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Reversal of Rocuronium-induced Neuromuscular Blockade with Sugammadex in Pediatric and Adult Surgical Patients

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Background: **Sugammadex reverses neuromuscular blockade by chemical encapsulation of rocuronium. This phase IIIA study explored efficacy and safety of sugammadex in infants (28 days to 23 months), children (2–11 yr), adolescents (12–17 yr), and adults (18–65 yr).**

Methods: **Anesthetized patients (American Society of Anesthesiologists class 1–2) received 0.6 mg/kg rocuronium and were randomized to receive sugammadex (0.5, 1.0, 2.0, or 4.0 mg/kg) or placebo at reappearance of T2. Neuromuscular monitoring was performed using acceleromyography. Primary endpoint was time from sugammadex/placebo administration to recovery of the train-of-four ratio to 0.9. Adverse events and electrocardiograms were recorded, and blood samples were collected for safety and determination of sugammadex and rocuronium plasma concentrations.**

Results: **A dose-response relation was demonstrated in children (n = 22), adolescents (n = 28), and adults (n = 26), but not infants because of the small sample size (n = 8). After placebo, median recovery time of train-of-four to 0.9 was 21.0, 19.0, 23.4, and 28.5 min in infants, children, adolescents, and adults, respectively. After 2.0 mg/kg sugammadex train-of-four 0.9 was attained in 0.6, 1.2, 1.1, and 1.2 min, respectively. The sugammadex plasma concentrations were similar for the children, adolescent, and adult age groups across the dose range. Sugammadex was well tolerated: No reoccurrence of blockade, inadequate reversal, significant QT prolongation, or other abnormalities were observed.**

Conclusions: **Sugammadex is a new reversal agent that rapidly, effectively, safely, and with similar recovery times reverses rocuronium-induced neuromuscular blockade in children, adolescents, adults, and the small number of infants studied.**

NEUROMUSCULAR blocking agents (NMBAs) are frequently used during anesthesia to facilitate tracheal intubation, artificial ventilation, and surgical procedures. Reversal agents (*e.g.*, neostigmine or edrophonium) are often administered to accelerate recovery from neuromuscular blockade and prevent postoperative residual curarization.[1,2]

The use of acetylcholinesterase inhibitors, currently the only reversal agents available, is associated with undesirable muscarinic side effects. These side effects necessitate the use of anticholinergic drugs, which may be only partially effective unless used in large doses with possible side effects. In addition, use of acetylcholinesterase inhibitors is associated with residual blockade in both adults and children.[3–7]

Sugammadex, a modified gamma cyclodextrin, is a selective relaxant binding agent specifically designed to encapsulate the steroidal NMBAs rocuronium and vecuronium.[8] Sugammadex forms an inclusion complex with these NMBAs, thereby preventing their binding to nicotinic receptors at the neuromuscular junction, resulting in reversal of neuromuscular blockade.[9] Several clinical studies have shown sugammadex to be a rapid and effective agent for the reversal of rocuronium-induced neuromuscular blockade, including reversal of prolonged and profound rocuronium blockade.[10–16] These studies showed that sugammadex administration was associated with recovery times to a train-of-four (TOF) ratio of 0.9 in approximately 2 min for shallow blockade using doses of 2.0 mg/kg or higher.[10–13] Furthermore, because sugammadex does not bind to muscarinic receptors, it has the advantage that it is not associated with the side effects that may occur with the use of anticholinesterase agents.[17]

Pediatric patients differ from adult patients because the pharmacokinetic and pharmacodynamic profiles of NMBAs may vary as a function of age.[18] For example, the clinical duration of rocuronium is prolonged in infants compared with children,[19,20] and the potency of rocuronium is greater in infants and less in children as compared to adults.[21] Residual paralysis may occur in children,[6] but it occurs less frequently than in adults.[3]

This first study with sugammadex in pediatric patients was set up as an exploratory study to obtain a first indication for its effectiveness and safety in this patient group based on similar studies carried out in adults in phase II.[10,16] The aim of this study was to explore the dose-response relationship of sugammadex given at reappearance of the second twitch (T2) of the TOF stimulation for the reversal of rocuronium-induced neuromuscular blockade in infants, children, adolescents, and

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adults. The safety of sugammadex in this patient population was also studied.

Materials and Methods

Study Design

This was a multicenter, randomized, parallel-group, dose-finding, safety-assessor blinded study carried out between May 2005 and May 2006 at a total of six European centers (two each in France and the United Kingdom and one each in Finland and Germany). The study protocol was approved by the Independent Ethics Committee of each trial center (Nancy, France; Belfast, United Kingdom; Helsinki, Finland; Rostock, Germany) and the study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines, Good Clinical Practice, and current regulatory requirements.

Patients were enrolled in the study if they fulfilled the following inclusion criteria: categorized as American Society of Anesthesiologists class 1 or 2; aged between 28 days and 65 yr inclusive (2–65 yr in Germany and 6–65 yr in Finland); scheduled for general anesthesia with an anticipated duration of at least 60 min, requiring only a single bolus dose of rocuronium; scheduled for surgery in a supine position for facilitating monitoring of neuromuscular blockade. Patients were excluded from participation in the study if they had known or suspected neuromuscular disorders that impair neuromuscular blockade, were using medication known to interact with rocuronium, had significant renal dysfunction, had a family history of malignant hyperthermia or allergy to any medication used during general anesthesia, or were pregnant, breast-feeding, or using an inadequate method of contraception. Patients were also excluded if they had participated in a sugammadex or another trial within 30 days of entering into the study. All patients and/or parents/guardians, as appropriate, were required to give written informed consent.

Enrollment of patients was stratified among 4 age groups: infants (aged 28 days–23 months), children (aged 2–11 yr), adolescents (aged 12–17 yr), and adults (aged 18–65 yr). Neonates were not included in this study.

