Sugammadex for Rocuronium-Induced Neuromuscular Blockade

Subjects: Anesthesiology

Contributor: Young Sung Kim

Sugammadex (Bridion®, Merk Sharp and Dohme Corp., Kenilworth, NJ, USA) is a modified cyclodextrin designed to selectively encapsulate aminosteroidal neuromuscular blocking agents (NMBAs) such as rocuronium and vecuronium, which leads to the rapid reversal of neuromuscular block (NMB).

Keywords: kidney failure ; chronic ; renal insufficiency ; chronic ; rocuronium

1. Introduction

Sugammadex administered to the blood rapidly encapsulates the NMBA, leading to an increased gradient in the concentration of NMBA between the neuromuscular junction and plasma; subsequently, the NMBA present at the neuromuscular junction is rapidly released into the blood, and rapid NMB reversal is achieved [1]. The sugammadex-NMBA complex produced is inactive and hydrophilic and is mainly excreted by the kidney. In addition, NMBAs such as rocuronium or vecuronium are excreted mainly through the kidneys [2][3]. In patients with severe renal impairment, the pharmacokinetics of both rocuronium and sugammadex are altered, and, thus, the NMB reversal by sugammadex can be unpredictable or incomplete [2]. Therefore, the U.S. Food and Drug Administration does not recommend sugammadex for patients with a creatinine clearance of <30 mL min −1 [4].

Nevertheless, the use of sugammadex is often observed in clinical practice for surgical patients with chronic kidney disease in various clinical situations, and some prospective case-control or retrospective studies and case reports regarding the use of sugammadex in patients with end-stage renal disease (ESRD) have been published [5][6][7]. To date, no systematic review regarding the use of sugammadex in patients with severe renal impairment has been reported, while there have been several meta-analyses showing the effectiveness, safety, and superiority of sugammadex, compared to cholinesterase inhibitors for NMB reversal in adult patients without organ dysfunction; a systematic review would need to take into account the results of the studies that reported the use of sugammadex in patients with ESRD and analyze their pooled data.

2. Study Characteristics and Patient Demographics

The details of the selected studies are summarized in **Table 1** and **Table 2**. It identified nine studies with 655 patients, including six prospective, case-control studies with 179 patients (90 patients with ESRD and 89 patients with normal renal function) and three retrospective, observational studies with 476 patients with ESRD who required preoperative renal replacement therapy.

Table 1. Characteristics of the included prospective case-control studies.

Study	Journal	Study Design	Center/Country	Group R (*n*)	Group *N* (*n*)	Age	Sugammadex Dose	NMB Monitoring
de Souza et al., 2015 [8]	*European Journal of Anaesthesiology*	Prospective clinical trial	Two hospitals Brazil, and Spain	ClCr < 30 mL min^{-1} (20)	ClCr > 90 mL min^{-1} (20)	18–65	4 mg kg^{-1}	Acceleromyography at the adductor pollicis muscle
Panhuizen et al., 2015 [9]	*British Journal of Anaesthesia*	Case control comparative study	Eight centers in Europe	ClCr < 30 mL min^{-1} (35)	ClCr ≥ 80 mL min^{-1} (35)	≥18	4 mg kg^{-1}	Acceleromyography at the adductor pollicis muscle

Study	Journal	Study Design	Center/Country	Group R (*n*)	Group *N* (*n*)	Age	Sugammadex Dose	NMB Monitoring
Staals et al., 2008 [10]	*British Journal of Anaesthesia*	Prospective clinical trial	Three centers in Europe	ClCr < 30 mL min^{-1} (15)	ClCr ≥ 80 mL min^{-1} (15)	≥18	2 mg kg^{-1}	Acceleromyography at the adductor pollicis muscle
Staals et al., 2010 [2]	*British Journal of Anaesthesia*	Prospective clinical trial	Three centers in Europe	ClCr < 30 mL min^{-1} (15)	ClCr ≥ 80 mL min^{-1} (15)	≥18	2 mg kg^{-1}	Acceleromyography at the adductor pollicis muscle
Maeyama et al., 2014 [11]	*European Journal of Anaesthesiology*	Prospective clinical trial	University hospital, Japan	ClCr < 15mL min^{-1} (13)	ClCr > 90 mL min^{-1} (14)	≥18	4 mg kg^{-1}	Not mentioned
Min et al., 2017 [12]	*International Journal of Clinical Pharmacology and Therapeutics*	Open label, two parts, phase 1 study	Clinical pharma-cology of Miami, USA	ClCr < 30 mL min^{-1} (6)	ClCr ≥ 80 mL min^{-1} (6)	≥18	4 mg kg^{-1}	None

