

## CLINICAL PRACTICE

# Reversal of rocuronium-induced neuromuscular block with sugammadex is faster than reversal of cisatracurium-induced block with neostigmine

E. A. Flockton<sup>1\*</sup>, P. Mastronardi<sup>2</sup>, J. M. Hunter<sup>1</sup>, C. Gomar<sup>3</sup>, R. K. Mirakhur<sup>4†</sup>, L. Aguilera<sup>5</sup>,  
F. G. Giunta<sup>6</sup>, C. Meistelman<sup>7</sup> and M. E. Prins<sup>8†</sup>

<sup>1</sup>University Department of Anaesthesia, School of Clinical Sciences, Duncan Building, Daulby Street, Liverpool L69 3GA, UK. <sup>2</sup>Department of Anaesthesia, University Federico II, Napoli, Italy. <sup>3</sup>Hospital Clinico y Provincial de Barcelona, Barcelona, Spain. <sup>4</sup>Queens University Belfast, Belfast, Northern Ireland. <sup>5</sup>Hospital de Basurto, Bilbao, Spain. <sup>6</sup>Ospedala Santa Chiara Pisa, Pisa, Italy. <sup>7</sup>Hôpital Brabois, Vandoeuvre les Nancy, France. <sup>8</sup>NV Organon, a part of Schering-Plough Corporation, Oss, The Netherlands

\*Corresponding author. E-mail: lizzy@lizzyflockton.fsnet.co.uk

**Background.** Reversal of the residual effect of rocuronium or cisatracurium by neostigmine may be slow and associated with side-effects. This randomized, safety-assessor-blinded study compared the efficacy of sugammadex, a selective relaxant binding agent for reversal of rocuronium-induced neuromuscular block, with that of neostigmine for reversal of cisatracurium-induced neuromuscular block. The safety of sugammadex and neostigmine was also evaluated.

**Methods.** Adult surgical patients (ASA class I–III) were randomized to sugammadex 2.0 mg kg<sup>-1</sup> for reversal of block induced by rocuronium 0.6 mg kg<sup>-1</sup>, or neostigmine 50 µg kg<sup>-1</sup> for reversal of block induced by cisatracurium 0.15 mg kg<sup>-1</sup>. Anaesthesia was induced and maintained using i.v. propofol and remifentanyl, fentanyl, or sufentanil. Neuromuscular function was monitored using acceleromyography (TOF-Watch<sup>®</sup> SX). Sugammadex or neostigmine was administered at reappearance of T<sub>2</sub>. The primary efficacy variable was time for recovery of the train-of-four (TOF) ratio to 0.9.

**Results.** Eighty-four patients were randomized, 73 of whom received sugammadex (n=34) or neostigmine (n=39). Time from start of administration of reversal agent to recovery of the TOF ratio to 0.9 was 4.7 times faster with sugammadex than with neostigmine (geometric mean=1.9 vs 9.0 min, *P*<0.0001). Reversal of block was sustained in all patients. There were no serious adverse effects from either reversal agent and no significant changes in any measure of safety, except for similar elevations in urinary *N*-acetyl glucosaminidase in both groups.

**Conclusions.** Sugammadex 2.0 mg kg<sup>-1</sup> administered at reappearance of T<sub>2</sub> was significantly faster in reversing rocuronium-induced blockade than neostigmine was in reversing cisatracurium-induced block.

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Cisatracurium and rocuronium are commonly used non-depolarizing neuromuscular blocking agents (NMBAs) for facilitating tracheal intubation and providing muscle relaxation during surgery. Patients receiving NMBAs are at risk of residual curarization, a factor in the development of postoperative pulmonary complications and increased

postoperative mortality.<sup>1 2</sup> Cholinesterase inhibitors such as neostigmine are used as reversal agents for NMBAs.

<sup>†</sup>*Declaration of interest:* M.E.P. is an employee of N.V. Organon, a part of Schering-Plough Corporation, Oss, The Netherlands. R.K.M. is a member of the Scientific Advisory Board of N.V. Organon, a part of Schering-Plough Corporation.

