Role of Baseline Parameters in Determining Indirect Pharmacodynamic Responses

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Abstract □ Indirect Response Models account for the pharmacodynamics of numerous drugs which inhibit or stimulate the production (k_{in}) or loss (k_{out}) of the response variable (R). The dose and pharmacokinetics, capacity (S_{max}, I_{max}), and potency (SC_{50}, IC_{50}) factors of the Hill function incorporated in these models are the primary determinants of overall responsiveness. However, the initial or baseline value for the response ($R_0 = k_{in}/k_{out}$) should also be considered as an important factor for the net response. Using Indirect Response Model III (stimulation of input) as an example, the net area under the effect curve ($AUEC_{NET}$) can be proportional to the R_0 values. Such a feature is demonstrated in this report by computer simulations, by examination of the integral of the simulated response vs time profiles, and with examples from the literature. Also shown is an adjustment of R_0 when the therapeutic agent is an endogenous substance. These analyses show that the role of R_0 and k_{in} should not be overlooked as determinants of indirect responses and source of variation among subjects or patient groups.

Introduction

The role of the initial or baseline value of a pharmacological response is often overlooked in considering factors which control pharmacodynamics. For indirect responses where drugs alter the production or loss of the response, the initial or baseline value (R_0) is a dependent variable which is usually described as the ratio of k_{in} (zero-order formation rate constant) ÷ k_{out} (first-order elimination rate constant).[1] The k_{in} is under the direct control of many drugs and subject to physiological and pathophysiologic alterations. Many biotech products produce their pharmacodynamic effects in a similar fashion: Interleukin-10 (IL-10) increases the blood monocyte and neutrophil counts,[2] growth hormone (GH) stimulates the formation for insulin-like growth factor I (IGF-I),[3] interferon α-2a (INF α-2a) induces the production of MX protein,[4] and erythropoeitin stimulates reticulocyte/red blood cell production,[5] and soluble transferrin receptor.[6] Drugs with actions according to Indirect Response Models,[1] especially Model III which accounts for stimulation of k_{in} when k_{out} remains unchanged, can exhibit variable responses in patients when there are marked interindividual differences in R_0 and k_{in} values.[4,6] This report provides simulations to demonstrate how differences in R_0 and k_{in} among patients or different groups will affect net responses to pharmacological agents and points out how this is of particular concern for the drugs which are intended to stimulate natural physiologic processes.

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Experimental Section

Methods—Computer simulations were performed using the ADAPT II program.[7] The pharmacokinetic/pharmacodynamic (PK/PD) relationships for a hypothetical drug concentration (C) and the induction of the response (R) were simulated.

Pharmacokinetics—The pharmacokinetics were described by the Bateman Function with a baseline value (C_{BL}):

$$C_p = C_{BL} + \frac{k_a \text{dose}}{V(k_a - k_{el})}(e^{-k_{el}t} - e^{-k_a t}) \quad (1)$$

The assigned PK parameter values were as follows: dose = 250, 500, 1000, and 2000 μg; absorption rate constant $k_a = 0.693\ h^{-1}$; elimination rate constant $k_{el} = 4\ h^{-1}$; CL = 10 L/h; volume V = 2.5 L. Simulations were performed with both $C_{BL} = 0$ and 1 ng/mL.

Pharmacodynamics—Assuming that the drug stimulates the formation rate of R, Indirect Response Model III (1) was applied:

$$\frac{dR}{dt} = k_{in}(1 + S(t)) - k_{out}R \quad (2a)$$

where

$$S(t) = \frac{S_{max}C_p}{SC_{50} + C_p} \quad (2b)$$

and

$$k_{in} = k_{out}R_0 \quad (3a)$$

where S_{max} is the maximum effect and SC_{50} is the drug concentration which can produce 50% of the maximum stimulation of the formation rate.

When the therapeutic agent is an endogenous substance, the basal response occurs when $C_p = C_{BL}$. As a result, the relationships between k_{in}, k_{out}, and R_0 should be defined as follows:[3]

$$k_{in} = \frac{k_{out}R_0}{(1 + S(BL))} \quad (3b)$$

where

$$S(BL) = \frac{S_{max}C_{BL}}{SC_{50} + C_{BL}} \quad (3c)$$

The assigned PD parameter values for the simulations were $R_0 = 25$, 50, 100, or 200 ng/mL; $k_{out} = 0.4\ h^{-1}$; $S_{max} = 5$; $SC_{50} = 4$ ng/mL.

