

# Dialysability of sugammadex and its complex with rocuronium in intensive care patients with severe renal impairment

G. Cammu<sup>1\*</sup>, B. Van Vlem<sup>2</sup>, M. van den Heuvel<sup>4</sup>, L. Stet<sup>5</sup>, R. el Galta<sup>6</sup>, S. Eloot<sup>2</sup> and I. Demeyer<sup>3</sup>

<sup>1</sup> Department of Anaesthesiology and Critical Care Medicine, <sup>2</sup> Renal Unit, and <sup>3</sup> Department of Emergency Medicine, Onze-Lieve-Vrouw Ziekenhuis, Moorselbaan 164, 9300 Aalst, Belgium

<sup>4</sup> Clinical PKPD, <sup>5</sup> CNS Global Clinical Trial Management, and <sup>6</sup> Biostatistics and Research Decision Sciences, MSD, Oss, The Netherlands

\* Corresponding author. E-mail: guy.cammu@olvz-aalst.be

## Editor's key points

- The action of both sugammadex and rocuronium is prolonged in renal failure patients.
- Study of the effect of haemodialysis on the sugammadex–rocuronium complex.
- Dialysis with a sustained low-efficiency daily dialysis technique in 6 renal failure patients.
- Sugammadex and the sugammadex–rocuronium complex were removed by high-flux dialysis.

**Background.** Renal excretion is the primary route for the elimination of sugammadex. We evaluated the dialysability of sugammadex and the sugammadex–rocuronium complex in patients with severe renal impairment in the intensive care unit (ICU).

**Methods.** Six patients in the ICU with acute severe renal impairment received general anaesthesia for transoesophageal echocardiography, to replace their tracheal tubes, or for bronchoscopy. Five of the six patients were in the ICU after cardiac/vascular surgery and one for pneumonia-induced respiratory failure. They all received rocuronium 0.6 mg kg<sup>-1</sup>, followed 15 min later by sugammadex 4.0 mg kg<sup>-1</sup>. Two patients were studied for two dialysis episodes and four patients for four episodes. Rocuronium and sugammadex concentrations were measured in plasma and dialysate at several time points before, during, and after high-flux dialysis. Dialysis clearance in plasma and dialysate, and reduction ratio (RR) (the extent of the plasma concentration reduction at the end of a dialysis episode when compared with before dialysis) were calculated for each dialysis episode.

**Results.** Dialysis episodes lasted on average 6 h. Observed RRs indicated mean reductions of 69% and 75% in the plasma concentrations of sugammadex and rocuronium, respectively, during the first dialysis episode. Reductions were around 50% during sequential dialysis episodes. On average, dialysis clearance of sugammadex and rocuronium in blood was 78 and 89 ml min<sup>-1</sup>, respectively.

**Conclusions.** Haemodialysis using a high-flux dialysis method is effective in removing sugammadex and the sugammadex–rocuronium complex in patients with severe renal impairment.

**Keywords:** kidney failure; neuromuscular block; renal dialysis; rocuronium; sugammadex

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Sugammadex specifically binds with high affinity to the steroidal neuromuscular blocking agents rocuronium and vecuronium.<sup>1</sup> Phase I–III trials have shown that sugammadex is generally well tolerated and effectively antagonizes both moderate [return of the second twitch (T<sub>2</sub>)] and deep (1–2 post-tetanic counts) rocuronium- and vecuronium-induced neuromuscular block (NMB).<sup>2–8</sup> Sugammadex is excreted in an unchanged state in the urine, with more than 90% of the dose excreted via the renal route within 48 h of administration.<sup>9 10</sup>

The effects of rocuronium may be prolonged in patients with renal disease, because of decreased clearance of the drug;<sup>11</sup> clearance of rocuronium is reduced by 39% in end-stage renal failure patients compared with healthy controls.<sup>12</sup> Interestingly, renal excretion of rocuronium is

increased by the use of sugammadex: the median cumulative excretion of rocuronium in the urine over a 24 h period increases from 26% with placebo to 58–74% of the administered dose after treatment with 4–8 mg kg<sup>-1</sup> of sugammadex.<sup>13</sup>

