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Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function

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Background. Sugammadex, a modified γ-cyclodextrin, is the first selective relaxant binding agent that specifically encapsulates the steroidal neuromuscular blocking agent, rocuronium. The action of rocuronium is prolonged in patients with renal failure. As sugammadex is primarily cleared renally, this phase III trial investigated the efficacy and safety of sugammadex for reversal of rocuronium-induced neuromuscular block (NMB) in patients with end-stage renal failure.

Methods. Thirty adult patients were studied: 15 renally impaired [creatinine clearance (CL_{CR}) <30 ml min^{-1}] and 15 controls ($CL_{CR}>80$ ml min^{-1}). Anaesthesia was induced and maintained using i.v. opiates and propofol. Neuromuscular monitoring was performed by acceleromyography and train-of-four (TOF) nerve stimulation. 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 TOF. The primary efficacy variable was time from administration of sugammadex to recovery of the TOF ratio to 0.9. Safety variables included clinical evidence of reoccurrence of NMB.

Results. After sugammadex administration, the mean (SD) time to recovery of the TOF ratio to 0.9 was 2.0 (0.72) min in renal patients and 1.65 (0.63) min in controls (NS). Recurrence of NMB was not observed in any patient. No sugammadex-related serious adverse events were reported.

Conclusions. Sugammadex administered at reappearance of T_2 rapidly and effectively reverses NMB induced by rocuronium in renal failure and healthy patients. Sugammadex was well tolerated by all patients. Further safety studies on sugammadex in patients with severe renal impairment are warranted.

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Rocuronium is a non-depolarizing aminosteroidal neuromuscular blocking agent (NMBA), with a rapid to intermediate onset of action and an intermediate duration of effect.[1] Recovery from neuromuscular block (NMB) occurs as the NMBA diffuses away from the neuromuscular junction (NMJ) and is eliminated. Use of an acetylcholinesterase inhibitor, such as neostigmine or edrophonium, enhances recovery and reduces the risk of residual block after operation.[2] However, residual NMB remains a potential problem in anaesthesia, as it is a risk factor for postoperative pulmonary complications and antagonists are not always administered.[3] In addition, acetylcholinesterase inhibitors do not effectively reverse profound NMB, particularly in the presence of volatile anaesthetics, and are

ineffective when reversal is attempted before spontaneous recovery.[4–6]

Sugammadex is a modified γ-cyclodextrin, designed to selectively reverse the effects of rocuronium. It is also the first selective relaxant binding agent (SRBA). Cyclodextrins are cyclic oligosaccharides which can encapsulate a lipophilic guest molecule, such as an aminosteroidal NMBA, to form a stable host–guest inclusion complex.[7] Sugammadex forms a stable complex with rocuronium in the plasma, resulting in a rapid decrease in effector site concentration of the unbound relaxant.[7] Owing to the concentration gradient of rocuronium molecules between the NMJ and the plasma, the drug can diffuse away from the nicotinic receptor, giving rapid recovery from NMB.[8 9]

Prolonged NMB has been reported in patients with renal failure after administration of older non-depolarizing NMBAs (gallamine, tubocurarine, and pancuronium), all of which are excreted, in part, by the kidney.[1] In addition, the mean time to spontaneous recovery [train-of-four (TOF) ratio of 0.7] from rocuronium-induced NMB has been shown to be significantly prolonged in patients with end-stage renal failure in comparison with patients with normal renal function.[10] As sugammadex and the sugammadex–rocuronium complex are cleared by the kidneys,[11] this Phase III investigation compared the efficacy and safety of sugammadex for the reversal of rocuronium-induced NMB in patients with normal or severely impaired renal function.

Methods

The study was approved by the Independent Ethics Committee of each trial centre 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 informed written consent. Thirty patients aged ≥18 yr were included in the trial: 15 ASA class II–III patients with end-stage renal failure [creatinine clearance (CL_{CR}) <30 ml min^{-1}] and 15 ASA class I–II control patients (CL_{CR}≥80 ml min^{-1}). CL_{CR} was calculated using the serum creatinine value and the Cockroft and Gault formula.[12]

Patients were undergoing elective surgical procedures in the supine position under general anaesthesia where it was anticipated that only one dose of rocuronium given before tracheal intubation would be required. Pregnant and breast-feeding women, patients with known or suspected neuromuscular disorders, a history of malignant hyperthermia, or allergy to narcotics, NMBAs, or other medication used during general anaesthesia were excluded, as were patients receiving medication known to interfere with the action of rocuronium, for example, aminoglycoside antibiotics, anticonvulsants, or Mg^{2+}.

