Sugammadex for Reversal of Neuromuscular Blockade in a Patient With Renal Failure

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Residual neuromuscular blockade following the use of non-depolarizing neuromuscular blocking agents (NMBAs) can lead to postoperative respiratory complications, including oxygen desaturation, atelectasis, and pneumonia. Sugammadex rapidly reverses steroidal NMBAs by encapsulating them in a highly stable water-soluble complex. This NMBA-sugammadex complex then undergoes renal elimination. In patients with renal insufficiency or failure, concern has been expressed regarding the elimination of the NMBA-sugammadex complex. We present a 19-year-old patient with renal failure who received sugammadex for reversal of neuromuscular blockade. The use of sugammadex in patients with renal dysfunction is discussed and safety concerns are reviewed.

ABBREVIATIONS NMBA, non-depolarizing neuromuscular blocking agents; TOF, train of four

KEYWORDS neuromuscular blockade; renal failure; reversal; sugammadex

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Introduction

Neuromuscular blocking agents (NMBAs) are used intraoperatively to facilitate endotracheal intubation, provide surgical relaxation, ensure a motionless surgical field, and facilitate controlled ventilation during surgical procedures. However, during the recovery period, residual neuromuscular blockade can lead to postoperative respiratory complications, including oxygen desaturation, atelectasis, and pneumonia.^{1–4} In an effort to prevent such problems, a novel pharmacologic agent, Sugammadex (Bridion, Merck & Co, Whitehouse Stations, NJ) has been developed and introduced into clinical practice. Sugammadex rapidly reverses steroidal NMBAs, specifically rocuronium or vecuronium, by encapsulating them in a stable, water-soluble complex. By doing so, there is a decrease in effector site concentration of the unbound NMBA and hence a reversal of its effects.^{5,6} The NMBA-sugammadex complex then undergoes renal elimination.⁷ In patients with renal insufficiency or failure, concern has been expressed regarding the elimination of the NMBA-sugammadex complexes. Plasma clearance of the sugammadex-rocuronium complex has been shown⁸ to be reduced 17-fold in patients with impaired renal function. The median elimination of sugammadex and rocuronium in the urine over 72 hours in patients with renal impairment was 29% and 4%, respectively, versus 73% and 42% in control patients with normal renal function.⁹

Given the evidence of reduced NMBA-sugammadex complex clearance in patients with renal impairment, concern has been expressed regarding the safety of the administration of sugammadex in patients with renal dysfunction. We present a 19-year-old with renal failure

who received sugammadex for reversal of neuromuscular blockade. The use of sugammadex in patients with renal dysfunction is discussed, safety concerns presented, and reports of adverse effects regarding its use in this patient population investigated.

Case

Institutional review board approval is not required at Nationwide Children's Hospital (Columbus, OH) for the presentation of single case reports. A 19-year-old, 82.2-kg female with end-stage chronic kidney disease presented to the emergency department via ambulance for an emergent revision of a ventriculoperitoneal shunt. Her past medical history included myelomeningocele, hydrocephalus, neurogenic bowel and bladder, lower extremity paralysis, end-stage renal disease with a glomerular filtrate rate less than 15 mL/min, anemia, and secondary hyperparathyroidism. She was listed for a cadaveric kidney transplant but had not received dialysis. Her past surgical history included myelomeningocele repair, a left ventriculoperitoneal shunt insertion, left clubfoot repair, debridement of a foot wound with skin grafting, and adenotonsillectomy. Current medications included ergocalciferol (4000 units orally [PO] daily), ferrous fumarate (325 mg PO twice a day), sodium bicarbonate (PO BID), sevelamer (800 mg PO TID), docusate sodium (100 mg PO QD), calcitriol (0.25 mcg PO twice a day), oxybutynin (10 mg, take 2 PO daily), and amlodipine (10 mg PO daily). Following admission to the emergency department, she had also received morphine (2 mg) and ondansetron (4 mg).

Review of systems on arrival noted severe frontal headache, nausea, emesis, photophobia, blurred vi-

Table. Reports of Sugammadex Use in Patients With Renal Dysfunction

Reference	Patients (n)	Age, yr (Range)	Findings
de Souza ⁷	40	18–65	After sugammadex (4 mg/kg), time for recovery of the TOF ratio to 0.9 was prolonged in the renal failure group (5.6 ± 3.6 versus 2.7 ± 1.3 min, $p = 0.003$). No adverse events or evidence of recurrence of neuromuscular block were observed.
Panhuizen ²⁴	67	≥ 18	Sugammadex provided rapid reversal of deep rocuronium-induced neuromuscular blockade with no difference in patients with normal versus abnormal renal function.
Staals ²⁵	30	29–81	Sugammadex (2 mg/kg) administered at reappearance of train 2 of the TOF rapidly and effectively reverses rocuronium in renal failure and healthy patients.
Carlos ²⁶	2	7–14	Sugammadex allows rapid and complete reversal of neuromuscular blockade in patients undergoing renal transplantation.

