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A Dose-ranging Study of Rapacuronium in Pediatric Patients

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Background: **The aim of this study was to determine the dose or doses of the new rapid-onset, short-acting, neuromuscular blocking drug rapacuronium that would provide satisfactory conditions for tracheal intubation at 60 s in infants and children.**

Methods: **Sixty-five infants (< 1 yr), 51 younger children (1–6 yr), and 49 older children (7–12 yr) were studied. Anesthesia was induced with thiopental–nitrous oxide–oxygen. Tracheal intubation was attempted 60 s after administration of one of five doses of rapacuronium (0.5, 1.0, 1.5, 2.0, or 2.5 mg/kg) and intubating conditions were assessed using a four-point scale. Following tracheal intubation, anesthesia was maintained with nitrous oxide–oxygen and alfentanil (12.5–50 μg/kg) as necessary. Neuromuscular transmission was monitored in an uncalibrated fashion using an acceleromyograph.**

Results: **Intubating conditions were good or excellent at 60 s in all infants after doses of 1.5 mg/kg or more and in all younger and older children after doses of 2.0 mg/kg or more. The duration of action of rapacuronium was dose- and age-dependent. Mean times to reappearance of the third twitch of the train-of-four (TOF; T_3) were less than 10 min in infants at doses of 1.5 mg/kg or less and in younger and older children at doses of 2.0 mg/kg or less. Recovery of T_3 after 1.0–2.0 mg/kg rapacuronium was significantly slower in infants compared with younger ($P = 0.001$) and older ($P = 0.02$) children. Five adverse experiences were related to rapacuronium administration: Bronchospasm (two instances), tachycardia (one instance), and increased salivation (two instances). None were serious.**

Conclusions: **Doses of 1.5 and 2.0 mg/kg rapacuronium can produce satisfactory intubating conditions at 60 s in anesthetized infants and children, respectively, and are associated with a short duration of action. (Key words: Muscle relaxants; pediatric anesthesia; tracheal intubation.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

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RAPACURONIUM (ORG 9487; Organon Teknika, Boxtel, The Netherlands) is a rapid-onset, short-acting, nondepolarizing neuromuscular blocking drug undergoing investigation as a possible alternative to succinylcholine for rapid tracheal intubation.[1-4] Succinylcholine is characterized by many side effects relating to its depolarizing action including cardiac dysrhythmias, hyperkalemia, increased intraocular or intragastric pressure, muscle fasciculations, and postoperative muscle pain. Consequently, the use of succinylcholine may be undesirable in some cases in which rapid tracheal intubation is necessary.

In a recent study, doses of 1.5-2.0 mg/kg rapacuronium provided good or excellent tracheal intubation conditions in most young-adult subjects at 60 s, with mean clinical durations of 14-18 min.[4] The main aim of the current study was to determine the doses of rapacuronium that would provide good or excellent tracheal intubation conditions 60 s after administration in three

groups of pediatric patients. One of five doses of rapacuronium was administered in a randomized manner during general anesthesia, and tracheal intubation conditions were assessed by a blinded observer. We also determined the time course of action of these various doses using an acceleromyograph. The studies were performed in infants (< 1 yr), younger children (1-6 yr), and older children (7-12 yr) because the potency and time course of action of the other aminosteroidal neuromuscular blocking drugs vecuronium[5-7] and rocuronium[8-11] have been shown to vary among these age groups.

Methods

This was a prospective, randomized, assessor-blinded, multicenter, descriptive study. After approval by the local institutional review board and after obtaining written informed consent of a parent, 165 pediatric patients consisting of 65 infants (< 1 yr), 51 younger children (1-6 yr), and 49 older children (7-12 yr) were enrolled. All children were American Society of Anesthesiologists physical status 1 or 2 and were free of drugs or diseases known to interfere with neuromuscular transmission. Patients with clinical signs suggesting possible difficult tracheal intubation or whose body weight deviated more than 20% from the ideal for their age were excluded.[12] All were scheduled for elective surgery not requiring rapid sequence tracheal intubation.

