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Neuromuscular effects of rapacuronium in pediatric patients during nitrous oxide-halothane anesthesia: comparison with mivacurium

Purpose: To describe neuromuscular effects of rapacuronium in pediatric patients during N₂O-halothane anesthesia and compare them with mivacurium in children.

Methods: 103 pediatric patients, seven days - 12 yr, received rapacuronium or mivacurium during N₂O-halothane anesthesia. Onset and recovery of block were measured using EMG (Datex). Block was compared between groups based on drug treatment and age. Children < two years received 1 or 2 mg·kg⁻¹ rapacuronium; 2 - 12 yr received either 2 mg·kg⁻¹ or 3 mg·kg⁻¹ rapacuronium, or 0.2 mg·kg⁻¹ mivacurium.

Results: There were no differences in onset (1.7 ± 1.8 min) or maximum block (T1 2.4 ± 8%) among neonates, infants, and toddlers after either dose of rapacuronium. There was no difference between 1 and 2 mg·kg⁻¹ of rapacuronium block at 60 sec. Train-of-four ratio (T4/T1) > 0.7 occurred later after 2 mg·kg⁻¹ than 1 mg·kg⁻¹ in these patients (P < 0.05). There was no difference in T25 among neonates, infants and toddlers for 1 mg·kg⁻¹ or 2 mg·kg⁻¹ doses. Rapacuronium, 3 mg·kg⁻¹, produced maximum block 1.5 min earlier than did mivacurium, 0.2 mg·kg⁻¹ (P < 0.001). There was no difference in block at 60 sec, maximum block or time to maximum block between 2 and 3 mg·kg⁻¹ rapacuronium for children > two years of age. Maximum block occurred 1.0 ± 0.5 min after 2 or 3 mg·kg⁻¹ when T1 was 0.2 ± 1.1% of baseline. T25 and T4/T1 > 0.7 occurred 10 to 11 min later after this dose of rapacuronium than after mivacurium.

Conclusion: Rapacuronium produces block earlier than mivacurium. Recovery from rapacuronium block is dose related and slower than that following mivacurium during halothane anesthesia.

Objectif : Décrire les effets neuromusculaires du rapacuronium pendant l'anesthésie avec N₂O et halothane et les comparer avec ceux du mivacurium chez des enfants.

Méthode : Cent trois enfants, de 7 jrs à 12 ans, ont reçu du rapacuronium ou du mivacurium pendant une anesthésie avec N₂O et halothane. Le début et la fin du bloc ont été mesurés à l'aide de l'EMG (Datex). Le bloc a été comparé sur la base du traitement médicamenteux et de l'âge. Les enfants < 2 ans ont reçu 1 ou 2 mg·kg⁻¹ de rapacuronium; ceux de 2-12 ans ont reçu 2 ou 3 mg·kg⁻¹ de rapacuronium, ou 0,2 mg·kg⁻¹ de mivacurium.

Résultats : Le rapacuronium, peu importe la dose administrée et l'âge des patients, n'a pas présenté de différence quant au début d'action (1,7 ± 1,8 min) du bloc ou au temps du bloc maximal (T1 2,4 ± 8 %). À 60 s, les blocs provoqués par 1 et 2 mg·kg⁻¹ de rapacuronium étaient semblables. Le rapport du train-de-quatre (T4/T1) > 0,7 s'est produit plus tard après 2 mg·kg⁻¹ qu'après 1 mg·kg⁻¹ (P < 0,05). Aucune différence non plus au T25 entre les doses de 1 ou 2 mg·kg⁻¹. La dose de 3 mg·kg⁻¹ de rapacuronium a produit le bloc maximal 1,5 min plus tôt que celle de 0,2 mg·kg⁻¹ (P < 0,001) de mivacurium. Il n'y a pas eu de différence de bloc à 60 s, de temps pour le bloc maximal ou de temps pour atteindre ce bloc maximal chez les enfants > 2 ans qui ont reçu 2 et 3 mg·kg⁻¹ de rapacuronium. Le bloc maximal a été noté 1,0 ± 0,5 min après 2 ou 3 mg·kg⁻¹ quand T1 était à 0,2 ± 1,1 % de la mesure de base. T25 et T4/T1 > 0,7 sont survenus de 10-11 min plus tard après cette dose de rapacuronium qu'après le mivacurium.

