Comparison of Twitch Depression of the Adductor Pollicis and the Respiratory Muscles

Pharmacodynamic Modeling without Plasma Concentrations

Paul Bragg, M.D.,* Dennis M. Fisher, M.D.,† Jun Shi, M.D.,‡ Francois Donati, Ph.D., M.D.,§ Claude Meistelman, M.D.,‖ Marie Lau, B.S., Lewis B. Sheiner, M.D.**

Background: Although the respiratory muscles (the diaphragm and the laryngeal adductors) recover from paralysis more rapidly than does the adductor pollicis, patients can develop complete paralysis of the respiratory muscles, but not of the adductor pollicis, after bolus administration of vecuronium. The authors used a pharmacodynamic model not requiring muscle relaxant plasma concentrations to reconcile these findings.

Methods: The pharmacodynamic model is based on the traditional model, in which: (1) vecuronium concentration at the neuromuscular junction (C_{mus}) is a function of the plasma concentration versus time curve and a rate constant for equilibration between plasma and the neuromuscular junction (k_{eq}); and (2) effect is a function of C_{effect}, the steady-state plasma concentration that produces 50% effect (C_{50}), and a factor to explain the sigmoid relationship between concentration and effect. In the absence of vecuronium plasma concentrations, an empiric model (rather than the usual effect compartment model) can be used to mimic the time delay (proportional, but not identical, to 1/k_{eq}) between dose and effect. The model can be used to estimate the steady-state infusion rate that produces 50% effect (IR_{50}), equal to the product of C_{50} and vecuronium plasma clearance; IR_{50} for different muscle groups can then be compared to assess relative sensitivity. The authors applied this model to published effect data for subjects given 40–70 µg/kg vecuronium in whom paralysis of three muscle groups was measured during opioid/propofol anesthesia.

Results: For IR_{50}, the ratio of values for the larynx:dia
gastric: adductor pollicis was 1.4:1:2:1:1 for the equilibrium constant (inversely proportional to the time delay), the ratio for the respiratory muscles to the adductor pollicis was 2.5:1.

Conclusions: Vecuronium concentrations peak earlier at the respiratory muscles than at the adductor pollicis, possibly the result of greater perfusion to these organs, leading to earlier onset of paralysis. The observation that bolus injection of vecuronium produces greater paralysis of the respiratory muscles than of the adductor pollicis, despite greater resistance of the respiratory muscles, can be explained by differential rates of equilibration between plasma and various muscles.

(Key words: Neuromuscular relaxants; vecuronium. Pharmacodynamics: adductor pollicis; diaphragm; larynx; models. Respiratory effects: muscle relaxants.)

BOTH the diaphragm and the adductor muscles of the larynx recover from paralysis induced by muscle relaxants more rapidly than does the adductor pollicis.¹ These observations suggest that the respiratory muscles are more resistant to the effects of muscle relaxants than is the adductor pollicis. In contrast, Donati et al.¹,² demonstrated that complete blockade of the diaphragm or laryngeal muscles can develop in patients without complete blockade of the adductor pollicis. These latter findings could be interpreted to suggest that the respiratory muscles are less resistant than the adductor pollicis to the effects of muscle relaxants.³ If resistance

* Research Fellow in Anesthesia, University of California. Current position: University of Ottawa, Ottawa, Canada.
† Professor of Anesthesia and Pediatrics, University of California.
‡ Research Fellow in Clinical Pharmacology, Division of Clinical Pharmacology and Experimental Therapeutics, University of California. Current position: Department of Clinical Pharmacology, Berlex Laboratories, Wayne, New Jersey.
§ Professor of Anesthesia, McGill University.
‖ Attending Anesthesiologist, Institut Gustave-Roussy.
# Staff Research Associate, Department of Anesthesia, University of California.
** Professor of Laboratory Medicine, Medicine, and Pharmacy, University of California.

Received from the Departments of Anesthesia and Laboratory Medicine, University of California, San Francisco; Department of Anesthesia, McGill University, Montreal, Quebec, Canada; and the Institut Gustave Roussy, Villejuif, France. Accepted for publication September 30, 1993. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, October 29, 1991. Additional analyses referred to in the manuscript and code for the NONMEM analysis can be obtained from the corresponding author.

