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The pharmacodynamics of rocuronium in pediatric patients anesthetized with halothane

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Abstract: The aim of this study was to determine the neuromuscular blocking potency of rocuronium (ORG 9426) in 4- to 14-year-old children anesthetized with halothane. After induction of anesthesia, the ulnar nerve was stimulated with electrical impulses of 0.2 ms duration every 12 s and the force of contraction of the thumb (P) was continuously recorded. Doses of 0.12, 0.16, 0.20, and 0.24 mg·kg^{-1} rocuronium were administered, in a randomized fashion, to 4 groups of 12 patients each. The ED_{50}, ED_{90}, and ED_{95} of rocuronium determined from the log dose-probit regression lines were 0.18, 0.34, and 0.40 mg·kg^{-1}, respectively. To facilitate tracheal intubation, after the development of the maximal effect of the first dose, a variable second dose of rocuronium was administered to increase the total dose to 0.3 mg·kg^{-1}. If after the second dose P was greater than 10% of control, additional 0.025–0.1 mg·kg^{-1} increments of rocuronium were administered until P became less than 10% of control. At this time the trachea was intubated. Muscular relaxation was maintained with 0.075, 0.1, or 0.125 mg·kg^{-1} rocuronium, administered whenever P recovered to 25% of control. The clinical duration of these doses was 6.9 ± 2.8, 6.1 ± 0.4, and 8.1 ± 0.6 min, respectively. On repeated administration of three 0.1 or 0.125 mg·kg^{-1} doses, rocuronium showed little cumulative tendency. Time for spontaneous recovery of P from 25% to 75%, 8.4 ± 0.39 min and from 10% to 90%, 16.19 ± 0.15 min, of control, were relatively short. When at termination of anesthesia T4/T1 ratios were lower than 0.75, the residual neuromuscular block could be antagonized with 0.5 mg·kg^{-1} edrophonium in 2 min. Rocuronium, 0.3 mg·kg^{-1} caused a 13.5% increase of heart rate but had no effect on blood pressure. In conclusion, in 4 to 14-year-old children, rocuronium appears to have a more rapid onset and shorter duration of action than other steroid-type muscle relaxants.

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Introduction

Rocuronium is a steroid base, monoquaternary, nondepolarizing neuromuscular (NM) blocking agent (muscle relaxant; MR). Under halothane anesthesia, the ED_{90} was reported to be 0.259 [1] and 0.230 [2] mg·kg^{-1} in adults and 0.284 mg·kg^{-1} in children between 1 and 5 years of age (calculated from [3]). There may be considerable differences in the potency and other pharmacodynamic characteristics of the same MR in different pediatric age groups [4]. Therefore, in the present study, the pharmacodynamics of rocuronium were investigated in patients between 4 and 14 years of age.

Methods

Sixty ASA classification 1 to 3 children, 4–14 years of age, were enrolled in this study. Informed consent was obtained from the parents or guardians, and the study protocol was approved by the Institutional Review Board. Patients who had renal, hepatic, metabolic, or neuromuscular disorders, were grossly overweight, or received drugs, in the perioperative period, which might have influenced NM activity, were excluded from the study.

Premedication consisted of 0.01 to 0.015 mg·kg^{-1} atropine administered intramuscularly. Anesthesia was induced with a mixture of 3L N_2O and 2L O_2 containing up to 3% (v/v) halothane. During the determination of the dose-response, end-expiratory halothane concentration was kept at 1.5%. Subsequently anesthesia was maintained with 0.8% to 1.5% halothane, as indicated. During induction of anesthesia and the determination

of the dose-response of rocuronium, ventilation was assisted or controlled through a face mask. End-expiratory Pco_2 was maintained between 32 and 42 mmHg.

After induction of anesthesia, the ulnar nerve was stimulated at the wrist through surface electrodes, with supramaximal square wave impulses of 0.2 ms duration, administered every 12 s. Occasionally, trains-of-four (TOF) of the above described electrical impulses were administered at 2 Hz. Depending on the weight of the patient, 75–250 g resting tension was applied to the thumb and the indirectly evoked force of contraction (P) of the thumb was continuously recorded on a Relaxometer 2 [5]. This apparatus also continuously records the resting tension and the surface temperature of the thumb.

