Molar Potency Is Predictive of the Speed of Onset of Neuromuscular Block for Agents of Intermediate, Short, and Utrahshort Duration

Aaron F. Kopman, M.D.*, Monica M. Kiewicka,† David J. Kopman, B.S.,‡ George G. Neuman, M.D.§

Background: The times to peak effect of rocuronium, vecuronium, cisatracurium, mivacurium, and succinylcholine were evaluated to confirm that the correlation between potency and onset time observed for long-acting relaxants also held for drugs of intermediate and short duration.

Methods: The authors recruited 99 patients classified as American Society of Anesthesiologists physical status score 1 or 2 for the study. After anesthesia was induced, tracheal intubation was accomplished without relaxants. Anesthesia was maintained with nitrous oxide and 3% or 4% end-tidal desflurane plus intravenous narcotic supplementation. The evoked electromyographic response to single stimuli administered at 0.10 Hz was recorded continuously. Drug doses were selected to produce approximately 95% twitch depression. If peak twitch depression did not fall in the range of 90% to 98%, the patient was excluded from the study. The time to 50% to 90% of peak effect was plotted as a function of the administered dose.

Results: There was no difference in the onset profiles of mivacurium and vecuronium, or in the time to 50% of peak effect between succinylcholine and rocuronium. For all other parameters, onset times ranked as follows: succinylcholine < vecuronium < mivacurium < cisatracurium (P < 0.05). When the log of the ED₉₅ in micromoles per kilogram for all five drugs was plotted against the log of onset time to 50% peak effect, the R² value for the best fit line was more than 0.98.

Conclusions: The inverse correlation between the molar potency and speed of onset previously described for agents of long duration also applies to nondepolarizing agents of intermediate and short duration. The onset time of succinylcholine also appears to be compatible with this relation. (Key words: Cisatracurium; mivacurium; rocuronium; succinylcholine; vecuronium.)

In 1988, Bowman et al.,1 after studying a series of desacetyl analogs of vecuronium in cats, reported that fast onset, coupled with brief duration, may be achieved only with compounds of relatively low potency. Shortly thereafter, Kopman2 administered equipotient doses (=ED₉₅) of gallamine, d-tubocurarine, and pancuronium in humans and observed the rate of onset of neuromuscular block. When the log of the ED₉₅ dose (μg/kg) was plotted against the log of the onset time (to 50% twitch depression), the coefficient of correlation of the best-fit line had a value 0.99. More recently, Bartkowski et al.3 studied onset times after ED₉₀-₉₅ doses of vecuronium, atracurium, and rocuronium and concluded that the relation between low potency and rapid onset previously demonstrated for long-acting neuromuscular blockers also held for drugs of intermediate duration. Cisatracurium was not available for study when their investigation was performed. Although vecuronium and cisatracurium have ED₉₅ values expressed in milligrams per kilogram that are similar, cisatracurium is 50% more potent on a micromoles-per-kilogram basis. If molar potency is the major determinant of onset time, then cisatracurium should have the slowest onset of action of any of the relaxants of intermediate duration.

We decided to evaluate the times to peak effect of rocuronium, vecuronium, cisatracurium, and mivacurium, because no onset studies have compared these neuromuscular blockers. In addition, we wished to confirm that the close correlation between molar potency and onset time observed for long-acting neuromuscular blockers also held for nondepolarizing drugs of short and intermediate duration.

Finally, although the speed of action of rocuronium is frequently compared with that of succinylcholine, we are unaware of any studies that have compared the onset...
times of these two drugs when administered in subparal- 
yzing doses. Therefore, we included succinylcholine in 
the protocol for comparative purposes because it still 
represents the "gold standard" for rapid onset of neuromuscular block.

Materials and Methods

Ninety-nine adult patients (ages 21–60 yr) classified as 
American Society of Anesthesiologists physical status 1 
or 2 and undergoing elective surgical procedures were 
included in the study. None of the patients had neuromuscular disease, and all were within 20% of ideal body 
weight. The protocol was approved by our hospital's 
Human Subject Review Committee, and informed con- 
sent was obtained. At the outset of the study patient 
selection was randomized. This process eventually broke 
down because only 11 patients needed to be recruited 
into the vecuronium group, but 37 patients were neces- 
sary to meet the inclusion criteria in the succinylcholine group.

