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Pharmacodynamic Modeling of Muscle Relaxants

Effect of Design Issues on Results

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Background: **Pharmacodynamic studies of muscle relaxants use different dosing regimens (such as administration by bolus *vs.* infusion and doses that produce complete *vs.* incomplete paralysis). The authors used published data to evaluate the effect of modeling assumptions on pharmacodynamic estimates.**

Methods: **The authors used a pharmacokinetic–pharmacodynamic dataset in which patients received cisatracurium, 75 or 300 μg/kg (1.5 or 6 × ED_{95}), to generate plasma concentration (Cp) and twitch depression (effect) curves. They then evaluated the impact of the following: assuming that Cp decreased monotonically *versus* increasing initially before decreasing monotonically; misrecording effect data by 6 s or less; and doses targeting incomplete *versus* complete paralysis. Parameters evaluated were the steady state Cp depressing twitch tension 50% (C_{50}) and the rate constant for equilibration between plasma and effect site concentrations (k_{e0}).**

Results: **With the large dose, increasing the time at which Cp peaked from 0.0 to 1.5 min decreased C_{50} and increased k_{e0} markedly; with the small dose, changes in both were small. Misrecording the timing of effect had a larger impact with the large dose compared with the small dose. Doses smaller than ED_{50} or those producing prolonged, complete twitch depression yielded biased and variable estimates.**

Conclusion: **The erroneous assumption that Cp decreases monotonically after bolus administration affects accuracy of pharmacodynamic estimates with doses producing rapid, complete twitch depression. Other errors (*e.g.*, misrecording the time of drug administration) impact on pharmacodynamic estimates, particularly with large doses. The authors' findings suggest that investigators performing neuromuscular (and other) pharmacodynamic studies should carefully consider the impact of study design on their parameter estimates.**

IN the 1970s, Hull *et al.*[1] and Sheiner *et al.*[2] proposed that the relation between plasma concentration (Cp) and effect for muscle relaxants needed to account for the time lag between concentrations in plasma and those at the effect site. Sheiner *et al.*[2] administered *d*-tubocurarine by infusion, typically achieving less than complete twitch depression, and suggested that effect data at complete twitch depression contribute little information to the estimation of the pharmacodynamic parameters. Pharmacodynamic modeling has since been applied to many muscle relaxants as well as other anesthetic and nonanesthetic drugs. Some investigators replicate the design of Sheiner *et al.*,[2] whereas others do not.

We were concerned that these design issues (administration by infusion *vs.* bolus, magnitude of dose) might affect the results of pharmacodynamic analyses. One issue, mode of administration, has been addressed previously: Zhu *et al.*[3] demonstrated that for one muscle relaxant (doxacurium), administration by bolus *versus* infusion yielded the same pharmacodynamic estimates. However, several studies[4–7] reported that the effect site concentration depressing twitch tension 50% (C_{50}) varies as a function of dose. We were concerned that the results (or at least some portion thereof) of two of these studies[4,7] might be an artifact of the analysis: these studies gave a bolus rather than an infusion of the muscle relaxant, obtained few Cp measurements before twitch depression was complete, and assumed that Cp of the muscle relaxant decreased monotonically after its administration.

To address whether C_{50} varying with dose could be an artifact of the assumptions of the analysis, we used published pharmacokinetic and pharmacodynamic values[4] to simulate the Cp of a muscle relaxant and the resulting twitch depression. We examined whether a pharmacokinetic model that assumes that concentration peaks instantly (*i.e.*, at 0.0 min) after drug administration and then decreases monotonically (as described by a sum of exponential terms) yields the same pharmacodynamic parameters as a model that assumes that concentration peaks later (as is known to be true).

We also were concerned about the effect of other design and analysis issues in studies of muscle relaxants on the results of a pharmacodynamic analysis. Using the same simulated dataset, we explored two additional issues. First, we examined the magnitude of influence that a systematic 3- or 6-s misspecification of the timing of the effect data has on the resulting pharmacodynamic parameters. Second, we examined whether the magnitude of the administered dose and the resulting peak effect (ranging from 20% twitch depression to ablated twitch for a prolonged period) affect reliability of the pharmacodynamic estimates.

