British Journal of Anaesthesia **104 (1):** 31–9 (2010)
doi:10.1093/bja/aep340

BJA

Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study†

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Background. Sugammadex is a selective relaxant binding agent designed to encapsulate the neuromuscular blocking agent, rocuronium. The sugammadex–rocuronium complex is eliminated by the kidneys. This trial investigated the pharmacokinetics (PKs) of sugammadex and rocuronium in patients with renal failure and healthy controls.

Methods. Fifteen ASA class II–III renal patients [creatinine clearance (CL_{CR}) $<$30 ml min^{-1}] and 15 ASA I–II controls ($CL_{CR} \geq$80 ml min^{-1}) were included. After induction of anaesthesia, a single i.v. dose of rocuronium 0.6 mg kg^{-1} was given, followed by a single i.v. dose of sugammadex 2.0 mg kg^{-1} at reappearance of the second twitch of the train-of-four response. Plasma concentrations of rocuronium and sugammadex were estimated and PK variables determined using non-compartmental analyses. Percentages of sugammadex and rocuronium excreted in the urine were measured.

Results. PK data were obtained from 26 patients. Mean total plasma clearance (CL) of sugammadex was 5.5 ml min^{-1} in renal patients and 95.2 ml min^{-1} in controls ($P<0.05$). Rocuronium CL was 41.8 ml min^{-1} in renal patients and 167 ml min^{-1} in controls ($P<0.05$). The median amount of sugammadex and rocuronium excreted in the urine over 72 h in renal patients was 29% and 4%, respectively, and 73% and 42% over 24 h in controls.

Conclusions. Large differences in the PKs of sugammadex and rocuronium between patients with renal failure and healthy controls were observed. The effect of renal impairment on the PK variables of rocuronium was less than with sugammadex. Urinary excretion of both drugs was reduced in renal patients.

Clinicaltrials.gov identifier: NCT00482599 [URL: http://www.clinicaltrials.gov/ct2/show/NCT00482599 (accessed November 4, 2008)].

Br J Anaesth 2010; **104**: 31–9

Keywords: kidney, failure; neuromuscular block, antagonism; neuromuscular block, rocuronium; pharmacokinetics, kidney; pharmacokinetics, rocuronium

Accepted for publication: November 1, 2009

Sugammadex is a modified γ-cyclodextrin and the first selective relaxant binding agent designed to encapsulate the aminosteroidal neuromuscular blocking agent (NMBA) rocuronium.[1–3] Cyclodextrins are cyclic oligosaccharides, capable of encapsulating lipophilic guest molecules such as steroids.[1] Sugammadex forms a 1:1

†Meetings at which the work has been presented: the 14th World Congress of Anaesthesiologists (WCA), Cape Town, South Africa, March 2–7, 2008. Staals L, Snoeck M, Hunter J, Heeringa M, Driessen J. Pharmacokinetics of rocuronium and sugammadex in patients with normal and impaired renal function. http://www.wca2008.com/images/abstractWCA/Pharmacology.pdf (accessed November 6, 2008).

host–guest inclusion complex with rocuronium in the plasma. Free rocuronium molecules in the plasma are captured by sugammadex, resulting in a rapid decrease in the free rocuronium plasma concentration. This creates a concentration gradient between free rocuronium in the effect compartment [the neuromuscular junction (NMJ)] and the central compartment (the plasma and extracellular fluid). As a result, free rocuronium molecules return to the plasma, where they are captured by sugammadex, leading to a rapid reversal of neuromuscular block (NMB).[4]

Rocuronium is an NMBA with an intermediate duration of effect,[5] which is widely used in anaesthesia. Recovery from NMB occurs spontaneously as rocuronium diffuses away from the NMJ and is redistributed before being metabolized by the liver and/or eliminated in the bile and urine.

Administration of sugammadex leads to altered elimination of rocuronium. Sugammadex is a water-soluble molecule which is cleared mainly by the kidneys.[6] After encapsulation by sugammadex, rocuronium is confined to the space in which sugammadex resides and the plasma clearance of rocuronium assimilates into the plasma clearance of sugammadex.[6] Human studies have shown that the percentage urinary excretion of a dose of rocuronium increases up to a maximum of 68% over 24 h with increasing doses of sugammadex.[6]

This phase III trial was conducted to determine the efficacy, safety, and pharmacokinetics (PKs) of sugammadex in patients with chronic renal failure, including patients on dialysis. The pharmacodynamic and safety findings of this study have already been reported.[7] This article describes the effect of severe to end-stage renal failure on the PKs of sugammadex and rocuronium and on the elimination of rocuronium encapsulated by sugammadex.

Methods

Patient selection

The study protocol was approved by the Independent Ethics Committee of each trial centre (one in the UK, two in the Netherlands) and was conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, Good Clinical Practice and current regulatory guidelines. All patients provided written informed consent.

