Anesthesiology
1999; 91:1285–92

Intramuscular Rapacuronium in Infants and Children

Dose-ranging and Tracheal Intubating Conditions

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Background: **Intravenous rapacuronium's rapid onset and short duration suggest that intramuscular rapacuronium might facilitate tracheal intubation without prolonged paralysis. Accordingly, the authors injected rapacuronium into the deltoid muscle to determine the optimal dose and time for intubation in pediatric patients.**

Methods: **Unpremedicated patients (aged, 2 months to 3 yr) were studied. Part I: Spontaneous minute ventilation ($\dot{V}_E$) and twitch tension were measured during N_2O/halothane anesthesia. Rapacuronium (2.2–5.5 mg/kg, given intramuscularly, n = 23), succinylcholine (4 mg/kg, given intramuscularly, n = 12), or vecuronium (0.1 mg/kg, given intravenously, n = 15) was given. Time to 50% depression of $\dot{V}_E$ and 10% recovery of twitch were measured. Dose for each patient was changed 10–20% according to the previous patient's response. Part II: In 22 patients anesthetized with 0.82–1.0% halothane, the optimal rapacuronium dose determined in part I (infants, 2.8 mg/kg; children, 4.8 mg/kg) was given intramuscularly. Laryngoscopy was scored. Time to laryngoscopy was increased or decreased 0.5 min according to the previous patient's response.**

Results: **Part I: Rapacuronium typically depressed ventilation in ≤ 2 min with 10% twitch recovery in 20–60 min. With succinylcholine, median time to ventilatory depression was 1.3 and 1.1 min for infants and children, respectively; for vecuronium, 0.7 and 0.6 min. Part II: Intubating conditions were good–excellent at 3.0 and 2.5 min in infants and children, respectively; time to 10% twitch recovery (mean ± SD) was 31 ± 14 and 36 ± 14 min in the two groups.**

Conclusions: **This pilot study indicates that deltoid injection of rapacuronium, 2.8 mg/kg in infants and 4.8 mg/kg in children, permits tracheal intubation within 2.5–3.0 min, despite a light plane of anesthesia. Duration of action is intermediate. (Key words: Intramuscular drug administration; ORG9487; pediatrics; succinylcholine; vecuronium.)**

RAPACURONIUM'S (ORG9487, Organon Inc., W. Orange, NJ and Organon Teknika, Boxtel, The Netherlands) rapid onset and short duration of action with intravenous administration in adults[1] suggest that intramuscular administration of rapacuronium might facilitate tracheal intubation in children without producing prolonged paralysis. Accordingly, in part I of this pilot study in infants and children, we measured onset of effect at the respiratory muscles and recovery of twitch tension to determine the optimal dose of rapacuronium. Because comparable data are lacking for other commonly used muscle relaxants, we measured the onset of effect at the respiratory muscles in patients given either intramuscular succinylcholine or intravenous vecuronium. In part II, we gave the optimal dose of rapacuronium determined in part I to determine the optimal time for tracheal intubation.

Methods

The protocol was approved by our institutional review board. Studies in which patients received rapacuronium were conducted using Organon Inc.'s Investigational New Drug Application. After obtaining informed consent from parents, we studied 95 pediatric patients, American Society of Anesthesiologists (ASA) physical status I or II, undergoing elective surgery. Of these, 68 received rapacuronium (45 intramuscularly and 23 intravenously), 15 vecuronium (all intravenously), and 12 succinylcholine (all intramuscularly); assignment was not randomized. Patients were stratified into two groups by age: infants (2–11 months, n = 47) and children (1–3 yr, n = 48). Fifty patients (24 infants, 26 children) were

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Received from the Department of Anesthesia and Perioperative Care, University of California, San Francisco, California. Submitted for publication November 9, 1998. Accepted for publication June 21, 1999. Supported in part by Organon Inc., West Orange, New Jersey. Studies involving rapacuronium were conducted under Organon's Investigational New Drug Exemption. Dr. Fisher is periodically a paid consultant to Organon.

