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Sugammadex 4.0 mg kg^{-1} Reversal of Deep Rocuronium-Induced Neuromuscular Blockade: A Multicenter Study in Chinese and Caucasian Patients

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Abstract

Objective: Maintenance of deep neuromuscular blockade (NMB) until the end of surgery may be beneficial in some surgical procedures. The selective relaxant binding agent sugammadex rapidly reverses deep levels of rocuronium-induced NMB. The purpose of this study was to evaluate the efficacy and safety of sugammadex 4.0 mg kg^{-1} for reversal of deep rocuronium-induced NMB in Chinese and Caucasian patients.

Methods: This was an open-label, multicenter, prospective Phase III efficacy study in adult American Society of Anesthesiologists Class 1-3 patients scheduled for surgery under general anesthesia and requiring deep NMB. All patients received intravenous propofol and opioids for induction and maintenance of anesthesia, and a single intubation dose of rocuronium 0.6 mg kg^{-1}, with maintenance doses of 0.1-0.2 mg kg^{-1} as required. Sugammadex 4.0 mg kg^{-1} was administered after the last dose of rocuronium, at a target blockade depth of 1-2 post-tetanic counts. The primary efficacy endpoint was time from sugammadex administration to recovery of the train-of-four (TOF) ratio to 0.9. Safety was also evaluated.

Results: Overall, 115 Chinese and 36 Caucasian patients were treated. Geometric mean (95% confidence interval) times to recovery of the TOF ratio to 0.9 were 2.3 (2.1 to 2.6) minutes and 1.4 (1.3 to 1.6) minutes in Chinese and Caucasian patients, respectively. Adverse events were reported in 57% of Chinese patients and 64% of Caucasian patients.

Conclusion: This study demonstrates that sugammadex 4.0 mg kg^{-1} provides effective and rapid reversal of deep rocuronium-induced NMB in Chinese and Caucasian patients. Efficacy equivalence between the two populations cannot be claimed.

Keywords: Sugammadex; Rocuronium; Neuromuscular blockade; Chinese; Asian; Caucasian; Efficacy; Safety

Introduction

Maintenance of deep neuromuscular blockade (NMB) until the end of surgery may be beneficial in surgical procedures that require deep levels of muscular relaxation or complete absence of movement, such as robotic, [1] abdominal, [2] and laparoscopic bariatric [3] procedures. It has been shown that deep levels of NMB may facilitate improved surgical access and an enhanced visual field [4]. NMB reversal has traditionally been performed using an acetylcholinesterase inhibitor such as neostigmine; however, neostigmine cannot adequately reverse deep levels of NMB, [5] and recovery of neuromuscular function may be prolonged and unpredictable [6]. Moreover, if the maximum dose of neostigmine has been administered and recovery of muscle function is not achieved, administration of additional neostigmine will not be of benefit as acetylcholinesterase has been maximally inhibited and may even cause an increase in the depth of blockade [7,8]. The introduction of the selective relaxant binding agent sugammadex means that rapid reversal of both moderate and deep levels of rocuronium-induced NMB can be achieved at the end of surgery [5,9].

Sugammadex has been extensively studied in patients in Europe and the USA, and is marketed for use in more than 40 countries worldwide. However, further data on the efficacy and safety of sugammadex in Chinese patients are required. While no differences in performance of sugammadex are expected in Chinese patients, it is important to investigate sugammadex in a variety of patient populations, as ethnic background and geographic location may potentially affect the potency of some drugs [10-13].

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The primary objective of the study was to demonstrate that time to recovery from deep rocuronium-induced NMB (target depth of 1 to 2 post-tetanic counts [PTC], train-of-four [TOF] 0) [14] after reversal with sugammadex 4.0 mg kg^{-1} is within 10 minutes in 95% of Chinese patients undergoing elective surgery under propofol anesthesia. The key secondary objective was to show equivalence between the Chinese and Caucasian patients in terms of time to recovery. Other secondary objectives were to demonstrate reversal (as defined in the primary objective) within 10 minutes in 95% of Caucasian patients, and to evaluate the safety of sugammadex 4.0 mg kg^{-1} in all patients undergoing rocuronium-induced deep NMB under propofol anesthesia.

Methods

Study design

This was an open-label, multicenter, prospective Phase III efficacy study (Liang study, NCT00826176, sponsor protocol number P05775), conducted from January to August, 2010.

Ethics

The study was conducted in accordance with the International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice, [15] and in compliance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board/Independent Ethics Committee at each of the eight sites in this study.

All patients were required to provide written informed consent.