A prolonged and increased exposure to the sugammadex–rocuronium complex was expected in patients with impaired renal function, although the efficacy of sugammadex was expected to be similar to that in patients with normal renal function. A study of 15 patients with chronic severe renal impairment who received sugammadex for the reversal of moderate rocuronium-induced block was consistent with these expectations.<sup>14 15</sup> As anticipated, different pharmacokinetics over time were observed for total rocuronium and sugammadex in these patients in comparison

with patients with normal renal function. For sugammadex, plasma clearance was reduced by  $\sim 17$ -fold, terminal half-life increased by 16-fold, and distribution volume increased by 20%, resulting in a prolonged and 16-fold higher exposure to sugammadex in renally impaired patients. However, peak plasma concentrations were similar between the two groups. For rocuronium, plasma clearance was reduced by  $\sim 4$ -fold, terminal half-life increased by 2.5-fold, and distribution volume increased by 15%, which resulted in a prolonged and 3.5-fold higher exposure to rocuronium (bound and unbound). The clearance of sugammadex and, to a lesser extent, rocuronium exhibited a highly significant correlation with creatinine clearance, which confirms the importance of renal elimination for the clearance of sugammadex.<sup>15</sup> Despite the altered kinetics of sugammadex and rocuronium in these patients with chronic severe renal impairment, there were no apparently related adverse events (AEs).

A dedicated *in vivo* study of haemodialysis of the sugammadex–rocuronium complex has not been conducted. In the study by Staals and colleagues,<sup>14 15</sup> some patients received haemodialysis within the first 72 h after surgery. As only two patients underwent high-flux haemodialysis, no conclusions regarding dialysability with these membranes could be drawn; low-flux filters ( $n=7$ ) appeared to be ineffective in the removal of sugammadex from the circulation. The current study was designed to evaluate the dialysability of the sugammadex–rocuronium complex, after administration of rocuronium  $0.6 \text{ mg kg}^{-1}$  and subsequent sugammadex  $4.0 \text{ mg kg}^{-1}$ , in patients with severe renal impairment on haemodialysis and to evaluate the efficacy of sugammadex in this patient group. The  $4.0 \text{ mg kg}^{-1}$  sugammadex dose was chosen as this represents the highest recommended dose for routine reversal in clinical practice.

## Methods

This study, the Filter study (NCT00656799; sponsor protocol number P05773), was approved by the independent ethics committee of the trial centre and was conducted in accordance with Good Clinical Practice and current regulatory requirements. Written informed consent was obtained from each patient or legal representative before any study-related activity. A total of six patients were selected from patients in the intensive care unit (ICU) and undergoing a procedure under general anaesthesia that required neuromuscular relaxation (Table 1). Patients were eligible for participation in the study if they were  $>18$  yr of age, ASA class  $\leq$ IV, and with severe renal impairment (creatinine clearance  $<30 \text{ ml min}^{-1}$ , requiring dialysis). Dialysis was performed using a sustained low-efficiency daily dialysis (SLEDD) technique. This method uses a high-flux dialysis membrane, but keeps the flow of blood and dialysate low. The Fresenius 4008H haemodialyser (Fresenius Medical Care AG, Bad Homburg, Germany) was used, with an FX 600 haemodiafilter standard helixone membrane (surface  $1.5 \text{ m}^2$ ). The ultrafiltration coefficient of the FX 600 membrane was  $52 \text{ ml h}^{-1} \text{ mm Hg}^{-1}$ .

Unfractionated heparin, activated clotting time adjusted (120–150 s), was used for anticoagulation.