Anaesthesia was induced and maintained using i.v. infusions of propofol and opiates. Blood pressure, heart rate, ECG, oxygen saturation, central core temperature (measured by a nasopharyngeal or rectal probe), and end-tidal CO_2 were recorded throughout. After induction of anaesthesia, neuromuscular function was monitored continuously by acceleromyography (AMG) at the adductor pollicis muscle using the TOF-Watch® SX (Organon Ireland Ltd, a part of Schering-Plough Corporation, 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.[13] Central core temperature was maintained above 35°C. The AMG transducer was attached to the distal phalanx of the thumb, perpendicular to its movement. The arm and other fingers were immobilized on an arm board. After induction of anaesthesia, a 5 s of 50 Hz tetanic stimulation was performed to reduce the time required to stabilize the response to subsequent TOF stimulation. This was followed by 2–5 min of TOF pulses at 2 Hz, repeated every 15 s, until the twitch response stabilized. The TOF-Watch® SX device was then calibrated. After stabilization of the TOF signal and calibration, repetitive TOF stimulation was performed every 15 s using supramaximal stimuli of 0.2 ms.

A single i.v. dose of rocuronium (0.6 mg kg^{-1}) was administered. After maximal NMB was obtained, tracheal intubation was performed followed by mechanical ventilation with a mixture of oxygen and air. End-tidal CO_2 was maintained within a range of 4.0–5.3 kPa. At reappearance of the second twitch response (T_2), a single i.v. dose of sugammadex (2.0 mg kg^{-1}) was given. Anaesthesia and neuromuscular monitoring were continued until recovery of the TOF ratio to 0.9, and for a minimum of 30 min after the administration of sugammadex.

The primary efficacy variable was the time from administration of sugammadex to recovery of the TOF ratio to 0.9.[14] Secondary efficacy variables were the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.7 (which was previously considered satisfactory clinical recovery)[15] and 0.8. Recurrence of NMB was defined as a decrease in the TOF ratio to <0.9 after full recovery had been detected, or as a deterioration in the clinical signs of recovery from block.

After operation, oxygen saturation and respiratory rate were monitored for 7 h after administration of sugammadex in patients with normal renal function and for at least 24 h in patients with impaired renal function. All patients were assessed for clinical signs of recovery (5 s head lift test, diplopia, general muscle weakness, and tongue depressor test)[15] after admission to the recovery room and 1, 2, 4, 6, 8, 12, 18, and 24 h after administration of sugammadex. Renal patients were also assessed for clinical signs of recovery 36 and 48 h after administration of sugammadex. All subjects were assessed for adverse events (AEs) and serious adverse events (SAEs).[16]

For safety analysis, a urine sample for chemistry and sediment analysis was collected the day before surgery. Blood samples for blood biochemistry (sodium, potassium, chloride, ionized calcium, ionized magnesium, creatinine, blood urea nitrogen, alanine transaminase, aspartate transaminase, gamma-glutamyl transpeptidase, alkaline phosphatase, creatine kinase, lactate dehydrogenase, total bilirubin, total protein, albumin, fasting glucose, total cholesterol, fasting triglycerides, and haptoglobin) and haematology (haematocrit, haemoglobin, erythrocyte count, leucocyte count, differential count, and platelet count), were collected at induction of anaesthesia, and at 20 min and 4–6 h after administration of sugammadex. Assessment of vital signs, blood chemistry, and haematology analysis and urinalysis were repeated on the day after surgery and during a follow-up visit 2–4 weeks after surgery. All clinically relevant abnormal laboratory tests or vital signs were reported as AEs.

Statistical analysis

In previous trials (Organon database) in which a dose of 2.0 mg kg^{-1} sugammadex was administered at reappearance of T_2, the standard deviation (SD) of the times to recovery of the TOF ratio to 0.9 was 45 s. Thirteen patients per group would be required to show equivalence at a power of 81% (significance level $P=0.05$). Assuming a 10–15% dropout rate, 15 patients per group were required.