Infants younger than 1 month of age received no premedication; infants aged 1-11 months and children older than 1 yr of age were given midazolam 0.2 mg/kg intranasally or 0.5 mg/kg orally 15-45 min preoperatively. Routine monitoring consisted of electrocardiography (ECG), noninvasive blood pressure, and pulse oximetry. Anesthesia was induced with 5-8 mg/kg thiopental followed by inhalation of a mixture of 66% N_2O in oxygen. After tracheal intubation, anesthesia was maintained with nitrous oxide in oxygen and 12.5- to 50-μg/kg doses of alfentanil as clinically indicated.

Neuromuscular transmission was monitored in an uncalibrated fashion using a TOF-Guard acceleromyograph (Organon Teknika) to record the acceleration of the adductor pollicis in response to train-of-four (TOF) supramaximal stimulation of the ulnar nerve at 15-s intervals.[13] The acceleromyograph apparatus was attached to the patients before induction of anesthesia, and TOF stimulation of the ulnar nerve was begun as soon as the patient was asleep. Immediately after the first TOF response was recorded, one of five doses of rapacuronium (0.5, 1.0, 1.5, 2.0, or 2.5 mg/kg) was administered by rapid intravenous injection according to a predetermined randomization schedule. Laryngoscopy was started 45-50 s later, followed by tracheal intubation at 60 s. Intubating conditions were graded according to a four-point scale by a blinded observer (table 1). Neuromuscular transmission was monitored until recovery of the TOF ratio to 0.7, during which period the temperature over the adductor pollicis was maintained above 32°C. Digitized data were recorded onto a memory card supplied with the acceleromyograph and subsequently transferred to a 486 series personal computer. Recovery times were measured from injection of rapacuronium to reappearance of the third twitch of TOF (T_3) and until the TOF ratio was 0.7.

Table 1. Grading Scheme for Intubating Conditions

I	Excellent	Jaw relaxed, vocal cords immobile, no diaphragmatic movement
II	Good	Jaw relaxed, vocal cords moving but not closing, minor diaphragmatic movement
III	Poor	Jaw relaxed, vocal cords closing, marked coughing/"bucking"; or jaw not relaxed, vocal cords immobile, no or minor diaphragmatic movement
IV	Impossible	Jaw not relaxed, vocal cords not visualized; or jaw relaxed or not relaxed and vocal cords closed

After a planned interim analysis of tracheal intubation data from 35 patients, it was decided to discontinue the 2.5 mg/kg dose of rapacuronium for infants and the 0.5 mg/kg dose for younger and older children. New randomization schedules were constructed for the remaining 130 patients.

An *adverse experience* was defined as any complaint or symptom emerging or increasing in frequency or intensity during the study period, whether or not it was related to the study drug. A serious adverse event was any experience that was fatal, life-threatening, permanently disabling, necessitating hospital admission, or an overdose. Investigators were required to state whether they considered the adverse experience to be related to the administration of rapacuronium.

Statistical Analysis

Demographic data were summarized as the mean ± SD and compared using analysis of variance (ANOVA). Tracheal intubation data were summarized as frequency distributions with corresponding 95% confidence intervals. Mean times to appearance of T_3 and recovery of