Anesthesia was induced with 40 μg/kg alfentanil plus 
2 to 2.5 mg/kg propofol given intravenously, and tracheal intubation was accomplished without using muscle relaxants. Anesthesia was maintained with nitrous oxide (65% to 70% inspired), and 2% to 4% end-tidal desflurane plus intravenous narcotic supplementation if needed. End-tidal concentrations of desflurane did not exceed 4%. This concentration (and the duration of stabilization before drug administration) was identical in all groups. Ventilation was controlled, and the end-tidal carbon dioxide tension was maintained between 34 and 40 mmHg.

The indirectly evoked integrated compound action po- tential of the first dorsal interosseous muscle to supra- 
maximal stimulation of the ulnar nerve at the wrist was 
measured and recorded using an NMT 221 monitor (Da- 
tex, Tewksbury, MA). Single stimuli at 0.10 Hz were 
administered during the period of observation, and 
twitch depression was recorded continuously. Control 
twitch height was established after a 15- to 20-min pe- 
riod of baseline stabilization.

Immediately after baseline calibration, one of five neuromuscular blocking drugs were administered: 0.25 mg/kg succinylcholine, 0.35 mg/kg rocuronium, 0.045 mg/kg vecuronium, 0.050 mg/kg cisatracurium, or 0.08 mg/kg mivacurium. These dosages (based on published potency data) were selected to produce approximately 95% twitch depression.8-8 As we gained experience, these doses were adjusted if necessary. If peak twitch depression in an individual patient did not fall in the range of 90% to 98%, the patient was excluded from the study.

Average twitch depression at 10-s intervals after drug 
administration was calculated for all groups. The esti- 
ated onset times to 50% and 90% peak effect in each 
patient were obtained by interpolating these data points. 
These individual values were averaged and the mean 
values were compared using one-way analysis of vari- 
ance and the Scheffé F procedure for post hoc compar- 
isons. Observed differences were considered significant 
at $P < 0.05$.

The time interval from drug administration to 50% and 
90% of peak effect was also plotted against molar po- 
tency of the individual drugs to examine the relation 
between these parameters. The coefficient of determi- 
ation of the best-fit line of regression was determined. 
In calculating this relation, we assumed that the average 
dose of neuromuscular blocking drug administered in 
each of our test groups was equal to the drug's true 
ED$_{50}$.

Results

Ninety-nine patients were initially recruited for this 
study (table 1). Forty-nine patients were excluded from 
analysis because initial drug-induced twitch depression 
was less than 90% or more than 98% of control. The

<table>
<thead>
<tr>
<th>Table 1. Effect of Applying Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Subjects initially recruited</td>
</tr>
<tr>
<td>Peak effect ≥99% (n)</td>
</tr>
<tr>
<td>Peak effect &lt;90% (n)</td>
</tr>
</tbody>
</table>