After an adequate level of anaesthesia was ensured, patients received an i.v. single bolus dose of rocuronium  $0.6 \text{ mg kg}^{-1}$  for NMB. Exactly 15 min after the rocuronium, a single bolus dose of sugammadex  $4.0 \text{ mg kg}^{-1}$  was given for reversal. Both sugammadex and rocuronium were given within 10 s into a fast-running infusion. Doses were based on the actual body weight of each patient. Blood and dialysate samples were collected before, during, and after each episode of haemodialysis in order to calculate the clearance of the sugammadex–rocuronium complex. Haemodialysis did not start until after the end of the distribution phase, that is, at least 1 h after administration of sugammadex. Rocuronium and sugammadex concentrations in plasma and dialysate were evaluated using validated liquid chromatographic assay methods with mass spectrometric detection at the Department of Bioanalytics, MSD, Oss, the Netherlands, in compliance with Good Laboratory Practice regulations.<sup>16 17</sup> The concentrations of rocuronium and sugammadex in plasma and dialysate were assessed in samples obtained before, during (at 15 min, 1, and 2 h after the start of dialysis, and before the end of dialysis), and at 15 min and 6 h after dialysis. Blood samples were obtained from ports in the arterial and venous tubing of the dialyser, whereas dialysate samples were taken from a port in the outflow of the dialyser. As pre-specified, the clearance of the rocuronium–sugammadex complex was to be considered effective if the mean clearance was  $\sim 50 \text{ ml min}^{-1}$  or more.

The assay methods used to determine sugammadex and rocuronium levels did not discriminate between complexed and non-complexed sugammadex and rocuronium, as during sample processing and analysis, the sugammadex–rocuronium complexes are disrupted.<sup>16 17</sup> Therefore, plasma and dialysate concentrations and also pharmacokinetic parameters indicate total concentrations of sugammadex and rocuronium.

The dialysis clearance for each patient was calculated from the sugammadex and rocuronium plasma concentration [the plasma concentrations in the arterial line in the dialyser ( $C_{in}$ ) and in the venous line of the dialyser ( $C_{out}$ )] and dialysate concentrations ( $C_d$ ). The dialysis clearance was calculated in blood (CL<sub>b</sub>) and in dialysate (CL<sub>d</sub>).

CL<sub>b</sub> was calculated from  $C_{in}$  and  $C_{out}$  using the formula:  $CL_b = Q_b \times (C_{in} - C_{out}) / C_{in}$ , where  $Q_b$  is the effective rate of blood flow. The means of the minimum and maximum blood flow rates for each dialysis episode were used for the calculation. No replacements of clearance values were made in the event that the concentration was below the lower limit of quantification (LLOQ). The dialysis clearance in plasma was calculated from the dialysis clearance in blood as:  $CL_p = CL_b \times (1 - Hct)$ , where Hct represents the haematocrit value (%). CL<sub>d</sub> was calculated from  $C_{in}$  and  $C_d$  using the formula:  $CL_d = Q_d \times C_d / C_{in}$ , where  $Q_d$  represents the dialysate flow rate (set to  $300 \text{ ml min}^{-1}$  during the trial). No replacements of clearance values were made in

**Table 1** Patient clinical data. AVR, aortic valve replacement; MVR, mitral valve replacement; TVP, tricuspid valve plasty; CABG, coronary artery bypass grafting; IABP, intra-aortic balloon pump; MVP, mitral valve plasty; TT, tracheal tube; TOE, transoesophageal echocardiography

No.	Sex	Age (yr)	Weight (kg)	Diagnosis	Admission SAPS II score	Haematocrit (%)	Creatinine clearance (ml min <sup>-1</sup> )	Inotropic agents	Interventional procedure	Anaesthetic technique	Time interval between administration of sugammadex and starting dialysis (h:min)
1	F	80	52	AVR–MVR–TVP	38	26.5	10.47	Dobutamine; norepinephrine	Re-intubation (replacement TT)	Propofol	1:28
2	F	81	62	CABG–AVR	41	26	16.95	Dobutamine; norepinephrine	Re-intubation (replacement TT)	Propofol; morphine	1:06
3	M	80	80	Respiratory failure (pneumonia)	55	22.8	22.09	Dobutamine	TOE (suspected myocardial infarction)	Propofol; remifentanyl	2:08
4	M	76	95	Urgent CABG–IABP	56	30.4	17.31	Dobutamine; norepinephrine	TOE (cardiac evaluation after CABG)	Midazolam; sufentanyl	1:26
5	M	77	70	Replacement of infected thoracic aortic prosthesis	30	25.4	18.08	Dobutamine; norepinephrine	Bronchoscopy for bronchial aspiration	Midazolam	1:07
6	M	63	84	CABG–AVR–MVP	47	26.9	25.90	Epinephrine	TOE (postoperative heart failure)	Propofol; remifentanyl	1:01

the event that the concentration was below the LLOQ. For calculations of CL<sub>b</sub> and CL<sub>d</sub>, the ultrafiltrate flow rate was ignored because a standard haemodialysis method was used. For each patient and each dialysis episode, the CL<sub>b</sub> and CL<sub>d</sub> were averaged across time points if at least two assessments were available.

