Anesthesiology
1999; 91:633–8

Intramuscular Rocuronium in Infants and Children

A Multicenter Study To Evaluate Tracheal Intubating Conditions, Onset, and Duration of Action

Richard F. Kaplan, M.D., T. Uejima, M.D.,† G. Lobel, M.D.,‡ N. Goudsouzian, M.D., M.S.,§ B. Ginsberg, M.D.,‖ Raafat Hannallah, M.D.,# Charles J. Coté, M.D.,** William Denman, M.D.,†† Renny Griffith, M.D.,‡‡ Chris Clarke, M.D.,‡‡ Kelly Hummer, R.N.§§*

Background: **This multicenter, assessor-blinded, randomized study was done to confirm and extend a pilot study showing that intramuscular rocuronium can provide adequate tracheal intubating conditions in infants (2.5 min) and children (3 min) during halothane anesthesia.**

Methods: **Thirty-eight infants (age range, 3–12 months) and 38 children (age range, 1 to 5 yr) classified as American Society of Anesthesiologists physical status 1 and 2 were evaluated at four investigational sites. Anesthesia was maintained with halothane and oxygen (1% end-tidal concentration if < 2.5 yr; 0.80% end-tidal concentration if > 2.5 yr) for 5 min. One half of the patients received 0.45 mg/kg intravenous rocuronium. The others received 1 mg/kg (infants) or 1.8 mg/kg (children) of intramuscular rocuronium into the deltoid muscle. Intubating conditions and mechanomyographic responses to ulnar nerve stimulation were assessed.**

Results: **The conditions for tracheal intubation at 2.5 and 3 min in infants and children, respectively, were inadequate in a high percentage of patients in the intramuscular group. Nine of 16 infants and 10 of 17 children had adequate or better intubating conditions at 3.5 and 4 min, respectively, after intramuscular rocuronium. Better-than-adequate intubating conditions were achieved in 14 of 15 infants and 16 of 17 children given intravenous rocuronium. Intramuscular rocuronium provided ≥ 98% blockade in 7.4 ± 3.4 min (in infants) and 8 ± 6.3 min (in children). Twenty-five percent recovery occurred in 79 ± 26 min (in infants) and in 86 ± 22 min (in children).**

Conclusions: **Intramuscular rocuronium, in the doses and conditions tested, does not consistently provide satisfactory tracheal intubating conditions in infants and children and is not an adequate alternative to intramuscular succinylcholine when rapid intubation is necessary. (Key words: Muscle relaxant; neuromuscular relaxants; pediatric.)**

SUCCINYLCHOLINE is the only clinically accepted muscle relaxant that, when given intramuscularly to children, provides satisfactory relaxation in 3 or 4 min.[1] Rare occurrences of hyperkalemia[2] and its association with cardiac dysrhythmias, increased intraocular pressure, muscle fasiculation, and malignant hyperthermia have prompted the Food and Drug Administration to revise the package insert for succinylcholine in the United States to read "the use of succinylcholine in children should be reserved for emergency intubation or for instances where immediate securing of the airway is necessary . . . or for intramuscular use when a suitable vein is inaccessible."‖‖‖‖ A nondepolarizing muscle relaxant that is rapidly effective when given intramuscularly could replace the need for intramuscular succinylcholine and obviate its unwanted side effects.[3]

* Associate Professor of Anesthesiology and Pediatrics, Children's National Medical Center.

† Assistant Professor of Anesthesiology, Children's Memorial Hospital.

‡ Fellow in Anesthesiology, Children's Memorial Hospital.

§ Associate Professor of Anesthesiology, Massachusetts General Hospital.

‖ Associate Professor of Anesthesiology, Duke University Medical Center.

Professor of Anesthesiology and Pediatrics, Children's National Medical Center.

** Professor of Anesthesiology and Pediatrics, Children's Memorial Hospital.

†† Assistant Professor of Anesthesiology, Massachusetts General Hospital.

‡‡ Fellow in Anesthesiology, Children's National Medical Center.

§§ Anesthesiology Research Nurse, Children's National Medical Center.

Received from the Departments of Anesthesiology, Children's National Medical Center, Washington, DC; Children's Memorial Hospital, Chicago, Illinois; Massachusetts General Hospital, Boston, Massachusetts; and Duke University Medical Center, Durham, North Carolina. Submitted for publication December 22, 1998. Accepted for publication April 12, 1999. Sponsored in part by Organon, Inc. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Diego, California, October 1997.