Address reprint requests to Dr. Fisher: Department of Anesthesia, University of California, San Francisco, 521 Parnassus Avenue, San Francisco, California 94143-0618.
PHARMACODYNAMIC MODELING OF RESPIRATORY MUSCLES

is defined as the need for a higher concentration of the muscle relaxant in the muscle, neither of these clinical observations permits one to determine relative sensitivity—differences in onset and recovery may result from inherent differences in end-organ sensitivity or differences in the rate at which drug is delivered to or removed from each muscle group.

One approach to resolving the apparent contradiction would be to administer vecuronium, measure its plasma concentration and the time course of paralysis at the various muscle groups, and analyze these data using combined pharmacokinetic/pharmacodynamic modeling. This analysis would yield values for the steady-state plasma concentration producing 50% paralysis, an estimate of muscle sensitivity not affected by delivery or removal of muscle relaxant from the neuromuscular junction. However, because simultaneous measurements of the time course of vecuronium-induced paralysis of the adductor pollicis and the respiratory muscles and plasma concentrations have not been reported, we were unable to use a combined pharmacokinetic/pharmacodynamic modeling approach. Instead, we used a recently described modeling approach in which plasma concentration measurements are not necessary to compare the time course of neuromuscular blockade of the adductor pollicis and the respiratory muscles. Using this approach, we can explain the apparent paradox that the respiratory muscles can be more resistant than the adductor pollicis to nondepolarizing muscle relaxants, yet develop more intense neuromuscular blockade after bolus administration.

Methods

The data used for this analysis were published previously by Donati et al. Briefly, 36 subjects were anesthetized with alfentanil and propofol. In all subjects, the adductor pollicis was stimulated via surface electrodes with supramaximal train-of-four stimuli at the ulnar nerve, and twitch tension was measured using a force transducer. Sixteen of these subjects had their right phrenic nerve stimulated supramaximally via surface electrodes at the base of the neck and the evoked response of the diaphragm was recorded electromyographically from surface electrodes placed in the eighth or ninth intercostal spaces. In the remaining 20 subjects, the recurrent laryngeal nerve was stimulated supramaximally at the notch of the thyroid cartilage; its evoked tension response was measured using the cuff of a tracheal tube positioned to record the maximal positive deflection with stimulation. After obtaining stable recordings for the adductor pollicis and either the diaphragm or the laryngeal muscles, 40 or 70 μg/kg vecuronium was administered intravenously, and neuromuscular function was recorded until full recovery.

An effect compartment pharmacodynamic model, derived in appendix 1, was fit to these data for the time course of paralysis of the adductor pollicis and the respiratory muscles to estimate:

1. the infusion rate that produces 50% effect at steady state (IR50): IR50 is the product of plasma clearance (Cl) and the steady-state plasma concentration that produces 50% effect (C50)
2. the time constant for equilibration of effect (k2, equivalent to k1 in the traditional effect compartment model)
3. the Hill factor (γ) that governs the sigmoidicity of the relationship between concentrations in the effect compartment and effect
4. the pharmacokinetic time constant (k1)

The model cannot determine usual pharmacokinetic (distribution or elimination half-lives, plasma clearance, volumes of distribution) or pharmacodynamic (C50) parameters, unless vecuronium plasma concentrations are measured.

The effect data were modeled using NONMEM, a program to analyze population pharmacokinetic/pharmacodynamic data. We tested various models. First, we compared a biexponential pharmacokinetic model (n = 2 in equations A1, A2, and A4) with a monoeXponential pharmacokinetic model (n = 1 in equations A1, A2, and A4). When the monoeXponential pharmacokinetic model fit the data as well as the biexponential pharmacokinetic model (i.e., both the objective function—NONMEM's equivalent to the residual sum of squares—and the pattern of the weighted residuals changed minimally), we performed subsequent analyses with the monoeXponential model. These models included as many as ten pharmacokinetic/pharmacodynamic parameters—IR50, k2, and γ for each of the three muscles and k1. All models also contained four parameters for interindividual variation, one each for k1, IR50, k2, and γ (i.e., we assumed that the magnitude of interindividual variation for IR50, k2, and γ was the same for all muscles).
Next, we evaluated whether separate values for $k_{50}$, $k_{2}$, and $\gamma$ were needed for each of the three muscle groups, i.e., would a simpler model in which the same $k_{50}$, $k_{2}$, or $\gamma$ was used for two or three muscle groups be adequate. The need for separate values for $k_{50}$, $k_{2}$, and $\gamma$ for each muscle group was determined by comparing two models, one in which separate values were used (e.g., $R_{50}$(larynx) and $R_{50}$(diaphragm)) to a model with a single value ($R_{50}$(respiratory muscles)). If the model with additional parameters was not statistically required by the likelihood ratio test* (using a conservative $P$ value of $<0.01$), the simpler model was selected.