The study was performed between June 2005 and April 2006. Thirty patients aged $\geq$18 yr were included in the trial: 15 ASA class II–III patients (American Society of Anesthesiologists physical status classification) with severe to end-stage renal failure [creatinine clearance (CL_{CR}) $<$30 ml min^{-1}] and 15 ASA class I–II control patients (CL_{CR} $\geq$80 ml min^{-1}). CL_{CR} was calculated using the serum creatinine value and the Cockcroft and Gault formula.[8] The pharmacodynamic and safety findings of this study have been reported previously.[7]

Patients were undergoing elective surgical procedures in the supine position under general anaesthesia, where it was anticipated that only one dose of rocuronium 0.6 mg kg^{-1} would suffice. Pregnant and breast-feeding women, patients with known or suspected neuromuscular disorders, those with a history of malignant hyperthermia, or allergy to narcotics, NMBAs, or other medication used during general anaesthesia were excluded, and also patients receiving medication known to interfere with the action of rocuronium, for example, aminoglycoside antibiotics, anticonvulsants, or magnesium (Mg^{2+}).

Study procedures

An i.v. cannula was inserted solely for the administration of all anaesthetic drugs, including rocuronium and sugammadex. Anaesthesia was induced and maintained using i.v. infusions of propofol and opiates. Another i.v. cannula was inserted for blood sampling.

After induction of anaesthesia, a single i.v. dose of rocuronium 0.6 mg kg^{-1} was given. When maximal block had been achieved, tracheal intubation was performed and the lungs were ventilated with a mixture of oxygen and air. End-tidal CO_2 was maintained within 4.0–5.3 kPa. No potent inhalation agents were used.

Neuromuscular monitoring was performed continuously using acceleromyography of the adductor pollicis muscle and the TOF-Watch® SX (Schering-Plough, Dublin, Ireland). Surface paediatric ECG electrodes (Neotrode®, Conmed, Utica, NY, USA) were placed over the ulnar nerve near the wrist. A temperature sensor was attached to the ball of the thumb: peripheral temperature was maintained above 32°C.[9] Core body temperature was measured using a nasopharyngeal or rectal probe and maintained between 35°C and 37°C.[10]

At reappearance of the second twitch (T_2) of the train-of-four (TOF) response, a single i.v. dose of sugammadex 2.0 mg kg^{-1} was administered. Anaesthesia and neuromuscular monitoring were continued until the end of surgery and at least until recovery of the T_4/T_1 ratio of the TOF to 0.9, and for a minimum of 30 min after administration of sugammadex.

Patients received dialysis during the study if indicated, according to usual practice.

Pharmacokinetic assessments

Plasma and urine sampling were conducted to determine the plasma concentration and the percentage of the administered dose of sugammadex and rocuronium excreted in the urine. Venous blood samples for determination of rocuronium concentration were obtained pre-dose and at 2, 3, 5, 10, 15, and 20 min after administration of rocuronium. If reappearance of T_2 occurred before all the post-rocuronium samples had been obtained, the remaining

post-rocuronium samples were ignored. Venous blood samples to assess total rocuronium and sugammadex plasma concentrations were obtained directly before administration of sugammadex and at 2, 3, 5, 10, 15, 20, 30, and 60 min and 2, 4, 6, 8, 12, 18, and 24 h after administration of sugammadex. In patients with renal failure, further plasma concentrations of rocuronium and sugammadex were also determined at 36 and 48 h after sugammadex administration. The actual time of blood sampling was recorded in each instance. Additional pre- and post-dialysis samples were obtained if the patient underwent haemodialysis within 72 h of administration of sugammadex.

Plasma samples were stored in 4 ml heparin collection tubes. Within 15 min of collection, the plasma samples were centrifuged. If centrifugation could not be performed within 15 min, the tubes were stored in ice (0–4°C). The heparin tubes were centrifuged for 15 min (2000−3000*g*). Centrifuged plasma was stored in two hard plastic tubes (one for rocuronium and the other for sugammadex) at −20°C.

Urinary rocuronium and sugammadex concentrations and total amounts excreted were assessed from all healthy patients and those renal patients who still produced urine. Urine was collected at 6 h intervals, starting from administration of rocuronium to 6 h after administration of sugammadex and for 6–12, 12–18, and 18–24 h after administration of sugammadex. In patients with renal failure, urine was also collected 24–36, 36–48, and 48–72 h after administration of sugammadex. The actual collection times and volumes were recorded.

The collected urine was stored at 4°C. Two samples of 1.0 ml of the collected urine for each interval were stored in a hard plastic tube: one for rocuronium and the other for sugammadex. These tubes were stored at −20°C. No preservatives were used.

Rocuronium and sugammadex concentrations in plasma and urine were determined using validated liquid chromatographic assay methods with mass spectrometric detection by the Department of Clinical Pharmacology and Kinetics, Schering-Plough, Oss, The Netherlands. The assays were carried out in full compliance with Good Laboratory Practice regulations. The lower limits of quantification (LLOQ) for the assays were: sugammadex 0.1 μg ml^{-1} (plasma) and 5 μg ml^{-1} (urine); and rocuronium 2.0 ng ml^{-1} (plasma) and 50 ng ml^{-1} (urine). The upper limits of quantification (ULOQ) for the assays were: sugammadex 40 μg ml^{-1} (plasma) and 200 μg ml^{-1} (urine); and rocuronium 1000 ng ml^{-1} (plasma) and 10 000 ng ml^{-1} (urine). All samples with a concentration >ULOQ were processed and analysed after an appropriate dilution to bring the concentration within the calibration range.

