SIGNA VITAE 2008; 3(1): 35 - 38

REVIEW

Emerging considerations in the reversal of neuromuscular blockade and residual block

WAYNE T. NICHOLSON (✉) •
JURAJ SPRUNG •
CHRISTOPHER J. JANKOWSKI
Mayo Clinic College of Medicine
Mary Brigh 2-752, 200 First Street SW
Rochester, Minnesota 55905, USA
Phone: (507) 255-3298
Fax: (507) 255-6463
E-mail: nicholson.wayne@mayo.edu

WAYNE T. NICHOLSON • JURAJ SPRUNG • CHRISTOPHER J. JANKOWSKI

ABSTRACT

Incomplete recovery following reversal of neuromuscular blockade can present as a clinical problem in surgical patients. Emerging pharmacologic solutions may prevent such adverse outcomes in the future. We briefly review two methods of pharmacologic reversal of neuromuscular blockade. Both methods of reversal are effective. However the early studies of the new compound, sugammadex has been shown to achieve a more rapid, stable reversal of steroidal based neuromuscular blocking agents compared to neostigmine. Due to the novel mechanism of action of this agent, sugammadex has been demonstrated to be effective even when administered during profound neuromuscular block, without evidence of recurarization.

Key words: sugammadex, Org 25969, cyclodextrin, rocuronium, cholinesterase inhibitor

Introduction

Spontaneous recovery from neuromuscular block occurs through redistribution, buffered diffusion, or metabolism of the neuromuscular blocking agent (NMBA) administered (1) Acetylcholinesterase inhibitors (e.g. neostigmine) are often given at the end of surgery to speed the rate of recovery from non-depolarizing NMBAs. However, residual block may persist. In the absence of such reversal agents, residual paralysis may persist for 2 hours or more after the administration of an intermediate duration muscle relaxant. (2) Concomitant use of magnesium (3), local anesthetics (4), antibiotics (5-8), and calcium channel blockers (9) has also been shown to increase the risk of prolonged paralysis after reversal of neuromuscular blockade.

Residual block may be associated with serious adverse events, such as respiratory depression, pharyngeal dysfunction, hypoxemia and prolonged length of stay in the recovery room. (10) While the use of acetylcholinesterase inhibitors may reduce these risks by accelerating reversal of neuromuscular blockade, they are themselves associated with unwanted effects resulting from muscarinic receptor activation. (11) Co-administration of anticholinergic agents (e.g. glycopyrrolate) may attenuate these effects but at the potential cost of further side effects, such as tachycardia and QT interval prolongation. (12,13)

Sugammadex (Organon, USA Inc.) is a new reversal agent currently under clinical investigation. A modified gamma cyclodextrin, sugammadex is a selective relaxant binding agent (SRBA) specifically designed to reverse the effects of the aminosteroidal non-depolarizing NMBA, rocuronium. Unlike the acetylcholinesterase inhibitors, sugammadex does not achieve reversal via competitive cholinergic mechanisms but, rather, acts non-competitively by forming a complex with rocuronium, thereby lowering its effective concentration. (14) As a result, sugammadex does not require the co-administration of anticholinergic agents for the management of muscarinic side effects.

Pharmacology

Pharmacological considerations explain the clinical differences between the two agents with regard to the onset and stability of reversal. Acetylcholinesterase inhibitors are agonists that act indirectly to increase endogenous concentrations of acetylcholine. This excess acetylcholine competes with the non-depolarizing NMBA at the nicotinic receptor at the neuromuscular junction. At the same time, these agents inevitably increase the availability of acetylcholine at muscarinic receptors,