Patients

Male and female patients were eligible for inclusion in the study if they were 18-64 years, American Society of Anesthesiologists Class 1 to 3, and scheduled for elective surgery under general anesthesia allowing stable neuromuscular monitoring, using rocuronium for deep NMB. Chinese patients had to be of Chinese descent, born in China, never emigrated out of China and have a Chinese home address. Similarly, Caucasian patients had to be of Caucasian descent, born in Europe, never emigrated out of Europe and have a European home address. All female patients of child-bearing potential had to agree to use an accepted method of contraception while receiving study medication and for 7 days thereafter. Pregnancy was excluded by human chorionic gonadotrophin test within 24 hours prior to surgery.

Patients were excluded from the study if they had anatomical malformations leading to an expected difficult intubation, neuromuscular disorders affecting NMB, significant renal or hepatic dysfunction that would prevent participation in the study (as determined by the investigator), or anticipated surgery requiring the use of a pneumatic tourniquet. Other exclusion criteria were (family) history of malignant hyperthermia, suspected or known allergy to neuromuscular blocking agents (NMBAs) or their excipients, or other medication used during general anesthesia, and contraindication to use of neostigmine and/or atropine. Patients who were breast-feeding, pregnant, had already participated in this or any previous sugammadex study, had a clinically significant condition that may have interfered with the trial, or were members (or family members) of the study or sponsor staff were also excluded.

Study procedures

Anesthesia was induced and maintained with intravenous propofol and opioids as required to ensure an adequate level of anesthesia. Opioids were also administered, with the choice of opioid according to local practice. Volatile inhalational agents were not used. Other adjunctive anesthetic measures (e.g. use of opioids, and oxygen in air or nitrous-oxide) were also in accordance with routine practices at the individual study sites. A single intubation dose of rocuronium 0.6 mg kg^{-1}, was administered within 10 seconds into a fast-running venous infusion, after which tracheal intubation was performed. Maintenance doses of rocuronium 0.1 to 0.2 mg kg^{-1} could be given as required to maintain a target depth of blockade of 1 to 2 PTC. After the last dose of rocuronium, at the target blockade depth of 1 to 2 PTC, sugammadex 4.0 mg kg^{-1} was administered within 10 seconds into a fast-running venous infusion for reversal of NMB. Rocuronium and sugammadex were both administered based on actual body weight.

Neuromuscular monitoring was performed continuously by acceleromyography using the TOF-Watch® SX (Organon Ireland Ltd., a subsidiary of Merck & Co., Inc., Swords, Co. Dublin, Ireland) according to the neuromuscular transmission monitoring guidelines version 5, and in accordance with guidelines for good clinical research practice in pharmacodynamic studies of NMBAs. [14,16] Monitoring was performed at the adductor pollicis muscle, in the same arm as the intravenous cannula for drug administration, and the monitored arm was immobilised. Peripheral temperature was monitored at the skin above the adductor pollicis. The TOF-Watch® SX was calibrated after induction of anaesthesia and a 50 Hz tetanic stimulation applied for 5 seconds. Repetitive TOF stimulation was applied every 15 seconds, and/or PTC stimulation, by the TOF-Watch® SX at the ulnar nerve until the end of anaesthesia. In order to administer sugammadex at a target depth of NMB of 1 to 2 PTC after the last maintenance dose of rocuronium, the PTC was repeated at 2 to 4-minute intervals. Neuromuscular data were collected via a transducer affixed to the top of the thumb and transferred online via an interface to a computer by means of the TOF-Watch® SX Monitoring Program, version 2.3.

After tracheal intubation, mechanical ventilation was started and anesthesia was maintained with propofol continuous infusion. Neuromuscular monitoring was continued until the end of anesthesia or at least until recovery of the TOF ratio to 0.9. In the event of recurrent NMB after extubation, patients were to receive adequate ventilation and, if clinically indicated, treatment with neostigmine.

Efficacy

The primary efficacy variable was time from sugammadex 4.0 mg kg^{-1} administration to recovery of the TOF ratio to 0.9. A series of three consecutive readings of TOF ≥ 0.9 were required to confirm this point had been reached. Secondary efficacy variables were times to recovery of the TOF ratio to 0.7 and 0.8, and were evaluated as additional, supportive, measures of evaluation of efficacy allowing comparison between the two groups.

Safety

Safety assessments were performed by a safety assessor who was blinded to the treatment received, and included monitoring of adverse events (AEs) which were coded using the Medical Dictionary for Regulatory Activities version 13.1. An AE was defined as any untoward medical occurrence (i.e. unfavourable or unintended sign, symptom or abnormal laboratory finding) in a patient administered sugammadex, regardless of whether considered related to treatment. Serious AEs (SAEs) were defined as those that resulted in death, were life-threatening, required new or prolonged hospitalization, or resulted in persistent or significant disability or incapacity, or a congenital

anomaly or birth defect.