The assay methods do not differentiate between sugammadex and rocuronium in their free or complexed forms, as the sugammadex–rocuronium complex dissociates on the liquid chromatography column. Thus, plasma concentrations, urine concentrations, and PK parameters pertain to total plasma and urine concentrations of sugammadex and rocuronium only and do not indicate the degree of encapsulation.

Pharmacokinetic parameter calculation

PK parameters were calculated using conventional non-compartmental analysis methods. For determination of terminal half-life, the slope ($-\lambda_z$) of the terminal log-linear phase of the concentration *vs* time curve was determined by linear regression. The log-transformed concentrations were fitted to a model with intercept and slope, starting with the last three points with measurable concentration (concentrations lower than LLOQ in the elimination phase were ignored). The procedure continued, adding preceding data points one at a time and fitting the regression equation sequentially. The terminal log-linear portion was defined by the data yielding the smallest mean square error term in the regression analysis. The elimination half-life ($t_{1/2,\ \beta}$) was then calculated as $\log_e 2/\lambda_z$.

The area under the concentration *vs* time curve (AUC) from time zero to t_{last} ($AUC_{0-tlast}$) was calculated by means of the linear trapezoidal rule, where t_{last} represents the last time point with a measurable concentration above the LLOQ within a subject. When a renal patient received dialysis during the study, t_{last} was the last pre-dialysis time point. This time point differed for each of the renally impaired patients. The AUC from time zero to infinity was calculated as $AUC_{0-\infty}=AUC_{0-tlast}+C_{tlast}/\lambda_z$, where C_{tlast} was the fitted concentration at time t_{last} using the regression line from which λ_z was calculated. With respect to the dialysed patients in the renally impaired group, $AUC_{0-\infty}$ was calculated by extrapolating from the pre-dialysis sample, ignoring plasma concentrations during and after dialysis.

The total plasma clearance (CL) was calculated as dose/$AUC_{0-\infty}$. The mean residence time (MRT) was calculated as (AUMC/$AUC_{0-\infty}$)−(duration administration dose/2), where AUMC is the area-under-the-moment-curve which is calculated from the product of concentration and time by means of the linear trapezoidal rule until t_{last} plus $(C_{tlast}\times t_{last}/\lambda_z)+(C_{tlast}/\lambda_z^2)$. The effective half-life ($t_{1/2,\ effective}$) was calculated as $\log_e 2\times MRT$. The apparent volume of distribution at steady state was calculated as $V_{ss}=CL\times MRT$.

In patients with renal failure who were treated with haemodialysis within 72 h after administration of sugammadex, the rocuronium and sugammadex plasma concentrations were assessed pre-dialysis ($C_{pre\text{-}dialysis}$) and post-dialysis ($C_{post\text{-}dialysis}$). A *post hoc* analysis was performed on the reduction ratio (RR) during dialysis, which was calculated as $RR=C_{post\text{-}dialysis}/C_{pre\text{-}dialysis}$.

From the sugammadex and rocuronium concentrations in urine and the urine volumes recorded for each collection interval, the amount excreted in urine (Ae) was

calculated for each interval, assuming a urine density of 1.0 g ml^{-1}. The cumulative amount excreted in urine up to any time t ($Ae_{cum,\ t}$), where time t is the endpoint of a collection interval, was obtained by adding the total amounts excreted in each collection interval up to that time.

Statistical analysis

A power calculation was performed to calculate the number of patients needed to show pharmacodynamic equivalence.[7] A separate power analysis was not performed for the PK part of the study.

PK assessments were performed in the population of patients who received study medication, had no protocol violations interfering with the PK analysis, and for whom at least one PK parameter could be calculated. Linear regression analyses were performed of sugammadex and rocuronium CL *vs* CL_{CR} as a measure of renal function. Renal patients undergoing haemodialysis were excluded from this calculation, as CL_{CR} may be overestimated in this patient group, when calculated using the Cockroft and Gault formula. Correlation plots were made of CL *vs* CL_{CR} including regression lines.

The PK variables in the renal failure and control groups were compared using Student's *t*-test on log_e-transformed values. Point estimates and 95% confidence intervals for the ratio of renal failure to control means were calculated using geometric means. If there were no significant group effects, then the PKs were considered comparable between the renal failure group and the control group.

PK evaluation was performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) on a PC running under Windows XP v5.1 (Microsoft Corporation, Redmond, WA, USA).

Comparison of the physical characteristics and patient details of the two groups were performed by *post hoc* analysis using Student's *t*-test. Effects were considered statistically significant if $P \leq 0.05$.

Results

Patients

Thirty patients were enrolled; 15 patients with renal failure [seven in Radboud University Nijmegen Medical Centre (RUNMC), six in Canisius-Wilhelmina Ziekenhuis (CWZ), Nijmegen, and two in Liverpool] and 15 controls (seven in CWZ, six in RUNMC, and two in Liverpool). In four patients (two renal patients and two controls), the data on the plasma and urine samples (time, date and patient number) did not correspond with those recorded on the Case Report Forms. These samples may have been reversed. For these subjects, no PK variables were calculated. Thus, 13 patients in each group were evaluable for PK assessment.