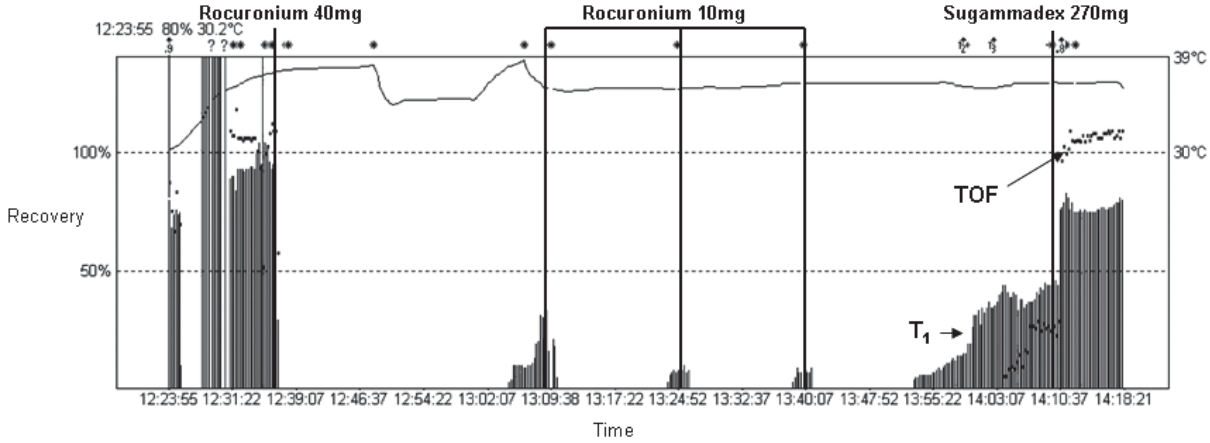

Figure 1. Acceleromyographic tracing example of the reversal of a rocuronium-induced neuromuscular block with sugammadex under general anesthesia. Vertical lines indicate T1 height. Dots indicate train-of-four (TOF) ratio.

resulting in parasympathetic adverse effects such as bradycardia and hypersalivation. Furthermore, there is a relative "ceiling effect" with acetylcholinesterase inhibitors, such that some recovery of neuromuscular function is required prior to their administration. (15) If these conventional agents are given to patient with a higher degree of neuromuscular blockade, inadequate reversal may ensue.

Sugammadex is a selective relaxant binding agent (SRBA) that is pharmacologically unrelated to conventional methods of reversal. Since its mechanism of action does not involve an endogenous increase in acetylcholine, reversal of neuromuscular block by sugammadex is not accompanied by the side effects associated with acetylcholinesterase inhibitors. (16) Sugammadex acts, instead, by encapsulating the NMBA, lowering its effective concentration. (17) By acting as a "pharmacologic sink", sugammadex prevents the interaction between the aminosteroidal NMBA and the nicotinic receptor at the neuromuscular junction. (18) Due to the specificity of the sugammadex molecule, NMBAs of the benzylisoquinolinium class are not antagonized.

Clinical Trials

Several clinical studies have illustrated the effectiveness of this mechanism of action for rapid reversal of rocuronium-induced neuromuscular blockade without evidence of recurarization. Efficacy was measured by acceleromyography (figure 1) and the time to achieve the train of four (TOF) ratio of 0.9 was the endpoint. Gijsenbergh et al.(19) showed full reversal without recurarization within 2 min, when sugammadex 8mg/kg was administered 3 min after rocuronium 0.6mg/kg. Other studies have demonstrated similar efficacy with sugammadex at doses of 2.0 mg/kg or higher, administered at reappearance of T_2 following rocuronium 0.6 mg/kg. (20,21)

The onset and stability of reversal with sugammadex appear to be related to several factors: the dose of NMBA administered, the timing of sugammadex administration in relation to NMBA administration, and the dose of sugammadex. In a dose-finding study by Groudine et al. (22), the two lowest doses of sugammadex (0.5 and 1.0mg/kg) were found to achieve inadequate reversal of profound neuromuscular block. Although there was some variability in effectiveness between the doses administered in this study, reversal of profound rocuronium-induced block was more successful with sugammadex $\geq$ 2 mg/kg. Low-dose sugammadex was also the topic of a recent case report (23) which described a transient decrease in train of four (TOF) response after a small dose (0.5mg/kg) of sugammadex for reversal of neuromuscular block induced by rocuronium 0.9 mg/kg. Using the data from this patient, the investigators developed a simple pharmacokinetic-pharmacodynamic model of rocuronium, sugammadex and their interaction. Simulations using this model indicated that rebound of muscle relaxation may occur with sugammadex doses "in a limited critical range". The authors concluded that administration of sugammadex in a sufficiently large dose eliminates the possibility of muscle relaxation rebound.