Conclusion : Le rapacuronium agit plus rapidement que le mivacurium. Pendant l'anesthésie avec de l'halothane, le renversement du bloc suivant l'utilisation de rapacuronium est relié à la dose et est plus lent que celui qui suit le mivacurium.

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RAPACURONIUM is a new aminosteroid neuromuscular blocker with relatively rapid time course of block in adults.¹ The purpose of this study is to describe the neuromuscular effects of rapacuronium in neonates and older pediatric patients during halothane-nitrous oxide anesthesia. This study was undertaken in two parts. Part I reports the effects of 1 and 2 mg·kg⁻¹ rapacuronium in neonates, infants and toddlers. Part II compares the effects of 2 and 3 mg·kg⁻¹ rapacuronium with those of 0.2 mg·kg⁻¹ mivacurium in children two through 12 yr of age, because mivacurium is the currently available nondepolarizing blocker with the shortest duration of action. Comparison with mivacurium was limited to conditions of use that have been approved by the Food and Drug Administration: for children over two years and maximum dose of 0.2 mg·kg⁻¹. Previous observations of the effects of 1 and 2 mg·kg⁻¹ rapacuronium in pediatric patients² suggest that these two doses will facilitate intubation in patients less than one year of age, but that < 2 mg·kg⁻¹ may not be effective in older children. Rapidity of onset and duration of block are of interest following the smallest doses likely to facilitate intubation. Therefore, 1 or 2 mg·kg⁻¹ rapacuronium were given to patients less than two years of age and 2 or 3 mg·kg⁻¹ to older children. Two doses of rapacuronium were administered in each age group so that the increase in duration of action of the larger dose, which might be chosen to facilitate intubation, could be documented.

Methods

Nine neonates (< 29 dy after birth), 17 infants (one month to < 12 mo), 12 toddlers (12 mo to < two years) and 65 children (two to < 13 yr), ASA physical status I-III, undergoing elective surgery were studied after obtaining institutional review board approval and signed parental informed consent. At Children's Hospital of Pittsburgh 44 patients were studied, including eight neonates. At Jackson Memorial Hospital at the University of Miami 31 were studied, including one neonate, and at Duke University 28 were studied. All patients were within the 10th to 90th percentiles in body weight and height. No patients had known impairment of renal or hepatic function or had received aminoglycoside antibiotics or antihistamines within 48 hr of this study. All neonates and infants were born after at least 37 wk gestation. No premedication was given.

Anesthesia was induced in neonates, after 80 to 120 µg atropine *iv*, with either 3 mg·kg⁻¹ thiopental, or halothane (up to 3% inspired), and nitrous oxide (50%-70%) and oxygen (30%-50%) as indicated by

clinical judgement. When an increase in heart rate or movement followed nerve stimulation, 1 µg·kg⁻¹ fentanyl was given to neonates during anesthetic induction. Halothane was reduced to 0.5% inspired in neonates when intravenous access was secured and ventilation controlled. For children aged one month to 12 yr, anesthesia was induced with halothane (up to 5% inspired), nitrous oxide (70%), in oxygen (30%). Following loss of eye lash reflex and lack of response to inflation of the blood pressure cuff, the inspired halothane was reduced to 2% and an intravenous catheter placed. No other drugs were given prior to administration of the blocker. Monitors for all patients included precordial stethoscope, electrocardiogram, pulse oximeter, temperature probe, and blood pressure cuff. Normothermia and normal minute ventilation were maintained.

The electromyogram of the adductor pollicis was recorded with a Datex neuromuscular transmission monitor (Helsinki, Finland). The sensing electrode was placed on the palmar aspect of the web space between the first finger and the thumb.³ The ulnar nerve was supramaximally stimulated at 2 Hz for two seconds (train-of-four, TOF) every 10 sec for less than one minute prior to injection of neuromuscular blocker, and continually thereafter. All muscle relaxants were administered after hemodynamic stabilization and observation of three stable TOF responses.