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Table 1. Criteria for Selecting a Dose of Rapacuronium in Part I

Time to Ventilatory Depression (min)	Time to 10% Recovery of Twitch Tension (min)	Dose for Next Patient
< 4	> 60	↓ 20%
< 4	30–60	↓ 10%
< 4	< 30	↑ 10%
4–5	—	↑ 10%
> 5	—	↑ 20%

All doses were rounded to the nearest 0.1 mg/kg.

studied in part I, and 45 (23 infants, 22 children) were studied in part II. No patient had a history of bleeding disorder, neuromuscular disease, or hepatic or renal insufficiency. Patients were excluded if they received anticonvulsants or aminoglycoside or polypeptide antibiotics perioperatively.

Part I: Determination of Optimal Dose of Rapacuronium and Onset of Ventilatory Depression with Intravenous Vecuronium and Intramuscular Succinylcholine

Patients were unpremedicated, and anesthesia was induced with N_2O and halothane. No opioids or intravenous anesthetics were given. N_2O was discontinued, and the trachea was intubated without the use of muscle relaxants. Anesthesia was maintained with 60% N_2O and halothane. End-tidal halothane concentrations were 1.0–1.2% for infants < 6 months of age, 0.8–1.0% for patients aged 7–30 months, and 0.7–0.9% for children > 30 months of age. Patients breathed spontaneously *via* a pediatric circle system. When anesthetic conditions and baseline twitch and ventilation recordings were stable, rapacuronium (20 mg/ml) was injected *via* a 21-gauge needle 1–2 cm into a single deltoid muscle after negative aspiration for blood.

The dose of rapacuronium was 3.0 mg/kg for the first infant and 5.0 mg/kg for the first child. The dose for each subsequent patient in each age group was based on the previous patient's time to ventilatory depression (defined as spontaneous minute ventilation [$\dot{V}_E$] decreasing 50% from the control value, a 10-mmHg increase in end-tidal PC_{O_2}, or arterial oxygen saturation [Sp_{O_2}] < 90%) and time to 10% recovery of twitch tension (table 1). This "up-down" technique, similar to that used to determine MAC,[2] was designed to bracket the rapacuronium dose, depressing ventilation within 4 min and permitting 10% recovery of twitch tension within 30–60 min. Once ventilation became depressed, mechanical ventilation was instituted, and anesthesia was maintained with the same concentrations of N_2O and halothane.

To determine the onset of ventilatory depression with intramuscular succinylcholine and intravenous vecuronium, an additional 27 patients were studied using similar anesthetic and monitoring techniques. When anesthetic conditions and baseline twitch and ventilation recordings were stable, 4 mg/kg of intramuscular succinylcholine (six infants, six children) or 0.1 mg/kg intravenous vecuronium (six infants, nine children) was administered.

Part II: Determination of Optimal Time for Tracheal Intubation Using Intramuscular Rapacuronium

Patients were unpremedicated, and anesthesia was induced with N_2O and halothane. After induction of anesthesia, ventilation was controlled manually to maintain normocapnia, N_2O was discontinued, and the inspired halothane concentration was adjusted to produce end-tidal halothane concentrations of 1.0% in children < 2.5 yr and 0.82% in children > 2.5 yr. No opioids or intravenous anesthetics were administered. When end-tidal halothane concentrations and baseline twitch recordings were stable for > 5 min, rapacuronium was injected either intramuscularly or intravenously (as a rapid bolus into a peripheral vein), as determined by randomization. The intramuscular dose of rapacuronium was 2.8 mg/kg for infants and 4.8 mg/kg for children; the intravenous dose was 2.0 mg/kg for infants and 3.0 mg/kg for children.

