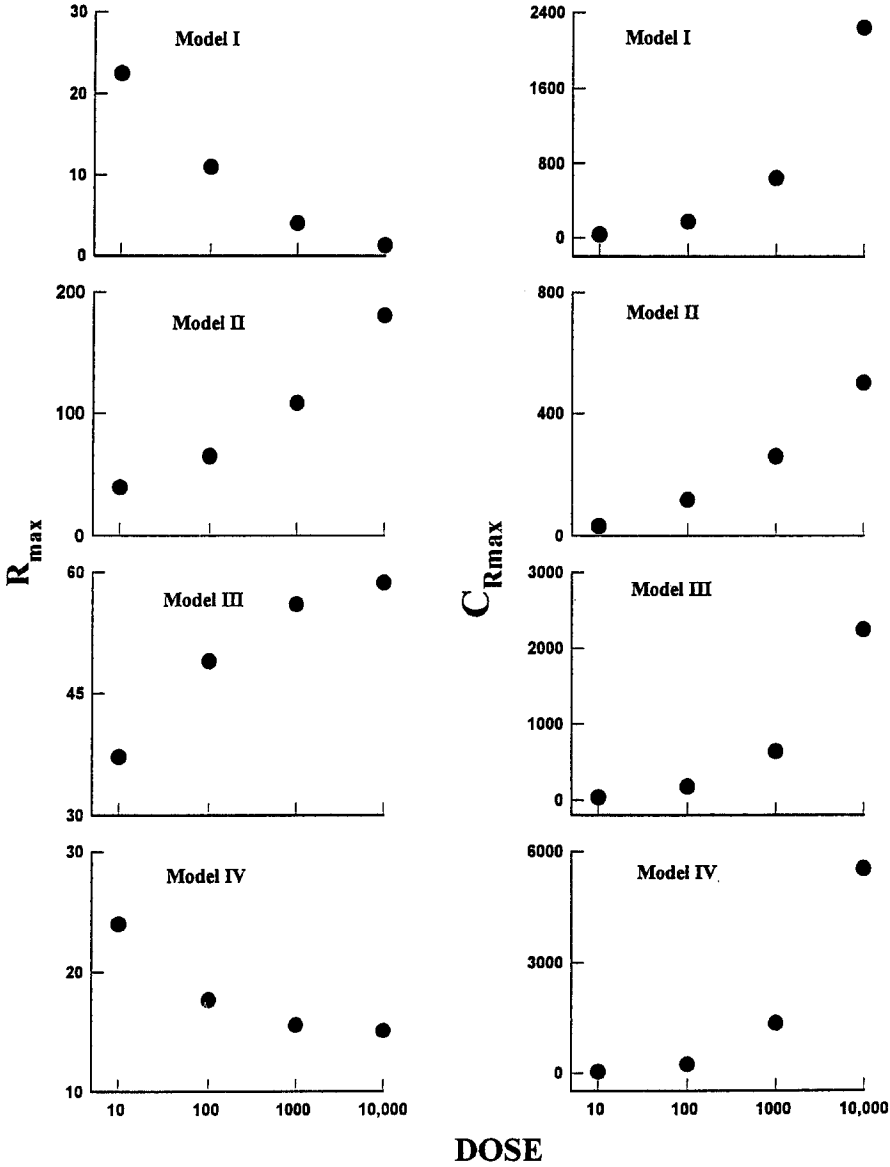


Fig. 7. The maximum effect (R_{max}) and the plasma concentration of drug at the time of maximum effect ($C_{R_{max}}$) vs. the log of drug dose for Models I to IV. Values of $I_{max} = 1.0$, $S_{max} = 1.0$, $IC_{50} = 100$ ng/ml, and $SC_{50} = 100$ ng/ml were used.

Model Identification

For pharmacodynamic modeling with a mechanistic basis, it is essential to assign appropriate models to pharmacodynamic data based on the fundamental actions of the drug. It is also helpful to anticipate the nature of expected model behavior. Pharmacodynamic response patterns occur downward for Model I and IV, and upward for Model II and III. For instance, if the drug causes a decrease in the pharmacodynamic response from its baseline value, either Model I or IV may be able to characterize the general pattern of response for one dose level. Similarly, if response increases from its baseline value in presence of drug, either Model II or III may appear to be applicable.

While an understanding of the mechanism of action of the drug is the best approach to construction of the model, the following two methods can be used for complete experimental identification of an appropriate indirect response model: (i) a single iv dose study at more than one dose level; and (ii) a steady-state iv infusion study at more than one administration rate.