Using these models, we determined whether sensitivity of muscle groups differed. Although this would traditionally be accomplished by comparing $C_{50}$s of different muscle groups, $C_{50}$ cannot be estimated in the absence of plasma concentration data. In that $R_{50} = C_{50}$ (Cl, total body clearance, cannot differ among muscle groups), the ratio of sensitivities of the diaphragm and the adductor pollicis

\[
\frac{C_{50} \text{ (diaphragm)}}{C_{50} \text{ (adductor pollicis)}}
\]

is approximated by the ratio

\[
\frac{R_{50} \text{ (diaphragm)}}{R_{50} \text{ (adductor pollicis)}}
\]

Therefore, if $R_{50}$ (diaphragm) exceeds $R_{50}$ (adductor pollicis), the diaphragm is resistant compared to the adductor pollicis. Similar calculations were used to compare sensitivity of the laryngeal muscles to each of the adductor pollicis and the diaphragm. Comparisons of $k_{50}$s enabled us to determine whether equilibration varied between muscle groups (equivalent to comparisons of $k_{50}$s); comparisons of $\gamma$ indicated whether the sigmoidicity of the concentration-effect (or dose-effect) relationship varied between muscles.

During these analyses, the need for one additional parameter appeared. When data for the two doses of vecuronium were fit separately, values for $k_{1}$ differed; when data for the two doses were analyzed together (i.e., assuming the same $k_{1}$ for the two doses), residual differences between measured values and those predicted by the model were consistently negative with data from one dose and positive with the other. This suggested a flaw in fitting the model to the data. This model misspecification was improved by allowing $R_{50}$ to vary with dose, i.e., $R_{50}(70 \mu g/kg) = \text{dose factor} \cdot R_{50}(40 \mu g/kg)$; the model was similarly improved by allowing $k_{2}$ to vary with dose. Thus, our final model also included a dose factor for $R_{50}$. From this model, we also simulated the typical time to peak effect for each muscle group.

Variability between individuals was modeled by assuming that each individual’s pharmacokinetic/pharmacodynamic parameters can be expressed as the sum of the typical value for the population and a factor for that individual. For example, interindividual variability for $k_{1}$ was modeled as:

\[
k_{1i} = k_{1} \cdot (1 + \eta_{i}),
\]

where $k_{1i}$ is the estimate for the pharmacokinetic rate constant for the $i^{th}$ individual, $k_{1}$ is the typical value for the population, and $\eta_{i}$ is a random variable with mean 0. Interindividual variability for $R_{50}$, $\gamma$, and $k_{2}$ were modeled in a similar manner, assuming the same proportionality for all muscles. Residual intrindividual variance (variance of the effect measurements) was modeled as:

\[
\text{Effect}_{ij} \text{ (measured)} = \text{Effect}_{ij} \text{ (actual)} + \epsilon_{ij},
\]

where $\text{Effect}_{ij}$ is the $j^{th}$ value for the $i^{th}$ subject, and $\epsilon_{ij}$ is the associated error.

**Results**

Models in which $R_{50}$ differed between each of the three muscle groups improved the objective function and the pattern of residual differences between measured and predicted values compared to models in which $R_{50}$ was similar for two or more muscle groups. In contrast, a model in which $k_{2}$ differed between the two respiratory muscles did not improve the objective function compared to a model in which $k_{2}$ was identical for the two respiratory muscle groups. Similarly, $\gamma$ was identical for the two respiratory muscle groups. Therefore, our final model contained one pharmacokinetic parameter common to the muscle groups ($k_{1}$), $R_{50}$s for each of the three muscle groups, two values for $k_{2}$ (one for the adductor pollicis, the other for the two respiratory muscles), the same two values for $\gamma$, and the dose factor for $R_{50}$ described in methods. The results with this model (fig. 1) demonstrate that, for each dose, the pharmacokinetic/pharmacodynamic parameters predict the central location of the data. Goodness
Fig. 1. Data for responses of the adductor pollicis, the diaphragm, and the laryngeal muscles to vecuronium are shown. Dashed lines display the data from each subject. The solid line represents the time course of paralysis for the “typical” individual, i.e., the individual whose pharmacokinetic/pharmacodynamic parameters are those estimated by the model.
of fit also can be assessed by examining a plot of weighted residuals (i.e., residual differences between observed and predicted values, normalized to units equivalent to standard deviations) versus time (fig. 2). To simplify examination of these plots, only those weighted residuals exceeding ±3 (SD) are shown; remaining values are represented by a smoothed plot obtained using Super smoother.†† These plots suggest that the model fits the data well with the possible exception of the 40-μg/kg dose for the adductor pollicis.

