

Onset of action and intubating conditions after administration of rocuronium or mivacurium in children

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ABSTRACT

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The objective of this study was to evaluate onset times and tracheal intubating conditions after administration of rocuronium or mivacurium in children of different ages. In this randomized double-blind study, 40 healthy (ASA I) children aged 1 to 14 years were studied. They were divided, according to age, into two groups: Group A (n=20) included patients 1 to 3 years of age and Group B (n=20) 4 to 14 years of age. After general anesthesia induction patients in both groups were further divided into two subgroups. So, half of patients (n=10) of each group were randomly assigned to receive a bolus of either rocuronium 0.6 mg*Kg⁻¹ or mivacurium 0.2 mg*Kg⁻¹. The onset time of neuromuscular blockade (from 100% to 0% response) was assessed by the accelerographic response (100-0%) of the adductor pollicis, stimulating the ulnar nerve with single twitch stimuli. Tracheal intubating conditions were assessed as good, excellent or poor, 60 sec after the initial dose of relaxant by an anaesthetist who was unaware of patient group. Statistical analysis was performed with Student t-test or Fisher's exact test, where appropriate. Statistical significance was assumed at the level of p<0.05. Demographic data were similar between subgroups of each range of age. Intubating conditions did not differ significantly between groups although the incidence of excellent grade intubations was higher with rocuronium. The onset time of neuromuscular blockade was found significantly shorter in the subgroup of rocuronium compared with mivacurium, while for the same drug regimen no significant difference was found between groups A and B. This study demonstrates that, regardless children's age, the onset time of rocuronium is shorter than mivacurium, while both drugs provide within 60 sec excellent intubating conditions in the majority of cases.

Neuromuscular agents are given to children to facilitate tracheal intubation, to relax the abdominal muscles during surgery, to assure immobility during critical portions of surgery and to facilitate mechanical ventilation. During the last decades of years several factors have influenced the practice of giving neuromuscular blo-

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cking agents to children. These include introduction of new drugs with different degrees of desirable qualities, concerns about the potential of severe adverse events of succinylcholine and the introduction of new anesthetic techniques and equipment, such as laryngeal mask airway, that might obviate the need for tracheal intubation[1].

Rocuronium is a nondepolarizing, steroidal muscle relaxant with an ED₉₅ -the dose that pro-

duces 95% depression of the first twitch height of $0.3 \text{ mg} \cdot \text{Kg}^{-1}$, intermediate duration of action, no histamine release, and a rapid onset time[2]. The major advantage of rocuronium is its rapid onset of action, which is useful for facilitating tracheal intubation. In adults, satisfactory intubating conditions developed between 60 and 90 sec after injection of twice the 95% effective dose of rocuronium[3,4], but there are few data about onset of neuromuscular blockade and tracheal intubation conditions after rocuronium in young children[5].

Mivacurium is a nondepolarizing relaxant of benzylisoquinolinium structure resembling that of atracurium and doxacurium[6]. Dose-response studies have shown the potency of mivacurium in terms of its ED_{95} to be $0.06\text{-}0.08 \text{ mg} \cdot \text{Kg}^{-1}$ [7,8]. Mivacurium is marketed on the basis of its short duration of action due to rapid hydrolysis by plasma cholinesterase⁷, its suitability as an infusion and the fact that it does not require routine reversal[7]. At equipotent doses, its duration of action is approximately twice that of succinylcholine and approximately 35-40% that of atracurium and vecuronium[9,10].

The characteristics of those two neuromuscular agents mentioned above have led to various studies with a proved safety and efficacy in children[11,12,13].

The effects of neuromuscular blocking drugs with intermediate duration, such as atracurium, mivacurium and vecuronium, are somewhat different in children compared with adults. Decreasing age is associated with a faster onset of action of vecuronium[14], whereas no substantial variation of onset times exists between children and adolescents with atracurium and mivacurium[15].

The aim of this randomized double-blind study was to evaluate the development of clinically acceptable tracheal intubating conditions and to compare the onset of neuromuscular blockade in children of different ages after administration of rocuronium and mivacurium.

