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Time Course of Rocuronium-Induced Neuromuscular Blockade in Pediatric Patients: A Phase III, Randomized, Dose-Response Study

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Abstract

Background: We evaluated the time course of neuromuscular blockade (NMB) of three intubating doses of rocuronium in pediatric patients.

Methods: This multicenter, randomized, assessor-blinded study included surgical patients aged 0 to 17 years. Anesthesia was induced with sevoflurane, continued until intubation, and maintained with isoflurane. Neuromuscular function was monitored by acceleromyography. Patients received a rocuronium dose of 0.45, 0.6 or 1.0 mg/kg, and intubation was attempted 60 sec later. Primary outcome variable was time from end of rocuronium administration to reappearance of the third twitch (T_3). Time to onset of peak NMB was assessed. Safety assessments included monitoring adverse events.

Results: A total of 207 patients were enrolled and randomized. Median times from rocuronium administration to NMB onset were <1.2 minutes in all age groups for each dose in the per-protocol population (n=175). Median time from rocuronium administration to reappearance of T_3 ranged from 21 to 114 minutes overall, and was longer in the higher dose groups across age groups, and longer in neonates and infants compared with other age groups. There were no adverse events considered related to rocuronium.

Conclusions: Rocuronium at intubating doses of 0.45, 0.6, or 1.0 mg/kg is effective in producing rapid-onset neuromuscular blockade with an intermediate duration of action in pediatric patients during sevoflurane induction/isoflurane maintenance anesthesia. Longest duration of blockade occurred with the highest dose within all age groups, and in neonates and infants compared with other age groups.

Keywords: Rocuronium; Pediatric; Sevoflurane; Isoflurane; Neuromuscular blockade

Introduction

There are differences between pediatric and adult patients in the responses to neuromuscular blocking agents (NMBAs), with variations in potency and duration of action having been observed among infants, children, and adults for most NMBAs [1]. Age-related differences in body composition, physiological function, and acetylcholine receptor density/distribution contribute to the observed differences in sensitivity to NMBAs [1-4].

Rocuronium is a steroidal nondepolarizing NMBA with a rapid onset and intermediate duration of action, and good tolerability in adults at doses up to 1.2 mg/kg [5-8], which has been available for use in pediatric patients since 1994. A small study [9] of 18 infants aged 2–11 months undergoing halothane anesthesia and receiving rocuronium 0.6 mg/kg for intubation reported a longer duration of rocuronium activity in infants compared with results published for children 1–5 years [10]. However, there are relatively limited data in pediatric patients, particularly in neonates and young infants, and in pediatric patients undergoing induction of anesthesia with sevoflurane, which is now more commonly used in this patient group than more traditional agents such as halothane and propofol.

The aim of this multicenter, dose-response study was to evaluate the duration of neuromuscular blockade (NMB) of three intubating doses of rocuronium (the standard 0.6 mg/kg intubating dose, and a dose above [1.0 mg/kg], and below this [0.45 mg/kg]) in pediatric patients during induction of anesthesia with sevoflurane and maintenance with isoflurane.

Methods

Study design

This was a multicenter, randomized, assessor-blinded, Phase IIIB study evaluating three different intubating doses of rocuronium (Zemuron®, Merck, Whitehouse Station, NJ, USA) in pediatric pa-

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tients between December 2004 and July 2007 (ClinicalTrials.gov, NCT00124722). A total of 19 sites participated in the trial (Children's Hospital of Pittsburgh, Pennsylvania, US; Albany Medical Center Hospital, New York, US; Arkansas Children's Hospital, Arkansas, US; Children's Healthcare [Children's Hospitals and Clinics of Minnesota], Minnesota, US; Miami Children's Hospital, Florida, US; Thomas Jefferson University Hospital, Pennsylvania, US; The Children's Hospital, Colorado, US; Stanford University School of Medicine, Lucile Packard Children's Hospital, California, US; Weill Medical Colllege of Cornell University, New York, US; Women and Children's Hospital of Buffalo, New York, US; Children's Hospital Los Angeles, California, US; Saint Peter's University Hospital, CARES Surgicenter, New Jersey, US; The Children's Hospital of Philadelphia, Pennsylvania; University Medical Center, Arizona, US; University of Miami, Florida, US; University of Iowa Hospital and Clinics, Iowa, US; Massachusetts General Hospital, Massachusetts, US; Universitair Ziekenhuis Antwerpen Edegem, Belgium; and Deutsches Herzzentrum München, Germany). The study was designed to provide additional data in pediatric subjects receiving rocuronium, and was conducted in accordance with principles of Good Clinical Practice and approved by the appropriate institutional review boards and regulatory agencies. Randomization took place in blocks of six, using a pre-prepared randomization list, with the study coordinator responsible for the randomization of each patient at their site.