Table 1 Physical characteristics and patient data by patient group. BMI, body mass index; CL_{CR}, total plasma creatinine clearance; SD, standard deviation. *Mean creatinine clearance may be overestimated in haemodialysis patients, when calculated using the Cockroft and Gault formula

	Patient group		
	Renal failure CL_{CR} <30 ml min^{-1} (n=13)	**Control CL_{CR} ≥80 ml min^{-1} (n=13)**	
Age (yr) [mean (range)]	61 (29–81)	54 (32–70)	P=0.23
Weight (kg) [mean (SD)]	76.8 (13.8)	83.4 (16.0)	P=0.24
Height (cm) [mean (SD)]	170 (8.7)	168 (9.1)	P=0.68
BMI (kg m^{-2}) [mean (SD)]	26.6 (4.1)	29.5 (5.5)	P=0.06
CL_{CR} (ml min^{-1}) [mean (SD)]*	12.3 (5.7)	103.8 (26.0)	P=0.00

Table 1 shows the baseline characteristics of the 26 patients. There were no significant differences in age, weight, height, or BMI between the two groups. The CL_{CR} in the renal failure group ranged from 4.3 to 24.1 ml min^{-1}.

All patients received propofol for induction and maintenance of anaesthesia, an intubating dose of rocuronium (median 0.6 mg kg^{-1}; range 0.59–0.61 mg kg^{-1}), and one dose of sugammadex (median 2.0 mg kg^{-1}; range 1.99–2.05 mg kg^{-1}). The most frequently administered analgesic drugs were i.v. fentanyl and morphine. All patients were receiving concomitant medication. The drugs most frequently taken were alfacalcidol (10 of 15 renal patients) and acetaminophen (11 renal patients and 14 controls). None of the patients received an NMBA other than rocuronium, a second dose of rocuronium, or a reversal agent other than sugammadex.

As previously reported, the mean (standard deviation) time from administration of rocuronium to reappearance of T_2 was 53.8 min (22.4 min) in the renally impaired group and 40.6 min (13.9 min) in the control group.[7] Mean time (standard deviation) from the start of administration of sugammadex at reappearance of T_2 to recovery of the TOF ratio to 0.9 was 2.0 min (0.72) for renal patients and 1.65 min (0.63) in healthy controls (not significant).[7] No clinical signs of recurarization were observed in any of the patients for up to 48 h.[7]

Plasma pharmacokinetics

In one control patient, the rocuronium plasma concentration after 24 h was considered to be a PK outlier (laboratory error). The concentration at this time point was 3.94 ng ml^{-1}, although the plasma concentration after 12 h was 2.1 ng ml^{-1} and after 18 h was <2.00 ng ml^{-1}. This sample was excluded from all calculations. In one renal patient undergoing haemodialysis, the pre-dialysis plasma rocuronium concentration (24 h after administration of sugammadex) was also considered an outlier: the

plasma concentration was 28.6 ng ml^{-1}, which was lower than the post-dialysis concentration (270 ng ml^{-1}). Therefore, the pre-dialysis sample was excluded from all calculations. For those patients in the renal failure group undergoing haemodialysis (nine patients), the samples obtained at time points after haemodialysis was started were excluded from the descriptive statistics.

Median plasma concentrations for sugammadex (Fig. 1A and B) and rocuronium (Fig. 2A and B) are presented by group. For the first 60 min after administration, median plasma concentrations of sugammadex were similar in the control and renally impaired groups (Fig. 1A). At later time points, plasma concentrations of sugammadex showed a slower decline in the renally impaired group compared with the control group (Fig. 1B). A similar effect was seen for rocuronium (Fig. 2A and B). For both groups and both compounds, the concentration *vs* time curves showed a log-linear terminal decline.

