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Pharmacodynamics of High-dose Vecuronium in Children during Balanced Anesthesia

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To compare the speed of onset, intubating conditions, duration of action, and recovery from neuromuscular blockade with vecuronium to those with succinylcholine, 40 ASA physical status 1 or 2 children (ages 2–9 yr) were studied during N_2O–O_2–opioid anesthesia. Each child was randomly assigned to receive a bolus dose of one of the following muscle relaxants: succinylcholine 2.0 mg/kg (n = 10), vecuronium 0.1 mg/kg (n = 10), vecuronium 0.2 mg/kg (n = 10), or vecuronium 0.4 mg/kg (n = 10). The evoked electromyogram of the abductor digiti minimi to train-of-four stimulation was monitored. We found that with succinylcholine, the time to 95% twitch depression (speed of onset, mean ± SD), 24 ± 7 s, was significantly less than that with each dose of vecuronium: 0.1 mg/kg, 83 ± 21 s; 0.2 mg/kg, 58 ± 17 s; and 0.4 mg/kg, 39 ± 11 s, respectively ($P < 0.05$). The time to laryngoscopy and intubation did not differ significantly between succinylcholine (48 ± 10 s) and vecuronium 0.4 mg/kg (57 ± 13 s); however, both were significantly less than than with vecuronium 0.1 and 0.2 mg/kg ($P < 0.005$). The intubating conditions were excellent in 100% of patients. The duration of action was least with succinylcholine (5.7 ± 1.5 min) and increased with increasing doses of vecuronium: 0.1 mg/kg, 23.9 ± 5.1 min; 0.2 mg/kg, 55.2 ± 11.6 min; and 0.4 mg/kg, 74.6 ± 9.9 min, respectively ($P < 0.001$). The recovery index was most rapid with succinylcholine (1.6 ± 0.4 min) and was slowest with vecuronium 0.4 mg/kg (22.6 ± 2.1 min) ($P < 0.005$). In conclusion, vecuronium 0.4 mg/kg reliably depresses the twitch response to 5% of control within 60 s in 95% of children. The rapid speed of onset is associated with an increased duration of action, which is less than 90 min. (Key words: Anesthesia: pediatric. Anesthetic techniques: balanced. Measurement techniques: electromyography. Neuromuscular relaxants: succinylcholine; vecuronium. Pharmacodynamics.)

RAPID-SEQUENCE INDUCTION is used in emergency surgical procedures in order to prevent aspiration of gastric contents. Currently, succinylcholine is considered the preferred muscle relaxant for this purpose. However, succinylcholine is contraindicated in many clinical situations. It increases intragastric pressure,[1] intraocular pressure,[2] and the concentration of serum potassium[3] and thereby may lead to adverse reactions in some patients. For these reasons, the newer nondepolarizing muscle relaxants have been evaluated as alternatives to succinylcholine.

Vecuronium bromide is a nondepolarizing neuromuscular blocking compound that has a relatively rapid onset of paralysis and an intermediate duration of action and causes minimal hemodynamic instability.[4,5] The speed of onset of vecuronium at the recommended intubating dose (0.1 mg/kg) is slower than that of succinylcholine. Previous studies in adult patients demonstrated that, when given in bolus doses of up to 0.4 mg/kg,[6,7] vecuronium decreases the onset time of paralysis and maintains hemodynamic stability. It is therefore a reasonable alternative to succinylcholine for rapid-sequence induction. However, the effectiveness of vecuronium for rapid-sequence induction in children has not been studied. Therefore, we undertook this study to assess the speed of onset, duration of action, and recovery from neuromuscular blockade after administration of high-dose vecuronium (up to 0.4 mg/kg) during N_2O–O_2–opioid anesthesia in children and to compare these data to those of succinylcholine under similar conditions.

