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

Pharmacodynamic Modeling without Plasma Concentrations

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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_{effect}) is a function of the plasma concentration *versus* time curve and a rate constant for equilibration between plasma and the neuromuscular junction (k_{e0}); 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 $1/k_{e0}$) 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 then can 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:diaphragm:adductor pollicis was 1.4:1.2:1; for the equilibration 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

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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[4] 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.*[1,2] 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.[5] 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 (IR_{50}): IR_{50} is the product of plasma clearance (Cl) and the steady-state plasma concentration that produces 50% effect (C_{50})
2. the time constant for equilibration of effect (k_2, equivalent to k_{e0} in the traditional effect compartment model[6])
3. the Hill factor (γ) that governs the sigmoidicity of the relationship between concentrations in the effect compartment and effect[6]
4. the pharmacokinetic time constant (k_1)

The model cannot determine usual pharmacokinetic (distribution or elimination half-lives, plasma clearance, volumes of distribution) or pharmacodynamic (C_{50}) parameters, unless vecuronium plasma concentrations are measured.

The effect data were modeled using NONMEM, a program to analyze population pharmacokinetic/pharmacodynamic data.[7] 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—IR_{50}, k_2, and γ for each of the three muscles and k_1. All models also contained four parameters for interindividual variation, one each for k_1, IR_{50}, k_2, and γ (*i.e.*, we assumed that the magnitude of interindividual variation for IR_{50}, k_2, and γ was the same for all muscles).

Next, we evaluated whether separate values for IR_{50}, k_2, and γ were needed for each of the three muscle groups, *i.e.*, would a simpler model in which the same IR_{50}, k_2, or γ was used for two or three muscle groups be adequate. The need for separate values for IR_{50}, k_2, and γ for each muscle group was determined by comparing two models, one in which separate values were used (*e.g.*, IR_{50}(larynx) and IR_{50}(diaphragm)) to a model with a single value (IR_{50}(respiratory muscles)). If the model with additional parameters was not statistically required by the likelihood ratio test[8] (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 $IR_{50} = Cl \cdot C_{50}$ (and 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

$$\frac{IR_{50}\text{ (diaphragm)}}{IR_{50}\text{ (adductor pollicis)}}.$$

Therefore, if IR_{50} (diaphragm) exceeds IR_{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_2s enabled us to determine whether equilibration varied between muscle groups (equivalent to comparisons of k_{e0}); comparisons of γ 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 IR_{50} to vary with dose, *i.e.*, IR_{50}(70 μg/kg) = dose factor · IR_{50}(40 μg/kg); the model was similarly improved by allowing k_1 to vary with dose. Thus, our final model also included a dose factor for IR_{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:

$$k_{1_i} = k_1 \cdot (1 + \eta_{1_i}),$$

where k_{1_i} is the estimate for the pharmacokinetic rate constant for the i^{th} individual, k_1 is the typical value for the population, and η_{1_i} is a random variable with mean 0. Interindividual variability for IR_{50}, γ, and k_2 were modeled in a similar manner, assuming the same proportionality for all muscles. Residual intraindividual variance (variance of the effect measurements) was modeled as:

$$\text{Effect}_{ij}\text{ (measured)} = \text{Effect}_{ij}\text{ (actual)} + \varepsilon_{ij},$$

where Effect_{ij} is the j^{th} value for the i^{th} subject, and ε_{ij} is the associated error.

Results

Models in which IR_{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 IR_{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, γ was identical for the two respiratory muscle groups. Therefore, our final model contained one pharmacokinetic parameter common to the muscle groups (k_1), IR_{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 γ, and the dose factor for IR_{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

