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Efficacy, safety and pharmacokinetics of sugammadex 4 mg kg⁻¹ for reversal of deep neuromuscular blockade in patients with severe renal impairment

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Abstract

Background: This study evaluated efficacy and safety of sugammadex 4 mg kg⁻¹ for deep neuromuscular blockade (NMB) reversal in patients with severe renal impairment (creatinine clearance [CL_{CR}] <30 ml min⁻¹) *vs* those with normal renal function (CL_{CR} ≥80 ml min⁻¹).

Methods: Sugammadex 4 mg kg⁻¹ was administered at 1–2 post-tetanic counts for reversal of rocuronium NMB. Primary efficacy variable was time from sugammadex to recovery to train-of-four (T_4/T_1) ratio 0.9. Equivalence between groups was demonstrated if two-sided 95% CI for difference in recovery times was within −1 to +1 min interval. Pharmacokinetics of rocuronium and overall safety were assessed.

Results: The intent-to-treat group comprised 67 patients (renal *n*=35; control *n*=32). Median (95% CI) time from sugammadex to recovery to T_4/T_1 ratio 0.9 was 3.1 (2.4–4.6) and 1.9 (1.6–2.8) min for renal patients *vs* controls. Estimated median (95% CI) difference between groups was 1.3 (0.6–2.4) min; thus equivalence bounds were not met. One control patient experienced acceleromyography-determined NMB recurrence, possibly as a result of premature sugammadex (4 mg kg⁻¹) administration, with no clinical evidence of NMB recurrence observed. Rocuronium, encapsulated by Sugammadex, was detectable in plasma at day 7 in 6 patients. Bioanalytical data for sugammadex were collected but could not be used for pharmacokinetics.

Conclusions: Sugammadex 4 mg kg⁻¹ provided rapid reversal of deep rocuronium-induced NMB in renal and control patients. However, considering the prolonged sugammadex-rocuronium complex exposure in patients with severe renal impairment, current safety experience is insufficient to support recommended use of sugammadex in this population.

Clinical trial registration: NCT00702715.

Key words: neuromuscular blockade; renal failure; rocuronium; sugammadex

Editor's key points

- Sugammadex was given to reverse rocuronium- induced deep NMB in 35 patients with renal impairment.
- The median time to recovery was 3.1 min in renal patients, and 1.9 min in controls.
- Sugammadex clearance is reduced in renal impairment.
- In view of prolonged sugammadex exposure in renal impairment, the current safety data are insufficient.

Sugammadex is a modified γ-cyclodextrin designed selectively to reverse the effects of the neuromuscular blocking agents (NMBAs) rocuronium and vecuronium. Sugammadex and the sugammadex-NMBA complex are excreted predominantly via the kidneys.[1] A previous study showed that sugammadex 2 mg kg^{-1} was well tolerated and effective in reversing moderate (administration at reappearance of second twitch [T_2] of the train of four) rocuronium-induced neuromuscular blockade (NMB) in patients with severe renal impairment. Sugammadex-mediated reversal of NMB was slower in patients with severe renal impairment and plasma clearance of sugammadex was reduced, compared with those with normal renal function.[2 3]

Sugammadex has been shown safely and effectively to antagonize deep rocuronium and vecuronium-induced NMB (1–2 post tetanic count [PTCs]).[4 5]

The aims of this study were to evaluate the efficacy, safety and pharmacokinetics of sugammadex 4 mg kg^{-1} for reversal of deep NMB in patients with severe renal impairment, and to compare the results with a control group of patients with normal renal function.

Methods

This was an open-label, case control, comparative study, known as the Firefly study (www.clinicaltrials.gov; NCT00702715; sponsor protocol number P05769) conducted at eight centres in Europe, between October 2008 and March 2010. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate ethics committees, institutional review boards and regulatory agencies.

Patients aged $\geq$18 years scheduled to undergo a surgical procedure using rocuronium for neuromuscular relaxation were included in the study. The aim was to enrol 35 patients with severe renal impairment (creatinine clearance [CL_{CR}] <30 ml min^{-1}), of ASA class I-III, with no anticipated need for haemodialysis during the first 24 h after sugammadex, and 35 control patients with normal renal function (CL_{CR} $\geq$80 ml min^{-1}). CL_{CR} was calculated using the Cockcroft & Gault formula,[6] assuming CL_{CR}=0 in renal patients on haemodialysis without urine production. Patients undergoing renal transplant surgery, those who were pregnant or breast-feeding women, or with neuromuscular disorders, hepatic dysfunction, a history of malignant hyperthermia, or allergy to narcotics, NMBAs or other medication used during general anaesthesia were excluded, as were patients receiving fusidic acid, toremifene and/or flucloxacillin, as these drugs have the potential to displace rocuronium from the sugammadex-NMBA complex.

