Efficacy, Safety, and Pharmacokinetics of Sugammadex for the Reversal of Rocuronium-induced Neuromuscular Blockade in Elderly Patients

David L. McDonagh, M.D.,* Patrick E. Benedict, M.D.,† Anthony L. Kovac, M.D.,‡
David R. Drover, M.D.,§ Neil W. Brister, M.D., Ph.D.,‖ Jovino B. Morte, M.D.,# Terri G. Monk, M.D., M.S.**

ABSTRACT

Background: The management of elderly patients can be challenging for anesthesiologists for many reasons, including altered pharmacokinetics and dynamics. This study compared the efficacy, safety, and pharmacokinetics of sugammadex for moderate rocuronium-induced neuromuscular blockade reversal in adult (aged 18–64 yr) *versus* elderly adult (aged 65 yr or older) patients.

Methods: This phase 3a, multicenter, parallel-group, comparative, open-label study enrolled 162 patients aged 18 yr and older, American Society of Anesthesiologists class 1–3, scheduled for surgery with general anesthesia and requiring neuromuscular blockade. After anesthesia induction, patients received rocuronium, 0.6 mg/kg, before tracheal intubation, with maintenance doses of 0.15 mg/kg as required. At the end of surgery, patients received sugammadex, 2.0 mg/kg, at reappearance of the second twitch of the train-of-four (TOF) for reversal. The primary efficacy variable was time from sugammadex administration to recovery of the TOF ratio to 0.9 or greater. Pharmacokinetics and safety were also evaluated.

Results: Overall, 150 patients were treated and had at least one postbaseline efficacy assessment; 48 were aged 18–64 yr (adult), 62 were aged 65–74 yr (elderly), and 40 were aged 75 yr or older (old-elderly). The geometric mean time (95% confidence interval) from sugammadex administration to recovery of the TOF ratio to 0.9 increased with age, from 2.3 (2.0–2.6) min (adults) to 2.9 (2.7–3.2) min (elderly/old-elderly groups combined). Recovery of the TOF ratio to 0.9 was estimated to be 0.7 min faster in adults compared with patients aged 65 yr or older ($P = 0.022$). Sugammadex was well tolerated by all patients.

Conclusion: Sugammadex facilitates rapid reversal from moderate rocuronium-induced neuromuscular blockade in adults of all ages.

What We Already Know about This Topic

- The pharmacokinetics and pharmacodynamics of many drugs, including neuromuscular blocking and reversal agents, are altered in elderly persons, although sugammadex has not been studied in this regard

What This Article Tells Us That Is New

- Reversal of rocuronium neuromuscular blockade with sugammadex was rapid in elderly patients in doses similar to nonelderly adults, although it was slightly slower in the elderly patients

THE proportion of elderly people in the population is growing faster than any other age group, and the number of older patients requiring surgical procedures during general anesthesia is increasing. Approximately 50% of elderly patients will require anesthesia for a surgical intervention,[1] and increasing age may be associated with greater morbidity and mortality after anesthesia.[2,3] Indeed, using the Cox proportional hazards model, the risk of postoperative long-term mortality increases 1.42 times per decade of age.[3]

Several factors may contribute to this increased risk of postoperative morbidity and mortality in elderly persons. Aging results in physiologic changes within all organ systems, with changes to the cardiovascular, respiratory, and renal systems of particular importance to anesthesia. Physiologic aging is linked to a progressive decline in resting organ func-

* Assistant Professor of Anesthesiology and Medicine, Department of Anesthesiology, Duke University Medical Center and Durham Veterans Affairs Medical Center, Durham, North Carolina. † Assistant Professor of Anesthesiology, Department of Anesthesiology, University of Michigan Health System, Ann Arbor, Michigan. ‡ Professor of Anesthesiology, Department of Anesthesiology, University of Kansas Medical Center, Kansas City, Kansas. § Associate Professor, Stanford University Medical Center, Stanford, California. ‖ Professor, Department of Anesthesiology, Temple University Hospital, Philadelphia, Pennsylvania. # Senior Clinical Scientist, Merck, Summit, New Jersey. ** Professor, Department of Anesthesiology, Duke University Medical Center and Durham Veterans Affairs Medical Center.

Received from the Duke University and Durham Veterans Affairs Medical Centers, Durham, North Carolina. Submitted for publication November 21, 2009. Accepted for publication October 6, 2010. Supported by Merck, Summit, New Jersey. Dr. Morte is employed by Merck, Rahway, New Jersey. The design and conduct of the study, as well as analysis of the study data and opinions, conclusions, and interpretation of the data, were the responsibility of the authors. Presented at the American Society of Anesthesiologists 2007 Annual Meeting, San Francisco, California, October 13–17, 2007.

Address correspondence to Dr McDonagh: Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, North Carolina 27710. david.mcdonagh@duke.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

 Anesthesiology 2011; 114: 318–29

tion,[4] which can cause several challenges when dealing with older patients. Furthermore, aging is accompanied by an increased risk of chronic disease, which may further limit organ function and accelerate impairment of the reserve capacity of the affected organ.[4]

Drug disposition, metabolism, and excretion may be altered in elderly patients as the result of several factors, including altered pharmacokinetics and dynamics, changes in receptor sensitivity, and impairment of the body's normal homeostatic mechanisms.[1] For example, several neuromuscular blocking agents (NMBAs), including pancuronium, vecuronium, rocuronium, and doxacurium, all display an increased onset time in elderly patients, possibly as the result of a less dynamic circulation in elderly persons and, thus, an increased transfer time to the effector site.[5–7] Furthermore, rocuronium has an increased duration of action in elderly patients[7–9] as the result of decreased elimination of the drug,[7] which may be due to the decreased total body water and decreased liver mass that often accompany aging.

The selective relaxant binding agent sugammadex, a modified γ cyclodextrin, was designed specifically to encapsulate the steroidal NMBAs rocuronium and vecuronium to result in rapid reversal of neuromuscular blockade.[10–12] Clinical data have already demonstrated the efficacy and tolerability of sugammadex for the reversal of moderate[13–15] and deep neuromuscular blockade.[16–18] This study was designed to assess the impact of advanced age (65 yr or older) on the efficacy, safety, and pharmacokinetics of sugammadex for reversal from moderate rocuronium-induced neuromuscular blockade.

Materials and Methods

Study Design

This was a phase 3a, multicenter, parallel-group, comparative, open-label study (designated the Diamond study; NCT00474617) set up to compare the efficacy, pharmacokinetics, and safety of sugammadex in adult (aged 18–64 yr) *versus* elderly-adult (aged 65 yr or older) patients. The study was performed at 14 centers in the United States between October 2005 and September 2006 (appendix 1). The protocol was approved by the institutional review board of each study center and conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines, Good Clinical Practice, and current regulatory requirements.

Patients

Patients aged 18 yr and older, categorized as American Society of Anesthesiologists class 1–3, who were scheduled to undergo elective surgery in the supine position during general anesthesia and requiring neuromuscular relaxation were eligible for the study. The enrollment of patients was stratified according to three age groups: 18–64 yr (adult), 65–74 yr (elderly), and 75 yr and older (old-elderly). Patients were excluded from the study for the following reasons: they were expected to have a difficult intubation for anatomic reasons; they had a neuromuscular disorder, significant renal dysfunction (defined by a creatinine clearance of 30 ml/min or less), a personal or family history of malignant hyperthermia, or known allergy to narcotics, muscle relaxants, or other medication used during general anesthesia; or were receiving medication known to interfere with NMBAs, such as antibiotics and anticonvulsants. Female patients who were pregnant, breastfeeding, or of childbearing potential and not using an adequate method of contraception were also excluded; in female subjects of childbearing potential (*i.e.*, not at least 2 yr menopausal or not having undergone a hysterectomy or bilateral tubal ligation), pregnancy was excluded within 24 h before surgery (preferably on the day of surgery) by testing a urine sample with a human chorionic gonadotropin pregnancy test. All subjects were required to give written informed consent before enrollment into the study.

