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Intramuscular Rapacuronium in Infants and Children

A Comparative Multicenter Study to Confirm the Efficacy and Safety of the Age-related Tracheal Intubating Doses of Intramuscular Rapacuronium (ORG 9487) in Two Groups of Pediatric Subjects

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Background: **This multicenter, assessor, blinded, randomized study was conducted to confirm and extend a pilot study in which intramuscular rapacuronium was given to infants and children to confirm efficacy and to evaluate tracheal intubating conditions.**

Methods: **Ninety-six pediatric patients were studied in two groups: infants aged 1 to 12 months (n = 46) and children aged 1 to 3 yr (n = 50). Infants received 2.8 mg/kg and children 4.8 mg/kg of intramuscular rapacuronium during 1 minimum alveolar concentration halothane anesthesia. These two groups were studied in three subgroups, depending on the time (1.5, 3, or 4 min) at which tracheal intubation was attempted after the administration of intramuscular rapacuronium into the deltoid muscle. Neuromuscular data collected included onset time, duration of action, and recovery data during train-of-four stimulation at 0.1 Hz. Data were analyzed by the Cochran-Mantel-Haenszel procedure.**

Results: **The tracheal intubating conditions were deemed acceptable in 17, 36, and 64% of infants and 20, 47, and 71% of children at 1.5, 3, or 4 min, respectively. The mean values for % of control twitch height (T1) 2 min after rapacuronium in both groups were similar. The mean (SD) time required to achieve more than or equal to 95% twitch depression in infants was 6.0 (3.7) *versus* 5.5 (3.8) min in children.**

Conclusions: **Only 27% of patients achieved clinically acceptable tracheal intubating conditions at 1.5 or 3 min after administration of 2.8 mg/kg and 4.8 mg/kg rapacuronium during 1 minimum alveolar concentration halothane anesthesia. Tracheal intubation conditions at 4 min were acceptable in 69% of subjects. The duration of action of 4.8 mg/kg of rapacuronium in children was longer than 2.8 mg/kg of rapacuronium in infants.**

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RAPACURONIUM (Raplon; Organon, Inc., West Orange, NJ) is a recently introduced nondepolarizing muscle relaxant. It has a relatively rapid onset and short duration of action when given intravenously with adequate tracheal intubating conditions occurring within 90 s when administered intravenously in a dose of 1.0–1.5 mg/kg to both children and adults.[1–5] Presently, the recommended dose for tracheal intubation is 1.5 mg/kg in adults and 2 mg/kg in children.[6,7]

Succinylcholine is presently the only recommended muscle relaxant for intramuscular use in infants and children providing satisfactory tracheal intubating conditions in 3–4 min.[8,9] However, the side effects of succinylcholine—hyperkalemia, cardiac dysrhythmias, increased intraocular pressure, muscle fasciculations, and a triggering agent for malignant hyperthermia—have prompted the Food and Drug Administration to issue a warning for its elective use in children.[10] Therefore, a nondepolarizing muscle relaxant for intramuscular use would be useful. A recent study showed that intramuscular rapacuronium, at doses of 2.8 mg/kg in infants and 4.8 mg/kg in children, provided adequate tracheal intubating conditions in infants and children within 2.5–3.0 min.[11] This multicenter study was undertaken to corroborate and elicit further the intubating conditions for these subject groups and to define the optimum intubation time.

Methods

The Institutional Review Boards at each center approved this study (Massachusetts General Hospital, Boston, MA; Children's National Medical Center, Washington, DC; Children's Hospital Medical Center, Chicago, IL; Duke University Medical Center, Durham, NC). Informed written consent was obtained from the parents or legal guardians of the 96 patients enrolled. All subjects were classified as American Society of Anesthesiologists physical status I or II. Of these 96 subjects, 46 were infants (aged 1–12 months) and 50 were children (aged 1–3 yr; table 1). Of the 46 infants, 15 were randomized

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Table 1. Subject Demographic Information (N = 96)

	Infants (n = 46)	Children (n = 50)
Age (months)*	6 ± 3	22 ± 11
Weight (kg)*	7.5 ± 1.9	11.9 ± 2.0
Height (cm)*	65.3 ± 7.8	82.3 ± 9.0
Gender (M/F)	30/13 (70%/30%)	33/13 (72%/28%)
ASA classification I	38 (88%)	41 (89%)
ASA classification II	5 (12%)	5 (11%)

There were no statistically significant differences between the intubation groups within infant or children groupings.