By random assignment, subjects < two years old received either 1 or 2 mg·kg⁻¹ rapacuronium, while those two to 12 yr of age received either 2 mg·kg⁻¹ rapacuronium, 3 mg·kg⁻¹ rapacuronium, or 0.2 mg·kg⁻¹ mivacurium administered as a bolus given over less than five seconds into the T-connector of a rapidly running intravenous line. Following neuromuscular blocker administration, inspired halothane was reduced to 1.5% for subjects older than 29 dy and kept at 0.5% for neonates. Tracheal intubation was performed two to three minutes after administration of blocker in neonates and after three to four minutes in infants, toddlers, and children. After tracheal intubation anesthesia was maintained with nitrous oxide (up to 70%) in oxygen, halothane (0.8% to 1% end-tidal), and 1 µg·kg⁻¹ increments of fentanyl when heart rate increased in response to surgical stimulation in all subjects.

Neuromuscular assessments included the degree of depression of the first response (T1) to the TOF stimuli at 60 sec after injection of blocker; maximum block of T1; time to maximum block; time to 25% recovery of T1 (clinical duration, T25); and times to T4/T1 ratios of 0.4, and 0.7. Recovery of T1 to 25% was referenced to the initial baseline signal since this usually occurred in less than 20 min.

Subjects were compared based on age categories and dose of blocker. Analysis of variance or chi-square analysis was used to compare differences in neuromuscular block between groups. A $P < 0.05$ was considered significant. Data is presented as mean $\pm$ standard deviation.

NEUROMUSCULAR DATA

Part I - Neonates, infants, and toddlers

There were no differences in the average duration of halothane exposure before the administration of neuromuscular blocker [9.4 ± 3.4 min (mean $\pm$ standard deviation), range 5-11 min] in the six groups of subjects $<$ two years old. Table I and Figures 1 and 2 summarize the neuromuscular data in these subjects. Of those who received $1 \text{ mg}\cdot\text{kg}^{-1}$ rapacuronium, in 80% of neonates, 78% of infants and 75% of toddlers, T1 was $<$ 10% of the baseline 60 sec after injection. Of those who received $2 \text{ mg}\cdot\text{kg}^{-1}$ rapacuronium, in 75% of neonates, 88% of infants, and 75% of toddlers T1 was $<$ 10% of baseline 60 sec after injection. There were no differences in block 60 sec after injection ($P > 0.6$), maximum block ($P > 0.149$), or time to maximum block ($P > 0.20$) between doses of rapacuronium in neonates, infants, and toddlers or among ages groups at these doses. The average maximum block occurred 1.7 ± 1.8 min after injection 1 or $2 \text{ mg}\cdot\text{kg}^{-1}$ of rapacuronium when T1 was $2.4 \pm 8\%$ of the base-

line in subjects $<$ two years of age.

There were no differences in T25 between neonates, infants, and toddlers ($P > 0.24$) (Table I). The end-tidal halothane concentration was $0.83 \pm 0.17\%$ in these patients at the time T25 was observed. However, in both infants and toddlers there was a dose related increase in duration of block with respect to T25 ($P = 0.02$). The time to T4/T1 ratio of 0.7 was longer in infants than in neonates after $2 \text{ mg}\cdot\text{kg}^{-1}$ rapacuronium (Table I). The interval in which T4/T1 was greater than 0.4 and less than 0.7 was longer in infants (14.2 ± 6.1 min) than in neonates (6.5 ± 3.9 min) or toddlers (7.1 ± 2.6 min) after $2 \text{ mg}\cdot\text{kg}^{-1}$ dose rapacuronium (Figure 2). The final baseline was $78 \pm 12\%$ of the initial baseline electromyogram in these patients.

Part II - Children two to 12 yr old

There were no differences in the average duration of halothane exposure before the administration of neuromuscular blocker [9.5 ± 3.6 min, range 3.3-17.5 min] in the three groups of children 2-12 yr old. Table II and Figures 2 and 3 summarize the neuromuscular data in these subjects. In all who received $2 \text{ mg}\cdot\text{kg}^{-1}$ rapacuronium, T1 was $<$ 10% of baseline 60 sec after injection. Of those who received $3 \text{ mg}\cdot\text{kg}^{-1}$ rapacuronium, in 90% T1 was $<$ 10% of baseline 60 sec after injection. Of those who received $0.2 \text{ mg}\cdot\text{kg}^{-1}$ mivacurium, in 27% T1 was $<$ 10% of baseline 60 sec after

