
Regular article

Reversibility of rocuronium-induced deep neuromuscular block with sugammadex in infants and children– a randomized study.

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Summary

Sugammadex 4 mg·kg⁻¹ is recommended for reversal from rocuronium-induced deep neuromuscular block. However, there is limited data regarding the dose-response of sugammadex required for reversal from deep neuromuscular block in pediatric patients. The aim of this study was to determine the reversibility of rocuronium-induced deep neuromuscular block with sugammadex in infants and children. Seventy-five children (48 infants and 27 children, mean (SD) age: 11.6 (6.7)) were enrolled in this study. After induction of anesthesia and administration of 0.6 mg·kg⁻¹ rocuronium, neuromuscular block was acceleromyographically evaluated by observing contractions of the adductor pollicis muscle to ulnar nerve train-of-four (TOF) stimulation. Subsequently, the intensity of rocuronium-induced block was determined every 6 min using post-tetanic count (PTC) stimulation during sevoflurane and remifentanil anesthesia. When the first response to the PTC stimulus was detected, either 1, 2 or 4 mg·kg⁻¹ sugammadex was administered and the time required for facilitated recovery to a TOF ratio of 0.9 following each dose was compared. The time [mean (SD)] from the administration of 1 mg·kg⁻¹ sugammadex until recovery to a TOF ratio of 0.9 was significantly longer [129.1 (83.5) s, \( P<0.001 \)] than that with 2 mg·kg⁻¹ and 4 mg·kg⁻¹ sugammadex [70.3 (26.7) s and 68.2 (34.5) s, respectively]. Incomplete reversal was seen in 3 patients in the 1 mg·kg⁻¹ group. The results suggested that a 4 mg·kg⁻¹ sugammadex dose is recommended for reversal from rocuronium-induced deep neuromuscular block even in infants and children.

**Keywords**: neuromuscular blocking drugs; antagonism; sugammadex; child; monitors
Introduction

Sugammadex is a selective reversal agent that directly binds to rocuronium and can promptly restore neuromuscular function with incremental doses, regardless of the intensity of neuromuscular block [1, 2]. Chemical encapsulation of the rocuronium molecule by sugammadex results in a rapid decrease in plasma concentration of free rocuronium, which induces extensive diffusion of rocuronium from the neuromuscular junction into plasma along the concentration gradient of free rocuronium [3]. Reportedly, the time for antagonism with sugammadex is in inverse proportion to cardiac output in the elderly [4, 5]. Therefore, a more rapid increase in the plasma concentration of sugammadex near the neuromuscular junction and a faster facilitated recovery by sugammadex would be expected in pediatric patients who have a greater cardiac output when compared with adults. Still, infants and younger children are more sensitive to non-depolarizing neuromuscular blocking agents because of the immaturity of their neuromuscular synapses [6] and elimination function [7], and hence, the reversibility of sugammadex may be different in them as compared to other age groups. However, there is limited data regarding this from prospective trials, and the relationship between the efficacy and dose of sugammadex in infants and children has not been fully investigated. Especially in infants and younger children, additional studies are needed to determine the efficacy of sugammadex, particularly when deeper neuromuscular block is present. We hypothesized that 4 mg·kg⁻¹ sugammadex is necessary to completely antagonize rocuronium-induced deep neuromuscular block and smaller dose of sugammadex may result in incomplete reversal even in infants and children. The aim of this study was to clarify the appropriate dose of sugammadex required to rapidly reverse a deep rocuronium-induced neuromuscular block in infants and children.
Methods

The study protocol was approved by the Hospital Ethics Committee on Human Rights in Research. Following written informed parental consent, 75 pediatric patients participated in this study in Tokyo Metropolitan Children’s Medical Center. Patients were ASA physical status I-II, aged between 2-23 months, and undergoing elective orthopedic or plastic surgery under general anesthesia. None of the patients had neuromuscular, hepatic or renal disorders, nor were they taking any drug known to interact with neuromuscular blocking agents. On arrival at the operating room, all patients were monitored with ECG, non-invasive blood pressure and pulse oximetry. General anesthesia was induced with sevoflurane with oxygen via a facemask or intravenously using thiopental and fentanyl.

After induction of anesthesia, neuromuscular monitoring was commenced using an acceleromyograph (TOF-Watch SX™, Organon Ltd, Dublin, Ireland). To enhance stabilization of neuromuscular responses, 1 Hz twitch stimuli were applied for 1 min over the ulnar nerve at the wrist. Thereafter, the nerve was stimulated with square-wave stimuli of 0.2 ms duration, which were delivered in a TOF mode at 2 Hz every 15 s, and contractions of the ipsilateral adductor pollicis muscle were measured. When the response to TOF was stabilized, calibration and supramaximal stimulation was ensured by the built-in calibration function (CAL2) of the acceleromyograph. After obtaining stable baseline responses for at least 2 min, all patients received 0.6 mg·kg⁻¹ rocuronium intravenously. Patients’ tracheae were intubated or laryngeal mask insertion was performed after rocuronium-induced complete neuromuscular block, and anesthesia was maintained with sevoflurane and a continuous infusion of remifentanil or fentanyl, as required.