Patients

Males and nonpregnant (determined by pregnancy test), non-nursing females from birth to 17 years of age of American Society of Anesthesiologists Class 1–3 scheduled for surgery under general anesthesia were included. Patients were classified as follows: neonates (birth to <28 days); infants (28 days to ≤3 months); toddlers (>3 months to ≤2 years); children (>2 years to ≤11 years) and adolescents, (>11 to ≤17 years). Patients were excluded if they were preterm neonates (<37 weeks gestational age at birth), had congenital anomalies or airway obstructions which would preclude visualization or intubation of the trachea; or had known significant renal, hepatic, or neuromuscular disorders, or a history/family history of malignant hyperthermia. Patients were also excluded if they were receiving medications that could modify the action of rocuronium, including anticonvulsant, aminoglycoside, macrolide, or polypeptide antibiotic medications during the pre-study or study period.

Written informed consent (and assent, when applicable) was required from the parent(s) or legal guardian(s) of every patient before randomization took place.

Anesthesia, neuromuscular blockade and neuromuscular monitoring

Anesthesia was induced with sevoflurane (2.0–2.5 minimal alveolar concentration to up to 7–8% inspired concentration) in 0–70% nitrous oxide until loss of consciousness. At loss of consciousness, nitrous oxide at 0–70% and sevoflurane of up to 5% end-tidal concentration was to be administered. Sevoflurane was continued until the tracheal tube was positioned.

Neuromuscular function was monitored by acceleromyography at the adductor pollicis muscle, using the TOF-Watch® SX (Organon Ireland Ltd., a subsidiary of Merck and Co., Inc., Swords, Co. Dublin, Ireland). Following induction of anesthesia, the TOF-Watch® SX (version 1.6) was stabilized, and calibrated automatically. The peripheral temperature at the thenar eminence was maintained at ≥32°C during the entire neuromuscular transmission monitoring. The baseline neuromuscular examination included three responses to train-of-four (TOF) stimulation with a variability of <10% from first to last. After this baseline examination, anesthetized patients received a dose of 0.45, 0.6, or 1.0 mg/kg rocuronium, according to their randomized assignment, administered over 5 sec into a fast-flowing intravenous infusion.

Following intubation, anesthesia was maintained with inhalation of isoflurane (1.0 ± 0.2% expired end-tidal concentration) in 0–70% nitrous oxide. If clinically necessary, patients were also permitted to receive intermittent bolus dose(s) of 0.5–2.0 mg/kg propofol or 50–150 µg/kg min propofol infusion. Patients were also allowed to receive fentanyl (1–2 µg/kg, intravenous bolus doses), acetaminophen (25–40 mg/kg per rectum), or a combination of these agents to provide perioperative analgesia.

Efficacy analysis

The primary outcome variable was the time from the end of administration of rocuronium to the reappearance of the third twitch (T_3) of the TOF. Secondary outcome variables included: onset time (time from the end of administration of rocuronium to NMB] and maximum NMB achieved. Maximum NMB was defined as 100% minus the amplitude of the first T_1 (i.e., the first response to a TOF stimulation expressed as a percent of the T_1 amplitude at baseline) which showed no further decline over three consecutive TOF stimulations.

Safety assessments

All adverse events (AEs) and serious AEs (SAEs) were recorded and coded using Medical Dictionary for Regulatory Activities (MedDRA version 10.0, International Federation of Pharmaceutical Manufacturers and Associations, Chantilly, Virginia, USA). Heart rate, blood pressure, and electrocardiogram (ECG) parameters were monitored regularly from pre-study physical examination until 30 minutes after the dose of rocuronium. Clinically significant abnormal heart rate was assessed according to pre-defined age-specific criteria and considered abnormal if outside the following ranges (≥110 to ≤170 beats per min [bpm] for neonates; ≥70 to ≤150 bpm for infants and toddlers; and ≥50 to ≤130 bpm for children and adolescents). For evaluation of QTc intervals, Bazett's correction was used. QTcB values were considered to be abnormal if they lay outside the following pre-defined age-specific bounds: neonates, infants and toddlers, 201–489 msec; children and adolescents, 201–439 msec. Ventilatory compliance and oxygen saturation were also assessed.

