Pharmacodynamic Modeling of Vecuronium-induced Twitch Depression

Rapid Plasma–Effect Site Equilibration Explains Faster Onset at Resistant Laryngeal Muscles than at the Adductor Pollicis

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Background: After bolus doses of nondepolarizing muscle relaxants, the adductor pollicis recovers from paralysis more slowly than the diaphragm and the laryngeal adductors, suggesting that the adductor pollicis is more sensitive than the respiratory muscles to effects of those drugs. In contrast, during onset, the respiratory muscles are paralyzed more rapidly than the adductor pollicis, suggesting that the respiratory muscles are more sensitive than the adductor pollicis. To reconcile these apparently conflicting findings, we determined vecuronium’s pharmacokinetics and its pharmacodynamics at both the adductor pollicis and the laryngeal adductors.

Methods: Six volunteers were studied on two occasions during anesthesia with propofol. Mechanical responses to train-of-four stimulation were measured at the adductor pollicis and at the laryngeal adductors. Vecuronium (15–60 μg/kg) was given and arterial plasma samples were obtained from 0.5–60 min. Vecuronium doses differed by twofold on the two occasions. A pharmacokinetic model 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 relative sensitivities and rates of equilibration between plasma and effect site concentrations.

Results: The steady-state plasma concentration depressing laryngeal adductor twitch tension by 50% was approximately 1.5 times larger than that for the adductor pollicis. The equilibration rate constant between plasma and laryngeal adductor concentrations was about 1.5 faster than that between plasma and adductor pollicis concentrations. The Hill factor (γ) that describes the steepness of the laryngeal adductor concentration–effect relation was approximately 0.6 times that of the adductor pollicis.

Conclusions: More rapid equilibration between plasma and laryngeal adductor vecuronium concentrations explains why onset is more rapid at the laryngeal adductors than at the adductor pollicis. During recovery, both rapid equilibration and lesser sensitivity of the laryngeal adductors contribute to earlier recovery. (Key words: Measurement techniques; larynx. Neuromuscular relaxants: vecuronium. Pharmacodynamics: adductor pollicis; diaphragm; larynx; models. Respiratory effects: muscle relaxants.)

DURING recovery from the effects of nondepolarizing muscle relaxants, the diaphragm and the adductor muscles of the larynx recover before the adductor pollicis.1,2 This suggests that the respiratory muscles are resistant to the effects of muscle relaxants compared with the adductor pollicis. In contrast, during onset, the respiratory muscles become paralyzed earlier, and sometimes more intensely, than the adductor pollicis.1,2 This latter finding might suggest that the respiratory muscles are more sensitive than the adductor pollicis to the effects of muscle relaxants.3 Previously, we reconciled these apparently conflicting findings using an approach in which the pharmacodynamic characteristics of vecuronium were modeled in the absence of values for its plasma concentration.1 In the present study, we re-examine this issue using plasma concentration data. In addition, because our previous investigation indicated that the vecuronium infusion rate calculated to maintain 50% twitch depression of the adductor pollicis (IR50[adductor pollicis]) varied with the bolus dose administered (suggesting that vecuronium’s pharmacokinetic or pharmacodynamic characteristics varied with dose),
we studied each subject twice with different doses of the muscle relaxant.

**Methods**

After obtaining institutional review board approval and informed consent, we studied six right-hand-dominant volunteers, aged 22-55 yr, weighing 66-76 kg, and all classified as American Society of Anesthesiologists physical status 1. Each volunteer was studied on two occasions separated by 1 week. An intravenous catheter was placed in the left antecubital fossa to administer fluids and drugs, and a catheter was placed in the left radial artery to sample blood. Anesthesia was induced with \(3-5\) \(\mu g/kg\) fentanyl and \(2-3\) \(mg/kg\) propofol and maintained with \(150-200\) \(\mu g \cdot kg^{-1} \cdot min^{-1}\) propofol. After loss of consciousness, a left-sided double-lumen tracheal tube (Mallinckrodt Medical, St. Louis, MO) was positioned with the proximal cuff at the vocal cords; this positioned the distal cuff and the end of the tracheal tube above the carina. The distal cuff was inflated to seal the trachea, and both lungs were ventilated mechanically through the distal lumen. Normocapnia (end-tidal partial pressure of carbon dioxide, 30-35 mmHg) and normothermia (esophageal temperature >36.5°C) were maintained.