Other safety assessments included vital signs (heart rate and blood pressure), oxygenation (oxygen saturation by pulse oximetry), signs of drug hypersensitivity (e.g. flushing or erythematous rash), physical examination, and TOF-Watch® SX- and arm board-related events. Patients were also assessed for evidence of residual NMB or recurrence of NMB using the TOF-Watch® SX (decline in TOF ratio from ≥ 0.9 to <0.8 in at least three consecutive TOF values, if neuromuscular monitoring continued after the TOF ratio 0.9 was reached) and/or clinical signs, (e.g. respiratory problems) within 60 minutes of sugammadex administration). Prolonged recovery to a TOF ratio of 0.9 was predefined as >6 minutes.

All AEs, SAEs, and any other events considered to be clinically relevant in the opinion of the safety assessor, including details of residual or recurrent NMB, were recorded in the electronic case report form (eCRF). Any evidence of events due to a possible interaction of sugammadex with endogenous compounds, or with exogenous compounds other than steroidal NMBAs, was also recorded on the eCRF.

The relationship of any AE relative to the use of sugammadex was assessed by an investigator and recorded as unlikely, possibly, or probably related.

Statistical Analysis

For regulatory considerations of a new pharmaceutical compound in China, 100 evaluable patients per treatment group are required. Assuming a maximum drop-out rate of 13%, the target number of patients to be enrolled at the Chinese sites should therefore be 115. For the present study, using data from previous sugammadex studies, the sample size calculation for Caucasian patients was based on having 90% power to show existing equivalence in time to recovery of the TOF ratio to 0.9 between Chinese and Caucasian patients. Using a standard deviation (SD) of 1.25 minutes, equivalence margin of 1 minute, and a 95% confidence interval (CI), it was calculated that at least 32 European and 100 Chinese patients would need to be reversed at a target NMB depth of 1 to 2 PTC. Assuming a 5% to 10% drop-out rate, the total number of patients needed was calculated to be 151 (115 Chinese and 36 Caucasian patients).

The primary efficacy analysis was performed on the full analysis set (equivalent to an intent-to-treat population), which included all patients who received sugammadex and had at least one efficacy assessment. To address the primary objective, a one-sided tolerance interval (TI) was calculated for recovery of the TOF ratio to 0.9. The TI refers to a fixed proportion (95% in this study) of the population achieving the primary objective with a stated confidence (95% in this study), and was calculated using the CAPABILITY procedure from the statistical software package SAS® (SAS Institute, Cary, NC, USA). In line with other deep blockade studies within the sugammadex clinical trial program, efficacy was concluded if the upper limit of the TI was <10 minutes.

To investigate equivalence in the time to recovery of the TOF ratio to 0.9 between Chinese and Caucasian patients (key secondary objective), analyses were performed using a non-parametric CI approach, which enabled a quantitative measure of any differences between the groups.

The estimated median difference between the two patient groups and the corresponding two-sided 95% CI were calculated using the Hodges-Lehmann estimator for treatment effect and Moses estimator for CI of estimated treatment effect. Equivalence in efficacy between Chinese and Caucasian patients was considered to be demonstrated when the 95% CI for the median difference (for time to recovery of TOF ratio to 0.9) between the groups was within a -1 to +1 minute interval. The same methods (ANOVA, Hodges-Lehman and Moses, as applicable) were used for the evaluation of times to recovery of TOF ratios to 0.7 and 0.8. Comparison of mean duration of surgery between Chinese and Caucasian patients was analyzed (post-hoc) using an ANOVA model with European/Chinese as the main factor and site as a nested factor within the main factor. Demographic data were compared between the two patient groups using ANOVA or Fisher's exact test, as applicable.

Safety analyses were performed for the all-patients-treated set, and included all patients who received a dose of sugammadex.

Results

The study was conducted at five sites in China (three sites in Shanghai, one in Guangdong, and one in Jiangsu) and three sites in Europe (one site each in Belgium, Denmark, and Norway). A total of 128 Chinese patients were enrolled, of whom 13 discontinued prior to any treatment (nine for administrative reasons, three due to withdrawal of consent, and one who was lost to follow-up [patient could not be contacted]) and one patient was treated but no efficacy data were recorded (Figure 1). Therefore, 114 Chinese patients were included in the full analysis set. All 36 enrolled Caucasian patients had evaluable data and were included in the full analysis set (Figure 1).

Overall, there were more female than male patients included in the study (p=0.02). On average, Chinese patients weighed less (p=0.001) and were slightly shorter (p<0.001) than Caucasian patients (Table 1).