R: patients with end-stage renal disease; Group N: patients with normal renal function; NMB: neuromuscular blockade; ClCr: Creatinine clearance.

Table 2. Characteristics of the included retrospective observational studies.

Study ID	Journal	Study Design	Center/Country	Enrolled Criteria (*n*)	Age	NMB Reversal Agent
Adams et al., 2020 [6]	*Anaesthesia*	Two centers retrospective study	Pittsburgh Medical Center, Memorial Sloan Kettering Cancer Center, USA	End-stage renal disease which is mandatory for renal replacement therapy (158)	≥18	sugammadex
Paredes et al., 2020 [13]	*Canadian Journal of Anaesthesia*	Historical cohort study, three-distinct geographic locations	Scottsdale, AZ, Jacksonville, FL, Rochester, MN, USA	eGFR value < 15 mL min^{-1} (219)	≥18	sugammadex
Ono et al., 2018 [5]	*Journal of Anesthesia Clinical Reports*	Retrospective study	Aichi Medical University, Nagakute, Japan	Diagnosed severe with renal failure and underwent renal transplantation (99)	not mentioned	sugammadex

eGFR = estimated glomerular filtration ratio. NMB = neuromuscular blockade.

Staals et al. published two articles, reporting on the same patients, in 2008 and 2010 [2][10]. Regarding post-anesthetic adverse events, de Souza et al. [8] defined the recurrence of NMB as a decrease in the TOF ratio below 0.9, after complete recovery was detected, and they monitored the arterial oxygen saturation (SaO_2), blood pressure, and heart rate until 2 h after the administration of sugammadex. Panhuizen et al. [9] assessed data associated with patient safety, including post-anesthetic adverse events, heart rate, blood pressure, and laboratory data, as well as data associated with the physical examination of patients for four weeks after surgery. In the studies of Staals et al. [2][10], oxygen saturation was monitored for 7 h after the administration of sugammadex for group N and 24 h for group R; they assessed for clinical signs of recovery until 48 h after sugammadex administration and collected data about the vital signs, blood chemistry, and hematology analysis for 2–4 weeks after surgery. The 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 NMB. Min et al. [12] evaluated the safety and tolerability of sugammadex through a clinical assessment of adverse events and other safety measures, including vital signs, medical history, physical examination, 12-lead electrocardiography, and standard laboratory tests obtained at pre-specified time points throughout the study.

Pharmacokinetic parameters were evaluated in three trials, and each study used liquid chromatography–mass spectrometry to measure the plasma concentration of sugammadex and rocuronium, and the assays in the three trials were carried out in full compliance with Good Laboratory Practice regulations.

In one study (Min et al., 2017) [12], blood samples were obtained before sugammadex administration (pre-dose) through 48 h after sugammadex administration (post-dose) for group N, and pre-dose through day 10 (216 h) post-dose for group

R (flexibility was included to extend pharmacokinetic assessment as needed for up to three additional samples [days 14, 18, and 21]). In another trial (Panhuizen et al., 2015) [9], plasma concentrations of rocuronium and sugammadex were assessed using blood samples pre-dose through 24 h post-dose for group N. For group R, blood samples were obtained pre-dose through 28 h post-dose. Unfortunately, the validity of the sugammadex bioanalytical data failed to reach quality standards since sample-to-sample carryover could not be ruled out and re-assay was not possible because of unavailable duplo samples and stability issues. Thus, in this study, all sugammadex bioanalytical data were considered invalid and could not be used for pharmacokinetic analysis.

