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Neuromuscular recovery following rocuronium bromide single dose in infants

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Summary

Background: Rocuronium bromide, a steroid nondepolarizing muscle relaxant, has a rapid onset and an intermediate duration of action in infants, children and adults. However, clinical evidence shows a longer duration of recovery in small infants. The aim of this study was to investigate the influence of age on rocuronium recovery during the first year of life.

Methods: ASA I–II infants, scheduled for elective surgery under general anaesthesia and intubation were included after ethics committee approval and parents' written consent. According to age the patients were randomly allocated to receive either 0.45 $mg \cdot kg^{-1}$ or 0.6 $mg \cdot kg^{-1}$ rocuronium bromide in three age-groups: (A) 0–1 month, (B) 2–4 months and (C) 5–12 months. After induction with thiopentone (5–7 $mg \cdot kg^{-1}$), anesthesia was maintained with isoflurane without opioids. Prior to surgery, caudal block with bupivacaine (0.125%) 1.0 $ml \cdot kg^{-1}$ and paracetamol 25 $mg \cdot kg^{-1}$ rectally were given for analgesia. Efficacy variables were intubation conditions 60 s after administration of muscle relaxant (T_0) and recovery of neuromuscular blockade measured as T_1 at 10, 25, 50 and 75 % of baseline, train-of-four (TOF) of 0.7 and Recovery Index (RI). Data were characterized by summary statistics and analysis of variance.

Results: A total of 61 infants with a median age range of 67 (2–364) days were included. Intubation conditions were excellent or good in all dose and age groups. T_0 in group A was reached in a range of 15–30 s, in others up to 60 s. T_1 recovery (T75) after 0.45 $mg \cdot kg^{-1}$ was 56.4 ± 16 (A), 62.7 ± 32 (B) and 45.8 ± 18 (C) min. Recovery times for of 0.6 $mg \cdot kg^{-1}$ were 100.8 ± 35 (A), 70.6 ± 19 (B) and 63.4 ± 21 (C) min, respectively. The TOF ratio (0.7) was 62.3 ± 18 (A), 64.1 ± 27 (B) and 43.7 ± 12 (C) min using 0.45 $mg \cdot kg^{-1}$ compared with 94.8 ± 31 (A), 63.8 ± 14 (B) and 67.5 ± 18 (C) min with 0.6 $mg \cdot kg^{-1}$. The differences of T75 and TOF 0.7 in A and C were significant ($P \leq 0.05$).

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Conclusions: Recovery of muscle relaxation using rocuronium bromide under isoflurane anesthesia in infants differs widely and shows great differences between age groups as well as dose regimen. A dose of 0.6 $mg \cdot kg^{-1}$ resulted in a significantly longer duration of action in group A. The reduced dose of 0.45 $mg \cdot kg^{-1}$ resulted in rapid and good relaxation in all infants without very long lasting effects. Reduced doses of rocuronium should be used in newborns and small infants.

Keywords: muscle relaxant; recovery*:* rocuronium bromide, infants, newborn

Introduction

Rocuronium bromide, a steroid nondepolarizing muscle relaxant, has a rapid onset and an intermediate duration of action in infants, children and adults. Satisfactory intubation conditions are achieved in both infants and children in 60 s following a single dose of rocuronium 2 ED_{95} (1–4). In newborn and small infants (age below 4 months) there is clinical evidence of variation in duration and recovery time after a single dose of rocuronium.

The aim of this study was to investigate the influence of different rocuronium doses in infants during the first year of life. The underlying hypothesis of this study was the immature myoneural junction in newborn and infants during the first weeks of life, its development at this time and possibly prolonged recovery after relaxation (5). Few studies, examining the age group below 1 year of age, with respect to intubation conditions and recovery from neuromuscular blockade after rocuronium have been published. They differ in methods, age or anesthetics used (6–8). Moreover, there are no recent studies including a reasonable number of patients below 1 year of age.

Methods

Onset and recovery times of intravenous bolus doses of rocuronium bromide 0.45 $mg \cdot kg^{-1}$ or 0.6 $mg \cdot kg^{-1}$ were studied in three age groups.