With intramuscular administration, the time at which intubation was attempted for the first patient in each age group was 2.5 min. For each subsequent patient, the time of attempted intubation was based on the previous patient's intubating conditions (table 2): if intubating conditions were good or excellent (*i.e.*, each of jaw tone, vocal cord position, and coughing was scored as good or better), intubation was attempted 0.5 min earlier; if intubating conditions were poor, intubation was attempted 0.5 min later. With intravenous administration, intubation was attempted at 1.0 min. All intubations were assessed by the same investigator who was not

Table 2. Scale Used to Assess Intubating Conditions in Part II

Score	Jaw Tone	Vocal Cords	Coughing
Excellent	Relaxed	Abducted, immobile	None
Good	Relaxed	Moving	Vigorous
Poor	Not relaxed	Closing	Sustained > 10 s

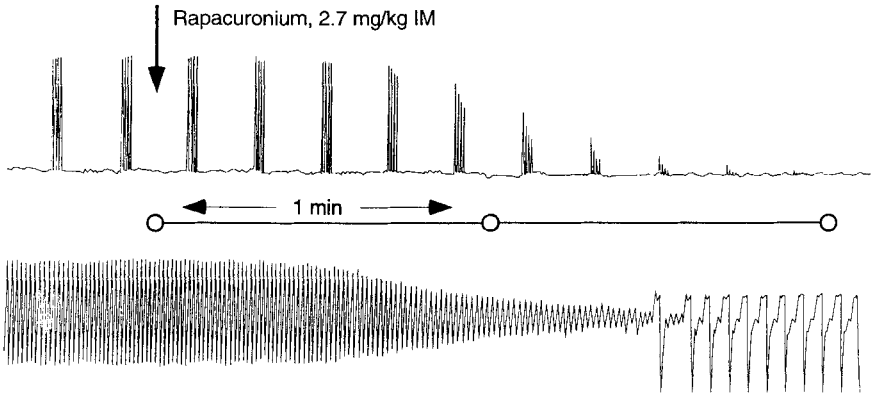

Fig. 1. Time course of twitch tension (*top*) and ventilatory flow (*bottom*) for an infant in part I given 2.7 mg/kg rapacuronium intramuscularly. Ventilatory flow was integrated in 12-s epochs to determine $\dot{V}_E$. The arrow indicates the time of rapacuronium administration. At 1.5 min after administration of rapacuronium, spontaneous ventilation was depressed more than 50% from the control value, and mechanical ventilation was instituted.

blinded to the route of rapacuronium administration or the rapacuronium dose.

Observations and Measurement Techniques

For all patients, supramaximal square-wave train-of-four stimuli were administered at 2 Hz every 12 s to the ulnar nerve *via* needle electrodes at the wrist. Evoked tension of the adductor pollicis was measured using a Grass FT-03 force transducer (Grass Instruments, Quincy, MA) with preload maintained at 50–100 g. The force signal was amplified (DC Bridge Signal Conditioner, Gould Electronics, Valley View, OH), digitized (NB-MIO-16, National Instruments, Austin, TX) on a Macintosh computer (Cupertino, CA), and displayed (LabView, National Instruments). The ratio of the first component of the train-of-four (T1) to its control value was determined. Each train-of-four was also recorded on a strip-chart (TA240, Gould).

Respiratory gas was sampled at the wye-connector to determine PC_{O_2} and anesthetic concentrations by infrared analysis (Capnomac Ultima, Datex, Helsinki); end-tidal values during each 12-s epoch were determined using LabView. Arterial oxygen saturation (Sp_{O_2}) was measured continuously (N200 Oximeter, Nellcor, Hayward, CA).

In part I, $\dot{V}_E$ was measured using a calibrated Fleisch pneumotachograph (A. Fleish Instrumentation Associates, New York, NY) placed between the breathing circuit and the tracheal tube (fig. 1). The flow signal was amplified (CD 15 Carrier Demodulator, Validyne, Northridge, CA), digitized on a Macintosh computer, and the inspiratory flow signal (corrected for flow to the capnograph) was integrated in 12-s epochs (LabView).

The injection site and the skin of the trunk and face were observed for erythema; signs consistent with histamine release were sought. At the end of surgery, 20 μg/kg atropine and 70 μg/kg neostigmine were administered, if necessary, to antagonize residual paralysis. In the post-anesthetic recovery room, patients were examined for signs of weakness such as inability to sustain leg lift[3]; the injection site was examined for signs of tissue inflammation or damage.