Values for $k_2$ (respiratory muscles) exceeded $k_2$ (adductor pollicis) (tables 1 and 2). The ratio of $k_2$ (respiratory muscles) to $k_2$ (adductor pollicis) was 2.5:1 when all data were analyzed together; similar ratios were obtained using data for each dose alone and for each muscle pair tested alone. Similarly, values for $IR_{50}$ (larynx) and $IR_{50}$ (diaphragm) exceeded $IR_{50}$ (adductor pollicis), the ratio being 1.4:1:2:1 for pooled data; the ratios were similar for individual doses or muscle pairs. Values for $γ$ (larynx) and $γ$ (diaphragm) did not differ; values for $γ$ (respiratory muscles) were greater than those for $γ$ (adductor pollicis). Predicted times to peak effect for the adductor pollicis and for the respiratory muscles were similar to that observed by Donati et al., 6.4 ± 1.5 min and 3.3 ± 0.8 min, respectively (excluding those subjects for whom time to peak effect could not be determined, e.g., those who developed 100% blockade).

### Discussion

We applied a newly described modeling technique to data for the neuromuscular effects of vecuronium in three muscle groups and found two differences between the respiratory muscles and the adductor pollicis.

### Table 1. Values for the Pharmacokinetic and Pharmacodynamic Parameters and Times to Peak Effects for 36 Subjects Given 40–70 μg/kg Vecuronium

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population Mean</th>
<th>Standard Error (Percent of Population Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$ (min⁻¹)</td>
<td>0.025</td>
<td>14</td>
</tr>
<tr>
<td>$k_2$ (adductor pollicis, min⁻¹)</td>
<td>0.44</td>
<td>14</td>
</tr>
<tr>
<td>$k_2$ (respiratory muscles)/$k_2$ (adductor pollicis)*</td>
<td>2.48</td>
<td>6</td>
</tr>
<tr>
<td>$IR_{50}$ (adductor pollicis, 40-μg/kg dose, μg · kg⁻¹ · min⁻¹)</td>
<td>0.692</td>
<td>9</td>
</tr>
<tr>
<td>$IR_{50}$ (70-μg/kg dose)/$IR_{50}$ (40-μg/kg dose)</td>
<td>1.42</td>
<td>5</td>
</tr>
<tr>
<td>$IR_{50}$ (diaphragm)/$IR_{50}$ (adductor pollicis)*</td>
<td>1.17</td>
<td>2</td>
</tr>
<tr>
<td>$IR_{50}$ (larynx)/$IR_{50}$ (adductor pollicis)†</td>
<td>1.36</td>
<td>4</td>
</tr>
<tr>
<td>$γ$ (adductor pollicis)</td>
<td>6.16</td>
<td>13</td>
</tr>
<tr>
<td>$γ$ (respiratory muscle)/$γ$ (adductor pollicis)*</td>
<td>1.23</td>
<td>4</td>
</tr>
</tbody>
</table>

* Respiratory muscles differ from adductor pollicis ($P < 0.001$).
† Laryngeal muscles differ from adductor pollicis, diaphragm ($P < 0.001$).
ND = not determined.

### Table 2. Values for Interindividual Variation for $k_1$, $k_2$, $IR_{50}$, and $γ$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Interindividual Variation (% of Population Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$</td>
<td>54</td>
</tr>
<tr>
<td>$k_2$</td>
<td>41</td>
</tr>
<tr>
<td>$IR_{50}$</td>
<td>41</td>
</tr>
<tr>
<td>$γ$</td>
<td>42</td>
</tr>
</tbody>
</table>

---

Fig. 3. Simulations of plasma concentrations (Cp) and concentrations at the effect site (Ce) are shown; all values are normalized to Cp at time 0. The dashed line shows Cp versus time following bolus administration. The solid lines demonstrate the effect of varying $k_{oe}$ on the time to peak Ce, the peak Ce, and the decline of Ce during recovery. With a higher $k_{oe}$, peak concentrations are attained more quickly; in addition, this earlier peak is greater because it is proportional to a greater simultaneous arterial plasma concentration. During recovery, the muscle with a higher $k_{oe}$ has a more rapid decline in its muscle relaxant concentration. (The shape of the plasma concentration versus time curve is based on published two-compartment data for vecuronium.)