Study Procedures

An IV cannula was inserted into the vein of a hand, forearm, or arm. Through this IV line, anesthetic medications, rocuronium, and sugammadex were administered in a three-way stop cock. A second IV cannula was inserted into the opposite hand, forearm, or arm for blood sampling. Through this line, blood was drawn at predefined time points during anesthesia for pharmacokinetic and safety analysis.

Anesthesia was induced and maintained with IV induction agents, IV opioids, inhaled anesthetics, and other agent(s), according to each patient's clinical need. After the induction of anesthesia, but before the administration of rocuronium, monitoring neuromuscular function was initiated and performed continuously using a commercially available system (TOF-Watch® SX, version 1.6; Organon Ireland Ltd, a division of Merck and Co. Inc, Swords, Co. Dublin, Ireland) at the adductor pollicis muscle. Repetitive train-of-four (TOF) stimulation was applied every 15 s at the ulnar nerve until the end of anesthesia, at least until recovery of the TOF ratio to 0.9 after administration of sugammadex. Data were collated and processed using a program (TOF-Watch SX Monitoring Program; TOFMON Program, version 2.1). When difficulties were experienced in recording TOF traces (*e.g.*, when a stable baseline could not be established or when recordings were unstable because of patient movement), but the results were considered valid by the investigator, recordings were sent to a Central Independent Adjudication Committee (CIAC). The members of the CIAC were contracted external physicians (anesthesiologists) who were experts with ample experience in neuromuscular monitoring and the evaluation of acceleromyographic traces. The CIAC was not blinded to patient grouping but accepted or rejected the recordings according to prespecified standards and/or their expert opinion. If a difference in opinion between the inves-

tigator and the CIAC occurred, the judgment of the CIAC was used for statistical analysis.

Each patient received a single IV bolus dose of rocuronium, 0.6 mg/kg, administered for less than 10 s into a fast-running IV infusion, after which tracheal intubation was performed. Maintenance doses of rocuronium, 0.15 mg/kg, were permitted as required and administered at the reappearance of the second twitch in the TOF. On reappearance of the second twitch at the end of surgery, patients received a single IV bolus dose (administered for less than 10 s into a fast-running IV infusion) of sugammadex, 2.0 mg/kg, for reversal. Patients were not permitted to receive any muscle relaxant other than rocuronium, a second dose of sugammadex, or any other reversal agent during monitoring of neuromuscular function. If renewed muscular relaxation was required after administration of sugammadex, a nonaminosteroidal muscle relaxant could be administered if necessary.

Study End Points

Efficacy and Safety. The primary efficacy variable was time from the start of sugammadex administration to recovery of the TOF ratio to 0.9 for the intent-to-treat (ITT) group (*i.e.*, patients who were treated and had one or more postbaseline efficacy measurements).

Secondary efficacy variables included time from the start of sugammadex administration to recovery of the TOF ratio to 0.7 and 0.8 and clinical signs of recovery before transfer to and discharge from the recovery room. An exploratory efficacy analysis was also performed to compare time from the start of sugammadex administration to recovery of the TOF ratio to 0.9 in subjects who received only an intubating dose of rocuronium *versus* those who also received at least one maintenance dose of rocuronium.

Safety was assessed in the all subjects–treated group by incidence of adverse events (AEs), *serious AEs* (defined as any untoward medical occurrence that at any dose resulted in death, was life threatening, or required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; or was a congenital anomaly/birth defect), serious trial procedure– and medical device–related events, laboratory parameters, vital signs (heart rate and blood pressure), and physical examination results. Abnormal heart rates were defined as 50 beats/min or less or 120 beats/min or greater and a relative change of ±15 beats/min from baseline.

Pharmacokinetics. Plasma rocuronium and sugammadex concentrations for assessment of pharmacokinetics were evaluated from before the administration of rocuronium to the postanesthetic visit in patients from the all subjects–pharmacokinetically evaluable group (all subjects–treated group with one or more measurable plasma concentration and no protocol violations that may have interfered with pharmacokinetics).

Study Assessments

Each patient underwent a physical examination (including height and body weight measurements) at screening and at the postanesthetic visit (the day after surgery, at least 10 h after sugammadex administration). Similarly, vital signs (heart rate and blood pressure) were recorded at screening and at the postanesthetic visit. Vital signs were also recorded during stable anesthesia (after the intubation dose of rocuronium) and at 2, 5, 10, and 30 min after the administration of sugammadex; these vital signs were monitored continuously. Continuous cardiac monitoring was performed throughout anesthesia and postoperatively, in accordance with the routine practice of each trial site. Core body temperature was also measured continuously in the distal esophagus, tympanic membrane, or nasopharynx; and was maintained at 35°C or greater. Oxygen saturation, measured by pulse oximetry, and respiratory rate were monitored for at least 60 min after recovery of the TOF ratio to 0.9.

Blood samples for pharmacokinetic evaluation from a randomized subset of patients in each age group were taken before rocuronium administration; immediately before the administration of sugammadex (*i.e.*, at reappearance of the second twitch after the last dose of rocuronium); at 2, 5, 15, and 60 min, and 4–6 h after sugammadex administration; and at the postanesthetic visit. Patients were randomized for pharmacokinetic analysis on a 1:1 ratio (pharmacokinetic: nonpharmacokinetic group) within each center and age group using permuted-block randomization. These randomized pharmacokinetic subsets aimed to include approximately 20 subjects for the adult group, approximately 30 subjects for the elderly group, and approximately 20 subjects for the old-elderly group for the determination of rocuronium and sugammadex plasma concentrations. Plasma rocuronium and sugammadex concentrations were determined using liquid chromatographic assay methods with mass spectrometric detection following solid-phase extraction (performed by the Department of Clinical Pharmacology and Kinetics, MSD, Oss, The Netherlands).[19,20] These methods were validated according to US Food and Drug Administration guidelines on bioanalytical method validation. The methods do not discern between free and complexed sugammadex and rocuronium, and they provide an assessment of total sugammadex or rocuronium concentration only. Compartmental pharmacokinetic modeling was then used to analyze sugammadex plasma concentrations.

All pretreatment events, serious trial procedure– and medical device–related events, AEs, and serious AEs were assessed and recorded throughout the procedure; at the postanesthetic visit; and at follow-up 7 days after surgery, with all events coded using the Medical Dictionary for Regulatory Activities, version 9.1 (MedDRA Maintenance and Support Services Organization, Chantilly, VA). Blood samples were collected from each patient for laboratory safety analysis before the administration of rocuronium, 4–6 h after the ad-

ministration of sugammadex, and at the postanesthetic visit. Similarly, urine samples were collected for subsequent laboratory safety evaluation 24 h before surgery or on the day of surgery before leaving for the operating room and at the postanesthetic visit. Clinical signs of a possible interaction of sugammadex with endogenous or exogenous compounds other than rocuronium (*e.g.*, unusual or unexpected drug results and a greater or lesser than expected response to a given drug dose) were also recorded.

After the discontinuation of anesthesia, assessments of neuromuscular recovery were performed using clinical signs of recovery for the duration of each patient's stay in the recovery room to complement the results of objective neuromuscular monitoring. Subjects were assessed for level of consciousness and, if awake and cooperative, were evaluated by a 5-s head-lift test and a general muscle weakness check (scale, 1–9 [from extreme impairment to close to no impairment]).[18] Evidence for residual neuromuscular blockade or recurrence of neuromuscular blockade was gauged by clinical assessment, the evaluation of any respiratory problems, or a significant decrease in the TOF ratio to less than 0.8 in patients who were still under anesthesia.

