J Anesth (2011) 25:855–859
DOI 10.1007/s00540-011-1236-y

ORIGINAL ARTICLE

Comparison of recovery times from rocuronium-induced muscle relaxation after reversal with three different doses of sugammadex and succinylcholine during electroconvulsive therapy

Yuji Kadoi · Hiroko Hoshi · Akiko Nishida · Shigeru Saito

Received: 22 May 2011 / Accepted: 5 September 2011 / Published online: 24 September 2011

Abstract
Purpose This study was conducted to compare recovery times from rocuronium-induced muscle relaxation after reversal with three different doses of sugammadex with succinylcholine during electroconvulsive therapy (ECT).
Methods Seventeen patients who were scheduled to undergo ECT were studied. Anesthesia was induced by use of propofol (1.0 mg/kg) followed by either succinylcholine (SCC) (1 mg/kg) or rocuronium (0.6 mg/kg). Assisted mask ventilation was initiated with 100% oxygen. After T1 was assessed as being zero by neuromuscular monitoring, an electroshock stimulus was applied bilaterally. Patients receiving rocuronium were infused with 16, 8, or 4 mg/kg sugammadex immediately after the seizure stopped to reverse the muscle relaxation. Neuromuscular monitoring was continued until recovery of the train-of-four ratio to 0.9 at the tibial nerve in the leg. The times to recovery of T1 to 10 and 90% with both relaxants were compared.
Results The time to recovery of T1 to 90% after 16 mg/kg sugammadex was shorter than that in subjects treated with SCC ($p = 0.046$), whereas that after 4 mg/kg sugammadex was longer than that in subjects treated with SCC (SCC group: 429 ± 65 s, 16 mg/kg sugammadex group: 387 ± 63 s*, 8 mg/kg sugammadex group: 462 ± 66 s, 4 mg/kg sugammadex group: 563 ± 45 s*,#; $^{*}p < 0.05$ compared with SCC, $^{\#}p < 0.01$ compared with 16 mg/kg sugammadex).
Conclusions This study demonstrates the efficacy of rocuronium–sugammadex as an alternative to SCC for muscle relaxation during ECT, and indicates that 8 mg/kg sugammadex produces equally rapid recovery from rocuronium muscular relaxation compared with spontaneous recovery from 1 mg/kg SCC during ECT.

Keywords Electroconvulsive therapy · Muscle relaxant · Rocuronium · Sugammadex · Succinylcholine

Y. Kadoi (✉) · H. Hoshi · A. Nishida · S. Saito
Department of Anesthesiology, Gunma University, School of Medicine, 3-39-22 Showa-Machi, Maebashi, Gunma 371-8511, Japan
e-mail: kadoi@med.gunma-u.ac.jp

Introduction

Succinylcholine (SCC) is commonly used as a muscle relaxant during electroconvulsive therapy (ECT) because of its rapid onset and short duration of action [1]. However, SCC has many side effects, for example myalgia, a small increase in plasma potassium, and increase in intra-gastric and intra-ocular pressures [1].

Sugammadex has recently been introduced as a fast-acting, selective relaxant-binding agent that was designed to rapidly reverse rocuronium-induced neuromuscular block. Lee et al. [2, 3] reported that reversal of profound rocuronium (1.0–1.2 mg/kg)-induced neuromuscular block with a large dose of sugammadex (16 mg/kg) was significantly faster than spontaneous recovery from SCC. Previously, we showed the potential benefit of using rocuronium (0.6 mg/kg)–sugammadex (16 mg/kg) as an alternative to SCC (1 mg/kg) for muscle relaxation during ECT [4]. A large dose of rocuronium (1.0–1.2 mg/kg) is usually not needed for muscle relaxation during ECT, as shown in our previous study [4] and that of others [1]. Hence, we speculated that a slightly smaller dose of sugammadex would be required for equally rapid recovery from 0.6 mg/kg rocuronium-induced muscle relaxation as from relaxation with 1 mg/kg SCC.