licis—a faster equilibration and a greater resistance of the former compared to the latter. These findings can explain the clinical observation that the respiratory muscles recover more quickly than the adductor pollicis from paralysis induced by nondepolarizing muscle relaxants. First, our model suggests that muscle relaxants wash out from the respiratory muscles more rapidly than from the adductor pollicis (a result of their more rapid equilibration rate constant; fig. 3); thus, at any time during recovery, the muscle relaxant concentration in the respiratory muscles will have decreased relatively more from its peak value than in the adductor pollicis. Second, for any given concentration of muscle relaxant in the muscle, paralysis is less in the respiratory muscles. Thus, more rapid recovery of the respiratory muscles from paralysis results from both more rapid washout of muscle relaxant from these muscles during recovery and greater resistance of these muscles. The physiologic basis of the greater resistance of the respiratory muscles is unknown but might result from differences in receptor density in the postjunctional motor endplate.9

The expected finding of greater resistance of the respiratory muscles might be considered inconsistent with Donati et al.'s1,2 observation that some subjects developed 100% depression of the diaphragm or the laryngeal muscles but not of the adductor pollicis or the observation that patients given muscle relaxants stop breathing because their respiratory muscles are paralyzed, well before a peripheral nerve stimulator demonstrates significant neuromuscular blockade.3 This apparent inconsistency can be reconciled by considering the factors that influence peak neuromuscular effect. After a bolus dose of a muscle relaxant, the muscle with the more rapid equilibration develops its peak concentration earlier (fig. 3); in addition, peak concentration at the muscle group with more rapid equilibration is greater than that at the muscle group with the slower equilibration (peak effect compartment concentrations are proportional to simultaneous arterial concentrations—a peak concentration occurring later will correspond to a lower arterial concentration). Even if the muscle group with the more rapid equilibration were resistant (i.e., required a greater concentration to produce comparable effect), the greater peak concentration might offset this to produce a more intense peak effect (fig. 4). Conversely, during a steady-state infusion or during recovery from neuromuscular blockade, arterial concentration and concentrations at

Anesthesiology, V 80, No 2, Feb 1994
the two muscle groups are in equilibrium or pseudo-equilibrium, and the resistant muscle group consistently will demonstrate a lesser effect. Thus, more rapid equilibration of the respiratory muscles results in higher peak concentrations, producing paralysis earlier, and possibly of greater magnitude, compared to the adductor pollicis.

The reason for the more rapid equilibration of the respiratory muscles is unknown. In principle, if the effect of a drug is rapid once it binds to the receptor (as is believed to be the case for the neuromuscular effects of nondepolarizing muscle relaxants), then differences in the onset of paralysis should reflect differences in equilibration between input drug (presumably in arterial blood) and drug in the effect compartment. This equilibration is influenced by two factors, the partition coefficient between blood and the effect site, and either perfusion of the effect site or (capillary/cellular) permeability of this site (whichever is rate-limiting). Although no studies have related vecuronium's partition coefficient to its $k_{iso}$, Stanski et al. demonstrated that values for $k_{iso}$ for d-tubocurarine were consistent with known values for muscle perfusion and $d$-tubocurarine partitioning between plasma and skeletal muscle. This suggests that tissue uptake for muscle relaxants is perfusion-limited (rather than permeability-limited). Thus, our finding that the respiratory muscles equilibrate more rapidly than does the adductor pollicis is likely to result from either greater perfusion of the respiratory muscles or a lower partition coefficient for vecuronium in these tissues.

To our knowledge, no studies have compared perfusion of the respiratory muscles and the adductor pollicis. Although diaphragmatic blood flow has been measured, its marked variation with ventilatory activity limits the applicability of those results to the present study. In addition, no studies have examined the partitioning of muscle relaxants into the respiratory muscles; thus, why the respiratory muscles equilibrate more rapidly than does the adductor pollicis remains unknown. However, we speculate that different muscles do not differ sufficiently to have different partition coefficients, that uptake is primarily perfusion-limited, and hence, that differences in equilibration result from differences in perfusion. We recognize that our absolute values for $1/k_2$ are not biased estimates of the actual time constants for equilibration between arterial blood and the muscles studied (even assuming no post-receptor delays), because we did not sample arterial blood for vecuronium concentrations. However, additional simulations (not reported) show that the ratio of $k_{iso}$ for two muscle groups is similar to the ratio of $k_{iso}$. As we are interested only in the relative magnitude of equilibration delays for different muscle groups, any biases apply equally across muscle groups and should not, therefore, affect our conclusions.