The proximal cuff of the tracheal tube was inflated to 20-30 mmHg; baseline pressure in the cuff varied by less than 2 mmHg during the experiment. Supramaximal square-wave train-of-four stimuli were administered at 2 Hz every 12 s to the recurrent laryngeal nerve at the notch of the thyroid cartilage. The evoked response was quantified by pressure changes in the proximal cuff of the tracheal tube.²

The right hand was placed in a padded grip and the thumb adducted. Preload was adjusted to 200-350 g; preload values for the two occasions differed less than 10%. Supramaximal square-wave train-of-four stimuli were administered at 2 Hz every 12 s to the right ulnar nerve via needle electrodes at the wrist, and evoked tension of the adductor pollicis was measured using a force transducer (Myotrace, Houston, TX).

The force signals of the adductor pollicis and laryngeal adductor twitch tensions were amplified (DC Bridge Signal Conditioner, Gould Electronics, Valley View, OH), digitized (NB-MIO-16, National Instruments, Austin, TX) on a Macintosh computer (Apple Computers, Cupertino, CA), and displayed (Lab View; National Instruments). The ratio of the first component (T1) of the train-of-four to its control value was recorded on a spreadsheet (Excel; Microsoft, Redmond, WA). Each train-of-four was recorded on a strip chart (TA240, Gould).

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 full recovery. On the first occasion, the vecuronium dose was 30 \(\mu g/kg\). Complete paralysis at the adductor pollicis and approximately 50% block at the laryngeal adductors developed in one participant; on his second occasion, he received 15 \(\mu g/kg\) vecuronium. The remaining participants received 60 \(\mu g/kg\) vecuronium on their second occasion. For each volunteer, both vecuronium doses were from the same manufacturing lot. Vecuronium was placed in solution less than 30 min before its administration and was given during 1-2 s.

Blood samples (5 ml each) were obtained before and 0.5, 1, 2, 3, 4, 5, 7, 10, 15, 20, 25, 30, 45, and 60 min after vecuronium administration. Samples were drawn over less than 5 s, the mid-point of the sampling period being the target sampling time. Samples were placed on ice immediately, and plasma was separated within 60 min. Plasma was stored at −70°C until vecuronium and 3-desacyetylvecuronium (the major metabolite of vecuronium) concentrations were determined by gas-liquid chromatography.³ This assay can detect concentrations of both vecuronium and 3-desacyetylvecuronium of 5 ng/ml with a 12% coefficient of variation at that concentration.

The pharmacokinetic/pharmacodynamic analysis had several components. First, we compared the plasma concentrations obtained for each of the doses of vecuronium. To compare the pharmacodynamics of vecuronium at the two muscle groups, we used both parametric and semiparametric approaches, with data from each individual and dose analyzed separately. To determine if the pharmacodynamics of vecuronium at the adductor pollicis varied with dose, we used a parametric approach in which adductor pollicis twitch tension data from each individual and dose were analyzed separately. We also used a semiparametric approach for pharmacodynamic data involving only the adductor pollicis muscle; data from both doses were analyzed simultaneously for each individual. All individual pharmacokinetic and pharmacodynamic analyses were performed using NONMEM.⁴

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¹ Beal SL, Sheiner LB. NONMEM Users Guides. San Francisco, NONMEM Project Group, UCSF. 1992

² Blumenfield D. Anesthesiology, V 86, No 3, Mar 1997

³ Blumenfield D. Anesthesiology, V 86, No 3, Mar 1997

⁴ Blumenfield D. Anesthesiology, V 86, No 3, Mar 1997

⁵ Blumenfield D. Anesthesiology, V 86, No 3, Mar 1997

⁶ Blumenfield D. Anesthesiology, V 86, No 3, Mar 1997

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Dose Linearity of Pharmacokinetics of Vecuronium

To determine whether the pharmacokinetics of vecuronium varied as a function of dose, we calculated for each subject the ratio of plasma concentrations for each sampling time (large dose/small dose). Mean values of this ratio at each sampling interval were compared with 2.0 (the ratio of the doses administered) using a one-sample t test; differences from the value 2.0 would suggest a pharmacokinetic nonlinearity as a function of dose.