In the last study (Staals et al., 2010) [2], for pharmacokinetic parameters, blood sampling was obtained pre-sugammadex, as well as 2, 3, 5, 10, 15, 20, 30, and 60 min and 2, 4, 6, 8, 12, 18, and 24 h after sugammadex administration. In group R, further blood samples were obtained at 36 and 48 h after sugammadex administration, and in the case of hemodialysis (within 72 h after the operation), additional blood samples were obtained pre- and post-dialysis.

3. Main Results: The Primary and Secondary Outcomes of the Included Prospective Studies

In total, three studies were analyzed for the time taken to reach a TOF ratio ≥0.9, 0.8 and 0.7, and all variables were significantly longer in group R than in group N, although the heterogeneity was high (WMD [95% CI] [min]: 1.14 [0.29 to 2.00]; I^2 = 86%, 0.9 [0.24 to 1.57]; I^2 = 87%, 0.89 [0.20 to 1.57]; I^2 = 92%, respectively) (**Figure 2**).

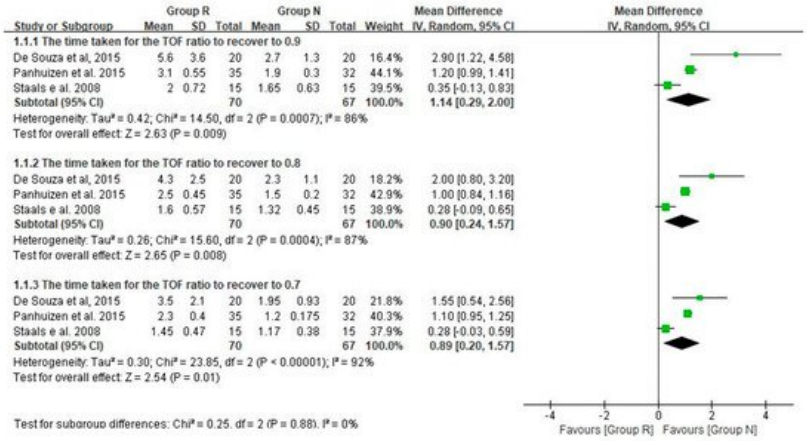

Figure 2. The time taken to reach a TOF ratio ≥ 0.9, 0.8, and 0.7 (min). SD = standard deviation; IV = inverse variance; CI = confidence interval.

The results of analysis on the pharmacokinetic parameters are as follows (**Figure 3**): Two studies [2][12] reported the total plasma clearance of sugammadex and rocuronium. The total plasma clearance of sugammadex was significantly lower in group R than in group N (WMD [95% CI] [mL min^{-1}]: −87.18 [−136.34 to −38.01]; I^2 = 0%). One study (Staals et al., 2010) [2] analyzed the total clearance of rocuronium. The total clearance of rocuronium was significantly lower in group R than in group N (MD [95% CI] [mL min^{-1}]: −125.2 [−153.59 to −96.81]). Two studies [2][9] analyzed the plasma concentration of rocuronium after 12 h of sugammadex injection and found it was significantly higher in group R than in group N (WMD [95% CI] [ng mL^{-1}]: 1023.32 [260.04 to 1786.6]; I^2 = 97%). One study (Staals et al., 2010) [2] analyzed the plasma concentration of sugammadex after 6 h of sugammadex injection and found it was significantly higher in group R than in group N (MD [95% CI] [μg mL^{-1}]: 7.7 [6.63 to 8.77]).