Methods

Recreation of Dataset

Our simulations were based on an investigation by Bergeron *et al.*,[4] who gave bolus doses of cisatracurium ranging from 75 to 300 μg/kg (approximately 1.5–6.0 times the ED_{95} reported in adults during barbiturate,

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N_2O–opioid anesthesia.[8,9] Bergeron *et al.*[4] sampled arterial blood at 1, 2, 3, 4, and 6 min after bolus administration of cisatracurium, followed by increasing intervals until 480 min. Their pharmacokinetic analysis was based on a two-compartment model that assumed that cisatracurium Cp peaked immediately after bolus administration and then decreased monotonically.

Because Bergeron *et al.*[4] did not report individual Cp and twitch tension data, we reconstructed their Cp and effect data for the 75- and 300-μg/kg doses based on their publication. We used their mean pharmacokinetic parameters to simulate a single Cp-*versus*-time curve (at intervals of 3 s) for each of the 75- and 300-μg/kg doses, assuming monotonic decay. These Cp-*versus*-time curves and the values of Bergeron *et al.*[4] for each dose for the equilibration rate constant (k_{e0}) between Cp and those at the effect site for each dose were then used to simulate concentrations of cisatracurium (Ce) at the effect site (the neuromuscular junction). The resulting values of Ce and the values of Bergeron *et al.*[4] for C_{50} and the Hill factor (γ) governing the sigmoidicity of the concentration–effect relation for each dose were then used to simulate the resulting twitch depression (effect) data.

To evaluate whether these simulated effect data were consistent with those obtained clinically by Bergeron *et al.*,[4] we determined the time to 98% twitch depression and compared it to the value for onset of Bergeron *et al.*[4]. Our values for time to 25 and 75% twitch recovery for each of the two doses were compared to those of Bergeron *et al.*[4]

Varying Time at Which Plasma Concentration Peaks

The time at which cisatracurium Cp peaks after bolus administration is not known. Previous studies show that Cp of vecuronium[10] and atracurium[11] peaks approximately 0.6 min (range, 0.4–0.9 min) after their bolus administration. Therefore, we tested seven additional models in which cisatracurium's Cp peaked at 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, and 1.5 min after its bolus administration. To create these Cp-*versus*-time curves, we assumed that the model with monotonic decay of Cp yielded accurate values for Cp at all times after Cp peaked (fig. 1); we also assumed that Cp increased in a linear manner from time 0.0 min to the time of its peak.

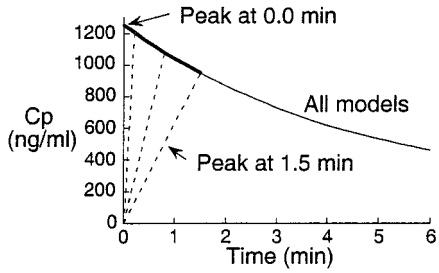

Fig. 1. Schematics of selected plasma concentration (Cp)-*versus*-time curves that were used in the simulations are displayed; some curves were omitted for clarity. After 1.5 min, all models used the same Cp values. Before 1.5 min, different approaches assumed that Cp decreased monotonically (thick line) or increased in a linear manner during the first 0.2–1.5 min (dashed lines are shown for 0.2, 0.8, and 1.5 min) before decreasing monotonically.

We then used a semiparametric convolution approach (Appendix) to relate each of the eight Cp-*versus*-time curves (*i.e.*, Cp peaking at 0.0 min plus the seven models in which Cp peaked at 0.2–1.5 min) to the corresponding effect curve for each of the two doses. Each analysis yielded values for C_{50} and k_{e0}. For each cisatracurium dose, these values were plotted against the time to peak Cp.

Misspecification of the Time of Cisatracurium Administration

In muscle relaxant studies, twitch depression is typically quantified by recording the evoked mechanical (or electrical) response of the adductor pollicis muscle on a strip chart.[12] To synchronize twitch recording with administration of the muscle relaxant, the investigator might mark the strip chart recording when the drug is administered. These markings might be erroneous; we tested systematic errors of −6 to +6 s.

