Characteristics of indirect pharmacodynamic models and applications to clinical drug responses

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This review describes four basic physiologic indirect pharmacodynamic response (IDR) models which have been proposed to characterize the pharmacodynamics of drugs that act by indirect mechanisms such as inhibition or stimulation of the production or dissipation of factors controlling the measured effect. The principles underlying IDR models and their response patterns are described. The applicability of these basic IDR models to characterize pharmacodynamic responses of diverse drugs such as inhibition of gastric acid secretion by nizatidine and stimulation of MX protein synthesis by interferon α -2a is demonstrated. A list of other uses of these models is provided. These models can be readily extended to accommodate additional complexities such as nonstationary or circadian baselines, equilibration delay, depletion or accumulation of a precursor pool, sigmoidicity, or other mechanisms. Indirect response models which have a logical mechanistic basis account for time-delays in many responses and are widely applicable in clinical pharmacology.

Keywords: pharmacodynamics, indirect response models

Introduction

In order to understand and predict the pharmacologic behaviour of drugs, it is important to quantify the time course of pharmacodynamic responses in relation to the plasma drug concentrations. The selection of an appropriate model should, if possible, be based on the mechanism of action of the drug and other facets of biological reality. In addition, mechanism-based physiologic models can be useful for estimating inaccessible pharmacodynamic steps and parameters. Reversible pharmacodynamic effects of drugs can be broadly classified as direct and indirect responses.

Direct responses are effects produced by drugs that act immediately on measured variables, and are observed in relation to drug concentrations at the site of action (biophase). A static function such as a linear model, an $E_{\max}$ model, or a sigmoid $E_{\max}$ model can often be applied to characterize the relationship between plasma concentrations and pharmacodynamic profiles of drugs. However, for some drugs, responses take time for their development and are not apparently related to plasma concentrations because of an equilibration delay between the plasma compartment and biophase. In such cases, a hypothetical effect-compartment ('link') type approach can sometimes account for the equilibration delay [1]. D-tubocurarine is a drug that appears to produce its pharmacodynamic response by a direct mechanism and exhibits onset and offset equilibration delays [2].

In contrast, for indirect pharmacodynamic responses, there is a lag time for development of a response even after the drug reaches the site of action. Indirect responses need time

for their elaboration because of processes such as inhibition or stimulation of the production or dissipation of factors controlling the measured effects. In these cases, there is always a mechanistic delay with or without an equilibration delay. The latter is primarily dependent upon the physico-chemical properties of the drug such as lipophilicity and the actual site of action. Thus, IDR models may be appropriate for many drugs that produce responses with a time lag between biophase drug concentrations and the time course of responses. The mechanism by which drugs cause indirect responses was originally described by Ariens in 1964 [3]. He noted that '... A number of drugs induce effects not because of an interaction with receptors related to the effector, but on the strength of endogenous compounds. That is, via their protection or release.' Warfarin is a classic example of a drug with an indirect mechanism of action; it inhibits the synthesis of prothrombin complex activity to produce an anticoagulant effect [4].

This report reviews basic IDR models that may be suitable for describing the effects of drugs produced by indirect mechanisms. We have also demonstrated the effect of dose on the response profiles of drugs for each of the IDR models, and described experimental designs and procedures to estimate the pharmacodynamic parameters of all four models. Furthermore, methods for experimental identification of an appropriate IDR model are discussed and some complexities, which require extension of these models, are described. Several studies which applied these models to clinical response data are reviewed.

Indirect pharmacodynamic response model

A fundamental physiologic model for drugs that produce pharmacologic effects by indirect mechanisms is shown in

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Figure 1. In this model, the precursor is converted into or secreted as the response variable or mediator which, in turn, is then removed from the system. Drugs with indirect actions can produce their effects by acting on one or more of the indicated steps shown in this model. The agent can cause inhibition or stimulation of the synthesis or secretion of the response variable or of its removal, or of processes leading to the production of precursor.