If the baseline level (C_{BL}) = 0, then $k_{in} = k_{out}R_0 = 10$, 20, 40, or 80 ng/mL/h.

If $C_{BL} = 1$ ng/mL, then

$$k_{in} = \frac{k_{out}R_0}{(1 + S(BL))} = \frac{k_{out}R_0}{2} = 5, 10, 20, \text{or } 40 \text{ ng/mL/h}$$

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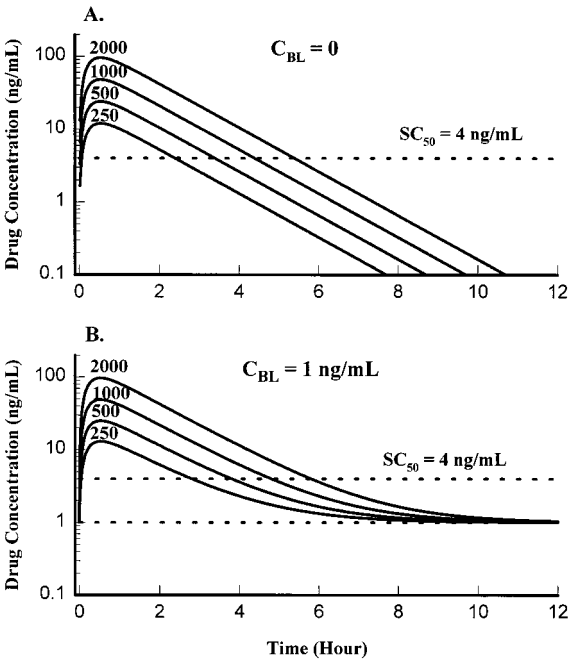

Figure 1—Simulated values for the pharmacokinetic profile of a hypothetical drug at doses of 250, 500, 1000, and 2000 μg. Top (Figure 1A): $C_{BL} = 0$ when the baseline value is negligible. Bottom (Figure 1B): $C_{BL} = 1.0$ ng/mL when the drug is an endogenous substance with a constant baseline value.

Area Analysis—The total areas under the response curves ($AUEC_{total}$) from time 0 to 20 h after drug dosing were obtained by integrating eq 2 in the ADAPT II program.[7] The net AUEC values ($AUEC_{NET}$) = $AUEC_{total} - AUEC_{base}$, where $AUEC_{base} = R_0(20\ h)$.

Results

Pharmacokinetics—Simulations for drug concentration vs time profiles after four different doses are shown in Figures 1a ($C_{BL} = 0$) and 1B ($C_{BL} = 1$ ng/mL). The curves show an expected up-curve, a C_{max} proportional to dose, a t_{max} at 0.5 h, and monoexponential decline. The presence of the baseline adds curvature to the lower profiles.

Pharmacodynamics—*No Baseline*—Simulations for the response vs time profiles are shown in Figure 2. When R_0 (or k_{in}) is a constant, the maximum response as well as the time to reach the maximum response increases when the dose increases. These are the basic characteristics of Indirect Response Model III.[8] As shown in Figure 2, R_0 (or k_{in}) has a profound effect on the magnitude of the overall response. When the dose is constant, the maximum response is proportional to R_0 (or k_{in}).

Presence of Baseline—Simulations for the response vs time profile are shown in Figure 3. Since R_0 is now regulated by the endogenous drug concentration (C_{BL}), the k_{in} value is a fraction of $k_{out}R_0$ as defined in eq 3b. In this particular case, $(1 + S(BL)) = 2$. These response profiles are similar to the results shown in Figure 2. However, the magnitudes of the responses are approximately one-half of those with $C_{BL} = 0$ owing to the lower k_{in} values.

Area Analysis—$AUEC_{NET}$ vs log dose profiles are shown in Figures 4a ($C_{BL} = 0$) and 4b ($C_{BL} = 1$ ng/mL). Within the dose range of 250 to 2000 μg, all curves show linear relationships ($r^2 = 0.9991-0.9997$). The slopes obtained by linear regression are listed in the figure legend.