These analyses were based on the simulated twitch tension data generated for the 75- and 300-μg/kg doses of cisatracurium. Four new twitch tension-*versus*-time

Table 1. Onset and Recovery Times Reported by Bergeron *et al.*[4] (Mean ± SD) and Those Simulated Based on the Mean Pharmacokinetic and Pharmacodynamic Parameters Reported by Bergeron *et al.*[4]

	Dose (μg/kg)			
	75		300	
	Reported by Bergeron *et al.*[4]	Simulated	Reported by Bergeron *et al.*[4]	Simulated
Time (min) to				
98% Twitch depression	4.8 ± 2.3*	4.8	1.8 ± 0.5*	1.8
25% Recovery	35.3 ± 5.8	35.3	81.5 ± 15.4	79.9
75% Recovery	48.0 ± 7.0	45.6	95.6 ± 16.4	92.3

* Bergeron *et al.*[4] reported onset rather than time to 98% twitch depression.

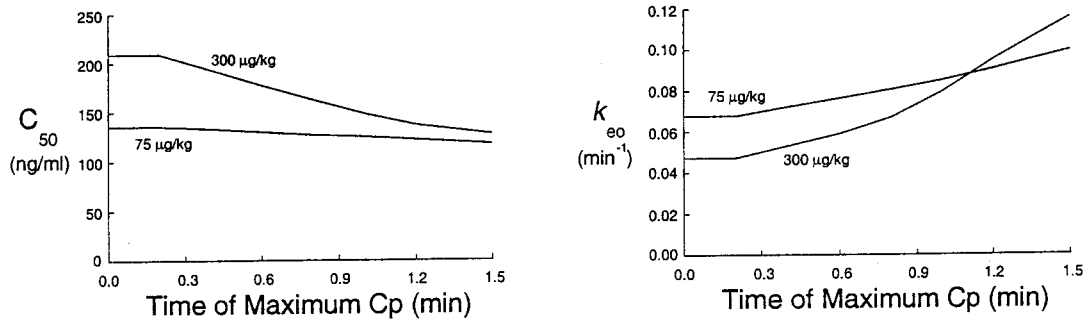

Fig. 2. Estimates of C_{50} (*left*) and k_{e0} (*right*) are plotted against the time at which plasma concentration (Cp) peaks. Values are shown for two doses of cisatracurium, 75 and 300 μg/kg.

datasets were created by shifting the time base −6, −3, +3, and +6 s. Plasma concentration of cisatracurium was assumed to peak at 0.2, 0.8, or 1.5 min after injection, as above. We then used the semiparametric convolution approach described earlier to relate each of the three Cp-*versus*-time curves (*i.e.*, Cp peaking at 0.2, 0.8, or 1.5 min) to each of the five effect curves (four time-shifted effect curves plus one with no shift in time base) for each of the two doses. Each analysis yielded values for C_{50} and k_{e0}. For each cisatracurium dose, these values were plotted against the shift in time base.

Magnitude of the Administered Dose

A typical strip chart recorder (TA240; Gould Electronics, Valley View, OH) has a 40-mm width for full-scale recording. The width of a recorded signal is approximately 1 mm (2.5% of full scale). The baseline signal may fluctuate several percent of full scale, a result of venous pulsations in the hand and movement artifact. In that investigators typically determine twitch depression by measuring distance from the twitch baseline to the peak of each evoked twitch, small inaccuracies in these measurements are inevitable. We were concerned that administering too small or too large a dose might impact on accuracy of the pharmacodynamic estimates. If the dose is small, the resulting "signal" is small (*i.e.*, peak effect is < 25% twitch depression); this error ("noise") represents a larger fraction of the signal than if peak effect were larger. If the administered dose is sufficiently large, few measurements are available during onset. Also, if twitch is ablated for a long period, changes in twitch tension that occur during the drug's distribution phase (*e.g.*, a decrease from 99.9% twitch depression to 99.1%) cannot be measured accurately. Hence, error in effect measurements might affect estimates of k_{e0} and, therefore, C_{50}. Therefore, we examined whether the magnitude of peak effect (ranging from 20% twitch depression to ablated twitch for a prolonged period) affects the reliability of the pharmacodynamic estimates. Based on the pharmacokinetic–pharmacodynamic data of Bergeron *et al.*[4] for the 75-μg/kg dose, we estimated that the doses producing 20% (ED_{20}), 50% (ED_{50}), 80% (ED_{80}), and 99% (ED_{99}) effect were approximately 30, 37.5, 45, and 75 μg/kg, respectively. Using the pharmacokinetic and pharmacodynamic parameters for the 75-μg/kg dose, we simulated the time course of Cp, Ce, and effect for each of these doses as well as 2 × ED_{99} (150 μg/kg) and 4 × ED_{99} (300 μg/kg). To simulate different degrees of "noise," 10 random sets of values of homoscedastic error‡ with an SD of either 2.5 or 10% of full scale (representing 1 or 4 mm, respectively, on a 40-mm twitch recording scale) were generated (Excel; Microsoft, Redmond, WA), *i.e.*, a different error was simulated for each time interval from 0.0 min to complete recovery of twitch tension. These errors were added to the "true" effect measurements. If the resulting twitch was less than 0 (*i.e.*, > 100% twitch depression), it was set to 0 (100% twitch depression).

