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ARTICLE

Reversal of rocuronium-induced intense neuromuscular blockade by sugammadex in Korean children: A pharmacokinetic and pharmacodynamic analysis

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Abstract

Sugammadex, a selective antagonist of steroidal non-depolarizing neuromuscular blocking agents, has been used in children in limited circumstances. However, neither pharmacokinetics (PKs) nor recovery profile of sugammadex for intense neuromuscular blockade reversal in children have been reported. This prospective study aimed to obtain a PK model of sugammadex and evaluate its efficacy and safety for intense neuromuscular blockade reversal in children. Forty children (age, 2–17 years) who underwent surgery that required early neuromuscular blockade reversal were enrolled. After neuromuscular blockade with 1 mg·kg^{-1} of rocuronium, sugammadex (2, 4, and 8 mg·kg^{-1}) or a conventional dose of neostigmine (0.03 mg·kg^{-1}) was administered randomly after confirmation of zero post-tetanic count. The plasma concentrations of rocuronium and sugammadex were measured 2 min after rocuronium injection; immediately before, 2, 5, 15, 60, 120, 240, and 480 min after the study drug injection. Response to train-of-four stimulation was continuously recorded. Noncompartmental analysis and population PK modeling were performed. For pharmacodynamics, the recovery profile was measured. Three-compartment PK model was established for sugammadex. The median (interquartile range [IQR]) time from injection of 8 mg·kg^{-1} of sugammadex to recovery of T_4/T_1greater than or equal to 0.9 at train-of-four stimulation was 1.1 (IQR: 0.88–1.8) min. No adverse events related to sugammadex were observed. We present a PK analysis of sugammadex for rocuronium-induced intense neuromuscular blockade reversal in children with its recovery profile. The time to recover T_4/T_1 greater than or equal to 0.9 at train-of-four stimulation with 8 mg·kg^{-1} of sugammadex was less than 3 min and comparable to that in adults.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Sugammadex is indicated for reversal of rocuronium-induced neuromuscular blockade in children after the appearance of second twitch by train-of-four stimulation.

WHAT QUESTION DID THIS STUDY ADDRESS?

There are no data about pharmacokinetics (PKs) and recovery profile for intense neuromuscular blockade reversal by sugammadex in children, and its use in this scenario is still off-label in most countries.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

We present a PK analysis of sugammadex and rocuronium in the scenario of reversal of intense neuromuscular blockade in children. Sugammadex at a dose of 8 mg·kg−1 appears to safely reverse intense neuromuscular blockade with comparable recovery time to that in adults.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides a rationale for using sugammadex for reversal of rocuronium-induced intense neuromuscular blockade in children. Further study is needed to evaluate the most appropriate dose.

INTRODUCTION

Non-depolarizing neuromuscular blocking agents are commonly used during general anesthesia to facilitate endotracheal intubation and ensure immobility during surgery. In situations where neuromuscular blockade reversal is required, such as when extubation is attempted at the end of surgery, acetylcholinesterase inhibitors have been the most commonly used agents. Sugammadex, an agent that encapsulates rocuronium by forming one-to-one complex,[1] was developed as a selective antagonist of steroidal non-depolarizing neuromuscular blocking agent, with marked efficacy and without muscarinic adverse effects or risk of residual neuromuscular blockades.[1,2] Sugammadex is applicable to the entire spectrum of neuromuscular blockade in a dose-dependent manner, whereas acetylcholinesterase inhibitors are ineffective for intense or deep neuromuscular blockade.[3–5] Intense neuromuscular blockade is defined as zero response to post-tetanic count stimulation, and deep neuromuscular blockade is defined as one or more response to post-tetanic count stimulation but zero response to train-of-four stimulation.[6] Use of sugammadex is increasing in various clinical situations, such as surgery requiring electrophysiological monitoring, immediate reversal of neuromuscular blockade in emergent cases where ventilation is impossible by any means, and reversal and prevention of residual blockade. In adults, the recommended dose of sugammadex is 4 $mg \cdot kg^{-1}$ at a post-tetanic count of 1 or 2, and 16 $mg \cdot kg^{-1}$ for the immediate reversal of intense neuromuscular blockade.

Pharmacokinetic (PK) and pharmacodynamic studies of sugammadex have revealed that sugammadex can be used in pediatric patients.[7–12] However, to date, PK studies of sugammadex in children are rare, with only one published study[7] in which sugammadex was administered on the appearance of T_2 by train-of-four stimulation. Many studies have evaluated the pharmacodynamics of sugammadex and rocuronium for deep neuromuscular blockade reversal; however, data for intense blockade reversal is rare, and the PKs of sugammadex and rocuronium in this scenario remain unclear.

Data for the use of sugammadex in deep neuromuscular blockade reversal in pediatric patients remains limited, and no data describes the efficacy and safety of sugammadex for reversal of intense neuromuscular blockade in children. Therefore, we planned a prospective study aiming to obtain a PK model of sugammadex and evaluate its efficacy and safety for the reversal of intense neuromuscular blockade in children.

METHODS

Study design and population

This study was designed as a randomized, controlled, single-blinded, exploratory study to examine the PKs of sugammadex and compare the pharmacodynamics of 2, 4, or 8 $mg \cdot kg^{-1}$ of sugammadex against 0.03 $mg \cdot kg^{-1}$ of neostigmine. This study was conducted at a single center. The study protocol was approved by the Institutional Review Board of the Seoul

National University Hospital (1904-149-1029, approval date: July 31, 2019) and the Ministry of Food and Drug Safety of the Republic of Korea (approval no.: 32285, approval date: July 9, 2019). This study was registered at http://clinicaltrials.gov (NCT03943888, principal investigator: Hee-Soo Kim, published date: August 13, 2019). The study was conducted in accordance with the Good Clinical Practice guidelines by the International Council for Harmonization and the Declaration of Helsinki. Participants were recruited between August 2019 and February 2020.