The purpose of this study was to determine the dose of sugammadex that would produce an equal recovery time

from 0.6 mg/kg rocuronium-induced muscle relaxation as from spontaneous recovery from relaxation with 1 mg/kg SCC during ECT.

Materials and methods

Informed consent was obtained from patients or their families. All protocols were approved by the local Institutional Clinical Study Committee and the Institutional Review Board. Seventeen patients who were scheduled to undergo ECT were studied. None of the patients had a history of cardiovascular, hepatic, renal, or neuromuscular disease, or were obese (BMI >35).

Anesthetic management

All patients underwent at least 10 sessions of ECT (three times per week at 1 or 2-day intervals). To avoid induction of the parasympathetic reflex, the patients received atropine (0.01 mg/kg IM) 30 min before the ECT procedure.

Data measured during the procedure included blood pressure (BP), heart rate, oxygen saturation (SpO_2; measured by pulse oximetry on the left or right index finger), end-expiratory partial pressure of carbon dioxide (end-tidal CO_2:$PetCO_2$) at the nostrils (Capnomac Ultima; Datex, Helsinki, Finland) and electrocardiogram (ECG; lead II). Measurements were initiated before ECT and were terminated at the end of the procedure.

Anesthesia was induced by use of propofol (1.0 mg/kg intravenously over 5 s), followed by either SCC (1 mg/kg intravenously) or rocuronium (0.6 mg/kg intravenously) over 5 s, followed by a 10-ml saline bolus. Assisted mask ventilation was initiated with 100% oxygen. After T1 was assessed as being zero by neuromuscular monitoring, an electroshock stimulus was applied bilaterally for 5 s.

$PetCO_2$ was maintained at 30–35 mmHg and the SpO_2 value was maintained above 98% by manual mask assistance throughout the therapy. Patients who received rocuronium were infused with 16, 8, or 4 mg/kg sugammadex with a 10-ml saline bolus immediately after the seizure stopped.

During the first and second ECT sessions, we confirmed that 1 mg/kg propofol and 1 mg/kg SCC could provide adequate anesthetic conditions and muscle relaxation to all patients. In addition, the intensity of the ECT stimulus required to achieve a minimum seizure duration of more than 20 s was determined during these sessions.

All patients received 1 mg/kg SCC as the muscle relaxant agent for first three of the subsequent ECT sessions and 0.6 mg/kg rocuronium during the next three sessions. In the remaining sessions (from 7 to 10 or 12 sessions) 1 mg/kg SCC was used as the muscle relaxant agent. When rocuronium was used as the muscle relaxant, patients received one of three sugammadex dosages (16, 8, or 4 mg/kg), with a 10-ml saline bolus immediately after the seizure stopped, the dose of sugammadex to be used in a particular session being decided by a lottery system. Administration of sugammadex was in a non-blinded manner. Electroencephalographic (EEG) seizure duration was recorded by a two-channel EEG after administration of the electrical stimulus.

Neuromuscular assessment

Neuromuscular monitoring was performed using the TOF-watch SX (Organon, Roseland, NJ, USA). The tibial nerve in the leg was supramaximally stimulated at the inferolateral aspect of the medial malleolus with square pulses of 0.2-ms duration, delivered as train-of-four (TOF) pulses, at intervals of 15 s. The resulting contractions of the great toe muscles were quantified by an acceleromyographic monitor. Calibration was performed and baseline responses were recorded after propofol administration and before muscle relaxant administration. A 50-Hz titanic stimulus was applied for 5 s and followed after 1 min by TOF stimulation every 15 s. When the response to TOF stimulation was stable, calibration and supramaximal stimulation were ensured by the in-built calibration function. Neuromuscular monitoring was continued until recovery of the TOF ratio to 0.9. Following the protocol of our previous study [4], we compared the time to recovery of T1 to 10 and 90% between relaxants. T1 was zero in all patients when sugammadex was administered. We used recovery of T1 to 10% (instead of TOF ratio) for its simplicity, its common usefulness between depolarizing and non-depolarizing relaxants, and because the TOF ratio has uncertain significance with a single dose of SCC.