Data Analysis

In part I, time to ventilatory depression, magnitude of peak twitch depression, and time to 10% recovery of twitch tension were recorded. In part II, magnitude of peak twitch depression (expressed as a percentage decrease from the control value); times to 10% (latency), 50%, 90%, and peak twitch depression (onset); and time to initial (first twitch detectable on the strip chart recording), 10%, 25% (clinical duration), and 90% spontaneous recovery of twitch tension (duration of action) were determined. For the intramuscular group, we determined twitch tension at 2.0, 2.5, and 3.0 min after administration of intramuscular rapacuronium. Recovery of twitch tension was referenced to the value before rapacuronium administration. Values with intramuscular administration were compared to those with intravenous administration using Student *t* test for unpaired data or the Mann–Whitney U test. A P value < 0.05 was considered statistically significant. Values are reported as median and range or as mean ± SD.

Results

Part I

Twenty-three patients (12 infants, 11 children) received intramuscular rapacuronium (table 3). Doses ranged from 2.2 to 3.4 mg/kg in infants (median, 2.8 mg/kg) and from 4.0 to 5.5 mg/kg in children (median,

Table 3. Demographic Data and Onset of Respiratory Depression for Infants and Children Given Intramuscular Rapacuronium or Succinylcholine or Intravenous Vecuronium as Determined in Part I

	Infants			Children		
	IM Rapacuronium	IM Succinylcholine	IV Vecuronium	IM Rapacuronium	IM Succinylcholine	IV Vecuronium
N	12	6	6	11	6	9
Dose (mg/kg)	2.8 (2.2–3.4)	4.0	0.1	4.8 (4.0–5.5)	4.0	0.1
Age (infants in months, children in years)	7.2 ± 3.3	7.9 ± 4.0	6.0 ± 3.3	2.0 ± 0.7	2.1 ± 0.9	2.7 ± 1.0
Weight (kg)	7.4 ± 1.2	7.5 ± 2.6	6.7 ± 2.3	12.5 ± 3.0	12.4 ± 2.6	15.1 ± 5.3
Time to ventilatory depression (min)	1.6 (1.2–5.4)	1.3 (0.8–1.8)	0.7 (0.4–1.8)	1.6 (1.0–8.4)	1.1 (0.4–1.4)	0.6 (0.4–2.0)
Time to 10% recovery of twitch tension (min)	25.4* (20.3–66.6)	12.6 (11.4–19.4)	48.0 (31.0–89.2)	28.9† (21.6–60.0)	11.0 (7.2–19.4)	35.2 (21.8–44.6)

Values are median (range) or mean ± SD.

IM = intramuscular; IV = intravenous.

* N = 11.

† N = 9.

4.8 mg/kg). Median time to 50% depression of $\dot{V}_E$ (fig. 2) was 1.6 min for infants and children. Twitch depression exceeded 95% in all patients, except for one infant given 2.6 mg/kg and one child given 4.0 mg/kg. Median time to 10% recovery of twitch tension was 25.4 min in infants and 28.9 min in children (fig. 3). Based on these findings, we selected rapacuronium doses of 2.8 mg/kg for infants and 4.8 mg/kg for children for part II.

After intramuscular succinylcholine administration (six infants, six children), median time to ventilatory depression was 1.3 min for infants and 1.1 min for children. With intravenous vecuronium administration (six infants, nine children), median time to ventilatory depression was 0.7 min for infants and 0.6 min for children.

Part II

Twenty-two patients (11 infants, 11 children) received intramuscular rapacuronium, and 23 (12 infants, 11 children) received intravenous rapacuronium.

Injection of Rapacuronium and Tracheal Intubation. Intramuscular injection of rapacuronium elicited vigorous movement (*e.g.*, extremity movement against gravity) in 37% of patients. In infants, intubation was attempted at 1.0–3.0 min (fig. 4). At 2.5 or 3.0 min, four of five infants had good or excellent intubating conditions; at 1.0–2.0 min, four of six had poor conditions. In children, intubation was attempted at 1.5–2.5 min. All three children in whom intubation was attempted at 2.5 min had good conditions. At 2.0 min, three of five children had good conditions, and two had poor conditions. All three children in whom intubation was attempted at 1.5 min had poor conditions. With intravenous adminis-