METHODS

After obtaining institutional approval and informed consent, 40 paediatric patients between 1 and 14 years of age and ASA physical

status I were enrolled in the study. The children underwent a variety of elective minor or moderate surgical procedures, requiring general anaesthesia. Children were divided, according to age, into two groups: **Group A** (n=20) included patients 1 to 3 years of age and **Group B** (n=20) 4 to 14 years of age. Children were excluded from the study, if they or their family had a history of neuromuscular disease, malignant hyperthermia, and paralysis or muscle atrophy. Additional exclusion criteria were therapy with drugs known to interfere with neuromuscular transmission (antibiotics), liver disease, renal disease, and plasma cholinesterase deficiency.

Children were premeditated orally with midazolam $0.5 \text{ mg} \cdot \text{kg}^{-1}$, and a local anaesthetic cream (EMLA[®], Astra Chemicals, Wedel, Germany) was applied to the previewed puncture site 1 h before anaesthesia induction. An infusion of lactated Ringer's solution was started before induction of anaesthesia in the arm contralateral to that used to monitor neuromuscular function. Monitors consisted of ECG, noninvasive blood pressure cuff, pulse oximeter, end-tidal CO_2 , oesophageal stethoscope, and temperature.

Anaesthesia was induced with midazolam $0.03 \text{ mg} \cdot \text{kg}^{-1}$, fentanyl $4 \mu\text{g} \cdot \text{kg}^{-1}$, propofol $2\text{-}3 \text{ mg} \cdot \text{kg}^{-1}$, titrated to loss of consciousness and loss of eyelash reflex. The lungs were ventilated manually with oxygen 100% via facemask.

Neuromuscular function was measured at the adductor pollicis by a TOF-GUARD[™] accelerometer (Organon, Teknika). Two surface electrodes were applied over the ulnar nerve at the wrist and a piezoelectric device measuring acceleration was placed on the corresponding thumb. The onset time of blockade (from 100% to 0% response) was recorded in the adductor pollicis by accelerometry.

Patients in groups A and B were further randomized into two subgroups. Half of patients (n=10) of each group were assigned to receive, in a random fashion, a blinded bolus of either rocuronium $0.6 \text{ mg} \cdot \text{Kg}^{-1}$ or mivacurium $0.2 \text{ mg} \cdot \text{Kg}^{-1}$, diluted in volume of 10 ml and administered with rapid iv infusion, as soon as the

Table 1: Scoring of Endotracheal Intubating Conditions

Score	Jaw relaxation	Vocal cords	Diaphragmatic response
Excellent	Complete	Open	None
Good	Moderate	Slight moving	Slight movement
Poor	None	Closed	Coughing

stimulator was functioning. Laryngoscopy and tracheal intubation were tried and performed 60 sec after the initial dose of the relaxant.

An observer (unaware of which drug had been given) assessed intubating conditions. Those were assessed as excellent, good, or poor based on jaw relaxation, position of the vocal cords, and response of the diaphragm to intubation (Table 1) using a previously described, modified score[4]. The completion of endotracheal intubation was not performed until intubating conditions were assessed. Intubating scores in cases of good jaw relaxation and easy laryngoscopy were further judged by touching the vocal cords with the tip of the tube. Closing of vocal cords and/or coughing triggered by this manoeuvre was designated to be a sign of unacceptable intubating conditions; if there was such a sign, the intubation attempt was stopped and subsequent intubation attempts were made at 30-s intervals until intubation could be achieved with acceptable conditions. Endotracheal intubation was performed by an experienced anaesthesiologist who was blinded to the muscle relaxants.

After intubation, the lungs were ventilated mechanically with N₂O 60% and sevoflurane 1-1.5%. Ventilation was adjusted to keep P_{ET}CO₂ in the range 4.5-5.5 pKa.