Pharmacodynamic parameters were estimated for each simulated dataset, assuming that plasma concentration of cisatracurium peaked 0.0 min after injection. For each level of error, mean and SD were determined. Then, bias and variability (both expressed as a percentage of the "true" value) in the estimates of C_{50} and k_{e0} were plotted against dose.

Pharmacokinetic–pharmacodynamic simulations and analyses were performed for each individual dataset using NONMEM.[13] Values are reported as mean ± SD.

Results

Recreation of Plasma Concentration and Effect Data

The pharmacokinetic and pharmacodynamic parameters used to simulate the onset and recovery data yielded values consistent with those reported by Bergeron *et al.*[4] (table 1).

‡ With homoscedastic error, the error is assumed to have a similar magnitude at all points on the measurement scale. In contrast, heteroscedastic error has a different magnitude at different points on the measurement scale, as might be the case for a pharmacokinetic analysis in which error may be proportional to the predicted concentration (and therefore of larger magnitude with larger concentrations).

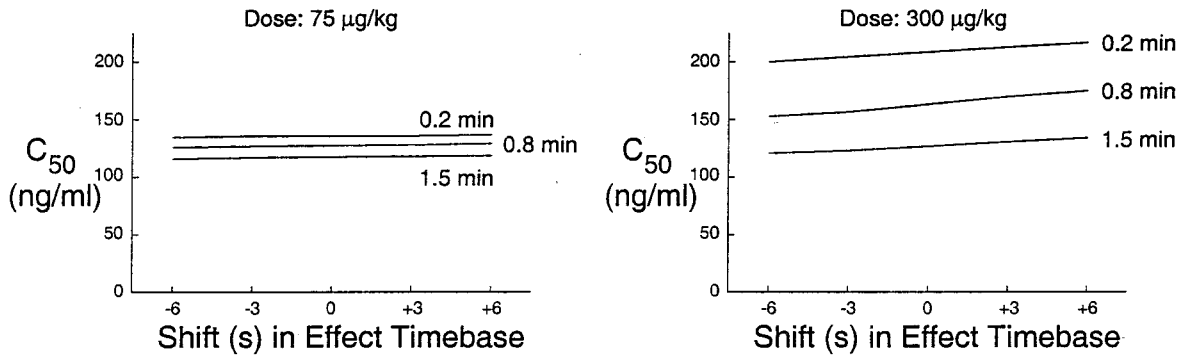

Fig. 3. Estimates of C_{50} are plotted against the timing error (in seconds) in the recording of effect data. Values are shown for two doses of cisatracurium, 75 (*left*) and 300 (*right*) μg/kg. Labels refer to the time at which plasma concentration peaks.

Varying Time at Which Plasma Concentration Peaks

As the simulated time to peak Cp increased from 0.0 to 1.5 min, estimates of C_{50} for the 300-μg/kg dose decreased; values of C_{50} for the 75-μg/kg dose varied minimally (fig. 2). For the 300-μg/kg dose, values for k_{e0} increased more than twofold as the time of peak Cp increased from 0.0 to 1.5 min. The magnitude of increase was smaller with the 75-μg/kg dose.

Misspecification of the Time of Cisatracurium Administration

Estimates for C_{50} resulting from a shift of pharmacodynamic data by −6, −3, +3, and +6 s vary more with the 300-μg/kg dose than with the 75-μg/kg dose (fig. 3). The effect of the timing error is similar for Cp peaking at 0.2, 0.8, and 1.5 min after injection. Similarly, shifting the time base of the pharmacodynamic data by ± 6 s affected k_{e0} more with the large dose than with the small dose (fig. 4).