The confidence interval (CI) approach was used to demonstrate equivalence between patients with normal renal function and those with impaired renal function for the time to recovery of the TOF ratio to 0.7, 0.8, and 0.9 after reversal with sugammadex. With respect to induced recovery, a difference of 60 s or less between the two patient groups in the time to recovery of the TOF ratio to 0.7, 0.8, and 0.9 was considered not to be clinically relevant. Equivalence was established if the two-sided 95% CI for the difference between the two groups lay entirely within the range of −60 to +60 s. The 95% CI for the difference between the two groups was calculated from a two-way full analysis of variance (ANOVA), with patient group and trial site as factors. If the patient group by centre interaction was not statistically significant (significance level of 5%), a *post hoc* two-sided additive ANOVA model was also used to calculate the 95% CI.

Comparison of the physical characteristics of the two patient groups was performed by *post hoc* analysis using Student's *t*-test, χ^2 test, and Fisher's exact test. A statistically significant difference was defined as $P<0.05$.

Results

Fifteen renally impaired patients and 15 controls were enrolled and completed the trial between June 2005 and April 2006. The number of renally impaired and control patients was evenly distributed within each study site. There were no significant differences in age, weight, height, sex, or ethnicity between the two groups (Table 1). The majority of the renal patients were ASA III (93%), whereas in the control group all patients were ASA I or II. The CL_{CR} in the renal failure group ranged from 4.3 to 24.1 ml min^{-1}. Ten of the 15 patients with end-stage renal failure were undergoing dialysis; one patient was having peritoneal dialysis and nine were undergoing haemodialysis at the time of the investigation. The mean CL_{CR} in the renally impaired group was 12 ml min^{-1}, whereas in the control group it was 103 ml min^{-1}.

Table 1 Physical and baseline characteristics by patient group. ASA, American Society of Anesthesiologists; CL_{CR}, total plasma creatinine clearance; SD, standard deviation

	Patient group	
	CL_{CR}<30 ml min^{-1} ($n=15$)	**$CL_{CR}\geq$80 ml min^{-1} ($n=15$)**
Age (yr), mean (range)	61 (29–81)	54 (32–70)
Weight (kg), mean (SD)	76 (13)	84 (15)
Height (cm), mean (SD)	170 (9)	170 (11)
Sex [*n* (%)]		
Female	7 (47)	9 (60)
Male	8 (53)	6 (40)
Ethnicity [*n* (%)]		
Asian	2 (13)	0 (0)
White/Caucasian	13 (87)	15 (100)
ASA class [*n* (%)]		
Class I	0 (0)	5 (33)
Class II	1 (7)	10 (67)
Class III	14 (93)	0 (0)
CL_{CR} (ml min^{-1})		
Mean (SD)	12 (5)	103 (24)
Min–max	4–24	81–181

The time from administration of rocuronium to reappearance of T_2 was 53.8 min (SD=22.4 min) in the renally impaired group and 40.6 min (SD=13.9 min) in the control group ($P=0.06$). The coefficient of variation in the renally impaired group was 41%.

In one subject (control), the TOF traces and recovery variables were unreliable due to poor recording. Data from this subject were excluded. Administration of sugammadex at reappearance of T_2 after a bolus dose of rocuronium resulted in a mean time to recovery of the TOF ratio to 0.9 of 2.0 min for renal patients and 1.65 min for control patients (Table 2). The estimated mean absolute difference in time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9 between the renal patients and the controls was +27.3 s. The corresponding 95% CI for this difference ranged from −10.9 to +65.5 s. The CI was not completely within the predefined equivalence interval of −60 to +60 s and equivalence could therefore not be claimed. However, since the interaction between trial site and subject group was not statistically significant ($P=0.73$), the *post hoc* additive ANOVA model excluding the group-by-centre interaction was applied. Using this approach, the estimated mean absolute between-group difference was 20.1 s and the 95% CI (−12.1 to +52.3 s) was within the predefined equivalence interval.