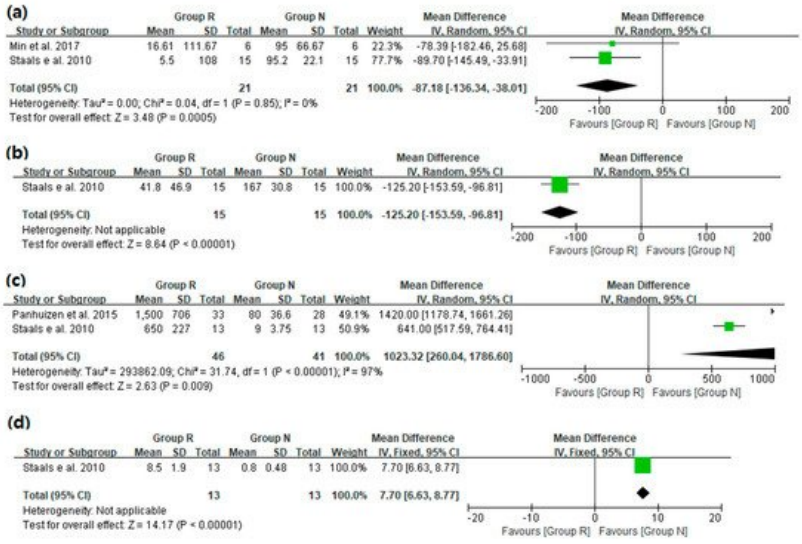

Figure 3. Pharmacokinetic parameters: (**a**) the total plasma clearance of sugammadex (mL min^{-1}), (**b**) the total plasma clearance of rocuronium (mL min^{-1}), (**c**) the plasma concentration of rocuronium 12 h after sugammadex injection (ng mL^{-1}), (**d**) the plasma concentration of sugammadex 6 h after sugammadex injection (μg mL^{-1}). SD = standard deviation; IV = inverse variance; CI = confidence interval.

Regarding the safety outcomes, there was no significant difference in the incidence of recurrence of NMB or prolonged time to recovery of a TOF ratio to 0.9 between the two groups (risk difference [95% CI]: −0.01 [−0.07 to 0.04]; I^2 = 0%, risk ratio [95% CI]: 2.87 [0.61 to 13.53]; I^2 = 0%, respectively) (**Figure 4**).

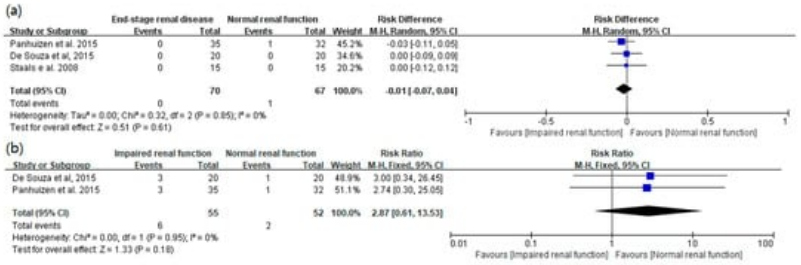

Figure 4. (**a**) Incidence of recurrence of neuromuscular blockade. (**b**) Incidence of prolonged time to recovery of a train-of-four ratio to 0.9. M-H = Mantel-Haenszel; CI = confidence interval.

For the other adverse events, three trials presented no clinically meaningful evidence (hemodynamic instability, such as a significant change in blood pressure, heart rate, and hypersensitivity) related to sugammadex administration [8][9][12]. Staals et al. [2] reported that two patients had low systolic pressure, and one patient had low diastolic pressure in group R, whereas in group N, one had high diastolic pressure, and one had low diastolic pressure. However, in all patients, the blood pressure changes were considered to be clinically insignificant and returned to baseline after anesthesia, and no markedly abnormal heart rates were observed. No laboratory abnormality related to sugammadex injection was reported in any of the studies, and there was no desaturation or other clinical signs of the inadequate recovery of neuromuscular function in any of the studies.

4. The Results of the Included Retrospective Studies

The results of post-anesthetic adverse events presented in the three retrospective observational studies with 476 patients with ESRD are as follows: Adams et al. [6] reported that there were 22 cases out of 158 patients (14%) with deferred tracheal extubation due to surgical or pre-existing medical conditions. Three of the 158 patients (2%) were re-intubated within 48 h postoperatively, but all of them were re-intubated due to their own medical problems and no incidence of recurrence of NMB after sugammadex injection was observed. This suggests that there is a very slim possibility of NMB recurrence after sugammadex injection in patients with ESRD. Paredes et al. [13] demonstrated that nine cases out of 219 patients (4.1%) were re-intubated, and of these, three (1.4%) patients were not excluded because of the possibility of sugammadex-related residual NMB. However, there was no mortality associated with sugammadex. Ono et al. [5] reported that there were no complications related to sugammadex administration in 99 patients.