Comparison of Laryngeal Adductors to Adductor Pollicis Using the Parametric Approach

Initial evaluations indicated that a three-compartment model was preferred (P < 0.05) over a two-compartment model to fit the vecuronium concentration versus time data; therefore, all subsequent analyses used three-compartment models. Because of limited information regarding disposition of 3-desacyctyvecuronium, it was assumed to distribute to a single compartment, the volume of which equaled vecuronium’s central compartment volume (Vc). The pharmacokinetic model allowed for metabolic conversion of vecuronium to 3-desacyctyvecuronium in the central compartment.

Based on previous pharmacokinetics and pharmacodynamics studies, we assumed that concentrations of vecuronium and 3-desacyctyvecuronium equilibrated between plasma and the effect compartment with the same rate constant (k[e]) and that 3-desacyctyvecuronium was 80% as potent as vecuronium. The relation between each effect (adductor pollicis, laryngeal adductors) and concentrations of vecuronium and its metabolite was described by the equation:

\[
\text{Effect} = \frac{C_{\text{active}}}{(C_{\text{active}} + C_{\text{m}}}^\gamma)\]

where \(C_{\text{active}}\) is the active concentration of the muscle relaxant in the effect compartment (the sum of vecuronium concentration and 0.8 × concentration of the metabolite), \(\gamma\) is the Hill factor that describes sigmoidicity (steepness) of the concentration-effect relation, and \(C_{\text{m}}\) is the steady-state plasma concentration of the muscle relaxant producing 50% effect. We defined the effect compartment as having a trivial volume (arbitrarily fixed at 0.001 × Vc) so as not to influence estimates of pharmacokinetic parameters.

Comparison of Laryngeal Adductors to Adductor Pollicis Using the Semiparametric Approach

One limitation to the parametric approach is that the compartmental model assumes that plasma concentrations decrease monotonically after bolus drug administration. However, Ducharme et al. found that arterial vecuronium concentrations increase during the initial 30 s after drug administration and then oscillate before decreasing monotonically. Therefore, even though the semiparametric model fits the observed vecuronium plasma concentration data well (fig. 1), it presumably misspecifies the vecuronium plasma concentration versus time course during the initial 30 s. A second limitation of the parametric approach is that it fails to account for peak concentrations of 3-desacyctyvecuronium 0.5–1.0 min after vecuronium administration, a result of the small quantity of 3-desacyctyvecuronium in the administered dose (personal communication, Mitchell Weinberger, Ph.D., Organon Inc., 1994). To address these problems, we modified a semiparametric approach described previously by Unadkat et al. We assumed that the plasma concentration of vecuronium could be described by linear interpolation of the preceding and subsequent measured values. For example, a measured vecuronium concentration of 150 ng/ml at 10 min and 100 ng/ml at 15 min would yield an interpolated 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 time versus time profile observed by Ducharme et al. 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-desacyctyvecuronium concentrations was then used in a pharmacodynamic analysis identical to that used in the parametric approach described earlier.

For each of the parametric and the semi-parametric approaches, we determined the relative sensitivities (ratio of \(C_{\text{m}}\) [laryngeal adductors] to \(C_{\text{m}}\) [adductor pol-
Comparison of the Parametric and Semiparametric Approaches

To determine whether the parametric and semiparametric analyses yielded different values for the pharmacodynamic parameters, we determined the ratio of values for \( k_{\text{r,}} \) (adductor pollicis), \( C_{\text{so}} \) (adductor pollicis), and \( \gamma \) (adductor pollicis) obtained from the parametric analyses to those obtained from the semiparametric analyses. Mean values of these ratios (\( n = 12 \)) were compared to 1.0 using a one-sample \( t \) test.

Dose-related Changes in the Pharmacodynamics of the Adductor Pollicis

To determine whether the pharmacodynamics of vecuronium at the adductor pollicis muscle varied as a function of dose, we used results from both parametric and semiparametric approaches. For the parametric approach, values for \( C_{\text{so}} \) (adductor pollicis) determined for each dose (see the section Comparison of Laryngeal Adductors to Adductor Pollicis with the Parametric Approach) were compared using a paired-sample \( t \) test.