Table 2 Time (min) from the start of administration of sugammadex to recovery of the TOF ratio to 0.7, 0.8, and 0.9 by patient group. *One patient was excluded from the control group due to poor recording resulting in unreliable TOF traces and recovery variables. ANOVA, analysis of variance; CL_{CR}, total plasma creatinine clearance; NS, not significant; SD, standard deviation; TOF, train-of-four

	Patient group		
	CL_{CR}<30 ml min^{-1} (n=15)	CL_{CR}≥80 ml min^{-1} (n=14)*	ANOVA
Recovery to TOF ratio 0.7, mean (SD)	1.45 (0.47)	1.17 (0.38)	NS
Recovery to TOF ratio 0.8, mean (SD)	1.60 (0.57)	1.32 (0.45)	NS
Recovery to TOF ratio 0.9, mean (SD)	2.00 (0.72)	1.65 (0.63)	NS

The mean times from start of administration of sugammadex to recovery of the TOF ratios to 0.7 and 0.8 were 1.45 *vs* 1.17 min and 1.60 *vs* 1.32 min for renal patients and controls, respectively (Table 2). The estimated mean absolute difference between renal patients and controls for the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.7 and 0.8 was +20.6 and +22.5 s, respectively. The corresponding 95% CI for these differences ranged from −2.4 to +43.6 s and −4.9 to +49.9 s, respectively. Both CIs were within the predefined equivalence interval of −60 to +60 s.

Recurrence of NMB was not observed in any of the patients during the neuromuscular monitoring or postoperative clinical monitoring period. In one control patient, a decrease in oxygen saturation was reported after operation. This was not considered a clinical sign of recurrence of NMB, but was attributed to the i.v. administration of meperidine on the recovery ward. This mild opioid-induced respiratory depression was successfully treated with oxygen (2 litre min^{-1}).

Blood biochemistry analysis showed hypocalcaemia in four patients (three renal patients and one control). The lowest serum calcium measured, in a renal patient, was 1.17 mmol $litre^{-1}$ at 20 min after administration of sugammadex. In one control patient, elevated alanine transaminase (144 U $litre^{-1}$), aspartate transaminase (177 U $litre^{-1}$), bilirubin (44.5 μmol $litre^{-1}$), and gamma-glutamyl transpeptidase levels were recorded a day after surgery. At the follow-up assessment (postoperative day 19), the levels were within the safety ranges. One control patient had thrombocytopaenia (68×10^9 $litre^{-1}$) 4–6 h after administration of sugammadex. The platelet counts at baseline, post-anaesthetic, and follow-up visit were within normal ranges. None of these abnormal values was considered to be related to sugammadex. Haematology and blood biochemistry results were comparable between the two groups, except for serum creatinine and blood urea nitrogen levels, for which the differences existed at baseline.

The urinary variables were comparable between the two groups, except for *N*-acetyl glucosaminidase, beta-2 microglobulin, and microalbumin, which are indicators of renal damage. For these variables, values above the safety ranges were seen predominantly in the renally impaired group and were already present at the screening assessment.

Twenty patients had at least one AE perioperatively: eight patients in the renally impaired group and 12 patients in the control group. The most frequently reported AEs were nausea (n=6), procedural pain (n=6), pain (n=3), anaesthetic complications (coughing and movement during anaesthesia shortly after administration of sugammadex) (n=3), and hypocalcaemia (n=4). Five patients, two in the renally impaired group and three in the control group, experienced a total of eight AEs possibly related to sugammadex. These were diarrhoea (n=2), nausea (n=1), anaesthetic complications (n=3), headache (n=1), and decreased oxygen saturation (n=1). None of the patients was discontinued from the trial because of an AE.

SAEs were reported in two patients. One patient (renally impaired) experienced hypocalcaemia after parathyroidectomy and was re-admitted to hospital before recovering satisfactorily. The other (control) was involved in a road traffic accident on day 6 and suffered a high impact trauma, contusion of the knee, and a forearm fracture. Neither SAE was considered to be related to the administration of sugammadex.

Five patients had abnormal changes in blood pressure from baseline (>20% decrease or increase) after administration of sugammadex. In the renally impaired group, two patients had a low systolic and one patient had a low diastolic blood pressure, whereas in the control group, one patient had a low and another patient had an elevated diastolic blood pressure. In all subjects, the blood pressure changes were considered to be clinically unimportant and returned to baseline after anaesthesia. No markedly abnormal heart rate values were observed.

Discussion

NMB induced by rocuronium (0.6 mg kg^{-1}) was rapidly and effectively reversed by administration of sugammadex (2.0 mg kg^{-1}), both in renally impaired and in control patients. Although reversal of NMB by sugammadex tended to be slower in renal patients (not statistically significant), a mean value of 2.0 min for recovery of the TOF ratio to 0.9 in patients with impaired renal function is still good, especially as clinical signs of recurrence of NMB were not observed in any of the 30 patients. Furthermore, equivalence between the groups was demonstrated with the *post hoc* statistical analysis.