The reduction ratio (RR) was calculated for each patient and each dialysis episode as the ratio of the total reduction in plasma concentration relative to the pre-dialysis concentration:

$$RR = [C(\text{pre-dialysis}) - C(15 \text{ min after end of dialysis})] / C(\text{pre-dialysis})$$

The rebound ratio was calculated for each patient and each dialysis episode as the ratio of the concentration rebound relative to the arterial concentration just before the discontinuation of dialysis: rebound ratio = (C<sub>post-dialysis</sub> - C<sub>end</sub>) / C<sub>end</sub>, where C<sub>end</sub> is the observed concentration that was obtained from the arterial port of the dialyser circuit just before the discontinuation of dialysis, and C<sub>post-dialysis</sub> is the observed plasma concentration 15 min and 6 h after the completion of dialysis. For the calculations, the LLOQ value was used when concentrations were below the LLOQ; the LLOQ for sugammadex in both the plasma and dialysate assays is 0.1 µg ml<sup>-1</sup>, while for rocuroonium, it is 2.0 ng ml<sup>-1</sup> in plasma and 1.0 ng ml<sup>-1</sup> in dialysate.

Descriptive statistics for the pharmacokinetic variables included mean, standard deviation, median, minimum, and maximum. The tables, plots, parameters, and descriptive statistics pertaining to the pharmacokinetic evaluation were generated using SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Neuromuscular function was monitored by acceleromyography using the TOF-Watch<sup>®</sup> SX (Organon Ireland Ltd, a subsidiary of Merck and Co., Swords, Co., Dublin, Ireland) at the adductor pollicis muscle. Monitoring started after the induction of anaesthesia (before rocuroonium administration) and continued for at least 10 min after recovery of the train-of-four (TOF) ratio to 0.9. Repetitive TOF stimulation was applied every 15 s at the ulnar nerve. Neuromuscular data were collected via a transducer that was fixed to the thumb and the TOF-Watch<sup>®</sup> SX monitoring programme. TOF-Watch<sup>®</sup> SX calibration was performed >3 min after a 5 s, 50 Hz tetanic stimulation and was preceded by a 1 min repetitive TOF stimulation. In addition, peripheral body temperature was continuously measured by a thermistor at the thenar eminence of the palm and maintained at ≥32°C during neuromuscular transmission monitoring. The times from the initiation of sugammadex treatment to T<sub>4</sub>/T<sub>1</sub> ratios of 0.7, 0.8, and 0.9 were measured.

Safety measurements included assessment of pre-treatment events, AEs, vital signs (arterial pressure and heart rate), and physical examination. Patients were also evaluated for signs of residual block or the recurrence of block, which was defined as a decline in the T<sub>4</sub>/T<sub>1</sub> ratio to

≤0.8 in at least three consecutive TOF values after sugammadex treatment.