After obtaining institutional ethics committee approval and parental written informed consent, we studied 61 infants aged 2 days to 12 months. All patients were of ASA physical status I–II undergoing elective surgery requiring general anaesthesia and tracheal intubation. Patients known or suspected to have neuromuscular diseases, metabolic disorders, impaired kidney or liver function and patients receiving medication, known to interfere with neuromuscular transmission, were excluded from the study.

Three age groups were defined: (A) 0–1 month, (B) 2–4 months and (C) 5–12 months. Each patient was randomly allocated to one of the two dose regimens to receive either rocuronium 0.45 $mg \cdot kg^{-1}$ (group 0.45) or 0.6 $mg \cdot kg^{-1}$ (group 0.6) using the Microsoft Excel™ chance figure generator.

Infants older than 6 months were premedicated with midazolam 0.4 $mg \cdot kg^{-1}$ rectally. Standard monitoring included precordial stethoscope, ECG, pulse oximetry, capnography and endtidal concentrations of volatile anesthetics as well as noninvasive blood pressure at 5-min intervals. Skin temperature (upper thenar) and esophageal temperature were monitored continuously. Anesthesia was induced using 0.02 $mg \cdot kg^{-1}$ atropine and 5–7 $mg \cdot kg^{-1}$ thiopentone, and thereafter manual ventilation was performed with O_2 (FiO_2 1.0) and isoflurane (1.0 vol% endtidal) via facemask.

Neuromuscular transmission was monitored using accelerography with a TOF-Guard® (Organon GmbH, Oberschleißheim, Germany). At a deep level of anesthesia, the hand and forearm were fixed on a plexiglass base in a manner to reduce movement of the hand and fingers and to enable optimal movement of the thumb. The surface electrodes were placed at the forearm near the wrist. Supramaximal stimulation of the ulnar nerve was performed with train-of-four (TOF) stimulation in square wave

pulses of 0.2 ms duration at a frequency of 2 Hz every 15 s. The acceleration of the thumb movement was registered via an acceleration transducer fixed on the dorsal side of the thumb. All data were recorded on a memory card and stored as Microsoft Excel® files.

After a 5 min stabilization of neuromuscular response, the patients received at random either 0.45 mg·kg^{-1} or 0.6 mg·kg^{-1} rocuronium as a single bolus dose into a peripheral forearm vein. Intubation of the trachea was attempted 60 s after rocuronium administration.

In the first part of this study intubation conditions were graded according to the following criteria (Table 1) of the Copenhagen Consensus Conference (9,10). Variables were: ease of laryngoscopy, position and movement of vocal cords and reaction to insertion of tube (coughing/movement of the limb). After tracheal intubation anesthesia was maintained with N_2O/O_2 (2 : 1) and isoflurane 0.6% inspired concentration. For analgesia, prior to surgery, caudal block with bupivacaine (0.125%) 1.0 ml·kg^{-1} was performed and paracetamol (25 mg·kg^{-1}) was given rectally.

In the second part of this study the time course of neuromuscular recovery to $T_1 < 75\%$ and TOF ratio <0.7 were recorded.

Statistical analysis

All values are expressed as mean ± SD and range, in Figure 1 as mean ± SEM. Differences in $T_1 = 75\%$ and TOF 0.7 were evaluated using a two factor analysis of variance (SAS statistical analysis software, Heidelberg, Germany) for the terms age and dose. Intergroup differences were evaluated using the Scheffé test. The level of statistical significance was set to $P \leq 0.05$.

Table 1
Intubating criteria of infants recovering from rocuronium bromide single dose relaxation

	Clinically acceptable		*Clinically not acceptable*
Variables	*Excellent*	*Good*	*Poor*
Laryngoscopy		Fair	Difficult
Vocal cords			
Position	Abducted	Intermediate	Closed
Movement	None	Moving	Closing
Reaction to intubation			
Movement limbs	None	Slight	Vigorous
Coughing	None	Slight	Sustained (>10 s)