Address reprint requests to Dr. Kaplan: Department of Anesthesiology, Children's National Medical Center, 111 Michigan Avenue, N.W., Washington, DC 20010. Address electronic mail to: rkaplan@cnmc.org

‖‖‖‖ Package insert for succinylcholine. Research Triangle Park, NC, Burroughs Wellcome Co., November 1994.

Table 1. Demographic Information of Study Children (n = 75*)

	Infants (3 mo–<1 yr)		Children (1–6 yr)	
	Intramuscular Rocuronium 1.0 mg/kg (n = 19)	Intravenous Rocuronium 0.45 mg/kg (n = 18)	Intramuscular Rocuronium 1.8 mg/kg (n = 19)	Intravenous Rocuronium 0.45 mg/kg (n = 19)
Age†	7 ± 2 mo	7 ± 3 mo	2 ± 2 yr	3 ± 1 yr
Height (cm)†	65 ± 8.6	70 ± 9.2	91 ± 13.6	97 ± 10.0
Weight (kg)†	7.9 ± 1.8	7.7 ± 2.1	13.5 ± 3.0	15.7 ± 3.0
Male [n (%)]	13 (68)	12 (67)	14 (74)	13 (68)
Female [n (%)]	6 (32)	6 (33)	5 (26)	6 (32)
ASA PS 1 [n (%)]	18 (95)	13 (72)	17 (89)	16 (84)
ASA PS 2 [n (%)]	1 (5)	5 (28)	2 (11)	3 (16)

ASA PS = American Society of Anesthesiologists physical status.

* Five of the originally selected 80 subjects had protocol violations and are not included in data analysis. Protocol violations included incorrect doses of rocuronium (n = 3) and administration of an inhalation agent other than halothane (n = 2).

† Values are mean ± SD. There were no statistically significant differences between intramuscular and intravenous groups.

Intramuscular mivacurium has been studied but was found to have a time-to-peak twitch depression of more than 15 min.[4] A pilot study investigated intramuscular rocuronium (Zemuron; Organon, West Orange, NJ) in children.[5] That study found that infants, ages 3–12 months (n = 10), given 1 mg/kg intramuscular rocuronium (to the deltoid muscle) under light halothane anesthesia, had 100% twitch depression in 6.4 min and spontaneous recovery to 90% twitch height in 104 min. Children, ages 1–5 yr (n = 10), given 1.8 mg/kg rocuronium had 100% twitch depression in 5.2 min and 90% recovery in 124 min. Light halothane anesthesia in this study was defined as end-tidal concentrations of 1% in children younger than 2.5 yr and 0.82% in children older than 2.5 yr. All patients had adequate or good-to-excellent tracheal intubating conditions at 2.5 min in infants and at 3 min in children.

The objectives of this multicenter, assessor-blinded, randomized study was to confirm and extend the findings of the previous study[5] by examining the neuromuscular blocking effects and tracheal intubating conditions of intramuscular rocuronium in a larger group of infants and children under light halothane anesthesia. Neuromuscular effects and intubating conditions were also compared with intravenous doses of rocuronium (control).

Methods

The study was approved by the institutional review boards of each center. After parents gave their informed consent, 80 patients classified as American Society of Anesthesiologists physical status 1 or 2 who were 3 months to less than 6 yr and undergoing surgery with nitrous oxide–oxygen–halothane anesthesia were enrolled in the study. Infants (ages 3 to 12 months) and children (ages 1 through 5 yr) were evenly distributed among the four study sites. Patients were excluded if they (1) weighed > 20 kg; (2) had abnormalities of the airway; (3) had renal, hepatic, metabolic, or neuromuscular disorders; (4) had bleeding disorders; or (5) were receiving anticonvulsants, antibiotics, or other drugs known to effect neuromuscular activity. Protocol violations included incorrect doses of rocuronium (n = 3) and administration of an inhalation agent other than halothane (n = 2), and these resulted in available data for analysis from only 75 of the original 80 patients. Table 1 shows the demographic data of these 75 patients.