Pulse oximetry, electrocardiogram, and noninvasive arterial blood pressure monitoring was commenced on arrival in the operating room. An intravenous cannula was inserted into one arm for the administration of anesthetic drugs, rocuronium, and sugammadex or placebo. In pediatric patients, a volatile agent could be administered to facilitate venous cannulation. This was followed by a washout period of 10 min before administration of rocuronium to ensure that the volatile agent had no effect on neuromuscular blockade. A second intravenous cannula was inserted into the opposite arm for the collection of blood samples for measurement of rocuronium and sugammadex plasma levels and safety analyses. Anesthesia was induced and maintained with an intravenous opioid and propofol according to the requirement of the patient. All the infants and one child received caudal analgesia with a mixture of 1 ml/kg ropivacaine 2 mg/ml and 1 μg/kg clonidine.

Monitoring of neuromuscular function at the adductor pollicis muscle was performed using acceleromyography (TOF-Watch SX; Schering-Plough, Swords, Co. Dublin, Ireland), and was initiated after the induction of anesthesia but before the administration of rocuronium. A transducer was placed over the thumb (in infants and children the transducer was attached with tape with the lead upwards; a thumb extensor could be used if required). No preload was used. Stabilization and calibration of the TOF-Watch SX were performed in the operating room after the induction of anesthesia in a standard manner as used in previous studies.[10–13] Default settings of CAL2 were used, delivering a 60mA current over 200 μs. At the start of the stabilization procedure, the arm was immobilized with an arm board, but the fingers were still free to move. Stabilization was done using a 5-s 50-Hz tetanic stimulation. One minute later, the fingers were fixed. Repetitive TOF stimulation was done every 15 s for at least 3 min, followed by calibration. After calibration, repetitive TOF stimulation was again applied for 3 to 4 min before rocuronium administration and subsequent data collection. In this period, the set-up was evaluated (to check the stability of the trace, scatter, supramaximal stimulation, and sensitivity). Repetitive TOF stimulation was then continued every 15 s. All neuromuscular data were transferred on-line to a computer using the TOF-Watch SX Monitoring Program version 1.2 (Schering-Plough, Oss, The Netherlands).

Patients received a single intravenous bolus dose of 0.6 mg/kg rocuronium, and tracheal intubation was performed after the maximum neuromuscular blockade had been attained. Using a central randomization system, patients were randomized to receive a single intravenous bolus dose of sugammadex 0.5, 1.0, 2.0, or 4.0 mg/kg or placebo within 2 min of reappearance of T2 (measured as the first time point from a series of three that the T2 response was recorded). The randomization was stratified by age group with a fixed block size of five, and it was accessible *via* a website. Rocuronium, sugammadex, and placebo were each administered as a single intravenous bolus dose over 10 s into a fast-running venous infusion. For the infants, sugammadex was diluted with 0.9% saline to a concentration of 25 mg/ml (initial solution 100 mg/ml) to allow more accurate administration of the calculated dose.

The primary efficacy endpoint was the time to attain a TOF ratio of 0.9, which was defined as the first time point of three consecutive readings of 0.9 or above. The times to attain TOF ratios of 0.7 and 0.8 were also recorded. Stable recovery was indicated by the time after

which there was no or very little change in the height of the twitches (plateau) after attainment of a TOF ratio of at least 0.8. TOF values were not related to baseline values.

No other reversal agents or additional NMBAs were administered during the 30-min period immediately after administration of sugammadex/placebo or before recovery of the TOF ratio to 0.9. A nonamino steroidal muscle relaxant could be administered if further muscle relaxation was needed beyond this time. Neuromuscular monitoring was continued until the end of anesthesia or at least until recovery of the TOF ratio to 0.9 and for a minimum of 30 min after the administration of sugammadex or placebo.

Patients were monitored for any evidence of inadequate reversal (TOF ratio < 0.9) or reoccurrence of blockade, defined as a decline in the TOF ratio from at least 0.9 to less than 0.8 in response to at least three consecutive TOF stimulations. Oxygen saturation (using a pulse oximeter with saturation alarm set at $< 90\%$ Spo_2) and respiratory rate were measured for at least 7 h after administration of sugammadex or placebo. The patients' level of consciousness and signs of clinical recovery of neuromuscular function (sustained 5-s head-lift test, absence of diplopia, ability to resist removal of a tongue depressor between clenched teeth, absence of general muscle weakness, and leg lift in infants) were recorded in the postanesthesia care unit whenever possible.

Efficacy

The primary efficacy variable was the time from the start of administration of sugammadex/placebo to recovery of the TOF ratio to 0.9. Secondary efficacy variables included time from the start of administration of sugammadex/placebo to recovery of the TOF ratio to 0.7 and 0.8. Times from start of administration of rocuronium until reappearance of T2 were also recorded.

Safety

Adverse events (AEs), serious AEs (SAEs), and any medical device or trial procedure-related AEs were recorded after administration of study drug until the end of the follow-up period (visit or telephone contact at 7th postoperative day). Any abnormal laboratory values or vital signs that were considered to be clinically relevant in the opinion of the investigator were reported as AEs.

Three blood samples (10 ml per sample in adults and adolescents and 3 ml per sample in children and infants) were collected from each patient for safety analysis (including hematocrit, blood count, liver enzymes, creatine kinase, and electrolytes) at stable anesthesia before administration of rocuronium, at 60 min after administration of sugammadex or placebo (or at the end of surgery), and at a postanesthetic visit, which was performed on the day of or the day after surgery at least 10 h after the administration of the study drug. Samples were also collected for urinalysis (including pH, protein, N-acetyl glucosaminidase, and creatinine) before anesthesia and at the postanesthetic visit. Heart rate and blood pressure were recorded, and a baseline 12-lead electrocardiogram was obtained before administration of rocuronium. Heart rate and blood pressure were again recorded before administration of the study drugs and at 2, 5, 10, and 30 min later, and at the postanesthetic visit. A 12-lead electrocardiogram recording was also obtained at 2 and 30 min after administration of sugammadex or placebo. Clinically significant cardiovascular events were to be reported as AEs. The electrocardiogram recordings were transferred electronically to a contract research organization to be read in a blinded fashion for any QTc prolongation. During the postanesthetic visit, a physical examination was performed, blood and urine samples were collected for safety analysis, and vital signs were recorded. Any AEs and/or any concomitant medication received were also recorded at this time point. During the study, clinical signs of any possible interaction between sugammadex and any endogenous or exogenous compounds other than rocuronium were also recorded.

