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Are Plasma Concentration Values Necessary for Pharmacodynamic Modeling of Muscle Relaxants?

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Background: **The traditional approach to pharmacokinetic/pharmacodynamic modeling of muscle relaxants requires sampling of plasma to determine drug concentrations. The authors recently proposed that certain pharmacodynamic characteristics (IR_{50}, the steady-state infusion rate to maintain 50% twitch depression; k_{eo}, the rate constant for equilibration between plasma concentration and effect; and γ, the Hill factor describing sigmoidicity of the concentration–effect relation) could be estimated without plasma concentration data. Here estimates for IR_{50}, k_{eo}, and γ determined with and without plasma concentration data are compared.**

Methods: **Six volunteers were given 15–60 μg/kg vecuronium on each of two occasions during anesthesia with propofol. Mechanical responses to train-of-four stimulation were measured at the adductor pollicis and at the laryngeal adductors. Various pharmacokinetic models accounting for the presence and potency of vecuronium's 3-desacetyl metabolite and a sigmoid e-max pharmacodynamic model were fit to the resulting plasma concentration and effect (adductor pollicis and laryngeal adductors) data to determine IR_{50} k_{eo}, and γ for each effect. One model related dose to effect without plasma concentration data.**

Results: **Values for IR_{50}(adductor pollicis), IR_{50}(laryngeal adductors), γ(adductor pollicis), and γ(laryngeal adductors) were similar when determined with and without plasma concentration values. Values for k_{eo}(adductor pollicis) and k_{eo}(laryngeal adductors) were larger when determined without plasma concentration values compared with those determined with these values; however, the ratio of k_{eo}(adductor pollicis) to k_{eo}(laryngeal adductors) was similar when determined with and without plasma concentration values.**

Conclusions: **Certain pharmacodynamic parameters were estimated accurately in the absence of plasma concentration values. This suggests limited utility for plasma concentration data under conditions similar to those of the present study. (Key words: Modeling: pharmacodynamics; NONMEM. Neuromuscular relaxants: vecuronium. Pharmacodynamics: adductor pollicis; larynx; models.)**

A TRADITIONAL approach to pharmacodynamic modeling is to administer a drug, measure its effects, and sample plasma to determine the time course of drug concentration. Pharmacokinetic (distribution, elimination) and pharmacodynamic (equilibration, sensitivity) characteristics of the drug are then determined and, in combination, used to formulate dosing regimens to achieve a desired effect. Although plasma concentration data are essential to this approach, an alternative approach to determine dosing regimens without measuring of plasma concentration was proposed by Verotta and Sheiner.[1] We previously used their approach to estimate the steady-state infusion rate to maintain 50% twitch depression (IR_{50}) with vecuronium.[2] Two issues arose from that analysis. First, in the absence of plasma concentration data, we could not verify whether this new approach yielded the same values as the traditional approach. Second, using the new approach we observed that IR_{50} varied as a function of the bolus dose of vecuronium. The absence of plasma concentration data prevented us from determining whether this dose-related change resulted from a nonlinearity in pharmacokinetics or a dose-related change in pharmacodynamics or was an artifact of the new method of analysis. The present study was designed to examine these issues. By obtaining plasma concentration data after administering vecuronium, we could analyze twitch tension data with and without these plasma concentration values. By studying volunteers on two occasions with different doses of vecuronium, we could determine whether the pharmacokinetics and/or pharmacodynamics of vecuronium varied with dose.

Methods

Data were obtained from six healthy volunteers given vecuronium on two occasions each during propofol

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anesthesia. Details of the anesthetic management, neuromuscular monitoring, data recording, blood sampling, and vecuronium determinations have been reported previously.[3] Briefly, twitch tension of the adductor pollicis in response to supramaximal train-of-four stimulation every 12 s was measured. Twitch tension of the laryngeal adductors was measured using a modification of the technique of Donati *et al.*[4] After 30 min of stimulation at both the adductor pollicis and the recurrent laryngeal nerve, vecuronium was administered intravenously and neuromuscular function was recorded until subjects were fully recovered. On the first occasion, vecuronium dose was 30 μg/kg. Complete paralysis at the adductor pollicis and approximately 50% block at the laryngeal adductors developed in one subject; on his second occasion, he received 15 μg/kg vecuronium. The remaining subjects received 60 μg/kg vecuronium on their second occasion. On each occasion, plasma samples were obtained before and 0.5, 1, 2, 3, 4, 5, 7, 10, 15, 20, 25, 30, 45, and 60 min after vecuronium administration. Plasma concentrations of vecuronium and its metabolite, 3-desacetylvecuronium, were determined by gas-liquid chromatography. The pharmacokinetic/pharmacodynamic analysis was performed both with and without plasma concentration data.