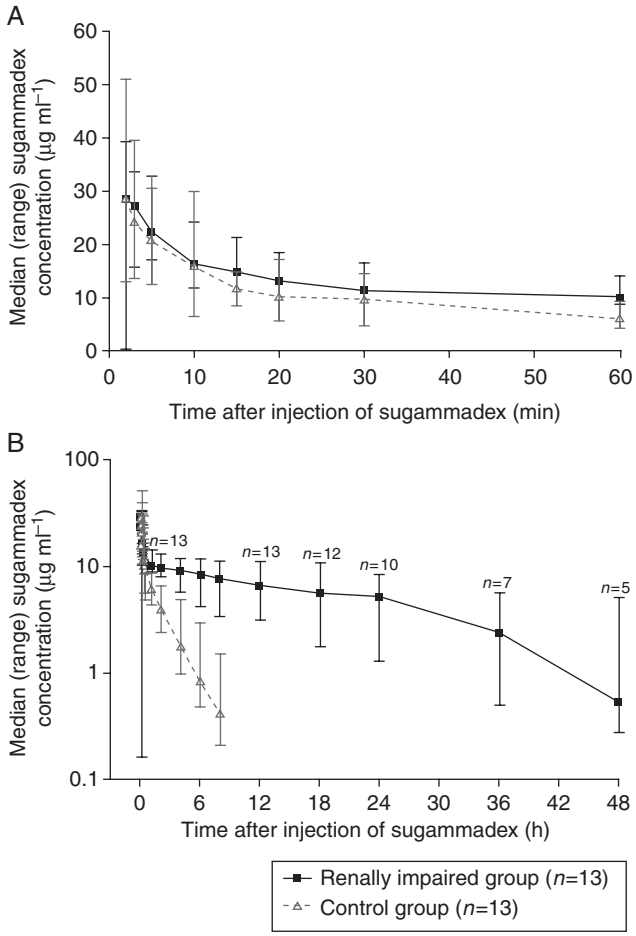

Fig 1 Sugammadex plasma concentration *vs* time plots for patients with renal failure and control patients. (A) Median (range) sugammadex plasma concentration (μg ml^{-1}) *vs* time (min), for time points up to 60 min after injection of sugammadex. (B) Semi-logarithmic plot: median (range) sugammadex plasma concentration (μg ml^{-1}) *vs* time (h), for time points up to 48 h after injection of sugammadex. Plasma concentrations were below the limit of quantification after 8 h in the control group. The numbers (*n*) of samples at each time point are given for the renally impaired group.

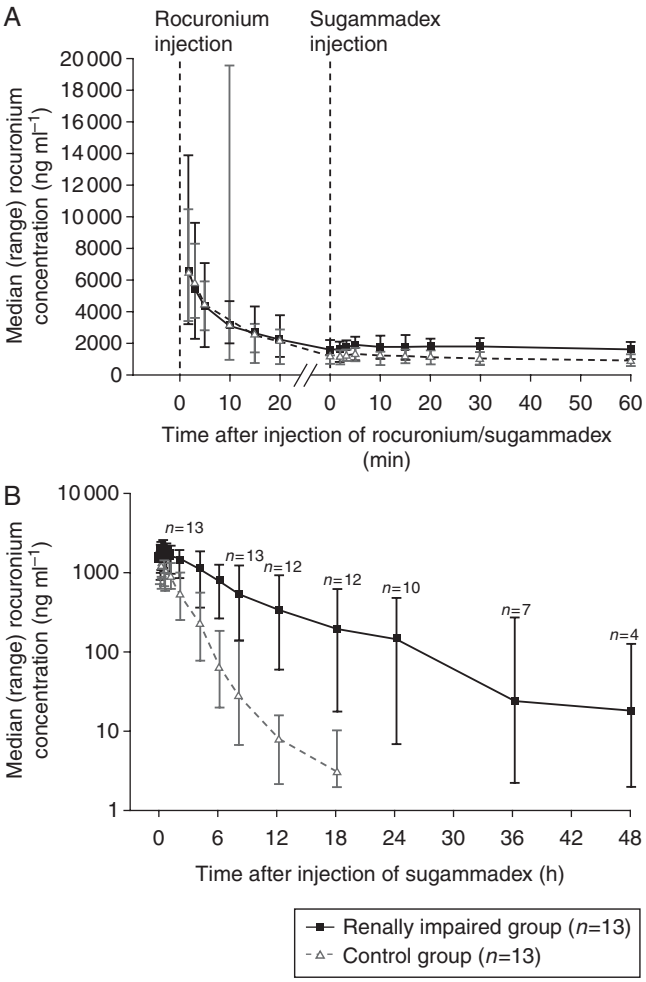

Fig 2 Rocuronium plasma concentration *vs* time plots for patients with renal failure and control patients. (A) Median (range) rocuronium plasma concentration (ng ml^{-1}) *vs* time (min) after administration of rocuronium and sugammadex, for time points up to 60 min after injection of sugammadex. (B) Semi-logarithmic plot: median (range) rocuronium plasma concentration *vs* time, for time points up to 48 h after administration of sugammadex. Plasma concentrations were below the lower limit of quantification after 18 h in the control group. The numbers (*n*) of samples at each time point are given for the renally impaired group.

The main PK variables for sugammadex and rocuronium are given in Table 2.

Statistically significant differences ($P<0.05$) were observed between the control and the renal failure groups for sugammadex in total plasma CL, and the related parameters, AUC, $t_{1/2,\ \beta}$, and MRT (Table 2). Exposure ($AUC_{0-\infty}$), $t_{1/2,\ \beta}$, and MRT were 15–20 times higher and the CL was 17 times lower in the renal failure group compared with the control group. The V_{ss} did not differ significantly between the renal failure and the control groups.

Statistically significant differences ($P<0.05$) were also observed in these variables for rocuronium (Table 2).