Materials and Methods

After obtaining approval from the Human Subjects Review committee and informed parental consent, 40 fasting and unpremedicated children were studied. All children were ASA physical status 1 or 2, were between the ages of 2 and 9 yr, and were scheduled for minor elective surgery. Children with a history of renal, hepatic, or neuromuscular disease and those in whom a difficult intubation was anticipated were excluded from the study. Children who had received aminoglycoside antibiotics within the 48 h preceding surgery also were excluded.

Patients were assigned randomly to one of four treatment groups (ten patients per group) to receive a single intravenous dose of either succinylcholine 2.0 mg/kg or vecuronium bromide 0.1, 0.2, or 0.4 mg/kg. Anesthesia was induced with intravenous thiopental 5.0 mg/kg, atropine 0.02 mg/kg, diazepam 0.15 mg/kg, and either morphine 0.15 mg/kg or fentanyl 2.0 μg/kg. After induction, the lungs were ventilated with 70% N_2O and 30% O_2 *via* mask. Continuous caudal anesthesia was maintained with bupivacaine 0.25% without epinephrine when appropriate for the surgical procedure.

After induction of anesthesia, the ulnar nerve in the forearm was stimulated with surface electrodes and a Da-

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TABLE 1. Demographic Data

	Succinylcholine 2.0 mg/kg	Vecuronium (mg/kg)		
		0.1	0.2	0.4
Age (months)	46.0 ± 13.3	64.8 ± 29.1	45.7 ± 16.3	55.8 ± 17.0
Weight (kg)	16.7 ± 2.0	20.4 ± 9.1	16.2 ± 2.5	18.0 ± 4.6

Data are means ± SD. No significant differences between groups.

tex Relaxograph electromyograph (EMG) monitor (Datex Instrumentarium, Helsinki, Finland). The Relaxograph delivered a supramaximal train-of-four (2 Hz for 2 s) stimulus every 10 s. The ratio of the heights of the first twitch (T1) to the control twitch (determined during the calibration sequence of the Relaxograph) and the ratio of the heights of the fourth twitch to T1 for each stimulus were collected on a PSION LZ64 (PSION UK PLC, London, England) hand-held computer. When a stable twitch response was obtained, the designated muscle relaxant was administered into a T-connector at the hub of the intravenous catheter and flushed with lactated Ringer's solution. The onset of paralysis was defined as the time when T1 was depressed to 5% of control. At this point, laryngoscopy and intubation were performed by an experienced anesthesiologist blinded to the relaxant given. The intubating conditions were assessed according to objective criteria adapted from Lund and Stovner:[8]

Excellent: jaw relaxed, vocal cords paralyzed; no diaphragmatic movement
Good: jaw relaxed, vocal cords paralyzed; slight diaphragmatic movement
Poor: vocal cords moving; "bucking"
Inadequate: jaw not relaxed, vocal cords closed

Ventilation was controlled after the muscle relaxant was administered. Anesthesia was maintained with 70% N_2O, 30% O_2, and incremental doses of opioids. End-tidal CO_2 concentration was maintained between 30 and 40 mmHg. Temperature was maintained within 1.0° C of the initial temperature during the study period.

Recovery from neuromuscular blockade was allowed to proceed spontaneously. The duration of action was defined as beginning at the time from 95% depression of T1 during the onset of neuromuscular blockade and lasting until 25% recovery of T1. The recovery index was the time for 25–75% recovery of T1.

Statistical analysis was performed with one-way analysis of variance (ANOVA) and the Student-Newman-Keuls test for intergroup differences. In order to calculate the onset times, linear regression analysis was used to extrapolate the straight-line portion of the recorded twitch response to a T1 of 5% of the control twitch height. A P value less than 0.05 was considered significant.

Results

There were no significant differences in the ages or weights of the four groups of patients (table 1). The onset of paralysis was significantly faster with succinylcholine than it was with any of the three doses of the vecuronium (table 2). Among the vecuronium doses, 0.4 mg/kg produced the fastest onset of neuromuscular blockade. In all patients, 100% blockade was achieved.

The time to laryngoscopy and intubation was significantly different among the vecuronium doses (table 2).