Statistical Analysis

Times from the start of sugammadex administration to recovery of the TOF ratio to 0.9, 0.8, and 0.7 were analyzed using a two-way ANOVA model, with recovery time taken as the response variable and the trial site and age group as factors in the model. Recovery times for adult subjects were compared with those for patients aged 65 yr or older. A 95% confidence interval (CI) for the difference between recovery in adults and elderly patients was used to determine whether they were equivalent for the time from the start of sugammadex administration to recovery of the TOF ratio to 0.9. Equivalence was concluded in the event that the corresponding two-sided 95% CI for the difference between the two age groups lay entirely within the range from −1 to 1 min.

In accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline E-7,[21] 100 elderly patients (65 yr or older) were to be enrolled in the trial, together with 40 younger adults (aged 18–64 yr) to ensure that the trial had high enough power (greater than 90%) to show equivalence in recovery times between elderly and younger adult subjects (*i.e.*, SD of less than 1.6 min for recovery of the TOF ratio to 0.9 in both age groups).

Because the efficacy results were expected to follow a skewed distribution, geometric mean times to recovery were calculated in addition to arithmetic mean and median. Although the arithmetic mean is prone to sampling error (because extreme observations can have a significant impact on arithmetic mean), the geometric mean is robust against extreme observations arising from data with a skewed distribution and is, therefore, more relevant to the current study.[22]

In case of missing recovery times, imputed times (*i.e.*, with imputation of missing recovery times) were used for the efficacy analysis of the ITT group, with imputed data calculated by age group and the two elderly groups combined into a geriatric group for imputation. The imputation method was developed so as not to potentially bias the results in the direction of a more rapid sugammadex reversal; the details of a similar imputation method have been reported previously, per the sugammadex grouping, by Jones *et al.*[18] Briefly, if the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9 was missing for patient X but the time to a TOF ratio of 0.8 was available, the difference between times to recovery to TOF ratios of 0.8 and 0.9 was calculated for all patients with these data who were in the same age group as patient X. The 95th percentile of these differences was then added to the time to recovery of the TOF ratio to 0.8 for patient X to give the imputed value. Similarly, if, for patient X, the times from the start of administration of sugammadex to recovery of the TOF ratios to 0.8 and 0.9 were missing, but the time to the TOF ratio of 0.7 was available, then for all subjects in the same age group as patient X with times to recovery of the TOF ratios to 0.7 and 0.9 available, the difference in time between these two recovery times was determined; the 95th percentile of these differences was calculated and then added to the time to recovery of the TOF ratio to 0.7 to give the imputed recovery time. Finally, if patient X had missing or unreliable times to recovery of the TOF ratios to 0.9, 0.8, and 0.7, the 95th percentile of the time to recovery of the TOF ratio to 0.9 observed in all subjects in the same age group as patient X was used to give an imputed time for recovery to a TOF ratio of 0.9. Statistical analyses were performed using SAS® version 9.1.3 (SAS Institute, Cary, NC).

The median rocuronium plasma concentration by age group and time point was derived from the observed rocuronium plasma concentrations. Pharmacokinetic modeling was applied to the observed sugammadex plasma concentration values to obtain estimates of several pharmacokinetic parameters, such as clearance and central and steady-state volumes of distribution. Sugammadex plasma concentrations at the lower limit of quantification or less (0.1 μg/ml or less) in samples taken at least 10 h postdose were substituted with 0.5 × lower limit of quantification. Pharmacokinetic data were analyzed using software (SAS version 9.1.3, S-Plus version 6.2, Professional Edition; Insightful Corporation, Seattle, WA) and with the nonlinear mixed-effects modeling program (NONMEM version V level 1.1; GloboMax LLC, Hanover, MD) using population analysis techniques. All NONMEM analyses were performed using the first-order conditional estimation method with interaction. Model selection was based on the following: the comparison of full with reduced models was based on the log-likelihood criterion, in which the difference in the minimum value of the objective function between hierarchical models is asymptotically χ^2 distributed, with *df* equal to the difference in num-

Table 1. Summary of Baseline Characteristics (All Subjects–Treated Population)

Characteristics	Adult Subjects Aged 18–64 yr (n = 48)	Elderly Subjects Aged 65–74 yr (n = 62)	Old-Elderly Subjects Aged 75 yr or Older (n = 40)	Subtotal Aged 65 yr or Older (n = 102)	Total (N = 150)
Age, yr*	45.5 (11.3)	69.2 (2.5)	80.1 (4.1)	73.5 (6.2)	64.5 (15.4)
Weight, kg*	84.2 (20.0)	84.1 (15.9)	73.9 (18.3)	80.1 (17.5)	81.4 (18.4)
Height, cm*	171.0 (10.7)	171.8 (10.5)	167.6 (12.0)	170.1 (11.3)	170.4 (11.1)
Sex					
Female	29 (60.4)	27 (43.5)	24 (60.0)	51 (50.0)	80 (53.3)
Male	19 (39.6)	35 (56.5)	16 (40.0)	51 (50.0)	70 (46.7)
Race					
Black (of African heritage)	14 (29.2)	7 (11.3)	1 (2.5)	8 (7.8)	22 (14.7)
White/Caucasian	33 (68.8)	53 (85.5)	38 (95.0)	91 (89.2)	124 (82.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (2.5)	1 (1.0)	1 (0.7)
Other	1 (2.1)	2 (3.2)	0 (0.0)	2 (2.0)	3 (2.0)
ASA class					
1	8 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	8 (5.3)
2	32 (66.7)	34 (54.8)	16 (40.0)	50 (49.0)	82 (54.7)
3	8 (16.7)	28 (45.2)	24 (60.0)	52 (51.0)	60 (40.0)
Creatinine clearance, ml/min†					
No. of patients‡	47	61	40	101	148
Mean (SD)	94.3 (26.9)	72.1 (37.4)	50.7 (21.5)	63.6 (33.6)	73.4 (34.6)

Data are given as number (percentage) of each group unless otherwise indicated.

* Data are given as mean (SD). † Calculated using the Cockcroft–Gault equation. ‡ No values were calculated for one patient in the 18–64-yr group and for one patient in the 65–74-yr group because no preoperative (baseline) specimens were collected.

ASA = American Society of Anesthesiologists.

ber of parameters between models; decrease in unexplained variability (extension of a model by adding independent variables should usually be accompanied by a decrease in random variability); acceptable basic goodness-of-fit plots; and scientific plausibility of the model.

Relationships between the covariates of body weight, age, and creatinine clearance and pharmacokinetic parameters were explored and retained in the model if statistically justified. The covariates were tested for their significance by inclusion in the model based on the previously described criteria.

Results

Patients

A total of 162 patients were enrolled, of whom 150 were treated (all subjects–treated group), comprising 48 in the adult age group (aged 18–64 yr), 62 in the elderly group (aged 65–74 yr), and 40 in the old-elderly group (75 yr or older) (table 1). The adult age group contained more black patients and fewer white patients than the elderly/old-elderly age groups, and there were fewer female patients in the elderly age group. Not surprisingly, old-elderly patients weighed approximately 10 kg less than the other age groups and most were class 3 according to the American Society of Anesthesiologists classification.

All 150 treated patients had at least one postbaseline efficacy assessment (ITT population), and 149 of these completed the trial. The single patient from the ITT population who discontinued the trial refused a postanesthetic evaluation and withdrew consent. The per-protocol population (all subjects from the ITT group without any major protocol violation) comprised 117 patients.