TABLE I Neuromuscular effects of rapacuronium in neonates, infants, and toddlers

Variable	Neonates		Infants		Toddlers	
	$1 \text{ mg}\cdot\text{kg}^{-1}$	$2 \text{ mg}\cdot\text{kg}^{-1}$	$1 \text{ mg}\cdot\text{kg}^{-1}$	$2 \text{ mg}\cdot\text{kg}^{-1}$	$1 \text{ mg}\cdot\text{kg}^{-1}$	$2 \text{ mg}\cdot\text{kg}^{-1}$
Subjects with T1<10% at 60 sec						
	4 of 5	3 of 4	7 of 9	7 of 8	3 of 4	6 of 8
T1 at 60 sec						
Mean $\pm$ SD	5.2 ± 9.6	7.6 ± 13.6	12.8 ± 20.1	1.8 ± 4.2	3.5 ± 7.0	13.3 ± 30.4
Median	0	1.3	4	0	0	1.3
Range	0-22	0-28	0-56	0-12	0-14	0-88
Time from injection of blocker to 25% recovery of T1						
n	4	4	8	8	4	8
Mean $\pm$ SD	9.8 ± 3.1	13.5 ± 2.8	10.2 ± 2.6^a	18.6 ± 9.1^b	8.1 ± 2.0^c	13.7 ± 3.0^d
Median	9.7	13.4	11.1	18.6	8.3	13.7
Range	6-13.7	10.3-16.8	5.5-13.0	1.7-32.4	5.7-10.2	9.5-19.0
Time from injection of blocker to T4/T1 $>$ 0.7						
n	3	4	8	8	4	8
Mean $\pm$ SD	19.7 ± 2.9	22.8 ± 5.9^e	21.8 ± 7.3	40.9 ± 10.3^f	15.2 ± 3.1	27.8 ± 13.0^e
Median	20.7	23.0	22.5	43.5	15.8	4.6
Range	16.5-22.0	16.5-28.7	11.5-29.9	28.0-53.6	10.7-18.5	17.5-57.9

T1 = the first response to the TOF as % of initial baseline

a and b, and c and d, are significantly different, $P = 0.02$

e and f are significantly different at $P < 0.05$

TABLE II Neuromuscular blocking effect of rapacuronium and mivacurium in children 2-12 yr old

Variable	Rapacuronium 2.0 mg·kg ⁻¹	Rapacuronium 3.0 mg·kg ⁻¹	Mivacurium 0.2 mg·kg ⁻¹
Subjects with T1 < 10% at 60 sec	23 of 23a	19 of 21a	6 of 21b
T1 at 60 sec			
Mean ± SD	1.0 ± 2.3a	5.4 ± 17.5a	44.5 ± 36.1b
Median	0	0	0
Range	0-8	0-80	0-100
Time from injection of block to 25% recovery of T1 (25)			
n	23	20	22
Mean ± SD	13.8 ± 7.2a	17.8 ± 3.2a	10.1 ± 3.0b
Median	12.7	17.4	9.4
Range	8.5-44.2	11.5-23.6	4.6-14.9
Time from injection of blocker to T4/T1 ratio = 0.7			
n	20	19	21
Mean ± SD	25.7 ± 9.3	37.1 ± 9.4a	15.9 ± 3.9b
Median	22.4	34.0	15.3
Range	17.5-50.5	22.5-54.2	9.4-23.9
Interval in which T4/T1 was greater than 0.4 and less than 0.7			
n	20	18	21
Mean ± SD	6.7 ± 4.8	11.0 ± 5.5	3.0 ± 1.0
Median	5.1	9.7	3.2
Variable	2.3-21.8	2.8-21.0	0.8-5.3

T1 = The first twitch of the TOF as % of baseline

Within each row a and b are significantly different from each other

FIGURE 1 This graph plots the time to maximal block vs the maximum block attained in pediatric patients < 2 yr old after 2 mg·kg⁻¹ (○) or 1 mg·kg⁻¹ (▲) rapacuronium.

injection (Table II). There were no differences in block 60 sec after injection ($P > 0.23$), maximum block ($P > 0.76$), or time to maximum block ($P > 0.35$) between 2 and 3 mg·kg⁻¹ doses of rapacuronium. Maximum block occurred 1.0 ± 0.5 min after injection of 2 or 3 mg·kg⁻¹ rapacuronium when average T1 was $0.2 \pm$

FIGURE 2 The interval in which occult residual block existed ($0.4 < T4/T1 < 0.7$) is plotted relative to the patient's age and blocker given: mivacurium, 0.2 mg·kg⁻¹ (X), rapacuronium, 3 mg·kg⁻¹ (●), 2 mg·kg⁻¹ (○), or 1 mg·kg⁻¹ (▲).