TABLE 2. Time Course of Neuromuscular Blockade after Succinylcholine or Vecuronium

	Speed of Onset (s)	Time to Laryngoscopy (s)	Duration of Action (min)	Recovery Index (min)
Succinylcholine 2.0 mg/kg	24 ± 7 (10–32)	48 ± 10 (36–62)	5.7 ± 1.5 (4.0–9.3)	1.6 ± 0.4 (1.0–2.3)
Vecuronium (mg/kg)				
0.1	83 ± 21* (62–126)	109 ± 23† (76–150)	23.9 ± 5.1§ (15.5–32.9) (n = 9)	7.9 ± 2.0† (4.8–12.2) (n = 9)
0.2	58 ± 17* (41–92)	81 ± 21† (52–117)	55.2 ± 11.6§ (42.0–72.3)	15.7 ± 6.8† (9.8–28.3) (n = 7)
0.4	39 ± 11* (31–61)	57 ± 13‡ (40–76)	74.6 ± 9.9§ (62.1–91.5) (n = 9)	22.6 ± 2.1† (19.8–24.5) (n = 4)

Data are means ± SD (range of responses in parentheses), n = 10 except as noted.
* $P < 0.05$ *versus* succinylcholine and other vecuronium doses.
† $P < 0.005$ *versus* succinylcholine and other vecuronium doses.
‡ $P < 0.005$ *versus* other vecuronium doses.
§ $P < 0.001$ *versus* succinylcholine and other vecuronium doses.

The time to intubation was significantly greater with vecuronium 0.1 and 0.2 mg/kg than it was with succinylcholine. However, the time to laryngoscopy with vecuronium 0.4 mg/kg did not differ significantly from that with succinylcholine. All intubating conditions were graded as excellent.

The duration of action of succinylcholine was significantly less than that of all three doses of vecuronium (table 2). The recovery index with succinylcholine was significantly less than the recovery index obtained with all three doses of vecuronium (table 2).

Discussion

We assessed the pharmacodynamics of high dose vecuronium during N_2O–O_2–opioid anesthesia in children and compared it to succinylcholine. As the dose of vecuronium was increased, the onset time for neuromuscular blockade decreased and the duration of action increased. There was a concomitant increase in the recovery index with the higher doses of vecuronium. All measurements with vecuronium were significantly longer than those with succinylcholine, with the exception of the time to laryngoscopy and intubation with vecuronium 0.4 mg/kg. This dose of vecuronium has characteristics that most closely approach those of succinylcholine.

Our results are consistent with those from previous studies[6,7,9,10] of high-dose vecuronium in adults. Those studies demonstrated similar dose-related decreases in onset time, increases in duration of action,[6,7,9,10] and increases in recovery time.[6] However, the speed of onset and duration of action of vecuronium 0.1–0.4 mg/kg were much shorter in this investigation than they were in studies in adults. In adults, the onset time ranged from 78 ± 19[7] to 106 ± 35 s,[6] and the mean duration of action ranged from 115 ± 19[7] to 138 ± 24 min.[6] In contrast, we found that the onset time was 39 ± 11 s and the duration of action was 74.6 ± 9.9 min with vecuronium 0.4 mg/kg. The more rapid onset and shorter duration of action (one half to two thirds of that in adults) of vecuronium in children are consistent with the results of previous studies of vecuronium in children.[11,12]

There may be pharmacokinetic reasons for the differences between adults and children. The greater cardiac output in children delivers muscle relaxants to the neuromuscular junction more rapidly and thus probably accounts for the faster onset of blockade. Fisher *et al.*[13] and Cronnelly *et al.*[14] demonstrated that the potency of vecuronium was the same in adults and children and that vecuronium clearance also was similar in adults and children (5.2 and 5.9 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively). However, children had a smaller volume of distribution than did adults (204 *vs.* 269 ml/kg). This results in a longer elimination half-life and mean residence time in adults. These values are almost two times those of the pediatric values and explain the longer duration of action of vecuronium in adults. The increased cardiac output in children may also contribute to the abbreviated duration of action by removing the drug from the neuromuscular junction more rapidly than in adults.[15]