Patients were also assessed for clinical signs such as the time interval between the first spontaneous breath and administration of muscle relaxant and the time to opening of eyes to verbal commands.

Statistical analysis

All data are expressed as mean ± standard deviation (SD). Before the study was started, sample size was evaluated. The sample size was calculated on the basis of the hypothesis that recovery of T1 to 10% with 4 mg/kg sugammadex would be prolonged to 60 s compared to that with SCC [4]. The sample size provided 80% power to detect a 20% difference between 4 mg/kg sugammadex and the SCC groups with a 5% probability of a type II error. A paired *t* test was used for comparison of the two groups. For multiple comparisons, one-way factorial ANOVA and the Bonferroni test were used for the

comparison. Values of $p < 0.05$ were considered statistically significant.

Calculations were performed by Stat View 5.0 software (Abacus Concepts, Berkeley, CA, USA).

Results

Patient age, height, and weight were 58 ± 14 years, 157 ± 7 cm, 57 ± 10 kg, respectively. Seven of the 17 patients were male.

Table 1 shows the comparison between the effects of SCC and rocuronium in terms of time from the start of administration of neuromuscular blocking agent to a T1 of zero. There was no significant difference between the groups.

Table 2 shows the time from commencement of administration of neuromuscular blocking agents to recovery of T1 to 10 and 90%, seizure duration, and time to first spontaneous breath in the two groups. The time to recovery of T1 to 90% in subjects treated with 16 mg/kg sugammadex was shorter than that in subjects treated with SCC ($p = 0.046$), and the time to recovery of T1 to both 10 and 90% in subjects treated with 4 mg/kg sugammadex was longer than that in subjects treated with SCC ($p < 0.01$). The time to first spontaneous breath in subjects treated with 16 mg/kg sugammadex was shorter than that in subjects treated with SCC ($p = 0.045$), and the time to first spontaneous breath in subjects treated with 4 mg/kg sugammadex was longer than that in subjects treated with SCC ($p < 0.01$). No significant difference in seizure duration was found among the four groups.

No adverse effects, such as nausea, vomiting, myalgia, or headache occurred with either relaxant. In addition, no symptoms of recurarization, for example respiratory depression (indicated by a decrease in SpO_2 less than 90% without supplementary oxygen supply) were seen in any of the patients treated with rocuronium–sugammadex (4, 8, or 16 mg/kg sugammadex) during the observation period of up to 12 h after the administration of rocuronium–sugammadex, when the patients were in the ward.

Table 1 Time from commencement of administration of neuromuscular blocking agents to a T1 of zero with each drug

	SCC	Rocuronium
Time to T1 of 0% (s)	109 ± 28	123 ± 28
p value	0.13	

Discussion

This study showed that:

1. the onset of action of 0.6 mg/kg rocuronium is equivalent to that of 1 mg/kg SCC for muscle relaxation during ECT; and
2. 8 mg/kg sugammadex is adequate for reversal of muscle relaxation induced by 0.6 mg/kg rocuronium during ECT.

Although Trollor and Sachdev [5] suggested the possible safety of the use of SCC in cases with neuroleptic malignant syndrome, SCC is thought to be a potent trigger for malignant hyperthermia (MH) [2]. Moreover, use of SCC is associated with a variety of adverse events and contraindications [2]. To avoid these, some researchers examined other neuromuscular agents, for example vecuronium [6, 7], mivacurium [8–10], rapacuronium [11] and rocuronium [12] during ECT. Kelly and Brull [10] demonstrated the safety of mivacurium as an alternative to SCC. In contrast, Cheam et al. [8] reported that a low dose of mivacurium was less effective than SCC. Another study of the safety of vecuronium reported that vecuronium shortened seizure duration and prolonged anesthetic time [6].