No premedicants were used. Anesthesia was induced with halothane and nitrous oxide delivered *via* face mask. A pulse oximeter, electrocardiograph, precordial stethoscope, and noninvasive blood pressure cuff were applied. An intravenous catheter was placed after loss of eyelid reflex. Anesthesia was maintained with halothane–oxygen (1% end-tidal concentration in patients < 2.5 yr; 0.80% end-tidal concentration in patients > 2.5 yr) for at least 5 min. Normocarbia was maintained by assisted ventilation and was assessed using clinical signs and the end-tidal carbon dioxide concentration. During this time, the ulnar nerve was stimulated at the wrist with surface electrodes using supramaximal square-wave train-of-four stimuli administered at 2 Hz every 20 s (Dual Stim Peripheral Nerve Stimulator, Life-Tech, Houston, TX). Baseline tension (50–100 g) was applied to the

Table 2. Intubating Conditions

Excellent:	Jaw relaxed, vocal cords apart and immobile; no diaphragmatic movement
Good:	Jaw relaxed, vocal cords apart and immobile, some diaphragmatic movement
Adequate:	Jaw relaxed, vocal cords immobile and vigorous coughing
Poor:	Jaw relaxed, vocal cords moving, "bucking"
Inadequate:	Jaw not relaxed, vocal cords closed

thumb. Mechanomyographic monitoring of the force of adduction of the thumb was recorded using a Myotrace adductor pollicus monitor (Professional Instruments, Houston, TX) and strip chart recorder. After 5 min of twitch stabilization, patients in each age group were randomly assigned to receive either intravenous or intramuscular rocuronium. All patients randomized to receive intravenous rocuronium received 0.45 mg/kg as a rapid bolus (in $<$ 5 s). Intramuscular rocuronium was administered as a rapid single injection into the deltoid muscle. Based on the results of the pilot study,[5] the intramuscular rocuronium doses for infants (ages 3 to 12 months) and children (1 to 5 yr) were 1 mg/kg and 1.8 mg/kg, respectively. Laryngoscopy and tracheal intubation was attempted by one of the two senior investigators at each site. The laryngoscopist entered the room after rocuronium administration. This person was blinded to the route of administration of rocuronium and the twitch response. Ten of 80 patients were enrolled in the initial period of this study. Laryngoscopy in these patients was initiated at 2.5 min (for infants) and 3 min (for children) after the muscle relaxant was administered. In the remaining patients, intubation was attempted at 3.5 min for infants and at 4 min for children. Intubating conditions were scored as shown in table 2. Anesthesia was maintained after intubation with nitrous oxide (60%), oxygen, and 0.8 to 1 MAC concentrations of halothane and fentanyl as clinically indicated. Atropine was not used during induction or maintenance. If clinically appropriate, spontaneous recovery of T_1 to 90% control was allowed. If necessary, residual neuromuscular blockade was antagonized at the end of surgery with 0.02 mg/kg atropine and 0.07 mg/kg neostigmine. The intramuscular injection site was assessed for redness, swelling, and bruising 5 min after injection and at the conclusion of surgery. Histamine-related clinical findings such as erythema, hives, or bronchospasm were recorded.

Pharmacodynamic parameters are expressed as the mean $\pm$ SD. Peak effect; onset time; time to 80% block; time from rocuronium injection to 25%, 50%, and 90% recovery; and return of T_4–T_1 to 70% between treatment groups, age groups, and centers were compared using a three-way analysis of variance. The Cochran–Mantel–Haenszel procedure (adjusted for age group and study center) was used to identify the difference in intubating conditions between treatment groups and age groups. Results were considered significant at $P < 0.05$.

Results

Patients in each age group and institution were comparable with respect to age, height, weight, gender, race, and American Society of Anesthesiologists physical status (table 1).

Neuromuscular Response

All groups had mean complete twitch depressions of $\geq$98% (table 3 and fig. 1). Time to complete twitch depression ("onset") was 7.4 $\pm$ 3.4 min and 8.9 $\pm$ 6.3 min for intramuscular injection in infants and children, respectively. Time to recovery of 25% of T_1 was 79 $\pm$ 26 min and 86 $\pm$ 22 min for intramuscular injection in infants and children, respectively. The time to complete twitch depression in the intravenous group was 2.5 $\pm$ 2.1 min and 2.4 $\pm$ 1.5 min for infants and children, respectively. 25% recovery of T_1 occurred in 27 $\pm$ 6 min and 18 $\pm$ 8 min in infants and children, respectively. All onset and recovery times between the intramuscular and intravenous groups were highly significant by analysis of variance ($P \leq 0.01$). There were no significant differences among the four investigational sites.