Statistical analysis

The primary analysis was based on the per-protocol (PP) group, defined as patients who received study medication, had an efficacy assessment, and no major protocol violations that would interfere with efficacy assessment.

This study was conducted to provide additional descriptive safety and efficacy information regarding the administration of differing doses of rocuronium in pediatric patients of different ages; therefore, neither the total sample size nor the sizes of the subgroups were intended to support statistical analyses. Furthermore, there were several major revisions to the protocol based upon regulatory input. Because of this, patients (n=6) enrolled in the study before the major changes contributed to the all-subjects-treated (AST) and intent-to-treat (ITT) groups but were excluded from the PP group.

No formal hypotheses were stated in the study protocol. Although the protocol indicated that analyses would be performed by age group

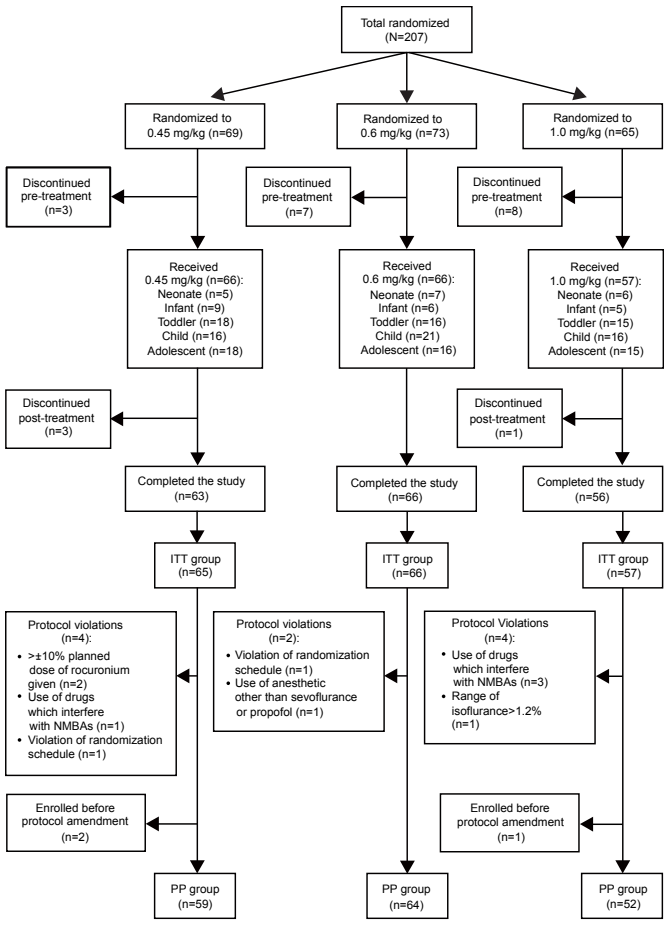
and by rocuronium dose using a model that included center as one of its terms, ultimately, the very small number of subjects within some groups markedly limits the interpretation that can be drawn from these analyses. Furthermore, for each parameter and each dose of rocuronium, six and ten pair-wise comparisons can be made (if comparing four and five groups, respectively); thus inflating the type I error. For this reason, descriptive rather than inferential analyses are presented.

Results

Patients

A total of 207 patients were enrolled and randomized. In total, 189 patients received treatment with rocuronium, of which 185 completed the study (Figure 1). Of the 189 treated patients, 188 had at least one efficacy assessment and were included in the ITT group (18 neonates, 20 infants, 49 toddlers, 52 children, and 49 adolescents), and 175 were included in the PP group. The most common reasons for exclusion from the PP group included violation of the randomization schedule, receiving a dose of rocuronium outside of the prespecified limits of ± 10% of the planned dose, and use of concomitant medications in a dose known to interfere with the action of rocuronium. Six patients were excluded due to enrollment before protocol amendment 2.

Baseline demographic information for all 189 patients who received rocuronium is shown in Table 1. Within each age group, baseline characteristics were similar between the rocuronium dose groups.