This finding confirms that reversal of rocuronium-induced NMB by sugammadex can be attributed to rapid binding of rocuronium, which prevents it from acting at receptors, and is not dependent on its elimination by renal excretion.

This is consistent with an animal study which demonstrated that after complete interruption of renal perfusion

in anaesthetized cats, sugammadex still caused a rapid reversal of rocuronium-induced NMB.[17] Although this animal model of acute renal failure is not a model for chronic renal insufficiency in humans, it did demonstrate that reversal of NMB by sugammadex is not dependent on renal excretion of the sugammadex–rocuronium complex.

Although available evidence suggests that the sugammadex–rocuronium complex will remain stable over time,[7 18] there may be concerns for patients with renal insufficiency, who will retain the complex for a longer period than patients with normal renal function. For this reason, we monitored the renal patients during 48 h for signs of recurarization, but none experienced recurrence of NMB.

It is of note that a recovery time of 2.0 min is quicker than the time to reversal of rocuronium-induced NMB by acetylcholinesterase inhibitors in healthy patients.[19 20] Sugammadex has already been shown to reverse rocuronium-induced NMB more rapidly than neostigmine. Sugammadex at a dose of 4 mg kg^{-1} for reversal of rocuronium-induced NMB achieved a TOF ratio of 0.9 in <5 min, compared with only 5% of patients given neostigmine 70 $\mu g\ kg^{-1}$.[20]

Mechanomyography (MMG) has for many years been considered as the 'gold standard' for quantification of NMB. An MMG TOF of 0.9 is considered necessary to exclude residual paralysis.[13 14] However, this method is now infrequently used and electromyography and AMG have largely replaced it in clinical research and practice.[13] The AMG and MMG methods cannot be used interchangeably, as a TOF ratio measured by AMG may overestimate recovery when compared with MMG.[21] Therefore, it must be accepted that slight levels of residual paralysis may not always be detected by the AMG.[21 22] The recently updated version of the Good Clinical Research Practice guidelines recommend that 'Investigators using AMG should always report the time to an uncorrected (not normalized) TOF ratio of 0.9 but are encouraged to report the times to TOF ratio of 1.0'. They also state that more comparative data are needed to determine the impact of the practice of normalization, whereby the final TOF ratio becomes the control value, to improve the accuracy of AMG-derived recovery data.[13] The final TOF ratio in our study was almost identical to the baseline. In seven patients (three renal patients and four control patients), reversed fade (TOF ratio>1.1) was recorded before administration of rocuronium. All patients returned to at least their baseline TOF level after administration of sugammadex.

As expected, the duration of clinical relaxation after rocuronium but before administration of sugammadex (time to reappearance of T_2) tended to be longer in patients with impaired renal function, although this finding was not statistically significant. This observation and large between-patient differences in clinical response to rocuronium in renal failure have been reported in other studies.[10 23 24] The efficacy of sugammadex in patients with renal failure reported in this trial indicates that it may be useful in this patient group, where a prolonged duration of action of rocuronium and increased risk of postoperative residual paralysis and respiratory complications are more likely.[1 10]

As cyclodextrins are water soluble and do not possess direct intrinsic biological activity, they are unlikely to cause side-effects, although drug interactions could occur. Of the severe AEs reported in this trial, none was considered to be related to sugammadex. AEs possibly related to sugammadex were diarrhoea, nausea, headache, and coughing or movement under anaesthesia. Coughing or movement after sugammadex has been reported in other studies.[8 25] This may be due to the rapid onset of effect of sugammadex in reversing NMB at a time of relatively light anaesthesia.

In conclusion, sugammadex at a dose of 2.0 mg kg^{-1} effectively and safely reverses NMB induced by rocuronium 0.6 mg kg^{-1}, in patients with normal or impaired renal function ($CL_{CR}<30$ ml min^{-1}). Recovery to the necessary TOF ratio of 0.9 before extubation occurred very rapidly and no signs of recurrence of NMB were reported. In patients with renal failure, sugammadex may be useful for limiting the risks of residual postoperative paralysis. Further safety studies on sugammadex in patients with severe renal impairment are warranted.