Comparisons were made among drug regimen within the same age group, and for the same drug regimen between groups A and B. Data are expressed as the mean±SD. Parametric data were compared between groups by student t-test. To compare gender distribution and intubation conditions, Chi Square test or Fisher exact test was used, as appropriate. A p value less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

There were no statistically significant differences in distribution of age, weight, and sex ratio between each age group and each subgroup (table 2).

There were no difficulties in visualizing the vocal cords in any patient. All tracheas were successfully intubated on the first attempt within 15 sec of beginning direct laryngoscopy.

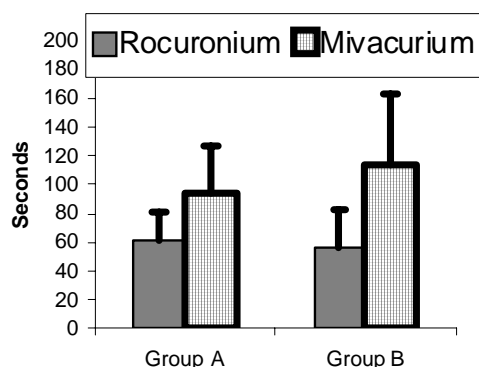
Table 2: Characteristics of the patients. Values are mean ± SD.

	Group A (n=20)		Group B (n=20)	
	Rocuronium (n=10)	Mivacurium (n=10)	Rocuronium (n=10)	Mivacurium (n=10)
Age (yr)	2.35±5.8	2.47±5.6	9.7±3.9	9.5±3.5
Weight (kg)	14.9±3.8	14.3±4.1	39.1±14.3	41.3±19.6
Gender(m/f)	8/2	7/3	6/4	8/2

All children achieved 100% blockade at the adductor pollicis.

The onset time of neuromuscular blockade was found significantly shorter ($p < 0.05$) in the subgroups of Rocuronium compared with these with Mivacurium (Figure 1), while the comparison for the same drug regimen between groups A and B appeared to have no significant

Figure 1: The onset time of neuromuscular blockade between Rocuronium and Mivacurium in different aged groups.



difference (Table 3).

Acceptable intubating conditions (excellent or good) did not differ significantly among groups at intubation attempts in 60 sec and all children had so, except one in the Mivacurium subgroup who had poor conditions (Group A). Excellent intubating conditions were observed in 18/20 patients in Group A, compared with 17/20 in Group B (Table 4).

DISCUSSION

The results of the present study showed that in

Table 3: The onset time of neuromuscular blockade between Rocuronium and Mivacurium in different aged groups. Values are expressed as mean ± SD.

	Rocuronium	Mivacurium	
Group A	61.4 ± 18.7	94.5 ± 31.8	$P < 0.05$
Group B	56.7 ± 25.1	113.6 ± 49.3	$P < 0.05$
	NS	NS	

children of different ages rocuronium ($0.6 \text{ mg} \cdot \text{Kg}^{-1}$), was associated with significantly faster onset of action than mivacurium ($0.2 \text{ mg} \cdot \text{Kg}^{-1}$), while both regimen provided excellent to good intubating conditions in almost all children.

The onset time of nondepolarizing muscle relaxants in the central airway musculature of the larynx, jaw and diaphragm is dependent on the presence of a critical number of drug molecules at the neuromuscular junction[1]. The rapid onset associated with rocuronium has been attributed to lower potency of this drug, which may allow more molecules to access the effector sites during the first few circulation times. The short duration of mivacurium is due to rapid hydrolysis by plasma cholinesterase[1].

Rocuronium in dose twice the ED_{95} produced maximal block in 61.4 sec (group A) and 56.7 sec (group B), compared to mivacurium (about 3-4 times the ED_{95}) 94.5 sec (group A) and 113.6 sec (group B). In addition, comparing the same neuromuscular blocking agent between the different aged groups appeared to have no difference on the onset time.