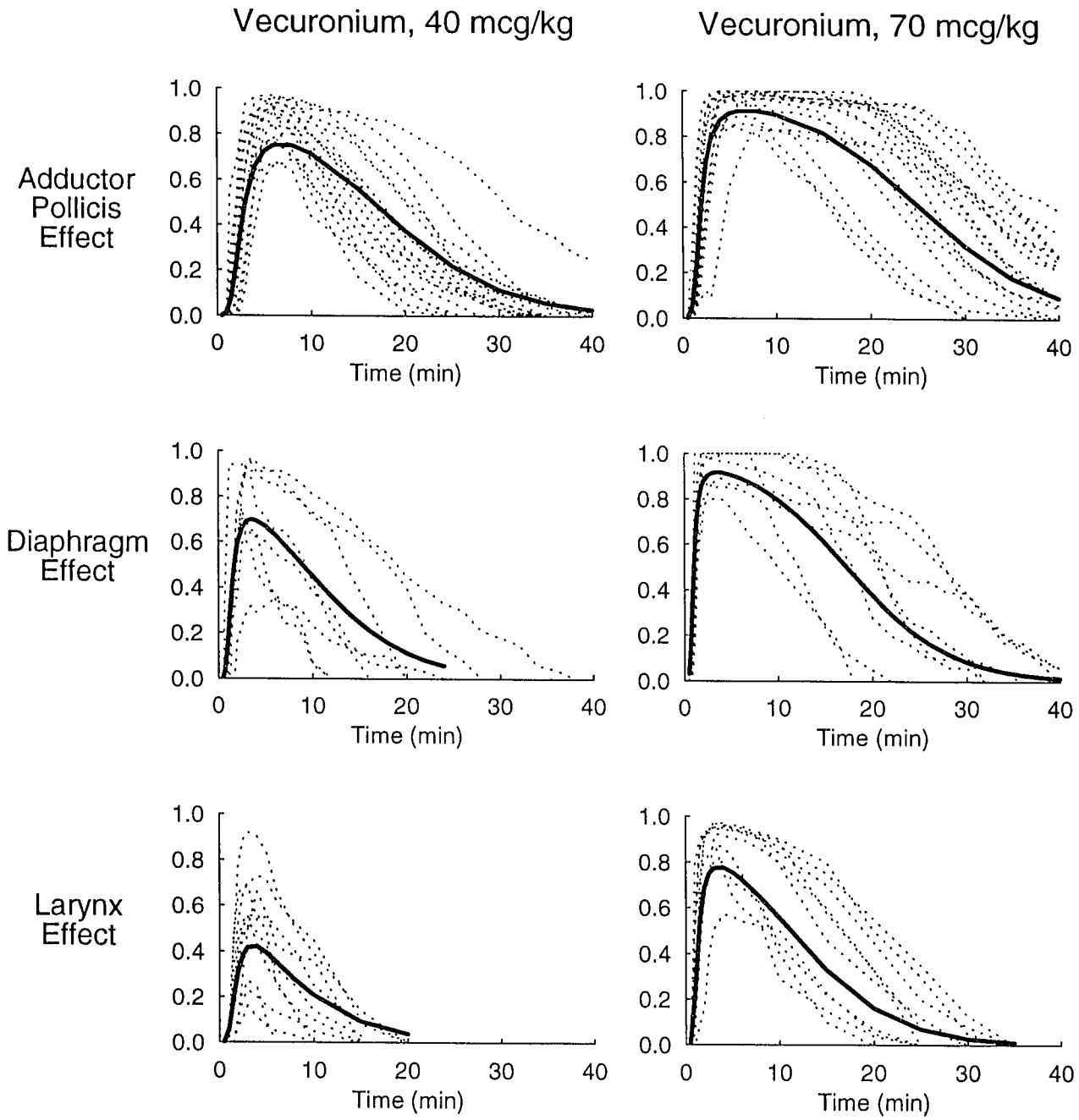

Fig. 1. Data for responses of the adductor pollicis, the diaphragm, and the laryngeal muscles to vecuronium are shown. Dashed lines display the data from each subject. The solid line represents the time course of paralysis for the "typical" individual, *i.e.*, the individual whose pharmacokinetic/pharmacodynamic parameters are those estimated by the model.