Plasma Levels

A graphical exploration of the pharmacokinetics of sugammadex and rocuronium was performed using sparse plasma concentrations. A maximum of six blood samples (3 ml per sample in adults and adolescents, and 0.25 ml per sample in children and infants) were collected from each patient (2 min after administration of rocuronium, just before administration of sugammadex/placebo [at reappearance of T2], and at 2, 5, 15, and 60 min [or end of surgery] after administration of sugammadex/placebo). Plasma concentrations were measured at the Department of Clinical Pharmacology and Kinetics, Schering-Plough, Oss, The Netherlands, using validated liquid chromatographic assay methods with mass spectrometric detection. The assays were conducted in full compliance with good laboratory practice regulations. Because the assay methods used to determine the plasma concentrations of sugammadex and rocuronium did not discriminate between complexed and noncomplexed sugammadex and rocuronium, the plasma concentrations reported relate to total plasma concentrations. The lower limit of quantification was 2 ng/ml for rocuronium and 100 ng/ml for sugammadex.

Sample Size

For the sample size calculation, it was assumed that the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9 for the different pediatric age groups was similar to that observed in earlier sugammadex studies in adults.[10–12] On the basis of these findings (estimated means and standard deviations for

different doses of sugammadex), trials were simulated using SAS version 8.2 (SAS Institute Inc., Cary, NC) in which, for each simulation, the data were fitted to an exponential model. The simulations (n = 5000) were performed to determine how many subjects per dose group were needed to find an adequate model fit. It was found that each dose group should comprise four patients to achieve a power of at least 95%. This means that an adequate dose response relationship could be determined in at least 95% of all 5000 simulations. However, assuming a discontinuation rate of 25%, it was decided to include six patients per dose and per age group, with five dose groups and four age groups, giving a total of 120 patients.

Statistical Analyses

The all-subjects-treated group comprised all treated patients (randomized patients who received a dose of sugammadex or placebo). This group was used to evaluate safety. The efficacy was evaluated for all patients in the intent-to-treat group (all treated patients who had at least one post-baseline efficacy measurement) and for all patients in the per-protocol group (all patients in the intent-to-treat group who had no protocol violation leading to exclusion of efficacy data). This was an exploratory study; therefore, the per-protocol group was primarily used to evaluate efficacy.

Efficacy data were summarized by age and dose groups. Summary statistics (mean, SD, median, and range) were used to describe continuous variables, and frequency counts and percentages were described for categorical variables.

For each age group, weighted nonlinear regression was used to explore the relation between the dose of sugammadex and time from the start of administration of sugammadex/placebo to recovery of the TOF ratio to 0.9 with the following equation: Estimated time to recovery of the TOF ratio to 0.9 = $a + b.\exp(c.\text{dose})$, where a represents the fastest achievable recovery time for the average subject, b represents the difference in time between mean spontaneous recovery (recovery after placebo administration in the present study) and mean recovery after an infinitely large dose of sugammadex, and c represents the extent of change in recovery time with sugammadex.[10] Descriptive statistics are presented for safety parameters.

Results

A total of 94 patients were randomized to receive sugammadex or placebo, of which 91 patients (8 infants, 24 children, 31 adolescents, and 28 adults) received the study medication (all-subjects-treated group). The number of patients per site ranged between 5 and 27. Major protocol violations were reported in two children, two adults, and two adolescent patients. These consisted of violation of the randomization schedule in three patients (one adolescent was considered by the Web site as a child and consequently randomized as a child, one adolescent and one adult received a higher dose of sugammadex than they should have had according to the randomization scheme), and administration of study medication more than 2 min after reappearance of T2 in the other three patients. Therefore, the per-protocol group comprised 85 patients. One adult patient who received sugammadex did not complete the study due to loss of contact after discharge from hospital. Table 1 presents a summary of the patient characteristics.

Table 1. Baseline Patient Characteristics (all-subjects-treated group)

	Infants	Children	Adolescents	Adults
N	8	24	31	28
Age, yr, mean (SD)	1 (0)	8 (2)	14 (1)	41 (13)
Weight, kg, mean (SD)	11 (2)	30 (10)	54 (12)	77 (13)
Height, cm, mean (SD)	78 (8)	130 (16)	164 (13)	172 (7)
Male/female, n	4/4	10/14	18/13	21/7
ASA class 1, n (%)	8 (100)	21 (88)	25 (81)	18 (64)
ASA class 2, n (%)		3 (13)	6 (19)	10 (36)

ASA = American Society of Anesthesiologists; SD = standard deviation.

Efficacy. The time to attain a TOF ratio of 0.9 decreased with increasing doses of sugammadex in all age groups by a similar magnitude. The times from the start of administration of sugammadex or placebo to recovery of the TOF ratio to 0.9 by dose group and age group for the per-protocol group are shown in table 2, and the estimated dose-response relationships are presented in table 3 and shown in figure 1 (with their 95% confidence intervals) for children, adolescents, and adults, respectively. A clear dose-response relationship was observed for children, adolescents, and adults with median times to a TOF ratio of 0.9 ranging from 4.6 to 0.6 min as the dose of sugammadex increased from 0.5 mg/kg upwards. A dose of 2.0 mg/kg was associated with recovery to this endpoint in all age groups in a median time of 1.1–1.2 min. The recovery was faster, at 0.6 min, in the only infant studied with the 2.0 mg/kg dose. The times were somewhat longer at 4.4 min in one child receiving the 4.0 mg/kg dose and in one adolescent at 5.2 min after the 2.0 mg/kg dose. Although the results from infants fit the exponential model, there were too few data to allow reliable interpretation of the results. A TOF ratio of 0.9 or higher was attained in a median time of less than 2 min with a sugammadex dose of 2.0 mg/kg in all age groups. Evaluation of the results from the intent-to-treat group showed that they were comparable to the per-protocol group.

The times from the start of administration of sugammadex/placebo to recovery of the TOF ratios to 0.7 and 0.8 for the four age groups showed the same trends as recovery of the TOF ratio to 0.9.