Table 2 PK variables for sugammadex 2.0 mg kg^{-1} and rocuronium 0.6 mg kg^{-1}. Blood samples obtained before and after sugammadex administration were used to determine the rocuronium PKs. AUC, area under the curve; CL, total plasma clearance; V_{ss}, volume of distribution at steady state; $t_{1/2,\ \beta}$, terminal elimination half-life; MRT, mean residence time. Data are presented as geometric mean [geometric coefficient of variation (%)] and overall ranges. *Statistically significant (Student's *t*-test), $P<0.05$ *vs* renal failure group

	Renal failure	Control
Sugammadex kinetic variables		
$AUC_{0-\infty}$ (μg min ml^{-1})	27 500 (114)	1730 (34.8)*
Range (μg min ml^{-1})	6480–147 000	1060–3330
CL (ml min^{-1})	5.5 (108)	95.2 (22.1)*
Range (ml min^{-1})	1.15–18.1	58.3–138
V_{ss} (litre)	16.0 (35.5)	13.8 (20.5)
Range (litre)	9.3–31.8	10.0–19.7
$t_{1/2,\ \beta}$ (h)	35.7 (121)	2.3 (44.4)*
Range (h)	10.7–282	1.6–7.5
MRT (h)	48.2 (132)	2.4 (25.5)*
Range (h)	13.2–399	1.8–4.0
Rocuronium kinetic variables		
$AUC_{0-\infty}$ (μg min ml^{-1})	1080 (53.8)	296 (37.4)*
Range (μg min ml^{-1})	412–2370	143–538
CL (ml min^{-1})	41.8 (46.9)	167 (30.8)*
Range (ml min^{-1})	23.2–88.8	108–314
V_{ss} (litre)	22.1 (29.9)	19.1 (28.3)
Range (litre)	14.0–41.6	12.2–30.7
$t_{1/2,\ \beta}$(h)	7.5 (39.9)	3.0 (67.5)*
Range (h)	3.4–13.3	1.2–8.2
MRT (h)	8.8 (52.7)	1.9 (29.2)*
Range (h)	3.7–19.7	1.2–3.3

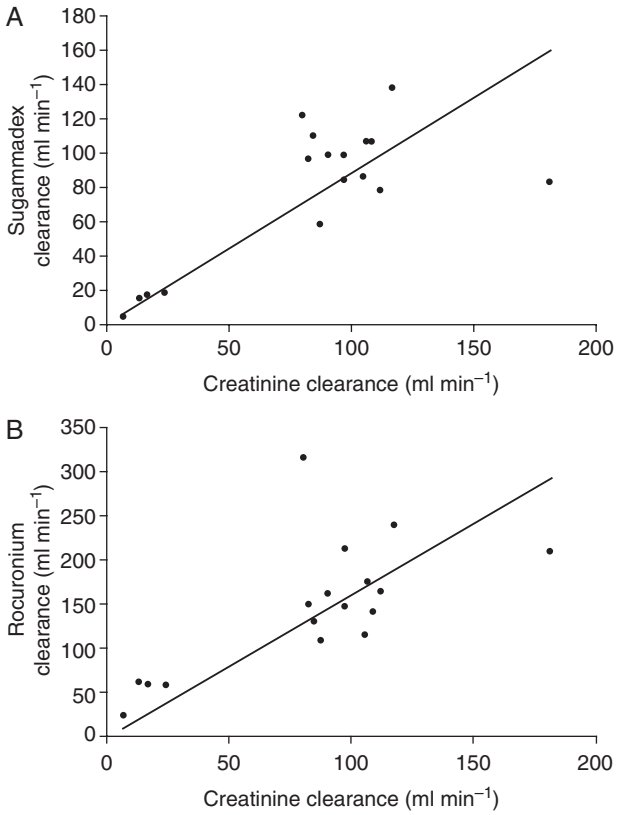

Fig 3 Regression plots of total plasma clearance (CL) of sugammadex and rocuronium *vs* CL_{CR} (creatinine clearance) in normal controls and patients with renal insufficiency not yet on dialysis. (A) Regression plot of sugammadex CL *vs* CL_{CR} ($r=0.72$) and (B) rocuronium CL *vs* CL_{CR} ($r=0.60$).

The exposure ($AUC_{0-\infty}$), $t_{1/2,\ \beta}$, and MRT were 2.5–5 times higher and the CL was four times lower in the renally impaired group compared with the control group. Again, the V_{ss} of rocuronium did not differ significantly between the two groups.

The effect of renal impairment on the PK variables was smaller for rocuronium than for sugammadex. The CL, AUC, $t_{1/2,\ \beta}$, and MRT of sugammadex were highly variable in patients with renal failure, with coefficients of variation >100%. The variability within renal failure patients in the PK parameters for rocuronium was smaller.

Correlation plots were made of CL of sugammadex and rocuronium against creatinine clearance in controls and patients with renal insufficiency not yet on dialysis (Fig. 3). Regression analyses showed that both for sugammadex and for rocuronium, the correlation between CL and CL_{CR} is highly significant ($P<0.0001$).

Urinary excretion

In six patients with renal failure and four control patients, urine sampling was incomplete. Two patients with renal failure did not produce urine. Nine of 13 patients with renal failure underwent haemodialysis during the period of urine collection, which may have influenced urinary excretion of the drugs.

Urinary excretions of sugammadex and rocuronium were much lower in the renal failure group than in the control group. In renal failure patients ($n=10$), the median (range) total amount of sugammadex excreted in urine (in 72 h) was 29% (3.9–121%) of the administered dose. In the control group ($n=11$), renal excretion of sugammadex was almost complete in 24 h; median (range) total amount of sugammadex excreted was 73% (56–101%).