Sample size was based on previous studies in which a dose of sugammadex 4 mg kg^{-1} was administered.[4 5 7 8] It was assumed that recovery data would follow a Gaussian distribution and that the standard deviation (SD) for recovery times would be equal in both subject populations. Consequently, the 95% confidence interval (CI) was based on Student's t distribution. It was calculated that 32 patients would need to be enrolled in each group to give ~80% (SD 1 min) probability of identifying equivalence in recovery times. Taking into account a 5–7% dropout rate, it was determined that a sample size of 35 patients per group would be required. Study sites enrolled renal and control patients in a 1:1 ratio. All patients provided written informed consent before enrolment.

Anaesthesia was induced and maintained with i.v. propofol and an opioid. Normothermia and normocapnia were maintained, and thenar skin temperature was measured continuously and maintained at 32°C throughout surgery. Neuromuscular monitoring was performed at the adductor pollicis muscle with acceleromyography (TOF-Watch® SX, Organon Ireland Ltd, a division of Merck and Co., Dublin, Ireland). After calibration of the TOF-Watch® SX, an i.v. bolus dose of rocuronium 0.6 mg kg^{-1} was given for tracheal intubation, with maintenance doses 0.1–0.2 mg kg^{-1} as necessary to maintain deep NMB at a target depth of 1–2 PTC. Patients received sugammadex 4 mg kg^{-1} i.v. for reversal after the last dose of rocuronium at a target depth of 1–2 PTC.

Efficacy endpoints

The primary efficacy endpoint was time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to $\geq$0.9. Based upon data from Phase II and IIIA sugammadex studies, a time to recovery of the T_4/T_1 ratio to 0.9 of >6 min was considered to be a prolonged recovery time. Secondary efficacy endpoints included the time from the start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.7 and 0.8.

Safety assessments

Safety was assessed from the screening period until four weeks post-surgery, and included adverse events (AEs), vital signs (heart rate and bp), laboratory data and physical examination. Patients were assessed for evidence of recurrence of NMB, both according to TOF-Watch® SX assessment (defined as a decrease in the T_4/T_1 ratio from $\geq$0.9 to <0.8 in at least three consecutive T_4/T_1 values) and clinically (assessed by routine measurement of oxygen saturation over 24 h after recovery to T_4/T_1 0.9 and breath frequency measurements).

Pharmacokinetic assessments

Blood samples to assess rocuronium concentrations before sugammadex administration were obtained pre-rocuronium dosing and at 2 and 15 min after the intubating dose of rocuronium. Sampling to assess both rocuronium and sugammadex concentrations was performed pre-sugammadex and at 5 and 20 min and 5, 10 and 24 h after administration of sugammadex. For renal patients, blood samples were also obtained 48 h after sugammadex and at days 7 and 28 post-surgery. For patients undergoing haemodialysis at time points 0–48 h after sugammadex, two additional samples were obtained pre- and post-dialysis.

Rocuronium and sugammadex concentrations in plasma were determined using validated liquid chromatographic assay methods with mass spectrometric detection by the Department of Bioanalytics-Waltrop, Merck Research Laboratories, Essex Pharma Development GmBH, Waltrop, Germany.[9] The assays were carried out in full compliance with Good Laboratory Practice

regulations. The assay methods do not differentiate between sugammadex and rocuronium in their free or complexed forms.

Statistical analysis

Efficacy analyses were performed using a non-parametric CI approach, which enables a quantitative measure of any differences between the groups. Median difference in recovery time between the groups and corresponding two-sided 95% CI were calculated using the Hodges-Lehmann estimator and Moses CI; as for previous studies of this type.[2][10] Equivalence in efficacy between the renal and control group was considered to be demonstrated when the CI for the difference between the groups was within a −1 to +1 min interval.