Modeling with Plasma Concentration Data

Two pharmacokinetic models were tested, one compartmental (parametric) and the other noncompartmental (semiparametric). Some results from these analyses were reported previously.[3]

Compartmental Approach, Pharmacokinetic Model. The first model was the traditional compartment model that relates plasma concentration (Cp) at time t after bolus drug administration to dose as

$$Cp = dose \cdot \sum_{i=1}^{n} A_i e^{-\lambda_i t} \quad (1)$$

where A_i is the (dose-normalized) intercept and λ_i is the rate constant associated with each of n exponential constants. Initial evaluations suggested that a three-compartment model (n = 3 in equation 1) was preferred ($P < 0.05$ by the likelihood ratio test) to a two-compartment model to fit the vecuronium concentration (Cp) *versus* time data; therefore, all subsequent analyses used three-compartment models. Because of limited information regarding disposition of 3-desacetylvecuronium, it was assumed to distribute to a single compartment, the volume of which equaled vecuronium's central compartment volume (V_1).[5] The pharmacokinetic model allowed for unidirectional metabolic conversion of vecuronium to 3-desacetylvecuronium in the central compartment. Residual error between measured and predicted values was modeled as being proportional to predicted values.

Compartmental Approach, Pharmacodynamic Model. Concentration in the effect compartment can be described as

$$Ce = k_{eo} \cdot dose \cdot \sum_{i=1}^{n} \frac{A_i \cdot (e^{-\lambda_i t} - e^{-k_{eo} t})}{k_{eo} - \lambda_i} \quad (2)$$

where k_{eo} is the rate constant for equilibration between plasma and the effect compartment.[6] Based on previous pharmacokinetic and pharmacodynamic studies,[5] we assumed that k_{eo} was identical for vecuronium and 3-desacetylvecuronium[6] and that 3-desacetylvecuronium was 80% as potent as vecuronium.[5] The relation between each effect (adductor pollicis, laryngeal adductors) and concentrations of vecuronium and its metabolite was described by the following equation:

$$Effect = \frac{C_{active}{}^{\gamma}}{(C_{active}{}^{\gamma} + C_{50}{}^{\gamma})} \quad (3)$$

where C_{active} is the active concentration of the muscle relaxant in the effect compartment (the sum of vecuronium concentration and 0.8 · concentration of the metabolite[5]), λ is the Hill factor that describes sigmoidicity (steepness) of the concentration-effect relation,[6] and C_{50} is the steady-state plasma concentration of the muscle relaxant producing 50% effect. In addition, the effect compartment has a trivial volume (arbitrarily fixed to one-thousandth of the volume of the central compartment) so as to not influence estimates of pharmacokinetic parameters.[6] Residual error between measured and predicted values for twitch tension was modeled as constant.

Area under the plasma concentration curve *versus* time curve was determined as

$$AUC = dose \cdot \sum_{i=1}^{n} \frac{A_i}{\lambda_i} \quad (4)$$

and plasma clearance (Cl) was determined as vecuronium dose divided by area under the curve. The steady-state infusion rate that produces 50% twitch depression (IR_{50}) was calculated as the product of Cl and C_{50}.

Noncompartmental Approach, Pharmacokinetic/Pharmacodynamic Model. Two problems

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are associated with application of the compartmental model to the plasma concentration data from this study. First, the model does not account for the peak in 3-desacetylvecuronium concentrations shortly after vecuronium administration, a result of each ampule of vecuronium containing this metabolite (<1%; personal communication, Mitchell Weinberger, Ph.D., Organon, Inc., West Orange, NJ, 1994). Second, the traditional model assumes that plasma vecuronium concentrations decline monotonically after bolus drug administration, whereas Ducharme *et al.*[7] showed that arterial vecuronium concentrations increase during the 30 s after drug administration and then oscillate before decreasing monotonically. Even though the traditional model fits the observed plasma concentration data well,[3] it presumably misspecifies the plasma concentration *versus* time course during the initial 30 s.