However, these drugs have a relatively slow onset of action and their use is associated with muscarinic side-effects, such as bradycardia, hypotension, bronchoconstriction, and emesis.<sup>3–5</sup> Thus, muscarinic receptor antagonists such as atropine or glycopyrrolate are used with cholinesterase inhibitors,<sup>6</sup> although these drugs also have adverse effects (AEs).<sup>7</sup> Importantly, cholinesterase inhibitors are ineffective for reversal of profound neuromuscular block or for use immediately after NMBA administration, and show reduced efficacy in the presence of potent inhalation anaesthetics such as sevoflurane and isoflurane.<sup>3 8 9</sup>

Sugammadex, a selective relaxant binding agent (SRBA), was developed specifically to bind the steroidal NMBA rocuronium.<sup>10</sup> Animal studies have shown that sugammadex rapidly reverses rocuronium-induced neuromuscular block by chemical encapsulation of unbound NMBA molecules in the plasma.<sup>10 11</sup> Sugammadex has been shown to be effective and well tolerated for the reversal of shallow and profound neuromuscular block induced by rocuronium or vecuronium,<sup>12–17</sup> and has been shown to reverse rocuronium-induced block more rapidly than does neostigmine.<sup>18</sup> The purpose of this study was to compare the efficacy and assess the safety of sugammadex for the reversal of neuromuscular block induced by rocuronium with that of neostigmine for the reversal of cisatracurium-induced neuromuscular block.

## Methods

### *Study design and patient selection*

This study, named the CRYSTAL trial, was a multicentre, randomized, safety-assessor-blinded, parallel-group, Phase IIIa study conducted at eight centres in Europe between November 2005 and May 2006. The protocol was approved by the Independent Ethics Committee at each centre and conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonization Guidelines, and Good Clinical Practice and current regulatory requirements.

Patients were included in the study if they were aged  $\geq 18$  yr, ASA class I–III, and undergoing surgery in the supine position under general anaesthesia requiring muscle relaxation. Patients were excluded if they were: expected to have a difficult intubation for anatomical reasons; had a neuromuscular disorder or significant renal dysfunction; a history or family history of malignant hyperthermia; or a known allergy to narcotics, NMBAs, or other medication used during general anaesthesia. Patients receiving antibiotics, anticonvulsants, or magnesium at a time likely to interfere with neuromuscular block were also excluded, as were those who had already participated in a previous sugammadex study or any other study within 30 days of entering this study. Female patients who were pregnant, breastfeeding or of childbearing potential, and not using

an adequate method of contraception were also excluded. All patients provided written informed consent.

Patients were randomized to study treatments (rocuronium/sugammadex or cisatracurium/neostigmine) using a central randomization system. Subject numbers were assigned to patients in sequential order of their enrolment into the study.

### *Anaesthesia and neuromuscular block*

Anaesthesia was induced with i.v. propofol and either remifentanyl, fentanyl, or sufentanyl, and maintained using a continuous infusion of propofol and further increments or infusions of analgesic as needed. After the establishment of neuromuscular monitoring, rocuronium  $0.6 \text{ mg kg}^{-1}$  or cisatracurium  $0.15 \text{ mg kg}^{-1}$  was administered as an i.v. bolus over 10 s into a fast running i.v. infusion. Tracheal intubation was performed on achieving maximum neuromuscular block and intermittent positive pressure ventilation commenced to achieve a normal end-tidal carbon dioxide concentration (4.5–5.5 kPa). Further doses of rocuronium  $0.1\text{--}0.2 \text{ mg kg}^{-1}$  or cisatracurium  $0.03 \text{ mg kg}^{-1}$ , up to a maximum of two doses, were administered if needed. The dose schedule was selected to achieve a similar level of neuromuscular block between the two groups. After administration of the last dose of NMBA and at reappearance of  $T_2$ , sugammadex  $2.0 \text{ mg kg}^{-1}$  (rocuronium group) or neostigmine  $50 \text{ } \mu\text{g kg}^{-1}$  (maximum of 5 mg) with glycopyrrolate  $10 \text{ } \mu\text{g kg}^{-1}$  (cisatracurium group) was administered within 10 s into a fast-running i.v. infusion. The time to recovery of the train-of-four (TOF) ratio to 0.9 was recorded. A non-steroidal NMBA could be given if further muscle relaxation was needed after administration of sugammadex.

### *Monitoring*

Neuromuscular function was monitored with acceleromyography, using the TOF-Watch® SX (Organon Ireland Ltd, Schering-Plough Corporation, Dublin, Ireland). Signal stabilization, calibration, and baseline responses were performed in accordance with accepted clinical research practice guidelines.<sup>19</sup> Supramaximal TOF stimuli were applied at the ulnar nerve every 15 s and acceleration of the thumb recorded by a transducer fixed to the ulnar side of the thumb just distal to the interphalangeal joint. The data were downloaded directly to a computer using the TOF-Watch® SX Monitoring Program (Organon Ireland Ltd). Stabilization, calibration, and baseline responses were obtained after induction of anaesthesia but before administration of the NMBA. Neuromuscular monitoring was continued until the end of anaesthesia. Patients were monitored for possible signs of inadequate recovery or re-occurrence of block (a decrease in TOF to  $<0.8$ ) until the end of anaesthesia. Central body and skin temperature were continuously monitored and maintained at  $\geq 35^\circ\text{C}$  and  $\geq 32^\circ\text{C}$ , respectively.