The distribution of types of surgery performed (categorized according to the Nordic Medico-Statistical Committee Classification of Surgical Procedures) [17] varied between the Chinese and Caucasian patient groups. Most of the Chinese patients (42%, 48/115) underwent surgery in the 'digestive system and spleen' category, compared with only 8% (3/36) of Caucasian patients. The most frequently performed procedure in Caucasian patients (58%, 21/36) was 'female genital organs' surgery, which was performed in only 16% (18/115) of Chinese patients. The second most frequent surgical procedure in both Chinese and Caucasian patients belonged to the 'ear, nose and larynx' category, and was performed in 23% (26/115) and 22% (8/36) of patients, respectively).

	Chinese (n=115)	Caucasian (n=36)	P-value[a]
Sex (Female : Male)	66 (57%) : 49 (43%)	29 (81%) : 7 (19%)	
Age (years)	47.9 (10.0)	47.2 (11.0)	p=0.02
Weight (kg)	63.8 (11.5)	71.0 (11.5)	p=0.72
Height (cm)	163.9 (7.0)	169.5 (8.4)	p=0.001
Body mass index (kg/m^2)	23.7 (3.5)	24.6 (3.0)	
ASA class			
1	55 (48%)	13 (36%)	p=<0.001
2	59 (51%)	23 (64%)	p=0.12
3	1 (1%)	0 (0%)	p=0.43

Data are mean (SD) or frequency
[a]p-values obtained from ANOVA or Fisher Exact test, as appropriate
ASA, American Society of Anesthesiologists; SD, standard deviation.

Table 1: Baseline characteristics (all-patients-treated set).

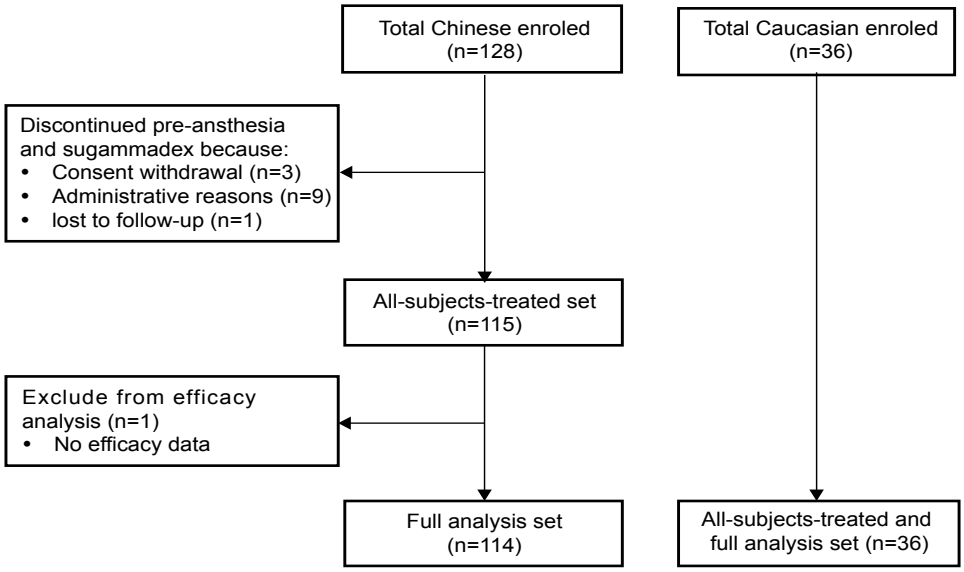

Figure 1: Patient disposition (in accordance with CONSORT guidelines).

	European sites			Chinese sites*					Pooled
Site number	1 (n=10)	2 (n=13)	3 (n=13)	4 (n=23)	5 (n=22)	6 (n=23)	7 (n=23)	8 (n=23)	(n=150)
Mean (SD)	54.3 (16.8)	97.3 (20.4)	45.3 (18.0)	103.4 (32.1)	122.7 (28.0)	34.8 (10.1)	207.5 (70.0)	107.1 (34.4)	103.4 (64.6)
Range	29.2-86.9	71.6-131.3	28.2-93.0	44.2-180.3	73.4-174.9	21.9-60.8	84.8-307.0	52.0-181.1	21.9-307.0

SD, standard deviation

*Mean duration of surgery across Chinese versus European sites: p<0.0001

Table 2: Summary of the duration of surgery (minutes) across participating study sites (full analysis set).