Table 2. Demographic Data for Infants, Younger Children, and Older Children

	Dose (mg/kg)				
	0.5	1.0	1.5	2.0	2.5
Infants (aged <1 yr)					
No.	18	18	16	11	2
Age (months)	4 ± 4	3 ± 3	4 ± 4	4 ± 2	6 ± 5
Weight (kg)	6.1 ± 2.6	5.9 ± 2.3	6.4 ± 2.9	7.0 ± 1.9	8.0 ± 2.9
Height (cm)	62 ± 10	60 ± 8	64 ± 11	65 ± 7	78 ± 6
Sex (M/F)	15/3	18/0	15/1	10/1	2/0
ASA physical status (I/II)	16/2	16/2	16/0	7/4	2/0
Younger children (aged 1–6 yr)					
No.	2	12	13	12	12
Age (yr)	4 ± 3	4 ± 2	3 ± 2	3 ± 2	3 ± 2
Weight (kg)	18.4 ± 6.5	15.7 ± 2.8	16.0 ± 4.7	15.7 ± 4.1	15.5 ± 5.3
Height (cm)	110 ± 22	102 ± 13	99 ± 14	96 ± 14	98 ± 16
Sex (M/F)	0/2	8/4	11/2	8/4	8/4
ASA physical status (I/II)	1/1	7/5	13/0	8/4	9/3
Older children (aged 7–12 yr)					
No.	3	12	11	11	12
Age (yr)	8 ± 2	9 ± 2	10 ± 2	9 ± 2	10 ± 2
Weight (kg)	24.1 ± 0.8	35.8 ± 9.7	36.3 ± 10.7	33.6 ± 7.5	33.4 ± 9.5
Height (cm)	129 ± 6	143 ± 13	142 ± 13	142 ± 10	141 ± 13
Sex (M/F)	1/2	9/3	6/5	10/1	8/4
ASA physical status (I/II)	3/0	9/3	8/3	11/0	12/0

Where appropriate, values are mean ± SD.

ASA = American Society of Anesthesiologists.

TOF ratio to 0.7 after various doses of rapacuronium were presented graphically and analyzed by analysis of covariance (ANCOVA). All statistical calculations were performed using SAS statistical software version 6.12 (SAS Inc., Cary, NC), under Windows NT, version 4 (Microsoft, Redmond, WA). Statistical significance was defined as $P < 0.05$.

Results

One hundred and sixty-five patients were enrolled in the study (table 2). There were no differences in age, weight, or height among the various dose groups within each of the three age groups. Protocol violations occurred in 37 patients, 35 of which were considered minor violations. The two major violations were admin-

Table 3. Frequency Distribution of Intubation Scores 60 s after Various Doses of Rapacuronium

		Dose (mg/kg)									
		0.5		1.0		1.5		2.0		2.5	
Age Group	Intubation Conditions	No.	%	No.	%	No.	%	No.	%	No.	%
Infants	Excellent	3	16	6	38	13	81	11	100	2	100
	Good	5	26	8	50	3	19	0	0	0	0
	Poor	11	58	2	12	0	0	0	0	0	0
	Impossible	0	0	0	0	0	0	0	0	0	0
Younger children	Excellent	0	0	4	33	6	50	8	67	10	83
	Good	0	0	2	17	3	25	4	33	2	17
	Poor	2	100	6	50	3	25	0	0	0	0
	Impossible	0	0	0	0	0	0	0	0	0	0
Older children	Excellent	0	0	1	8	3	25	8	73	7	58
	Good	0	0	6	50	8	67	3	27	5	42
	Poor	2	67	4	34	1	8	0	0	0	0
	Impossible	1	33	1	8	0	0	0	0	0	0

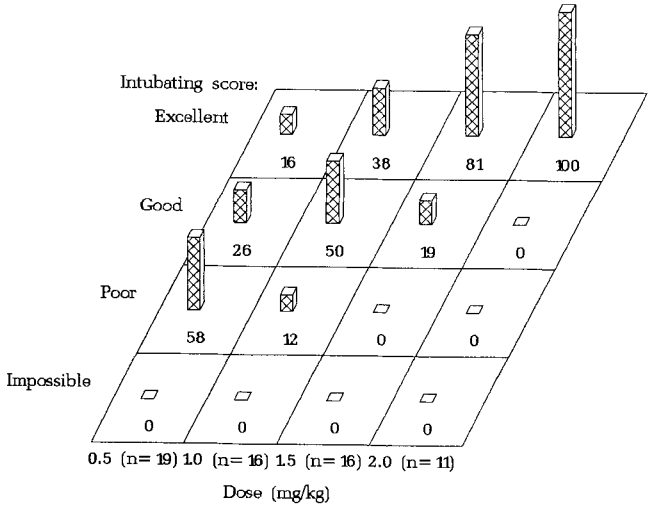

Fig. 1. Intubating scores at 60 s for dose groups of infants. Data in boxes are percentages; the total number in each group is given in parentheses after the dose.

