Neuromuscular Effects of Vecuronium (ORG NC45) in Infants and Children during N₂O, Halothane Anesthesia

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The authors determined the neuromuscular effects of vecuronium (ORG NC45, Norcuron®) during anesthesia with nitrous oxide and 0.9 MAC halothane. To determine potency, they administered vecuronium (15, 20, or 25 µg/kg) to 18 infants (<1 year old) and 18 children (1–8 years old). They then compared these dose-response relationships with values obtained for adults (>18 years old) under comparable anesthetic conditions. The ED₉₅₈ (dose producing 50% depression of adductor pollicis twitch tension) of 16.5, 19.0, and 15.0 µg/kg for infants, children, and adults, respectively, did not differ significantly. To determine the time course of neuromuscular blockade, the authors administered vecuronium, 70 µg/kg, to six infants, six children, and six adults. Onset time (time to maximal effect) was shortest for infants (1.5 ± 0.6 min, mean ± SD) compared with that for children (2.4 ± 1.4 min) and adults (2.9 ± 0.2 min). Duration (time from injection to 90% recovery) was longest for infants (73 ± 27 min) compared with that for children (35 ± 6 min) and adults (53 ± 21 min). The authors conclude that vecuronium can be used in infants and children in doses similar to those recommended for adults. The time interval for supplemental doses will be longest in infants and shortest in children. (Key words: Anesthesia: pediatric. Monitoring: neuromuscular blockade. Neuromuscular relaxants: vecuronium.)

Vecuronium, a nondepolarizing muscle relaxant having a molecular structure similar to that of pancuronium, is undergoing extensive clinical evaluation. In adults, the potency is similar to that of pancuronium; its duration of action is shorter and it has fewer, if any, cardiovascular effects. To determine its efficacy in pediatric anesthesia, we determined the neuromuscular effects of vecuronium in anesthetized infants and children.

Methods

After obtaining approval of the Committee on Human Research and informed consent, we studied 54 ASA I and II patients who were scheduled for elective non-hepatic, non-renal surgery. The patients were divided by age into three groups: 24 infants (7–45 weeks old), 24 children (1–8 years old) and six adults (18–58 years old). No patient had any disease known to alter neuromuscular function. Anesthesia was induced with nitrous oxide and halothane, and the trachea was intubated without the aid of muscle relaxants. Anesthesia was maintained with 65% nitrous oxide, and an age-adjusted end-tidal concentration of halothane of 0.9 MAC (measured by mass spectrometry). We controlled ventilation to keep end-tidal P₉₅₈ at 30–40 mmHg and maintained nasopharyngeal temperature at 35–37°C.

After induction of anesthesia, the ulnar nerve was stimulated with a Grass S-44® stimulator through 27-gauge needle electrodes inserted at the wrist. Single supramaximal square-wave stimuli of 0.15-ms duration were administered at 0.15 Hz. The mechanical response of the adductor pollicis was measured with a Grass FT-10® transducer. The electromyographic response (EMG) was monitored through an active electrode placed over the adductor pollicis; reference and ground electrodes were placed elsewhere on the hand. A microprocessor-controlled device records a compound muscle action potential during a 16-ms interval beginning 2.5 ms after the stimulus is applied. Through analog-to-digital conversion and digital memory storage, the EMG is slowed by a factor of 80, enabling transcription on a recorder at a paper speed of 5 mm/min. All studies were performed after 20–30 min of stabilization of the anesthetic and adductor pollicis twitch recordings.

To determine potency, we administered a single dose of vecuronium (15, 20, or 25 µg/kg) to 18 infants and 18 children. Maximal twitch depression was plotted against log dose, and least-squares regression lines were determined. Using analysis of covariance, we compared these dose-response curves with curves obtained under comparable anesthetic conditions for adults. To determine the time course of large doses, six infants, six children, and six adults were given a single dose of 70 µg/kg vecuronium. Onset time (time from injection to peak effect), duration (time from injection to 90% recovery of twitch tension), recovery time (time from 25% to 75% twitch tension), and peak effect (percent depression of twitch tension or EMG twitch height) were recorded. These values and the onset time of 20 µg/kg vecuronium were compared using analysis of variance and the Student-Newman-Keuls test.
Results