Data sets analysed

The intention-to-treat (ITT) group, which consisted of all treated patients who had at least one efficacy assessment, was used for the efficacy analyses. In the case of missing data, values were imputed using a relatively slow value (90th percentile) within each of the treatment groups. The all-subjects-treated (AST) group was used for the safety analysis. Pharmacokinetic analysis was performed for all subjects from the AST group who had measurable sugammadex or rocuronium concentration in ≥ 1 blood samples obtained at the specified sampling points and who did not have any protocol violations interfering with pharmacokinetics.

Results

A total of 69 patients were enrolled in the study, across eight European sites, of whom 68 received treatment with sugammadex (Nijmegen, Netherlands, n=24; Amsterdam, Netherlands, n=9; Zwolle, Netherlands, n=4; Manchester, UK, n=16; Cardiff, UK, n=1; Feldkirch, Austria, n=9; Wien, Austria, n=4; Créteil, France, n=1). Mean CL_{CR} in the renal failure group (n=35) was 13 ml min^{-1} (range 6–24 ml min^{-1}). Mean (range) CL_{CR} for the control group was 126 (61–230 ml min^{-1}). Twelve renal patients received haemodialysis after surgery. One patient in the control group received sugammadex rather than rocuronium, in error, and no efficacy measurements were performed; thus 67 patients were included in the ITT group and in all efficacy assessments (Fig. 1). Baseline characteristics of the AST group are shown in Table 1.

The median (range) total dose of rocuronium administered was 0.97 (0.59–2.10) mg kg^{-1} and 1.15 (0.59–2.90) mg kg^{-1} for renal and control group patients, respectively. Most renal patients (77%) underwent surgical procedures relating to dialysis.
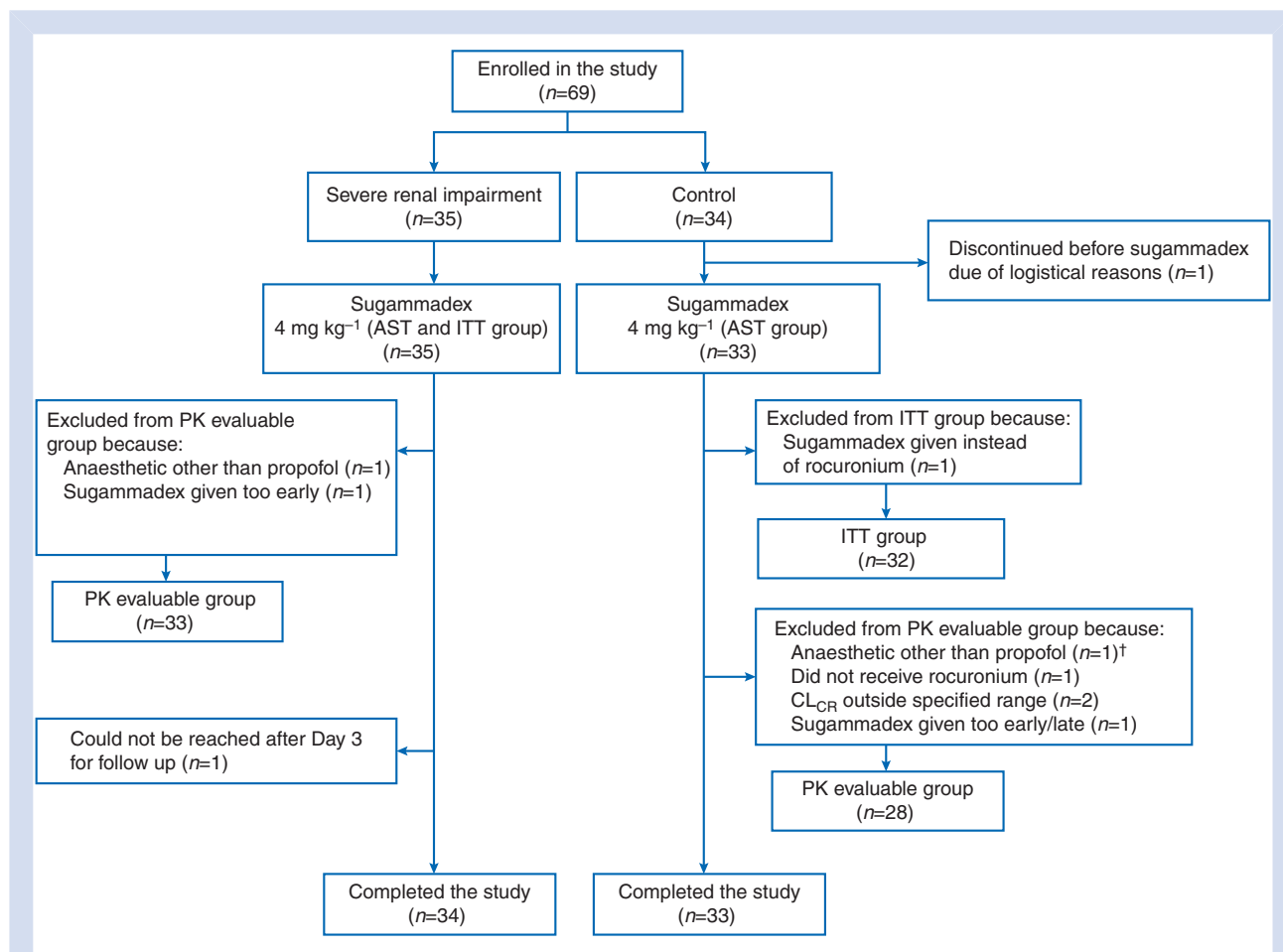
Fig 1 Patient flow through the study, in accordance with CONSORT guidelines. [†]This patient received sugammadex too early, which also constituted exclusion from the pharmacokinetically (PK) evaluable group; AST, all-subjects-treated; ITT, intent-to-treat.