After extubation, clinical assessments of level of consciousness and neuromuscular recovery (5 s head lift and general muscle weakness on a scale of 1–9) were performed every 15 min until the first sustained head lift for 5 s was achieved. Oxygen saturation using pulse oximetry and breathing frequency were monitored during anaesthesia and in the recovery room for at least 60 min after operation. Arterial blood pressure and heart rate were recorded at screening, before administration of rocuronium or cisatracurium, before and 2, 5, 10, and 30 min after administration of sugammadex or neostigmine, and during the post-anaesthetic visit, which was carried out within the first 24 postoperative hours. Systolic arterial pressure of  $\leq 90$  or  $\geq 160$  mm Hg, diastolic pressure of  $\leq 45$  or  $\geq 95$  mm Hg, and heart rates of  $\leq 50$  or  $\geq 120$  beats  $\text{min}^{-1}$  were accepted as clinically significant. The ECG was monitored continuously in the operating room and the recovery ward in a manner consistent with routine anaesthetic practice at the study sites. Physical examination was performed before surgery and at the post-anaesthetic visit.

Blood samples (10 ml each) were withdrawn from each patient for biochemistry and haematology assessments before administration of rocuronium or cisatracurium, 4–6 h after administration of sugammadex or neostigmine, and at the post-anaesthetic visit. Urine samples were collected for urinalysis on the day before surgery or on the day of surgery before anaesthesia and at the post-anaesthetic visit.

### *Efficacy and safety assessments*

The primary efficacy variable was the time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.9. In the sugammadex group only, an exploratory comparison of the primary efficacy variable between patients who received only an intubating dose of rocuronium and those receiving an intubating dose plus at least one maintenance dose was also performed.

Secondary efficacy variables were time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7 or 0.8 and clinical signs of recovery after extubation, but before transfer to the recovery room and before discharge from the recovery room. The time from administration of the intubating dose of rocuronium or cisatracurium to occurrence of maximum block was also recorded (i.e. onset time).

An assessor, who was blinded to study treatment, recorded any AEs or serious AEs (SAEs) during the post-anaesthetic visit and in the follow-up period (7 days later). Any cardiovascular event occurring during the study period that was considered by the investigator to be clinically significant was recorded as an AE. Safety assessments also included monitoring of incidents related to the use of the TOF-Watch® SX, laboratory variables, physical examination, and vital signs.

Blood samples were analysed for haematocrit, haemoglobin, blood counts, electrolytes, liver enzymes, creatine

kinase, lactate dehydrogenase, total bilirubin, total protein, albumin, total cholesterol, and haptoglobin levels. Urinalysis included assessment of urine chemistry and urine sediment analyses. Any clinical signs of possible interaction between sugammadex and endogenous or exogenous compounds (other than rocuronium) were also recorded.