5. Risk of Bias in the Prospective Case-Control Studies

Of the six prospective case-control studies, five studies were evaluated to have an overall “serious” risk of bias by ROBINS-I protocol, and only one study was evaluated as at an overall “moderate” risk of bias (**Table 3**).

Table 3. Risk of bias assessment of prospective case-control studies for meta-analysis by ROBINS-I* protocol.

Study	Confounding	Selection	Classification of Interventions	Deviation from Interventions	Missing Data	Measurement of Outcomes	Selection of the Reported Result	ROBINS-I Overall
de Souza et al., 2015 [8]	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Low	Serious
Panhuizen et al., 2015 [9]	Moderate	Low	Moderate	Low	Moderate	Serious	Low	Serious
Staals et al., 2008 [10]	Moderate	Moderate	Low	Low	Low	Serious	Low	Serious
Staals et al., 2010 [2]	Moderate	Moderate	Low	Low	Moderate	Serious	Low	Serious
Maeyama et al., 2014 [11]	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Min et al., 2017 [12]	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate

5. Discussion

In ESRD patients, the clearance of rocuronium may decrease and the duration of action may be prolonged, and similar changes may occur in the pharmacokinetics of sugammadex. It is very important to predict changes in the effect, but there is no clear knowledge of this. In particular, the administration of sugammadex is not recommended in ESRD patients, and its safety has not been clearly proven until now [14], making it difficult to apply sugammadex in clinical practice and proceed with clinical studies. Therefore, the number of clinical studies reported to date is limited [2][8][9][10][11][12], and only a few case reports have been reported [7][15][16]. Nevertheless, the demand and need for the administration of rocuronium and sugammadex in ESRD patients in actual clinical practice is increasing, and several recently reported retrospective studies dispute this need [5][6][13][17].

The incidence of post-anesthetic adverse events was generally small in the included studies. There was no significant difference between the two groups in the incidence of recurrence of NMB or prolonged time to recovery of TOF ratio to 0.9. In addition, there were no clinically meaningful hemodynamic instabilities such as hypotension, bradycardia, or hypersensitivity related to sugammadex administration. Moreover, no laboratory abnormalities related to sugammadex injection, desaturation, or other clinical signs of inadequate recovery of neuromuscular function have been reported in any of the studies. However, considering that safety assessments, including the reporting of items and observation periods related to the adverse events, varied for each study, further larger prospective studies are needed in this area. Four of the six prospective, case-control studies described monitoring items and observation periods related to the safety outcomes in detail; but one of the other two studies was abstract, and there was no mention of safety outcomes, and the other was a pharmacokinetic study that did not perform neuromuscular monitoring. Considering these points, it is difficult to completely exclude the possibility of residual NMB in the absence of quantitative NMB monitoring, particularly across the range of sugammadex doses employed [14]. Nonetheless, considering the fact that even three retrospective observational studies assessing 476 patients with ESRD reported few adverse events, the incidence of adverse events related to sugammadex reversal for rocuronium-induced NMB may not be much higher in ESRD patients than in normal patients