Table 2. Summary of the Time (min) from Start of Administration of Sugammadex or Placebo to Recovery of the TOF Ratio to 0.9 by Age Group and Dose Group (per-protocol group)

		Sugammadex Dose (mg/kg)			
	Placebo	0.5	1.0	2.0	4.0
Infants					
n	2	2	2	1	1
Mean (SD)	21.0 (11.3)	3.7 (0.6)	2.4 (0.7)	0.6 (—)	0.7 (—)
Median	21.0	3.7	2.4	0.6	0.7
Range	13.0–29.0	3.3–4.2	1.9–2.9	0.6–0.6	0.7–0.7
Children					
n	4	5	5	4	4
Mean (SD)	19.6 (11.0)	5.2 (3.5)	4.0 (3.2)	1.2 (0.4)	1.6 (1.9)
Median	19.0	3.7	2.7	1.2	0.6
Range	8.4–31.8	2.4–10.9	1.9–9.6	0.9–1.6	0.6–4.4
Adolescents					
n	5*	5	6	6	6
Mean (SD)	22.8 (13.1)	12.0 (17.7)	1.8 (0.4)	1.9 (1.7)	1.1 (0.2)
Median	23.4	4.6	1.7	1.1	1.1
Range	6.8–41.7	1.9–43.5	1.5–2.5	0.7–5.2	0.7–1.4
Adults					
n	6	5	5	5	5
Mean (SD)	29.5 (8.4)	3.8 (1.1)	1.6 (0.3)	1.3 (0.3)	1.4 (0.4)
Median	28.5	4.2	1.7	1.2	1.4
Range	19.6–44.0	2.3–4.8	1.2–2.0	0.9–1.6	1.0–2.0

* One patient had missing TOF data for 0.9.

SD = standard deviation; TOF = train-of-four.

The times from start of administration of rocuronium until reappearance of T2 are summarized in table 4. The mean (SD) time from the start of rocuronium to reappearance of T2 was 29.0 (11.2) min in the small group of infants studied. In children, this time was shortest, 21.8 (5.6) min; it was 26.0 (5.7) min in adolescents, and 32.9 (9.2) min in adults.

Safety. At least one AE was reported in seven of eight infants (87.5%), 15 of 24 children (62.5%), 21 of 31 adolescents (67.7%), and 16 of 28 adults (57.1%), with vomiting and pain related to surgery the most frequently reported AEs (table 5). AEs that were considered possibly related to the study drug according to the investigators were reported in seven patients. These consisted of bradycardia (procedural complication in table 5) in one infant (placebo), vomiting in one child (2.0 mg/kg sugammadex), muscle spasms (0.5 mg/kg sugammadex), paresthesia (1.0 mg/kg sugammadex), hot flush and vomiting (both 2.0 mg/kg sugammadex) in four adolescents, and decreased appetite 2.0 mg/kg sugammadex) in one adult. No dose-response relationship was observed for the occurrence of AEs. At least one of severe intensity was reported in two children (urinary retention and dysuria on 4.0 mg/kg sugammadex and pain on 0.5 mg/kg sugammadex), one adolescent (hypoesthesia and procedural pain on placebo) and one adult (pain on placebo).

One SAE (3 days of postoperative vomiting) was reported in an infant who received 0.5 mg/kg sugammadex, and another SAE (diarrhea and hematuria with vesicle clots, fever, weight loss, and oliguria) was reported in one child who received 4.0 mg/kg sugammadex. The intensity of these SAEs was described as moderate, and both patients recovered; neither of the SAEs was considered by the investigators to be related to sugammadex. No SAEs in the adolescent and adult patients or any deaths occurred in the study.

An AE due to a markedly abnormal laboratory value was reported in one infant and in one adult. These were hypoglycemia (glucose 1.39 mmol/l [lower limit of safety range = 2.664 mmol/l]) in the infant within 60 min of 0.5 mg/kg sugammadex administration, lasting

Table 3. Estimated Dose Response Relation for Different Age Groups (per-protocol group)

		Estimated Time to Recovery of the TOF Ratio to 0.9, min*			
Age Group	n	a [SE(a)], min	b [SE(b)], min	c [SE(c)], kg bodyweight/mg	Percentage of Variation Explained by Model†
Children	22	1.1 [0.24]	17.3 [5.2]	–2.5 [0.81]	89
Adolescents	28	1.1 [0.10]	22.0 [5.8]	–3.5 [0.37]	96
Adults	26	1.3 [0.09]	27.9 [3.3]	–4.8 [0.40]	97

* $a + b.\exp(c.\text{dose})$. † Percentage of variation explained by model (see Statistical Analyses section for explanations).

SE = standard error; TOF = train-of-four.