Anesthesia was induced with propofol in all Chinese and Caucasian patients. The mean (SD) total dose of propofol was 13.8 (10.0) mg/kg^{-1} in Chinese and 12.0 (6.7) mg/kg^{-1} in Caucasian patients, respectively. Analgesia was with fentanyl in 100% Chinese patients and remifentanil supplemented with fentanyl in 39% Chinese patients. In Caucasian patients, analgesia was with sufentanil, fentanyl, remifentanil, morphine and tramadol in 64%, 14%, 33%, 19% and 6% patients, respectively.

All patients received a rocuronium intubation dose within 10% of the dose prescribed in the protocol with the exception of one Caucasian patient, who received 0.52 mg/kg. In total, 89% (102/115) of Chinese and 75% (27/36) of Caucasian patients received one or more maintenance doses of rocuronium. The lowest maintenance dose of rocuronium was 0.09 mg kg^{-1}; administered on one occasion in one patient. The highest maintenance dose of rocuronium was 0.33 mg kg^{-1}: three patients received (on one occasion each) a maintenance dose of rocuronium >0.3 mg kg^{-1} (but ≤0.33 mg kg^{-1}). Ten Chinese and six Caucasian patients received one or more maintenance doses of rocuronium above the protocol-specified dose and two Chinese and one Caucasian patient received one or more lower than specified dose. The median (range) number of maintenance doses of rocuronium among patients who received them was 5 (1 to 20) in Chinese patients and 4 (1 to 15) in Caucasian patients.

The mean duration of surgery was longer in the Chinese sites, compared with mean duration in the European sites (p<0.0001, Table 2).

Efficacy

In Chinese patients, geometric mean (95% CI) time to recovery of the TOF ratio to 0.9 was 2.3 (2.1 to 2.6) minutes (Table 3). In Caucasian patients, the corresponding recovery time was 1.4 (1.3 to 1.6) minutes (Table 3). Times to recovery of the TOF ratios to 0.7 and 0.8 in Chinese and Caucasian patients are also shown in Table 3.

Geometric mean (95% CI) time to recovery of the TOF ratio to 0.9 was longer in patients who received at least one maintenance dose of rocuronium versus intubating dose only in Chinese patients (2.5 [2.2 to 2.7] vs. 1.5 [1.2 to 1.9] minutes, respectively) but not in Caucasian patients (1.4 [1.2 to 1.6] vs. 1.5 [1.1 to 2.1] minutes, respectively.

Four Chinese patients from the same site had prolonged recovery (pre-defined as >6 minutes) to a TOF ratio of 0.9. These patients each received between 15 and 20 maintenance doses of rocuronium, and recovery times from administration of sugammadex to a TOF ratio of 0.9 ranged from 6.4 to 14.6 minutes. At this particular site, the geometric mean time and range from start of administration of sugammadex to recovery of the TOF ratio to 0.9 was slower (3.6 [range 1.5 to 14.6] minutes) compared with those observed at the other four Chinese sites (2.1 [range 0.6 to 4.4] minutes, 2.6 [range 1.0 to 5.7] minutes, 1.6 [range 0.8 to 3.1] minutes and 2.2 [range 1.0 to 4.4] minutes, respectively). In addition, the fastest recovery time (1.5 minutes) at this site was slower than the fastest recovery time at the each of the other four Chinese sites, and the slowest recovery time (14.6 minutes) was slower than the slowest recovery time at the each of the other four Chinese sites. On average, the patients at this site underwent longer surgeries (Table 2)

	Chinese (n=114)	Caucasian (n=36)	Estimated difference (95%CI)	P-value
TOF 0.7				
Geometric mean (95% CI)	1.6 (1.5 to 1.8)	1.1 (1.0 to 1.2)	0.5 (0.2, 0.7)	p<0.0001
Median	1.6	1.1		
Range	0.6 to 9.3	0.6 to 2.8		
Upper limit of TI	4.3	2.2		
TOF 0.8				
Geometric mean (95% CI)	1.9 (1.7 to 2.1)	1.2 (1.1 to 1.3)	0.7 (0.4, 1.0)	p<0.0001
Median	1.8	1.2		
Range	0.6 to 10.1	0.6 to 3.0		
Upper limit of TI	5.0	2.4		
TOF 0.9				
Geometric mean (95% CI)	2.3 (2.1 to 2.6)	1.4 (1.3 to 1.6)	1.8 (0.5, 1.2)	p<0.0001
Median	2.3	1.4		
Range	0.6 to 14.6	0.6 to 3.3		
Upper limit of TI	6.4	3.2		

TI, tolerance interval; TOF, train-of-four.
Estimated difference and 95% CI were obtained according to Hodges-Lehmann and Moses.
p-values obtained from testing whether the ratio of the two geometric means is equal to 1 (ANOVA on log- transformed recovery times)

Table 3: Comparison of time (minutes) from administration of sugammadex to recovery of the TOF ratio to 0.7, 0.8 and 0.9 in Chinese and Caucasian patients (full analysis set).