ITT: intent-to-treat; NMBAs: neuromuscular blocking agents; PP: per-protocol.

Figure 1: Patient flow through the study.

All 175 patients in the PP group received sevoflurane for induction of anesthesia. Most patients received a range of sevoflurane concentrations. The concentration of sevoflurane given from initiation of induction to tracheal intubation, in patients receiving sevoflurane for induction and isoflurane for maintenance, ranged from 0.0 to 8.0%, with the overall range of duration of exposure to sevoflurane before intubation in these patients being 4.4–88.0 minutes. Isoflurane concentrations for anesthesia maintenance ranged from 0.0 to 2.9%.

Primary outcome variable

Of the patients included in the PP group (n=175), data for time to reappearance of T_3 were available for 159 patients. Data for the remaining 16 patients were either missing, or were considered unreliable by the investigator due to problems collecting accurate data in these cases. Median time from the end of administration of rocuronium to reappearance of T_3 was longer in the 1.0 mg/kg dose group across all age groups, with this dose producing a duration of action approximately double that of the 0.45 mg/kg dose (Table 2 and Figure 2). Across dose groups, the longest times from end of administration of rocuronium to reappearance of T_3 were seen in neonates and infants; the fastest median recovery time was seen in children (Table 2 and Figure 2).

Secondary outcome variables

Median times to onset of NMB (from end of administration of rocuronium to peak effect) were <1.2 minutes in all age groups for each of the three rocuronium doses, and appeared shorter in infants than the other age groups (n=175; Table 2 and Figure 3). Within each age group, rocuronium 1.0 mg/kg produced the fastest onset time (Table 2 and Figure 3). A maximum blockade of 100% (complete suppression of the T_1 response) was achieved in all except six subjects – four neonates (three of whom received rocuronium 0.6 mg/kg and the other 0.45 mg/kg), one infant (0.6 mg/kg), and one adolescent (0.6 mg/kg). Maximum level of blockade in these six patients ranged from 94 to 97%.

Safety analysis

At least one AE was reported for approximately 50% of patients. None were considered by the investigator to be related to rocuronium. The most commonly reported AEs across dose groups were procedural pain, vomiting and procedural hypotension. No dose-dependent relationship between the rocuronium dose and the occurrence of AEs was observed, regardless of age group.

Three patients experienced a total of four SAEs during the study (cardiac arrest during cardiac catheterization in an infant with a ventriculoseptal defect who received 0.45 mg/kg rocuronium, post-procedural hemorrhage in a toddler who underwent cleft lip/nose correction and received 0.45 mg/kg, and cerebrospinal fistula and lymphocele (both reported as a lymphatic malformation) in a child who underwent debulking of an orbital mass and received 0.6 mg/kg). All events were considered by the investigator to be unrelated to study medication.

One child in the rocuronium 0.45 mg/kg group discontinued the study due to an airway complication of anesthesia (reported as 'bucking' by the investigator). This was considered to be unrelated to rocuronium, which had been administered 38 minutes prior to the AE, with maximum blockade being achieved approximately 1 minute after rocuronium administration. The patient discontinued the study before data were recorded for any of the recovery parameters.