Basic indirect response models

Four basic IDR models (Figure 2) were proposed and characterized which may be applicable to describe the pharmacodynamic responses of drugs with indirect mechanisms of action [5, 6]. The basic premise of these IDR models 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:

$$\frac{dR}{dt} = k_{in}^0 - k_{out} \cdot R \quad (1)$$

where k_{in}^0 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 $R_0 (=k_{in}^0/k_{out})$. The response variable, R , can be a directly measured entity or it

Figure 1 Basic scheme for indirect pharmacodynamic responses. The response variable is affected by drugs which can alter the formation of precursor, and production or dissipation of response variable. Drugs can inhibit or stimulate any of these processes.

may be an observed response which is directly and immediately proportional to the concentration of a mediator. It is assumed that k_{in}^0 and k_{out} fully account for production and loss of the response. The equations for IDR cannot be fully integrated to explicit functions and thus must be handled as differential equations and solved by numerical integration algorithms.

Models I and II represent processes that inhibit the factors controlling drug response (Figure 2) where inhibition processes operate according to the inhibition function $I(t)$, which can be the sigmoid function:

$$I(t) = 1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p} \quad (2)$$

where the I_{max} and IC_{50} value and the plasma drug concentrations (C_p) control the dynamic function. I_{max} is the maximum fractional ability of the drug to affect the k_{in} or k_{out} processes and is always less than or equal to unity, i.e., $0 < I_{max} \leq 1$. IC_{50} is the drug concentration that produces 50% of maximum inhibition achieved at the effect site. The C_p values are determined by the pharmacokinetics of the drug. Any appropriate pharmacokinetic function can be used to obtain the C_p values.

Model I describes drug response resulting from inhibition of the factors regulating the production of the response variable (k_{in}^0). Inhibition with an I_{max} and IC_{50} is considered to act on k_{in}^0 according to:

$$\frac{dR}{dt} = k_{in}^0 \cdot I(t) - k_{out} \cdot R \quad (3)$$

In Model I, when plasma drug concentrations are high (i.e., $C_p \gg IC_{50}$), IC_{50} becomes insignificant and the C_p values cancel out, and if $I_{max} = 1$, then $I(t) = 0$. At high drug concentrations k_{in}^0 times zero is zero; thus, there is complete blockage of the production of the response variable. Later, when plasma concentrations decline to low values, C_p would be below IC_{50} ($C_p \ll IC_{50}$). When that happens, drug

Figure 2 Four basic indirect response models representing processes that inhibit or stimulate the factors controlling drug response.

effect would be zero and $I(t)=1$, meaning k_{in}^o would be back to its full value. The system returns toward its baseline as k_{in}^o will be refilling the pharmacodynamic compartment with the response variable.

Model II describes drug response resulting from inhibition of the factors governing the dissipation of response variable (k_{out}). Inhibition with an IC_{50} is considered to act on k_{out} according to:

$$\frac{dR}{dt} = k_{in}^o - k_{out} \cdot I(t) \cdot R \quad (4)$$

where $I(t)$ is the function shown as Equation 2.

Models III and IV represent processes that stimulate the factors controlling drug response (Figure 2) where stimulation processes operate according to:

$$S(t) = 1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p} \quad (5)$$

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

Model III describes drug response resulting from stimulation of the factors regulating the production of the response variable (k_{in}^o). Stimulation with SC_{50} is considered to act on k_{in}^o according to:

$$\frac{dR}{dt} = k_{in}^o \cdot S(t) - k_{out} \cdot R \quad (6)$$

where Equation 5 provides $S(t)$.

Model IV represents drug response resulting from stimulation of the factors controlling the dissipation of the response variable (k_{out}). Stimulation with SC_{50} is considered to act on k_{out} according to:

$$\frac{dR}{dt} = k_{in}^o - k_{out} \cdot S(t) \cdot R \quad (7)$$

The area between the baseline and effect curve (ABEC) can be calculated as a summary parameter to characterize the overall effect of drug.

$$ABEC = |R_o \cdot t_r - AUEC_{o-t_r}| \quad (8)$$

where R_o 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 $\rightarrow \infty$.

The ABEC summary parameter encompasses all of the determinants of drug action: pharmacokinetic (V , k_{el} for a monoexponential function, Equation 11) and dynamic (IC_{50} or SC_{50} , I_{max} or S_{max}). For Models I and III, ABEC is:

$$ABEC = R_o \cdot \frac{I_{max}}{k_{el}} \ln \left(1 + \frac{D/V}{IC_{50}} \right) \text{ Model I} \quad (9)$$

$$ABEC = R_o \cdot \frac{S_{max}}{k_{el}} \ln \left(1 + \frac{D/V}{SC_{50}} \right) \text{ Model III} \quad (10)$$

while it has a more complex relationship for Models II and IV [6]. These equations predict an initial threshold then a linear ABEC vs log dose profile for all drug responses.