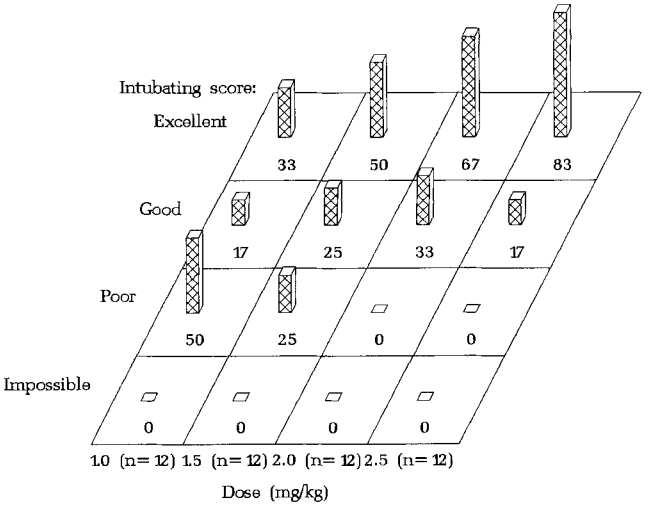

Fig. 2. Intubating scores at 60 s for dose groups of younger children. Data in boxes are percentages; the total number in each group is given in parenthesis after the dose.

istration of an incorrect dose of rapacuronium (n = 1) and allocation to the wrong age group (n = 1). The minor violations were introduction of a volatile anesthetic agent prior to recovery of the TOF ratio to 0.7 (n = 3), technical difficulties with the acceleromyograph, resulting in nonevaluability of recovery data (n = 2), and administration of a dose of thiopental above the upper protocol limit (n = 30). Despite the violations, analysis of the results showed no differences between the "per-protocol" group (all violators excluded) and the "intent-to-treat" group (all patients who received a dose of rapacuronium and had at least one postbaseline efficacy assessment). Accordingly, in the tables and figures, efficacy data (tracheal intubation conditions and time course of action) are based on the "intent-to-treat" group. Time to reappearance of T_3 could not be evaluated in 30 patients because the dose of rapacuronium administered was insufficient to abolish the response.

Tracheal intubation scores were evaluated in 164 patients (table 3 and figs. 1-3) Tracheal intubation conditions were good or excellent at 60 s in all infants after doses of 1.5 mg/kg and 2 mg/kg rapacuronium. Similarly, good or excellent tracheal intubation conditions were found in all younger and older children after doses of 2.0 mg/kg and 2.5 mg/kg. The percentage and 95% confidence interval of patients in each dose group with excellent or good intubating conditions are summarized in table 4.

Dose-related increases in mean times to reappearance of T_3 and recovery of TOF ratio to 0.7 were observed in all age groups (figs. 4 and 5). Mean times to T_3 recovery were less than 10 min in infants at doses of 1.5 mg/kg or less and in younger and older children at doses of 2.0 mg/kg or less. Mean times to a TOF ratio of 0.7 were less than 20 min in infants at doses of 1.5 mg/kg or less and in younger and older children at doses of 2.0 mg/kg or less. For doses between 1.0 and 2.0 mg/kg, the mean times to reappearance of T_3 were significantly longer in infants compared with both younger and older children (P = 0.001 and P = 0.02, respectively; fig. 4), The calculated difference in time to appearance of T_3 between infants and younger children was 2.2 min (95% confidence interval, 0.9-3.5 min), and that between infants and older children was 1.6 min (95% confidence interval, 0.3-2.9 min). Similarly, the times to TOF ratio recovery to 0.7 were significantly longer in infants compared with younger children (P = 0.007; fig. 5); the estimated difference was 2.9 min (95% confidence interval, 0.8-5.0 min).