In a direct comparison, sugammadex 4 mg/kg has been shown to reverse rocuronium-induced neuromuscular blockade more rapidly and effectively compared with neostigmine 70 μg/kg or edrophonium 1 mg/kg. (24) It has also been demonstrated that reversal of neuromuscular block achieved with sugammadex does not depend on the type of anesthetic maintenance employed. Vanacker et al. (25) studied reversal of rocuronium with sugammadex in patients receiving either propofol or sevoflurane, and found the recovery time of the TOF ratio to 0.9 to be comparable in both groups. In contrast, neostigmine has been shown to achieve slower reversal of rocuronium-induced block under sevoflurane compared to propofol anesthesia. (26)

Discussion

Recovery of the TOF ratio to 0.9 prior to tracheal extubation has been clinically advocated as important for patient safety. (2,27,28) Although the incidence

of "recurarization" declined with the introduction of shorter acting NMBAs in the 1990s (29), residual curarization may still occur. (30) In order to avoid complications related to the use of muscle relaxants, precise assessment of neuromuscular transmission would be beneficial. (31,32) However, acceleromyography is not currently used routinely to determine a TOF ratio but remains primarily a tool for research. More conventional spot monitoring with TOF stimulation is unlikely to provide the clinician with an adequate assessment of peri-operative neuromuscular function. The availability of a reversal agent with predictable effectiveness, and which fully prevents residual block, is therefore highly desirable.

Conclusions

The pharmacological comparison described here illustrates the rapid recovery of neuromuscular function permitted by the novel mechanism of action of sugammadex. Studies have also demonstrated the ability of sugammadex to reverse profound neuromuscular blockade, such that timing of sugammadex administration is not an issue, as it is with the use of conventional reversal agents. The rapid reversal can be attributed to the stability of the complex formed between sugammadex and the aminosteroidal NMBA. In conclusion, with the arrival of sugammadex in clinical practice, residual neuromuscular block may become extinct as a clinical feature.