These two problems with the compartmental model could be addressed by using a complicated compartmental model that permits absorption of vecuronium into the central compartment from a depot and also permits administration of a small dose (the magnitude of which is determined in the analysis) of 3-desacetylvecuronium into the central compartment or the same depot. These analyses were performed but are not reported because their results differ minimally from the results from the other analyses. An alternate approach is to describe the plasma concentration *versus* time profile using linear interpolation; that is, to estimate plasma concentration at each time point from the preceding and subsequent measured values.[8] For example, a measured vecuronium concentration of 150 ng/ml at 10 min and 100 ng/ml at 15 min would yield a concentration of 130 ng/ml at 12 min. Vecuronium (and its metabolite) concentration is assumed to increase in a linear manner from a concentration of 0 ng/ml at 0 min to the concentration observed at 30 s. This approach approximates the plasma concentration *versus* time profile observed by Ducharme *et al.*[7] and presumably describes the early time course better than the compartmental model does. The plasma concentration *versus* time profile described by linear interpolation of the measured vecuronium and 3-desacetylvecuronium concentrations was then used in a pharmacodynamic analysis identical to that used in the compartmental approach just described. Area under the curve from time 0 to the time of the final measured vecuronium concentration was determined using the trapezoidal rule, assuming that plasma concentration increased in a linear manner from a value of 0 ng/ml at 0 min to the observed value at 0.5 min; area under the curve after the final observed vecuronium concentration value (C_{final}) was estimated as C_{final} divided by $-\beta$, where β is the slope determined from linear regression of the logarithms of final 3–6 vecuronium concentration values *versus* time. Plasma clearance was calculated as vecuronium dose divided by area under the curve; IR_{50} was determined as the product of C_{50} and Cl.

Modeling without Plasma Concentration Data

This approach has been described in detail[2] and is described here briefly. If effect is related to effect site concentration as described in equation 2 and effect is related to effect site concentration as in equation 3, these equations can be combined to yield

$$\text{Effect} = \frac{\left[k_{eo} \cdot \text{dose} \cdot \sum_{i=1}^{n} \frac{A_i \cdot (e^{-\lambda_i t} - e^{-k_{eo} t})}{k_{eo} - \lambda_i}\right]^{\gamma}}{\left[k_{eo} \cdot \text{dose} \cdot \sum_{i=1}^{n} \frac{A_i \cdot (e^{-\lambda_i t} - e^{-k_{eo} t})}{k_{eo} - \lambda_i}\right]^{\gamma} + C_{50}{}^{\gamma}} \quad (5)$$

Equation 5 can be solved iteratively, yielding estimates for k_{eo} and for each of the values of λ_i. However, in the absence of values for plasma concentration, C_{50} cannot be estimated (note that changing each A_i twofold changes C50 twofold).

When the pharmacokinetic model has only one compartment (n = 1), equation 5 reduces to

$$\text{Effect} = \frac{\left[k_{eo} \cdot \text{dose} \cdot \frac{A \cdot (e^{-k_{elimination} t} - e^{-k_{eo} t})}{k_{eo} - k_{elimination}}\right]^{\gamma}}{\left[k_{eo} \cdot \text{dose} \cdot \frac{A \cdot (e^{-k_{elimination} t} - e^{-k_{eo} t})}{k_{eo} - k_{elimination}}\right]^{\gamma} + C_{50}{}^{\gamma}} \quad (6)$$

where A_1 and λ_1 are renamed A and $k_{elimination}$, respectively (appropriate equations are available for n > 1). The numerator and the denominator on the right side of equation 6 are then multiplied by $(k_{elimination}/A)^{\lambda}$, where $k_{elimination}/A$ equals Cl. In addition, the product of Cl and IR_{50} is replaced by IR_{50}. This changes equation 6 to

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$$\text{Effect} = \frac{\left[k_{eo} \cdot \text{dose} \cdot \frac{k_{elimination} \cdot (e^{-k_{elimination} t} - e^{-k_{eo} t})}{k_{eo} - k_{elimination}}\right]^{\gamma}}{\left[k_{eo} \cdot \text{dose} \cdot \frac{k_{elimination} \cdot (e^{-k_{elimination} t} - e^{-k_{eo} t})}{k_{eo} - k_{elimination}}\right]^{\gamma} + IR_{50}{}^{\gamma}} \quad (7)$$

In the absence of plasma concentration data, the parameters $k_{elimination}$ and k_{eo} do not have their traditional meanings of relating drug dose to elimination ($k_{elimination}$) and equilibration between plasma concentration and effect (k_{eo}). Instead, $k_{elimination}$ relates dose to the concentration in a hypothetical driving compartment‡ and k_{eo} relates concentration in that driving compartment to effect. In addition, if only a single effect were measured, then absence of plasma concentration data does not permit us to distinguish which of the two rate constants relates to elimination and which to equilibration. However, this problem does not exist when two effects are modeled simultaneously, as in the present study.