Children aged 2–17 years, with an American Society of Anesthesiologists (ASA) physical status classification of 1 or 2, who were scheduled to undergo surgery under general anesthesia, and required early reversal of neuromuscular blockade after induction because of electrophysiology monitoring were enrolled. Written informed consent was obtained from one parent of each participant aged younger than 7 years, whereas it was obtained from both the participant and one of their parents for children aged 7–17 years. The exclusion criteria were a history of hypersensitivity to any anesthetic agents, including rocuronium, the presence of underlying cardiovascular or genitourinary disease,; the use of a neuromuscular blocking agent or any other drug that can influence the effect of rocuronium before surgery, a history of malignant hyperthermia, anticipation of massive hemorrhage during surgery, and one or more parent or legal guardian declining to enroll.

Study protocol

Upon the participant's arrival in the operating room, electrocardiogram (ECG), noninvasive blood pressure at 1-min intervals, and pulse oximetry for peripheral capillary oxygen saturation (SpO_2) were monitored. Anesthesia was induced in a routine manner with sodium thiopental or propofol according to age. Intravenous propofol and remifentanil were continuously infused to maintain anesthesia while providing 100% oxygen via a fitting mask. Train-of-four stimulation was performed with four twitch stimulations over 2 s with an intensity of 50 mA every 15 s via ToFscan (IDMED) at the participant's unilateral ulnar nerve. Responses to the train-of-four stimulations were measured by acceleromyography and automatically recorded via a program provided by the manufacturer. After the start of the recording, 1 $mg \cdot kg^{-1}$ of rocuronium was intravenously injected. Arterial catheterization was performed at one of the four extremities, and continuous monitoring of blood pressure was initiated. After confirmation of a train-of-four count of zero, the post-tetanic count, which measures the number of responses to 15 twitch stimulations at 50 Hz for 5 s, was measured at another extremity. After confirmation of zero post-tetanic count, the study drug was administered intravenously. At the end of the surgery, the train-of-four monitoring was stopped.

Randomization and blinding

According to a randomization table obtained from the website https://sealedenvelope.com/, the participants were allocated to one of the four groups: 2, 4, or 8 $mg \cdot kg^{-1}$ of sugammadex or a control group with 0.03 $mg \cdot kg^{-1}$ of neostigmine. According to the allocation, the study drug was prepared by a single anesthesiologist (author J.H. Lee). The participants and their parents were blinded to the group allocation.

Pharmacokinetic measurements

Arterial blood was withdrawn nine times to measure the plasma concentrations of rocuronium and sugammadex at 2 min after rocuronium injection; immediately before study drug administration; and 2, 5, 15, 60, 120, 240, and 480 min after study drug administration. The concentration of rocuronium was measured at every timepoint, whereas sugammadex was excluded at the first point. In case of deviation from the scheduled time, the actual time of sampling was recorded.[13]

Measurement of plasma concentrations

At the previously described timepoints, 1 ml of arterial blood was drawn for each measurement, and the blood was immediately stored in a sodium heparin tube (BD Vacutainer sodium heparin [N] 75 USP Units, Becton Dickinson Korea). After centrifuging the samples at 1,167 times gravity for 10 min, the supernatant was collected and stored in a sterile internal cryogenic vial (Cryotain; SCILAB Korea). The cryovials were stored in a freezer below −70°C until analysis.

Plasma concentrations of sugammadex and rocuronium were measured using liquid chromatography–tandem mass spectrometry. The assays were conducted in full compliance with the Good Laboratory Practice regulations. As this assay could not discriminate the sugammadex-rocuronium complex from their free forms, all plasma concentrations were considered total plasma concentrations. The internal standard was donepezil base for sugammadex and 3-acetyl rocuronium bromide for rocuronium, respectively (Toronto Research Chemicals). The lower limit of quantification and upper limit of

quantification were set as 0.1 and 100 μg·ml^{-1} for sugammadex and as 10 and 10,000 ng·ml^{-1} for rocuronium. The intra-assay coefficient of variation was no more than 14.9%, and the percentage bias was −12.5–2.0% for sugammadex. The intra-assay coefficient of variation was no more than 5.7%, and the percentage bias was −5.6–5.0% for rocuronium.

Noncompartmental analysis

The noncompartmental PK parameters of sugammadex and rocuronium were calculated using a validated software, Phoenix WinNonlin (version 8.1; Certara USA). The maximum concentration (C_{max}) and time to reach C_{max} (T_{max}) were determined from the observed values. The area under the plasma concentration-time curve (AUC) from time zero to the last measurable concentration (AUC_{last}) was calculated using linear-up log-down trapezoidal method. Partial AUCs from time zero to 15 min ($AUC_{0\text{-}15m}$) and 1 h postdose ($AUC_{0\text{-}1h}$) were calculated using the same method. AUC from time zero to infinity (AUC_{inf}) was calculated as the sum of AUC_{last} and the last measurable concentration divided by the terminal elimination constant (λ_z) estimated by linear regression. Terminal-phase elimination half-life ($t_{1/2}$) was calculated as natural logarithm of 2 divided by λ_z. Clearance (CL) and terminal-phase volume of distribution (V_z) were calculated as dose·$AUC_{inf}{}^{-1}$ and dose·$(\lambda_z\, AUC_{inf})^{-1}$.