Magnitude of the Administered Dose

The ED_{20} dose was associated with more bias (fig. 5) and variability (fig. 6) in both C_{50} and k_{e0} compared with larger doses. There was minimal bias and variability with doses ranging from ED_{50} to 2 × ED_{99}. The largest dose, 4 × ED_{99}, yielded larger bias and variability than doses ranging from ED_{50} to 2 × ED_{99}. Both variability and bias were larger with the larger magnitude of error.

Discussion

Studies of muscle relaxants have provided important insights into various issues of pharmacokinetic–pharmacodynamic modeling, including the need for an effect compartment to accommodate the delay between plasma concentrations and effect and the need to consider that a polyexponential equation describes the initial plasma concentration-*versus*-time course poorly. We were concerned that certain methodologic issues in pharmacokinetic–pharmacodynamic modeling could impact on the results of these analyses. We used a published dataset to examine several issues, including the impact of different assumptions about the Cp-*versus*-time profile during the period immediately after drug administration, the impact of systematic error in the timing of effect data, and the impact of dose magnitude in estimating potency.

Varying Time at Which Plasma Concentration Peaks

Our simulations permitted the time of peak Cp to vary from 0.0 to 1.5 min. The latter of these values is larger

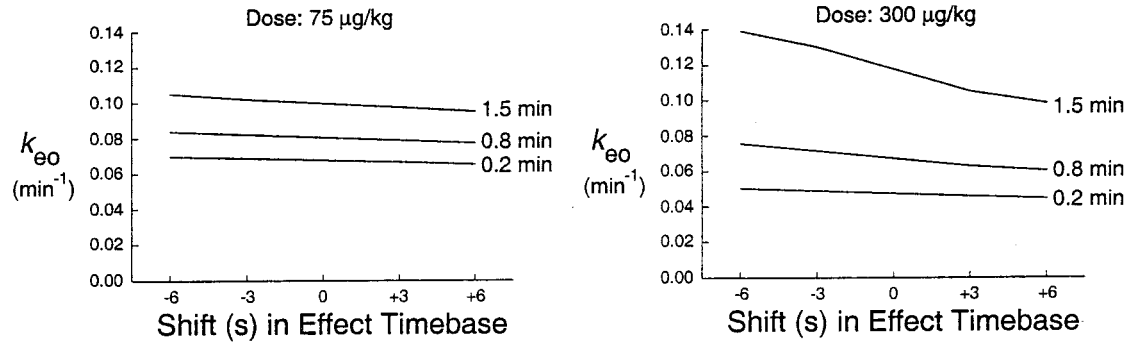

Fig. 4. Estimates of k_{e0} are plotted against the timing error (in seconds) in the recording of effect data. Values are shown for two doses of cisatracurium, 75 (*left*) and 300 (*right*) μg/kg. Labels refer to the time at which plasma concentration peaks.

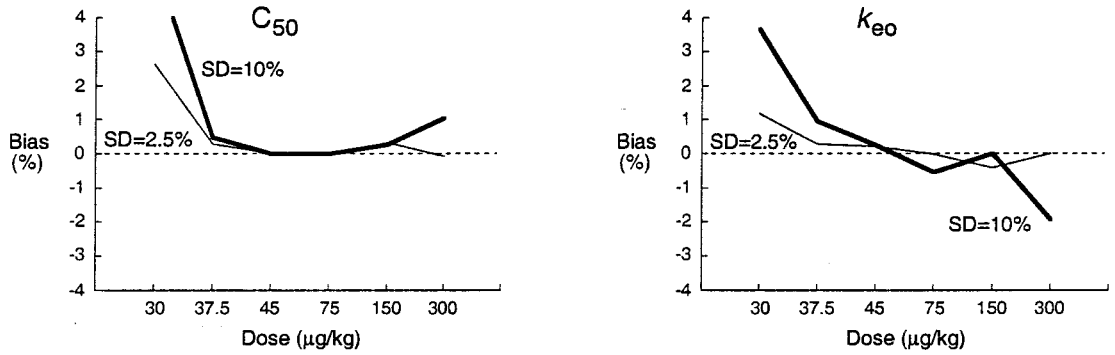

Fig. 5. Bias in the estimates of C_{50} (*left*) and k_{e0} (*right*) are plotted against the administered dose of cisatracurium. Values are shown for two levels of added error ([SD] of 2.5 and 10% of full scale) in the effect measurements.