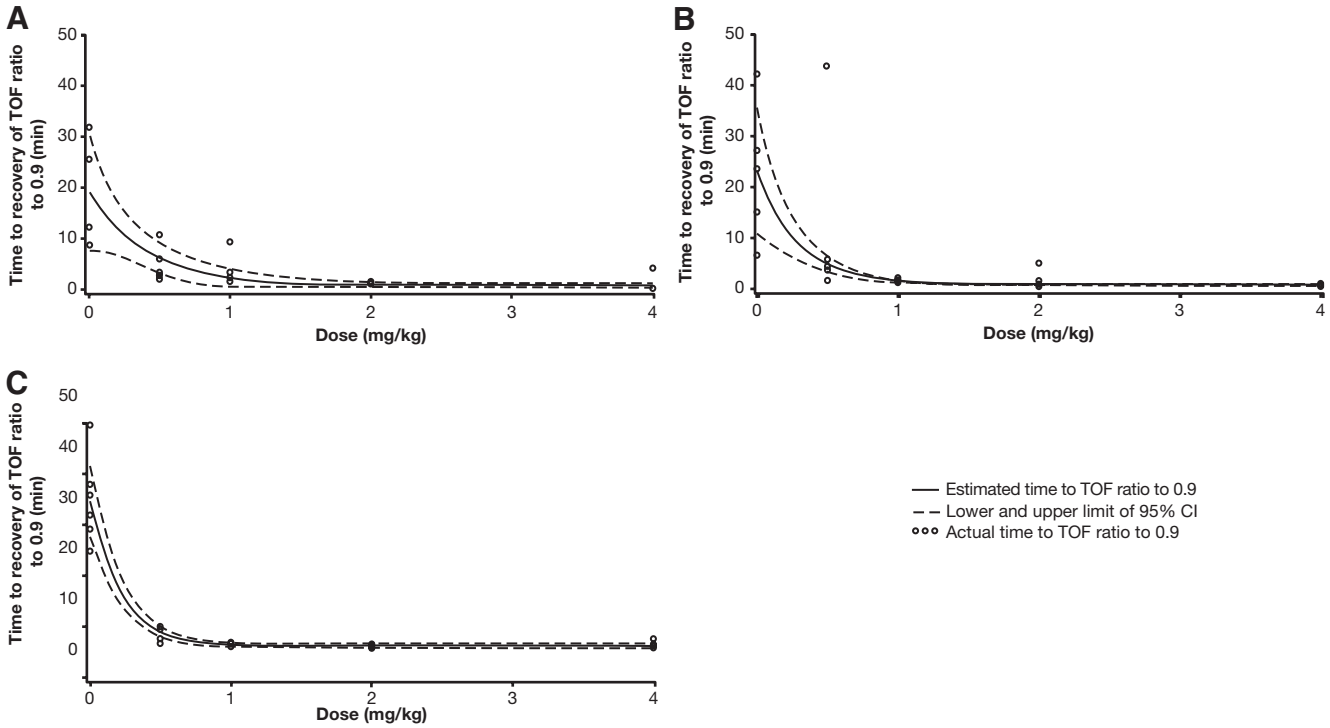

Fig. 1. Estimated dose-response relation between the time from the start of administration of sugammadex/placebo to recovery of the TOF ratio to 0.9 and the dose of sugammadex for (*A*) children (n = 22), (*B*) adolescents (n = 28), and (*C*) adults (n = 26) (per-protocol group). CI = confidence interval; TOF = train-of-four.

for approximately 18.5 h, and hyperglycemia (glucose level > 6.66 mmol/l, the upper limit of the safety range) in the adult subject 13 min after administration of 4.0 mg/kg sugammadex, lasting approximately 8 h. Both AEs were of moderate intensity and considered not likely to be related to sugammadex administration. Both patients recovered uneventfully. One child in the 4.0 mg/kg sugammadex group had an abnormal hemoglobin value (9.4 g/dl; safety range, 9.5–20.0 g/dl) on the morning of the first postoperative day, which was not considered an AE; however, the same patient developed anemia on the same evening, which was reported as an AE but not considered to be related to sugammadex administration.

Table 4. Summary of the Time (min) from Start of Administration of Rocuronium to Reappearance of T2 by Age Group (all-subjects-treated group)

	Time from Start of Administration of Rocuronium to Reappearance of T2, min
Infants	
n	8
Mean (SD)	29.0 (11.2)
Median	28.0
Range	13.1–42.7
Children	
n	24
Mean (SD)	21.8 (5.6)
Median	20.5
Range	13.2–34.7
Adolescents	
n	31
Mean (SD)	26.0 (5.7)
Median	25.3
Range	18.1–42.8
Adults	
n	28
Mean (SD)	32.9 (9.2)
Median	32.4
Range	18.3–52.6

SD = standard deviation; T2 = second twitch.

With the exception of one case of moderate bradycardia in an infant that was reported as an AE 2 min after placebo treatment and was considered possibly related to the placebo treatment, no other AEs relating to heart rate and blood pressure were reported. No clinically relevant differences were observed between the dose groups with respect to systolic and diastolic blood pressure and heart rate. No QTc prolongations were reported, and there was no indication of an association between QT/QTc prolongation and administration of sugammadex. There was no clinical evidence of any interaction between sugammadex and an endogenous or exogenous compound, other than rocuronium. None of the subjects experienced reoccurrence of blockade, either on neuromuscular monitoring or as determined by clinical signs.

Plasma Levels. Figures 2 and 3 show the median plasma concentration-time profiles for sugammadex and rocuronium, respectively, by age group and by dose after sugammadex administration. The median profiles indicate that, after sugammadex was dosed on body weight,

Table 5. Incidence (n) of the Most Common Adverse Events (at least 5% of patients) by Age Group and Dose Group, Regardless of Relationship to Study Drug (all-subjects-treated group)

		Sugammadex (mg/kg)				
	Placebo	0.5	1.0	2.0	4.0	Total
Infants, N	2	2	2	1	1	8
Vomiting, n	1	0	1	0	1	3
Diarrhea, n	0	0	0	1	0	1
Pyrexia, n	1	0	0	0	0	1
Viral gastroenteritis, n	0	1	0	0	0	1
Nasopharyngitis, n	0	0	0	1	0	1
Pharyngitis, n	0	0	0	0	1	1
Rhinitis, n	1	0	0	0	0	1
Procedural complication, n	1	0	0	0	0	1
Hypoglycemia, n	0	1	0	0	0	1
Children, N	4	6	5	5	4	24
Vomiting, n	2	3	2	1	3	11
Procedural pain, n	1	2	1	2	1	7
Constipation, n	0	1	1	0	0	2
Pain, n	0	2	0	0	0	2
Postoperative anemia, n	0	0	0	0	2	2
Adolescents, N	6	5	6	6	8	31
Procedural pain, n	3	1	3	3	4	14
Vomiting, n	3	0	1	3	2	9
Nausea, n	1	0	1	0	4	6
Adults, N	6	6	5	5	6	28
Procedural pain, n	1	1	2	1	1	6
Generalized pruritis, n	1	0	1	1	0	3
Constipation, n	1	0	0	0	1	2
Sleep disorder, n	0	0	2	0	0	2

N = total number of patients in each dose group; n = number of patients with adverse events.

similar levels of sugammadex in plasma were attained in the various age groups. The number of pharmacokinetic samples from infants was too small (n = 0, 1, or 2) to include in the median plasma concentration-time profiles.