The validity of our conclusions depends on the validity of our model. This can be evaluated in several ways. First, a data set containing both plasma concentration data and one or more effect measurements could be analyzed to determine IR$_{50}$ values with and without the plasma concentration data. The absence of plasma concentration data in the Donati et al. studies prevents such verification for those data. However, additional data sets with a single effect measurement exist for which this analysis can be performed. In appendix 2, we report such an analysis using plasma concentration and twitch tension data for vecuronium; these analyses demonstrate that IR$_{50}$ is similar regardless whether plasma concentration data are used in its determination. Second, plots of observed versus predicted effect should approximate each other well, as demonstrated in figure 1; in particular, the model accurately fits both the time to and the magnitude of peak effect for each muscle group, although figure 2 demonstrates minor systematic misfit, especially for the response of the adductor pollicis to the 40-µg/kg dose of vecuronium. Third, our parameter estimates for the adductor pollicis can be compared to those obtained previously using traditional study designs. Although IR$_{50}$(adductor pollicis) for vecuronium has not been reported, Cannon et al. determined the vecuronium infusion rate necessary to produce 90% twitch depression (IR$_{90}$) during fentanyl anesthesia. Their IR$_{90}$ (0.92 ± 0.37 µg·kg$^{-1}$·min$^{-1}$) is similar to the one that we estimate from our fit (1.0 µg·kg$^{-1}$·min$^{-1}$) during propofol/alfentanil anesthesia. Our present values for γ(adductor pollicis) are similar to those we reported previously. The present values for $k_2$(adductor pollicis) are greater than those we reported previously for $k_{iso}$, for vecuronium during anesthesia with nitrous oxide and halothane ($t_{1/2}/k_{iso} = 3.7$ min$^{15}$). There is at least one explanation, and possibly two, for this difference. First, simulations (not reported) reveal that when pharmacodynamic data are fit by models with fewer exponential constants than used to generate the data, resulting values for $k_2$ typically exceed those for the true $k_2$. We know that vecuronium pharmacokinetic/dynamic data gathered us-

Anesthesiology, V 80, No 2, Feb 1994
ing a design similar to that examined here require more than two exponential terms; hence, some of the bias we observe undoubtedly arises from this source. However, we reiterate that the bias for the various muscle groups should be similar (according to our simulations), and thus the ratios of $k_2$s are reasonable estimates of the ratios of $k_\infty$s. Second, Stanski et al. demonstrated that $k_\infty$ is greater during opioid-based anesthesia than during anesthesia with halothane, suggesting that values for difference between published $k_\infty$ values and the present values for $k_2$ also may be consistent, in part, with differences in study design.

We note two additional weaknesses of our model. First, we were unable to explain the dose-nonlinearity we observed (which also was seen in preliminary analyses in which data from individual subjects were analyzed separately), for which a scaling factor was needed. Additional analyses (not reported) suggest that this dose-nonlinearitly results from the data rather than from an artifact of the model, i.e., peak response to the 70-µg/kg dose was less than that predicted from the response to the 40-µg/kg dose. Investigations in which both plasma concentrations of the muscle relaxant and neuromuscular effects are measured may elucidate this anomaly.

A second weakness of our model is that the pharmacodynamic data appear to “need” only two exponential constants to account for all pharmacokinetic/dynamic time delays, whereas previous studies of vecuronium, whether administered by bolus or brief infusion and accompanied by plasma concentration measurements, have demonstrated the need for two or three pharmacokinetic exponents plus an exponential for the effect compartment delay. To address this issue, we performed simulations (not reported) in which pharmacodynamic data generated using typical parameters for vecuronium (i.e., three pharmacokinetic compartments) and “noise” of the same magnitude as in the Donati et al. studies were analyzed with and without pharmacokinetic data using the model used in the present study. Models with fewer than three exponential constants fit the data as well as models with the correct number of compartments by both visual inspection and goodness of fit. These findings suggest that, although two or three pharmacokinetic compartments may be needed to model the pharmacokinetics of vecuronium, when only “noisy” pharmacodynamic data are available (as in the Donati et al. studies), a more parsimonious model suffices. In addition, pharmacodynamic data were available for only a relatively short period (fig. 1)—multiple dosing regimens or an infusion of vecuronium could suggest a more complex model.