FIGURE 3 This graph plots time to maximum block vs the maximum block attained in children after 3 mg·kg⁻¹ rapacuronium (●), 2 mg·kg⁻¹ rapacuronium (○), or 0.2 mg·kg⁻¹ mivacurium (X).

1.1% of baseline. Maximum block occurred earlier by 1.5 minutes after 3 mg·kg⁻¹ rapacuronium than after 0.2 mg·kg⁻¹ mivacurium ($P < 0.001$).

There was a difference in T25 after 0.2 mg·kg⁻¹ mivacurium and 3 mg·kg⁻¹ rapacuronium ($P < 0.01$) (Table II). The end-tidal halothane concentration was $0.85 \pm 0.25\%$ in these patients at the time T25 was observed. The difference in T25 between 2 mg·kg⁻¹ rapacuronium and 0.2 mg·kg⁻¹ mivacurium was marginal ($P > 0.06$). The time to T4/T1 ratio of 0.7 was longer after 3 mg·kg⁻¹ rapacuronium, than after 0.2

mg·kg⁻¹ mivacurium ($P < 0.01$). The difference in time to T4/T1 ratio of 0.7 between 2 mg·kg⁻¹ rapacuronium and 0.2 mg·kg⁻¹ mivacurium was marginal ($P = 0.08$). The interval when T4/T1 was greater than 0.4 and less than 0.7 was longer after 2 mg·kg⁻¹ rapacuronium (6.7 ± 4.8 min) and 3 mg·kg⁻¹ rapacuronium (11.0 ± 5.5 min), than after mivacurium (3.0 ± 1.0 min) ($P < 0.05$) (Figure 2). The final baseline was $83 \pm 12\%$ of the initial baseline electromyogram in these patients.

Discussion

This study describes the neuromuscular effects of rapacuronium in pediatric patients from birth through 12 yr of age during N₂O/O₂/halothane anesthesia. In children over two years of age the larger dose of rapacuronium given here is greater than that given previously to facilitate tracheal intubation.² The degree of block present at the adductor pollicis 60 sec after injection of blocker is reported as a surrogate for the result of intubation attempts. It has been suggested that when neuromuscular function of the adductor pollicis is $< 10\%$ of baseline, tracheal intubation can be performed without resistance. Excellent intubation conditions 60 sec after injection would be an improvement over that observed after 0.3 mg·kg⁻¹ mivacurium during similar anesthetic conditions in children.⁴

It may be expected that increasing the dose of rapacuronium would produce block earlier. This was observed at the adductor pollicis, but not the laryngeal adductor, in adults during propofol/fentanyl anesthesia.⁵ In these pediatric patients during halothane anesthesia we did not observe differences in onset of block at the adductor pollicis with increasing dose. This may be because halothane produced changes in regional blood flow and block produced by rapacuronium is significantly altered by this. It has been demonstrated that the onset of block produced by another relatively low potency drug, rocuronium, is slowed by tourniquet inflation, whereas that produced by more potent drugs, vecuronium or mivacurium is not.⁶