Assumptions in the proposed models

In these four IDR models, it is assumed that the response to the drug is independent of the amount of the precursor, i.e., the precursor pool is very large and thus is not significantly affected by drug action. Therefore, k_{in}^o is an apparent zero-order rate constant. An assumption is also made that the baseline of the system is stationary, and k_{in}^o and k_{out} fully account for production and loss of response. The drug response (R) begins at a baseline value (R_o), changes with time following drug administration, and after dissipation of drug effects returns to R_o (i.e., $k_{in}^o = k_{out} \cdot R_o$). Another initial assumption is that drug effects correlate directly with plasma drug concentrations as the biophase; thus, functions such as $I(t)$ or $S(t)$ can be used to describe the intrinsic drug effect.

Effects of dose

Since dose is the most readily manipulated variable in a pharmacodynamic study, it is of interest to evaluate the effect of dose on the properties of the response profiles for each of the IDR models (See ref. 6 for details). The simulations presented in Figure 3 utilize a monoexponential function to describe the pharmacokinetics of the drug:

$$C_p = \frac{D}{V} e^{-k_{el} \cdot t} \quad (11)$$

where D =Dose, V =volume of distribution, and k_{el} =elimination rate constant.

The pharmacodynamic profiles of drugs that produce responses by indirect mechanisms described by Models I to IV exhibit grossly similar patterns with changes in dose (Figure 3). In all models an increase in dose causes the maximum response (R_{max}), initial slope (S_I), and the area between the baseline and effect curve (ABEC) values to increase, and the time of occurrence of R_{max} ($t_{R_{max}}$) to shift to later times. In addition, the ABEC and $t_{R_{max}}$ values continue increasing in proportion to log dose. For Models I and IV, R_{max} exhibits a lower limiting value with dose, while for Model III it shows an upper limiting value with dose. However, R_{max} continues increasing nonlinearly with log dose for Model II when $I_{max}=1$. If $I_{max}<1$, R_{max} has an upper limit of $R_o/(1-I_{max})$ with dose for Model II.

In the four IDR models, there is a considerable lag time between the occurrence of peak plasma concentrations and the maximum response (R_{max}) as shown in Figure 3. This is due to continuation of drug effects (inhibition or stimulation) for as long as $C_p > IC_{50}$ (or SC_{50}). After the R_{max} has been reached, the return to baseline is governed by both k_{in}^o and drug elimination (k_{el}). Therefore, even after drug concentrations have declined below IC_{50} (or SC_{50}), the response remains for some time owing to the time needed for the system to regain equilibrium (when $k_{in}^o = k_{out} \cdot R_o$).

Model identification

To assign an appropriate model to pharmacodynamic data, knowledge of the mechanism of drug action is essential.

Figure 3 Simulations of the pharmacodynamic response variables (solid lines) with respect to time after single i.v. bolus doses. Simulated pharmacokinetic profiles at the corresponding doses using Equation 11 are shown by dashed lines. The indicated values of doses (10 to 1000) were used to invoke pharmacodynamic responses for the four indirect response models. Values of $V = 90$ l, $k_{el} = 0.3$ h⁻¹, $I_{max} = 1.0$, $S_{max} = 1.0$, $IC_{50} = 100$ ng ml⁻¹, $SC_{50} = 100$ ng ml⁻¹, $k_{in}^o = 9$ unit h⁻¹, $k_{out} = 0.3$ h⁻¹, and $R_o = 30$ were used for simulations.

However, in cases where the mechanism is not known, experimental designs that can discriminate between models would be very useful. Furthermore, these study designs can also be used to validate the mechanism of action for drugs with known actions which, in turn, reinforces the biologic plausibility of the proposed model.

Among these four IDR models, response profiles show downward trends for Models I and IV, and upward behaviour for Models II and III (Figure 3). Models I and IV may be applicable if the drug causes a decrease in the response variable from its baseline value. Similarly, Models II and III may appear to be suitable for describing data if the response variable increases from its baseline value. Thus, it is useful to have method(s) that can be applied for experimental identification of an appropriate indirect response model. Two such methods have been proposed to assign an appropriate IDR model for drug response (6): (i) single i.v. dose study design; and (ii) a steady-state i.v. infusion study design.

