Dose–Response of Rocuronium Bromide in Children Anesthetized with Propofol
A Comparison with Succinylcholine


Background: The aim of this study was to determine the potency of rocuronium during propofol/fentanyl/\textsubscript{N}_2\textsubscript{O} anesthesia in children and to compare the time course of action of rocuronium at doses of two and three times the ED\textsubscript{50}, with that of succinylcholine.

Methods: Rocuronium (120, 160, 200, or 240 \textmu g/kg) was administered to 48 children aged 2–10 yr. Neuromuscular block was assessed by monitoring the electromyographic response of the adductor digit minimi to supramaximal stimulation of the ulnar nerve at 2 Hz for 2 s every 10 s. Potency was determined by log-probit transformation and least-squares linear regression analysis of dose and response. In a second group of 30 children, the onset and recovery profile of rocuronium at doses of two and three times the ED\textsubscript{50} was compared with that of succinylcholine (2 mg/kg).

Results: Values for ED\textsubscript{25} and ED\textsubscript{50} were 210 ± 24 and 404 ± 135 \textmu g/kg, respectively. The time to 90% neuromuscular block after 1.2 mg/kg rocuronium (three times the ED\textsubscript{50}), 35 ± 5 s (mean ± SD), did not differ significantly from that after succinylcholine, at 30 ± 7 s; however, both were significantly less than that after 0.8 mg/kg rocuronium, 46 ± 8 s (P < 0.05). The time to 25% recovery from 1.2 mg/kg rocuronium, 41 ± 13 min, was approximately 50% greater than that after 0.8 mg/kg, at 27 ± 6 min (P < 0.001), and eight times greater than that after succinylcholine, at 5.2 ± 1.9 min (P < 0.001).

Conclusions: Both 1.2 mg/kg rocuronium (three times the ED\textsubscript{50}) and 2 mg/kg succinylcholine provide 90% neuromuscular block within 45 s in 95% of children. The present dose–response data support the use of rocuronium at a dose of 1.2 mg/kg when rapid onset and intermediate-duration neuromuscular block are needed in children. (Key words: Anesthesia: pediatric. Anesthetics, intravenous: propofol. Neuromuscular relaxants: rocuronium; succinylcholine.)

PUBLISHED studies have shown that the neuromuscular block produced by rocuronium bromide is rapid in onset and intermediate in duration in adults.1–3 These characteristics have led to studies of rocuronium in children and to the notion that this nondepolarizing neuromuscular blocking agent might be an alternative to succinylcholine for rapid tracheal intubation. However, studies in children have focused mainly on the neuromuscular effects of rocuronium during halothane anesthesia.4 There is limited information on the potency and time course of action of rocuronium during intravenous anesthesia. Indeed, previous studies that try to evaluate the time course of action of rocuronium during intravenous anesthesia in children have used potency values derived during halothane anesthesia.5,6 Because halothane (end-tidal concentration of 0.7%) enhances the potency of vecuronium in children,7 potency values determined during halothane anesthesia should be applied to intravenous anesthesia with caution.

The objectives of the present study were to determine the potency of rocuronium during intravenous anesthesia with propofol, and to compare the onset and duration of action of two doses of rocuronium (two and three times the effective dose for 95% neuromuscular block [ED\textsubscript{50}]) with that of succinylcholine (2 mg/kg) during propofol anesthesia in children.

Methods

After approval of the study protocol by the research ethics board, informed consent was obtained from the parents of 78 children, classified as American Society of Anesthesiologists physical status I, aged 2–10 yr, who were having elective surgery that required tracheal
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intubation. Children were excluded if tracheal intubation was expected to be difficult; if they had received drugs that are known to affect the action of neuromuscular blocking agents; if there was a history of neuromuscular disease; or if the use of succinylcholine was contraindicated. All children fasted and were not premedicated.

Standard intraoperative monitors were used. Nitrous oxide (70%) in oxygen was administered before intravenous cannulation. Anesthesia was induced with fentanyl (5 μg/kg), propofol (4 mg/kg), and atropine (10 μg/kg). The trachea was intubated without neuromuscular paralysis. Anesthesia was maintained with nitrous oxide (70%) in oxygen and an infusion of propofol starting at a rate of 12 mg·kg⁻¹·h⁻¹ immediately after administration of the induction dose and decreasing at 10-min intervals to 10 mg·kg⁻¹·h⁻¹ and then to 8 mg·kg⁻¹·h⁻¹. Ventilation was controlled to maintain a normal end-tidal carbon dioxide partial pressure (35-40 mmHg).