Variable exposure to halothane within treatment groups prior to administration of blocker may have increased variability in the onset of block and thus prevented observation of a dose related change. However, it should be noted that in a study of 180 pediatric patients there was no difference in time to 90% block or to maximum block, produced by 0.3 mg·kg⁻¹ of mivacurium, between those who received halothane for an average of 4.4 min and those who received thiopental and fentanyl instead of halothane.⁷ The relatively short exposure to halothane in this study may not have produced much potentiation of

block. If halothane exposure had been continued long enough to reach equilibration in all patients, 30 to 45 min,⁸ the effect measured at the adductor pollicis would have been much greater than could be expected during induction of halothane anesthesia for clinical purposes. Similarly, description of onset of block acquired after three minutes of baseline stimulation, as has been suggested to be appropriate clinical research practice,⁹ may produce greater block than will be observed during clinical practice. For example, increasing the duration of stimulation prior to administration of mivacurium from one to five minutes, reduced the average time to onset of maximum block by 90 sec.¹⁰ The goal of this study was to describe drug effects during conditions as close to clinical practice as possible, not to describe drug effects during ideal monitoring conditions. Thus, this study is not a perfect study comparing the neuromuscular effects of rapacuronium and mivacurium. It is a study which illustrates for the clinician what can be observed when the effects of these drugs are monitored quantitatively during halothane anesthesia in pediatric patients.

Because the potency of rapacuronium in pediatric patients during halothane anesthesia has not been documented, it is not possible to compare equipotent doses of mivacurium and rapacuronium. Only preliminary studies of the potency of rapacuronium in pediatric patients are available.^{11,12} These report ED50s, the dose which would produce 50% block, of 0.3 or 0.4 mg·kg⁻¹ in infants one to 12 mo old and 0.4 to 0.8 mg·kg⁻¹ in children one to 12 yr old during nitrous oxide propofol anesthesia. The dose of mivacurium used in this study is the largest dose approved for use in children. It is equivalent to four times the ED50 of mivacurium.¹³ The onset of block after 0.2 mg·kg⁻¹ mivacurium, was slower than after rapacuronium in this study, but would 2 or 3 mg·kg⁻¹ rapacuronium produce block faster than mivacurium 0.3 mg? In a larger study of mivacurium the time to 90% block was found to be related to age, from an average of 1.0 minute at one month of age to 2.3 minutes at 12.5 yr of age.⁷ These data suggest that, in children, rapacuronium will often produce block of the adductor pollicis faster than 0.3 mg·kg⁻¹ of mivacurium.

Most nondepolarizing blocking drugs are more potent in neonates and young infants than in older children.¹⁴ Furthermore, neuromuscular function in neonates is more easily depressed than in the older child.¹⁵ However, this study could not identify age-related differences in most of the measures of spontaneous recovery in subjects from seven days to two years of age. This may be due to the small numbers of patients studied, to variability in neuromuscular function in the first months of life^{16,17} and to increasing

potentiation by halothane during the interval of observation.⁸

As the dose of rapacuronium increased, the time to any point in spontaneous recovery increased. Dose-related increases in clinical duration have also been documented after administration of vecuronium to children¹⁸ and rocuronium to adults.¹⁹ There was a difference in the interval in which the TOF ratio was greater than 0.4 and less than 0.7, between each dose of rapacuronium and mivacurium. This can be clinically important because fade in the TOF ratio is not palpable after the fourth response has reached 40% of the first.²⁰ Block which could be symptomatic,²¹ but undetectable by the usual clinical methods will persist an average of eight minutes longer during spontaneous recovery from 3 mg·kg⁻¹ rapacuronium than during recovery from 0.2 mg·kg⁻¹ of mivacurium. It may be advisable to administer anticholinesterase to reverse residual block during recovery from rapacuronium. If the same conservative recommendations, administration of anticholinesterase at T25, are applied to reversal of rapacuronium as were applied to vecuronium,²² anticholinesterase should be effective within 10 to 20 min after administration of 2 or 3 mg·kg⁻¹ rapacuronium to children during halothane anesthesia. Because T25 was referenced to initial baseline and the final baseline was about 80% of the initial baseline in this study, if T25 had been defined as time to 25% recovery of the final baseline it would have been slightly shorter than reported here. In the most extreme case T25 was less than 2.5 min earlier when it was referenced to the final rather than the initial baseline. Examination of the coefficients of variation (standard deviation/mean) of T25 and of the interval between T4/T1 > 0.4 and T4/T1 > 0.7 shows similar variability in spontaneous recovery after both mivacurium and rapacuronium.

In summary, rapacuronium produces block more rapidly than mivacurium, with a clinical duration less than 10 min longer. In this study, during halothane anesthesia, there was little difference in neuromuscular effects of rapacuronium in patients from one week to 12.5 yr of age.

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