than that reported for any of the muscle relaxants that have been sampled intensively during the initial minute after bolus dosing. For vecuronium,[10] atracurium,[11] mivacurium,[14] and doxacurium,[3] individual time to peak Cp ranges from 0.42 to 0.92 min, and mean values for each drug range from 0.47 to 0.67 min. Thus, it is likely that time to peak Cp for cisatracurium does not exceed 1.0 min. Regardless, as we permitted the time at which Cp peaked to increase from 0.0 to 1.0 min, estimates for C_{50} changed markedly with the 300-μg/kg dose of cisatracurium. In contrast, the same change in time at which Cp peaked after a 75-μg/kg dose of cisatracurium had a much smaller effect on C_{50}. As a result, for those analyses in which Cp was assumed to peak 1.0 min after bolus administration, the difference in C_{50} for the two doses was small; as Cp peaked earlier, the differences became larger (fig. 2). Therefore, if Cp actually peaks as late as 1.0 min after bolus administration of cisatracurium, it is likely that there is, at most, a minimal effect of dose size on C_{50}, a finding that contradicts that of Bergeron *et al.*[4] If Cp peaks at 0.6–0.8 min (as is the case for muscle relaxants for which early intense sampling has been performed[3,10,11,14]), then C_{50} may differ between doses. However, we speculate that the magnitude of difference predicted in our analyses (130 ng/ml for the 75-μg/kg dose and 178 ng/ml for the 300-μg/kg dose, assuming that Cp peaks at 0.6 min) is too small to detect with an unpaired study, as was performed by Bergeron *et al.*[4] When we used the flawed assumption that Cp peaks at 0.0 min (as is typical in most pharmacokinetic–pharmacodynamic studies), the difference in C_{50} between the two doses (136 ng/ml for the 75-μg/kg dose and 209 ng/ml for the 300-μg/kg dose) was sufficiently large for Bergeron *et al.*[4] to detect differences between groups. Our simulations suggest that if cisatracurium's C_{50} varies with dose and if the analysis of Bergeron *et al.*[4] were performed using a more appropriate method of analysis (*i.e.*, assuming that Cp peaked at a time later than 0.0 min), their study may not include sufficient subjects to support their conclusion. These results confirm the claim of Ducharme *et al.*[10] that estimation of pharmacodynamic parameters depends on an accurate description of the early time course of Cp. For example, to demonstrate that vecuronium's C_{50} varied with dose (as was suggested by Bragg *et al.*,[5] who modeled pharmacodynamics without plasma concentration data), Fisher *et al.*[6] sampled arterial plasma at 0.5 min (in addition to a sampling regimen similar to that of Bergeron *et al.*[4]) and analyzed the data using the "reasonable" assumption that vecuronium's Cp peaks at 0.5 min.

We observed that estimates of C_{50} for the smaller cisatracurium dose varied minimally as a function of the time at which Cp peaked. We presume that this occurs because the time at which twitch is ablated with this dose is sufficiently late (4.8 ± 2.3 min) that there is adequate information regarding the plasma concentra-

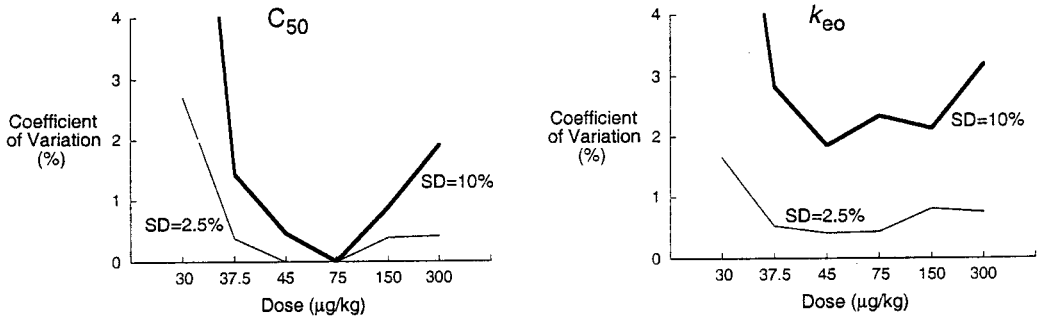

Fig. 6. Variability (coefficient of variation) in the estimates of C_{50} (*left*) and k_{e0} (*right*) are plotted against the administered dose of cisatracurium. Values are shown for two levels of added error ([SD] of 2.5 and 10% of full scale) in the effect measurements.