A total of 18 adverse experiences were reported in 14 patients, 5 of which were considered to be related to rapacuronium. Two of these events occurred in one 8-yr-old child in whom tachycardia and bronchospasm developed 60 s after administration of 2.5 mg/kg rapacuronium; the child was treated successfully by the administration 20 μg/kg alfentanil and addition of halothane to the inspired gas mixture. Bronchospasm developed in another 8-yr-old child shortly after receiving 2.5 mg/kg rapacuronium, but in this case, the symptoms subsided without treatment. The last two adverse events involved two children aged 4 and 5 yr in whom

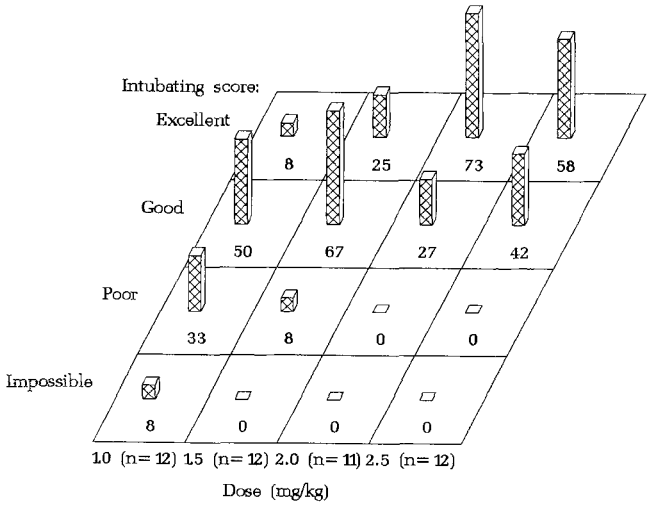

Fig. 3. Intubating scores at 60 s for dose groups of older children. Data in boxes are percentages; the total number in each group is given in parenthesis after the dose.

increased salivation developed after receiving 1.0 mg/kg and 2.0 mg/kg rapacuronium, respectively. Treatment consisted of removal of secretions by oral and pharyngeal suctioning. It is noteworthy that all five of these adverse events were observed after tracheal intubation, which could have contributed to the development of symptoms (particularly bronchospasm). None of the adverse events reported in the course of this study were considered to be serious.

Discussion

The primary objective of the current study was to determine the dose or doses of rapacuronium that would provide good to excellent tracheal intubation conditions at 60 s in pediatric patients so that the drug might be considered as a potential replacement for succinylcholine when rapid intubation of the trachea is necessary. Because doses of 1.0–1.5 mg/kg have been reported to produce excellent tracheal intubation conditions in adult patients,[1–3] we initially intended to evaluate five doses in the range 0.5–2.5 mg/kg. However, a planned preliminary analysis indicated that the dose of 0.5 mg/kg was ineffective in younger and older children, and the dose of 2.5 mg/kg in infants would not provide additional information. Accordingly, recruitment to these groups was discontinued. Although the number of patients in each dose group was small, the results suggest that satisfactory tracheal intubation conditions can be achieved at 60 s after a dose of at least 1.5 mg/kg in infants and 2.0 mg/kg in younger and older children (tables 3 and 4). The tracheal intubation scores achieved with these doses are comparable to those obtained at 60 s in anesthetized adults and children given 1–1.5 mg/kg succinylcholine[2,14–15] and those obtained at 60–90 s in anesthetized young-adult patients given 1.5–2.0 mg/kg rapacuronium.[4]