Equation 7 can be solved using iterative techniques to yield the "best fit." Three models with one, two, and three "pharmacokinetic" compartments (corresponding to n = 1, 2, and 3 in equation 5) were tested. Residual error between measured and predicted values for twitch tension was modeled as constant. A model with more compartments was accepted only if its objective function ($-2 \cdot$ log likelihood, equivalent to the residual sum of squares in traditional nonlinear regression) was statistically improved (a decrease of 3.8 units for each additional parameter in the new model) and if the model with more compartments was associated with a visual improvement in the residual differences between observed and measured values.

Comparison of the Three Approaches

Values for IR_{50}(adductor pollicis), IR_{50}(laryngeal adductors), the ratio of IR_{50}(laryngeal adductors) to IR_{50}(adductor pollicis), k_{eo}(adductor pollicis), k_{eo}(laryngeal adductors), the ratio of k_{eo}(laryngeal adductors) to k_{eo}(adductor pollicis), γ(adductor pollicis), γ(laryngeal adductors), and the ratio of γ(laryngeal adductors) to γ(adductor pollicis) for each of the three approaches were compared using repeated measures analysis of variance and the Student-Newman-Keuls test.

Comparison of the Two Muscle Groups

Values for the ratio of IR_{50}(laryngeal adductors) to IR_{50}(adductor pollicis), the ratio of k_{eo}(laryngeal adductors) to k_{eo}(adductor pollicis), and the ratio of γ(laryngeal adductors) to γ(adductor pollicis) were compared to 1.0 using a one-sample t test.

Dose-related Changes in Pharmacodynamics

The ratio of values for IR_{50}(adductor pollicis), k_{eo}(adductor pollicis), and γ(adductor pollicis) from the large dose of vecuronium to values from the small dose were determined. Mean values of these ratios were compared to 1.0 using a one-sample t test.

Except for the analyses of dose-related changes in pharmacodynamics (for which data on laryngeal muscle effect were not analyzed), data for both adductor pollicis and laryngeal muscle effect were fit simultaneously. All pharmacokinetic and pharmacodynamic analyses were performed simultaneously by individual participant and dose using NONMEM.§ All statistical tests were two tailed; $P < 0.05$ was assumed to be significant. Some statistical tests were performed after log transformation of the data. Values are reported as means ± SD.

Results

Modeling with Plasma Concentration Data

The compartmental model fit the vecuronium plasma concentration data well and resulted in an excellent fit of the pharmacodynamic model to the effect data for both muscle groups for all participants.[3] However, for six of the ten occasions when 3-desacetylvecuronium was identified, the model failed to account for the early peak in 3-desacetylvecuronium concentrations. Using the noncompartmental approach, linear interpolation of the plasma concentration data for vecuronium and 3-desacetylvecuronium necessarily resulted in an exact fit of the pharmacokinetic model to the plasma concentration data.

Modeling without Plasma Concentration Data

The pharmacodynamic model fit the effect data well for both muscle groups for all participants (fig. 1). For ten of 12 occasions (five of six participants), the model

‡ "Driving" compartment is the compartment on which k_{eo} "acts" to produce the concentration at the effect site. In the present model (and presumably in most situations), the plasma concentration (*i.e.*, the concentration in the central compartment) "drives" the concentration at the effect site.

§ Beal SL, Sheiner LB: NONMEM Users Guides. San Francisco, NONMEM Project Group, UCSF, 1992.