tion time course and effect time course before effect peaks so as to accurately describe the relation between Cp, Ce, and effect. In contrast, with the larger cisatracurium dose, twitch is ablated at 1.8 ± 0.5 min, so that patients studied by Bergeron *et al.*[4] typically had only one plasma sample obtained before twitch was ablated. In turn, the incorrect (but typical) assumption regarding the time at which Cp peaked markedly influenced the input function for the effect compartment, leading to flawed estimates of the pharmacodynamic parameters.

Our simulations indicate the importance of early samples when effect peaks early. If early samples cannot be obtained, pharmacodynamic modeling may be flawed. Another design issue that could lead to incorrect modeling of the early plasma concentration-*versus*-time course is the use of venous samples. For example, Donati *et al.*[15] demonstrated that atracurium's arterial Cp is markedly larger than venous Cp during the initial 2 min. In that arterial Cp accurately describes the input to the neuromuscular junction, use of venous samples may lead to inaccurate estimates of pharmacodynamic parameters. The inaccuracy of pharmacodynamic parameters is likely to be largest for those drugs with the largest difference between arterial and venous Cp values. If arterial blood cannot be sampled (*e.g.*, for ethical reasons), then the dosing regimen should be designed so as to minimize the difference between arterial and venous Cp during times critical for the pharmacodynamic analysis. This can presumably be accomplished by administering the muscle relaxant as a brief infusion, as was suggested originally by Sheiner *et al.*[2]

We assumed that Cp increased in a linear manner from time 0 to the time at which it peaked and then decreased in a monotonic manner. This assumption is slightly flawed. First, intensive sampling during the first minute after bolus administration of several muscle relaxants[3,10,11,14] reveals that concentrations of these drugs are not detectable in arterial blood for approximately the first 10 s. Second, the increase in Cp from the first detectable concentration to the peak is not exactly linear. Third, after the peak occurs, there may be several oscillations in Cp, presumably the result of recirculation. Regardless, our approach is markedly closer to the actual Cp-*versus*-time course than that used by most investigators. First, the commonly-used monotonic decay approach assumes that Cp is maximal at time 0. Second, we speculate that although oscillations exist, their magnitude, coupled with the damping effect of drug transfer to the effect compartment, is probably insufficient to impact on the time course of effect.

§ Of these nine measurements of twitch tension, several occur during the latency period (*i.e.*, before the first onset of twitch depression) and probably contribute minimally to the pharmacodynamic analysis.

Misspecification of the Time of Cisatracurium Administration

To examine the influence of systematic misspecification of the timing of effect data on pharmacodynamic parameter estimation, we simulated a shift of the effect measurements by ± 3 or ± 6 s. Such a shift would occur if the investigator systematically misrecorded the time of drug administration. This might occur under several circumstances. For example, the investigator might administer the drug, then make the notation on the recorder. Also, certain recorders are designed in a manner that prevents access to the paper that is presently being recorded; thus the investigator must wait until the strip chart advances and then make a mark at the estimated time of drug administration.

Although this timing error is trivial compared with the several-hour duration of a neuromuscular study (and it is even small compared with the 1.8 min to twitch ablation with the larger dose of cisatracurium), it influenced the estimates of the pharmacodynamic parameters for the larger dose of cisatracurium. In contrast, misspecification of the timing of effect data with cisatracurium administration influenced the pharmacodynamic estimates minimally with the small dose of cisatracurium, for which twitch was ablated much later, *i.e.*, at 4.8 min. The findings with the large dose of cisatracurium indicate the importance of accurate timing of dosing events in pharmacodynamic studies, particularly when the drug's onset is rapid.