* Values are mean ± SD.

ASA = American Society of Anesthesiologists.

for attempted tracheal intubation at 1.5 min, 15 were randomized to the 3-min tracheal intubation time, and 16 were randomized to the 4-min tracheal intubation time. Of the 50 children, 17 were randomized for attempted tracheal intubation at 1.5 min, 17 were randomized at 3 min, and 16 were randomized at 4-min tracheal intubation time. All subjects were undergoing surgery in which a nitrous oxide–oxygen, halothane anesthetic was appropriate. Patients were excluded if they weighed more than 16.5 kg; had abnormalities of their airway; had significant renal, hepatic, metabolic, or neuromuscular disorders; had bleeding disorders; or were receiving drugs known to interfere with neuromuscular function. Nine subjects were excluded from analysis because of protocol violation. Of the nine protocol violations, seven were subjects not receiving the investigational drug, one was excluded because of inappropriate randomization, and one was excluded because the wrong dose of rapacuronium was given (table 2).

No premedicants were used. Anesthesia was induced with halothane and nitrous oxide–oxygen *via* a face mask. A pulse oximeter, electrocardiogram, and noninvasive blood pressure cuff were applied. An intravenous catheter was placed after loss of eyelid reflex. Anesthesia was maintained with halothane and oxygen at an end-tidal concentration of 1% in patients younger than 2.5 yr and 0.80% end-tidal concentration in patients older than 2.5 yr. After anesthetic induction and intravenous placement, nitrous oxide was discontinued. Rapacuronium was given 5 min after the discontinuation of nitrous oxide. Rapacuronium was given in all cases within 15 min of starting the anesthetic. End-tidal carbon dioxide was monitored in all subjects, and normocapnia was maintained using assisted ventilation if required. After induction of anesthesia, the ulnar nerve was stimulated at the wrist with surface electrodes using supramaximal square-wave train-of-four stimulus administered at 2 Hz every 20 s (Dual Stim Peripheral Nerve Stimulator, Life-Tech, Houston, TX). Neuromuscular monitoring of the force of adduction of the adductor pollicis was recorded using a mechanomyograph. The transducer used was a Grass F20 (Grass Instruments, Quincy, MA) or Myotrace (Life-Tech, Inc.), and a strip chart recording was obtained. A baseline tension of 50–100 g was applied to the thumb. Before calibration of the strip chart recording, a 50-Hz tetanic stimulus was delivered for 2 s. After baseline stabilization, which required a minimum of 5 min, infants received 2.8 mg/kg rapacuronium intramuscularly and children received 4.8 mg/kg of rapacuronium intramuscularly into the deltoid as a single bolus injection. The arm on the opposite side to the neuromuscular monitoring equipment was used to administer the rapacuronium *via* a 22- or 23-gauge needle. The time at which tracheal intubation was attempted was determined from a randomization table. After the administration of rapacuronium, an experienced laryngoscopist (one of the principal investigators at each institution, who was blinded to the time of injection) entered the room and was told when to begin the laryngoscopy. The choice of laryngoscope blade was at the discretion of the laryngoscopist. Depending on the randomization schedule, laryngoscopy was attempted at 1.5 min, 3 min, or 4 min after administration of rapacuronium. The experienced laryngoscopist then scored the intubation using the criteria shown in table 3.

After laryngoscopy and tracheal intubation, anesthesia was maintained with 60% nitrous oxide in oxygen and 0.8–1 minimum alveolar concentrations of halothane. Fentanyl was used for analgesia as clinically indicated. If clinically appropriate, recovery of neuromuscular func-

Table 2. Patients Excluded from Analysis

Subject Group	Subject No.	Intubation Time (min)	Reason for Discontinuation
Infant	102	1.5	Fault with strip chart
Infant	155	1.5	Randomization error
Infant	201	3.0	Bradycardia or laryngospasm
Infant	202	4.0	Fault with recording machine
Infant	204	3	Wrong dose given
Child	151	1.5	Bradycardia or hypotension
Child	154	4.0	Fault with strip chart
Child	252	1.5	Study equipment not available
Child	356	4.0	Manpower availability issue

Patients 102, 201, 202, 151, 154, 252, 356 were not administered the investigational drug. Patients 356 and 155 were administered the drug but were not studied.