In a single iv dose study, it is important that one of the dose levels be sufficiently high to produce either full inhibition or stimulation of the system. Pharmacodynamic parameters such as I_{max} or S_{max} and IC_{50} or SC_{50} can be obtained by fitting the experimental data to two of the four models. These parameters, in turn, can be used to estimate the maximum responses (R_{max}) at large doses (Dose$\rightarrow\infty$) according to Eqs. (10)–(14). Thus in the absence of knowledge about the mechanism of action of the drug, one can determine which model is more suitable by comparing experimental R_{max} values obtained at larger doses with estimated R_{max} values for models which describe responses produced in the same direction.

In an infusion study, it is critical that the length of infusion be sufficiently long not only to produce steady-state pharmacokinetics but also steady-state conditions in the pharmacodynamic system. In other words, the time of infusion should be based on the k_{out} value. For instance, if k_{out} is small, a longer infusion time is required, and vice-versa.

Figure 8 shows the effects of change in the infusion rate on the time to reach the maximum response ($T_{R_{max}}$) for the four models. In Models I and III, the $T_{R_{max}}$ remained constant with the change in the infusion rate (Table IV; Fig. 8) because the drug affects k_{in} for these two models (inhibits for Model I and stimulates for Model III), and k_{in} has no influence on the time required by the pharmacodynamic system to reach steady-state under continuous drug infusion. However, in Models II and IV, the $T_{R_{max}}$ changed with the infusion rate (Table IV; Fig. 8) because the drug affects k_{out} for these models (inhibits for Model II and stimulates for Model IV). The k_{out}

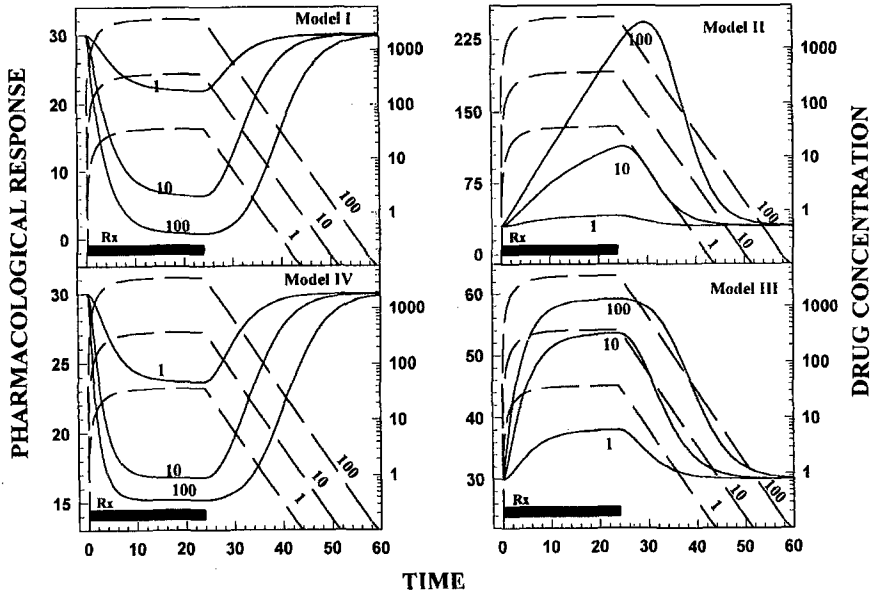


Fig. 8. Simulations of the pharmacodynamic response variables (solid lines) with respect to time during and after a 24 hr iv infusion for the four models. Pharmacokinetic profiles at the corresponding doses are shown by dashed lines. Values of $I_{max} = 1.0$, $S_{max} = 1.0$, $IC_{50} = 100$ ng/ml, $SC_{50} = 100$ ng/ml, and the indicated values of infusion rate (1 to 100 mg/hr) were used to produce pharmacodynamic response and pharmacokinetic profiles.

value influences the time required by the pharmacodynamic system to reach steady-state under continuous drug infusion. For instance, in Model II where a drug produces its pharmacodynamic response by inhibition of k_{out}, the $T_{R_{max}}$ shifted to later time (Table IV) because the decrease in k_{out} due to the drug would result in an increased time required by the pharmacodynamic system to reach steady-state under continuous infusion of the drug. Similarly, in Model IV, the $T_{R_{max}}$ shifted to earlier times (Table IV) because an increased k_{out} value produced an opposite behavior. Thus, one can determine

Table IV. Effect of Infusion Rate on $T_{R_{max}}$

Infusion Rate (mg/hr for 24 hr)	$T_{R_{max}}$ (hr) Model I	Model II	Model III	Model IV
1	24	24	24	23
10	24	25	24	20
100	24	29	24	16
1000	24	37	24	14

[a] I_{max} or $S_{max} = 1$; IC_{50} or $SC_{50} = 100$ ng/ml; $k_{in} = 9$ unit/hr; and $k_{out} = 0.3\ hr^{-1}$.

which model is suitable for a drug by comparing experimental $T_{R_{max}}$ values obtained at two steady-state infusion dose levels. However, a practical concern is whether the response data allows clear identification of $T_{R_{max}}$.