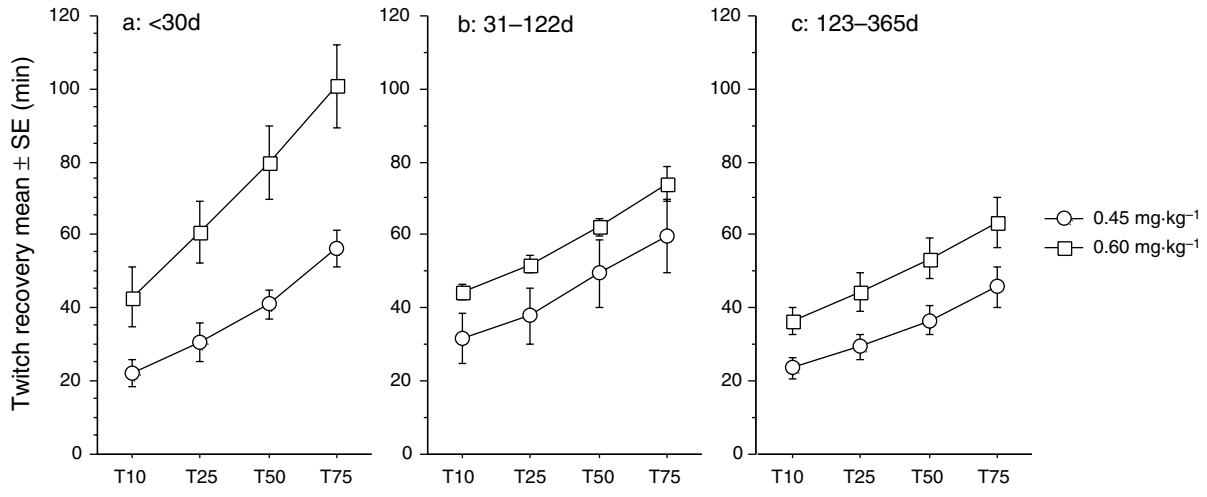

Figure 1
Recovery of twitch to 10, 25, 50 and 75% of baseline value (min) in infants after rocuronium bromide single dose relaxation ($n = 61$, mean ± SEM) significant differences between 0–1 month and 5–12 months. *$P \leq 0.05$ (0.45 mg·kg^{-1}) and **$P \leq 0.05$ (0.6 mg·kg^{-1}).

Results

Demographic data

Table 2 shows the demographic data of the three age groups. There were no statistically significant differences in distribution of age, weight, height, BMI (body mass index) and sex ratio between the groups. The surgical diagnoses comprised herniotomy, hydrocelectomy or procedures at the lower abdomen or lower limb.

Intubation conditions

The time from injection of rocuronium to the first attempt of intubation was 60 s in all patients. The data of intubating conditions are listed in Table 3. In group A (0–1 month), all patients were easily intubated 60 s following a dose of 0.45 mg·kg^{-1} rocuronium with excellent or good intubation conditions. In two of 10 patients the vocal cords were adducted at the moment of laryngoscopy. After 0.6 mg·kg^{-1} rocuronium nine of 10 patients were easily intubated, three of 10 patients had adducted vocal cords that could be passed without problems. In group B (2–4 months), intubating conditions after 0.45 mg·kg^{-1} rocuronium were rated good to excellent in seven of nine patients compared with 11 of 12 patients after 0.6 mg·kg^{-1} rocuronium. Two of 10 patients after 0.45 mg·kg^{-1} rocuronium and one of 12 patients after 0.6 mg·kg^{-1} rocuronium showed adducted vocal cords which could be passed for intubation without any problems. In group C (5–12 months), intubating conditions were good to excellent in both dose groups. Sixty seconds after injection of 0.45 mg·kg^{-1} rocuronium intubation was performed without problems. Three of 10 children showed slight movement of the limbs during intubation. After 0.6 mg·kg^{-1} two of 10 children showed slight movement of the limbs, respectively. There were no statistical differences between groups and dose regimen.