## Results

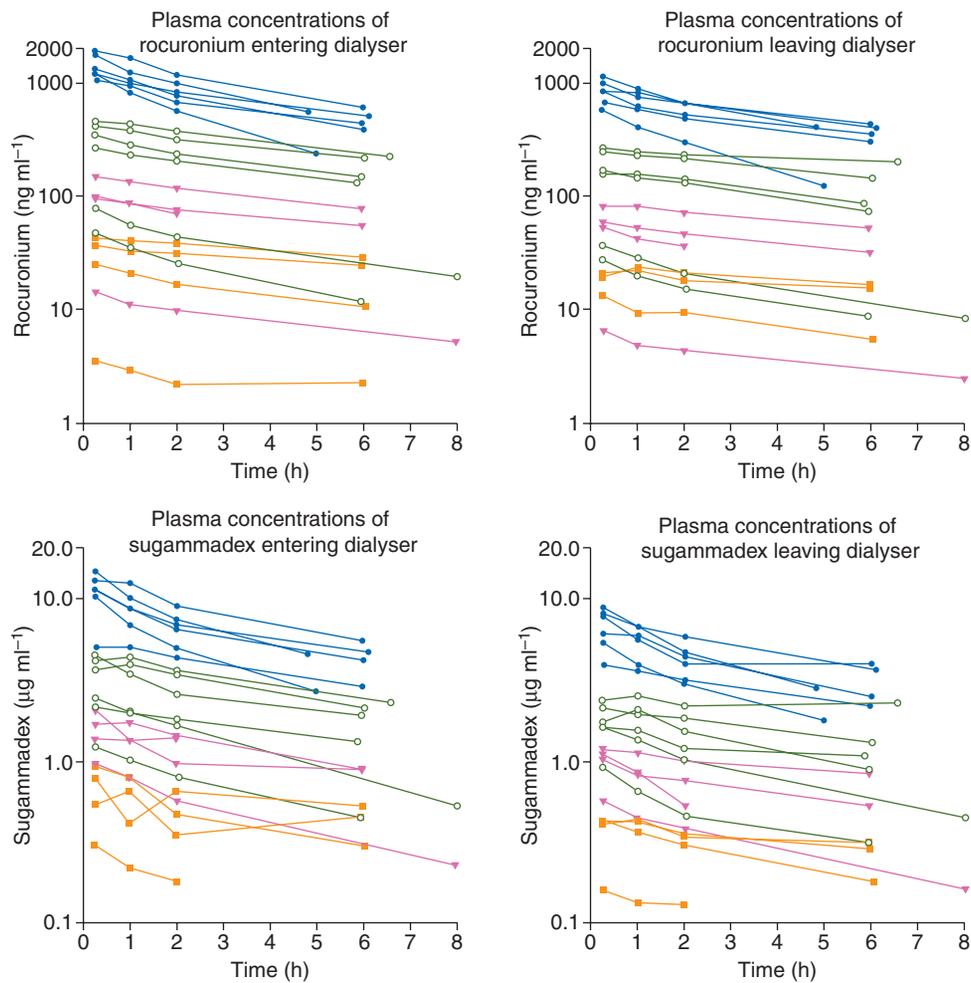
Six patients were included, all of whom received rocuroonium 0.6 mg kg<sup>-1</sup> followed by sugammadex 4.0 mg kg<sup>-1</sup>. At inclusion, all six patients were hospitalized on the ICU, had significant comorbidities in addition to the inclusion criterion of severe renal failure (estimated creatinine clearance of <30 ml min<sup>-1</sup>), and required dialysis. None of the patients had any residual urinary output, except for one who passed 36 ml of urine over 24 h. No pharmacokinetic analysis was performed on this single amount of urine. All patients were anaesthetized during the procedure for which they received sugammadex.

One patient was not dialyzed before the study started, two patients had one dialysis, and three patients had four dialyses before the study commenced. During the study period, two patients were studied for two episodes of haemodialysis and four patients were studied for four episodes. Except for one episode of one patient, all patients were dialysed daily. Dialysis episodes lasted for a median of 6 h (range: 4.9–8 h). Of the 20 dialysis episodes, an FX 600 high-flux dialysis helix-one membrane was used 19 times, while an FX 50 membrane (ultrafiltration coefficient: 33 ml h<sup>-1</sup> mm Hg<sup>-1</sup>) was erroneously used once. The results of the one dialysis episode performed with the FX 50 membrane were excluded from the evaluation because this type of membrane has a smaller surface area (1.0 m<sup>2</sup>).

Sugammadex and rocuroonium concentrations in plasma entering and leaving the dialyser vs time during the dialysis episodes are presented as overlay plots (Fig. 1). The RRs that were calculated for the first dialysis episodes indicate, on average, reductions of 69% and 75% in the plasma concentrations of sugammadex and rocuroonium, respectively, with reductions of around 50% during sequential episodes (Table 2). The mean per cent increases in concentrations 15 min and 6 h after the completion of dialysis were 9% and 19%, respectively, for sugammadex and 6% and 5%, respectively, for rocuroonium, indicating some rebound effects. Because of pre-study administration of rocuroonium (within 3–7 days), for five out of six patients, measurable pre-dose rocuroonium concentrations were detected in plasma (varying from 7.82 to 47.8 ng ml<sup>-1</sup>). These concentrations were ~0.3–2% of the rocuroonium concentration that was present at the time of sugammadex administration.