A post-tetanic count (PTC) mode was initially applied 5 min after obtaining maximal neuromuscular block, and repeated every 6 min for intraoperative monitoring. When the first detectable response to PTC stimulation was recorded, patients randomly
received either 1 mg·kg⁻¹, 2 mg·kg⁻¹ or 4 mg·kg⁻¹ sugammadex. Patients were assigned based on computer-generated randomization numbers into one of three study groups. The dose of sugammadex was correctly aspirated from the solution dissolved with 1 ml (100 mg) of sugammadex and 9 ml physiological saline.

The following variables were measured in all cases: neuromuscular blockade onset time, i.e. the time (s) from the administration of rocuronium to maximum depression of T1; time (min) from the administration of rocuronium to spontaneous recovery of the first response to PTC stimulation; and the time (s) required for facilitated recovery to a TOF ratio of 0.9. The TOF ratio of 0.9 normalized by the baseline TOF ratio was monitored.

In case where the TOF ratio did not reach 0.9 in 5 minutes, an additional dose of sugammadex was administered for adequate recovery of neuromuscular function and the time to a TOF ratio of 0.9 was not analyzed.

Statistical analyses
The primary outcome of the present study was average reversal times after sugammadex between groups. Based on data from our preliminary test, we estimated that a sample size of 22 patients per group would be required for comparison in a priori one-way analysis of variance with effect size of (f = 0.39), α = 0.05 and a power of 0.80. To allow for potential dropouts, we decided to recruit a total of 25 patients per group. Data are presented as mean (SD) and [range]. Statistical analysis was performed using the StatView™ software for Windows (SAS Institute, Cary, NC). ANOVA was used for multiple comparisons. If a significant P-value of <0.05 was obtained in multiple comparisons, further group comparisons were made using the Bonferroni post hoc test.
Results

Data of the reversal time after sugammadex administration obtained from three patients in the 1 mg·kg⁻¹ group were excluded from analysis because of incomplete recovery to a TOF ratio less than 0.9. Patient characteristics did not differ among the groups (Table 1). There were no significant differences in onset times of neuromuscular blockade from the administration of 0.6 mg·kg⁻¹ of rocuronium and the times required for recovery of PTC (Table 2). Facilitated recovery with sugammadex from the reappearance of PTC to a TOF ratio of 0.9 took significantly longer in the 1 mg·kg⁻¹ group as compared to the 2 mg·kg⁻¹ and 4 mg·kg⁻¹ groups (P<0.001), although no difference was seen between the 2 mg·kg⁻¹ and 4 mg·kg⁻¹ groups. Incomplete reversal was seen in 3 patients (age: 9, 17 and 18 months, respectively), in the 1 mg·kg⁻¹ group, although it was successfully treated with additional dosing of sugammadex.
Discussion

This study shows that 4 mg·kg⁻¹ of sugammadex completely and rapidly reverses rocuronium-induced deep neuromuscular block in infants and children, while a smaller dose, 1 mg·kg⁻¹ may result in a longer recovery period and incomplete antagonism. In 3 patients of 1 mg·kg⁻¹ group needed additional sugammadex, the times required for spontaneous recovery of PTC after an administration of 0.6 mg·kg⁻¹ rocuronium was normal (21 min, 26 min and 35 min, respectively). It was therefore judged that incomplete reversal was not due to higher sensitivity to rocuronium-induced neuromuscular block, but was due to underdosing of sugammadex.

So far, there is limited data regarding the dose-response of sugammadex required for reversal from deep neuromuscular block in infants and children. Plaud and colleagues [8] reported median reversal times of 3.7 (n=2), 2.4 (n=2), 0.6 (n=1) and 0.7 min (n=1) following 0.5, 1.0, 2.0 and 4.0 mg·kg⁻¹ sugammadex administered during moderate neuromuscular block induced by rocuronium in infants, and concluded that sugammadex exhibited comparable dose-dependent recovery times with adults. However, the number of patients in their study was very small and hence, the authors cautioned that additional pediatric studies, particularly in infants, will be required to fully determine the efficacy and safety of sugammadex, particularly when more profound levels of neuromuscular blockade are present. Since then, as far as we know, this issue has not been prospectively examined. We believe that our present study can contribute to determining the dose-efficacy of sugammadex in infants and children.