Population pharmacokinetic modeling of sugammadex

Population PK model for sugammadex was developed using nonlinear mixed-effect modeling software (NONMEM 7.4.4 software, ICON Development Solutions). Data processing and diagnostics were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) and Perl-Speaks-NONMEM (version 4.9.0, https://uupharmacometrics.github.io/PsN/). Plasma concentrations were fitted into one/two/three-compartment models via the ADVAN 6 subroutine and first-order conditional estimation with interaction. During model building, interindividual variabilities of parameters were assumed to be log-normally distributed and introduced as exponential. The residual error was described with a proportional model. The minimum objective function value was obtained, which was equivalent to the −2 log likelihood of the model. For an alpha-error probability of 0.05, a reduction in the objective function value by more than 3.84 was regarded as significant according to the χ^2 distribution at degrees of freedom = 1.

After determining the base PK models, covariates of age, sex, weight, height, and serum creatinine concentration[5] were evaluated for selection. The effect of bodyweight on CL was considered with allometric scaling as follows:

$$P_i = \theta_p \times \left(\frac{BW_i}{MeanBW_i}\right)^{0.75} \times e^{\eta_i}$$

where P_i denotes the individual value, θ_p represents the population estimates, BW_i represents the individual bodyweight, and η_i denotes the interindividual random effect.

After development, goodness-of-fit plots comparing observations and individual predictions, observations and population predictions, conditional weighted residuals and population predictions, conditional weighted residuals, and time after dosing were sketched. For internal validation, median values and their 95% confidence intervals for each parameter were obtained from a nonparametric bootstrap analysis of 1000 simulated datasets. Prediction-corrected visual predictive check[14] was performed with the R package "xpose." The prediction-corrected visual predictive check evaluated whether the observed data were within the median and 90% prediction interval of 1000 simulated datasets from the final model. The models were executed, and diagnostics were performed using Pirana (version 2.9.9, https://www.pirana-software.com). During the modeling, the rocuronium-sugammadex complex was not discriminated from the free form of sugammadex or rocuronium, because they were indistinguishable during the plasma concentration measurement. Referring to previous studies,[5,15] we assumed elimination constant of rocuronium-sugammadex complex as identical to that of sugammadex and built a PK model of sugammadex, regardless of complex formation.

Pharmacodynamic measurements

During or after surgery, neuromuscular blockade was monitored by evaluating the response to a peripheral nerve stimulation. Train-of-four stimulation, which consists of four successive supramaximal stimuli delivered at 2 Hz on the ulnar, facial, or posterior tibial nerve, is the most common means of monitoring. The count of responses to the stimuli and the ratio of the fourth twitch to the first twitch (T_4/T_1 ratio) represent the receptor occupancy by rocuronium. A T_4/T_1 ratio greater than 90% is considered sufficient for extubation.[2] Usually, the efficacy of the reversal agents for neuromuscular blockade is measured as the time after administration of reversal agents to recovery of the T_4/T_1 ratio greater than 90%.

The count of twitches and the T_4/T_1 ratio to the train-of-four stimulations were automatically recorded until the end of the surgery and were compared according to the group. The time elapsed from the study drug

administration to the attainment of a T_4/T_1 ratio greater than or equal to 0.9 was the primary pharmacodynamic outcome. To bind the PKs of sugammadex to pharmacodynamic measurements, the time to recovery of the train-of-four ratio larger than 0.9 was plotted against the C_{max} and AUC_{last} of sugammadex.

Monitoring of safety

Monitoring of the participants' ECG, mean blood pressure, pulse oximetry, and body temperature was started from the beginning of anesthesia and continued until 24 h after the end of surgery. The presence of hemodynamic instability (more than 30% change from baseline for heart rate and mean blood pressure), hypoxemia (<92%), hyperthermia (above 38.3°C), hypothermia (below 35.5°C), nausea, vomiting, urticaria, and any anaphylactic reactions were monitored and recorded.

Statistical analysis

Data for the baseline characteristics and pharmacodynamics were tested for normality using the Kolmogorov–Smirnov test for data from the whole study population and the Shapiro–Wilk test for data from individual study groups. For nonparametric comparison of baseline characteristics of individual study groups, the Kruskal–Wallis test and a consequent Mann–Whitney *U* test with Bonferroni correction for post hoc analysis were done using the SPSS version 22 (IBM). Differences in the PK parameters of rocuronium related to systemic exposure (i.e., C_{max}, AUC_{last}, and AUC_{inf}) according to the sugammadex dose groups were compared using the Kruskal–Wallis test, followed by the nonparametric post-hoc evaluation using the Dwass, Steel, Critchlow-Fligner procedure implemented in the SAS software (version 9.3; SAS Institute, Inc.).

RESULTS

Forty children aged 3.5–16 years were enrolled and yielded 342 points of plasma concentration data. No participants were excluded for PK modeling of sugammadex, although 19 plasma concentrations were excluded because of inevitable additional injection of rocuronium during anesthesia or failure to obtain blood samples. For pharmacodynamic data and noncompartmental analysis of rocuronium, three participants were excluded because of erroneous dosing of rocuronium. Figure 1 shows the Consolidated Standards of Reporting Trials flow diagram for the study protocol. The detailed demographic data are presented in Table 1. Histogram of participants' age who were included in the PK modeling of sugammadex is shown in Figure 2.

Noncompartmental PK analysis

The plasma concentrations of sugammadex exhibited a multiphasic elimination profile after a single intravenous administration. Sugammadex reached C_{max} immediately after administration with the median T_{max} of 0.02–0.03 h. Systemic exposure (C_{max}, AUC_{last}, and AUC_{inf}) of sugammadex was proportional to the administered dose. CL and volume of distribution of sugammadex were constant across the dose groups with the mean of 0.07–0.08 $L \cdot min^{-1}$ and 9.7–10.6 L, respectively (Table 2).