Efficacy

With increasing age, the geometric mean time from administration of sugammadex to recovery of the TOF ratio to 0.9 increased from 2.3 min (adults) to 3.6 min (old-elderly) (table 2). Imputed data were used to calculate the primary efficacy variable for 13 patients (three adults, five elderly persons, and five old-elderly persons); seven of these patients did not reach a TOF ratio of 0.9, whereas six had times to TOF of 0.9 that were considered unreliable by the CIAC. The recovery times to TOF ratios of 0.9, 0.8, and 0.7 were unavailable in eight patients (all in the elderly and old-elderly groups), and a recovery time to a TOF ratio of 0.9 of 5.9 min was imputed for these patients based on the 95th percentile of the recovery time to a TOF ratio of 0.9 observed in all elderly/old-elderly subjects (fig. 1). For patients with available data to TOF 0.9 only, geometric mean recovery times to TOF 0.9 were similar to the imputed results, with recovery times of 2.1, 2.4, and 3.4 min for the adult, elderly, and old-elderly age groups, respectively. Median times were similar to geometric mean times, with adults recovering in a median of 2.2 min and the old-elderly recovering in 3.6 min.

Table 2. Time from the Start of Administration of Sugammadex to Recovery of the TOF Ratio to 0.9, 0.8, and 0.7 by Age Group (ITT Population)

Time Variables	Adult Subjects Aged 18–64 yr (n = 48)	Elderly Subjects Aged 65–74 yr (n = 62)	Old-Elderly Subjects Aged 75 yr or Older (n = 40)	Subtotal Aged 65 yr or Older (n = 102)
Time to recovery of the TOF ratio to 0.9 (imputed analysis), No. of subjects	48	62	40	102
Geometric mean (95% CI)	2.3 (2.0–2.6)	2.6 (2.3–2.9)	3.6 (3.1–4.1)	2.9 (2.7–3.2)
Mean (SD)	2.5 (1.4)	2.9 (1.6)	3.9 (1.7)	3.3 (1.7)
Median	2.2	2.6	3.6	2.9
Minimum–maximum	1.2–7.4	0.9–8.8	1.0–9.9	0.9–9.9
P value*				0.022
Time to recovery of the TOF ratio to 0.9 (excluding patients with imputed data), No. of subjects	45	57	35	92
Geometric mean (95% CI)	2.1 (1.9–2.4)	2.4 (2.1–2.7)	3.4 (2.9–3.9)	2.7 (2.5–3.0)
Mean (SD)	2.3 (1.0)	2.7 (1.4)	3.7 (1.6)	3.1 (1.6)
Median	2.1	2.5	3.5	2.8
Minimum–maximum	1.2–6.2	0.9–8.8	1.0–9.9	0.9–9.9
P value*				0.017
Time to recovery of the TOF ratio to 0.8 (imputed analysis), No. of patients	48	62	40	102
Geometric mean (95% CI)	1.9 (1.7–2.1)	2.1 (1.8–2.4)	2.8 (2.4–3.3)	2.3 (2.1–2.6)
Mean (SD)	2.1 (1.0)	2.4 (1.6)	3.1 (1.4)	2.7 (1.5)
Median	1.7	2.0	2.9	2.2
Minimum–maximum	1.1–6.2	0.7–8.8	0.8–6.2	0.7–8.8
P value*				0.035
Time to recovery of the TOF ratio to 0.7 (imputed analysis), No. of patients	48	62	40	102
Geometric mean (95% CI)	1.6 (1.5–1.8)	1.8 (1.6–2.0)	2.4 (2.1–2.8)	2.0 (1.8–2.2)
Mean (SD)	1.8 (0.8)	2.1 (1.5)	2.7 (1.2)	2.3 (1.4)
Median	1.6	1.7	2.4	1.9
Minimum–maximum	0.9–4.9	0.7–8.3	0.8–4.9	0.7–8.3
P value*				0.027

Time data are given in minutes.

* Comparison between the adult group (aged 18–64 yr) and the elderly/old-elderly group combined (65 yr or older).

CI = confidence interval; ITT = intention-to-treat; TOF = train-of-four.

Fewer patients aged 65 yr or older achieved a time to recovery of the TOF ratio to 0.9 within 4 min compared with adult patients (75.5% *vs.* 85.4%) (fig. 1), although this difference was nonsignificant ($P = 0.166$) and all patients recovered within 10 min (table 2). Overall, the recovery time of the TOF ratio to 0.9 was estimated to be 0.7 min faster in the adult group compared with patients aged 65 yr or older (two-sided 95% CI, 0.1–1.3; $P = 0.022$). Major protocol violations had no impact on recovery to a TOF of 0.9, with data comparable between the per-protocol and ITT groups. Furthermore, the results of the exploratory analysis demonstrated that the number of rocuronium doses administered had no impact on the efficacy of sugammadex, with patients who received a single intubating dose *versus* maintenance doses of rocuronium having comparable times to recovery of TOF to 0.9 (table 3).

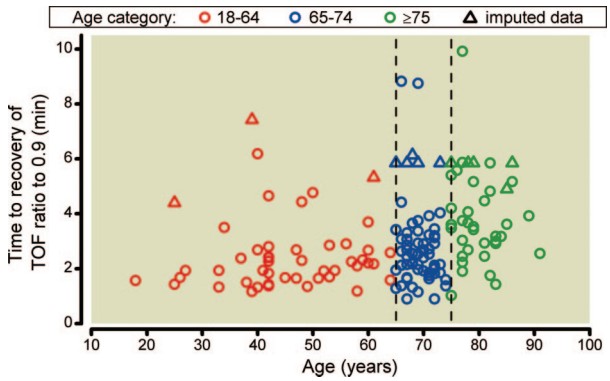

Fig. 1. Individual patient recovery times to a train-of-four (TOF) ratio of 0.9 (intent-to-treat [ITT] population; including imputed data shown with a triangle for 13 patients). Imputed data were calculated by age group, with the two elderly groups combined into a geriatric group for imputation.

As with recovery to TOF of 0.9, increasing age affected the recovery of the TOF ratios to 0.7 and 0.8 (table 2). In patients 65 yr or older, times to TOF ratios of 0.7 and 0.8 were both 0.5 min slower compared with adults (TOF 0.7: 95% CI, 0.1–1.0 [$P = 0.027$]; TOF 0.8: 95% CI, 0.0–1.1 [$P = 0.035$]).

Age had no impact on the clinical signs of recovery observed, with 93.5% of adult patients and 95.8% of patients 65 yr or older assessed as being awake and oriented before discharge from the recovery room. All subjects were cooper-

Table 3. Time from the Start of Administration of Sugammadex to Recovery of the TOF Ratio to 0.9 and T_1 at the Reappearance of T_2 after the Last Dose of Rocuronium*

Time Variables	Adult Patients Aged 18–64 yr (n = 48)	Elderly Patients Aged 65–74 yr (n = 62)	Old-Elderly Patients Aged 75 yr or Older (n = 40)	Subtotal Aged 65 yr or Older (n = 102)
Time to recovery of the TOF ratio to 0.9				
Intubating dose only, No. of patients	16	25	21	46
Geometric mean	2.3	2.5	3.4	2.8
Mean (SD)	2.6 (1.6)	2.7 (1.3)	3.8 (2.0)	3.2 (1.7)
Median	2.1	2.6	3.5	2.8
Minimum–maximum	1.2–7.4	0.9–6.1	1.0–9.9	0.9–9.9
Intubating plus maintenance doses, No. of patients	32	37	19	56
Geometric mean	2.3	2.7	3.9	3.0
Mean (SD)	2.5 (1.2)	3.0 (1.8)	4.1 (1.2)	3.4 (1.7)
Median	2.2	2.5	3.9	3.0
Minimum–maximum	1.2–6.2	0.9–8.8	1.8–5.9	0.9–8.8
T_1 at the time of reappearance of T_2 (%)				
Intubating dose only, No. of patients	16	25	21	46
Mean (SD)	17.3 (6.9)	14.4 (7.7)	13.1 (6.9)	13.8 (7.3)
Median	16.0	14.0	11.0	12.5
Minimum–maximum	7.0–34.0	4.0–29.0	3.0–30.0	3.0–30.0
Intubating plus maintenance doses, No. of patients	32	37	19	56
Mean (SD)	14.7 (7.4)	16.8 (7.9)	12.9 (6.3)	15.4 (7.5)
Median	13.5	16.0	12.0	14.0
Minimum–maximum	4.0–33.0	3.0–36.0	5.0–27.0	3.0–36.0

Time data are given in minutes.