Centers are delineated thus: 1 = Children's Hospital Medical Center, Chicago, Illinois; 2 = Duke University Hospital Medical Center, Durham, North Carolina; 3 = Massachusetts General Hospital, Boston, Massachusetts; 4 = Children's National Medical Center, Washington, DC.

Table 3. Scale Used to Assess Intubating Conditions

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

If all parameters were either good or excellent, conditions were rated as acceptable. If any parameter was poor, conditions were rated as poor. Subjects who failed intubation at first attempt were given a poor score.

Table 4. Intubating Conditions of Infants and Children at 1.5, 3.0, and 4.0 min after Intramuscular Rapacuionium

	Acceptable n (%) (Excellent/Good)	Unacceptable n (%) (Poor)
Infants (1 month–< 1 yr)		
1.5 min (N = 13)	2 (17)	10 (83)
3.0 min (N = 14)	5 (36)	9 (64)
4.0 min (N = 15)	9 (64)	5 (36)
Children (1–3 yr)		
1.5 min (N = 15)	3 (20)	12 (80)
3.0 min (N = 16)	7 (47)	8 (53)
4.0 min (N = 14)	10 (71)	4 (29)

n = total number of subjects within the intubation parameter; N = total number within the subject group/intubation time.

tion was allowed to proceed spontaneously to a twitch recovery of 90% as compared with final twitch response, if possible. However, if spontaneous neuromuscular recovery did not occur by the end of the procedure, residual neuromuscular block was reversed with 0.02 mg/kg atropine and 0.07 mg/kg neostigmine. The site of the intramuscular injection 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 were expressed as the mean (± SD), median, and range. Peak effect, onset time, time to 95% block, time from rapacuronium injection to 25%, 50%, and 90% recovery of the twitch height (T1), and the return of T4:T1 to 70% between treatment groups, age groups, and centers were compared using a three-way analysis of variance. The Cochran-Mantel-Haenszel procedure was used to identify the difference in intubating conditions between treatment groups and age groups. Results were considered significant at *P* less than 0.05.

Results

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

Tracheal Intubating Conditions

Intubating conditions were unacceptable in the majority of patients at 1.5 or 3 min after administration of rapacuronium in both groups. Tracheal intubating conditions were acceptable at 4 min in 64% of infants and 71% of children (table 4). Eleven subjects failed intubation at the first attempt and were all given a rating of poor.

Neuromuscular Data

In both infants and children, a mean twitch suppression more than or equal to 95% was achieved. Time to more than or equal to 95% twitch depression (onset) was 6.0 ± 3.7 min in infants and 5.5 ± 3.8 min in children. T1 (% of control) at 2 min was 67 ± 28% in infants and 67 ± 27% in children. The time for recovery of T1 to 25% of twitch height was 34.8 ± 11.7 min in infants (n = 33) and 43.8 ± 21.6 min in children (n = 29). The time for 90% spontaneous recovery of T1 to baseline twitch was 73.2 ± 21.3 min in infants (n = 17) and 106.0 ± 31.1 min in children (n = 6). The recovery index (T1, 25–75%) was 25 ± 12.4 min in infants (n = 22) and 56.2 ± 47.7 min in children (n = 11). Spontaneous recovery to a train-of-four ratio of 80% was obtained in 17 infants and 4 children and was 82.4 ± 18.5 in infants and 143 ± 16.1 in children. In assessing onset and recovery data, onset data were calculated using the initial twitch height of the initial train-of-four stimulus. Spontaneous recovery data were calculated using the final twitch height whenever possible. Reversal was administered if the T4/T1 ratio was less than 0.70 at the conclusion of the procedure (table 5).