For the semiparametric approach, data for adductor pollicis twitch tension for the two occasions (i.e., both doses) were analyzed simultaneously. Two analyses were performed for each individual: (1) Values for \( k_{\text{r,}} \), \( C_{\text{so}} \), and \( \gamma \) were assumed to be the same for both doses; and (2) values for \( k_{\text{r,}} \), \( C_{\text{so}} \), and \( \gamma \) were permitted to vary between doses.

These analyses suggested that \( k_{\text{r,}} \), \( C_{\text{so}} \), and/or \( \gamma \) varied between doses, as indicated by a marked improvement in the objective function and by visual inspection of the fits of predicted versus observed values. Therefore, results from the analyses in which \( k_{\text{r,}} \), \( C_{\text{so}} \), and \( \gamma \) were permitted to vary between doses were analyzed using a paired-sample \( t \) test to determine whether this dose-related effect was systematic. For example, did subjects consistently have a larger \( C_{\text{so}} \) with the larger dose?

Probability values less than 0.05 (two-tailed, adjusted for multiple comparisons) were assumed to be significant. Some statistical tests were performed after log transformation of the data. Values are reported as means ± SD.

Results

Dose Linearity of Pharmacokinetics of Vecuronium

Vecuronium plasma concentrations after the larger vecuronium dose were approximately twice those after
the smaller dose (fig. 2); mean values of the ratios of vecuronium concentrations with the two doses did not differ from 2.0 at any sampling time. Variability in the ratio of concentrations from the two doses decreased markedly by 2 min after drug administration. 3-Desacyetylvecuronium was detected on all occasions except in one participant given 15 μg/kg vecuronium and a different participant given 30 μg/kg vecuronium.

Comparison of Laryngeal Adductors to Adductor Pollicis with the Parametric Approach

The pharmacokinetic 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 subjects (fig. 1). However, for six of the ten occasions in which 3-desacyetylvecuronium was identified, the model failed to account for the early peak in 3-desacyetylvecuronium concentrations. Values for \( k_c \) and \( C_{50} \) were larger and \( \gamma \) smaller for the laryngeal adductors than for the adductor pollicis (table 1).

Comparison of Laryngeal Adductors to Adductor Pollicis with the Semiparametric Approach

The pharmacodynamic model fit the effect data well for both muscle groups for all subjects (fig. 3). Values for \( k_c \) and \( C_{50} \) were larger and \( \gamma \) smaller for the laryngeal adductors than for the adductor pollicis (table 2).

Comparison of the Parametric and Semiparametric Approaches

Values for \( k_c \) (adductor pollicis) were smaller and values for \( \gamma \) (adductor pollicis) larger with the parametric compared with the semiparametric analyses (table 3). \( C_{50} \) (adductor pollicis) did not differ between the parametric and semiparametric analyses.

Dose-related Changes in the Pharmacodynamics of the Adductor Pollicis

Values obtained from the parametric analyses showed a larger \( C_{50} \) (adductor pollicis) for the large dose than for the small dose. All participants had a larger \( C_{50} \) (adductor pollicis) for the large dose than for the small dose (fig. 4). The ratio of \( C_{50} \) (adductor pollicis) for the large dose to \( C_{50} \) (adductor pollicis) for the small dose averaged 1.28 (different from 1.0 by a one-sample t test).

Semiparametric analyses in which pharmacodynamic parameters were assumed to be identical for both doses failed to fit the pharmacodynamic data. Permitting \( k_c \), \( C_{50} \), and/or \( \gamma \) to vary between doses markedly improved

Table 1. Values (Mean ± SD) for the Pharmacodynamic Parameters Determined Using the Parametric (Compartmental) Approach

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Small Dose</th>
<th>Large Dose</th>
<th>Both Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 6</td>
<td>N = 6</td>
<td>N = 12</td>
</tr>
<tr>
<td>( k_c ) (adductor pollicis) (min⁻¹)</td>
<td>0.12 ± 0.07</td>
<td>0.12 ± 0.03</td>
<td>0.12 ± 0.05</td>
</tr>
<tr>
<td>( k_c ) (laryngeal adductors)/( k_c ) (adductor pollicis)</td>
<td>1.56 ± 0.37</td>
<td>1.49 ± 0.43</td>
<td>1.52 ± 0.38*</td>
</tr>
<tr>
<td>( C_{50} ) (adductor pollicis) (ng/ml)†</td>
<td>147 ± 60</td>
<td>186 ± 68</td>
<td>166 ± 64</td>
</tr>
<tr>
<td>( C_{50} ) (laryngeal adductors)/( C_{50} ) (adductor pollicis)</td>
<td>1.54 ± 0.40</td>
<td>1.47 ± 0.76</td>
<td>1.50 ± 0.58*</td>
</tr>
<tr>
<td>( \gamma ) (adductor pollicis)</td>
<td>11.0 ± 5.7</td>
<td>7.1 ± 1.9</td>
<td>9.1 ± 4.5</td>
</tr>
<tr>
<td>( \gamma ) (laryngeal adductors)/( \gamma ) (adductor pollicis)</td>
<td>0.73 ± 0.78</td>
<td>0.56 ± 0.13</td>
<td>0.64 ± 0.54*</td>
</tr>
</tbody>
</table>