Laryngoscopy and Tracheal Intubation

Laryngoscopy and tracheal intubation in the first 10 patients was attempted at 2.5 min for infants and 3 min for children. All patients given intravenous rocuronium had adequate or excellent intubating conditions. In contrast, four of five patients in the intramuscular group had poor or inadequate intubating conditions (table 4). Considering that neuromuscular blockade at the thumb was not fully developed at this stage, the time for laryngoscopy and tracheal intubation in all remaining patients was extended by 1 min to 3.5 min for infants and to 4 min for children. Laryngoscopy and tracheal intubation attempts at these extended times resulted in 9 of 16 infants and 10 of 17 children having adequate or good-to-excellent

Table 3. Pharmacodynamic Response of Infants and Children Given Rocuronium

	Infants		Children	
	Intramuscular	Intravenous	Intramuscular	Intravenous
Dose (mg/kg)	1.0 (n = 19)	0.45 (n = 18)	1.8 (n = 19)	0.45 (n = 19)
Peak effect–% twitch depression				
Mean	100 ± 0	99 ± 2	100 ± 0	98 ± 5
Range	98–100	91–100	99–100	80–100
Onset (min)	7.4 ± 3.4	2.5 ± 2.1	8.9 ± 6.3	2.4 ± 1.5
Range (min)	(3.3–11.5)	(0.7–3.7)	(4.0–31)	(0.4–5.3)
80% twitch depression range (min)	5.3 ± 2.9 (1.6–8.7)	1.4 ± 0.8 (0.6–4.0)	6.3 ± 3.5 (3.7–18)	1.6 ± 1.4 (0.5–5.1)
Spontaneous recovery				
25% recovery (min)	79 ± 26	27 ± 6	86 ± 22	18 ± 8
Range (min)	(47–139) (n = 18)	(15–38) (n = 15)	(55–129) (n = 16)	(3–26) (n = 19)
50% recovery (min)	91 ± 30	34 ± 7	98 ± 25	21 ± 9
Range (min)	(53–160) (n = 18)	(18–48) (n = 14)	(61–146) (n = 14)	(11–36) (n = 18)
90% recovery (min)	112 ± 36	52 ± 20	120 ± 29	32 ± 13
Range (min)	(66–187) (n = 15)	(21–93) (n = 12)	(83–182) (n = 12)	(8–60) (n = 16)
70% T_4/T_1 ratio	124 ± 37	54 ± 18	125 ± 35	32 ± 16
Range	(71–190) (n = 13)	(29–99) (n = 11)	(88–106) (n = 11)	(10–76) (n = 15)

Values are mean ± SD (n = number of patients). All onset and recovery times between intramuscular and intravenous doses were statistically significant in each age group; ANOVA, $P \leq 0.01$.

intubating conditions in response to intramuscular rocuronium. The results were significantly different for the intravenous group, where 14 of 15 infants and 15 of 16 children had adequate or good to excellent intubating conditions (table 5).

Adverse Events

Twenty-eight percent of patients (11 of 39) given intramuscular rocuronium had localized injection site reactions (bruising, swelling, hives) noted 5 min after injection. All localized reactions caused by intramuscular