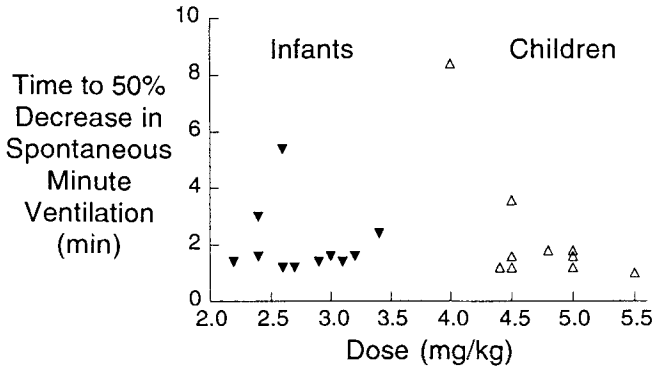

Fig. 2. Time to 50% depression of minute ventilation (*closed symbols* for infants, *open symbols* for children) in part I.

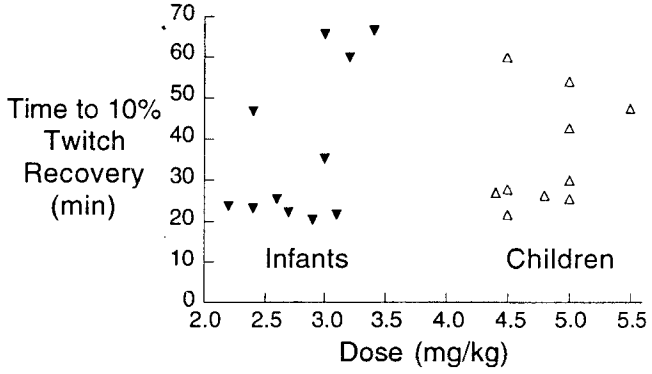

Fig. 3. Time to 10% recovery of twitch tension (*closed symbols* for infants, *open symbols* for children) in part I.

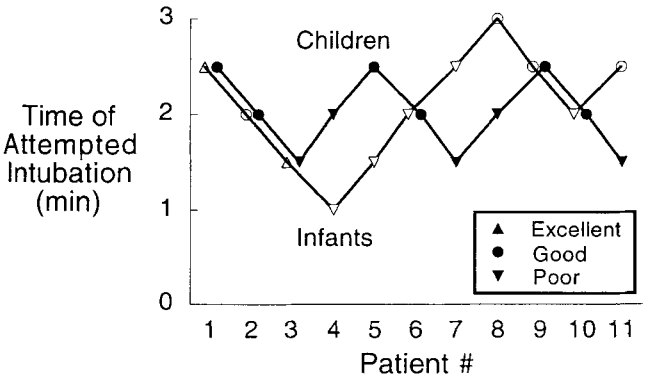

Fig. 4. Time (min) at which intubation was attempted in part II is plotted for each infant (*open symbols*) and child (*closed symbols*). If intubating conditions were good (*circles*) or excellent (*triangles*), time of attempted intubation for the next patient was decreased 0.5 min. If intubating conditions were poor (*inverted triangles*), time of attempted intubation for the next patient was increased 0.5 min.

tration, intubating conditions at 1 min were good in four infants and six children and excellent in the remaining patients.

Twitch Tension. With intramuscular administration, time to 10% twitch depression was 1.6 ± 0.7 min in infants and 1.6 ± 0.4 min in children (table 4). All but one infant and one child developed > 90% twitch depression; peak twitch depression was 89% in the remaining patients. Twitch depression peaked at 5.7 ± 2.9 min in infants and at 5.5 ± 2.7 min in children. Recovery began at 22 ± 11 min in infants and at 26 ± 10 min in children. Clinical duration was 39 ± 17 min in infants and 49 ± 17 min in children. In infants, median twitch tension 2.0 min after rapacuronium administration was 33% of control, decreasing to 16% by 3 min (table 5). In children, median twitch tension 2.0 min after rapacuronium administration was 63% of control, decreasing to 18% by 3 min.