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References

1 Hunter JM. New neuromuscular blocking drugs. *N Engl J Med* 1995; **332**: 1691–9

2 Caldwell JE. Reversal of residual neuromuscular block with neostigmine at one to four hours after a single intubating dose of vecuronium. *Anesth Analg* 1995; **80**: 1168–74

3 Berg H, Roed J, Viby-Mogenson J, *et al.* Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; **41**: 1095–103

4 Kirkegaard-Nielsen H, Helbo-Hansen HS, Lindholm P, Severinsen IK, Pedersen HS, Jensen EW. Optimum time for neostigmine reversal of atracurium-induced neuromuscular blockade. *Can J Anaesth* 1996; **43**: 932–8

5 Reid JE, Breslin DS, Mirakhur RK, Hayes AH. Neostigmine antagonism of rocuronium block during anesthesia with sevoflurane, isoflurane or propofol. *Can J Anaesth* 2001; **48**: 351–5

6 van den Broek L, Proost JH, Wierda JM. Early and late reversibility of rocuronium bromide. *Eur J Anaesthesiol* 1994; **9**: 128–32

7 Bom A, Bradley M, Cameron K, *et al*. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew Chem Int Ed* 2002; **41**: 265–70

8 Sorgenfrei IF, Norrild K, Larsen PB, *et al*. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex; a dose-finding and safety study. *Anesthesiology* 2006; **104**: 667–74

9 Hunter JM, Flockton EA. The doughnut and the hole: a new pharmacological concept for anaesthetics. *Br J Anaesth* 2006; **97**: 123–6

10 Robertson EN, Driessen JJ, Booij LHDJ. Pharmacokinetics and pharmacodynamics of rocuronium in patients with and without renal failure. *Eur J Anaesthesiol* 2005; **22**: 4–10

11 Gijsenbergh F, Ramael S, Houwing N, van Iersel T. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. *Anesthesiology* 2005; **103**: 695–703

12 Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41

13 Fuchs-Buder T, Claudius C, Skovgaard LT, Eriksson LI, Mirakhur RK, Viby-Mogenson J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. *Acta Anaesthesiol Scand* 2007; **51**: 789–808

14 Eriksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. *Anesthesiology* 2003; **98**: 1037–9

15 Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block (part II). *Br J Anaesth* 1971; **43**: 478–85

16 International Conference on Harmonization. *Guideline for Good Clinical Practice*. 1997

17 Bom AH, Van Egmond J, Hope F, Van de Pol F. Rapid reversal of rocuronium-induced neuromuscular block by Org 25969 is independent of renal perfusion. *Anesthesiology* 2003; **99**: A1158

18 Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg* 2007; **104**: 575–81

19 McCourt KC, Mirakhur RK, Kerr CM. Dosage of neostigmine for reversal of rocuronium block from two levels of spontaneous recovery. *Anaesthesia* 1999; **54**: 651–5

20 Sacan O, White PF, Tufanogullari B, Klein K. Sugammadex reversal of rocuronium-induced neuromuscular blockade: a comparison with neostigmine–glycopyrrolate and edrophonium–atropine. *Anesth Analg* 2007; **104**: 569–74

21 Capron F, Alla F, Hottier C, Meistelman C, Fuchs-Buder T. Can acceleromyography detect low levels of residual paralysis? A probability approach to detect a mechanomyographic train-of-four ratio of 0.9. *Anesthesiology* 2004; **100**: 1119–24

22 Samet A, Capron F, Alla F, Meistelman C, Fuchs-Buder T. Single acceleromyography train-of-four: 100-hertz tetanus or double-burst stimulation: which test performs better to detect residual paralysis? *Anesthesiology* 2005; **102**: 51–6

23 Cooper RA, Maddineni VR, Mirakhur RK, Wierda JM, Brady M, Fitzpatrick KT. Time course of neuromuscular effects and pharmacokinetics of rocuronium bromide (ORG 9426) during isoflurane anaesthesia in patients with and without renal failure. *Br J Anaesth* 1993; **71**: 222–6

24 Cooper RA, Mirakhur RK, Wierda JMKH, Maddineni VR. Pharmacokinetics of rocuronium bromide in patients with and without renal failure. *Eur J Anaesthesiol* 1995; **11**: 43–4

25 Sparr HJ, Vermeyen KM, Beaufort AM, *et al*. Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomized multicenter study. *Anesthesiology* 2007; **106**: 935–43