Table 1 Summary of patient baseline characteristics (AST group; *n*=68). SD, standard deviation; [a]Two patients in the control group had a CL_{CR} below the pre-defined range of ≥80 ml min^{-1} (61 and 64 ml min^{-1}, respectively). However, as in both patients the CL_{CR} was closer to the minimum CL_{CR} of the control group than to the maximum CL_{CR} of the renal group, they were assigned to the control group by the investigator

	Renal group CL_{CR} <30 ml min^{-1} (*n*=35)	Control group CL_{CR} ≥80 ml min^{-1} (*n*=33)
Gender		
Male, *n* (%)	18 (51)	20 (61)
Female, *n* (%)	17 (49)	13 (39)
Age, yrs		
Mean (SD)	57 (16)	45 (15)
Weight, kg		
Mean (SD)	73 (22)	86 (20)
Race, *n* (%)		
White	30 (86)	33 (100)
Black or African American	3 (9)	0 (0)
Other	2 (6)	0 (0)
Ethnicity, *n* (%)		
Hispanic/Latino	0 (0)	1 (3)
Non-Hispanic/Latino	35 (100)	32 (97)
ASA Class, *n* (%)		
I	0 (0)	16 (48)
II	3 (9)	14 (42)
III	32 (91)	3 (9)
CL_{CR}, ml min^{-1}		
Mean (SD)	13 (5)	126 (41)
Range	6–24	61–230[a]
0–15 ml min^{-1}, *n* (%)	24 (69)	0 (0)
15–30 ml min^{-1}, *n* (%)	11 (31)	0 (0)
Haemodialysis, *n* (%)	12 (34)	0 (0)

Table 2 Median (95% CI) time (min) from the start of administration of sugammadex to recovery of the TOF ratio to 0.7, 0.8 and 0.9 (ITT group, *n*=67)[a]. [a]Data for the four patients with prolonged recovery times (3 renal and one control) are included in the efficacy analysis

	Renal group CL_{CR} <30 ml min^{-1} (*n*=35)	Control group CL_{CR} ≥80 ml min^{-1} (*n*=32)	P-Value
TOF 0.7	2.3 (1.7–3.3)	1.2 (1.1–1.8)	<0.0001
TOF 0.8	2.5 (2.0–3.8)	1.5 (1.3–2.1)	<0.0001
TOF 0.9	3.1 (2.4–4.6)	1.9 (1.6–2.8)	0.0002

Table 3 Number (%) of patients with at least one serious AE (AST group; *n*=68). [a]Pretibial wound of leg because of patient fall; [b]The recorded onset date of the serious AE reflects the date of pathological diagnosis with onset occurring before sugammadex administration; [c]high urea (26 mmol^{-1}) and associated symptoms of vomiting, confusion, worsening constipation