There were significant differences in AUC_{last}, $AUC_{0\text{-}1h}$, and AUC_{inf} of rocuronium among the sugammadex dose groups. The post hoc analysis of AUC_{last} ($p = 0.0079$), $AUC_{0\text{-}1h}$ ($p = 0.0134$), and AUC_{inf} ($p = 0.0079$) revealed significant difference in the AUCs between the control and sugammadex 4 $mg \cdot kg^{-1}$ group. $AUC_{0\text{-}15m}$, C_{max}, and T_{max} of rocuronium were comparable across the sugammadex dose groups. Figure S1 shows the plasma concentrations of rocuronium after the administration of the study drug discriminated by the allocated groups.

Population pharmacokinetic model of sugammadex

A total of 203 sugammadex concentration data were used in the model development. A three-compartment model with first-order elimination was chosen as the base PK model of sugammadex. In the covariate analysis, bodyweight was a significant covariate for the central volume of distribution (V_1), volume of distribution of the rapid-equilibrating peripheral compartment (V_2), volume of distribution of the slow-equilibrating peripheral compartment (V_3), and CL. Population PK parameter estimates and the results of the nonparametric bootstrap replicates are shown in Table 3. The goodness-of-fit plots revealed that the model prediction was randomly scattered around the line of unity. No significant trend was observed at the plots of conditional weighted residuals versus population prediction or time (Figure S2). In the prediction-corrected visual predictive check, observed data mostly fell within the simulated 95% confidence intervals, consistently in 5%, median, and 95% quantiles of concentrations of sugammadex (Figure S3). For all the PK parameters, the bootstrap medians were close to the population estimates and the 95% confidence interval was relatively small (Table 3). This indicates that the population estimates of the parameters are accurate and precise.