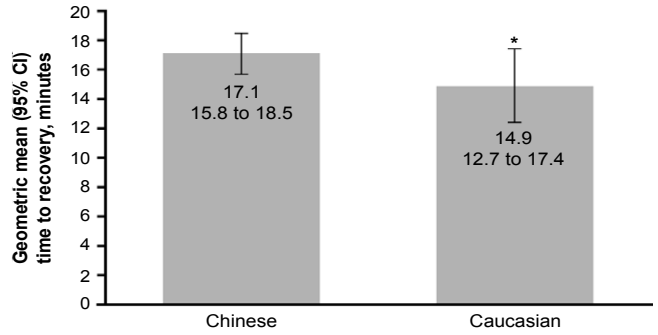

Figure 2: Time from last dose of rocuronium to recovery to a TOF ratio of 0.9 in Chinese (n=114) and Caucasian patients (n=36) (full analysis set).

*Estimated ratio of the geometric means (Chinese/Caucasian patients)=1.16, with 95% CI: 0.99, 1.35

and received a greater number of maintenance doses of rocuronium relative to other participating sites. In each of the four patients with delayed recovery to a TOF ratio of 0.9, it was reported that the onset of recovery was slow but that recovery thereafter was reasonably steep, and that one possible explanation might be injection of sugammadex into a slow-running infusion line.

The upper limit of the TI for time to recovery of the TOF ratio to 0.9 was 6.4 minutes in Chinese patients and 3.2 min in Caucasian patients. It can therefore be estimated, with 95% confidence, that 95% of patients would recover within these times in each group, respectively. In both groups, the upper limit of the TI was well within the pre-specified margin of 10 minutes for efficacy of sugammadex administered at 1 to 2 PTC in Chinese and Caucasian patients (Table 3).

There was an estimated median (95% CI) difference of 0.8 (0.5 to 1.2) minutes in time to recovery of the TOF ratio to 0.9 between Chinese and Caucasian patients (Table 3). Therefore, as the upper bound of the CI was above the pre-specified equivalence range of (-1 minute to +1 minute), efficacy equivalence between Chinese and Caucasian patients could not be claimed.

Geometric mean (95% CI) times from the last dose of rocuronium to recovery of the TOF ratio to 0.9 were also slightly longer in Chinese versus Caucasian patients (Figure 2).

Safety

Treatment-emergent AEs were reported in 66 (57%) Chinese patients and 23 (64%) Caucasian patients (Table 4). The most common AEs were incision site pain, abdominal pain, vomiting, and nausea and dizziness. AEs considered by the investigator to be at least possibly related to study treatment were reported in 21 (18%) Chinese patients: nausea (n=6), vomiting (n=12), dry mouth (n=3), sinus bradycardia (n=1), cardiac anesthetic complication (n=1) and tremor (n=1). Only one Caucasian patient had a possibly drug-related AE (nausea) according to the investigator. None of the above AEs were categorized as serious.

One SAE was reported. This was a post-procedural hemorrhage in a 61-year-old Caucasian female following laparoscopic-assisted vaginal hysterectomy with bilateralsalpingo-oophorectomy. At approximately 5 hours after administration of sugammadex for reversal of NMB, the patient experienced bleeding through the dressing. The event resolved spontaneously, with no treatment required. The SAE was considered by the investigator to be unlikely to be related to sugammadex.

Recurrence of NMB based on neuromuscular monitoring was reported in one Chinese patient. Although the TOF ratio had reached 0.9 at 3.5 minutes, NMB recurred to a lowest TOF value of 0.7 at 10.3 minutes, and did not return to TOF 0.9 during the study. Two minutes before the recurrence of NMB, the skin temperature dropped to <31.5°C until the end of monitoring. At about the same time, propofol was stopped, and an AE of 'light anesthesia' was reported which was considered by the investigator unlikely to be related to sugammadex.

There was no clinical evidence in any patient of residual NMB or recurrence of NMB from administration of sugammadex up to 60 minutes after recovery of the TOF ratio to 0.9.

A total of five Caucasian patients (all from one site) had events that were considered to be indicative of bleeding, all of which were considered by the investigator as unlikely to be related to the study medication. One patient had incision site hematoma and post-procedural hematoma; two patients had post-procedural hemorrhage

	Chinese (n=115)	Caucasian (n=36)
Abdominal pain[a]	1 (1)	12 (33)
Dizziness	3 (3)	5 (14)
Incision site pain	26 (23)	1 (3)
Post-procedural hemorrhage	0 (0)	2 (6)
Wound complication	0 (0)	3 (8)
Nausea	8 (7)	7 (19)
Vomiting	12 (10)	5 (14)
Cough	9 (8)	1 (3)
Rhinalgia	0 (0)	3 (8)

Data are number. [a]Includes Medical Dictionary for Regulatory Activities terms "abdominal pain" and "abdominal pain lower".