After intravenous administration, time to 10% twitch depression was 0.3 ± 0.1 min in infants and children. All patients developed complete twitch depression; in infants at 0.6 ± 0.3 min, and in children at 0.8 ± 0.3 min. Recovery began at 14 ± 8 min in infants and at 15 ± 3 min in children. Clinical duration was 20 ± 7 min in infants and 22 ± 4 min in children. Onset and recovery were more rapid with intravenous compared with intramuscular administration in infants and children.

Adverse Events. Six infants developed mild, transient erythema at the injection site 1–5 min after intramuscular administration of rapacuronium, resolving within 15 min. No erythema was noted in children or with intravenous injection. No other signs of histamine release (*e.g.*, bronchospasm) or tissue inflammation were observed. No patients demonstrated clinical signs of weakness during recovery.

Discussion

Recent changes in the package insert for succinylcholine have limited clinicians' opportunity to administer succinylcholine electively to children, *e.g.*, intramuscularly during induction of anesthesia. Several studies from our laboratory have examined whether nondepolarizing muscle relaxants have a time course appropriate for intramuscular administration in children. Mivacurium's onset was too slow to be clinically useful, despite doses as large as 800 μg/kg.[4] With rocuronium, tracheal intubation could be accomplished at 2.5 min in infants and at 3.0 min in children with anesthetic conditions similar to those of the present study.[5] However, time to 10% recovery was typically > 1 h, limiting intramuscularly administered rocuronium's clinical utility. The rapid onset and short duration of action of rapacuronium in adults[1] suggested that its intramuscular administration might result in a clinically appropriate time course in children. Therefore, we evaluated whether rapacuronium could be used to facilitate tracheal intubation in infants and children while permitting recovery of twitch tension in a time period appropriate for brief anesthetics. In infants, 2.8 mg/kg intramuscular rapacuronium permitted tracheal intubation within 3.0 min and 10% recovery at 31 ± 14 min. In children, 4.8 mg/kg intramuscular rapacuronium permitted tracheal intubation within 2.5 min and 10% recovery at 36 ± 14 min.

In the part I of our analogous study with rocuronium,[5] we adjusted the rocuronium dose exclusively based on onset and recovery times measured at the adductor pollicis. However, the ability to intubate the trachea may not be well predicted based on the time course at the adductor pollicis. Instead, studies by Donati *et al.*[6,7] demonstrate that the time course at the diaphragm or the laryngeal adductors better predicts intubating conditions. Therefore, in the present study we evaluated onset at the respiratory muscles. Whereas several studies have measured onset time at the laryngeal muscles, we considered that this technique (placement of a cuffed tracheal tube with the cuff at the vocal cords and measuring the time to change of laryngeal tone) would be difficult to implement in infants and small children. Instead, we measured the time course at the respiratory muscles. Unlike previous investigations of the time

Table 4. Onset and Spontaneous Recovery of Twitch Depression for Infants and Children Given Intramuscular or Intravenous Rapacuronium in Part II

	Infants		Children	
	Intramuscular	Intravenous	Intramuscular	Intravenous
N	11	12	11	11
Dose (mg/kg)	2.8	2.0	4.8	3.0
Age (infants in months, children in years)	6.7 ± 3.1	7.2 ± 2.4	2.6 ± 0.8	2.3 ± 0.9
Weight (kg)	7.9 ± 1.8	7.8 ± 1.6	13.4 ± 2.2	12.5 ± 3.0
Onset (min)*				
10% twitch depression	1.6 ± 0.7	0.3 ± 0.1	1.6 ± 0.4	0.3 ± 0.1
50% twitch depression	2.3 ± 0.9	0.3 ± 0.1	2.2 ± 0.6	0.4 ± 0.1
90% twitch depression	3.6 ± 1.6	0.4 ± 0.1	3.1 ± 1.0	0.5 ± 0.2
Maximum twitch depression	5.7 ± 2.9	0.6 ± 0.3	5.5 ± 2.7	0.8 ± 0.3
Spontaneous recovery (min)*				
Initial recovery	22 ± 11†	14 ± 7.9‖	26 ± 10	15 ± 3.1
10% recovery	31 ± 14†	17 ± 7.3‖	36 ± 14	18 ± 2.8
25% recovery	39 ± 17‡	20 ± 6.7‖	49 ± 17†	22 ± 3.5
90% recovery	82 ± 19§	48 ± 8.0‡	156 ± 31#	46 ± 6.5‡

Values are mean ± SD.