### *Statistics*

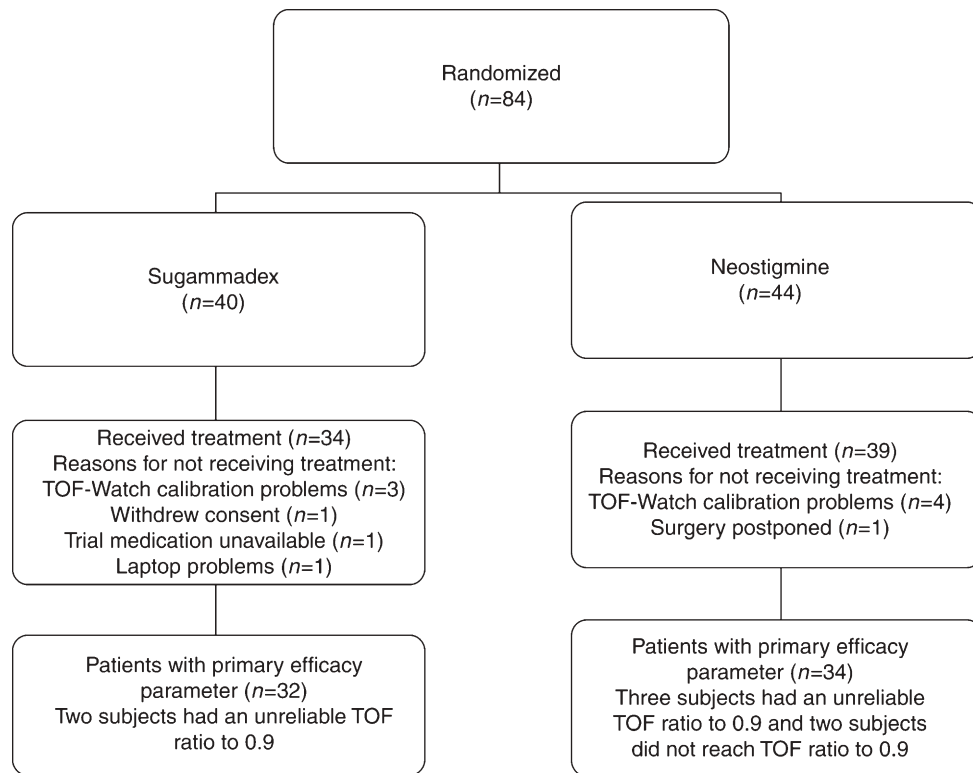
Efficacy analyses were performed using data from the intention-to-treat (ITT) population, which consisted of all randomized patients who received sugammadex or neostigmine, and had at least one post-baseline efficacy assessment carried out. The times from start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9 were analysed using two-way analysis of variance, with treatment group and study site as factors in the model. Since the times followed a skewed distribution in respect of recovery to TOF 0.7, 0.8, and 0.9, and between the two reversal agents, the logarithms of the recovery times were analysed statistically and the recovery times summarized using the geometric mean. The geometric mean was defined as  $\sqrt[n]{(t_1 * t_2 * \dots * t_n)}$ , where  $t_i$  is the recovery time of the  $i$ th of  $n$  subjects.

Safety analyses were performed on data from the all-subjects-treated (AST) group, which consisted of all randomized subjects who received a dose of sugammadex or neostigmine. Physical and baseline characteristics were summarized by treatment group and overall, with summary statistics [mean, median, standard deviation (SD), and range] for continuous variables. For categorical variables, frequency counts and percentages were presented. No statistical tests were performed on physical and baseline characteristics.

The sample size was based on the calculation that 40 patients in each treatment group would result in a power of 90% to detect a difference of at least 3 min in the mean time to recovery of the TOF ratio to 0.9 between the sugammadex and neostigmine groups, assuming an SD of 1.5 min in the sugammadex group and 5.5 min in the neostigmine group.<sup>3</sup> Assuming a dropout rate of 5% from the ITT evaluation, it was determined that 42 patients should be included in each treatment group.

## **Results**

Eighty-four patients were randomized to treatment (rocuronium–sugammadex,  $n=40$ ; cisatracurium–neostigmine,  $n=44$ ). Six patients did not receive sugammadex (inability to record a stable baseline TOF ratio in four patients, withdrawal of consent in one, and study medication unavailable in one). Five patients did not receive neostigmine (inability to record a stable baseline TOF ratio in four patients, and postponement of surgery in one) leading to their exclusion from the AST group ( $n=73$ ). All treated patients had at least one efficacy assessment carried out



**Fig 1** Flow diagram of attrition numbers in each group.

and therefore comprised the ITT population (sugammadex,  $n=34$ ; neostigmine,  $n=39$ ) (Fig. 1).

There were no clinically relevant differences in baseline characteristics between the sugammadex and neostigmine groups, although the sugammadex group included a higher proportion of women (59% vs 41%) and had a higher mean age than the neostigmine group (49 vs 42 yr) (Table 1). The sugammadex group also included a higher percentage of patients categorized as ASA class II or III compared with the neostigmine group (62% vs 46%).

The mean (SD) onset time of rocuronium was significantly faster than that of cisatracurium [1.5 (0.6) vs 2.9 (0.8) min,  $P<0.0001$ ].

**Table 1** Physical characteristics (AST group). ASA, American Society of Anesthesiologists; SD, standard deviation

	Rocuronium– sugammadex ( $n=34$ )	Cisatracurium– neostigmine ( $n=39$ )
Age (yr), mean (range)	49 (23–74)	42 (22–69)
Weight (kg), mean (SD)	72 (16)	78 (13)
Height (cm), mean (SD)	166 (10)	172 (9)
Male/female, $n$ (%)	14/20 (41/59)	23/16 (59/41)
Race		
Caucasian, $n$ (%)	34 (100)	38 (97)
Other, $n$ (%)	0	1 (3)
ASA class, $n$ (%)		
I	13 (38)	21 (54)
II	18 (53)	18 (46)
III	3 (9)	0 (0)