Subjects were given small (30 μg/kg) or large (60 μg/kg) doses of vecuronium except for one subject given 15 μg/kg vecuronium on one occasion and 30 μg/kg vecuronium on the other.

* Different from 1.0 (P < 0.05).
† Doses differ (P < 0.05).

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LARYNGEAL ADDUCTOR

Discussion

We found that vecuronium equilibrates more rapidly with the laryngeal adductors than with the adductor pollicis and that the laryngeal adductors are more resistant than the adductor pollicis to its effects. Resistance of the respiratory muscles is widely cited as the explanation for their more rapid recovery compared with the adductor pollicis. This fails to explain the observation that immediately after vecuronium is given the respiratory muscles are paralyzed more rapidly than are the adductor pollicis, reach their peak effect earlier, and, sometimes, peak at greater depression than do the adductor pollicis. These findings can be reconciled by considering the influence of equilibration rates on vecuronium’s concentration at each effect site. During onset, the faster equilibration (larger $k_{eq}$) of the laryngeal adductors results in effect site concentrations much larger than those at the adductor pollicis (fig. 5). Even if the laryngeal adductors require a 30% greater concentration than the adductor pollicis for 50% effect, the markedly greater concentration at the laryngeal adductors during onset results in earlier onset and a greater magnitude of paralysis. During recovery, more rapid equilibration at the laryngeal adductors results in smaller concentrations at the laryngeal adductors than at the adductor pollicis. Coupled with the greater resistance of the laryngeal adductors, this results in markedly earlier recovery at the laryngeal adductors. Although we previously proposed that equilibration delays explain the different time course at different muscles, the present study uses plasma concentration data for vecuronium to support this contention.

An additional finding of our study, that the concentration–effect relation is less steep for the laryngeal adductors than for the adductor pollicis, is also considered. During onset, when concentration at each muscle group reaches 80% of its $C_{eq}$, the muscle with the smaller value for $\gamma$ (the laryngeal adductors) would display greater effect (28% vs. 15% in fig. 6, based on values for $\gamma$ in table 2). Because $k_{eq}$ of the laryngeal adductors is larger than that of the adductor pollicis, $C_{eq}$ is reached at laryngeal adductors earlier than at the adductor pollicis; thus the difference in $\gamma$ further favors early development of paralysis at the laryngeal adductors. However, once concentrations exceed $C_{eq}$ for each muscle, the smaller $\gamma$ for laryngeal adductors limits peak effect for that muscle.

Similar findings regarding the time course of paralysis of the laryngeal adductors versus the adductor pollicis

the fit for all participants ($P < 0.01$). All volunteers had a larger $C_{eq}$ (adductor pollicis) for the large dose than for the small dose; the ratio of $C_{eq}$ (adductor pollicis) for the large dose to $C_{eq}$ (adductor pollicis) for the small dose averaged 1.31 (different from 1.0 by a one-sample $t$ test).