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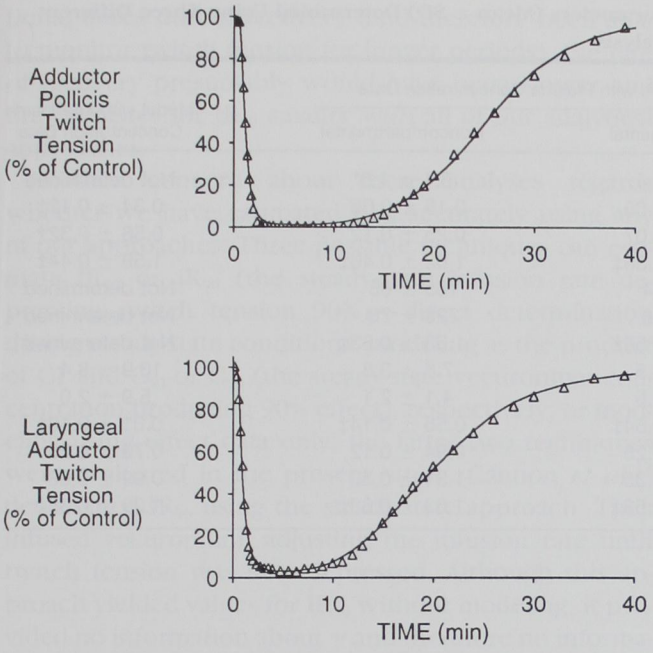

Fig. 1. Pharmacodynamic data from a representative study are shown; plasma concentration data from this participant were displayed in a previous report.[3] The volunteer received 60 μg/kg vecuronium at time 0. Measured values for twitch tension of the adductor pollicis (*top*) and the laryngeal adductors (*bottom*) are displayed as triangles; values predicted using the model without plasma concentration data are shown by the solid line.

with two "pharmacokinetic" compartments was associated with a markedly improved fit compared with the model with one "pharmacokinetic" compartment. In no volunteer was the model with three "pharmacokinetic" compartments statistically justified compared with the model with fewer "pharmacokinetic" compartments.

Comparison of the Three Approaches

Values for k_{e0}(adductor pollicis) and k_{e0}(laryngeal adductors) estimated without plasma concentrations were larger than values estimated with plasma concentration data (table 1). Values for γ(adductor pollicis), γ(laryngeal adductors), IR_{50}(adductor pollicis), and IR_{50}(laryngeal adductors) were similar with the three approaches.

Comparison of the Two Muscle Groups

The ratio of IR_{50}(laryngeal adductors) to IR_{50}(adductor pollicis) and the ratio of k_{e0}(laryngeal adductors) to k_{e0}(adductor pollicis) were larger than 1.0; the ratio of γ(laryngeal adductors) to γ(adductor pollicis) was less than 1.0.

Dose-related Changes in Pharmacodynamics

Values for C_{50}(adductor pollicis) for the large dose were larger than those for the small dose in each of the models with plasma concentration data (table 2). Values for IR_{50}(adductor pollicis) were larger for the large dose compared with those for the small dose in the noncompartmental model and in the model without plasma concentration data.

Discussion

We show that estimates for certain pharmacodynamic parameters—IR_{50}(adductor pollicis), IR_{50}(laryngeal adductors), γ(adductor pollicis), and γ(laryngeal adductors)—and the ratio of k_{e0}(laryngeal adductors) to k_{e0}(adductor pollicis) are similar regardless of whether values for plasma concentrations of vecuronium are used in the analysis. However, the model without plasma concentration values yielded estimates for k_{e0}(adductor pollicis) and k_{e0}(laryngeal adductors) larger than those from the model with plasma concentration data. In that k_{e0} describes equilibration between concentrations in plasma and at the effect site, we assume that the value obtained with plasma concentration values is correct and that the value obtained without plasma concentrations is therefore an overestimate. The flawed estimates for k_{e0} obtained without plasma concentration data may be due to the relative paucity of information regarding the shape of the concentration-effect relation during onset, a result of the brief period between initial and maximum effect (fig. 1).

There are several limitations to the utility of pharmacodynamic modeling without plasma concentration data. First, our approach to modeling without plasma concentration data requires *a priori* definition of a pharmacodynamic model (such as equation 3) and would not be applicable if other pharmacodynamic approaches (*e.g.*, Verotta and Sheiner's "collapse the loop" approach[9]) were necessary. Second, just as the traditional pharmacokinetic model misspecifies the plasma concentration *versus* time course during the initial 30–60 s after bolus drug administration, our model without plasma concentration data (see equation 1) assumes that the plasma concentration of vecuronium peaks instantly at time 0 and then decreases continuously after drug administration. Despite this incor-

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Table 1. Values for the Pharmacokinetic and Pharmacodynamic Parameters (Mean ± SD) Determined Using Three Different Models, Two of Which Used Plasma Concentration Data in the Analysis