### Efficacy

The time from the start of administration of the reversal agent to recovery of the TOF ratio to 0.9 was significantly faster with sugammadex after rocuronium than with neostigmine after cisatracurium [geometric mean=1.9 (95% confidence interval, CI: 1.6–2.2) min vs 9.0 (95% CI: 7.5–10.8) min,  $P<0.0001$  (Table 2)]. Five patients in the neostigmine group and two patients in the sugammadex group had missing recovery times as a TOF ratio of 0.9

**Table 2** Time (min) from start of administration of sugammadex or neostigmine to recovery of the train-of-four (TOF) ratio to 0.7, 0.8, and 0.9 (ITT population). SD, standard deviation. \* $P$ -value for geometric mean only

	Rocuronium– sugammadex ( $n=34$ )	Cisatracurium– neostigmine ( $n=39$ )	$P$ -value
Recovery of TOF ratio to 0.7			
$n$	32	36	
Geometric mean	1.4	5.1	$<0.0001^*$
Median (range)	1.2 (0.7–2.9)	4.7 (2.4–10.9)	
Recovery of TOF ratio to 0.8			
$n$	32	36	
Geometric mean	1.6	6.5	$<0.0001^*$
Median (range)	1.5 (0.7–3.4)	5.9 (3.2–15.6)	
Recovery of TOF ratio to 0.9			
$n$	32	34	
Geometric mean	1.9	9.0	$<0.0001^*$
Median (range)	1.9 (0.7–6.4)	7.3 (4.2–28.2)	



was either not attained or the measurement was considered unreliable (Fig. 1). These data were excluded from the analysis. Time to recovery of the TOF ratio to 0.9 was 4.7 times faster after reversal of rocuronium with sugammadex than after reversal of cisatracurium with neostigmine. Times to recovery of the TOF ratio to 0.7 and 0.8 were also significantly faster in the rocuronium–sugammadex group compared with the cisatracurium–neostigmine group ( $P < 0.0001$ ) (Table 2).

Exploratory analysis in the sugammadex group showed that time to recovery of the TOF ratio to 0.9 was similar in patients who received only an intubating dose of rocuronium ( $n=17$ ) to those who received an intubating dose and at least one maintenance dose ( $n=15$ ) (geometric mean=2.0 vs 1.8 min, respectively).

Twenty-two out of 34 patients (65%) in the sugammadex group and 27 out of 39 patients (69%) in the neostigmine group were awake and orientated before transfer to the recovery room. The majority of patients in both treatment groups were co-operative, able to perform a 5 s head lift, and did not report any general muscle weakness (Table 3). All but three evaluable patients (sugammadex,  $n=1$ ; neostigmine,  $n=2$ ) were awake and orientated before discharge from the recovery room (Table 3).