In a single i.v. dose study, administration at more than one dose level is required with one dose level high enough to produce either full inhibition or stimulation of the system. Depending on the nature of drug action (stimulation or inhibition), the experimental data obtained can be characterized using two of four IDR models to calculate pharmacodynamic parameters such as I_{max} or S_{max} and IC_{50} or SC_{50} . These parameters, in turn, can be used to estimate the maximum responses (R_{max}) at large doses ($Dose \rightarrow \infty$) according to:

$$R_{max} = R_o(1 - I_{max}) \quad (\text{Model I})$$

$$R_{max} = R_o/(1 - I_{max}) \quad (\text{Model II})$$

$$R_{max} = R_o(1 + S_{max}) \quad (\text{Model III})$$

$$R_{max} = R_o/(1 + S_{max}) \quad (\text{Model IV})$$

Therefore, for drugs with incomplete information on the mechanism of action, an appropriate IDR model can still be chosen by comparison of experimental R_{max} values obtained at larger doses with estimated R_{max} values for models with similar downward or upward responses. However, with Models II and III, it is difficult to know when the dose is sufficiently high to produce maximal responses (Figure 3). With Models I and IV, the range of responses has a clearer lower limit (e.g. zero).

In an infusion study, the length of infusion should be sufficiently long not only to produce steady-state pharmacokinetics but also steady-state conditions in the pharmacodynamic system. More than one administration rate is needed and 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*.

In Models I and III, the $t_{R_{max}}$ would remain constant with the change in the infusion rate because the drug affects k_{in}^o for these two IDR models (inhibits for Model I and stimulates for Model III), and k_{in}^o 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 $t_{R_{max}}$ would change with the infusion rate because the drug affects k_{out} for these models (inhibits for Model II and stimulates for Model IV). The k_{out} value influences the time required for the response to reach

steady-state during continuous drug infusion. For instance, in Model II where a drug produces its response by inhibition of k_{out} , the $t_{R_{max}}$ would shift to later times because the decrease in k_{out} due to the drug would result in an increased time required by the system to reach steady-state during continuous infusion of the drug. Similarly, in Model IV, the $t_{R_{max}}$ would shift to earlier times because an increased k_{out} value produces the opposite behavior. Thus, one can determine which IDR model is suitable for a drug by comparing experimental $t_{R_{max}}$ values obtained at two steady-state infusion rates.

Estimation of the pharmacodynamic parameters

The study design is critical for estimating the pharmacodynamic parameters of an IDR model. The following design is needed to elucidate fully the pharmacodynamic parameters of IDR models: (i) administration of two or more bolus i.v. doses of drug; (ii) one of the dose levels should be sufficiently high to produce either full inhibition or stimulation of the system; (iii) determination of the baseline value (R_o) and behaviour of the system.

The experimental values of the baseline (R_o), the initial slope (S_I), and maximum drug response (R_{max}) obtained at large doses can be first used to estimate maximum inhibitory (I_{max}) or stimulatory (S_{max}) factors as listed in the first row of Table 1. The estimated I_{max} (or S_{max}) and the initial slope (S_I) of the response versus time curve can then be used to calculate k_{in}^o values as indicated by the second row in Table 1. Then k_{out} is obtained from k_{in}^o/R_o for all models as indicated by the third row in Table 1.

The experimental value of the time to reach maximum response ($t_{R_{max}}$) and R_{max} obtained at a given dose can be used to interpolate the plasma drug concentration at $t_{R_{max}}$ ($C_{R_{max}}$) from the pharmacokinetic data. Very roughly, the IC_{50} or SC_{50} is the drug concentration at the time of R_{max} for a drug causing a moderate change in response. More exact IC_{50} or SC_{50} values can be estimated as shown in the fourth row of Table 1.

These equations provide a rationale for examining IDR profiles such as shown in Figure 3 and using graphical means of recovering the major parameters governing the overall system. However, because of the non-linearity and time-dependence of IDR, final estimation of parameters should be based on nonlinear least-squares regression analysis using computer programs (WinNonlin, Adapt II, P-Pharm, NonMem, and others) capable of performing numerical integration of differential equations.

Clinical examples

The applicability of IDR models has been demonstrated for diverse clinical pharmacodynamic responses such as those listed in Table 2. More specific responses that can be characterized with IDR models are demonstrated below. For the examples given below, we have used published data for the pharmacokinetics and pharmacodynamics of drugs with indirect responses, and data were reanalyzed with the most plausible of the IDR models shown in Figure 2.