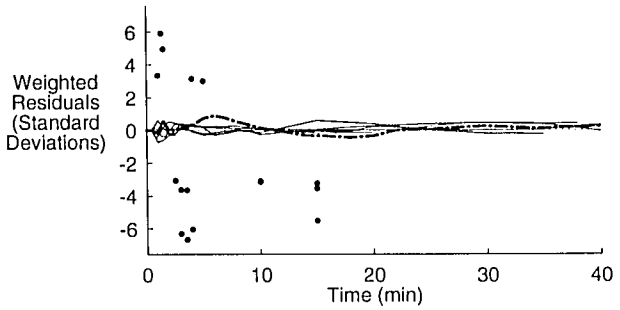

Fig. 2. Weighted residuals (*i.e.*, differences between observed and fitted values, normalized to units equivalent to standard deviations) are plotted against time. Circles represent the 15 weighted residual values exceeding ±3 (of a total of 1,633 data points). Lines summarize the remaining values for each of the muscle groups and doses, represented by a smoothed plot obtained using Supersmoother (see text). After 2.5 min, systematic deviations from the thin dashed line at zero (suggesting model misspecification) are small except for the adductor pollicis for the 40-μg/kg dose (shown with a thick dashed line).

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 Supersmoother.†† These plots suggest that the model fits the effect 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).

†† Modern Regression Methods. S-Plus User's Manual, Version 3.0. Seattle, Statistical Sciences, 1991, pp 1–46.

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

	Population Mean	Standard Error (Percent of Population Mean)
k_1 (min^{-1})	0.025	14
k_2 (adductor pollicis, min^{-1})	0.44	14
k_2 (respiratory muscles)/k_2 (adductor pollicis)*	2.48	6
IR_{50} (adductor pollicis, 40-μg/kg dose, $\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.692	9
IR_{50} (70-μg/kg dose)/IR_{50} (40-μg/kg dose)	1.42	5
IR_{50} (diaphragm)/IR_{50} (adductor pollicis)*	1.17	2
IR_{50} (larynx)/IR_{50} (adductor pollicis)†	1.36	4
γ (adductor pollicis)	6.16	13
γ (respiratory muscle)/γ (adductor pollicis)*	1.23	4
Time to peak effect at adductor pollicis (min)	6.89	ND
Time to peak effect at respiratory muscles (min)	3.53	ND

* Respiratory muscles differ from adductor pollicis ($P < 0.001$).

† Laryngeal muscles differ from adductor pollicis, diaphragm ($P < 0.001$).

ND = not determined.

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 pol-

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

	Interindividual Variation (% of Population Mean)
k_1	54
k_2	41
IR_{50}	41
γ	42

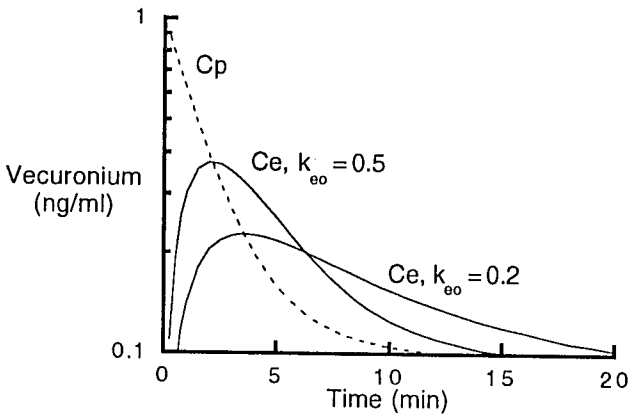

Fig. 3. Simulations of plasma concentrations (Cp) and concentrations at the effect site (Ce) are shown; all values are normalized to Cp at time 0. The dashed line shows Cp *versus* time following bolus administration. The solid lines demonstrate the effect of varying k_{eo} on the time to peak Ce, the peak Ce, and the decline of Ce during recovery. With a higher k_{eo}, 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_{eo} 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.*'s[1,2] 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