The observation that the infant group required a smaller dose of rapacuronium to produce satisfactory tracheal intubation conditions at 60 s compared with the two groups of children is in agreement with earlier studies that suggested that infants are sensitive to the effects of nondepolarizing muscle relaxants.[6,8,16] Evidence from laboratory animals suggests that this sensitivity may be caused by a reduction in the availability of acetylcholine in developing motor nerves.[17,18]

In the current study, the duration of action of rapacuronium was determined in an uncalibrated fashion so that the study could reflect the normal clinical practice of administering the muscle relaxant soon after induction of anesthesia. To calibrate the TOF-Guard, it would have been necessary to delay the injection of rapacuronium for at least 3 min to allow signal stabilization.[19] The times to reappearance of T_3 and recovery of TOF ratio to 0.7 are recovery indices that do not require the determination of a control twitch height. Furthermore, clinical experience suggests that the reappearance of T_3 should approximate the clinical duration of action of a nondepolarizing neuromuscular blocking drug (25% recovery of T_1). If the latter is accepted, our results indicate that rapacuronium is a short-acting neuromusclar blocking drug when used in doses suitable for tracheal intubation in children (clinical duration, 8–20 min).[20]

The finding that the duration of action of rapacuronium was dose-dependent confirms the results of previous studies in pediatric and adult patients.[4,21] Additionally, the observation that the duration of action of rapacuronium was longer in infants compared with children (figs. 4 and 5) agrees with the results of earlier studies of the aminosteroidal drugs vecuronium and rocuronium.[5,7,9,10] The longer duration of action of vecuronium and rocuronium in infants may be explained by a larger volume of distribution (extracellular fluid volume) with or without a lower plasma clearance.[22,23] The effect is most marked with vecuronium, which changes from being an intermediate-acting relaxant in children to being a long-acting drug in infants.[7] Although the results of our study suggest that the duration of effect of rapacuronium may be longer in infants compared with children, the difference in recovery times was not

Table 4. Numbers of Patients in Each Dose Group with Satisfactory Intubation Scores at 60 s

	Dose (mg/kg)				
	0.5	1.0	1.5	2.0	2.5
Infants					
Absolute numbers	8/19	14/16	16/16	11/11	2/2
%	42	88	100	100	
95% confidence interval	20–67	62–98	79–100	72–100	
Younger children					
Absolute numbers	0/2	6/12	9/12	12/12	12/12
%		50	75	100	100
95% confidence interval		21–79	43–95	74–100	74–100
Older children					
Absolute numbers	0/3	7/12	11/12	11/11	12/12
%		58	92	100	100
95% confidence interval		28–85	62–100	72–100	74–100

great, and the drug retained the characteristics of a short-acting muscle relaxant in doses suitable for tracheal intubation.

A comparison of the results of the current study with those of a recent study in adults suggests that recovery from the same dose of rapacuronium may be faster in pediatric patients.[4] In adult patients (19–64 yr), doses of 1.5 mg/kg and 2.0 mg/kg rapacuronium resulted in clinical durations of action of 14 and 18 min, respectively. The mean times to TOF ratio recovery to 0.7 were 30 min after the 1.5 mg/kg dose and 45 min after the 2.0 mg/kg dose. These recovery times were 51–181% longer than those observed after the same doses in infants, younger children, and older children in the current study (figs. 4 and 5). Faster recovery in pediatric patients compared with adults is a feature of many neuromuscular blocking drugs and probably reflects the greater cardiac output per kilogram of pediatric patients, which should result in a more rapid redistribution of the drugs from their site of action.[24]

The current study can be criticized for the use of acceleromyograph to monitor neuromuscular transmission, because this device does not meet the recommendations of the Copenhagen group for Good Clinical Research Practice, which specifies that mechanomyography should be used for phase II clinical trials.[20] The main problems