As shown in Figure 4, the slope coefficients are proportional to R_0 (or k_{in}) values. Krzyzanski and Jusko[9] provided an exact solution for the $AUEC_{NET}$ based on Indirect Response Model III:

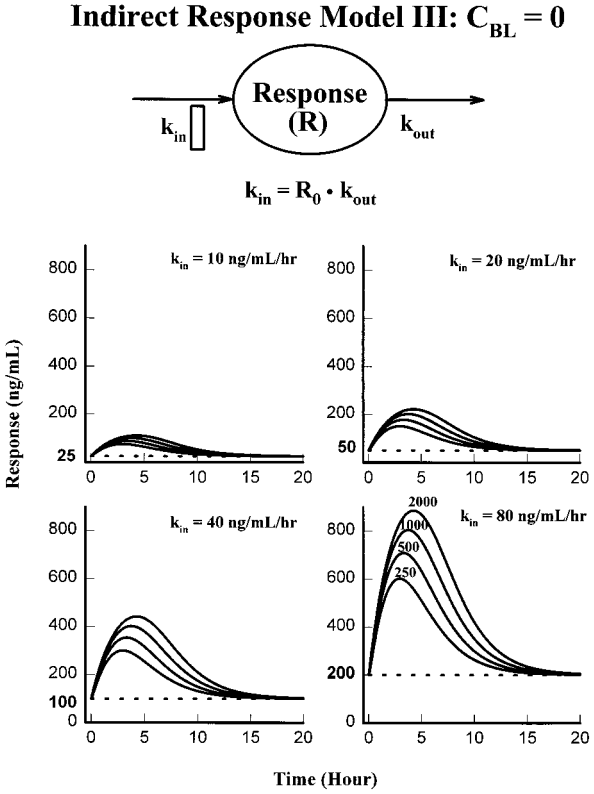

Figure 2—Simulations for drug effects on the production of responses based on the principles of Indirect Response Model III. Four dose levels were simulated: 250, 500, 1000, and 2000 μg. Assuming the baseline is negligible ($C_{BL} = 0$), four different R_0 values were utilized in the simulation: 25 (top, left), 50 (top, right), 100 (bottom, left), and 200 ng/mL (bottom, right). Based on the relationship described by eq 3a, the k_{in} values are 10, 20, 40, and 80 ng/mL/h, respectively.

$$AUEC_{NET} = R_0 \frac{S_{max}}{k_{el}} \ln\left(1 + \frac{dose/V}{SC_{50}}\right) \quad (4)$$

where k_{el} is the elimination rate constant for the function $C(t) = dose(e^{-k_{el}t})/V$. When doses are large, then

$$AUEC_{NET} \sim R_0 \frac{S_{max}}{k_{el}} \ln(Dose) \sim 2.3 R_0 \frac{S_{max}}{k_{el}} \log(Dose) \quad (5)$$

Therefore, the slope coefficient is approximately equal to $(2.3R_0S_{max}/k_{el})$. The k_{el} should be replaced by k_a when flip-flop kinetics occurs in eq 1. The estimates of slopes based on eq 5 for $R_0 = 25$, 50, 100, and 200 ng/mL are 415, 831, 1661, and 3323. These values are close to the results from linear regression for AUEC analysis, although they are slightly overestimated owing to the approximation and use of the Bateman Function.

The $AUEC_{NET}$ vs log dose profiles and the results for linear regression when $C_{BL} = 1.0$ ng/mL are shown in Figure 4B. The slope coefficients are also proportional to R_0 values. When the same R_0 values are compared, the slope coefficients are less than 50% of the estimates for which $C_{BL} = 0$. This disproportionality is due to the alteration of the definition for k_{in} (between eq 3a and 3b), and the different ratios of the stimulation factor, $S(t)$.

Application—The stimulating effects of a single sc dose of Interleukin-10 (IL-10) on monocytes in blood were characterized in normal volunteers[2] using Indirect Response Model III. Figure 5 shows the mean plasma concentrations of IL-10 and the time-course of monocyte numbers. The SC_{50} of IL-10 averaged 0.66 ± 0.70 ng/mL while the S_{max} was predetermined to be 1.5. The relation-