In the dose-finding phase of the study, when P became stable, 0.12, 0.16, 0.20, or 0.24 mg·kg^{-1} rocuronium was administered to four groups of three patients each in a nonrandomized fashion. Rocuronium was injected rapidly through a rubber port, located close to the vein, on a fast-flowing i.v. infusion set. After the development of its maximal effect, the variable initial dose of rocuronium was supplemented, by a second dose, to 0.3 mg·kg^{-1} (Fig. 1). If P was greater than 10% of control after the supplemental dose, additional 0.025–0.10 mg·kg^{-1} increments of rocuronium were injected until P became lower than 10% of control. At this time the trachea was intubated. When it became evident that the doses used in the range-finding phase were suitable for the determination of the dose-response of rocuronium, four groups of 12 patients each received an initial dose of 0.12, 0.16, 0.20, and 0.24 mg·kg^{-1} rocuronium, in a randomized fashion. The dose-response of rocuronium was determined from the observations made on those subjects, who received the various doses of rocuronium in randomized order. After development of the maximal effect of the first dose, patients were managed as described in the range-finding part of the protocol.

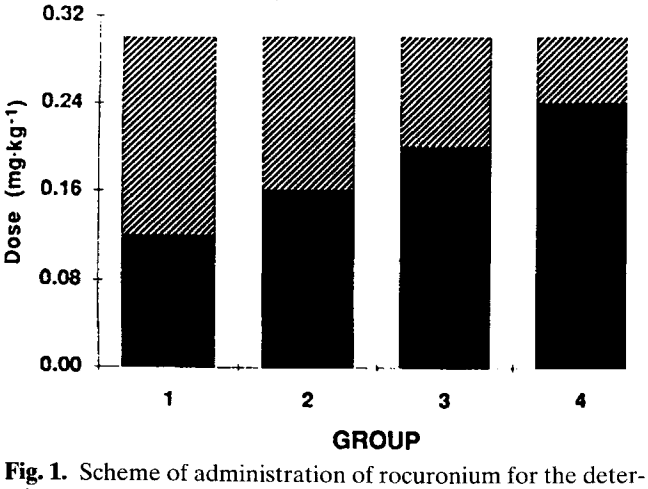

Fig. 1. Scheme of administration of rocuronium for the determination of its dose-response. Note that the dose-response was calculated from the neuromuscular blocking effect of the initial doses. The initial doses were supplemented to a total of 0.3 mg·kg^{-1} to facilitate tracheal intubation. *Hatched area*, supplemental dose; *closed area*, first dose

When the surgical procedure required prolonged muscular relaxation, increments of 0.075, 0.1, or 0.125 mg·kg^{-1} rocuronium were administered whenever P recovered to 25% of control. After the last dose of rocuronium, spontaneous recovery from the NM block was allowed to proceed for as long as possible. If the T4/T1 ratio (P elicited by the first and fourth impulse of TOF will be designated as T1 and T4, respectively, and expressed as percent of control P) was lower than 0.75 at the time of maximal spontaneous recovery, the residual NM block was antagonized with a mixture of 0.01 to 0.015 mg·kg^{-1} atropine and 0.5 mg·kg^{-1} edrophonium. Except for the determination of the dose-response, the observations made on the 12 subjects used for the range-finding phase and on the 48 subjects used in the dose response study were pooled. Data were statistically analyzed using analysis of variance (ANOVA) followed by Tukey's test [6], Student's *t*-test, or paired *t*-test as appropriate. $P < 0.05$ was accepted as significant.

Results

The demographic data of the four groups were similar (Table 1). Increasing doses of rocuronium caused a progressive decrease of P and the T4/T1 ratio (Table 2). The times of development of the maximal effect of different doses of rocuronium were similar. The ED_{50}, ED_{90}, and ED_{95} doses of rocuronium, determined from the log dose-probit response regression lines, were 0.18, 0.34, and 0.40 mg·kg^{-1}.

The total doses of rocuronium administered before intubation and the times required for the recovery of P to 25% of control were similar in all four groups (Table 3).

The clinical duration (time from the injection of a

Table 1. Demographic data

Group	Age	Weight	Sex M	Sex F
1	8.2 ± 0.8 (4–13)	30 ± 3 (15–62)	9	6
2	7.0 ± 0.8 (4–13)	23 ± 2 (15–38)	13	2
3	7.5 ± 0.8 (4–14)	28 ± 2 (17–49)	12	3
4	7.1 ± 0.7 (4–13)	28 ± 3 (17–64)	13	2

Mean ± SEM; n = 15 in each group; range in parentheses.