Patient group[a]	Neonate			Infant			Toddler			Child			Adolescent		
Rocuronium dose (mg/kg)	**0.45 (n=5)**	**0.6 (n=7)**	**1.0 (n=6)**	**0.45 (n=9)**	**0.6 (n=6)**	**1.0 (n=5)**	**0.45 (n=18)**	**0.6 (n=16)**	**1.0 (n=15)**	**0.45 (n=16)**	**0.6 (n=21)**	**1.0 (n=16)**	**0.45 (n=18)**	**0.6 (n=16)**	**1.0 (n=15)**
Gender, n (%)															
Female	1 (20.0)	1 (14.3)	1 (16.7)	4 (44.4)	0 (0.0)	2 (40.0)	5 (27.8)	3 (18.8)	6 (40.0)	6 (37.5)	14 (66.7)	7 (43.8)	7 (38.9)	7 (43.8)	7 (46.7)
Male	4 (80.0)	6 (85.7)	5 (83.3)	5 (55.6)	6 (100)	3 (60.0)	13 (72.2)	13 (81.3)	9 (60.0)	10 (62.5)	7 (33.3)	9 (56.3)	11 (61.1)	9 (56.3)	8 (53.3)
Age[b]															
Mean	0.26	0.46	0.41	2.05	2.45	1.72	10.69	12.82	11.99	5.12	6.03	5.77	15.05	14.32	14.60
(SD)	(0.14)	(0.23)	(0.25)	(0.82)	(0.37)	(0.73)	(4.59)	(6.06)	(4.98)	(2.65)	(2.18)	(2.34)	(1.73)	(1.54)	(1.82)
Weight (kg)															
Mean	3.48	3.61	3.37	5.19	5.48	4.62	8.74	9.56	9.10	22.38	22.89	19.98	58.98	55.98	55.13
(SD)	(0.22)	(0.25)	(0.32)	(1.09)	(1.06)	(0.37)	(1.51)	(1.97)	(1.46)	(14.89)	(10.26)	(6.22)	(14.15)	(15.08)	(13.72)
Race, n (%)															
Asian	0 (0)	1 (14.3)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	0 (0)	2 (13.3)	0 (0)	1 (4.8)	1 (6.3)	0 (0)	0 (0)	1 (6.7)
Black	1 (20.0)	1 (14.3)	0 (0)	0 (0)	1 (16.7)	0 (0)	2 (11.1)	2 (12.5)	1 (6.7)	2 (12.5)	8 (38.1)	4 (25.0)	3 (16.7)	2 (12.5)	2 (13.3)
White	4 (80.0)	5 (71.4)	6 (100)	9 (100)	4 (66.7)	5 (100)	16 (88.9)	14 (87.5)	12 (80.0)	14 (87.5)	12 (57.1)	11 (68.8)	15 (83.3)	14 (87.5)	12 (80.0)
ASA Class															
1	1 (20.0)	0 (0.0)	1 (16.7)	4 (44.4)	3 (50.0)	4 (80.0)	6 (33.3)	5 (31.3)	4 (26.7)	7 (43.8)	8 (38.1)	8 (50.0)	7 (38.9)	8 (50.0)	8 (53.3)
2	1 (20.0)	2 (28.6)	2 (33.3)	5 (55.6)	2 (33.3)	1 (20.0)	10 (55.6)	10 (62.5)	9 (60.0)	8 (50.0)	10 (47.6)	5 (31.3)	10 (55.6)	8 (50.0)	6 (40.0)
3	3 (60.0)	5 (71.4)	3 (50.0)	0 (0)	1 (16.7)	0 (0)	2 (11.1)	1 (6.3)	2 (13.3)	1 (6.3)	3 (14.3)	3 (18.8)	1 (5.6)	0 (0)	1 (6.7)

[a]Neonates: birth to <28 days, infants: 28 days to ≤3 months, toddlers: >3 months to ≤2 years, children: >2 years to ≤11 years, and adolescents: >11 to ≤17 years; [b]Age in months for neonates, infants and toddlers; in years for children and adolescents; ASA: American Society of Anesthesiologists.

Table 1: Summary of patient baseline characteristics (all subjects receiving rocuronium; n=189).