H₂-receptor antagonist: Inhibition of gastric secretion Nizatidine is an H₂-receptor antagonist that blocks the gastric acid secretion stimulated by histamine and other H₂-receptor agonists. Callaghan *et al.* [7] evaluated effects of nizatidine at four dose levels on gastric acid secretion in which one dose (250 mg) was high enough to produce full inhibition of the system (gastric acid secretion). In this study, healthy subjects received 5 min i.v. infusions of nizatidine at 25, 50, 100 or 250 mg dose levels. Gastric acid secretion was induced by i.v. infusion of pentagastrin at $2 \mu\text{g kg}^{-1} \text{h}^{-1}$ for 4.25 h starting 45 min before the nizatidine dose. Their data were reanalyzed using IDR Model I and are shown in Figure 4. In our proposed model the parietal cells in the stomach are assumed to produce gastric acid at a constant rate (k_{in}^o) under stimulation of H₂-receptor agonists such as histamine and the acid is removed from the stomach by gastric emptying via a first-order rate process (k_{out}). Nizatidine reduces the amount of gastric acid secretion by inhibiting the interaction of the H₂-receptor agonist with H₂-receptors. As the drug is eliminated from the body, gastric acid secretion returns gradually to baseline. The pharmacodynamic data were fitted to Model I (Figure 4). The fitted line shows that the proposed model adequately described the data. The pharmacodynamic parameters estimated were: $k_{in}^o = 184 \text{ mEq h}^{-2}$, $k_{out} = 5.6 \text{ h}^{-1}$, $I_{max} = 1.0$, and $IC_{50} = 164 \text{ ng ml}^{-1}$. The coefficients of variation (CV) of these parameters were reasonable, ranging from 2 to 6%.

Modeling IDR data such as this was and should be a two-stage process. The plasma drug concentration (or other biophase) data are first fitted to produce a suitable descriptive equation. This serves as a forcing function in Equation 2 or 5 to produce the inhibition or stimulation values. Then the dynamic data are fitted by nonlinear regression analysis where either k_{in}^o or k_{out} (NB $k_{in}^o = k_{out} \cdot R_o$), IC_{50} (or SC_{50}), and I_{max} (or S_{max}) are sought as regression parameters. Ideally, data from the baseline and several dose levels should be fitted simultaneously in order to generate one set of parameters to describe the effects of the drug. When one dose level is fitted alone, there may be inadequate discrimination of the model parameters. A Hill coefficient (γ) may be added once it is determined that lack of coefficient ($\gamma = 1$) is insufficient to characterize the data.

Induction of MX protein synthesis Interferon α -2a induces the synthesis of MX protein, a factor that interferes with viral replication. Nieforth *et al.* [8] used IDR Model III to characterize the pharmacodynamics of interferon α -2a after subcutaneous administration. It was assumed that MX protein is produced as a zero-order process (k_{in}^o), a first-order process (k_{out}) accounts for its degradation, and interferon α -2a stimulates k_{in}^o (Figure 5). There occurs an initial dose-proportional increase in MX protein in plasma and, as the drug is eliminated from the body, MX protein concentrations return to the baseline. Response data for four doses (3, 6, 9, and 18 MIU) of interferon α -2a [8] were simultaneously fitted to Model III (Figure 5). The pharmacodynamic parameters estimated were: $k_{in}^o = 0.65 \text{ ng ml}^{-1} \text{h}^{-1}$, $k_{out} = 0.013 \text{ h}^{-1}$, $S_{max} = 28.5$, and $SC_{50} = 29.9 \text{ units ml}^{-1}$. The coefficients of variation (CV) of these parameters ranged from 7 to 34%.

Table 1 Use of indirect response profiles to estimate model parameters. Measured characteristics: R_o , S_I , R_{max} , C_{Rmax} at large doses^a.