Table 2. The neuromuscular effect of increasing doses or rocuronium under halothane anesthesia

Dose ($mg \cdot kg^{-1}$)	T1[a] (% of control)	T4/T1 ratio	Time to development of maximal effect (min)
0.12	84.1 ± 4.9 (41 – 107)	0.60 ± 0.05 (0.14 – 0.94)	2.2 ± 0.14 (1.6 – 3.6)
0.16	69.5 ± 8.7 (11 – 120)	0.47 ± 0.05 (0.20 – 0.76)	2.5 ± 0.13 (1.6 – 3.4)
0.20	44.9 ± 7.5 (2 – 100)	0.22 ± 0.04 (0 – 0.25)	2.5 ± 0.20 (1.2 – 3.9)
0.24	35.1 ± 6.7 (5 – 71)	0.22 ± 0.03 (0 – 0.42)	2.4 ± 0.16 (1.0 – 3.2)

Mean ± SEM of 15 observations; range in parentheses.
[a] T1 = P elicited by the first of train-of-four impulses administered at 2 Hz.

Table 3. Duration of the neuromuscular blocking effect of intubating doses of rocuronium

Group	Total dose administered before intubating (mg/kg)	Time from intubation to recovery of P to 25% of control (min)
1	0.37 ± 0.02 (0.30 – 0.54)	8.9 ± 0.6 (6.2 – 13.8)
2	0.41 ± 0.03 (0.30 – 0.60)	10.9 ± 1.3 (4.8 – 26.0)
3	0.38 ± 0.03 (0.20 – 0.53)	9.3 ± 0.7 (4.4 – 16.2)
4	0.39 ± 0.03 (0.24 – 0.60)	10.0 ± 0.9 (4.6 – 16.2)

Mean ± SEM; $n = 15$ in each group.

Table 4. Clinical duration of repeat doses of rocuronium (three doses)

Dose	Clinical duration (min) of doses ($mg \cdot kg^{-1}$)	
	0.100 ($n = 7$)	0.125 ($n = 7$)
First	7.5 ± 1.0 (5.4 – 11.4)	7.0 ± 0.7 (4.2 – 8.8)
Second	8.7 ± 1.4 (5.2 – 15.0)	8.1 ± 0.8 (4.8 – 10.4)
Third	8.4 ± 1.0 (5.6 – 12.2)	9.3 ± 0.9 (5.8 – 11.2)

Mean ± SEM; ranges in parentheses.

dose to recovery of P to 25% of control) of 0.075, 0.1, and 0.125 $mg \cdot kg^{-1}$ incremental doses of rocuronium were similar, 6.9 ± 2.8 min ($n = 5$), 6.1 ± 0.4 min ($n = 32$) and 8.1 ± 0.6 ($n = 12$) min, respectively. There was no significant difference in the clinical duration of the first, second, or third 0.1 or 0.125 $mg \cdot kg^{-1}$ dose of rocuronium in patients who received all three doses (Table 4).

The observations of the spontaneous recovery of rocuronium induced NM block (Table 5) indicate that the time for 25% to 75% recovery of P is relatively short.

In 29 patients whose T4/T1 ratio was less than 0.75, at a time when they had to be removed from the operating room, the residual block could be antagonized with 0.5 $mg \cdot kg^{-1}$ edrophonium in 2 min (Table 6). There was no indication, in any patient, of recurrence of the NM block in the postanesthetic recovery room.

In 60 patients (Table 7), 0.3 $mg \cdot kg^{-1}$ rocuronium caused a 13.5% increase in heart rate ($P < 0.01$). Further increase of the dose of rocuronium up to 0.6 $mg \cdot kg^{-1}$ did not cause additional increase in heart

Table 5. Spontaneous recovery of the rocuronium-induced neuromuscular block

Variable	n	Mean ± SEM (range)
Recovery index[a]	45	8.41 ± 0.39 (4.2 – 14.6)
T4/T1 ratio at 75% recovery of T1	47	0.28 ± 0.02 (0.4 – 0.75)
Time (min) from 10% to 90% recovery of T1	37	16.20 ± 0.15 (8.4 – 28.6)
T4/T1 ratio at 90% recovery of T1	47	0.37 ± 0.03 (0.07 – 0.83)

[a] Recovery index = time (min) for recovery of T1 (P) from 25% to 75% of control.

Table 6. Antagonism of the residual rocuronium block

Time of observation	n	T4/T1
Before edrophonium	29	0.36 ± 0.02 (0.12 – 0.72)
After edrophonium		
2 min	28	0.90 ± 0.02 (0.66 – 1.02)
5 min	26	0.91 ± 0.01 (0.72 – 1.00)

T4/T1, ratios of the evoked force of contraction by the first and fourth impulses of train-of-four stimuli.