Nasopharyngeal temperature, N₂O concentration, and end-tidal P₉₀ did not differ for the three groups (table 1). End-tidal concentrations of halothane decreased with age, a result of the age-related changes in halothane MAC. Recordings of mechanical twitch tension were obtained in all studies, and all potency and time-course data refer to mechanical twitch tension. ED₉₀ was 16.5, 19.0, and 15.0 μg/kg for infants, children, and adults, respectively (table 2). The dose-response curves (fig. 1) did not differ in slope or position. In all subjects, 70 μg/kg vecuronium depressed twitch tension completely. Also, onset time of vecuronium, 20 and 70 μg/kg, was shorter in infants than in adults (table 3). Duration and recovery time of 70 μg/kg vecuronium, were longest in infants and shortest in children.

In 58 of 74 patients (which includes the 20 subjects used by Fahey et al.¹ in determining potency), we also obtained EMG recordings. Peak depression of EMG twitch height is compared with peak depression of mechanical twitch tension for all values between 0 and 100% in figure 2. There was good correlation between peak depression by the two techniques (r = 0.92, slope = 0.92). The correlation was familiar for the three groups (infants: r = 0.93; children: r = 0.91; adults: r = 0.92). Time to maximal depression of mechanical twitch tension and EMG twitch height was similar (r = 0.96, slope = 0.97; fig. 3). In 93% of these studies, peak changes in EMG twitch height occurred within 1.0 min of the peak change in mechanical twitch tension.

Discussion

Halogenated anesthetics potentiate neuromuscular blockade induced by nondepolarizing muscle relaxants in a dose-dependent manner.⁴ Therefore, the concentration of potent anesthetic must be considered in interpreting estimates of potency for muscle relaxants. Potency and duration of action of muscle relaxants, particularly d-tubocurarine (d Tc), have been studied in infants, children, and adults with widely inconsistent results. Many of these differences can be attributed to the inconsistent anesthetic conditions used in a particular study. For example, Goudsouzian et al.⁷ constructed cumulative dose-response curves for d Tc during nitrous-oxide–halothane anesthesia. Anesthesia was maintained with a 1.1% inspired concentration of halothane in neonates, increasing to a 1.5% inspired concentration in children 1–7 years of age. These results were then compared with dose-response curves obtained for adults during nitrous-oxide–narcotic anes-

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**Table 1. Clinical Data (Mean ± SD)**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age (yr)</th>
<th>End-tidal N₂O (%)</th>
<th>End-tidal Halothane (%)</th>
<th>End-tidal P₉₀ (mmHg)</th>
<th>Nasopharyngeal Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>24</td>
<td>0.4 ± 0.2</td>
<td>62 ± 4</td>
<td>0.96 ± 0.04*</td>
<td>34 ± 3</td>
<td>36.5 ± 0.5</td>
</tr>
<tr>
<td>Children</td>
<td>24</td>
<td>3.9 ± 2.0</td>
<td>63 ± 4</td>
<td>0.82 ± 0.06†</td>
<td>33 ± 3</td>
<td>36.3 ± 0.6</td>
</tr>
<tr>
<td>Adults</td>
<td>6</td>
<td>28.5 ± 6.5</td>
<td>64 ± 4</td>
<td>0.68 ± 0.04</td>
<td>33 ± 2</td>
<td>35.8 ± 0.6</td>
</tr>
</tbody>
</table>

* Different from children and adults (P < 0.05).  
† Different from adults (P < 0.05).

**Table 2. Onset Time, Magnitude of Peak Effect, and Potency of Vecuronium (at Three Doses) for Three Age Groups (Mean ± SD)**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Dose (μg/kg)</th>
<th>Onset Time (min)</th>
<th>Peak Depression (%)</th>
<th>ED₉₀ (μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>6</td>
<td>15</td>
<td>5.6 ± 1.7</td>
<td>41 ± 29</td>
<td>16.5</td>
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<tr>
<td></td>
<td>6</td>
<td>20</td>
<td>4.7 ± 0.8*</td>
<td>68 ± 12</td>
<td>19.0</td>
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<tr>
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<td>6</td>
<td>25</td>
<td>3.9 ± 1.7</td>
<td>92 ± 7</td>
<td>19.0</td>
</tr>
<tr>
<td>Children</td>
<td>6</td>
<td>15</td>
<td>5.4 ± 1.1</td>
<td>35 ± 29</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>20</td>
<td>4.8 ± 0.6*</td>
<td>50 ± 24</td>
<td>19.0</td>
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<tr>
<td></td>
<td>6</td>
<td>25</td>
<td>5.2 ± 1.6</td>
<td>72 ± 16</td>
<td>15.0</td>
</tr>
<tr>
<td>Adults†</td>
<td>7</td>
<td>10</td>
<td>6.7 ± 2.2</td>
<td>25 ± 11</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>14</td>
<td>6.3 ± 1.0</td>
<td>35 ± 18</td>
<td>15.0</td>
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<tr>
<td></td>
<td>7</td>
<td>20</td>
<td>6.0 ± 0.8</td>
<td>76 ± 15</td>
<td>15.0</td>
</tr>
</tbody>
</table>