Parameter	Model I	Model II	Model III	Model IV
I_{max} or S_{max}	$(R_o - R_{max})/R_o$	$(R_{max} - R_o)/R_{max}$	$(R_{max} - R_o)/R_o$	$(R_o - R_{max})/R_{max}$
k_{in}^o	$-S_I/I_{max}$	S_I/I_{max}	S_I/S_{max}	$-S_I/S_{max}$
k_{out}	k_{in}^o/R_o	k_{in}^o/R_o	k_{in}^o/R_o	k_{in}^o/R_o
IC_{50} or SC_{50}	$\frac{C_{Rmax} \cdot (R_{max} - (1 - I_{max}) \cdot R_o)}{(R_o - R_{max})}$	$\frac{C_{Rmax} \cdot (R_o - (1 - I_{max}) \cdot R_{max})}{(R_{max} - R_o)}$	$\frac{C_{Rmax} \cdot (R_o \cdot (1 + S_{max}) - R_{max})}{(R_{max} - R_o)}$	$\frac{C_{Rmax} \cdot (R_{max} \cdot (1 + S_{max}) - R_o)}{(R_o - R_{max})}$

^aSymbols are defined in Glossary.**Table 2** Drugs which produce indirect pharmacodynamic responses.

Drug	Mechanism of action	Measured PD response	Indirect model	Reference
Warfarin	Vitamin K epoxide reductase inhibitor	Decreased prothrombin complex activity	I	4
Nizatidine	H ₂ -receptor antagonist	Decreased secretion of gastric acid	I	7
Tolrestat	Aldose reductase inhibitor	Decreased RBC sorbitol	I	17
Methylprednisolone	Inhibits corticotropin and CRF	Decreased cortisol secretion	I	9, 30
Fluticasone propionate	Inhibits corticotropin and CRF	Decreased cortisol secretion	I	11
Prednisolone	Inhibits tissue efflux	Decreased basophil trafficking	I	30
Prednisolone	Inhibits tissue efflux	Decreased T-cell trafficking	I	27, 30
Prednisolone	Altered tissue efflux	Increased NK cells in blood	I	31
Prednisolone	Suppression of bone metabolism	Decreased serum osteocalcin concentration	I	32
Ibuprofen	Inhibition of prostaglandin E ₂	Reduced fever	I	28
DCN 203-922	Dopaminomimetic	Decreased plasma prolactin concentration	I	12
Pyridostigmine	Cholinesterase inhibitor	Increased muscle response	II	30
Frusemide	Inhibitor of Na ⁺ -K ⁺ -2Cl ⁻ symport	Increased urinary excretion of Na ⁺ , Cl ⁻	II	30
Cimetidine	H ₂ -receptor antagonist	Increased prolactin release	III	30
Interferon α -2a	Induces MX protein synthesis	Increased blood MX protein concentration	III	8
Terbutaline	β_2 -adrenergic receptor agonist	Increased pulmonary air flow	III	30
Terbutaline	β_2 -adrenergic receptor agonist	Hypokalaemia	IV	30

Figure 4 Composite graph showing the pharmacodynamic model, pharmacokinetics of nizatidine, and gastric acid secretion profiles after single i.v. administration of 25 (●), 50 (■), 100 (▲) and 250 (▼) mg nizatidine doses. Symbols are experimental data from Callaghan *et al.* [7], and lines are simultaneous least-squares regression fitting of all data to Model I.

These studies also included a comparison of the effects of interferon α -2a and pegylated interferon seeking to determine whether the latter, because of its longer $t_{1/2}$ (5.3 *vs* 11.9 h) would be suitable for once-weekly dosing. Unfortunately, pegylation also produced a reduction in $S_{\max}$ (67 *vs* 39) while SC_{50} remained the same (60 units ml^{-1}) as for interferon α -2a. Simulations demonstrated that an extension of the dosing interval was inadequate to maintain desired plasma concentrations of MX protein, thus leading to a company decision not to further develop this pegylated form of the drug. This was an excellent demonstration of the value of PK/PD modeling at a critical stage in drug development which saved considerable time and expense of further clinical trials.

Complexities and applications

The four models reviewed in this article are the most basic of IDR models and can be extended to incorporate additional complexities in pharmacodynamic systems. Several interesting applications of more complex IDR models will be described.

If the baseline is nonstationary such as for a circadian rhythm, a cosine function can be used to describe k_{in}^0 [9]. This approach has been used for assessing the effect of exogenous corticosteroids (methylprednisolone and prednisolone) on plasma concentrations of cortisol [9]. Rohatagi

et al. [10] used a ramp function consisting of a linear decrease of cortisol secretion during the day and a shorter linear increase at night as an alternative to the cosine function to handle the circadian behaviour of cortisol. It appears to handle better the rapid rise in cortisol which occurs in the early morning hours. Rohatagi *et al.* have modeled the cortisol suppressant effects of fluticasone propionate using an IDR model with the ramp function described above [11]. The mean IC_{50} values obtained in healthy volunteers were 0.171, 0.105 and 0.126 ng ml^{-1} for 0.5, 1, and 2 mg doses. A good correlation between *in vivo* pharmacodynamic response (decrease in cortisol levels) and *in vitro* receptor binding affinity of fluticasone propionate was observed.