Recovery from neuromuscular blockade

The recovery from neuromuscular blockade is shown in Table 4. We found a wide range of recovery data; the statistical evaluation however showed a dose and age dependency of the recovery times for T (75%) and TOF (0.7) ($P \leq 0.05$). After 0.45 mg·kg^{-1} rocuronium, recovery from

Table 2
Demographic data of infants recovering from rocuronium bromide single dose relaxation ($n = 61$)

	0–1 month		*2–4 months*		*5–12 months*	
	0.45 mg·kg^{-1}	*0.6 mg·kg^{-1}*	*0.45 mg·kg^{-1}*	*0.6 mg·kg^{-1}*	*0.45 mg·kg^{-1}*	*0.6 mg·kg^{-1}*
Age (days)	17 ± 9 (4–30)	19 ± 11 (2–30)	63 ± 22 (32–80)	74 ± 24 (41–117)	271 ± 93 (132–365)	225 ± 85 (125–359)
Weight (g)	3440 ± 489 (2450–4440)	3660 ± 522 (2400–4240)	4200 ± 1271 (3940–6570)	4812 ± 1529 (3380–7800)	8707 ± 975 (7350–10300)	8363 ± 1221 (7520–10470)
Height (cm)	52 ± 1 (50–54)	52 ± 2 (50–54)	54 ± 5 (54–64)	55 ± 8 (53–65)	72 ± 5 (61–78)	70 ± 5 (66–79)
BMI (kg·cm^{-2})	12.7 ± 1.2 (9.4–15.6)	13.5 ± 1.2 (9.2–15.1)	14.2 ± 2.4 (13.4–17.7)	15.8 ± 2.1 (13.3–18.5)	17.1 ± 2.3 (14.1–23.3)	17.1 ± 1.1 (16.3–20.0)

The values given are mean ± SD (range). No significant differences are observed.

Table 3
Intubation conditions of infants recovering from rocuronium bromide single dose relaxation ($n = 61$)

	0–1 month		*2–4 months*		*5–12 months*	
	n = *10* *0.45 mg·kg^{-1}*	n = *10* *0.6 mg·kg^{-1}*	n = *9* *0.45 mg·kg^{-1}*	n = *12* *0.6 mg·kg^{-1}*	n = *10* *0.45 mg·kg^{-1}*	n = *10* *0.6 mg·kg^{-1}*
1. Laryngoscopy						
Excellent	9	9	8	5	10	10
Good	1	1	1	7	0	0
Poor	0	0	0	0	0	0
2. Vocal cords (position and movement)						
Excellent	6	7	6	7	9	9
Good	2	0	1	4	1	1
Poor	2	3	2	1	0	0
3. Reaction to tube insertion (coughing)						
Excellent	8	10	9	12	7	8
Good	2	0	0	0	3	2
Poor	0	0	0	0	0	0

No significant differences are observed.

Table 4
Twitch response (minutes) of infants recovering from rocuronium bromide single dose relaxation ($n = 61$)

	0–1 month		*2–4 months*		*5–12 months*		*Total*	
	0.45 mg·kg^{-1}	*0.6 mg·kg^{-1}*	*0.45 mg·kg^{-1}*	*0.6 mg·kg^{-1}*	*0.45 mg·kg^{-1}*	*0.6 mg·kg^{-1}*	*0.45 mg·kg^{-1}*	*0.6 mg·kg^{-1}*
$T_1 = 10\%$	18.0 ± 12 (11.5–44.8)	43.0 ± 26 (11.3–97.5)	33.8 ± 22 (12.3–70.8)	41.8 ± 11 (13.8–54.3)	23.5 ± 9 (17.5–45.8)	36.4 ± 12 (19.8–50.2)	25.9 ± 15 (11.5–70.8)	41.4 ± 17 (11.3–97.6)
$T_1 = 25\%$	30.7 ± 16 (12.8–57.5)	60.8 ± 27 (24.5–114.3)	40.2 ± 25 (15.8–81.5)	48.9 ± 13 (16.5–63.8)	29.4 ± 11 (18.5–55.5)	44.4 ± 16 (22.8–73.0)	32.7 ± 18 (12.8–81.5)	52.4 ± 19 (22.8–114.3)
$T_1 = 50\%$	41.1 ± 12 (22.0–60.0)	79.9 ± 30 (45.5–129.0)	52.2 ± 30 (19.0–94.0)	59.1 ± 13 (25.5–72.0)	36.7 ± 13 (26.5–68.0)	53.6 ± 17 (30.0–76.0)	42.5 ± 20 (19.0–94.0)	64.6 ± 22 (30.0–129.0)
$T_1 = 75\%$	56.4 ± 16* (29.5–81.8)	100.8 ± 35** (66.8–159.5)	62.7 ± 32 (29.8–112.0)	70.6 ± 19 (33.3–112.0)	45.8 ± 18* (31.0–90.0)	63.4 ± 21** (33.3–95.8)	53.9 ± 23 (29.5–112.0)	79.2 ± 29 (33.3–159.5)