### Safety

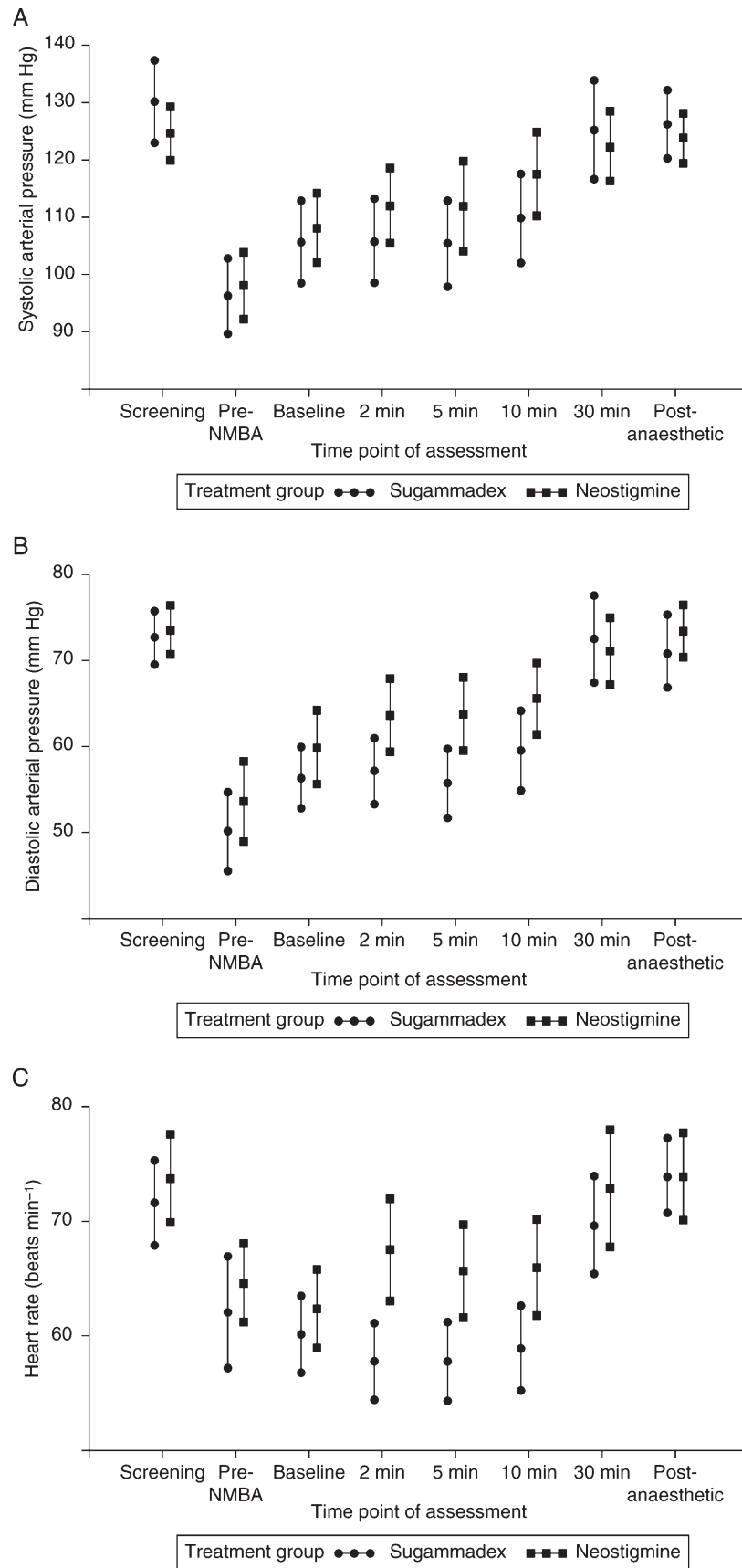
Mean systolic and diastolic arterial pressures and heart rates were similar in the two groups, with the exception of a higher mean diastolic pressure and mean heart rate at 2, 5, and 10 min after reversal in the neostigmine group (Fig. 2). Systolic arterial pressures of  $\geq 160$  or  $\leq 90$  mm Hg, diastolic pressures of  $\geq 95$  or  $\leq 45$  mm Hg, and heart rates of  $\geq 120$  or  $\leq 50$  beats  $\text{min}^{-1}$  were observed in six patients in the sugammadex group and in eight patients in the neostigmine group. None of these was considered clinically significant and was not therefore recorded as AEs.

Twenty-seven of the 34 patients (79%) in the sugammadex group and 28 of the 39 patients (72%) in the neostigmine group experienced at least one AE. The most frequent ( $\geq 10\%$  in either treatment group) AEs were pain due to surgery, nausea, dizziness, headache, increased urinary *N*-acetyl glucosaminidase (NAG) levels, insomnia, shivering, and vomiting (Table 4). No patient was discontinued from the study because of an AE. The majority of AEs were not considered to be study-drug related. However, four patients in the sugammadex group and one patient in the neostigmine group experienced at least one AE that was considered by the investigators to be possibly, probably, or definitely related to the study drug (sugammadex group: nausea in one, shivering in one, increased NAG level in two, tremor in one, and altered facial sensation in one patient; neostigmine group: nausea in one patient). All drug-related events were considered mild to moderate in intensity. There were no SAEs or deaths in the study.

There were no drug-related abnormalities in any haematological or biochemical variables in either treatment group and, overall, there were no clinically relevant differences between the groups with regard to safety. Increased urinary levels of NAG were reported in seven patients in the sugammadex group (two of these events were considered to be possibly drug related due to an increase above the upper safety limit from a previously normal level) and in one patient in the neostigmine group. Differences in NAG levels were not significant between the pre- and postoperative values. Overall, urinary variables were comparable between the treatment groups with the exception of urinary NAG (at the post-anaesthetic visit) and urinary creatinine, which were both higher in the sugammadex group, and  $\beta 2$  microglobulin, which was higher in the neostigmine group. The median (range) changes in NAG from baseline were  $0.31 \text{ U litre}^{-1}$  ( $-8.47$  to  $9.82 \text{ U litre}^{-1}$ ) in the sugammadex group, and  $-0.53 \text{ U litre}^{-1}$  ( $-14.51$  to  $16.89 \text{ U litre}^{-1}$ ) in

**Table 3** Assessment of clinical signs of recovery (ITT population). \*Data missing for two patients. †If a patient was uncooperative, 5 s head lift and general muscle weakness were not assessed