Serious AE, *n* (%)	Renal group CL_{CR} <30 ml min^{-1} (*n*=35)	Control group CL_{CR} ≥80 ml min^{-1} (*n*=33)
Pneumonia	1 (3)	0 (0)
Subdiaphragmatic abscess	0 (0)	1 (3)
Thrombophlebitis septic	1 (3)	0 (0)
Anastomotic leak	0 (0)	1 (3)
Incision site haematoma	1 (3)	0 (0)
Narcotic intoxication	1 (3)	0 (0)
Seroma	0 (0)	1 (3)
Wound[a]	1 (3)	0 (0)
Wound haemorrhage	2 (6)	0 (0)
Benign ovarian tumour	1 (3)	0 (0)
Ovarian cancer[b]	0 (0)	1 (3)
Azotaemia[c]	1 (3)	0 (0)
Pulmonary oedema	1 (3)	0 (0)
Respiratory failure	1 (3)	0 (0)
Necrosis as a result of vascular insufficiency	1 (3)	0 (0)
Blood creatinine increased	1 (3)	0 (0)

Efficacy analyses

Median (95% CI) time from the start of sugammadex administration to recovery of the T_4/T_1 ratio to 0.9 (primary efficacy endpoint) was 3.1 (2.4–4.6) and 1.9 (1.6–2.8) min for renal and control patients, respectively (Table 2). Times to recovery to T_4/T_1 ratios of 0.7 and 0.8 are also shown in Table 2. The median (95% CI) difference in recovery times to TOF ratio 0.9 between the two groups was 1.3 (0.6–2.4) min. As the CI of this difference in recovery times between the SRI and control groups did not lie entirely within the pre-specified –1 to +1 min interval, equivalence of efficacy between the patient groups could not be demonstrated.

Four patients (three renal patients and one control) had prolonged times to recovery of the T_4/T_1 ratio to 0.9. In the renal group, the prolonged recovery times were 6.3, 8.0 and 14.1 min. One patient in the control group had a recovery time of 6.4 min. All four patients were included in the ITT group, and efficacy analyses.

Safety analyses

In the AST group, at least one AE was experienced by 66% of renal patients and 70% of controls. The most frequently occurring AE in both groups was: procedural pain (*n*=9 for renal patients; *n*=11 for controls). Two patients in the control group experienced AEs that were considered by the investigator to be possibly related to sugammadex (recurrence of NMB [*n*=1] and diarrhoea [*n*=1]). The acceleromyographically determined recurrence of NMB was likely to be attributable to the administration of sugammadex (4 mg kg^{-1}) when 1 PTC was measured for the first time, only 5 min after the intubating dose of rocuronium was administered; in this onset phase of NMB, the recommended sugammadex dose is 16 mg kg^{-1}.[11] Both patients recovered fully from the AEs. No clinical evidence (i.e. respiratory problems) of residual NMB or recurrence of NMB was reported after extubation for any patient.

At least one serious AE was reported for nine renal patients and three patients in the control group; none were considered to be related to sugammadex (Table 3). Out of three renal patients receiving anticoagulant medication two had wound haemorrhage and one wound haematoma. One patient had a benign ovarian tumour and one had ovarian cancer; both had reported

onset of signs or symptoms before administration of sugammadex. All subjects with reported serious AEs recovered from the Serious AE, with the exception of the patient with ovarian cancer. There were no deaths during the study.

For three renal and two control patients, a total of six AEs were reported that were related to changes in pre-specified laboratory safety parameters. These were one patient each with increased: gamma GT, blood creatinine and blood creatine phosphokinase in the renal group, and two patients with increased neutrophils and a patient with increased white blood cells in the control group. The increased concentration of blood creatinine in a renal patient was considered a serious AE (Table 3). None of these AEs were considered to be related to sugammadex. In the renal group, mean liver enzyme values remained generally similar over time, with modest increases observed in alkaline phosphatase and gamma glutamyl transferase at Days 7 and 28. In the control group, in which patients underwent a higher frequency of intra-abdominal procedures (cholecystectomies), modest mean increases were observed in all liver enzyme parameters and were also most prominent at Days 7 and 28 (Table 4). No clinically meaningful changes in vital signs or haematology were observed in either group.

Pharmacokinetic analysis

In total, the data from 61 patients were evaluable for pharmacokinetic assessment (Fig. 1), including the four patients with prolonged recovery times. Unfortunately the validity of sugammadex bioanalytical data failed to reach quality standards at an internal audit conducted by Merck & Co., Inc. after closure of the study. Sample to sample carryover could not be ruled out. Re-assay was not possible because of unavailable duplo samples and stability issues. As a result all Sugammadex bioanalytical data are to be considered invalid and cannot be used for pharmacokinetic analysis. Median plasma concentrations for rocuronium are shown in Fig. 2. During the first 20 min after dosing sugammadex, plasma concentrations of rocuronium were similar in both groups. Thereafter, rocuronium concentrations decreased faster in the control than renal group.