On average, blood clearance of sugammadex over two to four dialysis episodes was 78 ml min<sup>-1</sup>, and dialysate clearance was 65 ml min<sup>-1</sup>, whereas blood clearance of rocuroonium was 89 ml min<sup>-1</sup>, and dialysate clearance was 94 ml min<sup>-1</sup> (Table 2).

The median time from the start of the administration of sugammadex to the recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.7 was 2.7 min (range 2.0–7.6 min), to 0.8 was 3.2 min (range 2.7–8.1 min), and to 0.9 was 4.2 min (range 3.4–9.8 min).



**Fig 1** Overlay plots of concentrations in plasma entering the dialyser and leaving the dialyser vs time for the sequential dialysis episodes. Each single line represents the measurements of one patient. Solid circles: first dialysis episode; open circles: second dialysis episode; solid triangles: third dialysis episode; and solid squares: fourth dialysis episode. Concentrations pertain to total sugammadex and total rocuronium. Time 0, start of dialysis.

Two patients had markedly long times for the recovery of the  $T_4/T_1$  ratio to 0.7 and, consequently, long times for the recovery of the  $T_4/T_1$  ratio to 0.8 and 0.9. For one of these two patients, the times for the recovery of the  $T_4/T_1$  ratio to 0.7, 0.8, and 0.9 were 7.6, 8.1, and 9.8 min, respectively. For the other patient, these were 6.3, 7.5, and 9.0 min, respectively. While the reasons for the delayed recovery are unknown, each of these patients had underlying low cardiac output associated with cardiac failure, which may result in longer circulation times. There were also technical issues with neuromuscular monitoring in one patient: although calibration and a relatively stable signal were maintained throughout the procedure, the signal of the measurement was not optimal; this 80-yr-old patient had bilateral oedema of the hands, which may have contributed to a suboptimal signal.

For all six treated patients, at least one AE was reported. None of the events was considered by the investigator as related to study drug. A total of four serious AEs occurred

in two patients. Both of these patients died. One of these patients (with an extensive medical history including diabetes mellitus, alcohol abuse, coagulopathy, ischaemic cardiomyopathy, heart failure, and oesophageal perforation) underwent replacement of an aortic endoprosthesis with a homograft 7 days before undergoing bronchoscopy for which rocuronium and sugammadex were administered. On day 5, this patient had a fatal pulmonary haemorrhage, considered to be major bleeding from the operative locus which eroded into the bronchus; concurrent illnesses included mediastinitis and multiorgan failure due to sepsis. The other patient (with an extensive medical history including diabetes mellitus, heart failure, increased liver enzymes, hepatic cirrhosis, and alcohol abuse) developed worsening heart failure on days 2–3, hepatic failure, and fatal intestinal ischaemia. This patient had undergone a mitral valve repair, an aortic valve replacement, and a coronary artery bypass graft ~6 days before enrolment in the study. To evaluate

**Table 2** Pharmacokinetic variables for sugammadex and rocuroonium. \*Only limited sugammadex dialysate clearance data were available for one patient; mean (SD) and range not calculated