The total number of subjects initially recruited for this study (n = 99) are given in row 1. Patients from whom data were analyzed are listed in row 4. Rows 2 and 3 list the numbers of patients excluded from study. The average drug doses administered to patients who did not meet inclusion criteria did not differ from those analyzed in table 2.
Table 2. Demographics and Onset Times from the Five Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Succinylcholine</th>
<th>Rocuronium</th>
<th>Vecuronium</th>
<th>Mivacurium</th>
<th>Cisatracurium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35.6 ± 13</td>
<td>34.8 ± 7.1</td>
<td>35.8 ± 6.9</td>
<td>37.0 ± 8.9</td>
<td>34.5 ± 8.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.1 ± 15.3</td>
<td>60.4 ± 10.6</td>
<td>57.0 ± 5.8</td>
<td>62.9 ± 7.6</td>
<td>62.7 ± 9.6</td>
</tr>
<tr>
<td>Male/female</td>
<td>3/7</td>
<td>1/9</td>
<td>1/9</td>
<td>1/9</td>
<td>2/8</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>0.260 ± 0.032</td>
<td>0.310 ± 0.021</td>
<td>0.041 ± 0.002</td>
<td>0.076 ± 0.001</td>
<td>0.046 ± 0.002</td>
</tr>
<tr>
<td>Time (s) to 50% maximal effect</td>
<td>(0.23–0.35)</td>
<td>(0.30–0.35)</td>
<td>(0.04–0.045)</td>
<td>(0.075–0.078)</td>
<td>(0.045–0.050)</td>
</tr>
<tr>
<td>Time (s) to 90% maximal effect</td>
<td>(41–61)</td>
<td>(34–83)</td>
<td>(113–136)</td>
<td>(94–143)</td>
<td>(128–221)</td>
</tr>
<tr>
<td>Time (s) to maximal effect</td>
<td>(60–90)</td>
<td>(64–170)</td>
<td>(168–230)</td>
<td>(150–255)</td>
<td>(201–340)</td>
</tr>
<tr>
<td>Time (s) to maximal effect</td>
<td>(80–130)</td>
<td>(180–320)</td>
<td>(324–51)</td>
<td>(317–54)</td>
<td>(420–77)</td>
</tr>
<tr>
<td>Maximal effect (%)</td>
<td>95.0 ± 2.7</td>
<td>95.0 ± 3.1</td>
<td>95.7 ± 2.2</td>
<td>95.3 ± 2.7</td>
<td>95.6 ± 2.4</td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

There was no statistical difference between succinylcholine and rocuronium in time to 50/90% peak effect (P > 0.05) or between vecuronium and mivacurium at any time. For all other parameters onset times ranked as follows: succinylcholine/rocuronium < vecuronium/mivacurium < cisatracurium (P < 0.001). Values represent the mean ± SD (range).

average drug doses administered to patients who were excluded from analysis did not differ from those given to patients who remained in the study. Twenty-seven of 37 patients who received succinylcholine and 14 of 24 who received mivacurium were excluded from the study. There were no differences in the demographics of the five study groups (table 2), and the peak twitch depression achieved did not differ between groups. The doses of blocking drugs needed to achieve 95% twitch depression are in keeping with the generally accepted relative potencies of these drugs.

There was no difference between succinylcholine and rocuronium in the time to 50% to 90% of peak effect. There were, however, significant differences in the time to 50% and 90% of peak effect among all other groups (table 2, fig. 1). The onset profiles of mivacurium and vecuronium essentially could be superimposed (fig. 2). The speed of onset ranked as follows: succinylcholine, rocuronium, or both < vecuronium, mivacurium, or both < cisatracurium (P < 0.001).

When the log of the dose administered for all five blocking agents, expressed in micromoles per kilogram of the cation (table 3) is plotted against the log of onset time to 50% or 90% of maximal effect, the coefficient of determination (R²) is more than 0.97 (fig. 3). This regression relation is not altered significantly by omitting succinylcholine, mivacurium, or both from the analysis.

Discussion

Why Use Molar Potency?

For clinical purposes, potency traditionally has been expressed in milligrams per kilogram, and this is unlikely to change. After all, vial-ampoule labels state the contents of the container in milligrams per milliliter of drug. However, this convention does not appear to be helpful when trying to predict onset times.

Fig. 1. The percentage of peak effect after a single ED₉₅ dose of succinylcholine, rocuronium, vecuronium, or cisatracurium as a function of time. For the sake of clarity, the onset curve for mivacurium was omitted from this graph (fig. 2). Succinylcholine shows more than 50% recovery at 5 min.
The rationale for expressing potency in moles per kilogram is simple. Ultimately, we have a variable number of molecules chasing a fixed number of nicotinic receptors. The fewer molecules it takes (per kilogram of body weight) to achieve a given degree of receptor occupancy, the greater the affinity the drug has for the receptor. This is best expressed in micromoles per kilogram rather than in milligrams per kilogram.