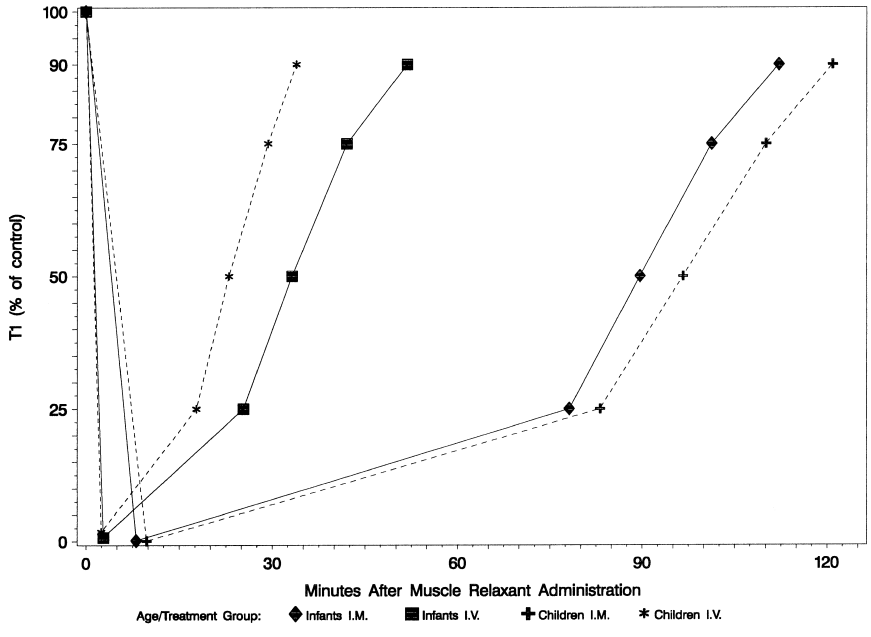

Fig. 1. The mean onset, peak effect, and recovery parameters of intravenous and intramuscular rocuronium for infants and children.

Table 4. Intubating Conditions at 2.5 min (Infants) and 3.0 min (Children) in Initial 10 Patients

Study Group		Excellent	Good	Adequate	Poor	Inadequate
Infants (n = 5)	Intramuscular rocuronium 1.0 mg/kg	0	0	0	3	0
	Intravenous rocuronium 0.45 mg/kg	2	0	0	0	0
Children (n = 5)	Intramuscular rocuronium 1.8 mg/kg	0	0	1	0	1
	Intravenous rocuronium 0.45 mg/kg	2	0	1	0	0

rocuronium resolved by the end of surgery. No patient exhibited clinical evidence of histamine release, such as systemic erythema, hives, or bronchospasm.

Discussion

We could not verify the observations of the earlier study[5] that showed that infants given 1 mg/kg and children given 1.8 mg/kg intramuscular rocuronium during light halothane anesthesia could have adequate or good-to-excellent tracheal intubating conditions at 2.5 and 3 min, respectively. Our multicenter, randomized study was specifically designed to confirm and extend these observations. Similar concentrations of halothane, the timing of deltoid injections, and the rating scale for the quality of intubation were used in both studies. In the previous study,[5] the person performing the intubation was not blinded to the timing of the muscle relaxant or neuromuscular response. Intubation in our multicenter study was performed only by senior investigators, who were unaware of the dose and route of rocuronium and the results of the train-of-four stimulation at the time of intubation. In the previous study, an "up-down" approach was used to determine the timing of intramuscular rocuronium, which was associated with adequate or better intubating conditions. The recommended time for intubation was based on the results of four infants at ≥2.5 min and five children at ≥3 min. The first three infants given intramuscular rocuronium in our study had poor intubating conditions after 2.5 min. Of the first children given intramuscular rocuronium, one had adequate and the other inadequate intubating conditions after 3 min. These preliminary findings after intramuscular rocuronium led us to extend the time from injection to laryngoscopy and intubation by one additional minute. This improved the incidence of adequate or good-to-excellent intubating conditions for the intramuscular group to 9 of 16 infants and 10 of 17 children. It still, however, resulted in poor or inadequate intubating conditions in more than 40% of the sample (seven infants and seven children). Additional prolongation of the time from injection to intubation might have improved intubating conditions, because the neuromuscular response was decreasing but was thought to be too long to be clinically relevant.

The poorer intramuscular intubating conditions in our study is consistent with a longer time to peak effect of intramuscular rocuronium compared with the previous study.[5] The current study showed a mean (± SD) time to peak effect of 7.4 ± 3.4 min in infants (n = 19) and 8.9 ± 6.3 min in children (n = 19). The previous study had times to peak effects of 6.4 ± 1.6 min in infants (n =

Table 5. Intubating Conditions of Infants and Children at 3.5 min and 4.0 min (n = 64)

Study Group		Excellent	Good	Adequate	Poor	Inadequate
Infants (n = 31)	Intramuscular rocuronium 1.0 mg/kg	3	1	5	5	2
	Intravenous rocuronium 0.45 mg/kg	10	3	1	1	0
Children (n = 33)	Intramuscular rocuronium 1.8 mg/kg	3	3	4	5	2
	Intravenous rocuronium 0.45 mg/kg	14	1	0	1	0

Intubating conditions were significantly better ($P < 0.01$) in the intravenous group than in the intramuscular group for both age groups. One child's intubation was attempted at a time other than the protocol-specified time and is not included in intubation conditions.

10) and 5.2 ± 0.8 min in children (n = 10). The differences between the results of the two studies occurred despite great care taken to duplicate the technique of intramuscular injection, the rating scale of intubation, the dose of intramuscular rocuronium, and administration of halothane.