Table 4: Treatment-emergent AEs occurring in ≥ 5% patients in either subject group (all-subjects-treated set).

(one of which was reported as an SAE because it resulted in prolonged hospitalization); and one patient each had wound hemorrhage and intra-abdominal hemorrhage. None of the Chinese patients had events indicative of bleeding.

There were no reports of drug hypersensitivity and no clinically meaningful post-treatment effects of sugammadex on blood pressure or heart rate in Chinese or Caucasian patients. Overall, Caucasian patients had notably lower mean systolic and diastolic blood pressures compared with Chinese patients up to the 30-minute time point after administration of sugammadex (~15 mm Hg difference), but these returned to screening values by the post-anesthetic visit.

Discussion

This is the first study evaluating efficacy and safety of sugammadex 4.0 mg kg^{-1} for reversal of deep rocuronium-induced NMB in Chinese patients and which compared the efficacy and safety of sugammadex in Chinese and Caucasian populations. In this study, sugammadex was shown to result in rapid (geometric mean 2.3 minute) NMB reversal in Chinese patients, with an upper limit of the TI of 6.4 minutes, well within the pre-specified margin of 10 minutes, thus meeting the study's primary objective and confirming efficacy in this patient population.

The upper bound of the CI for the estimated median difference between the two populations in the present study was 12 seconds above the pre-specified equivalence range (-1 minute to +1 minute), and thus equivalence for efficacy between Chinese and Caucasian patients could not be claimed based on these results. Upon further inspection it became clear that within the Chinese sites there was one site with relatively long recovery times on average; in this site there were four patients that had prolonged recovery times to a TOF ratio of 0.9 of >6 minutes. The reasons for the longer times are not entirely clear. It is notable that there was a greater median (range) number of maintenance doses of rocuronium administered at this site 12 (3 to 20) compared with the other sites (median [range] number was five [0 to 16] across Chinese sites and two [0 to 15] across European sites), which may have contributed to the longer recovery times observed. However, in line with the study protocol, and general clinical practice, maintenance doses of 0.1 to 0.2 mg kg^{-1} could be given as required throughout the procedure to maintain a target depth of 1 to 2 PTC (the depth at which sugammadex 4 mg kg^{-1} was to be administered). Moreover, a previous study in Caucasian patients found that the number of rocuronium doses administered has 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 to TOF ratio 0.9. [18] Another factor potentially contributing to the longer recovery times in one site may have been that, in this site, patients generally underwent more complex surgical procedures, with longer mean (SD) durations of surgery (207.5 [70.0] minutes, vs. 103.4 [64.6] minutes when duration of surgery is pooled across all sites). Indeed, duration of surgery was generally longer for Chinese versus European sites ($p<0.0001$; Table 2), potentially contributing to the slightly longer recovery times in Chinese patients. Additionally, it should be noted that there were more female than male patients included ($p=0.02$; Table 1), with a greater difference within the Caucasian group. However, no gender differences with regards to efficacy of sugammadex have previously been observed [19]. Chinese patients also weighed less on average than Caucasian patients in the present study ($p<0.0001$; Table 1). However, population pharmacokinetic analysis of adult