* Data are presented by age group for subjects who received an intubating dose of rocuronium only (0.6 mg/kg) and those who also received at least one maintenance dose (0.15 mg/kg) (intent-to-treat population; imputed data).

T_1 = first twitch of the TOF; T_2 = second twitch of the TOF; TOF = train-of-four.

ative and able to perform the head-lift test, and none of the subjects required ventilation in the recovery room. One patient in the old-elderly group exhibited signs of mild muscle weakness; the patient was awake and responsive and had grade 7 muscle weakness before transfer to the recovery room (on a scale of 1–9: 1 indicates extreme impairment; and 9, close to no impairment) and grade 8 muscle weakness before discharge from the recovery room. Although the possibility of recurrence of neuromuscular blockade cannot be eliminated for this patient because neuromuscular monitoring had ceased, recurrence of blockade was considered highly unlikely based on further clinical assessment by the investigator. Furthermore, there was no evidence of recurrence of neuromuscular blockade in any of the other patients.

Safety

At least one AE was reported in all patients in each age group, the most common of which are listed in table 4. Two patients (both in the elderly age group) had AEs considered by the investigator to be possibly related to sugammadex (*i.e.*, tachycardia, pyrexia, dizziness, and oliguria in one patient and procedural hypotension in the other patient). Patients in

Table 4. Most Common Adverse Events Reported by Patients Regardless of Relationship to Study Drug

Adverse Event	Adult Patients Aged 18–64 yr (n = 48)	Elderly Patients Aged 65–74 yr (n = 62)	Old-Elderly Patients Aged 75 yr or Older (n = 40)	Overall Total for All Ages (N = 150)
Procedural pain	44 (91.7)	57 (91.9)	36 (90.0)	137 (91.3)
Nausea	13 (27.1)	16 (25.8)	15 (37.5)	44 (29.3)
Pyrexia	6 (12.5)	11 (17.7)	6 (15.0)	23 (15.3)
Vomiting	7 (14.6)	9 (14.5)	5 (12.5)	21 (14.0)
Constipation	3 (6.3)	7 (11.3)	8 (20.0)	18 (12.0)
Postprocedural nausea	9 (18.8)	6 (9.7)	3 (7.5)	18 (12.0)
Headache	8 (16.7)	3 (4.8)	7 (17.5)	18 (12.0)

Data are given as number (percentage) of patients in each group (all subjects–treated population).

the elderly age groups had more AEs reported for laboratory values than younger patients (occurring in 16.1% and 20% in the elderly and old-elderly age groups *vs.* 6.25% in the adult age group).

Serious AEs were reported in 16 subjects: four in the adult age group (representing 8.3% of the group), eight in the elderly age group (12.9%), and four in the old-elderly age group (10.0%). None of the serious AEs were considered related to sugammadex treatment. After these serious AEs, three subjects needed further surgery, requiring neuromuscular relaxation. Two were in the elderly age group (one required an exploratory laparotomy 2 days after the initial surgery because of a marked decrease in hematocrit and the development of tachycardia and oliguria, and one required emergency intubation 9 h after surgery after experiencing acute respiratory distress as the result of edema of the neck, induced by malposition of the central line catheter) and one was in the old-elderly age group (a patient diagnosed as having a perforated colon 3 days after initial surgery, who required surgery for colonic anastomosis repair and double-barrel colostomy). In accordance with the study protocol for renewal of neuromuscular blockade, these patients received a nonaminosteroidal NMBA (succinylcholine) for relaxation. No serious procedure- or medical device–related events were reported, and no patient died or discontinued treatment because of an AE.

Three patients had abnormal heart rate values 10 min after sugammadex administration. Two patients (one each in the adult and old-elderly groups) experienced a reduction in heart rate from 72 or 75 beats/min, respectively, at baseline to 50 beats/min; and a third patient (adult group) experienced an increase in heart rate from 84 beats/min at baseline to 122 beats/min.

Pharmacokinetics

In total, 75 patients were evaluated in the pharmacokinetic analysis: 24 in the adult group, 32 in the elderly group, and 19 in the old-elderly group. The rocuronium plasma concentrations (individual observations and median) are presented by age group in figure 2. All three patient groups displayed a slight increase in total (*i.e.*, bound and unbound) plasma rocuronium concentrations after the administration of sugammadex, with the maximal increase in rocuronium concentrations being reached 5–15 min after sugammadex administration (insets to fig. 2 show data for the first hour).

Sugammadex plasma concentration–time data were best characterized by a three-compartment model with zero-order input and first-order elimination from the central compartment with (log–normally distributed) interindividual variability on clearance, central volume of distribution, first peripheral volume of distribution, intercompartmental clearance, and apparent infusion time and a combined proportional and additive residual error model. Covariate analysis to identify components of the model showed that

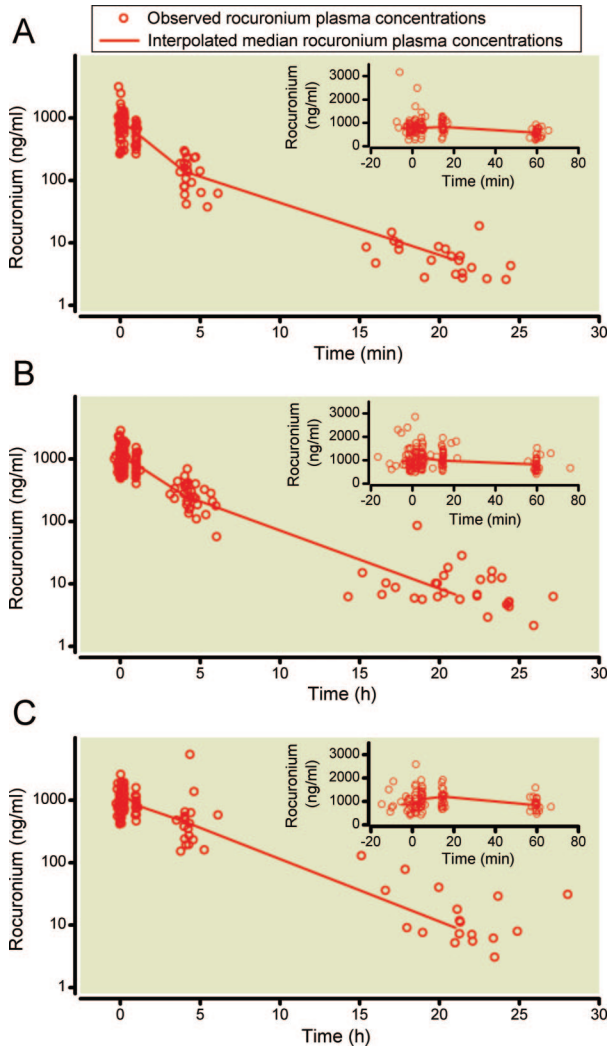

Fig. 2. Observed and median rocuronium plasma concentrations plotted on a logarithmic scale: (*A*) adult group, (*B*) elderly group, and (*C*) old-elderly group. Time 0 represents the time of sugammadex administration. Inset plots show data from the first hour after sugammadex administration on a linear scale.

increasing age and decreasing creatinine clearance were associated with decreased sugammadex clearance, whereas increasing body weight was associated with an increase in the central volume of distribution of sugammadex (table 5).