	After extubation but before transfer to recovery room		Before discharge from recovery room	
	Rocuronium/sugammadex ( $n=34$ ) $n$ (%)	Cisatracurium/neostigmine ( $n=39$ ) $n$ (%)	Rocuronium/sugammadex ( $n=34$ ) $n$ (%)	Cisatracurium/neostigmine ( $n=39^*$ ) $n$ (%)
Level of consciousness				
Awake and orientated	22 (64.7)	27 (69.2)	33 (97.1)	35 (94.6)
Arousable with minimal stimulation	7 (20.6)	7 (17.9)	1 (2.9)	2 (5.4)
Responsive only to tactile stimulation	5 (14.7)	5 (12.8)	0 (0)	0 (0)
Cooperative				
Yes	26 (76.5)	31 (79.5)	34 (100.0)	37 (100.0)
No	8 (23.5)	8 (20.5)	0 (0)	0 (0)
Able to perform 5 s head lift <sup>†</sup>				
Yes	25 (96.2)	31 (100.0)	34 (100.0)	37 (100.0)
No	1 (3.8)	0 (0)	0 (0)	0 (0)
General muscle weakness <sup>†</sup>				
No	23 (88.5)	29 (93.5)	34 (100.0)	37 (100.0)
Yes	3 (11.5)	2 (6.5)	0 (0)	0 (0)



**Fig 2** Mean (2 SEM) values for (A) systolic arterial pressure, (B) diastolic arterial pressure, and (C) heart rate in patients receiving sugammadex after rocuronium, or neostigmine after cisatracurium (AST group).

**Table 4** Most commonly reported AEs (i.e.  $\geq 10\%$  in either treatment group) and/or considered drug related (AST group)

Adverse event, <i>n</i> (%)	Rocuronium/sugammadex ( <i>n</i> =34)		Cisatracurium/neostigmine ( <i>n</i> =39)	
	All	Drug-related	All	Drug-related
Procedural pain	16 (47.1)	0	16 (41.0)	0
Nausea	7 (20.6)	1 (2.9)	10 (25.6)	1 (2.6)
$\beta$ -N-acetyl-D-glucosaminidase increased	7 (20.6)	2 (5.9)	1 (2.6)	0
Dizziness	6 (17.6)	0	4 (10.3)	0
Chills	5 (14.7)	1 (2.9)	0	0
Headache	2 (5.9)	0	6 (15.4)	0
Tremor	2 (5.9)	1 (2.9)	1 (2.6)	0
Insomnia	1 (2.9)	0	5 (12.8)	0
Altered facial sensation	1 (2.9)	1 (2.9)	0	0
Vomiting	0	0	4 (10.3)	0

the neostigmine group. The median (range) changes in urinary creatinine from baseline were  $-1.00$  mmol litre $^{-1}$  ( $-12.7$  to  $21.8$  mmol litre $^{-1}$ ) in the sugammadex group and  $-4.65$  mmol litre $^{-1}$  ( $-22.2$  to  $11.7$  mmol litre $^{-1}$ ) in the neostigmine group. Inability to adequately reverse neuromuscular block or re-occurrence of block was not observed in any patient. There was no clinical evidence of any interaction between sugammadex and endogenous or exogenous compounds other than rocuronium.

## Discussion

This multicentre, randomized, parallel-group study was the first comparative study, after several dose–response trials, of sugammadex to reverse rocuronium-induced neuromuscular block with neostigmine to reverse cisatracurium-induced neuromuscular block, when administered at reappearance of  $T_2$ . It increased the amount of safety data available about sugammadex, although this was not the prime reason for the study. The study showed that sugammadex reverses rocuronium-induced neuromuscular block significantly faster than neostigmine reverses a block of similar depth induced by cisatracurium. The time to recovery of the TOF ratio to 0.9 was almost five times faster with sugammadex than with neostigmine. A TOF ratio of  $\geq 0.9$  is considered necessary for full recovery of pharyngeal muscle function and is now generally accepted as the target for adequate reversal.<sup>20</sup> Recovery of the TOF ratio both to 0.7 and to 0.8 was also achieved more rapidly with sugammadex than with neostigmine. Clinical signs of recovery were similar with both treatments, which is to be expected since extubation and transfer to the recovery ward were carried out after recovery to a similar endpoint had been attained in both groups.

It is evident that there was a high rate of study exclusion due to technical problems with the TOF-Watch® SX. This may in part be due to time constraints limiting the time available to obtain a stable signal, although much effort was made in this respect. Accidental movement of the immobilized arm used for neuromuscular monitoring and faulty equipment may have been responsible for failure to record full recovery of the TOF response. However, when data from subjects who

failed to reach TOF 0.9 were imputed, similar results were obtained as for the 66 completed cases. This indicates that the results presented are realistic.