One renal patient was calculated to excrete 121% of the administered sugammadex dose, which reflects either an imprecision in the bioassay or in the urinary sampling. In nine of the 10 evaluable renal patients, the amount of sugammadex excreted over 72 h was <70%.

For rocuronium, a much smaller fraction of the dose was excreted in the urine than for sugammadex, both for the renally impaired group and for the control group. Median (range) total amount of rocuronium excreted in urine was 4.4% (0.8–18) of the administered dose in 72 h in the renal failure group ($n=10$) and 42% (14–75) in 24 h in the control group ($n=12$).

Haemodialysis

Nine renal patients underwent haemodialysis between 0 and 72 h after administration of sugammadex. The plasma concentrations of sugammadex and rocuronium

were measured pre- and post-dialysis. Median time for dialysis was 225 min.

In patients undergoing low-flux haemodialysis (n=7), no significant reductions in sugammadex plasma concentrations were observed after dialysis. The median (range) RR of sugammadex was 0.93 (0.87–1.20) and that of rocuronium was 0.65 (0.57–0.90). As there were only two patients undergoing high-flux haemodialysis, no conclusions regarding dialysability with these membranes can be presented from this study.

Discussion

This multicentre, parallel-group, comparative trial was the first to investigate the PKs of sugammadex and rocuronium in patients with severe to end-stage renal failure. This phase III study showed large differences in the PKs of sugammadex and rocuronium between patients with renal failure and healthy controls. Plasma concentrations of sugammadex showed a slower decline in the renal failure group compared with the control group. Total plasma CL of sugammadex was 17 times lower and mean $t_{1/2,\ \beta}$ was 16 times higher in the renal failure group.

The effect of renal impairment on PK variables was less for rocuronium. Figure 2A shows no significant differences between renal patients and controls in rocuronium plasma concentrations before the administration of sugammadex. This is probably because redistribution of rocuronium, rather than CL, determines its plasma concentration during the initial 30–45 min after administration. However, after administration of sugammadex, total plasma CL of rocuronium was four times lower in the renal failure group than the control group.

Urinary excretion of sugammadex and rocuronium was also much lower in patients with renal failure.

In this investigation, venous sampling was performed for 48 h in the renal failure patients and for 24 h in the control group, which may have influenced the PK calculations. In renal failure patients, the calculated half-lives are longer than the sampling period, potentially making them inaccurate. However, the terminal elimination half-life ($t_{1/2,\ \beta}$) and MRT for sugammadex are both greatly prolonged in renal failure compared with controls, suggesting a significant effect of renal impairment.

The major routes of elimination of rocuronium are biliary and urinary excretion.[11] Rocuronium is taken up by the liver and metabolized, excreted, or both in bile and faeces in high concentrations. The mean urinary recovery of rocuronium within 48 h of administration in subjects without a history of renal disease is 26%.[11] In patients with severe renal failure, CL of rocuronium is reduced by 33–39%, with a 66–84% increase in the MRT.[12 13]

For sugammadex, a water-soluble molecule, renal excretion is the main route of elimination. In pre-clinical and clinical studies, renal excretion of the unchanged product was observed.[4 6 14] The plasma CL of sugammadex in healthy non-anaesthetized volunteers is ~120 ml min^{-1}, which is similar to the glomerular filtration rate.[6]

As urinary excretion is the main route of elimination of the sugammadex–rocuronium complex, the extrarenal route of elimination is expected to be unavailable for encapsulated rocuronium. After administration of sugammadex, the percentage of rocuronium excreted in the urine increases with increasing doses of sugammadex.[6 15] These data indicate that encapsulation by sugammadex diverts the elimination of rocuronium from its normal primary pathway of hepatic clearance to less effective renal clearance.[14] Such PK behaviour should have no consequences in surgical patients with normal renal function. However, patients with renal insufficiency will retain the sugammadex–rocuronium complex for a longer period of time, and it is still unclear whether this prolonged exposure will have an impact on safety.

The plasma concentrations of rocuronium plateaued after administration of sugammadex. During the first hour after rocuronium injection, the plasma concentration of rocuronium decreased rapidly, mainly by redistribution and binding in the liver. After administration of sugammadex, the concentration of rocuronium showed a plateau or even an increase. This may be due to the fact that sugammadex attracts some rocuronium already bound in the liver back into the plasma, or that the assay cannot distinguish between free rocuronium and encapsulated rocuronium, thus leading to a higher total rocuronium concentration. In addition, the increased concentration gradient of non-encapsulated rocuronium molecules between the plasma and NMJ will result in free rocuronium at the NMJ returning to the plasma.

Available evidence suggests that the rocuronium–sugammadex complex remains stable over time.[1 16] The sugammadex–rocuronium complex exists in equilibrium with a very low dissociation rate (dissociation constant, K_d=0.1×10^{-6} M) because of strong binding.[1 16] No drug interactions have been described between sugammadex and other agents used in general anaesthesia, such as opioids or propofol. In this trial, renal patients were monitored for 48 h after administration of sugammadex for clinical signs of recurarization. None of them experienced recurrence of NMB. Despite the large differences in the PKs of rocuronium and sugammadex between patients with renal failure and healthy controls, reversal of rocuronium-induced NMB by administration of sugammadex was rapid and effective in both patient groups.[7] It is appreciated, however, that the number of patients studied was small.