Table 7. Heart rates

Time of observation	Beats·min^{-1}	Percent Increase[c]
Before induction of anesthesia	108 ± 1.9[b] (78 – 140)	
Before administration of rocuronium	111 ± 2.3 (70 –150)	
After 0.3 mg/kg rocuronium	126 ± 1.8 (90 – 152)	13.5*
Before intubation	125 ± 1.6 (90 – 156)	12.6*
At 5 min[a]	127 ± 1.8 (90 – 156)	14.4*
10 min	128 ± 1.6 (92 – 156)	15.3*
20 min	123 ± 1.7 (92 – 151)	10.8*
30 min	120 ± 1.7 (89 – 146)	8.1*
Before reversal[d]	115 ± 2.8 (112 – 120)	3.6

* Significantly different ($P < 0.01$) from control rate.
[a] After administration of the first increment of rocuronium.
[b] Mean ± SEM (n = 60).
[c] Compared to "before" rocuronium rate.
[d] Of residual neuromuscular block ($n = 29$).

rate. By the end of anesthesia, heart rates returned close to control values. Rocuronium caused no significant changes in systolic or diastolic blood pressure.

Discussion

In this study, the NM potency of rocuronium, under halothane anesthesia, was found to be lower, ED_{90} = 0.34 mg·kg^{-1}, than in 1- to 5-year-old children ED_{90} ± 0.28 mg·kg^{-1} [4], or in adults [1,2], ED_{90} ± 0.26 mg·kg^{-1}. The onset time of rocuronium in adults is defined as the time to the development of the maximal NM blocking effect after the administration of a 2 × ED_{90} dose, was much shorter, 1.5 ± 0.1 min (mean ± SEM), under balanced anesthesia [7], than that of pancuronium, 3.7 ± 0.5 min, vecuronium, 5.9 ± 1.0 min, or pipecuronium, 3.6 ± 0.4 min [8]. The maximal NM blocking effect of rocuronium also developed more rapidly than that of equipotent doses of vecuronium under halothane [9], enflurane [10], or isoflurane [11] anesthesia. Rocuronium, in 2 × ED_{90} doses, was not administered in this study, therefore its onset time could not be determined. However, the rapid development of the maximal effect of smaller than ED_{90} doses (Table 2) indicates that, after the administration of a 2 × ED_{90} dose, the onset time of rocuronium will also be shorter than the onset times of other non-depolarizing MR in clinical use.

The recovery indices (time for recovery of P from 25% to 75% of control) observed in this study, 8.4 ± 0.4 min, were similar to the 11.1 ± 1.6 min reported in 1- to 5-year-old children [4] and in adults [1], 8.0 ± 0.4 min. The time from 10% to 90% recovery of P observed in this study, 16.2 ± 0.15 min and in adults 15.0 ± 0.30 min [1], were also similar.

The increase in heart rate of about 18% found by Brandom et al. [4], following the injection of 0.6 mg·kg^{-1} rocuronium in 1 to 4-year-old children, was similar to the 13.5% increase observed in this study, in 4 to 14-year-old children, following the injection of 0.3 mg·kg^{-1}. In another study, on adults anesthetized with halothane, a 36% increase in heart rate was observed 1 min after the intravenous administration of 0.6 mg·kg^{-1} rocuronium [9]. In contrast, no increase in heart rate was observed following the administration of the 2 × ED_{90} [8] or the 3 × ED_{95} [12] dose of rocuronium in patients under balanced anesthesia. The discrepancy between the influence of rocuronium on heart rate in patients receiving halothane or balanced anesthesia may be due to the fact that halothane causes a preponderance of the vagal tone of the heart and decreases heart rate [13], especially in children [14]. It is conceivable that rocuronium has no effect on the nonstimulated vagus, but that it inhibits the elevated vagal tone. This assumption is corroborated by the finding that in the cat, the 2 × ED_{90} dose of rocuronium had no effect on heart rate. However, when the vagal tone was increased by electrical stimulation of the vagus, the stimulation-induced decrease of heart rate and blood pressure is antagonized by the ED_{90} dose of rocuronium (unpublished observations).

In conclusion, in 4 to 14-year-old children anesthetized with halothane, the NM potency of rocuronium is less than in adults [1,2] or in 1 to 5-year-old children. The NM blocking effect of rocuronium developed rapidly. On administration of 0.075 to 0.125 mg·kg^{-1} repeat doses, rocuronium showed no cumulative tendency. When necessary, the residual NM block at the end of anesthesia could be reliably antagonized by a single 0.5 mg·kg^{-1} dose of edrophonium. In this age group, 0.3 mg·kg^{-1} rocuronium caused a 13.5% increase in heart rate. Administration of additional increments of rocuronium, up to a total of 0.6 mg·kg^{-1}, caused no further increase in heart rate.

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