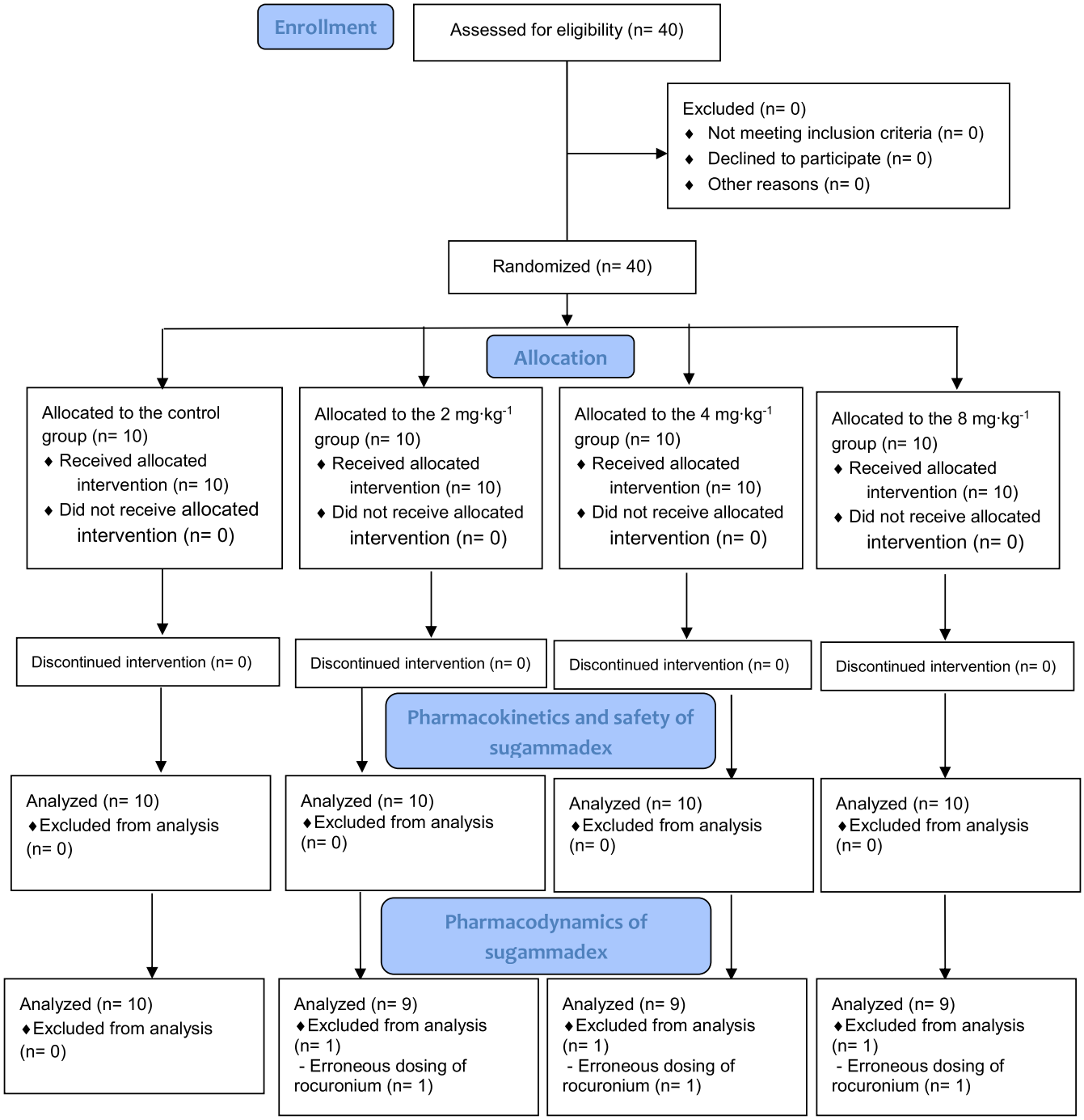

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram

Effect of sugammadex on the pharmacodynamics of rocuronium

Data from 37 children were included in the pharmacodynamic analysis. Three children were excluded because of erroneous dosing of rocuronium. The time interval (median [IQR]) between the injection of rocuronium and that of the study drug was 13.2 [IQR: 10.9–18.0] min, and no significant difference was observed between groups ($p = 0.074$). The elapsed time (mean ± SD or median [IQR]) from the administration of the study drug to the recovery of the T_4/T_1 ratio greater than or equal to 0.9 at train-of-four stimulation was 43.7 ± 28.2 min for the control group, 5.7 ± 4.7 min for 2 mg·kg^{-1} of sugammadex, 3.1 ± 1.0 min for 4 mg·kg^{-1} of sugammadex, and 1.1 [IQR: 0.88–1.8] min for 8 mg·kg^{-1} of sugammadex. Figure 3 shows the plasma concentrations of rocuronium and sugammadex along with T_4/T_1 ratio for each sugammadex dose group. Time to recovery of the T_4/T_1 ratio greater than or equal to 0.9 at train-of-four

TABLE 1 Demographic data

	Control (neostigmine) ($n = 10$)	Sugammadex 2 mg kg^{-1} ($n = 10$)	Sugammadex 4 mg kg^{-1} ($n = 10$)	Sugammadex 8 mg kg^{-1} ($n = 10$)	p value
Sex (male: female)	5:5	4:6	6:4	4:6	0.776
Age (years)	8.5 [7–11] (4–13)	6.5 [5–9] (3.5–15)	10 [6–12] (3.7–16)	6 [5–10] (3.5–15)	0.509
Height (cm)	134.2 ± 19.2	123.4 ± 31.7	133.8 ± 27.0	124.6 ± 25.9	0.621
Weight (kg)	40.4 [25.3–49.2] (15.0–58.9)	23.0 [18.5–40.3] (12.3–98.9)	33.8 [19.2–45.7] (14.7–51.9)	22.0 [16.8–50.3] (12.5–58.8)	0.418
Anesthesia time (min)	257.5 [240–330] (135–415)	305 [245–335] (215–420)	392.5 [375–505] (255–995)	335 [270–380] (235–570)	0.016
Operation time (min)	172.5 [140–235] (80–385)	220 [145–240] (140–330)	307.5 [285–435] (185–920)	260 [190–288] (170–490)	0.005
Type of surgery					0.036
Brain	10 (100%)	6 (60%)	4 (40%)	7 (70%)	
Spine	0 (0%)	4 (40%)	6 (60%)	3 (30%)	

Note: Data are shown as median [interquartile range] (range).

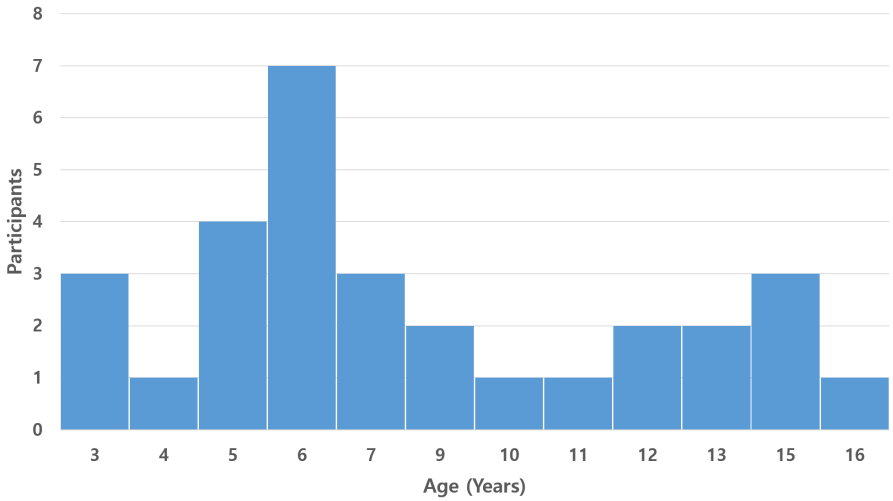

FIGURE 2 Histogram of participants who were included in the pharmacokinetic modeling of sugammadex

stimulation against dose were also shown as box plots in Figure 3.

Safety profiles of sugammadex

Six participants experienced seven incidences of adverse reactions in the period between the administration of sugammadex and 24 h after the end of surgery; however, none of the reactions were proven to be relevant to the administration of sugammadex. Detailed data are shown in Table 4. No residual blockade or respiratory depression was observed after surgery.

DISCUSSION

We established a PK model of sugammadex in children under intense neuromuscular blockade induced by rocuronium. In previous studies, Ploeger and colleagues[15] presented a three-compartment model without allometry, and Kleijn et al.[5] identified a two-compartment model with allometry. We used a three-compartment model with allometry, and its value is that the dataset was obtained solely from children.

In the PK model of sugammadex, interindividual variability of V_3 showed high residual standard error and shrinkage. However, when compared to the model without assumption of interindividual variability of V_3, the objective function value was reduced by 31.74 and there was an improvement in the goodness-of-fit plot. Therefore, we used the model with assumption of interindividual variability for V_3.