The sampling time points for the plasma rocuronium concentrations after administration of sugammadex varied between patients; therefore, the median plots for the plasma rocuronium concentrations should be interpreted in relation to the pre-sugammadex concentration

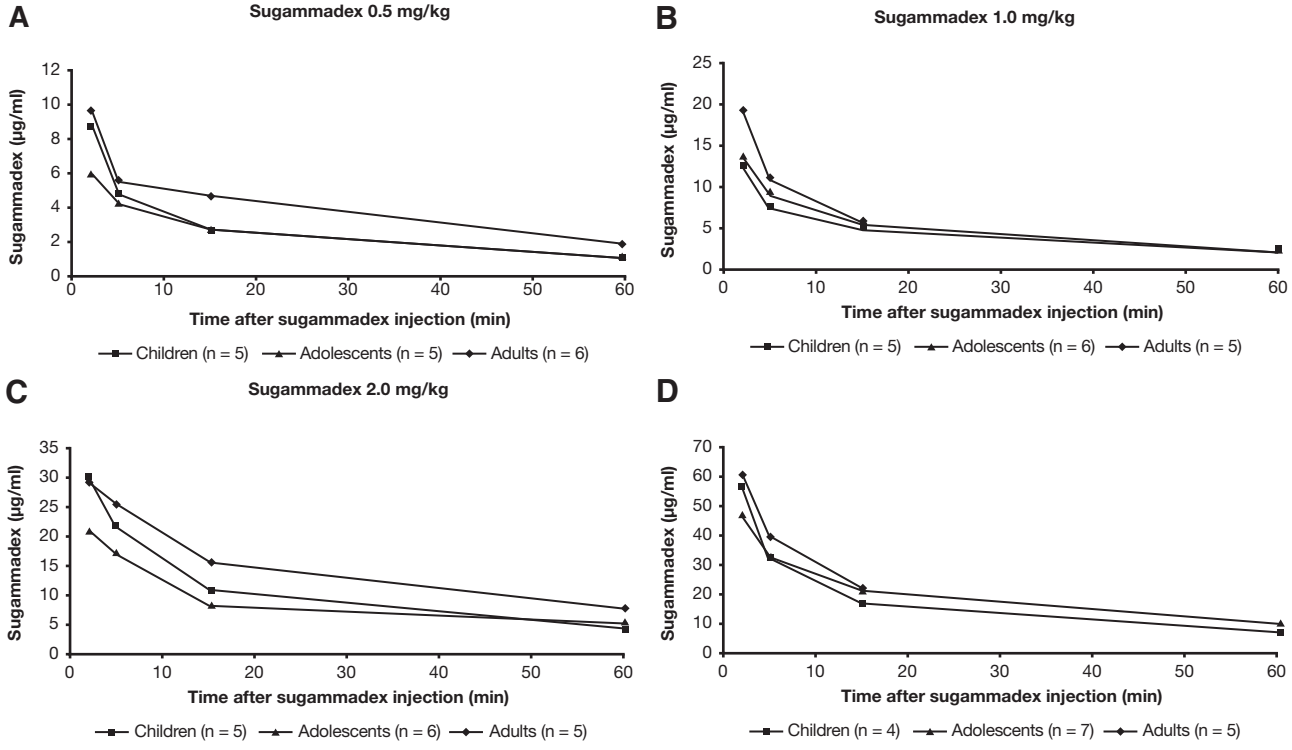

Fig. 2. Median plasma concentration-time profiles of sugammadex after administration of rocuronium (0.6 mg/kg) followed by (*A*) 0.5 mg/kg sugammadex, (*B*) 1.0 mg/kg sugammadex, (*C*) 2.0 mg/kg sugammadex, or (*D*) 4.0 sugammadex mg/kg, stratified by age group (all subjects pharmacokinetically evaluable group with a measurable reading at individual time points).