Magnitude of the Administered Dose

In that all physiologic measurements involve error, one responsibility of an investigator is to maximize the signal-to-noise ratio, thereby minimizing the impact of noise on parameter estimates. For neuromuscular studies, this noise can be minimized by accurate application of stimulation electrodes, establishing a control response that varies less than 2% for at least 3 min, and maintaining core temperature of 35°C or more and peripheral temperature of 32°C or more.[12] We were concerned that the impact of noise would be largest when the maximal effect was small, *e.g.*, if a small dose of cisatracurium produced only 20% twitch depression. Our simulations support this speculation. However, we also note that as the cisatracurium dose increased beyond the ED_{99}, thereby producing a prolonged period during which twitch was ablated, both bias and variability increased (figs. 5 and 6). We offer two possible explanations. First, as the dose increases, the period during which twitch is ablated increases; therefore, there is minimal "information" regarding the relation between changing Cp and effect (*i.e.*, Cp and Ce may be decreasing, but changes in effect cannot be measured). Second, as the dose increases, onset time shortens so the quantity of effect data during onset decreases (*e.g.*, during a 1.8-min onset period, there are only 9 measurements of twitch at 12-s intervals,§ whereas the 4.8-min onset period permits 24

measurements). Our analysis did not permit us to evaluate the impact of two additional factors that might influence the accuracy of pharmacodynamic estimates with larger doses. First, several investigators[16,17] demonstrated that an inadequate stabilization period before muscle relaxant administration results in twitch tension recovery exceeding the baseline value. Whether or not, and the manner in which, an investigator adjusts the data to correct for this overrecovery influences the pharmacodynamic parameters. Second, the longer the period from drug administration to complete recovery, the greater the likelihood is that the twitch tension signal will be unstable, *e.g.*, by movement of the arm or by changes in body temperature. In that a larger dose yields a longer time to complete recovery, this suggests a disadvantage to administration of doses larger than those necessary. Our simulations indicate that doses ranging from the ED_{80} to the ED_{99} are probably optimal. This is in contrast to recommendations by other authors, *e.g.*, Bergeron *et al.*[4] recommend that "doses relevant to the anesthetic practice [presumably in the range of $2 \times ED_{99}$] be used for the estimation of EC50 [termed C_{50} in the current article] values."

One issue of our study design warrants comment. For all pharmacodynamic analyses, we used abundant and "perfect" Cp data. This contrasts to the real-world situation in which many factors contribute to variability in Cp data. These include errors in the timing of blood samples, blood samples being obtained over lengthy intervals (so that their assigned time is not truly representative), contamination of blood samples by intravenous fluids, assay errors, and other factors. It is likely that including this variability in our analyses would have affected our results. In particular, estimates of variability in the estimation of the optimal dose for potency determination are likely to be larger than those reported here.

In summary, we examined several issues that potentially influence pharmacodynamic estimates in neuromuscular studies. We demonstrate that the typical assumption that Cp peaks at 0.0 min after bolus administration results in flawed pharmacodynamic estimates and may lead to misleading conclusions regarding the effect of dose magnitude on these parameters. We demonstrate that timing of effect measurements must be precise, particularly if the onset of effect is rapid. Finally, we demonstrate that doses outside of the range of ED_{80} to ED_{99} are more likely to yield flawed estimates of the pharmacodynamic parameters than doses within that range.

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Appendix

Semiparametric modeling of effect data. A typical approach to pharmacokinetic–pharmacodynamic modeling of muscle relaxants starts by using a compartmental model to describe the plasma concentration (Cp)-*versus*-time curve. Parameters from this compartmental model and effect data are then used to estimate the pharmacodynamic parameters. In this second step, the pharmacokinetic parameters are used to generate an idealized Cp-*versus*-time curve. A rate constant k_{e0} "acts" on these Cp values to generate a effect compartment concentration (Ce)-*versus*-time curve; the Ce values are then manipulated mathematically using the Hill equation (which involves C_{50} and γ) to estimate an effect-*versus*-time curve. The process starts with initial parameter estimates that are revised in successive iterations until the fit of the model to the data are optimized. The first of these steps, describing the Cp-*versus*-time curve, cannot always be optimized using a simple compartmental (polyexponential) model in which Cp decreases monotonically. Thus, the compartmental model in the first step can be replaced by one or more functions that describe the Cp-*versus*-time course. We chose a linear representation for the initial increase in Cp; other nonlinear approaches would also be acceptable. The remainder of the steps in fitting the effect data are identical with the traditional parametric approach and the semiparametric approach.