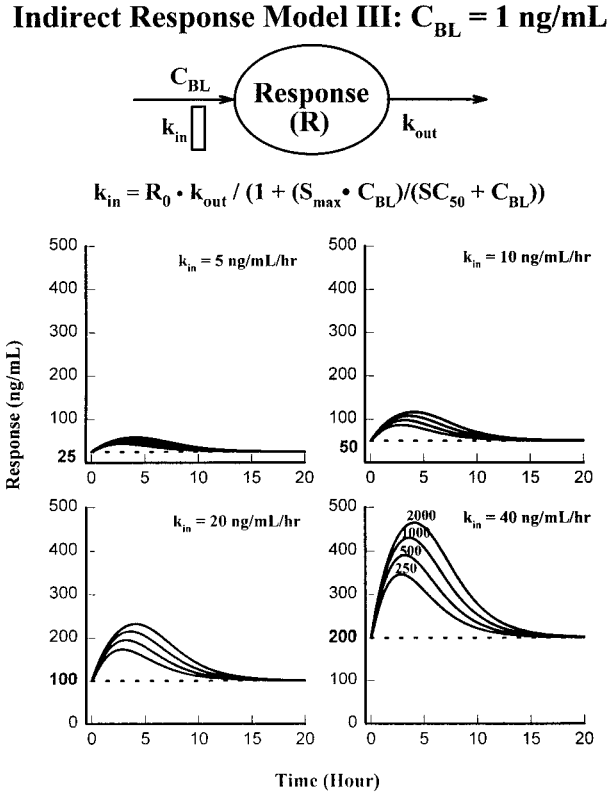

Figure 3—Simulations for drug effects on the production of responses based on the principles of Indirect Response Model III and eq 3b assuming that the drug is an endogenous substance with a constant baseline (C_{BL} = 1.0 ng/mL). Other conditions and simulations are the same as in Figure 2.

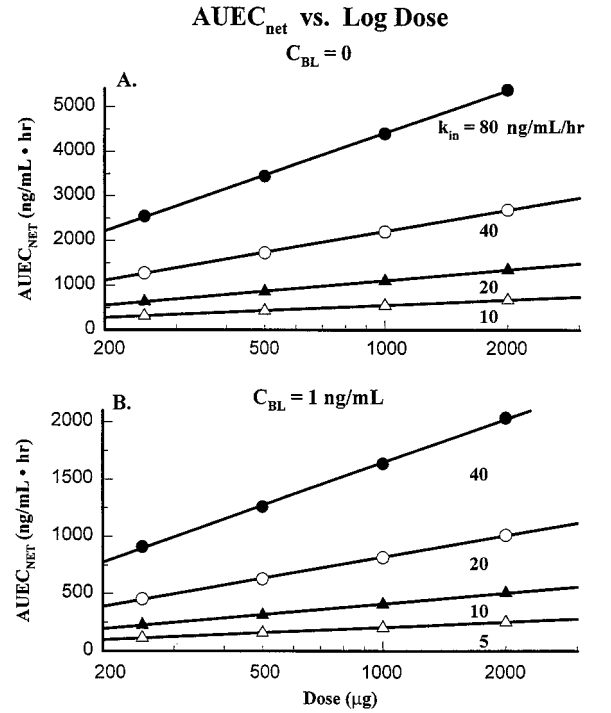

Figure 4—$AUEC_{NET}$ vs log dose for the response profiles in Figures 2 and 3. Top (Figure 4A): baseline is negligible (C_{BL} = 0). Slopes are 394, 787, 1574, and 3148. Bottom (Figure 4B): the drug is an endogenous substance with a constant baseline value (C_{BL} = 1 ng/mL). Slopes are 155, 310, 620, and 1248.