	Models with Plasma Concentration Data		Model without Plasma Concentration Data
	Compartmental	Noncompartmental	
Cl ($ml \cdot kg^{-1} \cdot min^{-1}$)	5.1 ± 2.4	6.1 ± 1.6*	Not determined
k_{eo} (adductor pollicis) (min^{-1})	0.12 ± 0.05	0.15 ± 0.06	0.34 ± 0.12†
k_{eo} (laryngeal adductors) (min^{-1})	0.18 ± 0.07	0.25 ± 0.12	0.56 ± 0.32†
k_{eo} (laryngeal adductors)/k_{eo} (adductor pollicis)	1.52 ± 0.38‡	1.62 ± 0.46‡	1.59 ± 0.44‡
C_{50} (adductor pollicis) (ng/ml)	166 ± 64	165 ± 66	Not determined
C_{50} (laryngeal adductors) (ng/ml)	227 ± 76	228 ± 78	Not determined
C_{50} (laryngeal adductors)/C_{50} (adductor pollicis)	1.50 ± 0.58‡	1.53 ± 0.63‡	Not determined
γ (adductor pollicis)	9.1 ± 4.5	7.6 ± 3.8	10.9 ± 8.4
γ (laryngeal adductors)	5.7 ± 5.5	4.1 ± 2.1	5.9 ± 2.6
γ (laryngeal adductors)/γ (adductor pollicis)	0.64 ± 0.54‡	0.55 ± 0.14‡	0.61 ± 0.18‡
IR_{50} (adductor pollicis) ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.73 ± 0.25	0.94 ± 0.12	0.73 ± 0.26
IR_{50} (laryngeal adductors) ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	1.04 ± 0.35	1.31 ± 0.32	0.99 ± 0.63
IR_{50} (largyngeal adductors)/IR_{50} (adductor pollicis)	1.50 ± 0.58‡	1.53 ± 0.63‡	1.29 ± 0.35‡

N = 12 (two doses for each of six subjects) for all values.

* Differs from compartmental model.

† Differs from model with plasma concentration data.

‡ Differs from 1.0.

rect assumption, all three approaches (two of which misspecified plasma concentrations during the period immediately after drug administration) yielded similar values for most pharmacodynamic parameters. This suggests that the model misspecification does not produce large errors in modeling certain pharmacodynamic parameters.

A third limitation to our analyses is that several of the approaches (the compartmental model and the model without plasma concentration data) ignore the small dose of vecuronium's metabolite in the drug administered. Because this metabolite accounted for less than 1% of the administered dose and the metabolite is only eight tenths as potent as vecuronium, it probably contributes minimally to the effect of these single doses of vecuronium. As a result, misspecifying the metabolite's plasma concentration *versus* time course does not limit accuracy of the pharmacodynamic estimates. A fourth limitation is the brief time period (typically 30–40 min) when we measured effect. With repeated administration, recovery from vecuronium is cumulative, presumably because of increasing concentrations of its metabolite[10] (the clearance of which is 69% that of vecuronium[5]). Thus our study design—administration of vecuronium doses smaller than typically used clinically—may underestimate the contribution of the metabolite to vecuronium's effect with prolonged administration.[10,11] Had we administered larger doses or addi-

Table 2. Ratio of the Pharmacodynamic Parameters (Mean ± SD) from Two Different Doses of Vecuronium

	Models with Plasma Concentration Data		Model without Plasma Concentration Data
	Compartmental	Noncompartmental	
k_{eo} (adductor pollicis)—large dose/small dose	1.52 ± 0.91	1.14 ± 0.73	1.00 ± 0.59
C_{50} (adductor pollicis)—large dose/small dose	1.28 ± 0.15*	1.33 ± 0.21*	Not determined
γ (adductor pollicis)—large dose/small dose	0.73 ± 0.22*	0.89 ± 0.34	0.82 ± 0.45
IR_{50} (adductor pollicis)—large dose/small dose	1.38 ± 0.76	1.31 ± 0.41*	1.50 ± 0.41*

Parameters were determined using three different models, two of which used plasma concentration data in the analysis. For each parameter, n = 6 for each of the large dose and small dose.

* Differs from 1.0.

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tional doses during recovery (and therefore been able to monitor twitch tension for longer periods), the rate of recovery presumably would have been slower and the estimates for IR_{50} smaller with all of our analytical approaches.