* Values for intramuscular and intravenous administration differ significantly ($P < 0.05$ by Student t test or the Mann-Whitney U test).

† N = 10.

‡ N = 9.

§ N = 3.

‖ N = 11.

N = 4.

course of muscle relaxants at the diaphragm that measured either electrical activity[6] or transdiaphragmatic pressure changes in response to phrenic nerve stimulation,[8] we chose a simpler measure, minute ventilation. We assumed that the time at which minute ventilation decreased 50% from pre-drug values indicates onset of diaphragmatic or intercostal muscle paralysis.

Average time to ventilatory depression with intramuscularly administered rapacuronium was 1.6 min in infants and children. These values are longer than with commonly used doses of intramuscular succinylcholine (median of 1.3 min for infants and 1.1 min for children) and intravenous vecuronium (median of 0.7 min for infants and 0.6 min for children), which suggests that tracheal intubation would not be possible as early with intramuscular rapacuronium as with these other two drugs. However, the magnitude of delay with intramuscular rapacuronium appears to be small—median time to ventilatory depression with intramuscular rapacuronium was only 0.5 and 1.0 min longer than with intramuscular succinylcholine and intravenous vecuronium, respectively. Our part I findings suggest that rapacuronium should permit tracheal intubation soon after its intramuscular administration, leading to the second part of our study. Of note, all patients who developed ventilatory depression more than 2.5 min after intramuscular administration of rapacuronium in part I received rapacuronium doses less than those given in part II.

Table 5. Values for Twitch Tension at Time Intervals after Intramuscular Administration of Rapacuronium to Infants (2.8 mg/kg) and Children (4.8 mg/kg) in Part II

Time Interval (min)	Infants	Children
2.0	33 (3–98)	63 (1–100)
2.5	20 (0–98)	33 (0–82)
3.0	16 (0–83)	18 (0–56)

Values are percent of control, median (range).

In part II, we determined the optimal intubation time with intramuscularly administered rapacuronium. Anesthetic doses were minimal, barely sufficient to prevent spontaneous movement and often inadequate to prevent movement in response to intramuscular injection. We selected these minimal anesthetic conditions to ensure that successful intubation could be attributed, at least partially, to the effect of the muscle relaxant and not merely to anesthetic depth.[9] We demonstrated that intramuscular rapacuronium allows tracheal intubation in 2.5–3.0 min, despite a light plane of anesthesia. This finding suggests that intramuscular rapacuronium is an

appropriate muscle relaxant to facilitate non-emergent securing of the airway. Initial recovery typically occurs within 30 min of intramuscular administration; this contrasts to initial recovery with intramuscular rocuronium occurring at ~ 1 h,[5] suggesting that intramuscular rapacuronium may have greater clinical utility compared with intramuscular rocuronium for brief procedures.

In part II, we also examined the time course of intravenous rapacuronium. We demonstrated that doses of 2 mg/kg in infants and 3 mg/kg in children typically depress twitch tension completely in < 1 min, permit tracheal intubation with good or excellent conditions at 1 min, and allow 25% recovery in < 25 min in infants and children. Although we did not obtain concurrent data for rocuronium (whose onset is presumably the fastest of presently available nondepolarizing muscle relaxants), these values for rapacuronium indicate that its onset and initial recovery are faster than those for rocuronium. For example, with 0.6 mg/kg rocuronium in children, onset time was 1.3 ± 0.7 min, and clinical duration was 26.7 ± 6.6 min,[10] both delayed compared with the values for intravenous rapacuronium in the present study. Intravenous rapacuronium's rapid onset and short duration of action will be particularly useful for children undergoing brief surgical procedures when muscle relaxants are desired to facilitate surgical conditions or tracheal intubation (when venous access has already been established).