Patient group[a]	Neonate			Infant			Toddler			Child			Adolescent		
Rocuronium dose (mg/kg)	**0.45 (n=4)**	**0.6 (n=7)**	**1.0 (n=4)**	**0.45 (n=9)**	**0.6 (n=6)**	**1.0 (n=5)**	**0.45 (n=16)**	**0.6 (n=15)**	**1.0 (n=14)**	**0.45 (n=13)**	**0.6 (n=20)**	**1.0 (n=16)**	**0.45 (n=17)**	**0.6 (n=16)**	**1.0 (n=13)**
Reappearance of T_3, n	4	6	2	8	6	3	15	14	12	12	20	14	16	16	11
Mean	49.5	55.7	114.4	46.4	62.3	116.5	35.3	41.8	76.1	23.6	38.3	53.5	37.0	41.8	61.6
SD	11.6	32.3	30.9	23.1	20.4	34.2	11.3	11.6	23.6	5.2	11.6	16.1	13.4	15.2	19.4
Median	48.2	50.4	114.4	49.1	57.9	103.3	39.1	41.5	72.5	21.3	38.9	53.1	36.7	41.7	65.6
Range	39.2–62.6	20.2–111.7	92.6–136.3	13.5–79.9	32.3–87.8	90.8–155.4	16.9–59.4	18.9–59.3	42.0–128.2	17.5–31.5	21.7–65.9	31.2–89.9	18.3–65.7	16.3–81.9	25.6–93.8
Onset of NMB, n	4	7	4	9	6	5	16	15	14	13	20	16	17	16	13
Mean	1.22	1.10	0.82	0.69	0.52	0.41	0.83	0.67	0.57	0.89	0.87	0.67	1.10	1.08	0.72
SD	0.67	0.67	0.67	0.35	0.21	0.19	0.47	0.30	0.32	0.42	0.33	0.21	0.38	0.47	0.17
Median	1.06	1.15	0.57	0.53	0.53	0.32	0.77	0.65	0.49	0.83	0.85	0.69	1.02	1.06	0.68
Range	0.58–2.17	0.32–2.07	0.33–1.82	0.35–1.25	0.23–0.82	0.23–0.70	0.32–1.92	0.27–1.55	0.23–1.52	0.40–1.92	0.32–1.70	0.38–1.17	0.53–1.67	0.18–2.08	0.53–1.17
Recovery to TOF 0.9, n	2	2	1	3	4	1	9	10	7	12	13	9	10	11	7
Mean	134.0	119.6	180.8	108.6	111.2	255.6	65.1	68.1	148.8	46.5	71.0	76.0	63.5	73.4	97.7
SD	59.5	42.7	–	4.7	30.6	–	31.3	19.9	22.2	15.2	29.0	26.8	32.0	24.8	34.4
Median	134.0	119.6	180.8	109.6	109.2	255.6	56.8	68.6	150.7	45.4	68.9	83.7	58.6	79.2	107.9
Range	91.9–176.1	89.4–149.8	–	103.5–112.7	77.5–148.8	–	28.2–125.2	28.4–96.6	104.6–172.7	26.7–82.5	33.4–137.9	44.0–120.2	26.2–133.5	28.6–123.9	47.8–143.1

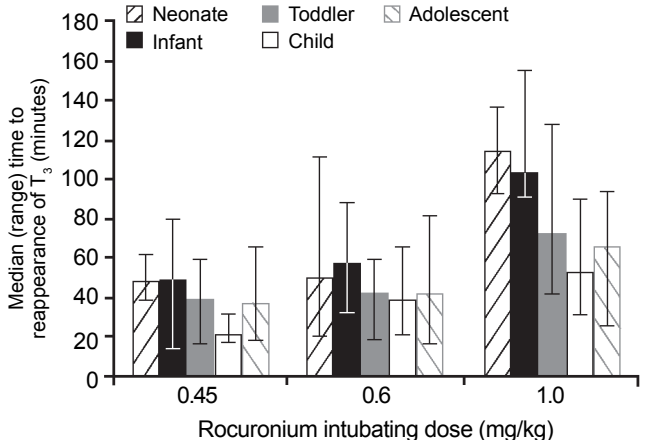
[a]Neonates: birth to <28 days, infants: 28 days to ≤3 months, toddlers: >3 months to ≤2 years, children: >2 years to ≤11 years, and adolescents: >11 to ≤17 years.

Table 2: Time (minutes) from end of administration of rocuronium to: reappearance of T_3, onset of neuromuscular blockade (NMB) and recovery to train-of-four (TOF) 0.9 (per-protocol group).

Following treatment, mean systolic and diastolic blood pressure values were generally higher in children and adolescents with mean heart rate values lower in these older age groups. Clinically significant (requiring intervention or medication within 120 minutes after administration of rocuronium) cardiovascular changes from baseline in blood pressure, heart rate and ECG parameters were reported by investigators in six neonates, no infants, one toddler, five children, and seven adolescents, but no relationship to dose was observed. The reasons given for such changes were anesthesia (n=12), surgical procedure (n=6) and unknown cause (n=2).