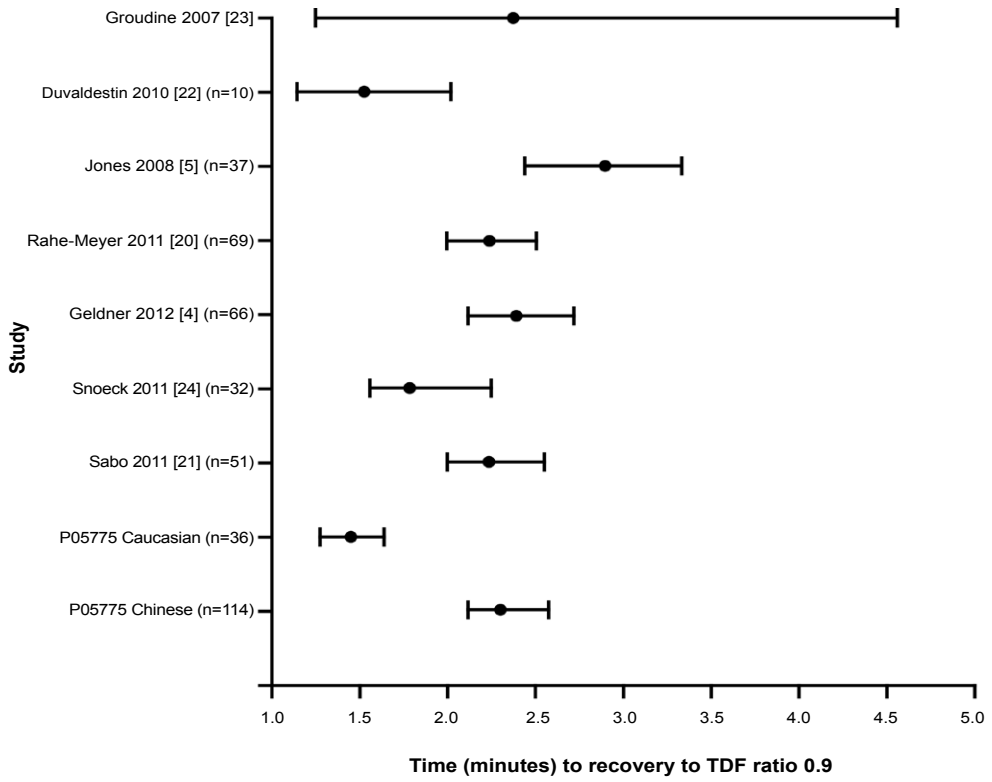

Figure 3: Geometric mean (95% CI) times from sugammadex administration to recovery to TOF ratio 0.9 in the current study (P05775), and seven other studies in which sugammadex was administered at deep NMB (1 to 2 post-tetanic count) for reversal of rocuronium-induced blockade.

and elderly patients has shown no clinically relevant relationship of sugammadex clearance and volume of distribution with body weight, when administered at recommended sugammadex doses and based on actual body weight. [18,19] Moreover, mean (SD) body mass index was comparable between groups in this study: 23.7 (3.5) kg/m^2 for Chinese patients and 24.6 (3.0) kg/m^2 for Caucasian patients. Additionally, while propofol dosing was performed according to routine site practices and individual doses of propofol permitted to be adjusted as necessary to provide optimal patient care, mean (SD) doses administered were similar between Chinese and Caucasian groups, suggesting no major differences in practice.

Another explanation emerges when we present average recovery times across studies; geometric mean (95% CI) recovery times for Chinese and Caucasian patients in this study are illustrated in Figure 3, together with eight other studies [4,5,20–24] in which sugammadex was administered at deep NMB for reversal of rocuronium-induced blockade. As is clear from the figure, geometric mean results for the Chinese population in the current study are similar to those observed for the other studies. If anything, recovery times for Caucasian patients (geometric mean 1.4 minutes) appeared to be particularly rapid in comparison with previous studies (Figure 3). Greater experience among the European versus Chinese investigators in use of the TOF-Watch® SX may have played a role. Importantly, while recovery times were slightly longer for Chinese versus Caucasian patients in this study, results for the Chinese population are in fact well within the expected range observed in clinical studies with similar conditions.

Sugammadex was generally well tolerated in this study and the AE profile was consistent with that seen in previous studies. [20,25,26] There were differences in the incidence of AEs reported between Chinese and Caucasian patients (Table 4), with AEs considered at least possibly drug-related reported in 21 (18%) Chinese patients versus one (3%) Caucasian patient. Differences including the types of pain reported may reflect the different surgical procedures undergone by the Chinese versus Caucasian patients. Furthermore, although Medical Dictionary for Regulatory Activities coding was used to ensure consistency wherever possible; differences in local practices also may have led to observed differences in the incidence of AEs.

Conclusions

It can be predicted with 95% confidence that 95% of Chinese patients will recover from deep rocuronium NMB within 6.4 minutes following sugammadex 4.0 mg kg^{-1} administration, and that 95% of Caucasian patients will recover within 3.2 minutes. Results of this study therefore demonstrate that sugammadex 4.0 mg kg^{-1} provides effective and rapid reversal of deep rocuronium-induced blockade in both Chinese and Caucasian patients. Efficacy equivalence between the two populations cannot be claimed. There was only one SAE reported following sugammadex 4.0 mg kg^{-1} (post-procedural hemorrhage in a Caucasian patient). This SAE was considered by the investigator to be unlikely related to sugammadex.

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Conflicts of interest: Henk Rietbergen is an employee of MSD, Oss, The Netherlands, and Tiffany Woo is an employee of Merck, Whitehouse Station, NJ, USA, both of whom may own stock and/or hold stock options in the Company. Esther Abels was formerly an employee of MSD, Oss, The Netherlands. The remaining authors work for institutions which received funding for performing the study from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ, USA.

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