References

1. Epemolu, O.; Bom, A.; Hope, F.; Mason, R. Reversal of neuromuscular blockade and simultaneous increase in plasma rocuronium concentration after the intravenous infusion of the novel reversal agent Org 25969. Anesthesiology 2003, 99, 632–637.
2. Staals, L.M.; Snoeck, M.M.; Driessen, J.J.; van Hamersvelt, H.W.; Flockton, E.A.; van den Heuvel, M.W.; Hunter, J.M. Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: A pharmacokinetic study. Br. J. Anaesth. 2010, 104, 31–39.
3. Peeters, P.; Passier, P.; Smeets, J.; Zwiers, A.; de Zwart, M.; van de Wetering-Krebbers, S.; van Iersel, M.; van Marle, S.; van den Dobbelsteen, D. Sugammadex is cleared rapidly and primarily unchanged via renal excretion. Biopharm. Drug Dispos. 2011, 32, 159–167.
4. U.S. Food and Drug Administration; Merck Sharp & Dohme Corp. BRIDION® (Sugammadex) Injection, for Intravenous Use; Initial U.S. Approval: Silver Spring, MD, USA, 2015. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022225lbl.pdf (accessed on 5 December 2019).
5. Ono, Y.; Fujita, Y.; Kajiura, T.; Okawa, H.; Nakashima, J.; Isobe, H.; Fujiwara, Y. Efficacy and safety of sugammadex in patients undergoing renal transplantation. JA Clin. Rep. 2018, 4, 56.
6. Adams, D.R.; Tollinche, L.E.; Yeoh, C.B.; Artman, J.; Mehta, M.; Phillips, D.; Fischer, G.W.; Quinlan, J.J.; Sakai, T. Short-term safety and effectiveness of sugammadex for surgical patients with end-stage renal disease: A two-centre retrospective study. Anaesthesia 2020, 75, 348–352.
7. Pfaff, K.; Tumin, D.; Tobias, J.D. Sugammadex for Reversal of Neuromuscular Blockade in a Patient With Renal Failure. J. Pediatr. Pharmacol. Ther. 2019, 24, 238–241.
8. De Souza, C.M.; Tardelli, M.A.; Tedesco, H.; Garcia, N.N.; Caparros, M.P.; Alvarez-Gomez, J.A.; de Oliveira, I.S., Jr. Efficacy and safety of sugammadex in the reversal of deep neuromuscular blockade induced by rocuronium in patients with end-stage renal disease: A comparative prospective clinical trial. Eur. J. Anaesthesiol. 2015, 32, 681–686.
9. Panhuizen, I.F.; Gold, S.J.; Buerkle, C.; Snoeck, M.M.; Harper, N.J.; Kaspers, M.J.; van den Heuvel, M.W.; Hollmann, M.W. Efficacy, safety and pharmacokinetics of sugammadex 4 mg kg-1 for reversal of deep neuromuscular blockade in patients with severe renal impairment. Br. J. Anaesth. 2015, 114, 777–784.
10. Staals, L.M.; Snoeck, M.M.; Driessen, J.J.; Flockton, E.A.; Heeringa, M.; Hunter, J.M. Multicentre, parallel-group, comparative trial evaluating the efficacy and safety of sugammadex in patients with end-stage renal failure or normal renal function. Br. J. Anaesth. 2008, 101, 492–497.
11. Maeyama, A.; Nagasaka, H.; Matsumoto, N. Prolonged recovery time from muscle relaxation due to rocuronium in patients with severe chronic renal disease using sugammadex: 9AP4-6. Eur. J. Anaesthesiol. EJA 2014, 31, 152.
12. Min, K.C.; Lasseter, K.C.; Marbury, T.C.; Wrishko, R.E.; Hanley, W.D.; Wolford, D.G.; Udo de Haes, J.; Reitmann, C.; Gutstein, D.E. Pharmacokinetics of sugammadex in subjects with moderate and severe renal impairment. Int. J. Clin. Pharmacol. Ther. 2017, 55, 746–752.
13. Paredes, S.; Porter, S.B.; Porter, I.E., 2nd; Renew, J.R. Sugammadex use in patients with end-stage renal disease: A historical cohort study. Can. J. Anaesth. 2020, 67, 1789–1797.
14. Magoon, R.; Kashav, R.; Kohli, J.K. Sugammadex in end-stage renal disease: Too early for a “free-pass”. Can. J. Anaesth. 2021, 68, 264–265.
15. Carlos, R.V.; Torres, M.L.; de Boer, H.D. The use of rocuronium and sugammadex in paediatric renal transplantation: Two case reports. Eur. J. Anaesthesiol. 2016, 33, 383–386.
16. Kurita, S.; Moriwaki, K.; Shiroyama, K.; Sanuki, M.; Toyota, Y.; Takebayashi, M. Rocuronium-sugammadex use for electroconvulsive therapy in a hemodialysis patient: A case report. JA Clin. Rep. 2016, 2, 28.
17. Renew, J.R.; Porter, S.B.; Porter, I.; Paredes, S. In reply: Sugammadex in end-stage renal disease: Too early for a “free-pass”. Can. J. Anaesth. 2021, 68, 266–267.

Retrieved from https://encyclopedia.pub/entry/history/show/39963