In a previous study at this institution, Cunliffe *et al.*[16] evaluated the pharmacodynamics of pancuronium 0.15 mg/kg and succinylcholine 1.5 mg/kg for rapid intubation in children. Using a force transducer to monitor single twitch response, we found a mean onset time of 40.8 ± 3.0 s with succinylcholine. This value for succinylcholine is approximately twice that obtained in the current study. The longer onset time that Cunliffe *et al.* obtained with succinylcholine was due most likely to the combination of a smaller dose of succinylcholine (1.5 mg/kg in their study *vs.* 2.0 mg/kg in this study) and the use of a force transducer rather than the evoked EMG to monitor muscle relaxation. Although the effect of a lower dose on the pharmacodynamics of succinylcholine is self-evident, the effect of the type of neuromuscular stimulator is less clear. Donati and Bevan demonstrated that the single-twitch response with a force transducer lags behind that of the EMG response during the onset of neuromuscular blockade with succinylcholine.[17] Hence, the discrepancies in results between this study and previous studies with succinylcholine may be understood.

The force transducer is considered the gold standard for assessing neuromuscular function during clinical research. However, many investigators now use the more recently available, compact and easy-to-use EMG apparatus. With respect to nondepolarizing muscle relaxants, several authors have investigated the relationship between the evoked mechanogram of thumb adduction and the EMG recorded from both the thenar eminence[18,19] and the hypothenar eminence.[20,21] Only small differences were demonstrated between the two methods of measurement, although the EMG underestimated the degree of neuromuscular blockade with nondepolarizing muscle relaxants. If this is the case, then the current study underestimated the actual extent of neuromuscular blockade, and therefore the speed of onset of blockade may be even faster than that reported.

Concerns regarding the use of high-dose nondepolarizing muscle relaxants have focussed on their prolonged duration of action. The mean duration of action (for 25% recovery) with pancuronium 0.13 mg/kg in children is 90 min.[22] In contrast, we found that the duration of action of vecuronium 0.4 mg/kg is 20–25% shorter than that of pancuronium 0.13 mg/kg. This shorter duration of action with vecuronium 0.4 mg/kg should facilitate reversal of neuromuscular blockade at the completion of most emergency surgical procedures.

Even though the time to onset of paralysis with vecu-

ronium 0.4 mg/kg was statistically different from that of succinylcholine, the time to laryngoscopy and intubation in these two groups was not different. Since we did not have one anesthesiologist perform all intubations, the difference between 95% twitch depression and laryngoscopy for succinylcholine is a reflection of the time it takes the individual anesthesiologist to perform laryngoscopy once the twitch response is ablated. We used objective criteria for judging intubating conditions. The intubating conditions were graded as excellent in all patients in this study. Even though the diaphragm and vocal cords were paralyzed in all patients, two patients moved their extremities during intubation. This may be a response to light anesthesia and partial paralysis, but it is also consistent with the observation that while peripheral muscles are more sensitive to relaxants than are central respiratory or upper airway muscles, the centrally located musculature is better perfused and as a result will be blocked more rapidly with larger doses of muscle relaxants.[23]

In conclusion, we found that vecuronium 0.4 mg/kg intravenous bolus reliably depresses the EMG twitch response to 5% of control within 60 s when given to children during N_2O–O_2–opioid anesthesia. The rapid speed of onset is accompanied by an extended duration of action that remains less than 90 min after even a single dose of vecuronium 0.4 mg/kg. Although the onset of neuromuscular blockade with 0.4 mg/kg vecuronium is still somewhat longer than that after 2 mg/kg succinylcholine, clinically, these differences are not significant. Thus, vecuronium 0.4 mg/kg is a reasonable alternative to succinylcholine in situations where rapid tracheal intubation is required and succinylcholine is contraindicated.

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