Rocuronium is potentially useful for muscle relaxation during ECT. However, before our previous study [4] there

Table 2 Time from commencement of administration of neuromuscular blocking agents to recovery of T1 to 10 and 90%, seizure duration, time to first spontaneous breath, and interval between rocuronium and sugammadex administration with each drug

	Recovery of T1 to 10% (s)	Recovery of T1 to 90% (s)	Time to first spontaneous breath (s)	Seizure duration (s)	Time from administration of rocuronium to administration of sugammadex (s)
SCC	310 ± 38	429 ± 65	273 ± 43	36 ± 6	
Sugammadex, 16 mg/kg	280 ± 54	387 ± 63*	233 ± 53*	38 ± 4	134 ± 7
Sugammadex, 8 mg/kg	324 ± 68	462 ± 66	267 ± 69	40 ± 7	132 ± 8
Sugammadex, 4 mg/kg	407 ± 74*,#	563 ± 45*,#	360 ± 59*,#	39 ± 5	134 ± 8

SCC, succinylcholine

* $p < 0.05$ compared with SCC

# $p < 0.05$ compared with sugammadex 16 mg/kg group

was only one report evaluating the effects of rocuronium versus SCC on clinical recovery from ECT [12]. Turkkal et al. [12] reported that although the time to first spontaneous breath was longer in the rocuronium group than in the SCC group, no significant differences were detected between the two groups in terms of eye opening, head lift, or tongue depressor testing. However, the dosage of rocuronium used in the study of Turkkal et al. [12] was relatively small (0.3 mg/kg), which is thought to be inadequate for muscular paralysis, because a dose of 0.3 mg/kg IV is rocuronium's ED_{50} dose for the laryngeal adductor muscles, this being half of the recommended intubating dose for rocuronium. Rocuronium (0.6–1.2 mg/kg) typically produces complete neuromuscular block within 2 min, compared with an average of 1 min with 1 mg/kg SCC [13]. High-dose rocuronium (1.0–1.2 mg/kg) has been recommended by some researchers as an effective alternative to SCC for rapid sequence induction. However, a meta-analysis of the Cochrane Review [14] concluded that intubation conditions do not statistically significantly differ with the administration of SCC and rocuronium when propofol is used to rapidly induce anesthesia. Indeed, in this study, no difference in the time from commencement of administration of neuromuscular blocking agents to T1 zero was found between the two groups. Hence, doses of 0.6 mg/kg rocuronium and 1 mg/kg SCC are appropriate for muscle relaxation during ECT.

Sluga et al. [15] compared tracheal intubation conditions with the use of 0.6 mg/kg rocuronium and 1 mg/kg SCC in emergency cases and showed that the time interval from injection of the neuromuscular blocking agents to the cessation of a visible motor response to continuous single-twitch nerve stimulation of the ulnar nerve was shorter in the SCC group (median time 40 s) than in the rocuronium group (median time 70 s). Although there was a tendency towards a longer interval between commencement of administration of neuromuscular blocking agents and T1 zero in the rocuronium group in this study, the difference between the two groups was not significant. The possible cause of this difference, as we previously showed [16], is that the onset of action of muscle relaxants is greatly affected by cardiac output before injection. Another possibility is that Sluga et al. [15] selected 1.5 mg/kg propofol with 2 μg/kg fentanyl for anesthetic induction. The difference in the anesthetic regime may also be responsible for the different results.