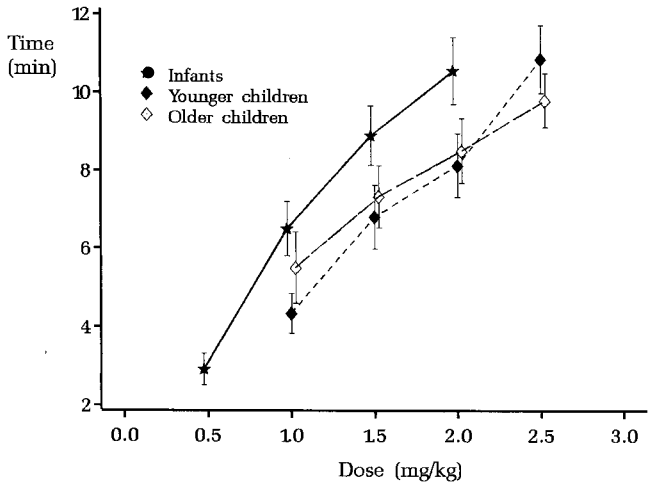

Fig. 4. Times to reappearance of T_3 after various doses of rapacuronium. Values are the mean ± SEM. Statistical differences obtained with analysis of covariance (ANCOVA): Three age groups simultaneously, $P = 0.003$; infants *versus* younger children, $P = 0.001$; infants *versus* older children, 0.02.

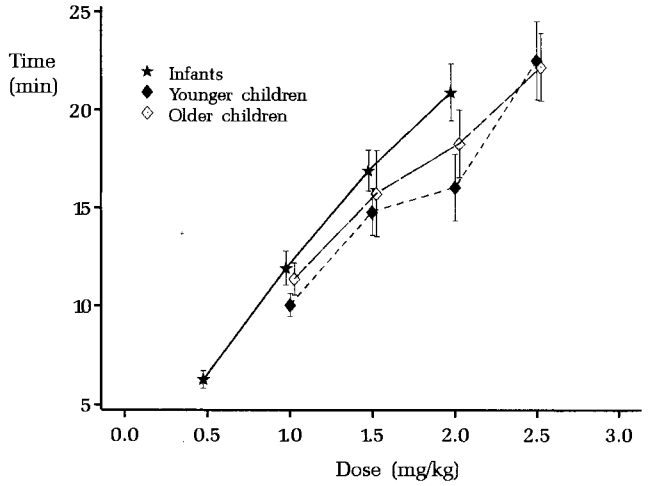

Fig. 5. Times to recovery of TOF ratio to 0.7 after various doses of rapacuronium. Values are the mean ± SEM. Statistical differences obtained with analysis of covariance (ANCOVA): Three age groups simultaneously, $P = 0.026$; infants *versus* younger children, $P = 0.007$.

with using acceleromyograph in place of the "gold standard" mechanomyography appear to be the relative underestimation of partial neuromuscular block and a greater tendency to down drift.[25,26] However, these problems should be less likely to affect measurements such as the reappearance of T_3 and the TOF ratio, which are not referenced to a control twitch. This suggestion is supported by the observations that a close relation exists between acceleromyograph and mechanomyography TOF ratios in the range 0-70%[27] and average times to TOF ratio recovery to 0.7 with the two monitors are similar.[13]

In the current study, five adverse experiences were reported to be possibly or probably related to administration of rapacuronium. These five events included bronchospasm and tachycardia in one patient, isolated bronchospasm in one patient, and increased salivation in two patients. None of the adverse experiences were considered serious, and none were definitively related to the study drug. Our finding of a low incidence of adverse experiences related to rapacuronium (3%) confirms the similar finding of a previous study in adult patients (1.7%).[4] Further studies are required to determine the cardiovascular effects and histamine-releasing properties of rapacuronium in children.

The results of our study indicate that rapacuronium can produce satisfactory conditions for tracheal intubation at 60 s in infants and children when given in doses of 1.5 and 2.0 mg/kg, respectively. It may therefore be a suitable alternative for succinylcholine in situations in which rapid tracheal intubation is required. At these doses, rapacuronium appears to be an effective and well-tolerated short-duration, nondepolarizing muscle relaxant for use in pediatric patients.

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