Traditionally, pharmacokinetic/pharmacodynamic modeling of muscle relaxants has required that plasma concentrations of the muscle relaxant be determined. Because this is costly and complicates the study design, a pharmacodynamic model that does not require values for plasma concentrations of the muscle relaxant might be desirable, if appropriate information could be obtained. The present analysis suggests that to determine the relative sensitivities of different muscles and to estimate the relative time delay between dose and effects at different muscle groups, the simpler design is adequate. However, the information obtained using the present methodology is limited compared to that provided by the more complex design. If relative pharmacodynamics of different effects are the object of the study (as in the present study), then the design can be useful. However, the proposed analysis does not provide the traditional results associated with pharmacokinetic or pharmacodynamic analyses.

In summary, we use a recently described approach to pharmacodynamic modeling in which effect data are analyzed independently of plasma concentration data. Using this model, we find that the rate of equilibration between plasma and effect is faster for the diaphragm and laryngeal muscles than for the adductor pollicis, a finding consistent with greater perfusion of the respiratory muscles. In addition, we find that the respiratory muscles are resistant to the effects of vecuronium compared to the adductor pollicis. The latter finding is consistent with the clinical observation that the respiratory muscles recover neuromuscular function more rapidly than do peripheral muscles. In addition, the pharmacodynamic model is able to explain the clinical observation that, after bolus doses of muscle relaxant, the respiratory muscles can develop more intense neuromuscular blockade than can the adductor pollicis during onset of paralysis, despite their resistance to neuromuscular blockade.

Appendix I: Derivation of the Pharmacodynamic Model

Although the pharmacodynamic model will be developed using a mechanistic justification, the reader should be aware that the model is empiric and that it should not, in itself, be overinterpreted. Assume
that, after bolus administration, the arterial plasma concentration of vecuronium (Cp) at time t can be expressed by the equation:

\[
C_p = \text{dose} \cdot \sum_{i=1}^{n} A_i e^{-\lambda_i t},
\]

where \(A_i\) is the (dose-normalized) intercept and \(\lambda_i\) the rate constant associated with each of \(n\) exponential constants. Next, assume that the concentration at the effect site takes time to equilibrate with \(C_p\). This can be modeled by postulating an effect compartment whose concentration \(C_e\) at time \(t\) is given by:

\[
C_e = k_{ee} \cdot \text{dose} \cdot \sum_{i=1}^{n} \frac{A_i (C_{p,0} - e^{-\lambda_i t})}{k_{ee} - \lambda_i},
\]

where \(k_{ee}\) is the rate constant for equilibration between plasma and the effect compartment. The leading \(k_{ee}\) in the right side of equation A2 causes \(C_e\) to equal \(C_p\) at steady state; this arbitrary scaling is required as \(C_e\) is never measured and the effect data provide no scale for \(C_e\). Next, assume that effect is related to \(C_p\) by:

\[
\text{Effect} = \frac{C_{e,0}}{1 + C_{e,0}}
\]

where \(C_{e,0}\) is the steady-state plasma concentration that results in 50% paralysis of the muscle, and \(\gamma\), the Hill factor, governs the sigmoidicity of the relationship between concentrations in the effect compartment and effect. By substituting the right side of equation A2 for \(C_e\) in equation A3, effect at time \(t\) can be expressed as a function of \(\text{dose}, A_i, \lambda_i, k_{ee}, \gamma, \) and \(C_{e,0}\):

\[
\text{Effect} = \frac{k_{ee} \cdot \text{dose} \cdot \sum_{i=1}^{n} \frac{A_i (C_{p,0} - e^{-\lambda_i t})}{k_{ee} - \lambda_i}}{k_{ee} \cdot \text{dose} \cdot \sum_{i=1}^{n} \frac{A_i (C_{p,0} - e^{-\lambda_i t})}{k_{ee} - \lambda_i}} + C_{e,0},
\]