Six renal patients had measurable rocuronium concentrations (above LLOQ of 2 ng ml^{-1}) at Day 7, with no patients having measurable rocuronium concentrations at Day 28.

Rocuronium pharmacokinetic parameters were not calculated as many subjects received maintenance doses of rocuronium in addition to the initial dose and calculation of pharmacokinetic parameters under these conditions according to non-compartmental pharmacokinetic methods was not appropriate.

Haemodialysis

Twelve patients received haemodialysis during the study (18–47 h post-surgery; duration 3–4 h), haemodialysis methods differed between centres. Pharmacokinetic effect of haemodialysis could not be analysed.

Discussion

Sugammadex 4 mg kg^{-1} resulted in complete, rapid and well-tolerated reversal of deep rocuronium-induced NMB both in patients with severe renal impairment and in controls with normal renal function. The estimated median (95% CI) difference in recovery times between groups indicated that time from start of sugammadex to recovery of the T_4/T_1 ratio to 0.9 was slower in the renal group. This finding is in line with a previous case-control study,[2] in which sugammadex 2 mg kg^{-1} was administered at reappearance of T_2; in this study the estimated mean (95% CI) difference in recovery times between the two groups was 0.5 min (0.2–1.1) min.[2] It was not expected that administration of sugammadex 4 mg kg^{-1} at deep NMB would result in prolongation of recovery time vs sugammadex 2 mg kg^{-1} at moderate NMB. In both studies, patients in the renal group had a high burden of underlying medical conditions that could have contributed to their longer recovery times. While cardiac output was not assessed in the current study, kidney disease is often associated with reduced cardiac function.[12 13] A study performed in elderly patients demonstrated that reduced cardiac output is correlated with slower recovery after sugammadex (2 mg kg^{-1}) for moderate rocuronium-induced NMB reversal.[14] Further data from studies investigating the onset and recovery of NMB with respect to cardiac output in selected populations will provide the required knowledge for clinical application.

In the present study, administration of sugammadex 4 mg kg^{-1} resulted in rapid recovery to a T_4/T_1 ratio of 0.9 in both groups; in total, 71% of patients in the renal group achieved a T_4/T_1 ratio of 0.9 in <5 min, compared with 97% of control patients (ITT group). However, as the median (95% CI) difference in recovery times between groups in the present study did not lie within the pre-specified –1 to +1 min interval, equivalence with respect to efficacy was not demonstrated. Nevertheless, it is important to note that the median 3.1 min recovery time observed in renal patients remains considerably more rapid compared with neostigmine reversal of deep[4] and moderately deep (in the presence of desflurane maintenance anaesthesia).[15]

Four patients included in the efficacy and pharmacokinetic analyses had prolonged times to recovery which were considered to be related to their clinical condition, old age and/or technical issues with neuromuscular monitoring. Importantly, there was no evidence of recurrence of NMB in any patient with severe renal impairment. Occasional outliers in NMB recovery can be expected in patients with severe renal impairment. The prolonged time to recovery in the control patient in this study, however, was considered to be exclusively related to technical issues with neuromuscular monitoring.

The efficacy findings in this study are comparable with findings from other studies where sugammadex was given at 1–2 PTC for reversal of deep rocuronium NMB.[4 8] These suggest that sugammadex may facilitate optimal surgical conditions in procedures benefiting from deep NMB by allowing the anaesthetist to maintain deep blockade until the end of surgery without the concern of prolonged recovery at the end of the procedure, which should thus help to improve patient safety.[16]

Sugammadex was generally well tolerated in both patient groups and no safety signals were observed in the renal patients. Two renal patients receiving anticoagulant medication had wound haemorrhage and one receiving anticoagulant medication had wound haematoma. Patients with severe renal impairment may be at increased risk of bleeding in general and the use of anticoagulants increases this risk. It is currently recommended that caution be exercised when considering the use of sugammadex in patients receiving therapeutic anticoagulation for a pre-existing or co-morbid condition.[11]

In the present study, performed pharmacokinetic analysis of sugammadex had to be considered invalid and clearance could not be calculated. Six renal patients still had measurable rocuronium concentrations above the LLOQ at Day 7. In the case of prolonged measurable rocuronium in combination with the assumption of reduced sugammadex clearance,[3] this is likely to be rocuronium which is encapsulated by sugammadex.