Francheteau *et al.* [12] characterized the prolactin suppressant effects of a dopaminomimetic drug DCN 203-922 using an IDR model which required both a link compartment and a 'fluctuation model' for the irregular rhythmic baseline of prolactin. The latter was handled using a spline fitting of the placebo response. They showed greater reductions in plasma concentrations of prolactin when giving the drug as 2 mg at 6 hour intervals rather than a single 6 mg dose. Therefore, diverse functions can be used easily to describe nonstationary baselines as part of k_{in}^0 or k_{out} in Equation 1 in application of IDR models for drug responses.

For some drugs, the production of the drug response may be dependent on the amount of precursor, which may

Figure 5 Composite graph showing the pharmacodynamic model, pharmacokinetics of interferon α -2a, and blood MX protein stimulation profiles after a single subcutaneous administration of 3 ($\circ$), 6 ($\square$), 9 ($\bullet$) and 18 ($\blacksquare$) MIU interferon α -2a doses. Symbols are experimental data from Nieforth *et al.* [8], and lines are simultaneous least-squares regression fitting of all data to Model III. Note difference in PK and PD time scales.

change significantly due to the drug. Ekblad & Licko [13] suggested a general model similar to that shown in Figure 1 to characterize transient responses for physiological substances. Basic IDR models can be extended to accommodate dependence of response on the amount of precursor by making k_{in} a first-order rate constant [13–15]. These extended IDR models can describe tolerance and rebound phenomena, and are appropriate for drugs that affect precursor pools and/or the amount of endogenous compounds that are required for the production of drug response. This approach was used to model the effects of the dopamine antagonist remoxipride on stimulation of prolactin release into circulation upon repeated administration [14,15]. When a second dose of drug is given before the precursor pool has refilled (refractory period), the response will be blunted and tolerance will appear to occur. A linear rather than sigmoid stimulation model was suitable for relating remoxipride plasma concentrations to release of prolactin.

IDR models were also extended by addition of a 'modifier' compartment where k_{out} was altered in relation to the measured response to cause development of furosemide tolerance [16]. This extended model well characterized the diuretic and natriuretic response patterns after administration of serial doses of furosemide where responses diminished with successive doses and allowed the estimation

of a lag-time for tolerance and a rate constant for tolerance development.

IDR modeling approaches were extended to handle multiple-dose kinetics and dynamics of drugs by Van Griensven and co-workers [17]. Model I was used to characterize the effects of tolrestat on RBC sorbitol levels after administration of single and multiple-doses. For modeling of multiple-dose dynamics, a continuous PK/PD relationship was generated by using the method of superpositioning to extrapolate the effects from the initial to the final tolrestat dose [17]. Like for many pharmacologic effects it was found that responses or IC_{50} values related better to free than total drug in plasma. There was close agreement of the *in vivo* IC_{50} for free tolrestat ($12\text{--}16\text{ ng ml}^{-1}$) with values obtained *in vitro* (13 ng ml^{-1}) measuring sorbitol production in human erythrocytes.

The classic example and the first quantitative modeling of an IDR was the measurement of warfarin effects on prothrombin complex activity (PCA) [4]. Pitsiu *et al.* [18] applied both population and two-stage analyses to examine PCA and factor VII activities after dosing warfarin in a group of 48 healthy volunteers. The IDR required both the γ shape factor and a lag time to allow for a delay in the onset of response after warfarin administration. The γ values were 1.03 for PCA and 2.63 for factor VII. The lag time was about 8 h for both responses. The population model

identified sources of both pharmacokinetic and pharmacodynamic variances with inter-individual differences in k_{out} and IC_{50} contributing most to variability in responses. A time analysis also showed when each parameter was most influential in the observed responses.

The equations used to describe the inhibitory (Equation 2) and stimulatory (Equation 5) effects of drugs need not be limited to the sigmoid or Hill equations. In fact, it is important to identify the biosensor process and to use an equation that best reflects the mechanism of action. A simple linear function served well for remoxipride stimulation of prolactin release [14]. When two agonists are present (C_1 and C_2), it is possible to describe their additive effects as: $C = C_1 + \varepsilon.C_2$ where ε is a potency ratio. This was done by Milad *et al.* [19] to describe the joint effects of cortisol and methylprednisolone on lymphocyte trafficking in studies in normal volunteers.