In the model by Kleijn et al.,[5] creatinine CL was included as a covariate for clearance, whereas our model did not include it. This may be because we enrolled only healthy children without renal impairment. Because alterations in CL have been reported in the renally impaired

TABLE 2 Summary of pharmacokinetic parameters

	Placebo ($n = 10$)	Sugammadex 2 mg kg^{-1} ($n = 10$)	Sugammadex 4 mg kg^{-1} ($n = 10$)	Sugammadex 8 mg kg^{-1} ($n = 10$)	p value[a]
Sugammadex					
C_{max} (μg ml^{-1})		28.4 ± 9.6	58.2 ± 12.5	118.9 ± 13	
AUC_{last} (h·μg·ml^{-1})		13.6 ± 3.7	28 ± 6.3	51 ± 9.6	
AUC_{inf} (h·μg·ml^{-1})		14.2 ± 3.8	29.1 ± 7	53.9 ± 13	
T_{max} (h)		0.03 [0.02–0.03]	0.02 [0.02–0.03]	0.03 [0.02–0.03]	
$t_{1/2}$ (h)		1.5 ± 0.4	1.7 ± 0.2	1.6 ± 0.2	
V_z (L)		9.9 ± 6.8	10.6 ± 2.8	9.7 ± 5.1	
CL (L·min^{-1})		0.07 ± 0.04	0.08 ± 0.03	0.07 ± 0.03	
Rocuronium					
C_{max} (μg·ml^{-1})	6.8 ± 3.1	5.3 ± 1.9	8.0 ± 2.1	5.4 ± 3	0.0875
AUC_{last} (h·μg·ml^{-1})	2.9 ± 0.9	3.7 ± 1	4.8 ± 1.1	4 ± 1.4	0.0100
$AUC_{0\text{-}15m}$ (h·μg·ml^{-1})	1.5 ± 0.4	1.7 ± 0.6	1.8 ± 0.3	1.4 ± 0.5	0.1920
$AUC_{0\text{-}1h}$ (h·μg·ml^{-1})	2.3 ± 0.6	2.6 ± 0.6	3.2 ± 0.5	2.5 ± 0.9	0.0143
AUC_{inf} (h·μg·ml^{-1})	2.9 ± 0.9	3.7 ± 1	4.9 ± 1.1	4.3 ± 1.8	0.0098
T_{max} (h)	0.08 [0.03–0.22]	0.1 [0.07–0.25]	0.07 [0.03–0.13]	0.12 [0.03–0.43]	
$t_{1/2}$ (h)	1.1 ± 0.4	1.2 ± 0.3	1.2 ± 0.2	1.3 ± 0.2	
V_z (L)	21.4 ± 10.8	14.5 ± 11.8	10.8 ± 3.5	13.0 ± 5.9	
CL (L·min^{-1})	0.22 ± 0.07	0.13 ± 0.08	0.11 ± 0.04	0.12 ± 0.05	

Note: Data were presented as mean ± SD except for T_{max}, for which median [minimum − maximum] was presented. Three participants (one participant in each group) who were administered of rocuronium 0.6 mg kg^{-1} were excluded from the analysis of rocuronium.

Abbreviations: AUC, area under the plasma concentration-time curve; $AUC_{0\text{-}15m}$, AUC from time zero to 15 min; $AUC_{0\text{-}1h}$, AUC for 1 h postdose; AUC_{last}, AUC from time zero to the last observable concentration; AUC_{inf}, AUC from time zero to infinity; CL, clearance; C_{max}, maximum plasma concentration; T_{max}, time to reach the maximum plasma concentration; $t_{1/2}$, terminal-phase elimination half-life; V_z, terminal-phase volume of distribution.

[a]Kruskal-Wallis test.

population,[16,17] further studies assessing children with decreased renal function are needed.

In previous studies by Ploeger et al.,[15] the plasma concentrations of rocuronium were higher than predicted in participants who received sugammadex with immediate increase after injection of sugammadex. This finding was explained by the movement of rocuronium from the tissue compartment to the plasma compartment to form a complex with sugammadex. Our noncompartmental analysis revealed a similar result, although the difference was not statistically significant, probably due to the small sample size (Figure S1).

In adults, the recommended dose of sugammadex for reversal of intense neuromuscular blockade is 16 mg·kg^{-1}. However, as many previous dose-finding studies[18,19] limited the dose to 8 mg·kg^{-1} and no safety data was available for greater than 4 mg·kg^{-1} of sugammadex in children, we decided to limit the dose to 8 mg·kg^{-1}, which is two-folds of the current maximum available dose. In our study, the median time to recover T_4/T_1 greater than or equal to 0.9 at train-of-four stimulation was much shorter than 3 min with 8 mg·kg^{-1} of sugammadex and differed significantly from that of the 4 mg·kg^{-1} group. According to Figure 3, a large spectrum of recovery time was observed in the 2 mg·kg^{-1} group, and we can expect a recovery time of up to 5 min in the 4 mg·kg^{-1} group. The most critical scenario of reversing intense neuromuscular blockade would be "cannot intubate, cannot ventilate" scenario during induction of anesthesia that immediate neuromuscular reversal is needed. These results show that 8 mg·kg^{-1} of sugammadex may be effective in reversal of intense neuromuscular blockade in less than 3 min in children. In a previous study on adults, the time to recover T_4/T_1 greater than or equal to 0.9 at train-of-four stimulation with 8 mg·kg^{-1} of sugammadex was 1.8 min, which is much shorter than that with 4 mg·kg^{-1} of sugammadex, when administered 15 min after 1 mg·kg^{-1} of rocuronium.[18] Our results are similar in that the dose of 8 mg·kg^{-1} was suitable for reversal of intense neuromuscular blockade, whereas 4 mg·kg^{-1} was not.