Another concern about these analyses regards whether we have estimated IR_{50} accurately using any of our approaches. Three possible techniques can estimate IR_{50} or IR_{90} (the steady-state infusion rate depressing twitch tension 90%)—direct determination during steady-state conditions; modeling as the product of C1 and C_{50} or C_{90} (the steady-state vecuronium concentration producing 90% effect), respectively; or modeling using effect data only; the latter two techniques were evaluated in the present study. Cannon *et al.*[12] determined IR_{90} using the steady-state approach: They infused vecuronium, adjusting the infusion rate until twitch tension was 90% depressed. Although this approach yielded values for IR_{90} without modeling, it provided no information about γ and therefore no information about dose requirements to maintain different magnitudes of effect (*e.g.*, IR_{50}). In addition, their approach was tedious and would have been further complicated if two effects (*e.g.*, both adductor pollicis and laryngeal adductor twitch tension) were measured. Finally, their approach provided no information about k_{eo} and thus offered no insight into time to peak effect after bolus doses. We recently modified Cannon *et al.*'s steady-state approach by infusing mivacurium to maintain two to three different levels of twitch depression, one to two bracketing 50% twitch depression, and a third near 90% twitch depression.[13] A modification of the Hill equation (equation 3) was then applied to these infusion rates *versus* steady-state twitch depression to estimate γ, permitting estimates of IR_{50} and IR_{90} (but not k_{eo}). Although IR_{50} and IR_{90} were estimated, rather than determined directly, we were confident of these estimates because steady-state twitch depression bracketed 50% twitch depression and was close to 90% twitch depression.

In contrast to these steady-state approaches, the present study compares two methods to model IR_{50} (each of which also permits estimation of IR_{90}),‖ one using both plasma concentration and effect data, the other using only effect data. The former approach requires that we estimate both Cl and C_{50} correctly. Presumably we have sufficient data during onset and offset for each participant to estimate C_{50} reliably. However, by sampling plasma for only 60 min,# we cannot estimate vecuronium's terminal half-life accurately and therefore might overestimate vecuronium's Cl. The potential for error in estimating Cl is suggested by differences in these values when determined with the compartmental and noncompartment models (table 1). If elimination half-life is underestimated and Cl is overestimated, values of IR_{50} estimated from C_{50} and Cl might be overestimated. Without direct measurement of IR_{50}, the magnitude of this potential error cannot be determined. However, the values of IR_{90} estimated in the present study during propofol anesthesia (0.97 ± 0.31 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 1.30 ± 0.41 $\mu g \cdot kg^{-1} \cdot min^{-1}$, or 1.08 ± 0.74 $\mu g \cdot kg^{-1} \cdot min^{-1}$ based on the compartmental model, the noncompartmental model, and the model without plasma concentration data, respectively) are similar to the values estimated directly by Cannon *et al.*[12] (0.92 ± 0.37 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during fentanyl anesthesia, suggesting accuracy of our modeling approach.

Several of the pharmacodynamic values in the present study (table 1) are similar to those from a previous study[2] (table 3) in which we analyzed data for adductor pollicis and laryngeal adductor twitch tension obtained by Donati *et al.*[14] in the absence of plasma concentration values. One exception is that the ratio of k_{eo}(laryngeal adductors) to k_{eo}(adductor pollicis) was reported previously as 2.48,[2] a value larger than that estimated either with or without plasma concentration values in the present study (~1.5). The second exception is the ratio of γ(laryngeal adductors):γ(adductor pollicis), reported as 1.23 in the previous study and ~0.6 in the present study. Both these exceptions suggest that esti-

Table 3. "Typical" Values for the Pharmacodynamic Parameters Determined in a Population Analysis in a Previous Study[2] in Which No Plasma Concentration Values for Vecuronium Were Available

	Value
k_{eo} (adductor pollicis)	0.44
k_{eo} (laryngeal adductors)/k_{eo} (adductor pollicis)	2.48
γ (adductor pollicis)	6.16
γ (laryngeal adductors)/γ (adductor pollicis)	1.23
IR_{50} (adductor pollicis)	0.692
IR_{50} (laryngeal adductors)/IR_{50} (adductor pollicis)	1.36

‖ The Hill equation can be rearranged to $IR_{90} = IR_{50} \cdot [90\%/(100\% - 90\%)]^{1/\gamma}$. Values for IR_{50} and γ for each individual can then be used to estimate IR_{90}.