Vecuronium, for example, has a potency approximately 1.9 times that of mivacurium if potency is expressed in milligrams per kilogram (of the cation). However, the potency ratio expressed in micromoles per kilogram is virtually unity (table 3). As noted in this study, these two drugs have nearly identical onset profiles. Thus, if potency is predictive of onset time, it is best expressed in micromoles per kilogram.

Methodologic Issues

When subparalyzing doses of relaxants are administered, computer simulation suggests that the time to 50% (or 90%) of peak effect is also a function of the maximal degree of block achieved. In our model for vecuronium, an ED_{50} dose will achieve 90% of its peak effect (85.5% block) in 2.8 min. However, a single ED_{50} dose will not result in 90% of peak effect (45% block) until 5 min have passed. It was for this reason that the inclusion criteria we used (90–98% block) were kept narrow.

We also understand that the dose–response curve in the range of 90% to 98% effect is not linear. In our computer model (which assumes a Hill coefficient of 5), a ± 15% error in the ED_{50} will produce responses ranging from 89% to 97.5% twitch depression. This is not very critical, because computer-projected peak onset times after dose variations of this magnitude are approximately normally distributed. In our model after an ED_{50} dose of vecuronium, 90% of peak effect (T1 = 85.5%) occurs at 3.1 min. A 1.15 · ED_{50} dose produces 90% of peak effect at 2.55 min, and a 0.85 · ED_{50} dose achieves 90% of peak effect at 3.8 min.

Our rigid exclusion criteria did have an unfortunate result: A high percentage of patients in the succinylcholine and mivacurium groups (table 1) were excluded from further analysis. However, because in both instances the proportion of patients excluded came almost equally from either side of the inclusion range, we are confident that our data are not unduly skewed toward one end of the spectrum.

An alternative protocol that might have reduced the potential for data loss did become apparent. We could have used ED_{50} rather than ED_{50} doses of each test drug. With this method, we also would have been working on a straighter portion of the dose–response curve. We ultimately rejected this approach for the following reason: Because of the very steep slope of the curve between 25% and 75% block, small errors in guessing the true ED_{50} for an individual will result in large variations in effect. Again assuming a Hill coefficient of 5, a ± 15% error in the ED_{50} would produce a range of responses from 31% to 67% twitch depression. In fact, in a small group of patients (n = 4) to whom we administered 0.02 mg/kg vecuronium (1 · ED_{50}), the twitch depression ranged from 33% to 70%. From a purely pragmatic perspective, the probability of collecting data with a narrow range of effects (45–55% or even 40–60%) with a reasonable number of patients did not seem promising.

Rocuronium, Vecuronium, and Cisatracurium

Our results with rocuronium, vecuronium, and cisatracurium indicate that the same close correlation between molar potency and onset time that was found for blocking agents of long duration also applies to relaxants of intermediate duration. The coefficient of determination \( R^2 \) for the best-fit line of regression, which plots the log of molar potency against the log of onset time, is more than 0.97. As predicted, cisatracurium has an onset time to 50%, 90%, and 100% of peak effect that is measurably longer than vecuronium. This confirms recent observations by Stevens et al.

The onset times noted in the current investigation cannot be compared directly with Kopman's earlier...
Table 3. Each Drug's Molecular Weight (MW) and Its Calculated Potency

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Weight (mg/kg)</th>
<th>MW Salt</th>
<th>MW Cation</th>
<th>ED50-cation (μM/kg)*</th>
<th>Log ED50-cation (μM/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine chloride</td>
<td>0.260</td>
<td>361</td>
<td>290</td>
<td>0.8950</td>
<td>-0.0480</td>
</tr>
<tr>
<td>Rocuronium bromide</td>
<td>0.310</td>
<td>610</td>
<td>530</td>
<td>0.5849</td>
<td>-0.2329</td>
</tr>
<tr>
<td>Vecuronium bromide</td>
<td>0.041</td>
<td>638</td>
<td>558</td>
<td>0.0735</td>
<td>-1.1338</td>
</tr>
<tr>
<td>Mivacurium chloride</td>
<td>0.076</td>
<td>1100</td>
<td>1029</td>
<td>0.0738</td>
<td>-1.1318</td>
</tr>
<tr>
<td>Cisatracurium besylate</td>
<td>0.046</td>
<td>1244</td>
<td>930</td>
<td>0.0495</td>
<td>-1.3055</td>
</tr>
</tbody>
</table>

The mean administered dose of each drug (in mg/kg) from Table 2 is assumed to equal the true ED50 dose under the conditions of this study.