Duration of action of intramuscular rapacuronium was longer than that of intravenous doses. Two factors contribute to this finding. First, the dose given intramuscularly was larger than the dose given intravenously; however, until data are available on the bioavailability of intramuscular administration, the magnitude of the difference between absorbed doses is unknown. Second, intramuscular administration delays absorption, thereby prolonging the effect.

Median time to 50% ventilatory depression with 4 mg/kg of intramuscular succinylcholine in the present study was 1.3 min in infants and 1.1 min in children. These results appear to differ from those of Mazze and Dunbar,[11] who reported apnea at 3.5 min with administration of 2.2 mg/kg intramuscular succinylcholine. It is likely that the larger dose in our study explains, at least partially, the difference between the two findings. In addition, Mazze and Dunbar did not report the criteria defining apnea, limiting comparison of the two studies.

Several aspects of our study warrant comment. First, in part I, we measured the time to 50% depression of ventilation to determine the optimal dose to be used in part II. We recognize that 50% depression of minute ventilation is not associated with sufficient muscle paralysis to ensure adequate intubating conditions. However, we chose 50%, rather than 90% or 95%, depression of ventilation so that the time at which ventilation was controlled was more likely a function of depression of minute ventilation rather than either hypoxemia or hypercapnia. In addition, the primary objective of the dosing regimen in part I was to ensure that the rapacuronium dose depressed ventilation but did not produce prolonged paralysis. As all but one infant and one child in part I (both of whom received doses smaller than those used in part II) developed > 95% twitch depression, we assumed that doses selected for part II would eventually ensure complete paralysis. Therefore, in part II, we determined the earliest time at which intubation could be accomplished consistently.

The second issue regarding our study is that the assessor was not blinded to the elapsed time between rapacuronium administration and tracheal intubation or to the response to tracheal intubation of the previous patient. Although blinding could have been accomplished by having the assessor enter the operating room immediately before the attempt at intubation, the assessor would not have been blinded to the drug administered or the dose. With this consideration, we performed the study without blinding. We recognize that acceptance of intramuscular rapacuronium for clinical use depends on confirmation of our results in a larger, assessor-blinded study.

The third issue is that halothane doses selected for part II were insufficient to permit tracheal intubation in the absence of muscle relaxants. Although nitrous oxide was used to facilitate induction of anesthesia, it was discontinued several minutes before tracheal intubation was attempted, and end-tidal concentrations at the time of tracheal intubation were minimal. The halothane doses, approximately 85% of the age-adjusted MAC for tracheal intubation,[12] would not be expected to permit tracheal intubation in the absence of paralysis and did not permit successful intubation when tracheal intubation was attempted at 1.5 min or earlier. However, with the onset of twitch depression and, presumably, paralysis of the respiratory muscles, attempts at tracheal intubation were generally successful at 2.5 min or later. Had we administered usual doses of anesthetics, it is likely that intubating conditions would be better than those in the present study—a larger dose of inhaled anesthetic would facilitate intubation both directly and by potentiating the effects of rapacuronium. In turn, administration of intra-

muscular rapacuronium might permit tracheal intubation at a lighter plane of anesthesia than in the absence of muscle relaxants, thereby permitting clinicians to avoid anesthetic overdose and the resulting cardiovascular depression.

The final issue regarding our study is that twitch was often not completely depressed at the time of tracheal intubation. However, with rapacuronium,[13] as with other muscle relaxants,[14,15] the respiratory muscles become paralyzed before the adductor pollicis, presumably because higher blood flow to these muscles delivers effective concentrations of the muscle relaxant earlier. Thus, the quantity of twitch depression observed in our patients at the time of tracheal intubation (table 5) likely underrepresents paralysis of the respiratory muscles.

In summary, our pilot study suggests that the onset and recovery characteristics of intramuscular rapacuronium make it a suitable alternative to the elective administration of intramuscular succinylcholine for brief anesthetics. However, the onset of intramuscular rapacuronium is too slow to be appropriate for emergency use (and is slower than that of intravenous rapacuronium) and its duration of action is longer than with intervenous administration. With intervenous administration, rapacuronium has a rapid onset and short-intermediate duration of action.

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