TOF, train of four

sion, and declining mental status. Physical examination demonstrated an altered mental status and nystagmus on upward lateral gaze. The patient's pulse was 113 beats/min, while the remainder of her vital signs were unremarkable. Airway, cardiovascular, and respiratory examination were unremarkable. Computed tomography imaging of the head demonstrated a shunt dysfunction, with an increase in size of the lateral and third ventricles, as well as a Chiari 2 malformation. Coagulation function (prothrombin time [PT], partial thromboplastin time [PTT], and international normalized ratio [INR]) and cerebrospinal fluid analysis were within normal limits. The basic metabolic panel showed significant abnormalities, with a blood urea nitrogen of 37 mg/dL (5–18 mg/dL) and a creatinine of 4.83 mg/dL (0.5–1.20 mg/dL). She was transported to the operating room, where routine American Society of Anesthesiologists' monitors were placed. Rapid sequence intubation and anesthetic induction were accomplished with propofol (200 mg), fentanyl (200 mcg), lidocaine (80 mg), and rocuronium (80 mg). Anesthesia was maintained with isoflurane in air and oxygen. Additional intraoperative medications included cefazolin (2000 mg), dexamethasone (4 mg), and ondansetron (4 mg). Mild hypotension after anesthetic induction was treated with incremental doses of phenylephrine (total intraoperative dose of 400 mcg). Blood loss was minimal, and intraoperative fluids included 500 mL of lactated Ringers. Two hours and 10 minutes after the administration of rocuronium, there were no twitches noted in the train of four (TOF), although there were 4 posttetanic twitches. The anesthesia team continued the maintenance anesthesia. Twenty minutes later (approximately 2 hours and 30 minutes after the administration of rocuronium), there was the return of one twitch on the TOF.

Sugammadex (4 mg/kg) was administered, and within 10 minutes there was complete reversal of residual neuromuscular blockade, with return of protective airway reflexes, TOF, demonstration of adequate spontaneous ventilation, and purposeful movements. The patient's

trachea was extubated without incident. She was then transported to the postanesthesia care unit with supplemental oxygen until she was fully awake, alert, and oriented. She was discharged to the inpatient ward, having returned to her normal baseline mental status. The remainder of her postoperative course was unremarkable, and she was discharged home that evening.

Discussion

Various challenges are presented for the perioperative care of patients with chronic renal failure. In particular, acute and chronic renal insufficiency affects the pharmacokinetic and pharmacodynamic parameters of most medications, including NMBAs. Given our patient's clinical status, the anesthetic plan for induction and securing the airway included rapid sequence intubation.¹⁰ Rapid sequence intubation involves the rapid, sequential administration of medications to induce general anesthesia and provide neuromuscular blockade. The medications chosen to provide neuromuscular blockade are chosen based on their onset. As such, the options include either the depolarizing agent succinylcholine or the non-depolarizing agent rocuronium. Although the onset time and conditions for endotracheal intubation may be superior with succinylcholine, the potential for adverse effects is higher.^{11,12} Furthermore, these adverse effects have a higher incidence in critically ill patients, those with increased intracranial pressure, and those with renal failure.^{13–16} The most serious of these complications is hyperkalemia, which remains a relative contraindication to the administration of succinylcholine in the setting of renal failure.^{14,16}

Given these concerns, rocuronium was chosen for our patient. Although the liver serves as the main route of metabolism and elimination for rocuronium, as noted in our patient, a prolonged duration of action has been reported in the patients with renal failure.¹⁷ With non-depolarizing NMBAs such as rocuronium, there is

a concern for postoperative residual neuromuscular blockade and its resultant clinical effects, as outlined above.¹⁻⁴ As several clinical trials have demonstrated the superiority of sugammadex in reversing residual neuromuscular blockade when compared to acetylcholinesterase inhibitors such as neostigmine, we chose this agent for reversal in our patient.¹⁸⁻²¹ This may be particularly relevant in our patient, who had profound residual neuromuscular blockade with only 1 twitch of the TOF at the time of reversal.

As noted above, concern has been expressed regarding the administration of sugammadex to patients with renal failure, given the potential for prolonged excretion of the sugammadex-rocuronium complex.⁹ The delayed excretion has led to the theoretical concern of the dissociation of rocuronium from the sugammadex-rocuronium complex with recurrence of neuromuscular blockade. However, dissociation is minimal, as it has been estimated^{4,6,22} that for every 25 million sugammadex-rocuronium complexes that are formed, only one complex dissociates. No change in renal function or alteration in renal biomarkers has been noted following its use in patients with renal dysfunction.²³ Additional data from the literature²³⁻²⁵ also support safety and efficacy of sugammadex in patients with altered renal function (Table).