One forearm and hand were washed with an alcohol solution, allowed to dry, and positioned for assessment of neuromuscular function by electromyography (Relaxograph; Datex Instruments, Helsinki, Finland). Stimulating electrodes were applied to the skin over the ulnar nerve, and recording electrodes were placed over the hypothenar eminence (active) and base of the fifth finger (indifferent). Supramaximal stimuli (0.1-ms duration) were delivered to the ulnar nerve in a train-of-four (2 Hz for 2 s) pattern every 10 s. The electromyographic response of the adductor digiti minimi was recorded. After 5 min of baseline stimulation, the neuromuscular blocking agent was administered into a rapidly flowing intravenous infusion of balanced salt solution. The degree of neuromuscular block was determined from the height of the first response of the train-of-four (T1). During the onset of block, T1 was referenced to the control T1 height. During recovery, T1 was referenced to the final T1 height, which was obtained after complete recovery. The skin temperature of the forearm being monitored was maintained using standard methods.

To establish the potency of rocuronium, 48 children were allocated to receive one of four doses of rocuronium (120, 160, 200, or 240 μg/kg) using a table of random numbers. The maximum degree of neuromuscular block attained was determined.

To compare the onset and recovery times of rocuronium with those of succinylcholine, a second group of 30 children were randomly allocated to receive either rocuronium two or three times the ED₉₅ (using the ED₉₅ value determined in the first part of the study) or 2.0 mg/kg succinylcholine. The onset (time to 90% and 100% block) and regression (time to 25% of clinical duration of action, 50%, 75%, and 95% recovery) of block were determined. Lag time (time to first decrement [≥ 5% of control value] in T1) was determined. All times were measured from the beginning of administration of the neuromuscular blocking agent. The 25%-75% recovery interval (T25-75 recovery index) was calculated.

Statistics

To detect a difference of 10 s in onset times, a sample size of 10 children per group was required, assuming α = 0.05, β = 0.05, and a SD of the time to 90% block after succinylcholine (2 mg/kg) of 6 s in children. The potency of rocuronium was determined by least-squares linear regression of the log-probit transformation of the initial dose and response, respectively. Parametric data were compared using one-way analysis of variance and the Student-Newman-Keuls test. Onset and recovery times were compared using the Kruskal-Wallis test and Dunn's test for multiple comparisons. Data are presented as mean ± SD. A probability value < 0.05 was considered significant.

Results

The age and weight of the 48 children in the first part of the study were 5.4 ± 2.2 yr and 20.3 ± 5.8 kg, respectively; those of the 30 children in the second part were 5.9 ± 2.7 yr and 21 ± 6.9 kg.

Linear regression analysis of the log-probit transformations yielded ED₉₅ and ED₉₅ values of 210 ± 24 μg/kg and 404 ± 135 μg/kg, respectively (fig. 1). There were no instances of 0 or 100% block after any of the four doses used in the potency determination.

At a dose of 1.2 mg/kg (three times the ED₉₅), the time to 90% neuromuscular block after rocuronium (35 ± 5 s) did not differ significantly from that after succinylcholine (30 ± 7 s); however, both were significantly less than that after 0.8 mg/kg (two times the ED₉₅). 46 ± 8 s (P < 0.05; fig. 2). Complete neuromuscular block was achieved in all children in the second part of the study. Complete block after 1.2 mg/kg rocuronium (39 ± 8 s) occurred an average of 8 s later than that after succinylcholine, but this difference was not significant.
Fig. 1. Maximal T1 depression and corresponding probit values after 120, 160, 200, and 240 μg/kg rocuronium (log scale). Data are individual (●) and mean (□) ± SD values for each dose. The slope was 5.8 (r² = 0.9). The ED₉⁵ and ED₉₅ values were 210 ± 21 and 404 ± 135 μg/kg, respectively.

(fig 2). Lag times after rocuronium (0.8 mg/kg: 23 ± 8 s; 1.2 mg/kg: 19 ± 3 s) did not differ significantly from those after succinylcholine (17 ± 5 s).