Median values of age, body weight, and creatinine clearance per age group (all subjects–pharmacokinetically evaluable group) were then used in the final model to calculate several pharmacokinetic parameters (clearance, central volume of distribution, steady-state volume of distribution, and effective half-life) for a typical subject in each age group (table 6). For a typical old-elderly patient, sugammadex clearance was decreased by half compared with an adult patient (0.052 *vs.* 0.103 l/min) and by approximately one-third compared with an elderly patient (0.052 *vs.* 0.076 l/min). For a typical patient in each age group, sugammadex concen-

Table 5. Summary of Parameter Estimates of the Final Pharmacokinetic Model for Sugammadex

Parameter	Units	Population Estimate	CV (%)	IIV (%)
CL	l/min	0.081	3.1	27.3
		−0.0010 × (age [yr] – 65.4)	21.8	
		+0.00038 × (CLcr [ml/min] – 88.8)	32.1	
V_C	l	4.29	4.5	28.2
		+0.030 × (Weight [kg] – 81.8)	32.7	
V_2	l	9.07	4.2	21.0
Q_2	l/min	0.27	6.3	31.3
V_3	l	7.56	29.4	
Q_3	l/min	0.0088	8.2	
D_1	min	3.47	23.8	64.3
Residual Error				
σ_1 (proportional)		0.049	22.1	
σ_2 (additive)		0.00031		0.018*

CL = clearance; CLcr = creatinine clearance; CV = coefficient of variation (100 × standard error/population estimate); D1 = apparent infusion time; IIV (ω^2) = interindividual variability expressed as a variance; Q_2 = intercompartmental clearance between central and first peripheral compartments; Q_3 = intercompartmental clearance between central and second peripheral compartments; SD = standard deviation; V_C = central volume of distribution; V_2 = first peripheral volume of distribution; V_3 = second peripheral volume of distribution. The CV of the proportional part of the residual error is $100 \cdot \sqrt{\sigma_1}$, and the SD of the additional part of the residual error is $\sqrt{\sigma_2}$ μg/mL.
* For the additive residual error, the last column is SD.

trations over time were simulated with the final model. As would be expected in patients with reduced sugammadex clearance, plasma concentrations exhibited a slower decline for older patients. The simulated sugammadex concentrations generated by the model for a typical subject within each group were consistent with the observed sugammadex plasma concentrations (fig. 3).

The lower sugammadex clearance in the typical old-elderly patient resulted in the effective half-life being almost double compared with the typical adult patient (4.6 *vs.* 2.4 h) and increased by nearly half compared with the typical elderly patient (4.6 *vs.* 3.2 h). No clinically significant age-related differences in sugammadex volume of distribution (defined as changes of more than 10%) were determined (table 6).

Discussion

To our knowledge, this was the first study to assess the efficacy, safety, and pharmacokinetics of sugammadex, 2.0 mg/kg, for the reversal of moderate rocuronium-induced neuromuscular blockade specifically in elderly patients.

The time from administration of sugammadex to recovery of the TOF ratio to 0.9 was within a geometric mean time of 4 min in all three age groups but was significantly faster in the adult group (2.3 min) compared with the elderly/old-elderly groups combined (2.9 min). These differences in time to recovery to TOF 0.9 were supported by the 95% CI data, which were not between −1 and 1 min, indicating that the groups were not clinically equivalent. A similar pattern was observed for recovery to TOF 0.7 and 0.8. One possible explanation for this slower recovery in elderly/old-elderly patients compared with adult patients may be a less dynamic circulation in older patients, which would result in a slower distribution of sugammadex. Elderly patients may also experience an altered perfusion within the muscles, thus changing the distribution and redistribution rates of rocuronium, sugammadex, and the rocuronium-sugammadex complex. Indeed, in elderly patients, the onset of rocuronium[7] and other NMBAs[6] is significantly slower and the duration of action is

Table 6. Baseline Characteristics and Sugammadex Pharmacokinetics in Three Typical Patients, One from Each Age Group

Patient Characteristics				Sugammadex Pharmacokinetics			
Age Group, yr	Age, yr	Weight, kg	CL_{cr}, l/min	CL, l/min	V_c, l	V_{ss}, l	$t_{1/2\_eff}$, h
18–64	49	84.0	0.104	0.103	4.36	21.0	2.4
65–74	68	86.1	0.085	0.076	4.42	21.0	3.2
75 or older	81	71.5	0.059	0.052	3.98	20.6	4.6

CL = clearance; CL_{cr} = creatinine clearance; $t_{1/2\_eff}$ = effective half-life; V_c = central volume of distribution; V_{ss} = steady-state volume of distribution.

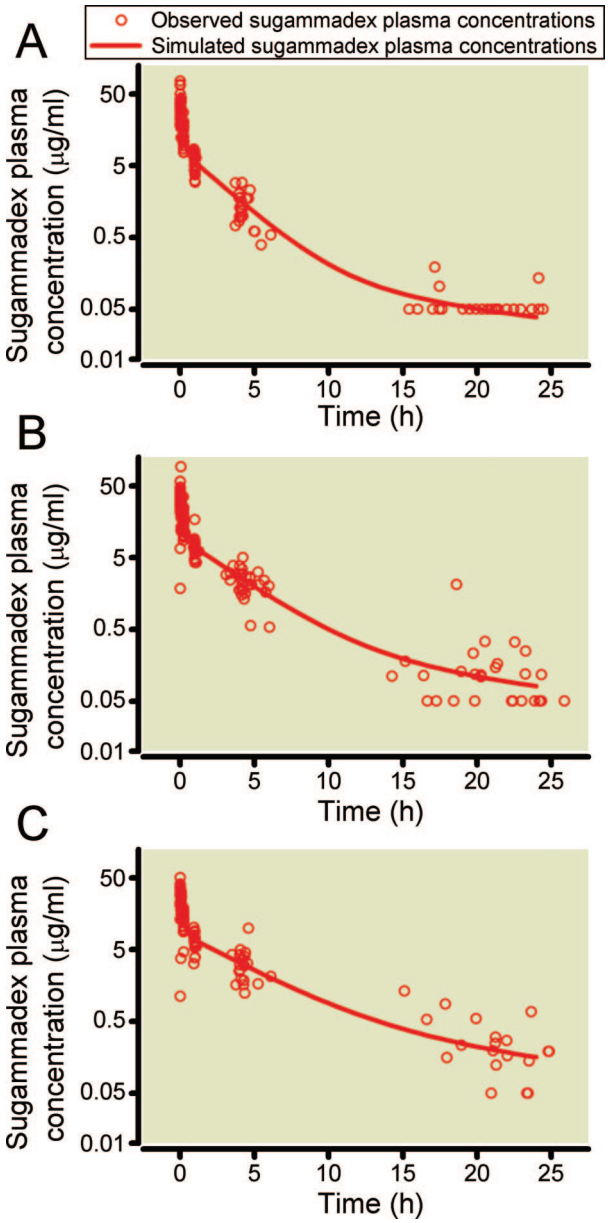

Fig. 3. Observed sugammadex plasma concentrations and simulated sugammadex plasma concentration for a typical subject plotted on a logarithmic scale: (*A*) adult group, (*B*) elderly group, and (*C*) old-elderly group. Time 0 represents the time of sugammadex administration. Lower limit of quantification (LLOQ) values of less than 0.1 were plotted as follows: 0.05 (1/2 × LLOQ).

prolonged compared with younger individuals; this potentially reflects a reduced blood flow to the muscles in elderly patients[23] or an increased volume of distribution, although the latter has not been reported for either rocuronium[7] or for other NMBAs.[6]

An alternative phenomenon, perhaps occurring simultaneously with altered blood flow, would be possible changes in receptor biologic features (*e.g.*, ligand affinity and kinetics), potentially resulting in a slower release of the NMBA from the receptor, delayed recovery of the receptor, or possibly altered receptor expression at the neuromuscular junction.[24,25] Further research is required in this area, but it may be that a combination of factors ultimately contributes to the somewhat slower recovery to a TOF ratio of 0.9 seen in elderly patients compared with younger adults.