Although many children undergoing anesthesia encounter situations that require the rapid reversal of neuromuscular blockade, its use in children remains off-label in many countries because of lack of data or safety issues. On published literatures, PK modeling of sugammadex solely from children is difficult to find. Our data and the

TABLE 3 Population estimates of parameters of the pharmacokinetic model of sugammadex

Base pharmacokinetic model – sugammadex					
Parameter	**Population estimate**	**RSE (%)**	**CV (%)**	ω^2	**Shrinkage (%)**
V_1 (L)	1.49	8	66.7	0.368	5
V_2 (L)	2.26	11	78.1	0.476	3
V_3 (L)	2.41	13	17.9	0.0317	30
CL (L·min^{-1})	0.0668	8	42.6	0.167	0
Q_1 (L·min^{-1})	0.188	21	–[a]	–[a]	
Q_2 (L·min^{-1})	0.0247	16	–[a]	–[a]	
Final model with covariates – sugammadex					
Parameter	**Population estimate**	**RSE (%)**	**Shrinkage (%)**	**Bootstrap median**	**Bootstrap 95% CI**
$V_1\,(\mathrm{L}) = \theta_1 \times \frac{\mathrm{WT}}{30}$	$\theta_1 = 1.46$	6.8		1.45	1.23–1.63
$V_2\,(\mathrm{L}) = \theta_2 \times \frac{\mathrm{WT}}{30}$	$\theta_2 = 2.22$	5.3		2.23	2.01–2.50
$V_3\,(\mathrm{L}) = \theta_3 \times \frac{\mathrm{WT}}{30}$	$\theta_3 = 2.80$	6.1		2.81	2.47–3.17
$\mathrm{CL}\,(\mathrm{L{\cdot}min^{-1}}) = \theta_4 \times \left(\frac{\mathrm{WT}}{30}\right)^{0.75}$	$\theta_4 = 0.0647$	3.7		0.0648	0.0603–0.0698
Q_1 (L·min^{-1})	0.187	18.1		0.190	0.142–0.263
Q_2 (L·min^{-1})	0.0227	13.0		0.0229	0.0169–0.0290
ω^2 for V_1 (%)	22.1	20	20	21.7	11.0–29.6
ω^2 for V_2 (%)	19.8	28	29	19.4	6.19–28.7
ω^2 for V_3 (%)	21.8	29	24	21.3	5.91–30.9
ω^2 for CL (%)	18.7	11	2	18.3	14.2–22.7
Residual proportional error (%)	13.0	10		12.5	10.1–15.1

Abbreviations: CI, confidence interval; CL, metabolic clearance; CV, Coefficient of variation calculated as $\sqrt{e^{(\omega^2)} - 1}$; Q_1, clearance from compartment 1 to compartment 2; Q_2, clearance from compartment 1 to compartment 3; RSE, residual standard error; V_1, central volume of distribution; V_2, volume of distribution of the rapid-equilibrating peripheral compartment; V_3, volume of distribution of the slow-equilibrating peripheral compartment; ω^2, untransformed value of interindividual variability.

[a]In the base pharmacokinetic model, interindividual variability of Q_1 and Q_2 were not estimated due to insignificance.

PK model of sugammadex would be valuable for studies in the pediatric population and would potentially provide evidence for use of sugammadex for reversal of deep or intense neuromuscular blockade in children. The use of sugammadex is associated to enhanced recovery after surgery as it prevents postoperative residual blockade, reduces anesthesia time, and ensures better surgical conditions as the anesthesiologist can use neuromuscular blocking agents without concern for delays in the reversal of neuromuscular blockade after surgery. Sugammadex is also considered potentially helpful in situations of rocuronium-induced anaphylaxis, although its use remains controversial.[20–22] We expect our study to serve as a basis for use of sugammadex in children.

Reported adverse effects of sugammadex include cardiovascular adverse effects, such as bradycardia, QTc prolongation, atrioventricular block, hypotension, and atrial fibrillation.[23] Other reported events include hypersensitivity and anaphylaxis.[24,25] In our study candidates, there was no incidence of these previously reported adverse events. As our study was conducted in patients under general anesthesia and surgery, our adverse event data of fever, hypertension, hypotension, and intra-operative seizure can be attributed to surgery or the effect of anesthetic agents. Considering this, the use of sugammadex during general anesthesia is considered to be well-tolerated in children.

Our study has some limitations. First, we did not perform an external validation of the PK model of sugammadex due to the limited number of participants. Second, our study did not include neonates or infants, as the use of sugammadex in these populations is also off-label in any of the scenario and data are scarce.[11,26] Third, it was technically difficult to make multiple PK sampling before recovery of T_4/T_1 ratio greater than or equal to 0.9. In addition, it was difficult to discriminate free form of rocuronium or sugammadex from rocuronium-sugammadex complex. These factors made PK-pharmacodynamic modeling difficult. Fourth, the