Lee et al. [3] compared the time required for sugammadex reversal of profound rocuronium-induced neuromuscular block with time to spontaneous recovery after SCC. In their study, either 1.2 mg/kg rocuronium or 1 mg/kg SCC was used for block of neuromuscular transmission and facilitation of tracheal intubation. Sugammadex (16 mg/kg) was administered 3 min after rocuronium administration. Mean times to recovery of T1 to 90% were significantly faster in the rocuronium–sugammadex group than in the SCC group. Hence, they concluded that reversal of profound high-dose rocuronium-induced neuromuscular block (1.2 mg/kg) with 16 mg/kg sugammadex was significantly faster than spontaneous recovery from 1 mg/kg SCC. In an earlier report from Gijsenbergh et al. [17] with an intubating dose of 0.6 mg/kg rocuronium, the TOF ratio returned to 0.9 within 2 min after administration of 8.0 mg/kg sugammadex given 3 min after the administration of rocuronium. Pühringer et al. [13] examined the dose-dependent effects of sugammadex for reversal of profound neuromuscular block. Sugammadex (2, 4, 8, 12, or 16 mg/kg) was administrated 3 min after the administration of 1.0 or 1.2 mg/kg rocuronium. The time to recovery of the TOF ratio to 0.9 with sugammadex was faster in a dose-dependent manner. These two reports showed that although the recovery speed of the TOF ratio to 0.9 with sugammadex was dose-dependent, its efficacy was unchanged. Our study showed that although 16 mg/kg sugammadex resulted in the fastest recovery of the TOF ratio to 0.9 in the case of 0.6 mg/kg rocuronium, 8 mg/kg sugammadex had equipotent effects on the recovery of the TOF ratio to 0.9 compared with the use of SCC during ECT.

Batistaki et al. [18] reported successful anesthetic management of a patient with pseudocholinesterase deficiency by use of rocuronium reversed by sugammadex in a series of ECT sessions. In a preliminary report, we showed the potential efficacy of the use of rocuronium–sugammadex as a muscle relaxant during ECT [4]. Hence, rocuronium–sugammadex could also be useful for muscle relaxation during ECT for patients for whom the use of SCC is contraindicated. Our report implies that a combination of rocuronium–sugammadex, using 0.6 mg/kg rocuronium, may be adequate for inducing muscle paralysis during ECT. In addition, 8 mg/kg sugammadex produced adequate recovery from the muscular relaxation induced by 0.6 mg/kg rocuronium during ECT.

In this study, the patients were administered a combination of rocuronium–sugammadex repeatedly once a day for a week during the study. Although this repeated administration may possibly have adverse effects on the patients, we did not find any adverse effects (nausea, vomiting, prolongation of the QTc interval), and more specifically, recurarization, with any of the three doses of sugammadex. Batistaki et al. [18] reported that a combination of rocuronium–sugammadex used every 48 h for 8 consecutive ECT sessions proved to be effective and safe in a situation where SCC was contraindicated. Our study also confirms the potential usefulness of rocuronium–sugammadex for muscle relaxation during ECT for patients for whom the use of SCC is contraindicated, for example those with severe osteoporosis, amyotrophic lateral sclerosis, and a history of neuroleptic syndrome.

Another consideration is that the combination of rocuronium–sugammadex is eliminated by the kidney, so that it is possible that its elimination could be prolonged in patients with impaired renal function, which could induce adverse effects in these patients. All patients included in this study had normal renal function, as shown by normal serum creatinine and BUN levels. However, care should be taken when using sugammadex for patients with impaired renal function. Use of the combination of rocuronium–sugammadex would also be disadvantageous compared with SCC in cases where re-use of rocuronium is required immediately after administration of sugammadex.

In conclusion, we demonstrated the efficacy of rocuronium–sugammadex as an alternative to SCC for muscle relaxation during ECT and showed that 8 mg/kg SG has equipotent recovery time from muscular relaxation compared with 1 mg/kg SCC during ECT.

Acknowledgments The authors wish to thank Forte (Tokyo, Japan) for assistance with manuscript preparation in English. This study was supported in part by grants to Dr Kadoi (no. 21591998) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Conflict of interest No authors have any conflicts of interest in association with this article.