Despite the slower recovery noted in the elderly/old-elderly patients, the results obtained for recovery to a TOF ratio of 0.9 were still rapid in relation to recovery times reported for other reversal agents administered to patients aged 18 yr and older at a comparable time point and depth of blockade: a previous study[26] comparing sugammadex, 2.0 mg/kg, with neostigmine, 50 μg/kg, administered at reappearance of the second twitch for reversal of moderate rocuronium-induced neuromuscular blockade reported a geometric mean recovery time to a TOF ratio of 0.9 of 18.6 min with neostigmine (1.5 min with sugammadex). A similar difference in recovery time between neostigmine and sugammadex may be anticipated in elderly patients, particularly because neostigmine has been shown to be less potent for the reversal of moderate vecuronium-induced neuromuscular blockade in patients older than 70 yr compared with younger adult patients (aged 18–50 yr).[27]

Although a correlation between advancing age and an increase in the proportion of patients with a higher American Society of Anesthesiologists class exists, no dose adjustment of sugammadex is required for either geriatric patients or patients with a higher American Society of Anesthesiologists class. The recovery times to TOF 0.9 reported in this study for the adult, elderly, and old-elderly age groups are consistent with those recorded previously using sugammadex, 2.0 mg/kg, after rocuronium, 0.6 mg/kg, in adult patients aged 18 yr and older.[13,14,16,28] In addition, despite differences between the groups for TOF recovery time, there were no differences for clinical recovery, with only one patient (from the old-elderly group) displaying mild muscle weakness before discharge from the recovery room. Based on further clinical tests, the muscle weakness was not considered related to residual neuromuscular blockade. However, it should be noted that clinical assessment of postoperative residual neuromuscular blockade is of limited sensitivity and should be used in conjunction with quantitative neuromuscular monitoring when available.[29]

Pharmacokinetic analysis showed a brief increase in total plasma rocuronium shortly after administration of sugammadex. This phenomenon has been reported previously and is because of the redistribution of free rocuronium from the peripheral compartments to the plasma once rocuronium in the plasma has been encapsulated.[13,17,30] The onset of this increase seems to be slower in the old-elderly age group compared with the adult group and may be related to changes in dynamic circulation associated with aging, resulting in a slower onset of sugammadex or possible alterations in receptor biologic features that slow the release of rocuronium from the receptor.

The slower sugammadex clearance seen in the elderly and old-elderly groups is unsurprising, particularly because these patients are more likely to have other comorbidities, such as impaired renal function. Previous studies[17,30] have demonstrated that the rocuronium–sugammadex complex is excreted predominantly *via* the kidneys. In the current study, the decrease in kidney function with increasing age, indicated by reduced creatinine clearance (table 1), would explain the slower clearance of sugammadex in elderly and old-elderly patients relative to adult patients. There were no differences determined between the age groups for sugammadex volume of distribution, as demonstrated by the values derived for a typical patient in each age group.

In patients with slower clearance of the rocuronium–sugammadex complex, there may be a concern for recurrence of neuromuscular blockade as the result of a longer retention of the agents involved, although the available data suggest that the complex will remain stable over time.[10] While recurrence of neuromuscular blockade may occur without disassociation of the sugammadex–rocuronium complex, this likely results from the redistribution of unbound rocuronium from peripheral to central and effect compartments. This may occur if sugammadex is underdosed; however, provided that the recommended dose of sugammadex is used for the relevant depth of neuromuscular blockade, the risk of recurrence of neuromuscular blockade is very low. In both the current study and in a study[31] of patients with impaired kidney function (and, thus, impaired clearance), reversal was rapid and effective, with no patients displaying evidence of recurrence of neuromuscular blockade.

Overall, sugammadex was well tolerated by all age groups, and the AE profile was consistent with previous studies[13–17,27,32–35] that have demonstrated the safety and tolerability of sugammadex at a range of doses up to 16.0 mg/kg.

In conclusion, sugammadex, 2.0 mg/kg, facilitated rapid recovery from moderate rocuronium-induced neuromuscular blockade in all age groups. Although older patients tended to recover more slowly than younger patients, those in the old-elderly group still recovered to a TOF ratio of 0.9 within a geometric mean time of 3.6 min from sugammadex administration. Sugammadex was well tolerated in adult patients of all ages during this study, including those in the old-elderly age group.

The authors thank the following investigators and colleagues for their help in the enrollment of patients: Tod Sloan, M.D., M.B.A., Ph.D. (Professor of Anesthesia, University of Colorado Health Sciences Center, Denver, CO); Nikolaus Gravenstein, M.D. (Professor of Anesthesiology, University of Florida, J. Hills Miller Health Center, Gainesville, FL); Salwa A. Shenaq, M.D. (Chief of Anesthesiology, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX); Laura Clark, M.D. (Director of Acute Pain and Regional Anesthesia, University of Louisville, Louisville, KY); Mohamed Naguib, M.D. (Professor, University of Texas, Houston, TX); R. Kevin Jones, M.D. (Attending Anesthesiologist, Saddleback Memorial Medical Center, Laguna Hills, CA; and Chief Executive Officer, Accurate Clinical Trials, Inc., Laguna Hills, CA); John Wills, M.B.B.S., F.A.N.Z.C.A., M.B.A. (Professor and Chair, University of New Mexico Health Sciences Centre, Albuquerque, NM); Harold Sydney Minkowitz, M.D. (Anesthesiologist, Memorial Hermann Memorial City Medical Center, Houston, TX); Mark Edward Hudson, M.D. (Associate Professor, University of Pittsburgh Medical Center-Shadyside Hospital, Pittsburgh, PA); Martin Angst, M.D. (Associate Professor of Anesthesia, Stanford University, Stanford, CA); Matthew McDaniel, M.D. (Resident Physician, Duke University Medical Center, Durham, NC); Dilipkumar Patel, M.D. (Associate Professor, Temple University Hospital, Philadelphia, PA). The statistical analysis of the study data was conducted by Mary C. Liu, Ph.D. (Statistician, Merck, Summit, NJ). The pharmacokinetic analysis was conducted by Marita Prohn, M.Sc. (Pharmacokineticist, MSD, Oss, The Netherlands). Medical writing assistance was provided by Neil Venn, Ph.D. (Medical Writer, Prime Medica, Knutsford, Cheshire, United Kingdom), during the preparation of the manuscript, supported by Merck (Kenilworth, NJ).