* Different from adults (P < 0.05).  
† From Fahey et al.¹  
See text for explanation of column headings.

**FIG. 1. Dose-response curves for vecuronium for three age groups.**  
Values for adults (from Fahey et al.) were obtained under comparable anesthetic conditions. Mean and standard error for twitch depression for each dose are represented by vertical lines.
thesis. In only one previous study, that of the pharmacokinetics and pharmacodynamics of \( d' Tc \), was anesthetic conditions comparable for neonates, infants, children, and adults. In that study, Fisher et al. found that dose requirements for \( d' Tc \) were similar for the different age groups, but that doses were required at longer and more variable intervals in patients less than one year of age.

In the present study, infants, children, and adults received equivalent MAC fractions of halothane. Under these anesthetic conditions, the potency of vecuronium did not differ for infants, children, and adults. However, if infants had received lower concentrations of halothane, larger doses of vecuronium presumably would have been required to achieve neuromuscular blockade, and estimates of potency might have differed for the three age groups. Under these comparable anesthetic conditions we were unable to demonstrate differences in potency; this result is similar to our findings for \( d' Tc \).

The onset of vecuronium-induced paralysis is more rapid in infants than in adults, possibly because the higher cardiac output during infancy causes vecuronium to be delivered to the neuromuscular junction more rapidly. Alternatively, if the doses were not truly equipotent, a larger dose in infants might result in a more rapid onset. However, table 2 reveals that the onset time is more rapid for infants than for adults, even for doses that do not produce complete paralysis. Because its onset is rapid in infants, vecuronium may be valuable in facilitating rapid endotracheal intubation.

The longer duration of neuromuscular blockade in infants might be attributed to the use of a larger dose for infants than for adults. However, recovery time, which was also longer, represents the rate of recovery from paralysis and depends less on the magnitude of the dose. These results suggest that vecuronium-induced neuromuscular blockade will last longer in infants than in older patients.

The longer duration of action of vecuronium in infants can be attributed to several factors. Of these, marked differences in dosage can be eliminated; we could demonstrate no difference in the potency of vecuronium based on age. Prolonged duration of action

| Table 3. Time Course for 70 \( \mu g/kg \) Vecuronium (Mean ± SD) |
|-----------------|-----------------|-----------------|-----------------|
|                 | Onset Time (min) | Duration (min)  | Recovery Time (min) |
| Adults          | 6               | 2.0 ± 0.2       | 53 ± 21          |
| Children        | 6               | 2.4 ± 1.4       | 35 ± 6           |
| Infants         | 6               | 1.5 ± 0.6*      | 73 ± 27†         |

* Different from adults (\( P < 0.05 \)).
† Different from children (\( P < 0.05 \)).
See text for explanation of column headings.

is probably due to a longer elimination half-life which may result from lower serum clearance or a larger volume of distribution. The first condition might result from age-related differences in excretion and metabolism. Studies in rats suggest that vecuronium is eliminated predominantly by hepatic excretion. Therefore, the relative immaturity of the liver in infants might account for age-related differences in clearance. A second explanation for a longer elimination half-life is a larger volume of distribution. The steady-state volume of dis-

![Fig. 2. Comparison of values for peak twitch depression obtained by two measurement techniques. The x-axis represents mechanical twitch tension; the y-axis is EMG twitch height. Also, the least-squares regression line is shown.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931433/)

![Fig. 3. Comparison of values for onset time obtained by two measurement techniques. The x-axis represents mechanical twitch tension; the y-axis is EMG twitch height. Also, the least-squares regression line is shown.](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931433/)
tribution for vecuronium is 0.27 l/kg in adults, a value similar to that for extracellular fluid (ECF). ECF decreases from 44% of body weight at birth to 26% at one year. Therefore, if vecuronium distributes into ECF, its volume of distribution would be expected to be greater in infants than in older subjects. Similar age-related changes in steady state volume of distribution have been demonstrated for d-Tc, another drug whose volume of distribution is similar to that of ECF. Thus, the longer duration of vecuronium-induced neuromuscular blockade may be explained by either age-related differences in clearance or volume of distribution.