Adverse Events

Adverse events occurred in 20 infants and 22 children. Two in the children's group were classified as serious. The serious adverse events were from one site: prolonged neuromuscular block in one patient and bronchospasm in another. In the subject who developed bronchospasm, it was rated as moderate in intensity, occurring as a response to tracheal intubation. Resolution of bronchospasm occurred after an increase in inspired halothane. The patient with prolonged neuromuscular block appeared weak postoperatively, despite full

Table 5. Pharmacodynamics of the Two Groups after Intramuscular Rapacoronium

	Infants (n = 42)	Children (n = 45)
Dose	2.8 mg/kg	4.8 mg/kg
Time to ≥95% twitch depression (min)		
n	39	39
Mean (SD)	60 (3.7)	5.5 (3.8)
Median	5.5	4.5
Range	1.9–22.1	2.4–24.6
T_1 (% of control) at 2 min		
n	40	44
Mean (SD)	67 (28)%	67 (27)%
Median	77%	44%
Range	4–100%	20–100%
Spontaneous recovery 25% Recovery (min)		
n	33	29
Mean (SD)	34.8 ± 11.7	43.8 ± 21.6
Range (min)	15.7–66.4	4.8–115.5
90% Recovery (min) of T_1		
n	17	6
Mean (SD)	73.2 ± 21.3	106.0 ± 39.1
Range (min)	39.8–125.0	62.1–160.5
70% T_4:T_1 ratio		
n	18	5
Mean ± (SD)	75.8 ± 16.5	153.0 ± 52.5
Range (min)	42.8–119.4	108.8–240.0

recovery of train-of-four response. In neither patient were there any long-term sequelae. All other adverse events noted were swelling or erythema at the injection site. The swelling and erythema had resolved by the end of surgery in all patients. There were no deaths during the study, and no subjects were discontinued from the study because of adverse events.

Discussion

In the present study, we did not obtain adequate intubating conditions in the majority of patients at 1.5 and 3 min after 2.8 mg/kg rapacuronium in infants and 4.8 mg/kg in children at 1 minimum alveolar concentration end-tidal halothane. When laryngoscopy was attempted 4 min after the administration of rapacuronium, the tracheal intubating conditions were acceptable in 64% and 71% of infants and children, respectively. Consequently, we do not recommend the use of intramuscular rapacuronium for tracheal intubation in infants and children while undergoing light halothane anesthesia.

This multicenter study could not confirm results of the previous study by Reynolds *et al.*,[11] in which 2.8 mg/kg intramuscular rapacuronium given to infants and 4.8 mg/kg intramuscular rapacuronium given to children provided adequate tracheal intubating conditions in 2.5–3.0 min after drug administration. We used similar concentrations of halothane and administered rapacuronium as a single dose intramuscularly into the deltoid and used the same scale for assessing the ease of laryngoscopy and tracheal intubation conditions (table 3). In the present study, only senior anesthesiologists performed the laryngoscopies and intubations at each center, and they were blinded as to the time elapsed from the rapacuronium administration. In the pilot study, it was shown that at 1.5 min after administration of rapacuronium, poor intubation conditions were present, but at 2.5 min good tracheal intubating conditions were obtained.[11] We could not confirm this finding.

In the pilot study, maximum twitch depression occurred at 5.7 ± 2.9 min in infants and 5.5 ± 2.7 min in children.[11] This is similar to the time taken for maximum twitch depression to develop in the subjects in the present study. However, despite the similarity of the times to twitch depression, we did not find tracheal intubating conditions to be as good in the multicenter trial as those in the pilot study. Recovery of T1 to 10% of initial twitch in both infants and children was comparable in both the pilot study and the multicenter study (table 6). This would imply that the uptake, distribution, and metabolism in the subjects from both studies were similar.[11,12]

This study was conducted in a similar manner to the previous multicenter study assessing intramuscular rocuronium.[13] That study, based on a pilot study, assessed onset, intubating conditions, and recovery after intramuscular rocuronium 1 mg/kg in infants and 1.8 mg/kg in children.[14] In that study, the conditions for tracheal intubation were poor in the majority of subjects at 2.5 min after intramuscular rocuronium. After extending the time before attempting tracheal intubation, conditions improved, with 56% of the infants having acceptable conditions at 3.5 min after rocuronium.[13] When tracheal intubation was attempted in the children at 4.5 min after rocuronium, 58% of the subjects had acceptable conditions.[13] This was despite the fact that the pilot study had found excellent intubating conditions using the same techniques.[14] Onset, or the time to maximum block, after intramuscular rocuronium was 7.4 ± 3.4 min and 8.9 ± 6.3 min in infants and children, respectively.[13] The onset after rapacuronium in our study was slightly faster at 6.0 ± 3.7 min and 5.5 ± 3.8 min in infants and children, respectively. The time for recovery after intramuscular rapacuronium tended to be faster than recovery after intramuscular rocuronium. The time for T1 to recover to 90% of initial twitch height after intramuscular rocuronium was 112 ± 36 min and 120 ± 29 min in infants and children, respectively.[13] In contrast, after intramuscular rapacuronium, recovery of T1 to 90% of initial twitch height took 73.2 ± 21.3 min and 106 ± 39.1 min in infants and children, respectively. These data confirm the observations from the intravenous studies that rapacuronium has a shorter duration of action than the intermediate acting relaxant rocuronium.[6,11,12]