References

1. Sear JW: Implication of aging on anesthetic drugs. Curr Opin Anaesthesiol 2003; 16:373–8
2. Manku K, Leung JM: Prognostic significance of postoperative in-hospital complications in elderly patients, II: Long-term quality of life. Anesth Analg 2003; 96:590–4
3. Manku K, Bacchetti P, Leung JM: Prognostic significance of postoperative in-hospital complications in elderly patients, I: Long-term survival. Anesth Analg 2003; 96:583–9
4. Priebe HJ: The aged cardiovascular risk patient. Br J Anaesth 2000; 85:763–78
5. Moore EW, Hunter JM: The new neuromuscular blocking agents: Do they offer any advantages? Br J Anaesth 2001; 87:912–25
6. Gariepy LP, Varin F, Donati F, Salib Y, Bevan DR: Influence of aging on the pharmacokinetics and pharmacodynamics of doxacurium. Clin Pharmacol Ther 1993; 53:340–7
7. Matteo RS, Ornstein E, Schwartz AE, Ostapkovich N, Stone JG: Pharmacokinetics and pharmacodynamics of rocuronium (Org 9426) in elderly surgical patients. Anesth Analg 1993; 77:1193–7
8. Bevan DR, Fiset P, Balendran P, Law-Min JC, Ratcliffe A, Donati F: Pharmacodynamic behavior of rocuronium in the elderly. Can J Anaesth 1993; 40:127–32
9. Motamed C, Donati F: Intubating conditions and blockade after mivacurium, rocuronium and their combination in young and elderly patients. Can J Anesth 2000; 47:225–31
10. Bom A, Bradley M, Cameron K, Clark JK, van Egmond J, Feilden H, MacLean EJ, Muir AW, Palin R, Rees DC, Zhang M-Q: A novel concept of reversing neuromuscular block: Chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. Angew Chem Int Ed Engl 2002; 41:266–70
11. Epemolu O, Bom A, Hope F, Mason RL: Reversal of neuromuscular blockade and simultaneous increase in plasma rocuronium concentration after the intravenous infusion of the novel reversal agent Org 25969. ANESTHESIOLOGY 2003; 99:632–7
12. de Boer HD, van Egmond J, van de Pol F, Booij A, Boij LHDJ: Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized rhesus monkeys. ANESTHESIOLOGY 2006; 104:718–23
13. Sorgenfrei IF, Norrild K, Larsen PB, Stensballe J, Ostergaard D, Prins ME, Viby-Mogensen J: Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: A dose-finding and safety study. ANESTHESIOLOGY 2006; 104:667–74
14. Shields M, Giovanelli M, Mirakhur RK, Moppett I, Adams J, Hermens Y: Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block. Br J Anaesth 2006; 96:36–43

15. Suy K, Morias K, Cammu G, Hans P, van Duijnhoven WG, Heeringa M, Demeyer I: Sugammadex, a selective relaxant binding agent, offers effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block. ANESTHESIOLOGY 2007; 106:283–8
16. Groudine SB, Soto R, Lien C, Drover D, Roberts K: A randomized, dose-finding, phase II study of the selective relaxant binding drug, sugammadex, capable of safely reversing profound rocuronium-induced neuromuscular block. Anesth Analg 2007; 104:555–62
17. Sparr HJ, Vermeyen KM, Beaufort AM, Rietbergen H, Proost JH, Saldien V, Velik-Salchner C, Wierda JM: Early reversal of profound rocuronium-induced neuromuscular block by sugammadex in a randomized multicenter study: Efficacy, safety, and pharmacokinetics. ANESTHESIOLOGY 2007; 106:935–43
18. Jones RK, Caldwell JE, Brull SJ, Soto RG: Reversal of profound rocuronium-induced blockade with sugammadex: A randomized comparison with neostigmine. ANESTHESIOLOGY 2008; 109:816–24
19. Staals LM, Snoeck MM, Driessen JJ, van Hamersvelt HW, Flockton EA, van den Heuvel MW, Hunter JM: Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: A pharmacokinetic study. Br J Anaesth 2010; 104:31–9
20. Plaud B, Meretoja O, Hofmockel R, Raft J, Stoddart PA, van Kuijk JH, Hermens Y, Mirakhur RK: Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients. ANESTHESIOLOGY 2009; 110: 284–94
21. FDA Guideline for Industry: Studies in Support of Special Populations: Geriatrics. ICH-E7 August 1994. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073131.pdf.
22. Bland JM, Altman DG: Transformations, means, and confidence intervals. BMJ 1996; 312:1079
23. Dinenno FA, Jones PP, Seals DR, Tanaka H: Limb blood flow and vascular conductance are reduced with age in healthy humans: Relation to elevations in sympathetic nerve activity and declines in oxygen demand. Circulation 1999; 100:164–70
24. Balice-Gordon RJ: Age-related changes in neuromuscular innervation. Muscle Nerve Suppl 1997; 5:S83–7
25. McMullen CA, Andrade FH: Functional and morphological evidence of age-related denervation in rat laryngeal muscles. J Gerontol A Biol Sci Med Sci 2009; 64:435–42
26. Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, Prins ME: Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: Results of a randomized, controlled trial. Eur J Anaesthesiol 2010; 27:874–81
27. McCarthy GJ, Cooper R, Stanley JC, Mirakhur RK: Dose-response relationships for neostigmine antagonism of vecuronium-induced neuromuscular block in adults and the elderly. Br J Anaesth 1992; 69:281–3
28. Vanacker BF, Vermeyen KM, Struys MMRF, Rietbergen H, Vandermeersch E, Saldien V, Kalmar AF, Prins ME: Reversal of rocuronium-induced neuromuscular block with the novel drug sugammadex is equally effective under maintenance anesthesia with propofol or sevoflurane. Anesth Analg 2007; 104:563–8
29. Plaud B, Debaene B, Donati F, Marty J: Residual paralysis after emergence from anesthesia. ANESTHESIOLOGY 2010; 112: 1013–22
30. Gijsenbergh F, Ramael S, Houwing N, van Iersel T: First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. ANESTHESIOLOGY 2005; 103: 695–703
31. Staals LM, Snoeck MM, Driessen JJ, Flockton EA, Heeringa M, Hunter JM: Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function. Br J Anaesth 2008; 101:492–7
32. Pühringer FK, Rex C, Sielenkämper AW, Claudius C, Larsen PB, Prins ME, Eikermann M, Khuenl-Brady KS: Reversal of profound, high-dose rocuronium-induced neuromuscular blockade by sugammadex at two different time points: An international, multicenter, randomized, dose-finding, safety assessor-blinded, phase II trial. ANESTHESIOLOGY 2008; 109: 188–93
33. de Boer HD, Driessen JJ, Marcus MA, Kerkkamp H, Heeringa M, Klimek M: Reversal of rocuronium-induced (1.2 mg/kg) profound neuromuscular block by sugammadex: A multicenter, dose-finding and safety study. ANESTHESIOLOGY 2007; 107:239–44
34. Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M: Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: A comparison with spontaneous recovery from succinylcholine. ANESTHESIOLOGY 2009; 110:1020–5
35. Sacan O, White PF, Tufanogullari B, Klein K: Sugammadex reversal of rocuronium-induced neuromuscular blockade: A comparison with neostigmine-glycopyrrolate and edrophonium-atropine. Anesth Analg 2007; 104:569–74

Appendix 1: Centers Involved in the Study

University of Colorado Health Sciences Center, Denver, Colorado; Department of Anesthesiology, University of Florida, College of Medicine, Gainesville, Florida; University of Kansas Medical Center, Kansas City, Kansas; Duke University Medical Center and Durham Veterans Affairs Medical Center, Durham, North Carolina; University of Michigan, Ann Arbor, Michigan; Department of Anesthesiology, Veterans Affairs Hospital, Houston, Texas; University of Louisville Hospital, Louisville, Kentucky; Temple University, Philadelphia, Pennsylvania; Stanford University Medical Center, Stanford, California; MD Anderson Cancer Center, Houston, Texas; Saddleback Memorial Medical Center, Laguna Hills, California; University of New Mexico Health Sciences Center Clinical Trials Center, Albuquerque, New Mexico; Memorial Hermann Healthcare System–Memorial City Hospital, Houston, Texas; and University of Pittsburgh Medical Center–Shadyside Hospital, Pittsburgh, Pennsylvania.