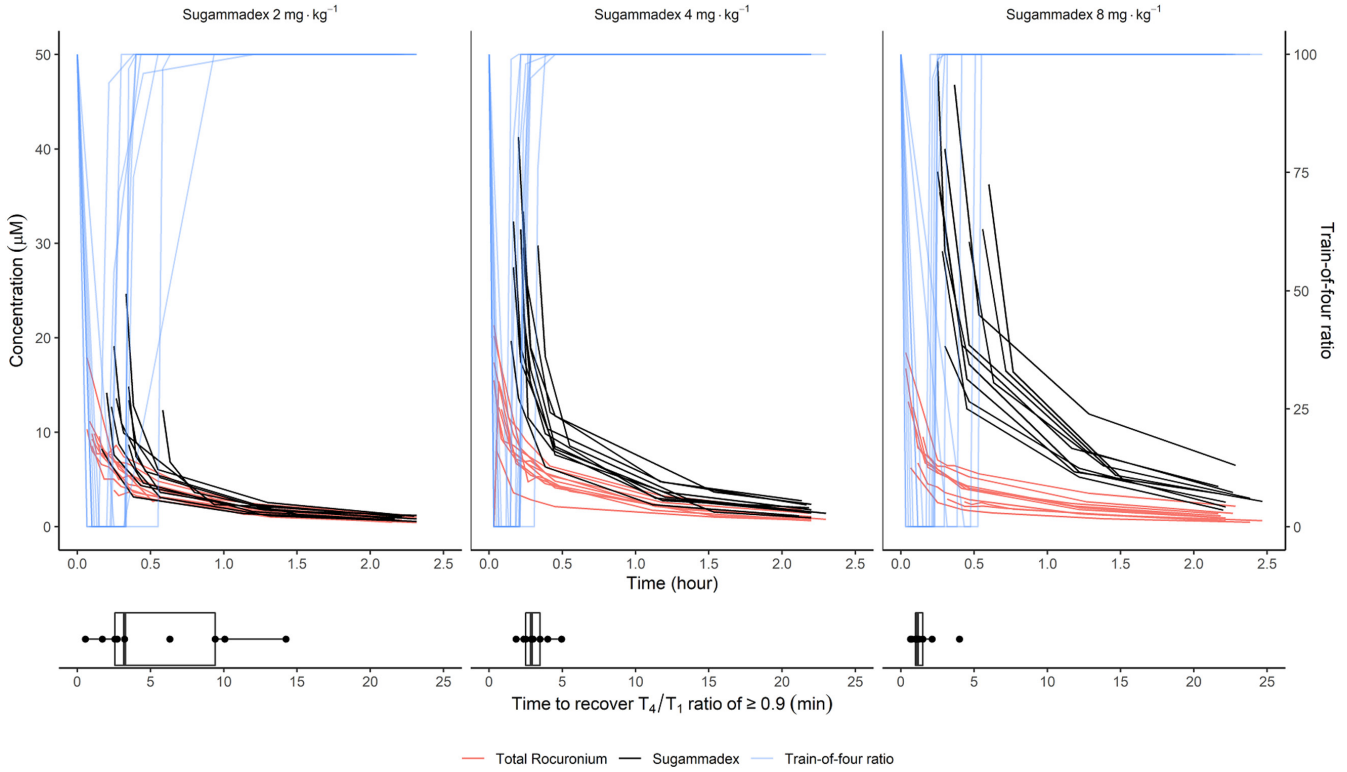

FIGURE 3 Response profiles of plasma concentration of rocuronium and T_4/T_1 ratio at train-of-four stimulation drawn together with plasma concentration of sugammadex. Box plots below are showing time from study drug administration to recovery of T_4/T_1 ratio greater than or equal to 0.9 at train-of-four stimulation. Molar concentration was calculated on the basis of the molecular weights of rocuronium (529.8 g mol^{-1}) and sugammadex (2002 g mol^{-1})

TABLE 4 Summary of adverse events after sugammadex administration

Group	Control ($n = 10$)	Sugammadex 2 mg·kg^{-1} ($n = 10$)	Sugammadex 4 mg·kg^{-1} ($n = 10$)	Sugammadex 8 mg·kg^{-1} ($n = 10$)
Number of participants with any adverse event	–	1 (10%)	3 (30%)	2 (20%)
Fever	–	1 (10%)	1 (10%)	1 (10%)
Nausea	–	–	1 (10%)	–
Hypotension	–	–	1 (10%)	–
Hypertension	–	–	–	1 (10%)
Intra-operative seizure	–	–	1 (10%)	–
Number of participants who received medication for adverse events	–	–	1 (10%)	–
Number of adverse events relevant to study drug	–	–	–	–

Note: Adverse events were recorded from the administration of sugammadex to 24 h after the end of surgery.

assumption that elimination constant of rocuronium-sugammadex complex is equal to that of free sugammadex is based on previous models, but firm evidence is lacking. Finally, we cannot directly compare our absolute value of recovery time with previous adult studies or conclude that 8 mg·kg^{-1} of sugammadex is also suitable for "immediate" reversal of rocuronium-induced neuromuscular blockade, because our time interval between administration of rocuronium and sugammadex of 13 min was considerably longer than that of those studies. Still, we can say that 8 mg·kg^{-1} of sugammadex seems to be effective in children even when the post-tetanic count was zero. As we observed safety in a dose of 8 mg·kg^{-1} and already obtained a PK model, a further pharmacodynamics-only study which includes a dose of 16 mg·kg^{-1} is encouraged to compare with adult data.

In conclusion, we report a PK model with recovery profile of sugammadex of children during intense neuromuscular blockade induced by rocuronium and observed no adverse event associated with sugammadex. The time to recover T_4/T_1 greater than or equal to 0.9 at train-of-four stimulation with 8 mg·kg^{-1} of sugammadex was less than 3 min and comparable to that in adults. Further studies, including external validation of PK models and pharmacodynamics of other reversal scenarios, are required.

AUTHOR CONTRIBUTIONS

S.H.J., K.Y.H., J.O., Y.E.J., E.H.K., J.H.L., J.T.K., and H.S.K. wrote the manuscript. S.H.J., K.Y.H., J.O., H.J.J., Y.E.J., and H.S.K. designed the research. S.H.J., H.J.J., Y.E.J., E.H.K., J.H.L., J.T.K., and H.S.K. performed the research. S.H.J., K.Y.H., J.O., E.H.K., J.H.L., and H.S.K. analyzed the data.

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CONFLICT OF INTEREST

The authors declared no competing interests from this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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