We have no specific explanation for the differences in the results of our current study and the previously described intramuscular rocuronium study.[5] Our study reinforces the concept that a single study should be confirmed by several independent studies or in a well-designed multicenter, randomized, blinded study.

Our study does not support the hypothesis that intramuscular rocuronium in the doses and conditions used is an appropriate alternative to intramuscular succinylcholine when satisfactory relaxation for intubation is needed in 3.5 to 4 min in infants and children, respectively. It should be emphasized that the dose of halothane used during this study produced light anesthesia such that many patients moved in response to intramuscular injection. This light level of inhalational anesthesia was picked so that the success of intubation would depend on the muscle relaxant and not the inhalational anesthetic. Higher concentrations of inhalational anesthetic, as frequently used by clinicians during inhalation inductions, would be expected to improve intubating conditions.

None of the patients in our study had evidence of postoperative residual neuromuscular blockade after reversal with neostigmine and atropine. This verifies the results of a previous intramuscular rocuronium[6] study. Children in that study who were given intramuscular deltoid rocuronium under halothane anesthesia had peak plasma concentrations at 13 min and 80% bioavailability from the intramuscular site. Simulation showed that less than 4% of the administered dose remained to be absorbed from the intramuscular site 30 min after injection. Thus there is no basis for the supposition that children might be "recurarized" from residual intramuscular rocuronium if more than 30 min elapses from the time of injection and adequate reversal and monitoring are used.

The intravenous doses of rocuronium used in our study are approximately 1.5 times the ED_{95} dose found in children during nitrous oxide–halothane anesthesia.[7] The time to 100% twitch depression and return to T_1 of 25% in our study is consistent with the results of other studies.[7] Patients given intravenous rocuronium served as a control to compare the effectiveness of intramuscular rocuronium and to verify our technique of neuromuscular monitoring.

In conclusion, intramuscular rocuronium in doses of 1 mg/kg in infants and 1.8 mg/kg in children provided complete neuromuscular blockade in 7.4 ± 3.4 and 8.9 ± 6.3 min, respectively. Twenty-five percent recovery in infants and children occurred in 79 ± 26 and 86 ± 22 min, respectively. This multicenter, assessor-blinded, randomized study could not verify the results of a previous intramuscular study[5] that showed that intramuscular rocuronium injected into the deltoid muscle produced adequate or good-to-excellent intubating conditions in 2.5 min in infants or in 3 min in children under light halothane anesthesia. In our study, 7 of 16 infants given a 1 mg/kg intramuscular injection of rocuronium had poor or inadequate intubating conditions 3.5 min after injection. Similarly, 7 of 17 children had poor or inadequate intubating conditions 4 min after a 1.8 mg/kg injection. Our study does not support the hypothesis that intramuscular rocuronium in the doses used and conditions of this study is an appropriate alternative to succinylcholine when satisfactory relaxation for intubation is needed in 3.5 and 4 min in infants and children, respectively.

The authors thank P. Abraham for additional technical support.

References

1. Liu LMP, DeCook TH, Goudsouzian NG, Ryan JR, Liu PL: Dose response to intramuscular succinylcholine in children. ANESTHESIOLOGY 1981; 55:599–602

2. Rosenberg H, Gronert GA: Intractable cardiac arrest in children given succinylcholine (letter). ANESTHESIOLOGY 1992; 77:1054

3. Berry FA: Intramuscular rocuronium in infants and children—Is there a need? ANESTHESIOLOGY 1996; 85:229–30

4. Cauldwell CB, Lau M, Fisher DM: Is intramuscular mivacurium an alternative to intramuscular succinylcholine? ANESTHESIOLOGY 1994; 80: 320–5

5. Reynolds LM, Lau M, Brown R, Luks A, Fisher DM: Intramuscular rocuronium in infants and children: Dose-ranging and tracheal intubating conditions. ANESTHESIOLOGY 1996; 85:231–9

6. Reynolds LM, Lau M, Brown R, Luks A, Sharma M, Fisher DM: Bioavailability of intramuscular rocuronium in infants and children. ANESTHESIOLOGY 1997; 87:1096–1105

7. Woelfel SK, Brandom BW, Cook RD, Sarner JB: Effects of bolus administration of Org9426 in children during nitrous oxide-halothane anesthesia. ANESTHESIOLOGY 1992; 76:933–42