	First dialysis	Second dialysis	Third dialysis	Fourth dialysis
Blood flow rate (ml min <sup>-1</sup> )				
<i>n</i>	5	6	4	4
Median	207	207	207	211
Range	200–210	202–210	204–211	199–218
Sugammadex				
Reduction ratio				
<i>n</i>	5	6	4	4
Mean (SD)	0.69 (0.11)	0.57 (0.15)	0.52 (0.23)	0.53 (0.14)
Range	0.51–0.80	0.32–0.76	0.22–0.78	0.38–0.67
Clearance in blood (ml min <sup>-1</sup> )				
<i>n</i>	5	6	4	4
Mean (SD)	79.1 (19.0)	76.5 (19.6)	72.4 (18.4)	83.4 (16.5)
Range	52.6–105	50.1–100	53.6–96.8	63.8–99.5
Clearance in plasma (ml min <sup>-1</sup> )				
<i>n</i>	5	6	4	4
Mean (SD)	57.9 (12.3)	56.2 (13.9)	53.0 (14.4)	60.6 (10.8)
Range	39.2–73.2	37.4–74.2	37.3–71.6	47.6–69.7
Clearance in dialysate (ml min <sup>-1</sup> )				
<i>n</i>	5	6	4	1*
Mean (SD)	63.0 (8.7)	65.1 (7.1)	66.8 (13.2)	—
Range	53.8–71.3	56.8–74.1	52.7–84.2	—
Rocuroonium				
Reduction ratio				
<i>n</i>	5	6	4	4
Mean (SD)	0.75 (0.08)	0.63 (0.14)	0.52 (0.05)	0.46 (0.12)
Range	0.65–0.85	0.45–0.80	0.49–0.59	0.38–0.63
Clearance in blood (ml min <sup>-1</sup> )				
<i>n</i>	5	6	4	3
Mean (SD)	80.2 (15.2)	86.3 (14.1)	94.1 (14.8)	94.8 (9.7)
Range	65.5–102	71.2–106	81.4–113	83.6–100
Clearance in plasma (ml min <sup>-1</sup> )				
<i>n</i>	5	6	4	3
Mean (SD)	58.9 (10.5)	63.6 (10.3)	68.7 (11.6)	68.8 (6.0)
Range	47.9–74.9	53.1–78.0	58.1–83.2	62.4–74.3
Clearance in dialysate (ml min <sup>-1</sup> )				
<i>n</i>	5	6	4	4
Mean (SD)	75.1 (5.8)	97.2 (32.4)	110 (36.4)	95.3 (19.2)
Range	65.8–81.8	67.8–142	70.6–146	72.3–115

underlying heart failure, this patient underwent transoesophageal echocardiography, for which rocuroonium and sugammadex were administered.

Residual NMB was not observed in any of the patients during the neuromuscular monitoring period, and recurrence of NMB was not observed based upon neuromuscular monitoring or clinical evidence.

## Discussion

Although not recommended for use in patients with severe renal impairment, sugammadex can effectively reverse

rocuroonium-induced NMB in these patients.<sup>14</sup> Urinary excretion of sugammadex and the sugammadex-rocuroonium complex is reduced in patients with severe to end-stage renal failure.<sup>15</sup> In this study, the dialysability of the sugammadex-rocuroonium complex was evaluated in patients with severe renal impairment, with a dose of 4.0 mg kg<sup>-1</sup> of sugammadex given 15 min after rocuroonium 0.6 mg kg<sup>-1</sup>. A dose of 4.0 mg kg<sup>-1</sup> is the highest recommended dose of sugammadex for routine reversal, and its administration at 15 min after rocuroonium has been shown to be generally well tolerated and associated with an effective recovery of NMB.<sup>13</sup>

In this study, the SLEDD technique of haemodialysis was utilized. This method uses a high-flux dialysis membrane, but keeps the flow of blood and dialysate low. SLEDD has evolved as a hybrid of continuous renal replacement therapy and intermittent renal replacement therapy, which provides stable renal replacement therapy and good clinical outcomes in critically ill patients,<sup>18 19</sup> and is becoming increasingly utilized. Our study indicates that haemodialysis using a SLEDD high-flux dialysis method is effective in removing the sugammadex-rocuronium complex in patients with severe renal impairment.

Of the two patients who died in this study, one had a fatal pulmonary haemorrhage, considered due to an aortobronchial fistulization or direct erosion of the bronchus by the thoracic aortic homograft. This haemorrhage did not occur during dialysis and the recorded activated clotting time at the end of the last dialysis session was 131 s. Concurrent illnesses in this patient included mediastinitis and multiorgan failure due to sepsis. Unfractionated heparin [activated clotting time adjusted (120–150 s)] was used for anticoagulation in conjunction with the high-flux haemodialysis in this study; however, taking the above factors into account, it is considered unlikely that this patient's haemorrhage was as a result of the method of anticoagulation used.