When the pharmacokinetic model has only one compartment (\(n = 1\)), equation A4 reduces to:

\[
\text{Effect} = \frac{k_{ee} \cdot \text{dose} \cdot \frac{A_1 (C_{p,0} - e^{-\lambda_1 t})}{k_{ee} - \lambda_1}}{k_{ee} \cdot \text{dose} \cdot \frac{A_1 (C_{p,0} - e^{-\lambda_1 t})}{k_{ee} - \lambda_1}} + C_{e,0},
\]

where \(A_1\) and \(\lambda_1\) are renamed \(A\) and \(k_{\text{elimination}}\), respectively. (Analogous equations exist for multiple pharmacokinetic compartments.) If effect is measured but plasma concentrations are not, there is no unique best-fitting solution to equation A5, i.e., it is said to be unidentifiable. If each possible solution to equation A5 will have the same values for \(k_{\text{elimination}}, k_{ee}, \) and \(\gamma\) (these parameters govern shape), but \(C_{e,0}\) can vary as long as their ratio remains constant. Next, recognize that \(k_{\text{elimination}}/A = C_l\) (where \(C_l\) is drug clearance). Multiplying both the numerator and the denominator on the right side of equation A5 by \((k_{\text{elimination}}/A)^2 = C_l^2\) and assigning the name \(C_{e,0}\) the infusion rate that produces 50% effect at steady state) to the product of \(C_l\) and \(C_{e,0}\), eliminates one parameter (i.e., \(C_{e,0}\) and \(A\) together have been replaced by \(C_{e,0}\)) and changes equation A5 to:

\[
\text{Effect} = \frac{k_{ee} \cdot \text{dose} \cdot \frac{k_{\text{elimination}} \cdot (C_{p,0} - e^{-\lambda_1 t})}{k_{ee} - k_{\text{elimination}}}}{k_{ee} \cdot \text{dose} \cdot \frac{k_{\text{elimination}} \cdot (C_{p,0} - e^{-\lambda_1 t})}{k_{ee} - k_{\text{elimination}}}} + C_{e,0},
\]

This equation is formally identifiable, although as with any nonlinear regression, there is no unique solution, only a "best fit." Thus, the absence of measured plasma concentrations permits estimation of certain descriptive pharmacodynamic parameters—\(k_{ee}, k_{\text{elimination}}, \) and \(\gamma\)—but does not permit absolute identification of \(A\) or \(C_{e,0}\).

To facilitate understanding of this model, we propose one additional, purely notational change to equation A6. The rate constant \(k_{\text{elimination}}\) usually is interpreted mechanistically as the rate of change of the plasma concentration and the rate constant \(k_{ee}\) as the rate of equilibration of plasma and effect compartment concentrations. However, in the absence of measured plasma concentrations, there is no assurance that these rate constants retain their usual meanings; only that the equation as a whole accounts for the shape and duration of the effect versus time course. Therefore, we rename the two rate constants \(k_{\text{elimination}}\) becoming \(k_1\), and \(k_{ee}\) becoming \(k_2\). In fitting the data, we restrict \(k_1\) to be the same for all muscle groups so that \(k_2\) captures all differences in effect dynamics between muscle groups. Equation A6 now reaches its final form:

\[
\text{Effect} = \frac{k_2 \cdot \text{dose} \cdot \frac{k_1 \cdot (C_{p,0} - e^{-\lambda_1 t})}{k_2 - k_1}}{k_2 \cdot \text{dose} \cdot \frac{k_1 \cdot (C_{p,0} - e^{-\lambda_1 t})}{k_2 - k_1}} + C_{e,0},
\]

This equation can now be fit to effect versus time data to estimate \(k_1, k_2, IR_{50}, \) and \(\gamma\).

**Appendix 2: Additional Studies to Validate the Proposed Pharmacodynamic Model**

Although our approach to analyzing effect data in the absence of plasma concentration data has been validated for several drugs, similar validation for vecuronium (or other muscle relaxants) is necessary. This validation was performed using published data for the pharmacokinetics and adductor pollicis pharmacodynamics of vecuronium for five infants. We used NONMEM to fit a two-compartment pharmacokinetic model with an effect compartment to the plasma concentration and effect data. Resulting values for \(C_l\) and \(C_{e,0}\) then were used to estimate \(IR_{50}\) with plasma concentration data (\(B_{\text{max}}\), 290 \(\mu g \cdot kg^{-1} \cdot min^{-1}\)). In addition, we used NONMEM to fit our proposed pharmacodynamic model with two exponentials to the same data to determine \(IR_{50}\) without plasma concentration data (\(B_{\text{max}}\), 354 \(\mu g \cdot kg^{-1} \cdot min^{-1}\)). Using a likelihood profile analysis, these values do not differ significantly. Therefore, we conclude that the proposed pharmacodynamic model provides reasonable estimates of \(IR_{50}\) for vecuronium.
References


2. Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. Anesthesiology 75:870–875, 1990