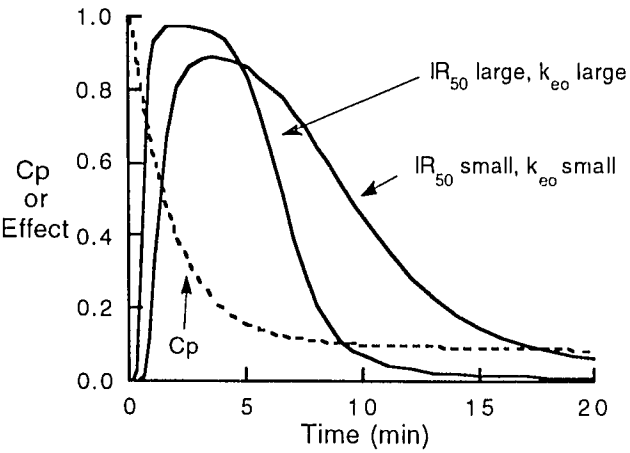

Fig. 4. Simulations of plasma concentrations (dashed line) and effect in two muscles with different sensitivities (solid lines) to vecuronium are plotted against time. The "resistant" muscle (*e.g.*, the diaphragm) has a greater IR_{50} (by a factor of 1.2) and a greater k_{eo} (by a factor of 2.5) compared to the "sensitive" adductor pollicis. Note that the resistant muscle group develops more intense neuromuscular blockade because of the greater k_{eo}. (The shape of the plasma concentration *versus* time curve is based on published two-compartment data for vecuronium.)

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[10]), 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_{e0}, Stanski *et al.*[11] demonstrated that values for k_{e0} 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[12,13] 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_2s for two muscle groups is similar to the ratio of k_{e0}s. 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.*[14] determined the vecuronium infusion rate necessary to produce 90% twitch depression (IR_{90}) during fentanyl anesthesia. Their IR_{90} (0.92 ± 0.37 $\mu g \cdot kg^{-1} \cdot min^{-1}$) is similar to the one that we estimate from our fit (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) during propofol/alfentanil anesthesia. Our present values for γ(adductor pollicis) are similar to those we reported previously.[15] The present values for k_2(adductor pollicis) are greater than those we reported previously for k_{e0} for vecuronium during anesthesia with nitrous oxide and halothane ($t_{1/2}k_{e0} = 3.7$ 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_{e0}. We know that vecuronium pharmacokinetic/dynamic data gathered us-

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_2s are reasonable estimates of the ratios of k_{e0}s. Second, Stanski *et al.*[11] demonstrated that k_{e0} is greater during opioid-based anesthesia than during anesthesia with halothane, suggesting that values for difference between published k_{e0} 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-nonlinearity 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 1: 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:

$$Cp = dose \cdot \sum_{i=1}^{n} A_i e^{-\lambda_i t}, \quad (A1)$$

where A_i is the (dose-normalized) intercept and λ_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 Cp. This can be modeled by postulating an effect compartment whose concentration Ce at time t is given by:

$$Ce = k_{e0} \cdot dose \cdot \sum_{i=1}^{n} \frac{A_i \cdot (e^{-\lambda_i t} - e^{-k_{e0} t})}{k_{e0} - \lambda_i}, \quad (A2)$$

where k_{e0} is the rate constant for equilibration between plasma and the effect compartment.[5] The leading k_{e0} in the right side of equation A2 causes Ce to equal Cp at steady state; this arbitrary scaling is required as Ce is never measured and the effect data provide no scale for Ce. Next, assume that effect is related to Cp by:

$$Effect = \frac{Ce^{\gamma}}{Ce^{\gamma} + C_{50}^{\gamma}}, \quad (A3)$$

where C_{50} is the steady-state plasma concentration that results in 50% paralysis of the muscle, and γ, the Hill factor, governs the sigmoidicity of the relationship between concentrations in the effect compartment and effect.[5] By substituting the right side of equation A2 for Ce in equation A3, effect at time t can be expressed as a function of dose, A_i, λ_i, k_{e0}, γ, and C_{50}:

$$Effect = \frac{\left[k_{e0} \cdot dose \cdot \sum_{i=1}^{n} \frac{A_i \cdot (e^{-\lambda_i t} - e^{-k_{e0} t})}{k_{e0} - \lambda_i}\right]^{\gamma}}{\left[k_{e0} \cdot dose \cdot \sum_{i=1}^{n} \frac{A_i \cdot (e^{-\lambda_i t} - e^{-k_{e0} t})}{k_{e0} - \lambda_i}\right]^{\gamma} + C_{50}^{\gamma}}. \quad (A4)$$