REFERENCES

1. Bevan DR. Monitoring and reversal of neuromuscular block. Am J Health Syst Pharm 1999;56:S10-3.
2. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. Anesthesiology 2003;98:1042-8.
3. Fawcett WJ, Stone JP. Recurarization in the recovery room following the use of magnesium sulphate. Br J Anaesth 2003;91:435-8.
4. Bruckner J, Thomas KC Jr, Bikhazi GB, Foldes FF. Neuromuscular drug interactions of clinical importance. Anesth Analg 1980;59:678-82.
5. Burkett L, Bikhazi GB, Thomas KC Jr, Rosenthal DA, Wirta MG, Foldes FF. Mutual potentiation of the neuromuscular effects of antibiotics and relaxants. Anesth Analg 1979;58:107-15.
6. Lee C, de Silva AJ. Interaction of neuromuscular blocking effects of neomycin and polymyxin B. Anesthesiology 1979;50:218-20.
7. Paradelis AG, Triantaphyllidis C, Giala MM. Neuromuscular blocking activity of aminoglycoside antibiotics. Methods Find Exp Clin Pharmacol 1980;2:45-51.
8. Rutten JM, Booij LH, Rutten CL, Crul JF. The comparative neuromuscular blocking effects of some aminoglycoside antibiotics. Acta Anaesthesiol Belg 1980;31:293-306.
9. Del Pozo E, Baeyens JM. Effects of calcium channel blockers on neuromuscular blockade induced by aminoglycoside antibiotics. Eur J Pharmacol 1986;128:49-54.
10. Beaussier M, Boughaba MA. Residual neuromuscular blockade. Ann Fr Anesth Reanim 2005;24:1266-74.
11. Booij LH, de Boer HD, van Egmond J. Reversal agents for nondepolarizing neuromuscular blockade: reasons for and development of a new concept. Seminars in Anesthesia. Perioperative Medicine and Pain 2002;21:92-8.
12. Annila P, Yli-Hankala A, Lindgren L. Effect of atropine on the QT interval and T-wave amplitude in healthy volunteers. Br J Anaesth 1993;71:736-7.
13. Saarnivaara L, Simola M. Effects of four anticholinesterase-anticholinergic combinations and tracheal extubation on QTc interval of the ECG, heart rate and arterial pressure. Acta Anaesthesiol Scand 1998;42:460-3.
14. 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;99:632-7.
15. Bartkowski RR. Incomplete reversal of pancuronium neuromuscular blockade by neostigmine, pyridostigmine, and edrophonium. Anesth Analg 1987;66:594-8.
16. Adam JM, Bennett DJ, Bom A, Clark JK, Feilden H, Hutchinson EJ, et al, editors. Cyclodextrin-derived host molecules as reversal agents for the neuromuscular blocker rocuronium bromide: synthesis and structure-activity relationships. J Med Chem 2002;45:1806-16.
17. Bom A, Bradley M, Cameron K, Clark JK, Van Egmond J, Feilden H, et al, editors. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. Angew Chem Int Ed Engl 2002;41:266-70.
18. Nicholson WT, Sprung J, Jankowski CJ. Sugammadex: a novel agent for the reversal of neuromuscular blockade. Pharmacotherapy 2007;27:1181-8.
19. 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.
20. Sorgenfrei IF, Norrild K, Larsen PB, Stensballe J, Ostergaard D, Prins ME, et al, editors. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. Anesthesiology 2006;104:667-74.

21. Shields M, Giovannelli M, Mirakhur RK, Moppett I, Adams J, Hermens Y. Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block. Br J Anaesth 2006;96:36-43.
22. Groudine SB, Soto R, Lien C, Drover D, Roberts K. A randomized, dose-finding, phase II study of the selective relaxant binding drug, Sugammadex, capable of safely reversing profound rocuronium-induced neuromuscular block. Anesth Analg 2007;104:555-62.
23. Eleveld DJ, Kuizenga K, Proost JH, Wierda JM. A temporary decrease in twitch response during reversal of rocuronium-induced muscle relaxation with a small dose of sugammadex. Anesth Analg 2007;104:582-4.
24. 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.
25. Vanacker BF, Vermeyen KM, Struys MM, Rietbergen H, Vandermeersch E, Saldien V, et al, editors. Reversal of rocuronium-induced neuromuscular block with the novel drug sugammadex is equally effective under maintenance anesthesia with propofol or sevoflurane. Anesth Analg 2007;104:563-8.
26. 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.
27. Eriksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. Anesthesiology 2003;98:1037-9.
28. Fuchs-Buder T, Mencke T. Use of reversal agents in day care procedures (with special reference to postoperative nausea and vomiting). Eur J Anaesthesiol Suppl 2001;23:53-9.
29. Caldwell JE. New skeletal muscle relaxants. Int Anesthesiol Clin 1995;33:39-60.
30. Bettelli G. Which muscle relaxants should be used in day surgery and when. Curr Opin Anaesthesiol 2006;19:600-5.
31. Baillard C, Clec'h C, Catineau J, Salhi F, Gehan G, Cupa M, et al, editors. Postoperative residual neuromuscular block: a survey of management. Br J Anaesth 2005;95:622-6.
32. Kopman AF, Sinha N. Acceleromyography as a guide to anesthetic management: a case report. J Clin Anesth 2003;15:145-8.

ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Ms. Shonie Buenvenida, R.N. from the Anesthesia Clinical Research Unit (ACRU) for her contributions to this publication.