Cyclodextrins are water-soluble molecules, which are used as solubilizing agents for many drugs and foods. Sugammadex is biologically inactive and has been shown to be well tolerated. Toxicity studies on γ-cyclodextrins after oral or parenteral administration show that the drugs are well tolerated and safe to use in the dose ranges

recommended for sugammadex.[17] No data based on prolonged follow-up are available on the safety of sugammadex in patients with renal failure, where elimination of the drug is compromised.

In this study, the effect of renal impairment on the kinetic variables was smaller for rocuronium than for sugammadex. These data suggest that in patients with renal failure, extrarenal clearance of rocuronium does take place, in spite of complexation. However, we did not measure biliary concentrations of rocuronium, which would be necessary to determine if elimination, metabolism, or both by the liver of encapsulated rocuronium was continuing. Even after encapsulation of rocuronium by sugammadex, there may still be a low concentration of rocuronium unbound and available for hepatic metabolism and elimination. However, since the assay method cannot differentiate between encapsulated and free rocuronium, it is not possible at present to determine the plasma concentration of unbound rocuronium. If a higher dose of sugammadex had been administered even more rocuronium would have been encapsulated, and rocuronium clearance in renal patients would have more closely approximated the clearance of sugammadex in this patient group.

We obtained PK data in only four pre-dialysis patients with severe to end-stage renal failure and nine dialysis patients. In the latter group, the time of the first postoperative haemodialysis was patient-specific and occurred before the last sampling time of 48 h after administration of sugammadex in eight patients. This might have influenced the PK parameters. The haemodialysis, together with the incomplete urine sampling, may have resulted in an underestimation of the urinary excretion of sugammadex and rocuronium.

Our study showed a significant correlation between sugammadex and rocuronium CL and creatinine clearance ($P<0.0001$), although it may not be linear. We did not investigate patients with mild renal failure (CL_{CR} 30–80 ml min^{-1}). Further PK studies in a larger patient group, in patients with different degrees of renal dysfunction, and population PK approaches are needed to determine a more detailed profile of these drugs in such patients.

After administration of sugammadex, an increase in rocuronium plasma concentration was detected. This has been described in other PK studies.[4 6 14 15] This is consistent with the rapid formation of the rocuronium–sugammadex complex in the plasma.[4] After administration of sugammadex, free rocuronium molecules in the plasma are encapsulated. This creates a concentration gradient of free rocuronium molecules between the NMJ and the central compartment. As they enter the plasma, more free rocuronium molecules are encapsulated by sugammadex. As the assay method cannot yet differentiate between free and encapsulated rocuronium, the complexation of rocuronium appears as an increase in total plasma rocuronium concentration.[14 15]

Dialysis membranes are classified into high and low flux, depending on their permeability. High-flux membranes are more porous non-cellulosic membranes with increased permeability, particularly to larger molecules.[18] Of the nine patients with renal failure who underwent haemodialysis during the investigation, seven were dialysed using low-flux membranes, which seemed almost ineffective in removing sugammadex from the circulation. However, the small number of subjects per filter type and the limited sampling means that the results must be viewed as preliminary. Further investigation is necessary to obtain more detailed information regarding dialysability of sugammadex and rocuronium.

In conclusion, large differences in the PKs of rocuronium and sugammadex were observed between patients with severe to end-stage renal failure and healthy controls. Total plasma CL of sugammadex and rocuronium was much lower in renal patients compared with controls. However, reversal of the NMB induced by rocuronium 0.6 mg kg^{-1} with sugammadex 2.0 mg kg^{-1} was rapid and effective in both patient groups. No patient showed signs of recurarization.[7] The sugammadex–rocuronium complex is retained in the body for longer in patients with severe to end-stage renal failure and no clinical data on its long-term disposition are yet available. Furthermore, detailed studies should be conducted with a longer follow-up period, preferably with a higher dose of sugammadex, to determine more accurately whether prolonged exposure to sugammadex and the rocuronium–sugammadex complex has an impact on safety in patients with end-stage renal failure.

Acknowledgements

This study was supported by Schering-Plough, Oss, The Netherlands. Bioanalysis of study samples and PK evaluation of the study were performed by M.A.H. de Zwart and C. Machielsen (Schering-Plough, Oss, The Netherlands). J. Wetzels (Department of Nephrology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands) and N.S. Houwing, R.A. Kroon and S.M.A. Peeters (Schering-Plough, Oss, The Netherlands) were involved in the design of the study. Editorial support was provided by Melanie More of Prime Medica Ltd, funded by Schering-Plough, Kenilworth, NJ, USA.

Funding

This work was supported by Schering-Plough, Oss, The Netherlands. The study sponsor was involved in the design of the trial, the data validation and the analysis of the trial. The authors were responsible for the interpretation of the data and for writing the report. One of the authors is employed by the sponsor (M.W.H.). The decision to submit the paper for publication to this journal was made by the authors.

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