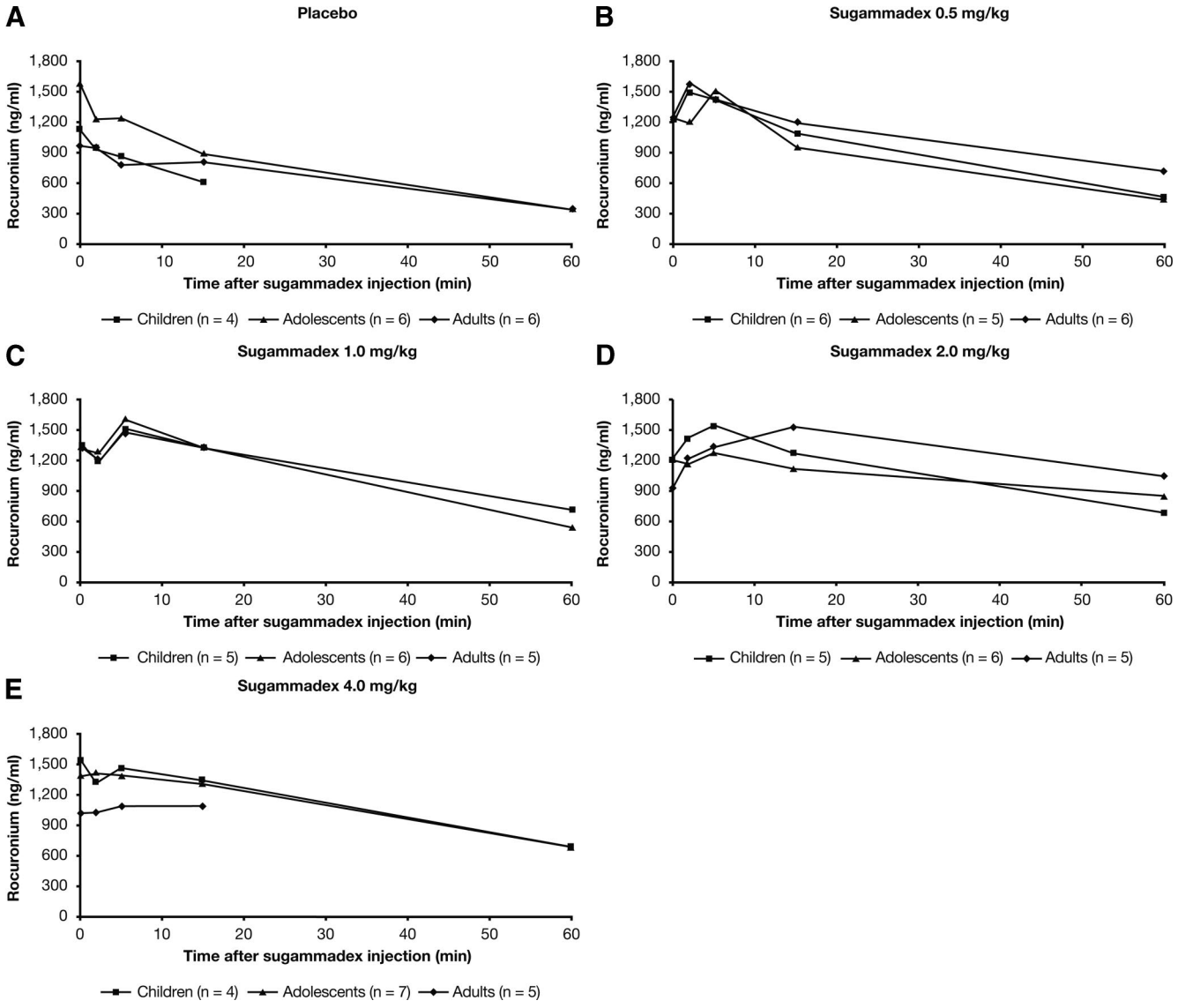

Fig. 3. Median plasma concentration-time profiles of rocuronium after administration of rocuronium (0.6 mg/kg) followed by (*A*) placebo or (*B*) 0.5 mg/kg sugammadex, (*C*) 1.0 mg/kg sugammadex, (*D*) 2.0 mg/kg sugammadex, or (*E*) 4.0 mg/kg sugammadex stratified by age group (all subjects pharmacokinetically evaluable group with a measurable reading at individual time points).

and not necessarily as absolute concentrations. In general, however, median plasma rocuronium concentrations increased temporarily after administration of sugammadex but not after placebo administration. Also, the median profiles for rocuronium indicate that after rocuronium and sugammadex were dosed on body weight, similar levels of rocuronium in plasma were attained in the children, adolescent, and adult age groups.

The sparse sampled data from the present study were added to a pooled pharmacokinetic-pharmacodynamic analysis with data from other trials for pharmacokinetic-pharmacodynamic evaluation.

Discussion

This multicenter, randomized, dose-finding study demonstrated a dose-response relationship in children, adolescents, and adults when sugammadex is administered at reappearance of T2 for the reversal of rocuronium-induced neuromuscular blockade. In the placebo group, spontaneous recovery of the TOF ratio to 0.9 occurred in a median time of 21.0, 19.0, 23.4, and 28.5 min in infants, children, adolescents, and adults, respectively. In contrast, the corresponding median times to recovery of the TOF ratio to 0.9 after sugammadex were markedly lower, ranging from 0.6–3.7 min (infants), 0.6–3.7 min (children), 1.1–4.6 min (adolescents), and 1.2–4.2 min (adults) in a dose-dependent manner (table 2). Because of the small sample size, median values have been presented to reduce the effect that possible outliers may have on mean values. Recovery times after doses of at least 2.0 mg/kg sugammadex seem comparable between children, adolescents, and adults. Doses of 2.0 mg/kg

sugammadex and above produced TOF ratios of 0.9 in a median time of less than 2 min.

As expected, the mean time taken to the reappearance of T2 from the start of administration of rocuronium was shorter in children and adolescents than in adults. No evidence of reoccurrence of blockade or inadequate reversal was observed in any patient.

The findings from the present study are consistent with those from two recent phase II studies.[10,11] Both studies showed a rapid and dose-dependent reduction in the mean time to recovery of the TOF ratio to 0.9 from approximately 4.0 to 1.1 min with sugammadex doses of 0.5–4.0 mg/kg, respectively, when administered at reappearance of T2 in adult patients with neuromuscular blockade induced by 0.6 mg/kg rocuronium.[10,11] The phase II dose-finding studies and the current study show that five doses are needed to achieve a good estimate of the exponential relationship between the recovery time and the dose of sugammadex (two measurements are needed on the first declining part, one close to the point of inflection and two on the plateau).

The time to achieve a TOF ratio of 0.9 was selected as the primary outcome measure in this study because normal muscle function, including normal pharyngeal function, is only present when the TOF ratio is 0.9 or greater. For this reason, a TOF ratio of at least 0.9 is now generally accepted as the endpoint of adequate recovery after administration of NMBA reversal agents.[22–24]

We used acceleromyography for monitoring of neuromuscular blockade in the present study as this has been used in the development program of sugammadex. While this may not be considered as gold standard, the use of this method of monitoring neuromuscular blockade is now widespread.[25] It has been the method of monitoring in other published studies on sugammadex.[10–16] While accepting that the values obtained with mechanomyography and acceleromyography may not be interchangeable, several workers have suggested that acceleromyography can be used with confidence for neuromuscular monitoring provided that a TOF ratio of 0.9 or more is used to denote adequate recovery.[26–28] Although some recent studies have suggested that a TOF ratio of 1.0 should be aimed for to denote adequate recovery using acceleromyography monitoring,[29] the general consensus is to attain a TOF ratio of 0.9 or more using this technique.[25,28,30] Finally, because the speed of the recovery curve from muscle relaxation with sugammadex is very rapid, the differences between the various techniques would be a matter of seconds rather than minutes. The TOF values obtained in this study were not related to baseline values; however, with good set up and consistent checking, the quality of the traces was confirmed. Recovery to TOF 0.9 was defined as three consecutive readings of a TOF value of at least 0.9, verifying the stability of the recovery. Two patients had somewhat longer recovery times: Times to TOF ratios of 0.9 of 4.4 min in a child receiving 4.0 mg/kg sugammadex and 5.2 min in an adolescent receiving 2.0 mg/kg sugammadex. The child recovered to a TOF ratio of 0.7 within 0.7 min and to a TOF ratio of 0.8 within 1.4 min. After this, the TOF ratio only gradually recovered to 0.9 and reached a plateau of 0.94. The adolescent recovered to a TOF ratio of 0.8 within 1.0 min but took another 4.2 min to recover to a TOF ratio of 0.9. Although these times appear longer in comparison with the median/mean value of the groups, these are still well within the times often observed when using neostigmine.