Table 4 Changes from baseline for liver function test parameters, (AST group; *n*=68)

| Liver function parameter % change from baseline	Renal group CL$_{CR}$ <30 ml min^{-1} (*n*=35)					Control group CL$_{CR}$ ≥80 ml min^{-1} (*n*=33)				
	20 min	5 h	Post-anaesthetic	Follow-up Day 7	Follow-up Day 28	20 min	5 h	Post-anaesthetic	Follow-up Day 7	Follow-up Day 28
Alanine aminotransferase										
n	35	35	34	33	34	33	32	32	33	31
Mean (SD)	1.83 (16.93)	6.67 (25.32)	−1.96 (29.38)	21.09 (84.19)	64.90 (177.94)	0.30 (14.50)	51.35 (114.16)	56.60 (140.50)	79.65 (118.07)	38.35 (91.68)
Range	−45.5–40.0	−50.0–100.0	−54.5–110.0	−72.7–300.0	−64.3–950.0	−31.6–31.6	−21.1–491.7	−46.2–626.7	−66.7–600.0	−55.6–500.0
Albumin										
n	35	35	35	33	34	33	32	32	33	31
Mean (SD)	−5.35 (7.20)	−1.28 (7.39)	0.45 (9.62)	7.79 (12.57)	11.79 (10.47)	−7.49 (10.71)	−0.45 (10.47)	0.43 (16.91)	14.34 (14.83)	16.71 (10.44)
Range	−22.1–12.5	−17.4–15.2	−13.4–33.0	−15.1–45.6	−13.7–32.6	−41.9–8.2	−39.6–17.4	−63.3–24.3	−43.7–38.0	−19.7–34.3
Alkaline phosphatase										
n	35	35	35	33	34	33	32	32	33	31
Mean (SD)	−4.63 (7.86)	−0.32 (10.17)	3.70 (14.83)	20.90 (35.67)	30.97 (67.34)	−6.77 (12.34)	1.05 (13.03)	1.64 (21.00)	29.17 (29.76)	23.70 (21.92)
Range	−23.2–14.6	−20.3–21.1	−33.3–30.4	−38.6–154.7	−72.5–366.7	−41.7–12.7	−38.3–24.1	−65.3–51.7	−11.8–149.2	−18.2–95.2
Aspartate aminotransferase										
n	35	35	35	33	34	33	32	32	33	31
Mean (SD)	−7.82 (19.65)	4.37 (23.86)	5.73 (31.94)	12.26 (53.99)	16.16 (45.39)	4.83 (22.89)	87.27 (174.09)	58.58 (128.36)	36.65 (101.05)	11.82 (29.05)
Range	−79.4–31.3	−76.5–66.7	−73.5–100.0	−73.5–166.7	−64.7–145.5	−23.1–87.5	−12.0–706.3	−38.5–500.0	−59.3–538.5	−23.1–92.3
Bilirubin										
n	35	35	34	33	34	33	32	32	33	31
Mean (SD)	−7.61 (22.14)	−0.05 (47.13)	15.98 (60.82)	−0.80 (50.13)	12.90 (56.07)	−2.06 (29.23)	24.32 (54.20)	40.18 (62.69)	24.28 (65.08)	23.67 (51.64)
Range	−50.0–51.5	−83.5–152.9	−83.5–200.0	−66.7–152.9	−62.8–200.0	−50.0–68.6	−66.7–168.6	−75.0–152.9	−50.5–202.9	−50.0–152.9
Gamma GT										
n	35	35	35	33	34	33	32	32	33	31
Mean (SD)	−6.95 (9.07)	3.74 (24.31)	3.85 (20.99)	25.74 (46.09)	74.57 (309.16)	−7.16 (12.92)	57.42 (176.70)	50.38 (148.87)	78.30 (114.17)	31.93 (46.13)
Range	−26.1–15.0	−22.2–128.6	−30.4–71.4	−38.5–182.6	−75.4–1805.9	−36.4–14.3	−36.4–900.0	−55.0–557.1	−18.3–627.3	−64.7–145.5
Protein total										
n	35	35	35	33	34	33	32	32	33	31
Mean (SD)	−4.99 (7.19)	−1.28 (7.61)	0.31 (9.43)	9.01 (11.62)	10.79 (9.62)	−7.66 (11.20)	−0.24 (10.45)	0.37 (17.46)	17.53 (13.74)	18.58 (8.59)
Range	−19.1–9.5	−18.6–13.9	−13.3–32.6	−11.7–38.3	−9.3–28.6	−43.9–9.5	−39.4–14.8	−64.1–29.5	−30.6–41.5	2.7–39.6
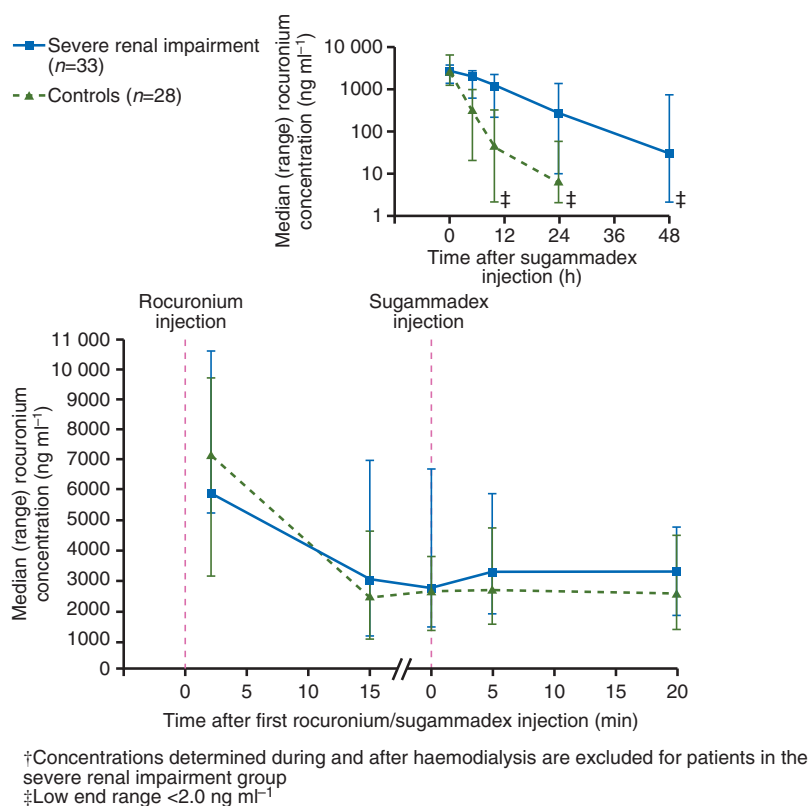
Fig 2 Median (range) rocuronium plasma concentration (ng ml^{-1}) *vs* time (min) after injection of rocuronium and sugammadex, for time points up to 20 min after injection of sugammadex. Inset shows a logarithmic plot of median rocuronium plasma concentration (ng ml^{-1}) *vs* time (h) for time points up to 48 h after injection of sugammadex[†].