The IDR models can accommodate an irreversible component as well. The antiplatelet effect of aspirin was modeled by Yamamoto *et al.* [20] with the relationship

$$\frac{dR}{dt} = k_{in} - k_{out} \cdot R - k \cdot C \cdot R$$

where the last term reflects a bimolecular drug-platelet interaction. The modeling yielded a realistic responses and regeneration rate constant (k_{in}^o) for platelet production. A similar concept is embodied in some simple cancer and antibiotic chemotherapy models [21, 22] where cell replication represent the k_{in} process.

The greatest complexities come with transduction processes. In the basic IDR models, the response is assumed to be directly proportional, in a linear and immediate manner, to a biosignal. The response and the biosignal become the same. However, in some pharmacodynamic responses, there may be signal transduction mechanisms involved which can cause nonlinearities and time-delays between the biosignal generated by the drug (bound receptor) and the response being measured. This occurs with corticosteroids [23]. Following receptor binding, processes involving nuclear binding, synthesis of mRNA, and synthesis of effector proteins are major steps in propagation of a response. The receptor-gene mediated actions of various steroids and the numerous signal-transduction processes of various drugs will

require more complex indirect models and represent a major frontier in the future of PK/PD modeling.

Comprehensive pharmacokinetic/pharmacodynamic model

A comprehensive scheme that accounts for the various steps involved in a complex PK/PD system is depicted in Figure 6 [24]. This diagram shows four intermediary components between drug in blood and the measured response, with drug action divided into pharmacokinetic and pharmacodynamic steps. Drug administration, distribution and elimination are considered under pharmacokinetics. In most cases, the drug response may be directly related to the plasma concentration or free drug in plasma. In others, the biophase may be relevant. For example, in the case of frusemide and most other diuretics, the biophase is urine [25, 26]. If drug concentrations in the biophase cannot be directly measured, then use of a link model may be appropriate in considering drug equilibration with a site separate from plasma.

For pharmacodynamic modeling, it is essential to have knowledge of the mechanism of action of the drug. In Figure 6, the mechanism of drug action is represented as biosignal flux. The biosignal may be a mediator, which undergoes altered synthesis or degradation due to drug action. The H indicates that the Hill equation might be applied as an inhibitory or stimulatory function to the k_{in}^o or k_{out} processes as used in Equations 2 and 5. The pharmacodynamic model based on biosignal flux may also be applicable to receptor-mediated action. For instance, one can consider k_{in} to be binding of drug to the receptor, k_{out} the rate constant for drug dissociating from the receptor, and bound receptor concentrations to be the biosignal. These IDR models can adequately describe the receptor-mediated processes.

Conclusions

Modeling pharmacodynamic effects requires a broad appreciation of pharmacology, pharmacokinetics, and dynamics. The mechanism of action of the drug should be known to define the appropriate pharmacodynamic model. It is important to understand the biophase responsible for the drug action, be it a real one or a hypothetical compartment. It is advisable to start with the simple models (observe

Figure 6 A comprehensive scheme proposed to include the major pharmacokinetic and pharmacodynamic processes governing drug action including distribution (rate constant, k_{eo}) to a biophase, inhibition or stimulation (H) of the production (k_{in}) or dissipation (k_{out}) of a mediator or biosignal, and transduction of the response (R). (Reprinted with permission from Jusko *et al.* *J Pharmacokinet Biopharm* 1995; 23: 5–8).

parsimony) and add complexities in an attempt to account for all sources of variability in drug action. The IDR models reviewed in this report are relevant to numerous drugs. They require numerical integration and nonlinear regression programs for data analysis and simulation and should be considered as a possible choice in modeling the time course of drug action.

Glossary

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
$I(t)$	Inhibitory function
IC_{50}	Drug concentration producing 50% of maximum inhibition
I_{max}	Maximum inhibitory factor attributed to drug ($0 < I_{max} \leq 1$)
IDR	Indirect pharmacodynamic response
k_{el}	First-order rate constant for drug elimination
k_{in}^o	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_o	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
$S(t)$	Stimulatory function
t	Time after drug administration
t_r	Time when response returns to baseline
t_{Rmax}	Time to reach maximum response following drug administration

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