The present study is the first to evaluate the efficacy of sugammadex for the reversal of rocuronium-induced neuromuscular blockade in pediatric patients. The planned sample size of six patients per dose and age group in our study was not achieved in the infant group nor, to a lesser extent, in the children's group because the expiration date of the sugammadex supply necessitated early termination of the study. It is recognized that recruitment in pediatric studies is more difficult than in adult studies. Nevertheless, because of differences in the clinical pharmacology of muscle relaxants between adult and pediatric patients,[18] it is necessary to conduct clinical trials in the pediatric population.[31,32] Neonates were not included in this study because there are insufficient data on the use of rocuronium in this age group. As in other age groups, the median time to recovery of the TOF ratio to 0.9 in the infant group decreased markedly with increasing doses of sugammadex. However, no formal dose-response relation was achieved because of the very small number of patients (n = 1 or 2) in each dose group.

Measurements of plasma concentrations of sugammadex showed these to be similar in the children, adolescent, and adult age groups across the dose range of 0.5–4.0 mg/kg. The plasma concentration of rocuronium (complexed plus free rocuronium) was increased after administration of sugammadex, and this was not evident in the placebo group. This finding is consistent with data from animal studies[33] and previous studies in humans showing an increase in plasma rocuronium concentrations with increasing doses of sugammadex in healthy volunteers[34] and surgical patients.[10] Redistribution of rocuronium from the tissue to the plasma compartment to form complexes with sugammadex molecules has been proposed as the mechanism responsible for the increased total plasma concentration of rocuronium.[34] This movement of rocuronium from the tissue compartment ultimately results in removal of rocuronium from the neuromuscular junction where it exerts its effect. It also leads to the creation of a rocuronium diffusion gradient, facilitating the movement of further rocuronium molecules to form sugammadex-rocuronium complexes in the plasma. Because the available assay method does not differentiate between free and complexed forms of sugammadex and rocuronium in the plasma, the movement of rocuronium manifests as

an increase in total rocuronium plasma concentration. The presence of complexed rather than free rocuronium is demonstrated by the fact that this increase in total plasma rocuronium concentration is not accompanied by an increased degree of blockade but, rather, by a recovery from neuromuscular blockade.[33,34] A pharmacokinetic analysis was not feasible because sparse samples were drawn in this study for only up to about 1 h, whereas the reported half-life of sugammadex is approximately 100 min in adults.[34]

Sugammadex was well tolerated in all patient groups in our study. The sample sizes were not big enough to draw firm conclusions, but the safety information collected in this study adds to the profile of the compound established in previously published studies.[10–16] No clinically relevant differences were observed between the dose and age groups with respect to the incidence of AEs. Although a large number of AEs were recorded, these were not considered to be related to sugammadex administration but had to be recorded as part of early clinical studies with any new compound. There was also no evidence of an association between sugammadex and QT/QTc prolongation with the doses of sugammadex used in this study. Neither of the two reported SAEs were considered by the investigator or the sponsor to be related to sugammadex. Although sugammadex also appeared to be well tolerated by the infants, these findings should be interpreted with caution because of the small number of infants enrolled in the study.

Conclusions

Sugammadex is a new selective relaxant binding agent that rapidly and effectively reverses rocuronium-induced neuromuscular blockade in adult and pediatric patients with similar recovery times to TOF 0.9 when doses of at least 2.0 mg/kg sugammadex are administered at reappearance of T2. Sugammadex was well tolerated overall in the children, adolescents, and adults in this study. Additional pediatric studies, particularly in infants (< 2 yr), will be required to determine fully the efficacy and safety of sugammadex in this special population, particularly when more profound levels of neuromuscular blockade are present.

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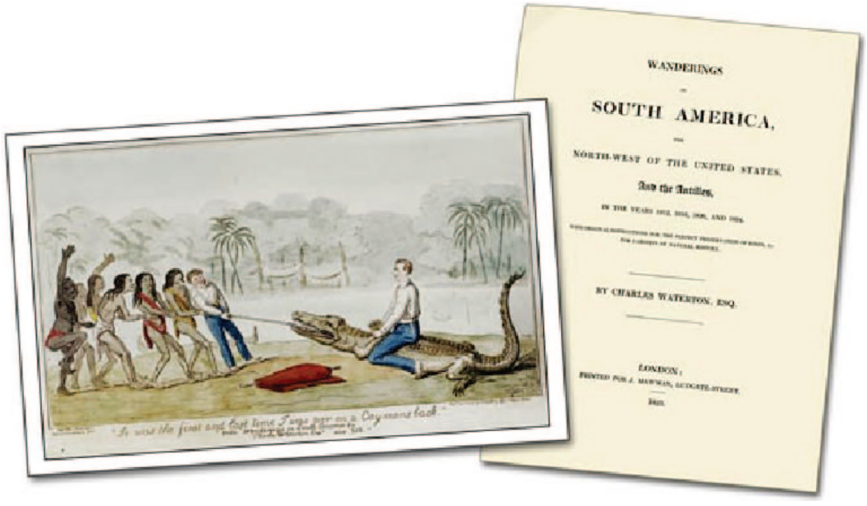
ANESTHESIOLOGY REFLECTIONS

Waterton Riding the Cayman



During his "first wandering" in South America, England's Charles Waterton, Esq. (1782–1865), searched in 1812 for "ourali" (curare) as a potential aid in capturing animal specimens intact for taxidermy. Eight years later, during his "third wandering," Waterton fished for a man-eating reptile with a wooden hook baited with rodent entrails as his South American guide, at day's end, drummed a tortoise carapace "as the cayman's dinner-bell." Determined "not to carry back a mutilated specimen," Waterton forsook bullets and arrows for a canoe mast, which the naturalist planned to "force …down the cayman's throat should he come open-mouthed." The next morning, as six companions began reeling in the hooked reptile, Waterton faced the cayman's "countenance of cruelty and malice" and "saw enough not to fall in love at first sight." Leaping on the reptile's back and twisting its forelegs back like a bridle, Waterton used skills acquired while hunting "with Lord Darlington's fox-hounds" to ride the cayman inland before dispatching and dissecting it with a knife. Years later, the Waterton Family's freed slave, John Edmonstone, would pass on the naturalist's taxidermy techniques to a disenchanted Edinburgh medical student named Charles Darwin. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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