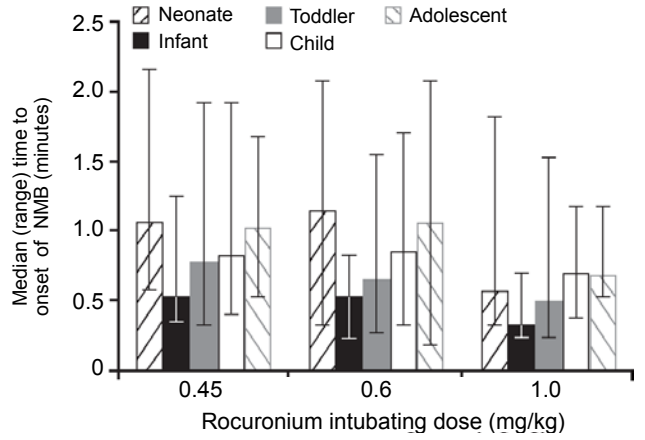
ECG tracings showed that following treatment, according to the pre-defined age-specific criteria, there was no clear effect of rocuronium dose on heart rate, although in infants, the percentage of subjects with high heart rate values was lower in the 0.45 mg/kg group (11%) versus the 0.6 and 1.0 mg/kg groups (67% and 60%, respectively).

Mean QTcB increased from the pre-sevoflurane anesthesia baseline to the post-anesthesia baseline (values increased from 411 to 425, 402 to 425 and 406 to 436 msec in the 0.45, 0.6 and 1.0 mg/kg groups, respectively). There was a further stable increase (during continued an-



T3: the third twitch of the train-of-four
Neonates: birth to <28 days; infants: 28 days to ≤3 months; toddlers: >3 months to ≤2 years; children: >2 years to ≤11 years; adolescents: >11 to ≤17 years

Figure 2: Time (minutes) from end of administration of rocuronium to reappearance of T_3 (per-protocol group with data available, n=159).



Neonates: birth to <28 days; infants: 28 days to ≤3 months; toddlers: >3 months to ≤2 years; children: >2 years to ≤11 years; adolescents: >11 to ≤17 years

Figure 3: Time (minutes) from end of administration of rocuronium to onset of neuromuscular blockade (NMB) (per-protocol group).

esthesia) across the whole patient group, with values at 30 minutes after rocuronium of 454, 440 and 454 msec in the 0.45, 0.6 and 1.0 mg/kg groups, respectively. The percentage of patients with clinically significant abnormal QTcB across treatment groups ranged from 0 to 17% in neonates, 0 to 20% in infants and 0 to 6.7% in toddlers. The proportion of patients with clinically significant abnormal values was greater in the two eldest age groups, ranging from 63 to 75% and 61 to 87% of patients in the child and adolescent groups, respectively. There was no apparent relationship between the rocuronium dose and the percentage of patients with clinically significant abnormal QTcB values.

Four patients from the PP group had clinically significant changes in ventilatory compliance or SaO_2 requiring a change in ventilatory settings during the study period. In each of these four cases, the changes were considered unrelated to rocuronium and were thought to be associated with difficulty in intubation (due to an anatomical malformation of subglottic stenosis, which became apparent when intubation was attempted), transesophageal echocardiogram probe pressing on chest, spontaneous breathing and hypoventilation, respectively.

Discussion

Our study showed that rocuronium at the approved intubating doses of 0.45, 0.6 or 1.0 mg/kg was generally well tolerated, and induced a rapid onset of NMB, during sevoflurane anesthesia. The study also showed, as with previous studies in adults [5-8], that rocuronium has an intermediate duration of action at these approved doses in pediatric patients during isoflurane maintenance anesthesia after induction with sevoflurane.

The clinical duration of action of rocuronium (time from end of rocuronium administration to reappearance of T_3), was approximately double with the 1.0 mg/kg dose compared with the 0.45 mg/kg dose across all age groups. However, there appeared to be only a very small increase in rocuronium duration with the 0.6 mg/kg dose compared with the 0.45 mg/kg dose. Across dose groups, the longest times from end of administration of rocuronium to reappearance of T_3 were seen in neonates and infants. This may be associated with age-related pharmacokinetic and pharmacodynamic differences between the groups as a result of differences in body composition, physiological function and acetylcholine receptor numbers and distribution [4]. Previous studies have shown that the potency of rocuronium is greater in infants and lower in children when compared with adults [4,9,11–14]. The fastest recovery in the present study was seen in children.