Conclusions

We describe a 19-year-old patient with renal failure who received sugammadex for reversal of rocuronium-induced neuromuscular blockade. Much of the concern for sugammadex use in renal failure patients stems from the delayed clearance of the sugammadex-rocuronium complex. Despite these concerns, our anecdotal experience and that from the literature demonstrate the safety and efficacy of sugammadex in this clinical setting.

ARTICLE INFORMATION

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REFERENCES

1. Ledowski T, Hillyard S, O'Dea B, et al. Introduction of sugammadex as standard reversal agent: impact on the incidence of residual neuromuscular blockade and postoperative patient outcome. *Indian J Anaesth.* 2013;57(1):46–51.
2. Tobias JD. Current evidence for the use of sugammadex in children. *Paediatr Anaesth.* 2017;27(2):118–125.
3. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg.* 2010;111(1):120–128.
4. Eikermann M, Vogt FM, Herbstreit F, et al. The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade. *Am J Respir Crit Care Med.* 2007;175(1):9–15.
5. Miller K, Hall B, Tobias JD. Sugammadex to reverse neuromuscular blockade in a child with a past history of cardiac transplantation. *Ann Card Anaesth.* 2017;20(3):376–378.
6. 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 Engl.* 2002;41(2):266–270.
7. de Souza CM, Tardelli MA, Tedesco H, et al. 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(10):681–686.
8. Cammu G, Van Vlem B, van den Heuvel M, et al. Dialysability of sugammadex and its complex with rocuronium in intensive care patients with severe renal impairment. *Br J Anaesth.* 2012;109(3):382–390.
9. Staals LM, Snoeck MM, Driessen JJ, et al. Reduced clearance of rocuronium and sugammadex in patients with severe to end-stage renal failure: a pharmacokinetic study. *Br J Anaesth.* 2010;104(1):31–39.
10. Tobias JD. Rapid sequence intubation: what does it really mean? *Saudi J Anesth.* 2014;8(2):153–154.
11. Sluga M, Ummenhofer W, Studer W, et al. Rocuronium versus succinylcholine for rapid sequence induction of anesthesia and endotracheal intubation: a prospective, randomized trial in emergent cases. *Anesth Analg.* 2005;101(5):1356–1361.
12. Tran DTT, Newton EK, Mount VAH, et al. Rocuronium vs. succinylcholine for rapid sequence intubation: a Cochrane Systematic Review. *Anaesthesia.* 2017;72(6):765–777.
13. Blanié A, Ract C, Leblanc PE, et al. The limits of succinylcholine for critically ill patients. *Anesth Analg.* 2012;115(4):873–879.
14. Martyn JA, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms. *Anesthesiology.* 2006;104(1):158–169.
15. Minton MD, Grosslight K, Stirt JA, Bedford RF. Increases in intracranial pressure from succinylcholine: prevention by prior nondepolarizing blockade. *Anesthesiology.* 1986;65(2):165–169.

16. Thapa S, Brull SJ. Succinylcholine-induced hyperkalemia in patients with renal failure: an old question revisited. *Anesth Analg*. 2000;91(1):237–241.
17. Khuenl-Brady KS, Pomaroli A, Pühringer F, et al. The use of rocuronium (ORG 9426) in patients with chronic renal failure. *Anaesthesia*. 1993;48(10):873–875.
18. Khuenl-Brady KS, Wattwil M, Vanacker BF, et al. Sugammadex provides faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine: a multicenter, randomized, controlled trial. *Anesth Analg*. 2010;110(1):64–73.
19. Lenz A, Hill G, White PF. Emergency use of sugammadex after failure of standard reversal drugs. *Anesth Analg*. 2007;104(3):585–586.
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(3):569–574.
21. Blobner M, Eriksson LI, Scholz J, et al. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. *Eur J Anaesthesiol*. 2010;27(10):874–881.
22. Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg*. 2007;104(3):575–581.
23. Isik Y, Palabiyik O, Cegin BM, et al. Effects of sugammadex and neostigmine on renal biomarkers. *Med Sci Monit*. 2016;22(3):803–809.
24. Panhuizen IF, Gold SJ, Buerkle C, et al. Efficacy, safety and pharmacokinetics of sugammadex 4 mg/kg for reversal of deep neuromuscular blockade in patients with severe renal impairment. *Br J Anaesth*. 2015;114(5):777–784.
25. Staals LM, Snoeck MM, Driessen JJ, et al. 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(4):492–497.
26. Carlos RV, Torres ML, de Boer HD. The use of rocuronium and sugammadex in paediatric renal transplantation: two case reports. *Eur J Anaesthesiol*. 2016;33(5):383–386.