DISCUSSION

We have characterized the four basic indirect response models (Fig. 1) with respect to changes in either I_{max} or S_{max}, IC_{50} or SC_{50}, and dose in order to determine whether there are identifying features that can help understand how these models function and to assign an appropriate model to experimental data. In a previous report (1), the inhibition models (Models I and II) assumed that the k_{in} or k_{out} process could be fully blocked and thus no I_{max} was used. This report extends our previous inhibition models by adding the I_{max} factor because partial dynamic responses (inhibition or stimulation) can occur for some drugs. For example, partial suppression of dihydrotestosterone production by finasteride has been described (10). The maximum inhibition or stimulation capacity (I_{max} or S_{max}) of the drug also affects the limiting value of the initial slope as well as the AUC of effect. In addition, we have sought methods of model identification, have shown the interchangeability of Dose and IC_{50} or SC_{50}, and have demonstrated the application of some new theoretical relationships (Eq. (10)–(26) and Appendix I).

There are several common features of the pharmacodynamic profiles of drugs which produce responses by indirect mechanisms described by Models I to IV. All four models show that the maximum response (R_{max}), S_I, and ABEC values increased, and the time of occurrence of R_{max} ($T_{R_{max}}$) shifted to later times with the increase in dose or with the decrease in IC_{50} or SC_{50}. Also, combinations of $Dose \cdot V^{-1}/IC_{50}$ (or $Dose \cdot V^{-1}/SC_{50}$) which have the same value produce identical and superimposable dynamic response patterns within each of the four models. The R_{max}, S_I, and ABEC values increased with the increase in I_{max} or S_{max} in all models. The ABEC and $T_{R_{max}}$ usually continue increasing in proportion to log dose (Fig. 6), while R_{max} has a limiting value at larger doses (Fig. 7) in all four models. As observed previously, the maximum observed response (R_{max}) occurs much later than the time of occurrence of maximum plasma drug concentrations (time 0) because the drug causes incremental inhibition or stimulation for as long as $C_p > IC_{50}$ (or SC_{50}). After the response reaches the maximum or minimum, the return to baseline is then a function of both k_{in} and drug elimination. Therefore, the response lasts beyond the presence of effective drug levels because of the time needed for the system to regain equilibrium (when $k_{in} = k_{out} \cdot R_0$).

In Models I and III, the response patterns appear similar though occurring in opposite directions. For instance, the $T_{R_{max}}$ remained constant with the change in I_{max} or S_{max} for both models. The values of $\%R_{max}$, S_I, ABEC, and $C_{R_{max}}$ were identical with changes in I_{max} or S_{max}, IC_{50} or SC_{50} or dose for both models. However, Model III allows for S_{max} to attain values >1 beyond which most similarities end. The reason for these identical properties is that the drug affects k_{in} in both models (inhibits k_{in} for Model I and stimulates k_{in} for Model III) and the inhibition function = −stimulation function [Eqs. (3) and (6)].

Models II and IV exhibit more distinctive dynamic response patterns as a function of I_{max} or S_{max}, IC_{50} or SC_{50} and dose. Besides occurring in opposite directions, an increase in these parameters produced values of $T_{R_{max}}$, $\%R_{max}$, S_I, ABEC, and $C_{R_{max}}$ which changed dissimilarity for the two models. In both models the drug affects k_{out} (inhibits k_{out} for Model II and stimulates k_{out} for Model IV). The explicit functions for ABEC indeed differ in structure between Model II and IV [Eqs. (20) and (22)].

In Models I and IV, although the response patterns occur in the same direction, the numerical values of the properties which characterize the response patterns were dissimilar because the drugs affect different components of the indirect effect model (inhibits k_{in} for Model I and stimulates k_{out} for Model IV). The values of $T_{R_{max}}$, $\%R_{max}$, S_I, ABEC, and $C_{R_{max}}$ were different as a function of I_{max} or S_{max}, IC_{50} or SC_{50} and dose for the two models. Similarly, in Models II and III, the response patterns occurred in same direction but with different curve properties.

For complete experimental identification of an indirect response model, the studies should be done at more than one dose level or administration rate of a drug. If two dose levels are used, the higher dose or rate should be sufficiently large to determine whether full or partial inhibition or stimulation occurs, and whether the initial rate of change of response represents the true value of $k_{in} \cdot I_{max}$ or $k_{in} \cdot S_{max}$ depending on the model. Alternatively, two administration rates can be used for experimental identification of a model by determining the effect of the infusion rate on $T_{R_{max}}$. If $T_{R_{max}}$ changes with the infusion rate then either Model II or IV may apply which can be distinguished by the direction of the response profile. In contrast, Models I and III do not exhibit any change in $T_{R_{max}}$ with the altered infusion rate.