The values given are mean ± SD (range). Significant differences are observed between 0–1 month and 5–12 months.
*$P \leq 0.05$ (0.45 mg·kg^{-1}).
**$P \leq 0.05$ (0.6 mg·kg^{-1}).

neuromuscular blockade was faster in all three age-groups than after 0.6 mg·kg^{-1} rocuronium. In the age groups A (0–1 month) and C (5–12 months) significant differences were found between doses ($P \leq 0.05$). For these patients the recovery time from neuromuscular blockade after 0.6 mg·kg^{-1} rocuronium was about twice as long as for 0.45 mg·kg^{-1}. A recovery to $T_1 = 75\%$ was reached after 56.4 ± 16 min with rocuronium 0.45 mg·kg^{-1} compared with 100.8 ± 35 min in the 0.6 mg·kg^{-1} group. In age group C (5–12 months), recovery to $T_1 = 75\%$ was achieved in 45.8 ± 18 min after 0.45 mg·kg^{-1} compared with 63.4 ± 21 min in the 0.6 mg·kg^{-1}.

In age group B, the differences between the two doses were not significant. Recovery to $T_1 = 75\%$ was reached in 62.7 ± 32 min following a dose of 0.45 mg·kg^{-1} and in 70.6 ± 19 min following 0.6 mg·kg^{-1}.

Related to age, Recovery Index (RI) after 0.45 mg·kg^{-1} decreased from 25.7 ± 13 (group A) to 22.4 ± 9 (group B) and 16.3 ± 10 (group C) min, respectively (Table 5). After 0.6 mg·kg^{-1}, RI decreases as well with increasing age from 40.2 ± 20 (group A) to 21.6 ± 15 (group B) and 19.0 ± 11 min (group C).

A TOF-ratio of 0.7 (TOF 0.7) was reached in all age- and dose-groups in close relation to the recovery time to $T_1 = 75\%$. There was a significant difference for TOF 0.7 ($P \leq 0.05$) between the two dose regimen in group A and C. With 0.45 mg·kg^{-1}, TOF 0.7 was 62.3 ± 18 (group A), 64.1 ± 27(group B) and 43.7 ± 12 (group C) min compared with

Table 5
Recovery Index (RI) and train-of-four (TOF 0.7) (min) of infants after rocuronium bromide single dose relaxation ($n = 61$)

	0–1 month		*2–4 months*		*5–12 months*		*Total*	
	0.45 mg·kg^{-1}	*0.6 mg·kg^{-1}*	*0.45 mg·kg^{-1}*	*0.6 mg·kg^{-1}*	*0.45 mg·kg^{-1}*	*0.6 mg·kg^{-1}*	*0.45 mg·kg^{-1}*	*0.6 mg·kg^{-1}*
RI 25–75 %	25.7 ± 13 (11.0–42.3)	40.2 ± 20 (17.5–71.3)	22.4 ± 9 (7.5–38.0)	21.6 ± 15 (9.3–63.8)	16.3 ± 10 (7.8–34.5)	19.0 ± 11 (5.5–43.8)	21.3 ± 11 (7.5–42.3)	26.9 ± 18 (5.5–71.3)
TOF = 0.7	62.3 ± 18* (35.5–102.0)	94.8 ± 31** (46.5–147.8)	64.1 ± 27 (35.8–105.5)	63.8 ± 14 (24.0–78.8)	43.7 ± 12* (33.8–72.0)	67.5 ± 18** (39.3–90.5)	55.4 ± 22 (24.0–105.5)	76.3 ± 24 (39.3–147.8)

The values given are mean ± SD (range). Significant differences between 0–1 month and 5–12 months are observed.
*$P \leq 0.05$ (0.45 mg·kg^{-1}).
**$P \leq 0.05$ (0.6 mg·kg^{-1}).