* The ED50 (row D) in μM/kg may be calculated as follows: D = A/C + 1.000.

Observations with pancuronium, d-tubocurarine, and gallamine because of differences in methods. In that previous study, trains-of-four were administered at 20-s intervals, and onset was expressed as the estimated time to 50% twitch depression rather than as a fraction of maximal effect. The current protocol (single stimuli at 0.10 Hz) is preferable because the interval between observations is reduced by half. This is a crucial advantage when the level of block is changing rapidly. In addition, we report times to a given percentage of peak effect rather than times to a fixed degree of twitch depression because we agree with Bartkowski et al.² that this interval appears to be a more sensitive method for comparing drugs, especially when differences in onset speed are small. This parameter can be obtained only when subparalyzing doses of relaxant are used.

Bowman¹ explained the observation that molar potency is a major determinant of the speed of action by invoking the "law of mass action." With impotent drugs, many molecules must be administered; the concentration gradient from plasma to end-plate was increased, and thus drug delivery was accelerated. Donati's¹⁰ initial interpretation was not greatly different. No matter what the potency of the relaxant, a large proportion of receptors must be occupied (75–80%) before the onset of neuromuscular blockade becomes apparent. Thus (if equipotent doses of relaxant are given), when a potent drug is administered, plasma concentration will be low, and the critical number of blocking molecules will be carried in a larger volume of blood. Because it takes more time to deliver this larger volume to muscle, potent drugs should have a slower onset time.¹⁰ More elaborate explanations have since been proposed. Donati and Meistelman¹¹ later hypothesized that because the density of receptors constitutes a significant drain of drug molecules for potent drugs, an inverse relation between speed of onset and potency can be anticipated. Variations of this concept have been invoked by Hull,¹² and other investigators¹³ in an attempt to reconcile onset time with biophase kinetics.

Mivacurium

Potency as defined by intrinsic receptor affinity or the equilibrium dissociation constant of drug-receptor binding cannot be the sole factor that establishes a drug's onset profile. A decade ago, Donati¹⁰ suggested that very rapid plasma clearance should also be associated with a rapid onset of action. Although this concept is not intuitively obvious, pharmacokinetic computer simulations suggest that the basic principle is valid.¹⁴,¹⁵ In addition, there is strong circumstantial clinical evidence to support this premise. The ED₅₀ for succinylcholine in patients who are homozygous for atypical plasma cholinesterase approximates only 0.04 to 0.07 mg/kg.¹⁶,¹⁷ In these patients after a subparalytic dose of succinylcholine, 6 or 7 min may elapse before the peak neuromus-
cular effect is achieved. Receptor affinity presumably remains normal, but a reduction in plasma clearance has slowed onset time and increased the apparent potency. Similar alterations in potency may be detected after the administration of mivacurium to patients with atypical or absent plasma cholinesterase. In these persons, the ED₉₅ for mivacurium approximates 0.015 to 0.02 mg/kg.¹⁸¹⁵

When administered to persons with normal plasma cholinesterase activity, the steady state clearances of the predominant isomers of mivacurium are 10 to 20 times greater than those of rocuronium, vecuronium, and cisatracurium.²⁰ In healthy persons, the drug has an ED₉₅ of approximately 0.08 mg/kg, not because of a change in the EC₅₀, but because a significant percentage of the drug is destroyed in plasma before it ever reaches the neuromuscular junction. In these patients, the reported time to peak effect after subparalyzing doses of mivacurium approximates 5 min.⁸ The latter figure is similar to our observed value of 5.3 min. Thus the onset profile that mivacurium exhibits in healthy persons appears to represent the net effect of two opposing properties: high receptor affinity and rapid plasma clearance.