Table 4: Grades of intubating conditions between groups and subgroups

	Group A (n=20)		Group B (n=20)	
	Rocuronium (n=10)	Mivacurium (n=10)	Rocuronium (n=10)	Mivacurium (n=10)
Excellent	100%	80%	90%	80%
Good	-	10%	10%	20%
Poor	-	10%	-	-

Paediatric patients differ from adults in certain pharmacokinetic and pharmacodynamic characteristics. It is known that maturation influence the response to neuromuscular blocking agents because age-related changes in body composition influence drug distribution. For example, the neuromuscular blocking agents are polar and therefore they distribute only to extracellular fluid space. This volume decreases markedly during the first year of life, thereafter reaching adult values. However, because maturational changes in certain of these characteristics counterbalance, dosing requirements do not differ markedly with age[16].

Sarner et al showed that the onset time of mivacurium in paediatric patients (0.25 mg kg^{-1}) had a mean of $1.1 \pm 0.3 \text{ min}$ during halothane anaesthesia, while during opioid anaesthesia, the onset was $1.6 \pm 0.4 \text{ min}$ [17]. The onset action of rocuronium is even faster during halothane anaesthesia, rocuronium $0.8 \text{ mg} \cdot \text{kg}^{-1}$ has an onset of $28 \pm 8 \text{ sec}$ [1]. A dose of rocuronium $0.6 \text{ mg} \cdot \text{kg}^{-1}$ depressed twitch tension by 90% (at which time trachea can presumably be intubated) at $0.8 \pm 0.3 \text{ min}$ and 100% at $1.3 \pm 0.8 \text{ min}$ [5].

It is well established that the frequency of stimulation can affect the evoked response. Therefore, the mode of stimulation used in this study (single-twitch) could result in an apparently lower potency of neuromuscular blockers compared with the TOF mode[18]. In this study, a single twitch stimuli monitoring of the hand was achieved. It has been suggested that monitoring of the facial nerve-orbicularis oculis muscle might be a better guide for determining onset of optimal intubating condition[2]. To test this hypothesis, Sayson and Morgan randomized patients to undergo tracheal intubation at either maximal depression of the orbicularis oculi or at maximal depression of the adductor pollicis, after mivacurium 0.15 mg/kg [19]. They reported that despite 100% orbicularis oculi blockade, 7 of 10 patients showed diaphragmatic activity. So in this study the adductor pollicis muscle was preferred, as monitoring of the facial nerve-orbicularis oculis muscle may not be accurate to predict onset of

tracheal intubating conditions following administration of mivacurium.

It is recognized that the determination of tracheal intubating conditions is dependent upon the skills and experience of the intubator, the anatomy of the patient, and upon subjective criteria. In the present study, an experienced anaesthetist, blinded to the relaxant, assessed the intubating conditions using the standardized scoring system mentioned above. It is unlikely that bias from different anaesthetists (which performed intubation) could have accounted for the differences in coughing and bucking after the tube insertion observed in the study. This is because the cough buck response represented the most objective of the criteria evaluated. This response was obvious and apparent and most likely represented incomplete paralysis of the muscles of the diaphragm, larynx. and/or abdominal wall.

Intubating conditions graded as excellent-good-poor, were judged to be good-excellent in all except in one patient of the mivacurium subgroup. It has been suggested that the use of mivacurium is associated with high incidence of moderate coughing after intubation, a response that is rarely seen with rocuronium[2]. This movement may be particularly undesirable in patients during surgery. Others reported similar observations even when doses of mivacurium up to $0.3 \text{ mg} \cdot \text{kg}^{-1}$ were administered to children[20].

In our patients anaesthesia was induced with propofol. Although it has been suggested that propofol produces greater depression of pharyngeal and laryngeal reactivity than thiopental[21], this finding has not been substantiated by others [22,23]. In any case the dose of propofol was similar between groups and subgroups.

Finally, this study demonstrated, that in the doses that were administered and regardless the children's age, a) the onset time of rocuronium was faster than mivacurium and b) both drugs provide within 60 sec excellent intubating conditions in the majority of cases and acceptable conditions in almost all cases, although the onset times (100%-0%) in some cases (espe-

cially with mivacurium) were longer than 60 sec.

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