0.6 mg·kg^{-1} and 94.8 ± 31 (group A), 63.8 ± 14 (group B) and 67.5 ± 18 (group C) min.

Discussion

A comparison with other studies regarding intubation conditions and recovery is difficult, because different regimes of patient age, anesthesia agents or measurement of recovery, as well as the duration of anesthesia and the individual reaction to volatile anesthetics before intubation were used (9).

Intubation conditions

In the first part the intubation conditions after a single dose of 0.45 mg·kg^{-1} or 0.6 mg·kg^{-1} rocuronium were investigated. In paediatric patients rocuronium has a more rapid onset at the adductor muscles of the larynx than at the adductor pollicis (11,12). Thus, good intubation conditions could be seen before a 100% neuromuscular blockade of peripheral muscles (1,3). However, some children showed 'poor' conditions with respect to the position and movement of the vocal cords. This was only seen in very young infants in age groups A and B. Presumably, the anatomical features of the infant rather than absence of relaxation, accounted for the adducted vocal cords.

Recovery from neuromuscular blockade

It is known that a higher dose of rocuronium leads to faster onset and greater neuromuscular blockade (1,13). A faster onset and more profound neuromuscular blockade after 0.6 mg·kg^{-1} rocuronium was noted and the same dose of rocuronium produced a longer duration of action in small infants than in older ones (6,14). The data from our study confirm that there are marked and significant age-dependent difference in duration of action and recovery following 0.45 mg·kg^{-1} or 0.6 mg·kg^{-1} rocuronium in small infants (group A; 0–1 month) compared with older ones group C (5–12 months). This supports the data of Driessen *et al*. (7), comparing patients below 7 months with children 2 years and older, which show a longer duration in younger children with the same dose of rocuronium. Other investigators (15–17) also showed that the individual ED_{95} is lower for infants than for children. Moreover there are no recent studies, including a reasonable number of patients below 1 year of age, taking into account newborns and infants up to 4 months.

The maturation of neuromuscular transmission occurs during the first 3 months (5,14). This includes transmission from fetal to adult acetylcholine-receptor as well as increased distribution and number of receptors. In addition to immature neuromuscular transmission, changes of body composition and immature elimination pathways (liver and renal function) or anesthetics (8,19,20) influence the duration of neuromuscular action (7,14). The subdivision in the different age groups in the present study shows a slower recovery in group A (0–1 month). In a previous study, Woelfel *et al*. (6) found a RI of 26.6 ± 2.7 min and a TOF-ratio 0.75 of 82.1 ± 6.9 min following 0.6 mg·kg^{-1} rocuronium. This should be compared with the present study where the RI was 26.9 ± 18 min and TOF-ratio (0.7) of 74.6 ± 25 min. The difference probably depends on the anesthetic agent and a wide standard deviation of the data resulting from large variations of the duration of neuromuscular blockade measured by electromyography, especially in newborns and less-aged infants, up to 3 months.

Despite some restrictions on a direct comparison of these data with the results of other studies, it is consistent that especially newborn and small infants up to 3 or 4 months have a significantly longer duration of recovery to T (75%) and TOF (0.7) for both doses than older infants. Thus, in newborn and small infants up to 3 or 4 months, a dose of 0.45 $mg \cdot kg^{-1}$ rocuronium bromide is sufficient for good neuromuscular blockade and satisfactory recovery times. Individual development of the neuromuscular junction should always be considered below the age of 4 months. Similar results for both dose regimens in group B (2–4 months) seem to be due to the fact that especially in the age of 2 to 4 months the development of muscles and neuromuscular function changes rapidly and with indivdial variability. A dose of 0.45 $mg \cdot kg^{-1}$ of rocuronium seems to result in satisfactory intubation conditions without unacceptably long lasting relaxation in newborn and small infants up to 4 months of age.

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