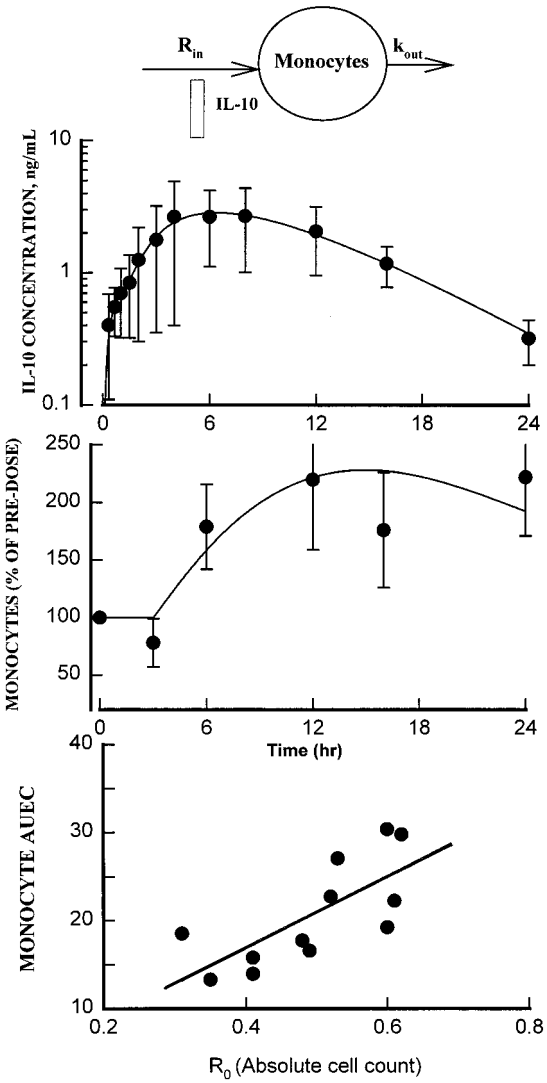

Figure 5—Pharmacokinetics of Interleukin-10 (IL-10) in normal volunteers (top), time course of stimulation of monocytes in blood (middle), and relationship of AUEC of monocytes to initial cell number in blood (R_0) (bottom). Adapted from ref 2.

ship between AUEC and R_0 was found to correlate strongly and indicated that R_0 was a major determinant of the net response.

Discussion

Our simulations show that the baseline value of the pharmacodynamic response (R_0) may play an important role in affecting the extent of the response if its PK/PD relationship can be described by Indirect Response Model III. When other factors remain unchanged (such as S_{max}, SC_{50}, k_{out}), the R_0 which intrinsically reflects the k_{in}/k_{out} ratio dictates the overall magnitude of the response. The same principles apply for drugs which inhibit k_{in} (Indirect Response Model I). The extent of the observed response is also jointly determined by k_{in} and the Hill Function,[1,8,9] and an equation analogous to eq 4 exists.[9] The net response ($AUEC_{NET}$) is also proportional to R_0 in a more complex fashion for drugs which inhibit or stimulate k_{out}.[9] However, such equations also indicate that the present simulations are generally applicable to all drugs with indirect mechanisms of action.

Many protein therapeutic agents stimulate natural physiological processes. For example, IL-10 increases the

blood monocyte and neutrophil counts.[2] GH stimulates the formation of IGF-I, which is a mediator for the growth effect and is often used as a surrogate measurement.[3] IFN α-2a induces the production of MX protein which exerts various antiviral activities.[4] EPO stimulates soluble transferrin receptor.[6] The PK/PD relationships for these biotech products were characterized by Indirect Response Model III.[2−4,6] The relationship between k_{in}, k_{out}, and R_0 can be adjusted accordingly using eq 3B when the pharmacodynamic effect is produced by an endogenous substance which is present at the time of dosing.[3]

Disease states, physiological conditions, medication history (treated vs naive patients, drug interactions, etc.), and other factors may affect the R_0 values of the response. Even for well-controlled studies, interindividual variation in R_0 values is often noticeable. For example, about a 2-fold difference of MX protein baseline values were observed among healthy subjects in a study where IFN α-2a effects were measured.[4] As a result, marked interindividual variation for MX protein production was found. For the effect of EPO on the increase of soluble transferrin receptors (sTfr) in athletes, interindividual variation in sTfr baseline values may be one reason there were large differences in responses observed among the subjects.[6]

These simulations show that the $AUEC_{NET}$ values are well correlated with log(dose) and R_0. The relationship is linear-log and predictable especially when $C_{BL} = 0$, and doses are relatively large.[6] Further investigations of the role of noticeable C_{BL} values on the response profiles are needed. These results suggest that dosages may have to be adjusted according to individual R_0 values. For example, a patient with a lower R_0 value may require higher doses compared to another patient with a higher R_0 value in order to produce similar overall responses. If pathophysiologic alterations of R_0 occur, dosage regimens designed for patients should not solely depend on the response profile obtained from healthy subjects. Finally, when indirect response models are applied to agents which are endogenous substances, the equations for the models will require utilization of eq 3b in order to account for the role of the naturally present active substance. In conclusion, for those therapeutic agents stimulating (or inhibiting) the production rate (or k_{out}) of the response, the R_0 and k_{in} are important determinants of the extent of the response and adjustment of model equations for baseline effects may be needed.

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Acknowledgments

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