In some cases, three doses may be necessary for model identification, since low drug doses may produce intermediate effects, and the properties of the model may not be fully clear. For instance, both Models II and III were able to characterize the general pattern of increased numbers of natural killer cells in blood following a low single dose of prednisolone (10 mg/day). It was difficult to determine which model was more suitable on the basis of curve fitting (11), and simulations of the expected effects of larger

doses showed dissimilar response profiles. However, Model II produced IC_{50} values which were in close concordance to dissociation constant (K_D) values for prednisolone receptors in lymphocytes.

An indirect pharmacodynamic response (R) will mimic that of a direct response occurring in a biophase outside of plasma when the kinetics of R are "fast" i.e. $k_{out} \gg k_{eo}$ where k_{eo} is the rate constant for drug equilibration between plasma and an effect site (12). For instance, the discrimination of a changing $T_{R_{max}}$ of some indirect pharmacodynamic responses at different dose levels would be less obvious if $k_{out} \gg k_{eo}$. For closer examination of such a drug and system, intensive sampling times with respect to the $t_{1/2}$ of k_{eo} will be required (6).

GLOSSARY

A	Ratio of D/IC_{50}
ABEC	Area between the baseline and the response curve (0 to t_r)
C_p	Plasma concentration of drug at any time
C_{Rmax}	Plasma concentration of drug at the time of maximal response
D	Dose of drug
$H_n(t)$	Hill function for Model n
IC_{50}	Drug concentration producing 50% of maximum inhibition
I_{max}	Maximum inhibitory factor attributed to drug ($0 < I_{max} \leq 1$)
k_{el}	First-order rate constant for drug elimination
k_{eo}	Rate constant for drug equilibration between plasma and a hypothetical effect compartment
k_{in}	Apparent zero-order rate constant for production of drug response
k_{out}	First-order rate constant for loss of drug response
R	Response variable
R_{max}	Maximal response
R_0	Baseline response prior to drug administration
SC_{50}	Drug concentration producing 50% of maximum stimulation
S_{max}	Maximum stimulatory factor attributed to drug ($S_{max} > 0$)
S_I	Initial slope of the response versus time curve
t	Time after drug administration
t_r	Time when response returns to baseline
T_{Rmax}	Time to reach maximum response following drug administration
V	Volume of distribution

ACKNOWLEDGMENTS

The review and comments of Dr. Wojciech Krzyzanski are appreciated.

APPENDIX

Identical and superimposable dynamic response profiles were observed when both the dose and IC_{50} or SC_{50} were changed in such a way that their ratio (i.e., D/IC_{50} or D/SC_{50}) remained constant. This can be anticipated for any linear pharmacokinetic function.

The inhibition function is

$$H_n(t) = -\frac{I_{max} \cdot C_p}{IC_{50} + C_p} \tag{A.1}$$

For a drug having linear, monoexponential pharmacokinetics, the plasma concentration C_p at any time t after iv bolus dose (D), can be described by

$$C_p = \frac{D}{V} e^{-k_{el} \cdot t} \tag{A.2}$$

Substituting Eq. (A.2) in Eq. (A.1)

$$H_n(t) = -\frac{I_{max} \cdot \frac{D}{V} e^{-k_{el} \cdot t}}{IC_{50} + \frac{D}{V} e^{-k_{el} \cdot t}} \tag{A.3}$$

Assuming $A = D \cdot V^{-1}/IC_{50}$, $L(t) = e^{-k_{el} \cdot t}$ and rearranging yields

$$H_n(t) = -\frac{I_{max} \cdot A \cdot L(t)}{1 + A \cdot L(t)} \tag{A.4}$$

Thus, any combination of IC_{50} and Dose/V which produce the same values of A will result in identical degrees of inhibition (or stimulation) as described by Eq. (A.4).

This expectation can be generalized further for any linear pharmacokinetic function. The Laplace transform of plasma (or any biophase) drug concentration can be written as (13,14):

$$\bar{C}_p = D \cdot (ins) \cdot (dis) \tag{A.5}$$

where ins and dis are Laplace transforms of general dose input and unit disposition functions. The latter applies to any multi-compartment model and ins functions have been identified for bolus, first-order, zero-order, and combined methods of drug administration (14). The dose is a constant which factors directly into the time domain and anti-transformation of Eq. (A.5)

$$C_p = D \cdot \text{Input} \cdot \text{Disposition} \tag{A.6}$$

thus yielding equations similar to Eq. (A.4).

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