References

1. Kadoi Y, Saito S. Anesthetic considerations for electroconvulsive therapy-especially hemodynamic and respiratory management. Curr Psychiatry Rev. 2009;5:276–86.
2. Lee C. Goodbye suxamethonium!. Anaesthesia. 2009;64:73–81.
3. Lee C, Jahr JS, Candiotti KA, Warriner B, Zornow MH, Naguib M. Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine. Anesthesiology. 2009;110:1020–5.
4. Hoshi H, Kadoi Y, Kamiyama J, Nishida A, Saito H, Taguchi M, Saito S. Use of rocuronium–sugammadex, an alternative to succinylcholine, as a muscle relaxant during electroconvulsive therapy. J Anesth. 2011;25:286–90.
5. Trollor JN, Sachdev PS. Electroconvulsive treatment of neuroleptic malignant syndrome: a review and report of cases. Aust N Z J Psychiatry. 1999;33:650–9.
6. Nishiyama M, Togashi H. Effects of anesthetic agents on seizure duration and hemodynamics in electroconvulsive therapy. Masui (Jpn J Anesthesiol). 2009;58:1266–9. (in Japanese with English abstract).
7. Setoyama K, Hirata T, Saeki H, Morimoto Y, Tsuruta S, Matsumoto M, Sakabe T. Anesthetic management for electroconvulsive therapy in the patients with a history of neuroleptic malignant syndrome. Masui (Jpn J Anesthesiol). 2009;58:633–6. (in Japanese with English abstract).
8. Cheam EW, Critchley LA, Chui PT, Yap JC, Ha VW. Low dose mivacurium is less effective than succinylcholine in electroconvulsive therapy. Can J Anesth. 1999;46:49–51.
9. Janis K, Hess J, Fabian JA, Gillis M. Substitution of mivacurium for succinylcholine for ECT in elderly patients. Can J Anesth. 1995;42:612–3.
10. Kelly D, Brull SJ. Neuroleptic malignant syndrome and mivacurium: a safe alternative to succinylcholine? Can J Anaesth. 1994;41:845–9.
11. Kadar AG, Kramer BA, Barth MC, White PF. Rapacuronium: an alternative to succinylcholine for electroconvulsive therapy. Anesth Analg. 2001;92:1171–2.
12. Turkkal DC, Gokmen N, Yildiz A, Iyilikci L, Gokel E, Sagduyu K, Gunerli A. A cross-over, post-electroconvulsive therapy comparison of clinical recovery from rocuronium versus succinylcholine. J Clin Anesth. 2008;20:589–93.
13. Pühringer FK, Rex C, Sielenkämper AW, Claudius C, Larsen PB, Prins ME, Eikermann M, Khuenl-Brady KS. Reversal of profound, high-dose rocuronium-induced neuromuscular blockade by sugammadex at two different time points: an international, multicenter, randomized, dose-finding, safety assessor-blinded, phase II trial. Anesthesiology. 2008;109:188–97.
14. Perry J, Lee J, Wells G. Rocuronium versus succinylcholine for rapid sequence induction intubation. In: The Cochrane Library. Issue 3. Hoboken: Wiley; 2004.
15. Sluga M, Ummenhofer W, Studer W, Siegemund M, Marsch SC. Rocuronium versus succinylcholine for rapid sequence induction of anesthesia and endotracheal intubation: a prospective, randomized trial in emergent cases. Anesth Analg. 2005;101:1356–61.
16. Matsumoto N, Tomioka A, Sato T, Kawasaki M, Kadoi Y, Saito S. Relationship between cardiac output and onset of succinylcholine chloride action in electroconvulsive therapy patients. J ECT. 2009;25:246–9.
17. 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.
18. Batistaki C, Kesidis K, Apostolaki S, Kostopanagiotou G. Rocuronium antagonized by sugammadex for series of electroconvulsive therapy (ECT) in a patient with pseudocholinesterase deficiency. J ECT. 2011;27:e47–8.