We understood this relation in general terms before beginning this investigation. What we did not anticipate was the accuracy with which the apparent ED₉₅ (in micromoles per kilogram) would predict onset time for this agent. Generally accepted ED₉₅ values for vecuronium and mivacurium are 0.045 and 0.08 mg/kg, respectively. These are similar to our administered doses of 0.041 mg/kg (0.0735 µg/kg) and 0.076 mg/kg (0.0738 µg/kg) for these two drugs. Consequently, in patients with normal plasma cholinesterase activity, mivacurium and vecuronium have essentially equal molar potencies. The times to 50% and 90% of peak effect for the two relaxants were nearly identical (table 2), and the onset profile of the two drugs may be virtually superimposed (fig. 2). Approximately 6% of mivacurium by weight consists of the relatively inactive cis-cis isomer. This may introduce a small error into the potency–onset relation plotted in figure 3.

**Succinylcholine**

Twenty-seven of 37 patients who received succinylcholine were excluded from the study because the administered dose of succinylcholine produced less than 90% or more than 98% single-twitch depression. The marked variance in response to an ED₉₅ dose of succinylcholine probably reflects the wide variability in plasma cholinesterase activity found in the healthy population.²¹

Several authors have proposed that the rapid onset of action of depolarizing blockers is based, in large part, on their action as agonists at the nicotinic acetylcholine receptor rather than as competitive antagonists.²²²³ They suggest that these drugs probably need to occupy only a small fraction of available receptors to produce neuromuscular block. This is in contrast to the case with nondepolarizing agents in which presumably more than 75% receptor occupancy must be attained before measurable block supervenes.²⁴

There is, however, compelling circumstantial evidence that succinylcholine’s rapid onset of effect may be explained by at least one other mechanism. In patients homozygous for atypical plasma cholinesterase, subparalyzing doses of succinylcholine may take as long as 7 min to achieve maximal block.²⁵²⁶ In contrast, we (table 2) and others²⁷ found that in patients with normal plasma cholinesterase activity, 1 × ED₉₅ doses of succinylcholine reach peak effect in less than 2 min. The speed of onset of succinylcholine, therefore, may be in large part a function of rapid plasma clearance and have nothing to do with its mode of action.

Our finding that succinylcholine adheres to essentially the same regression line relating onset and apparent molar potency as the four nondepolarizing relaxants tested was unexpected. We are unprepared to speculate about the theoretical significance of this observation, because the mechanism(s) by which succinylcholine produces neuromuscular block is controversial.²⁸

**Conclusions**

The regression relation illustrated in figure 3 suggests that any blocking agent that has an ED₉₅ (for the active moiety) of 1 µg/kg or more should rival the onset profile of succinylcholine. This is particularly intriguing because ORG9487, a nondepolarizing blocker currently being evaluated in clinical trials, would appear to meet this requirement. Although rigorous dose–response studies of ORG9487 have not been published, the ED₉₅ of the drug appears to approximate 0.75 mg/kg.²⁹ Because the molecular weight of the cation of ORG9487 is 598, the ED₉₅ is 1.25 µg/kg. Preliminary data suggest that ORG9487, when administered at 2.5 mg/kg (≈ 5 × ED₉₅), has an onset of effect similar to that of an approximately equipotent dose of succinylcholine (1 mg/kg).³⁰³¹ Comparative onset-time studies of succinylcholine and ORG9487 at doses equal to or less than a single ED₉₅ have not been performed but would be valuable.
MOLAR POTENCY AND ONSET OF NEUROMUSCULAR BLOCK

For the five neuromuscular blocking agents we tested, the speed of onset to 50% and 90% of maximal effect was a function of molar potency. The rate of plasma clearance, intrinsic receptor affinity, and perhaps the mechanism of neuromuscular block (depolarizing vs. nondepolarizing) doubtless influence the speed of action of neuromuscular blocking agents. However, the actual molar dose requirement (the $ED_{50}$) expresses the extent to which these various parameters cancel each other out.

References