Table 6. Recovery of T1 to 10% of Initial Twitch Height

	Infants	Children
Pilot study[8]	31 ± 14	36 ± 14
Multicenter study	29 ± 10	33.5 ± 17

Mean (±SD) in minutes.

Succinylcholine is the recommended intramuscular relaxant because of rapid onset and a relatively brief duration of action. However, to the best of our knowledge, there has not been a study that has properly studied intubating conditions when succinylcholine has been given intramuscularly. Clinical experience has shown that the drug is effective for tracheal intubation when given intramuscularly, but the experience of most pediatric anesthesiologists is very limited in this respect. Neuromuscular studies have shown that twitch depression of more than 90% occurs when succinylcholine is given intramuscularly at a dose of 3–4 mg/kg. The inspired halothane concentration in those studies was 2% in one study and not specified in the other.[8,9]

Based on present data, it is difficult to make a specific recommendation for the ideal muscle relaxant that can be used in the absence of intravenous sites. Clinical experience and neuromuscular data have shown that intramuscular succinylcholine has the fastest onset (4 min) and the fastest recovery. Of the relaxants tested, mivacurium was found to be ineffective when given

intramuscularly.[15] Rocuronium and rapacuronium have onset times that are relatively slow *i.e.*, 6–7 min, with durations of action of more than 1 h. Perhaps if the clinician were willing to wait more than 5 min before attempting tracheal intubation or increase the depth of anesthesia, the conditions would become satisfactory. In the scenario of laryngospasm, lack of intravenous access, and decreasing arterial oxygen saturation, intramuscular succinylcholine would be the decision of choice. However, if the situation is not urgent, muscle relaxation can be supplemented by intramuscular rapacuronium or rocuronium. Because laryngeal and respiratory muscles are affected before the peripheral muscles, tracheal intubation would be possible before the twitch response was ablated at the thumb.[16,17] This onset differential may allow easier face mask ventilation before tracheal intubation is possible.

Intramuscular relaxants may be needed less frequently with increasing use of long-term central venous access and the availability of anesthetic agents such as sevoflurane, which may have a safer profile (better cardiovascular stability) than halothane and produce less coughing or laryngospasm than older anesthetics.[18,19]

We have no specific explanation for the differences between this study and the pilot study. However, we would further reiterate that it is important that multicenter, well-controlled, blinded trials are used to verify and corroborate single-center studies.[20]

Our study does not support the hypothesis that rapacuronium in the doses used provides adequate intubating conditions within 3 min of drug administration when using 1 minimum alveolar concentration halothane anesthesia, thereby greatly diminishing the synergistic effect of the volatile agent. This was by design, as the investigators were keen to insure that the intramuscular neuromuscular blocking drug, rapacuronium, and not the inhalational anesthetic, was providing the intubating conditions.

Conclusion

This multicenter study showed that 27% of patients achieved clinically acceptable tracheal intubating conditions at 1.5 or 3 min after intramuscular administration of 2.8 mg/kg and 4.8 mg/kg rapacuronium during light halothane anesthesia. The tracheal intubations at 4 min were acceptable in 69% of subjects. The duration of action of 4.8 mg/kg rapacuronium in children was longer than 2.8 mg/kg rapacuronium in infants. We cannot recommend intramuscular rapacuronium at the doses studied as an acceptable muscle relaxant to facilitate tracheal intubation at 1.5 or 3 min after administration, because of its slow onset. Further study is needed to evaluate the role intramuscular rapacuronium in the relief of laryngospasm.

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