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Table 2. Values (Mean ± SD) for the Pharmacodynamic Parameters Determined Using the Semiparametric (Noncompartmental) Approach

<table>
<thead>
<tr>
<th></th>
<th>Small Dose</th>
<th>Large Dose</th>
<th>Both Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>$k_{oe}(\text{adductor pollicis})$ (min⁻¹)</td>
<td>0.17 ± 0.08</td>
<td>0.14 ± 0.03</td>
<td>0.15 ± 0.06</td>
</tr>
<tr>
<td>$k_{oe}(\text{laryngeal adductors})/k_{oe}(\text{adductor pollicis})$</td>
<td>1.72 ± 0.49</td>
<td>1.51 ± 0.44</td>
<td>1.62 ± 0.46*</td>
</tr>
<tr>
<td>$C_{50}(\text{adductor pollicis})$ (ng/ml)†</td>
<td>141 ± 56</td>
<td>188 ± 71</td>
<td>165 ± 66</td>
</tr>
<tr>
<td>$\gamma(\text{laryngeal adductors})/C_{50}(\text{adductor pollicis})$</td>
<td>1.55 ± 0.34</td>
<td>1.52 ± 0.87</td>
<td>1.53 ± 0.63*</td>
</tr>
<tr>
<td>$\gamma(\text{laryngeal adductors})/\gamma(\text{adductor pollicis})$</td>
<td>8.7 ± 5.1</td>
<td>6.6 ± 1.7</td>
<td>7.6 ± 3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects were given small (30 µg/kg) or large (60 µg/kg) doses of vecuronium except for one subject given 15 µg/kg vecuronium on one occasion and 30 µg/kg vecuronium on the other.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Different from 1.0 (P &lt; 0.05).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>† Doses differ (P &lt; 0.05).</td>
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</tbody>
</table>

have been reported for mivacurium, rocuronium, and succinylcholine and presumably result from similar differences between the adductor pollicis and the laryngeal adductors in sensitivity and equilibration rates as seen with vecuronium. However, only one study examined these issues using pharmacokinetic/pharmacodynamic modeling with plasma concentration data: Plaud et al. studied rocuronium using a design similar to ours, except that each individual was studied only once. They reported that rocuronium’s ratio of values for $k_{oe}(\text{laryngeal adductors})/k_{oe}(\text{adductor pollicis})$ is 1.55, a value similar to what we determined for vecuronium (1.52 and 1.62 for the parametric and semiparametric approaches, respectively). Plaud et al. observed that $C_{50}$ for the laryngeal adductors is 1.73 times as large as that for the adductor pollicis, a value slightly larger than that for vecuronium that we report here (1.50 and 1.53 for the parametric and semiparametric approaches, respectively). Plaud et al. also reported that $\gamma$ was 1.5 times smaller for the laryngeal adductors than for the adductor pollicis, a finding similar to ours.

Two factors simplified Plaud et al.’s pharmacokinetic/pharmacodynamic analysis compared with ours. First, unlike vecuronium, rocuronium’s metabolites are assumed to have no neuromuscular activity; modeling vecuronium’s metabolite confounded our pharmacokinetic and pharmacodynamic analysis by requiring us to use historical data about the relative potency and equilibration rates for vecuronium’s metabolites. Second, Plaud et al. gave rocuronium as a brief infusion, rather than as a bolus in the present study. It is likely that their brief infusion minimized the impact of recirculatory peaks, permitting them to use a compartmental model similar to the model used in our parametric approach. However, we chose to reproduce the bolus study design reported previously by Donati et al. to increase the likelihood of observing any dose-related changes in pharmacokinetics or pharmacodynamics. To address the problem of model misspecification resulting from recirculatory peaks, we evaluated both compart-

Table 3. Ratio (Mean ± SD) of Pharmacodynamic Parameters Determined from the Parametric Analyses to Those from the Semiparametric Analyses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{oe}(\text{adductor pollicis})$</td>
<td>0.78 ± 0.18*</td>
</tr>
<tr>
<td>$C_{50}(\text{adductor pollicis})$</td>
<td>1.00 ± 0.07</td>
</tr>
<tr>
<td>$\gamma(\text{adductor pollicis})$</td>
<td>1.19 ± 0.25*</td>
</tr>
</tbody>
</table>

* Different from 1.0 (P < 0.05).

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Fig. 4. Values for the concentration producing 50% effect on the adductor pollicis for the two doses are shown. Lines connect the two values obtained from each individual in the parametric analyses.
mental (parametric) and noncompartmental (semiparametric) approaches. Despite the parametric approach
presumably describing vecuronium concentrations poorly during the initial 30 s after drug administration,
values for $C_{50}$ (adductor pollicis) and values for the ratios of $k_0$, $C_{50}$, and $\gamma$ for the two muscle groups were
similar with the two approaches. However, values for $k_0$ and $\gamma$ differed slightly between the two analytic
approaches, presumably because of model misspecification with the compartmental approach.