Unfortunately, the assay methods used did not allow differentiation between sugammadex and rocuronium in their free or complexed forms. Toxicity studies indicate that γ-cyclodextrins are safe for use in the doses recommended for sugammadex[17]; however renal insufficiency can result in accumulation of many forms of cyclodextrin.[18] Considering the prolonged sugammadex exposure in patients with severe renal impairment, current safety experience is considered insufficient to support recommended use of sugammadex in this patient population.

Owing to its molecular size and charge, dialysability of sugammadex was expected to be good. In this study, only limited numbers of patients received haemodialysis, and parameters such as time spent on dialysis and the type of membranes used were not standardized between study centres. Indeed, there is a need for more controlled studies in dialysis patients in the future. High-flux haemodialysis filters appeared to be more effective than low-flux in removing sugammadex and its complex with rocuronium from the circulation. This has been described in a recent study in dialysis patients in which high-flux haemodialysis was shown to be effective in removing the sugammadex 4 mg kg^{-1} rocuronium 0.6 mg kg^{-1} complex in patients with severe renal impairment when sugammadex was administered 15 min after rocuronium.[19]

In summary, sugammadex 4 mg kg^{-1} provided rapid reversal of deep rocuronium-induced NMB in renal and control patients, including occasional prolonged times to recovery in renal patients as a result of underlying medical conditions. However,

considering the up to 7 days prolonged sugammadex complexed rocuronium exposure in patients with severe renal impairment in some cases, current safety experience is insufficient to support the use of sugammadex in patients with a creatinine clearance <30 ml min^{-1} at this time.

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Authors' contributions

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