The 60-min sampling period was dictated by sensitivity of the assay. Although we could consistently detect vecuronium until complete recovery of twitch tension, we assumed that rapid decreases in plasma concentration after small doses of vecuronium would prevent detection of vecuronium after 60 min.

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mates for certain pharmacodynamic parameters for the laryngeal adductors were flawed in the previous study. Although there are several differences between the two studies (investigators, drug doses, volunteers *versus* patients), we speculate that the most important difference involves the signal-to-noise ratio for twitch tension of the laryngeal adductors. By studying volunteers in whom interferences such as electrocautery were eliminated and by modifying Donati *et al.*'s technique to monitor laryngeal muscle function,** we obtained data for laryngeal adductor twitch tension that was affected minimally by noise. Because the parameter k_{eo} describes onset and offset of twitch depression, information regarding each of these phases is available only during the initial several minutes after drug administration and from the time of initial recovery until recovery is complete. Because of the brief duration of onset, any "noisy" signals during that period may markedly influence the ability to estimate k_{eo} and γ accurately. This difference between studies in k_{eo}(laryngeal adductors) and similarity between studies in k_{eo}(adductor pollicis) suggest further limitation to the utility of modeling without plasma concentration data—that estimates will be flawed if the signal-to-noise ratio for the effect measure is not large.

In the previous study that modeled adductor pollicis and laryngeal adductor twitch tension in the absence of plasma concentrations, we observed that IR_{50} differed as a function of the bolus dose of vecuronium.[2] This dose-related change in pharmacodynamics was confirmed in the present study as a dose-related change in C_{50} in the analyses with plasma concentration data and a dose-related change in IR_{50} in the analyses without plasma concentration data and the noncompartmental approach. We cannot explain this observation.

One additional consideration arises from the analyses without plasma concentration data. Consider a study design in which a single effect is modeled with two exponentials (*e.g.*, if we had measured only a single effect). The resulting analysis would yield two rate constants, one of which corresponds to the relation between dose and "concentration" in the driving compartment§ (analogous to $k_{elimination}$) and the other to the relation between concentration in the driving compartment and effect (analogous to k_{eo}). However, without plasma concentration data there is no means to identify which rate constant corresponds to $k_{elimination}$ and which to k_{eo}; this situation is similar to modeling pharmacokinetics of drugs given orally in which it is impossible to distinguish between the absorption and elimination rate constants. We overcome this problem by measuring two effects: one (or more) rate constants describe the relation between dose and the resulting driving compartment; the remaining two rate constants relate the common driving compartment to the two resulting effects. Finally, even if an analysis with only a single effect measure prevented identification of k_{eo} *versus* $k_{elimination}$, the resulting rate constants would be sufficient to describe the relation between dose and effect *versus* time.

We also note that in the analyses performed without plasma concentration data, despite estimates of k_{eo} for each of the muscle groups being flawed, the ratio of k_{eo} for the two muscle groups is estimated correctly (assuming that the values determined with plasma concentration data are correct). This supports our earlier claim that "any biases apply equally across muscle groups and should not, therefore, affect our conclusions (regarding the relative values of k_{eo})."[2]

Additional investigations with different drugs and other effect measures are necessary to validate that modeling without plasma concentration provides pharmacodynamic results similar to those obtained with plasma concentration data. However, risks associated with blood sampling, expense of measuring plasma concentrations of drugs, and potential delays in drug development if sensitive or specific assays are not available suggest a potential role for modeling pharmacodynamics without plasma concentration data. Regardless, this new approach does not obviate the need for measurements of plasma concentration if the intent is to determine traditional pharmacokinetic parameters such as plasma clearance or volume of distribution.

In summary, we estimated pharmacodynamic parameters for vecuronium using a traditional approach requiring both measured values for plasma concentration and twitch tension and using a novel approach requiring only values for twitch tension. Estimates for certain pharmacodynamic parameters were similar using the two approaches, suggesting limited utility of measured values of the plasma concentration of the muscle relaxant. If future studies confirm that modeling without plasma concentration data yields reliable estimates for certain pharmacodynamic parameters, the utility of measuring

** Whereas Donati *et al.*[14] used a traditional tracheal tube, we used a double-lumen tracheal tube positioned with the proximal cuff at the vocal cords. By placing the distal cuff in the trachea (rather than a bronchus) and ventilating through the distal lumen only, we eliminated the artifact from mechanical ventilation, thereby improving the signal-to-noise ratio.

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plasma concentrations of muscle relaxants and other drugs may be questionable.

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