The duration of neuromuscular block after rocuronium increased when the dose was increased (fig. 3). For example, the time to 25% recovery after 1.2 mg/kg rocuronium (41 ± 13 min) was approximately 50% greater than that after 0.8 mg/kg (27 ± 6 min; P < 0.01) and eight times greater than that after succinylcholine (5.2 ± 1.9 min; P < 0.001; fig. 3). The T25-75 recovery index did not change significantly when the dose of rocuronium was increased (0.8 mg/kg: 7.3 ± 3.2 min; 1.2 mg/kg: 8.3 ± 4.3 min).

Discussion

In the present study, an increase in the dose of rocuronium from two to three times the ED₉⁵ accelerated the onset of neuromuscular block by approximately 30% and prolonged recovery by approximately 50%. At three times the ED₉⁵ (1.2 mg/kg), the onset of action of rocuronium was similar to that of succinylcholine (2 mg/kg), whereas the clinical duration of action was eight times greater.

The dose of succinylcholine recommended for tracheal intubation in children is 2 mg/kg.⁸ Accordingly, this dose was considered a suitable reference dose with which to compare the neuromuscular effects of rocuronium. However, data from Meakin et al.⁸ suggest that the ED₉₅ of succinylcholine during thiopentone-nitrous
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Oxide anesthesia is 0.42 mg/kg. If this finding holds true during propofol anesthesia, then the dose of succinylcholine used in the present study is almost five times the ED₉₅; consequently, the use of this dose, although consistent with our clinical practice, might have precluded a comparison of equipotent doses of the neuromuscular blocking agents. If an equipotent dose of two or three times the ED₉₅ had been used, it is likely that the onset of succinylcholine block would have been slower than reported here.

Comparison of the onset times reported in the present study with those of previous studies is difficult, in part because study conditions and drug doses differ. At a dose of 0.6 mg/kg, the mean onset time of rocuronium at the adductor pollicis was 48 s when train-of-four stimulation at 10-s intervals was used, and it was nearly double that when the interval was increased to 20 s. Several aspects of study design profoundly affect onset time and may account for this discrepancy. One aspect is the frequency of neuromuscular stimulation: for a given pattern of stimulation, onset time decreases as the frequency increases. A second aspect is the duration of baseline stimulation. The onset times of atracurium and vecuronium decrease as the duration of baseline stimulation increases in adults. This finding, if applicable to rocuronium, might help to reconcile the results of the two previous studies, although its significance remains speculative because the duration of baseline stimulation was not reported in one of the studies.

A third aspect of study design is the site of neuromuscular monitoring. Measurement of the evoked electromyogram of the adductor digit minimi in response to supramaximal stimulation of the ulnar nerve is a well-recognized monitoring technique. During recovery of the block, the electromyogram of the adductor digit minimi reflects recovery of respiratory muscle function (as measured indirectly by inspiratory pressure, peak inspiratory flow rate, and vital capacity) better than does mechanomyography of the adductor pollicis. A potential problem with monitoring the adductor digit minimi is stimulus artifact. We positioned the stimulating electrodes proximally, at the mid-forearm level, and placed the ground electrode between the stimulating and recording electrode pairs to reduce stimulus artifact. In all instances, we obtained good-quality compound action potentials with good peak-to-peak amplitude and no evidence of stimulus artifact interference or baseline drift.

The onset time of rocuronium is more rapid than that reported previously for an equipotent dose of mivacurium or vecuronium. At an equipotent dose of three times the ED₉₅, the onset time of mivacurium during propofol anesthesia was more than double that reported here for rocuronium. To achieve an onset time that is comparable to that of rocuronium, approximately eight times the ED₉₅ of vecuronium was required, which resulted in a clinical duration of action that was nearly double that reported here.

Other investigators recently reported the potency of rocuronium during balanced anesthesia in children. Although the study design was similar to the present study in that volatile anesthetics were not used, it differed in that the time course of neuromuscular block was not determined and a cumulative two-dose rather than a single bolus technique was used to determine potency. The cumulative dose–response technique yielded mean ED₅₀ and ED₉₅ values of 205 and 409 µg/kg, respectively, which correspond closely to our results.

In conclusion, linear regression analysis yielded ED₅₀ and ED₉₅ values for rocuronium of 210 ± 24 µg/kg and 404 ± 135 µg/kg, respectively. The present dose–response studies support the use of rocuronium at a dose of 1.2 mg/kg (three times the ED₉₅) when rapid onset and intermediate-duration neuromuscular block are needed in children.

References