Our study was designed to replicate those of Donati et al.\*,** with plasma sampling added to determine vecuronium concentrations. Whereas Donati et al. selected vecuronium doses of 40 and 70 $\mu$g/kg, we chose smaller
doses at 30 and 60 $\mu$g/kg to increase the time between latency and maximal twitch depression, thereby
increasing our ability to model pharmacodynamics. Complete twitch depression developed in one volunteer
with the 30 $\mu$g/kg dose of vecuronium (this person had the smallest values for $C_{50}$ (adductor pollicis) for both
doses; fig. 4). Had this subject received 60 $\mu$g/kg vecuronium, complete twitch depression might have been protracted. Therefore, we selected a smaller vecuronium dose (15 $\mu$g/kg, also two times different from the original
dose) for the second dose.

One other difference from the technique described by Donati et al.\*,** is our use of a tracheal tube with two
cuffs; that is, a double-lumen tube. Because the tracheal tube was positioned with the distal cuff in the trachea
(rather than in a bronchus) and we ventilated only through the distal lumen, the distal cuff isolated the
proximal cuff (now used only for monitoring) from pressure changes during mechanical ventilation. This
eliminated the respiratory artifact reported by Donati et al.,\*,** thereby improving the signal-to-noise ratio and
permitting on-line data acquisition. In addition, because the proximal cuff was not used to seal the trachea, its
baseline pressure could be adjusted to optimize the laryngeal twitch signal. Fixation of the tracheal tube by
the distal cuff also increases stability, thereby minimizing the likelihood that subtle changes in tracheal tube
position will alter the resulting signal.

By replicating most conditions of the studies by Donati et al. and by studying each participant twice, we
found that $C_{50}$ (adductor pollicis) varied as a function of dose. Previously, when similar data for adductor pollicis
twitch tension were analyzed in the absence of plasma concentration data, we reported that $IR_{50}$ (adductor pollicis)
was 42% larger with a vecuronium dose of 70 $\mu$g/kg compared with a dose of 40 $\mu$g/kg.\* Assuming that
vecuronium’s pharmacokinetic characteristics were linear over this small range of doses, we previously attributed
the dose-related differences in $IR_{50}$ (adductor pollicis) to dose-related differences in pharmacodynamics
(presumably in $C_{50}$ (adductor pollicis)), rather than to nonlinearity in pharmacokinetics (e.g., clearance).
Results of the present study are consistent with that hypothesis—in the parametric analyses, $C_{50}$ (adductor pollicis)
licis) was 28% larger with the large dose than with the small dose (and vecuronium concentration values with the larger dose were, as expected, twice those with the smaller dose). We cannot explain this dose-related change in $C_{50}$; additional studies are needed to demonstrate whether it results from dose-related changes in neuromuscular junction sensitivity, local effects at the neuromuscular junction, or is an artifact of modeling. It is unlikely that nonlinear protein binding of vecuronium would explain our findings: A larger dose would yield larger initial plasma concentrations and larger unbound concentrations, thereby producing a smaller $C_{50}$, contrary to our findings. If the dose-related difference in pharmacodynamics is real (i.e., not a modeling artifact), it suggests that the clinical response to vecuronium should not vary as expected as a function of dose; however, no clinical evidence supports this supposition.

In summary, we report pharmacokinetic/pharmacodynamic modeling of the differences in sensitivity and rates of equilibration of the adductor pollicis and the laryngeal adductors. Unlike a previous study in which we examined this issue in the absence of plasma concentration data, the present analysis uses more traditional pharmacokinetic/pharmacodynamic approaches. We confirm our previous observation that the rate of equilibration between plasma and effect is faster for the laryngeal adductors than for the adductor pollicis. We also confirm that the laryngeal adductors are resistant to the effects of vecuronium compared with the adductor pollicis, requiring a steady-state vecuronium concentration of approximately 1.5 times as large to depress twitch tension by 50%. 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 can explain the clinical observation that, after bolus doses of muscle relaxant, the respiratory muscles develop more intense neuromuscular blockade than do the adductor pollicis during onset of paralysis, despite their resistance to neuromuscular blockade. Finally, we replicate our previous finding of a dose-related change in vecuronium’s pharmacodynamics, a finding that warrants additional study.

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References

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