We did not evaluate the duration of pancuronium in pediatric patients under comparable anesthetic conditions; however, Goudsouzian et al. found that after pancuronium, recovery time from 10–25% twitch height was 8.9 min for infants and children; for vecuronium, the value is 5.2 min. This supports the findings of Fahey et al. that duration of action is shorter for vecuronium than for pancuronium.

Fahey et al. demonstrated that the duration of neuromuscular blockade in adults following 70 μg/kg vecuronium was 34 ± 8 min (mean ± SD). We found a longer duration, 53 ± 21 min (P < 0.05, using Student’s t test for unpaired data). Fahey et al. administered vecuronium after thiopental but before halothane; in contrast, we administered halothane and achieved a steady-state alveolar concentration prior to vecuronium administration. Since vecuronium probably is eliminated by the liver, its longer duration of action in the present study may result from the halothane-induced decrease in hepatic blood flow.

Although our study was not designed to evaluate cardiovascular effects, we observed no changes in heart rate or blood pressure after vecuronium. This lack of cardiovascular effects also has been observed in adults. In contrast, increases in heart rate and blood pressure occur after bolus administration of pancuronium in children.

Both mechanical twitch tension and EMG twitch height have been used to evaluate neuromuscular function during anesthesia. Katz obtained recordings of both, using a variety of anesthetic agents and neuromuscular relaxants. He noted that “when the mechanical and electrical twitch responses were simultaneously recorded, they were quite similar and often superimposable.” However, mechanical twitch tension was increased by respiratory alkalosis and decreased with respiratory acidosis. In contrast, EMG twitch height was not affected by changes in pH. Katz also measured the integrated EMG of the abdominal muscles and found that its activity was increased by surgical stimulus despite the absence of other clinical signs of responsiveness.

Epstein and Epstein compared EMG twitch height and mechanical twitch tension for subjects anesthetized with nitrous oxide and halothane and paralyzed with d-Tc. They found that maximal mechanical twitch depression was almost always greater than the maximal depression of EMG twitch height. This is consistent with our finding of a slope less than 1.0 in the regression of peak EMG twitch height depression versus peak mechanical twitch depression (fig. 2). However, in some of the subjects in the Epstein study and our study, depression of EMG twitch height exceeded depression of mechanical twitch tension. In addition, we found that changes in mechanical twitch tension were rapidly reflected in EMG twitch height.

The clinical advantage of measuring EMG twitch height occurs when the anesthesiologist does not have access to the patient’s arms. Stimulating the facial nerve while monitoring the facial muscle has been suggested as an alternative. However, Stiffel et al. demonstrated poor correlation between train-of-four values obtained with stimulation of the ulnar and facial nerves. The use of a peripheral nerve stimulator and EMG recording device permits nonvisual monitoring of the response of the muscle group with which anesthesiologists are familiar.

Although we demonstrated a strong correlation between EMG twitch height and mechanical twitch tension, there were subjects for whom these two measurements were dissimilar. The question remains as to which measurement technique provides a more accurate assessment of the tone of the abdominal wall and respiratory muscles. If further study demonstrates that EMG provides adequate quantification of the conditions of neuromuscular blockade, it could become valuable as a clinical monitor.

In conclusion, during anesthesia with nitrous oxide and 0.9 MAC halothane, patients demonstrated no age-related difference in potency of vecuronium. Onset was most rapid in infants, while duration and recovery times were longest in infants and shortest in children. No cardiovascular effects were noted. The duration of action and the lack of cardiovascular effects of vecuronium should make it valuable as a muscle relaxant for pediatric patients. Dose requirements are similar to those for adults and supplemental doses will be required at longer intervals for infants and shorter intervals for children. Further investigation is necessary to determine whether the differences in duration and recovery times can be explained by age-related changes in clearance or volume of distribution.

References