Driessen et al. [11] evaluated duration of action of rocuronium 0.3 mg/kg in 51 children of different ages (0–6 months, 6–24 months, and >24 months) during halothane anesthesia. Young infants (0–6 months) had significantly faster NMB onset times versus the two older age groups, with the youngest two age groups having significantly longer duration of action versus the eldest age group. Thus, although this study utilized a lower dose of rocuronium and a different anesthetic compared with the present study, the results were generally consistent with those reported here. A study by Woelfel et al. [9] showed that in infants (2–11 months) undergoing halothane anesthesia and receiving rocuronium 0.6 mg/kg for intubation, rocuronium had a longer duration of action (recovery of T_1 to 25%) compared with children aged 1–5 years [10].

One study reported that with the dose predicted to produce 95% depression of evoked movement of the thumb (ED_{95}) the time-course of recovery after rocuronium is similar in all age groups [12]. This suggests that redistribution, rather than clearance, is the major factor determining the duration of action of a single ED_{95} dose of rocuronium. In the present study, however, doses up to three or four times the ED_{95} were administered. These larger doses are likely to result in recovery from blockade during the elimination phase of plasma decay when reduced hepatic clearance will prolong NMB. The increased sensitivity of the neonate and infant to non-depolarizing NMBAs during exposure to inhalation anesthetics is also significant [15,16].

In this study, onset of NMB was rapid, with median onset times of <1.2 minutes in all age groups for each of the three rocuronium doses. Similar results were obtained in a previous study in children aged 1–5 years which found that, during halothane-nitrous oxide anesthesia, rocuronium 0.6 mg/kg resulted in rapid (0.8 ± 0.1 [0.5–1.3] minutes) onset of 90% NMB, and complete blockade in 1.3 ± 0.2 (0.7–2.8) minutes [10]. Within each age group in the present study, rocuronium 1.0 mg/kg produced the fastest onset time (Table 2).

Sevoflurane was chosen for use as the induction anesthetic as this

agent tends to be used more commonly now in pediatric patients than traditional anesthetics such as halothane and propofol. The concentration of sevoflurane used varied somewhat between patients and reflected the practices of the hospitals participating in this study and the clinical needs of the patient. As reported in the literature, the concentration of sevoflurane may enhance the effect of rocuronium [17-19], with this potentiating effect of inhalational agents also reported to be time-dependant [20,21]. Onset of action of rocuronium may also potentially be shortened during anesthesia with sevoflurane [22], particularly when there is a very long duration of sevoflurane exposure [23]. It could be argued that the variable concentrations and lengths of sevoflurane exposure for induction of anesthesia make accurate evaluation of the NMB parameters difficult. However, following intubation in the present study, sevoflurane was stopped and anesthesia was maintained with a uniform concentration of isoflurane (1.0 ± 0.2% expired end-tidal concentration). While, as an inhalational anesthetic agent, isoflurane may also have a potentiating effect on NMBA pharmacodynamics, this effect is likely to be less pronounced compared with sevoflurane [17,18]. In addition, sevoflurane has a very low blood:gas partition coefficient of 0.69 in adults [22] and 0.66 in neonates, with no age-related effects [24], and this results in both its rapid uptake and elimination. Given this and the duration of the surgical procedures the patients underwent, it is likely that there would be negligible amounts of sevoflurane remaining, if any, to cause a potentiating effect on rocuronium.

All doses of rocuronium were well tolerated and no drug-related AEs or SAEs occurred. Sevoflurane is known to cause QT prolongation at induction concentrations in both adults and infants [25-27], and analysis of ECG data from the present study suggests that both sevoflurane and rocuronium at the doses employed may increase QTc interval. However, it was impossible to separate conclusively the effect of rocuronium from that of anesthesia or other factors because: (i) anesthesia was administered simultaneously with rocuronium; (ii) anesthetics and their doses were changed during rocuronium treatment; and (iii) ECGs were not performed immediately upon administration of rocuronium.

Conclusions

The results of this study provide additional data collected in the setting of a randomized, assessor-blinded study regarding the use of rocuronium in pediatric patients. Rocuronium at intubating doses of 0.45, 0.6, or 1.0 mg/kg is generally well tolerated, and effective in producing rapid-onset NMB with an intermediate duration of action in pediatric patients during sevoflurane induction/isoflurane maintenance anesthesia.

A 1.0 mg/kg dose of rocuronium produced a duration of action approximately double that of a 0.45 mg/kg dose, across all age groups, with the duration of action only slightly longer with the 0.6 mg/kg dose compared with the 0.45 mg/kg dose. The longest duration of blockade was observed in infants and neonates.

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