Consequent to the high dropout rate from the study (66 subjects achieved reliable recovery of TOF 0.9 out of the 84 subjects randomized to treatment), the number of evaluable subjects would have been insufficient to detect a 3 min difference between the two reversal agents in the mean time to recover to a TOF=0.9, which was the postulated time difference on which the sample size was calculated. However, the values of the mean time to recovery of TOF=0.9 were 1.09 and 6.20 min, yielding a 5.11 min difference between the two groups and hence the study was adequately powered.

The faster time to recovery with sugammadex compared with neostigmine in this study is consistent with that previously reported.<sup>21</sup> In that study, median (range) times to recovery of the TOF ratio to 0.9 were 1.4 (0.9–5.4) and 17.6 (3.7–106.9) min ( $P<0.0001$ ), respectively, after reversal of rocuronium-induced block at reappearance of  $T_2$  by sugammadex or neostigmine. The rapid time to recovery of the TOF ratio to 0.9 with sugammadex observed in our study (geometric mean of 1.9 min) is similar to that reported in previous studies, demonstrating a consistency in observed efficacy. For instance, in a placebo-controlled study of 27 male surgical patients, sugammadex reduced recovery time from moderate rocuronium-induced block in a dose-dependent manner, with median time to recovery of the TOF ratio to 0.9 of 1.3 min with sugammadex  $2.0$  mg kg $^{-1}$ .<sup>12</sup> Similarly, a mean recovery time of 1.8 min with sugammadex  $2.0$  mg kg $^{-1}$  in patients in whom a rocuronium-induced block had been maintained for 2 h or more has been reported.<sup>13</sup> The recovery times with sugammadex in these studies and the present study are a substantial improvement on reported recovery times for reversal of rocuronium or cisatracurium block with neostigmine.<sup>3 8 22 23</sup> In our analysis, administration of an intubating plus maintenance dose(s) of rocuronium compared with an intubating dose only had no significant effect on recovery time.

Compared with sugammadex, there was a relatively greater change in heart rate in the neostigmine group at

2–10 min after reversal (Fig. 2). The lack of any need for a muscarinic antagonist and hence minimal change in heart rate is an advantage of sugammadex. A similarly greater change in heart rate was observed for neostigmine–glycopyrrolate compared with sugammadex in the study by Sacan and colleagues.<sup>18</sup> Considerable fluctuations in heart rate are often observed with neostigmine, particularly when atropine is the anticholinergic agent used. These are less frequent with the use of glycopyrrolate but not completely eliminated.<sup>24–25</sup> Greater stability of heart rate is associated with greater cardiovascular stability and a lower risk of any associated ischaemic changes. The lack of a need to use a muscarinic antagonist with sugammadex should also result in fewer side-effects.

Both sugammadex and neostigmine were safe and well tolerated. Although AEs were recorded in a significant proportion of patients, the majority were not considered to be study-drug related and were only recorded because of adherence to the relatively strict definition of AEs as used in early clinical trials of new agents. There were no SAEs or discontinuations due to AEs in either treatment group. Laboratory variables were similar and within normal limits in both groups except for NAG values, which were outside the normal range in 16 patients in the sugammadex group and in 14 patients in the neostigmine group at the post-anaesthetic visit (day 1). They were not related to the age of the patients. The significance of these findings is unclear, but they were not accompanied by any clinical evidence of, or AEs relating to, renal dysfunction.

There was no evidence of inability to reverse the block or any re-occurrence of block in either group in this study and in particular with sugammadex. Sugammadex 2.0 mg kg<sup>-1</sup> appears to be an adequate dose to use at reappearance of T<sub>2</sub>, as has been reported in previous studies of sugammadex.<sup>12–17</sup> We compared the combination of rocuronium and sugammadex with cisatracurium and neostigmine in the present study, as rocuronium and cisatracurium are two commonly used NMBA.

In conclusion, the results of this study confirm that sugammadex 2.0 mg kg<sup>-1</sup> administered at reappearance of T<sub>2</sub> can rapidly and effectively reverse rocuronium-induced neuromuscular block in surgical patients. Sugammadex was significantly faster in reversing rocuronium-induced neuromuscular block than neostigmine was at reversing cisatracurium-induced block. Both sugammadex and neostigmine were safe and well tolerated. The combination of rocuronium and sugammadex provides clinicians with a rapid onset, rapid reversal combination, which is potentially advantageous in, for instance, a busy operating list.

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