The dialysability of other neuromuscular blocking agents may differ from that observed with rocuronium. Indeed, in contrast to the effective removal of the sugammadex-rocuronium complex by high-flux dialysis, only very limited elimination of atracurium (highly protein bound) has been observed with continuous venovenous haemofiltration.<sup>20</sup> However, as only ~10% of a bolus dose of atracurium is excreted in the urine over 24 h in healthy patients, there were no significant differences between the plasma clearances of atracurium and laudanosine in more critically ill patients with renal failure and those in patients with normal renal function.<sup>20</sup>

Anticholinesterases are often administered to reverse residual NMB. Although the clinical efficacy of anticholinesterases is not adversely affected by renal insufficiency,<sup>21</sup> adverse effects can occur even when anticholinergic agents, such as atropine and glycopyrrolate, are given. In patients with renal failure, neostigmine has a prolonged half-life and reduced clearance,<sup>22</sup> and may precipitate bradycardia or atrioventricular block, especially when combined with shorter-acting atropine. The elimination of glycopyrrolate in plasma has been found to be significantly prolonged in uraemic patients compared with non-uraemic control patients,<sup>23</sup> producing prolonged antisecretory effects. Anticholinergic drugs also disrupt bowel activity, and glycopyrrolate decreases gastric emptying by 40–50%, when used in doses of 4 µg kg<sup>-1</sup>; thus, in uraemic patients, delayed bowel function after surgery caused by opioids and other drugs may be aggravated by glycopyrrolate.<sup>23</sup> Sugammadex reversal of rocuronium-induced NMB results in faster recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 in comparison with that obtained via neostigmine,<sup>3 5 6 24</sup> and in contrast to neostigmine, sugammadex is also able to reverse deep block.<sup>5</sup> Given the

substantial inter-patient variability in response to rocuronium in patients with renal failure and hepatic cirrhosis, the ability to reverse deep block in such patients would be advantageous.<sup>25</sup>

The main pharmacokinetic variables of rocuronium in intensive care patients are different from those of surgical patients, with volume of distribution at steady state increased; plasma clearance decreased; and terminal half-life and mean residence time prolonged in ICU vs surgical patients. These disparities may reflect the differing physiological state between intensive care and surgical patients, such as impaired renal/hepatic function in the former group.<sup>26</sup> In a study of patients with ischaemic heart disease, chronic heart failure, or arrhythmia, undergoing non-cardiac surgery, sugammadex was effective in reversing rocuronium-induced block with mean recovery times comparable with those in healthy subjects.<sup>27</sup> However, no pharmacokinetic data were collected in this study.

In the current study, the times from the start of sugammadex administration to the recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 ranged from 3.4 to 9.8 min, with a median of 4.2 min. These recovery times are prolonged in comparison with those in a previous study using sugammadex 4.0 mg kg<sup>-1</sup> for the reversal of deep rocuronium-induced NMB (median 2.7 min).<sup>5</sup> The prolonged recovery times in our study may have been caused by the serious medical conditions and underlying comorbidities of the patients in this study. A recent study<sup>28</sup> found that sugammadex can adequately restore neuromuscular function in older patients, although the time to reach a TOF ratio of 0.9 after sugammadex was dependent on cardiac output in elderly patients.<sup>28</sup> Except for one, patients in our study were older than 75 yr. Five of the six patients in our study received vasoconstricting drugs, reducing peripheral blood flow even more. While the reversal of rocuronium-induced NMB by sugammadex is not dependent on the renal excretion of the complex, Staals and colleagues<sup>14</sup> also found reversal by sugammadex slower in renal patients, although the difference was not statistically significant. As in our study, that study<sup>14</sup> was not powered on efficacy parameters and thus, due to the small sample size, no firm conclusions can be drawn with respect to the prolonged recovery times observed in these patients. Although for five of the six patients, there were measurable pre-dose rocuronium concentrations due to pre-study administration of rocuronium, these small pre-dose measurements were not expected to impact the conclusions with respect to dialysability and recovery to a T<sub>4</sub>/T<sub>1</sub> ratio of 0.9.

In conclusion, in this study, sugammadex and the sugammadex-rocuronium complex were effectively removed from the body by haemodialysis using a high-flux dialysis method. Reversal of deep NMB by sugammadex appeared to be slower in these ICU patients with severe renal insufficiency than previously observed in surgical patients. Additional safety data are considered necessary to support the recommendation for the use of sugammadex in patients with severe renal impairment.

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## Declaration of interest

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