It has been suggested that 4 mg·kg⁻¹ sugammadex is required to facilitate recovery from deep rocuronium-induced neuromuscular block in adult patients [9]. However, 2 mg·kg⁻¹ sugammadex restored neuromuscular function in the infants and children in this study. The interval between rocuronium injection and reappearance of PTC is reportedly
significantly age-related. In adult patients, the average time to reappearance of PTC 1 after administration of 0.6 mg·kg⁻¹ rocuronium is approximately 12 min [10]. In our study, on the other hand, the duration of intense neuromuscular block was approximately three-fold longer (35 min). Although this could have been due to differences in the anesthetics used, immature neuromuscular function in infants and children is probably the most likely cause of the longer duration of action of rocuronium. In fact, in a previous study [11] comparing the same child at different ages, during infancy and after the age of two years, when significant muscular growth and maturation of the neuromuscular junction and its function had occurred [6], indicated that infants are more sensitive to rocuronium than older children. In children aged 2 to 5 years, PTC 1 can be detected in 29.8 min even after a high dose of 1 mg·kg⁻¹ of rocuronium [12]. In the light of the fact that the ED₉₅ of rocuronium in infants is significantly lower than that in older children (0.25 mg·kg⁻¹ vs. 0.41 mg·kg⁻¹) [11], the plasma concentration or number of molecules of rocuronium should be smaller in infants and younger children at the same PTC level. Since one sugammadex molecule encapsulates one rocuronium molecule, it is therefore speculated that a smaller dose of 2 mg·kg⁻¹ of sugammadex may reverse a deep rocuronium-induced neuromuscular block in this study.

Faster facilitated recovery with 2 and 4 mg·kg⁻¹ sugammadex to a TOF ratio of 0.9 was shown in infants and children in this study as well, when compared with adult patients. In younger adult and elderly patients, 4 mg·kg⁻¹ sugammadex could completely antagonize the deep neuromuscular block induced at the adductor pollicis muscle, but it took approximately 120 s and 178 s, respectively [13]. Faster recovery in infants and children surely depends on a relatively larger cardiac output. The finding that 0.6 mg·kg⁻¹ rocuronium also exhibited a shorter onset of block in the current study may support a relationship between the onset of drug action and cardiac output. A faster reversal effect of sugammadex could result in a cannot ventilate cannot intubate emergency situation in pediatric patients.
A limitation of our study is that we did not calibrate thenar muscle responses using recommended methods with a 5 s - 50 Hz tetanic stimulation [14]. The neuromuscular junction and its function in infants is in a developmental stage. Therefore, tetanic fade may be observed even without muscle paralysis. Further, the staircase phenomenon is of a shorter duration in pediatric than adult patients [15, 16]. Hence, we used lower frequency repetitive stimulation of 1 Hz for calibration. Further, although this calibration method might have influenced the onset of action of rocuronium, it would not have affected the reversal effects of sugammadex, which were the main results of this study. Next, we did not investigate sugammadex effect in adolescents. Hence, the present results cannot be applied to all pediatric patients. Further studies will be needed to verify our findings in different pediatric age groups.

As second limitation, the range of recovery time after 1 mg·kg⁻¹ of sugammadex widely varied and the minimum data was faster than the average times of 2 mg·kg⁻¹ and 4 mg·kg⁻¹. The faster recovery observed in 1 mg·kg⁻¹ group was not dose-dependent recovery of sugammadex. It was guessed that the exceptional data may result from the difference in pharmacokinetic factors, such as cardiac output because the recovery from neuromuscular block with sugammadex is negatively correlated with cardiac output [5].

In conclusion, a 4 mg·kg⁻¹ dose of sugammadex is generally recommended for reversal from deep rocuronium-induced neuromuscular block even in infants and children.

**Conflict of interest:** Takahiro Suzuki has received speaker fees from MSD Inc., JAPAN.
References


sugammadex in pediatric and adult surgical patients. Anesthesiology, 110, 284-294 (2009)
### Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Dose of sugammadex</th>
<th>1 mg·kg⁻¹</th>
<th>2 mg·kg⁻¹</th>
<th>4 mg·kg⁻¹</th>
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</thead>
<tbody>
<tr>
<td>Gender (m/f)</td>
<td>17 / 8</td>
<td>17 / 8</td>
<td>18 / 7</td>
</tr>
<tr>
<td>Age (months)</td>
<td>11.2 (6.9)</td>
<td>11.8 (7.5)</td>
<td>11.8 (6.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8.2 (2.5)</td>
<td>8.3 (2.9)</td>
<td>8.2 (2.0)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>70.2 (9.8)</td>
<td>70.6 (11.4)</td>
<td>70.9 (8.9)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD). No significant differences were seen among the groups.

### Table 2. Neuromuscular variables

<table>
<thead>
<tr>
<th>Dose of sugammadex</th>
<th>1 mg·kg⁻¹</th>
<th>2 mg·kg⁻¹</th>
<th>4 mg·kg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of rocuronium (s)</td>
<td>56.9 (33.9)</td>
<td>58.9 (33.3)</td>
<td>54.4 (20.4)</td>
</tr>
<tr>
<td>Time to reappearance of PTC (min)</td>
<td>35.3 (15.1)</td>
<td>35.5 (17.2)</td>
<td>35.3 (14.8)</td>
</tr>
<tr>
<td>Time to TOF 0.9 (s min)</td>
<td>129.1 (83.5) *</td>
<td>70.3 (26.7)</td>
<td>68.2 (34.5)</td>
</tr>
</tbody>
</table>

* P < 0.001 vs. other groups. Data are presented as mean (SD) and [range]. Time to TOF 0.9 in the group of 1mg/kg was analyzed from the data of 22 patients.