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

$$Effect = \frac{\left[k_{e0} \cdot dose \cdot \frac{A \cdot (e^{-k_{elimination} t} - e^{-k_{e0} t})}{k_{e0} - k_{elimination}}\right]^{\gamma}}{\left[k_{e0} \cdot dose \cdot \frac{A \cdot (e^{-k_{elimination} t} - e^{-k_{e0} t})}{k_{e0} - k_{elimination}}\right]^{\gamma} + C_{50}^{\gamma}}, \quad (A5)$$

where A_1 and λ_1 are renamed A and $k_{elimination}$, 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.‡‡ Each possible solution to equation A5 will have the same values for $k_{elimination}$, k_{e0}, and γ (these parameters govern shape), but A and C_{50} can assume any values as long as their ratio remains constant. Next, recognize that $k_{elimination}/A = Cl$ (where Cl is drug clearance). Multiplying both the numerator and the denominator on the right side of equation A5 by $(k_{elimination}/A)^{\gamma} = Cl^{\gamma}$ and assigning the name IR_{50} (the infusion rate that produces 50% effect at steady state) to the product of Cl and C_{50} eliminates one parameter (*i.e.*, C_{50} and A together have been replaced by IR_{50}) and changes equation A5 to:

$$Effect = \frac{\left[k_{e0} \cdot dose \cdot \frac{k_{elimination} \cdot (e^{-k_{elimination} t} - e^{-k_{e0} t})}{k_{e0} - k_{elimination}}\right]^{\gamma}}{\left[k_{e0} \cdot dose \cdot \frac{k_{elimination} \cdot (e^{-k_{elimination} t} - e^{-k_{e0} t})}{k_{e0} - k_{elimination}}\right]^{\gamma} + IR_{50}^{\gamma}}. \quad (A6)$$

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—IR_{50}, k_{e0}, and γ—but does not permit absolute identification of A or C_{50}.

To facilitate understanding of this model, we propose one additional, purely notational change to equation A6. The rate constant $k_{elimination}$ usually is interpreted mechanistically as the rate of change of the plasma concentration and the rate constant k_{e0} 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, $k_{elimination}$ becoming k_1, and k_{e0} 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:

$$Effect = \frac{\left[k_2 \cdot dose \cdot \frac{k_1 \cdot (e^{-k_1 t} - e^{-k_2 t})}{k_2 - k_1}\right]^{\gamma}}{\left[k_2 \cdot dose \cdot \frac{k_1 \cdot (e^{-k_1 t} - e^{-k_2 t})}{k_2 - k_1}\right]^{\gamma} + IR_{50}^{\gamma}}. \quad (A7)$$

This equation can now be fit to effect *versus* time data to estimate k_1, k_2, IR_{50}, and γ.

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,[4] 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.[15] We used NONMEM to fit a two-compartment pharmacokinetic model with an effect compartment[5] to the plasma concentration and effect data. Resulting values for Cl and C_{50} then were used to estimate IR_{50} with plasma concentration data (IR_{50with}), 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 ($IR_{50without}$), 354 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Using a likelihood profile analysis,[16] these values do not differ significantly. Therefore, we conclude that the proposed pharmacodynamic model provides reasonable estimates of IR_{50} for vecuronium.

‡‡ If both the numerator and denominator of the right side of equation A5 are divided by A^{γ}, the constant in the denominator becomes $(C_{50}/A)^{\gamma}$ and C_{50} and A are indistinguishable (any change in A can be compensated for by a proportional change in C_{50}).

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