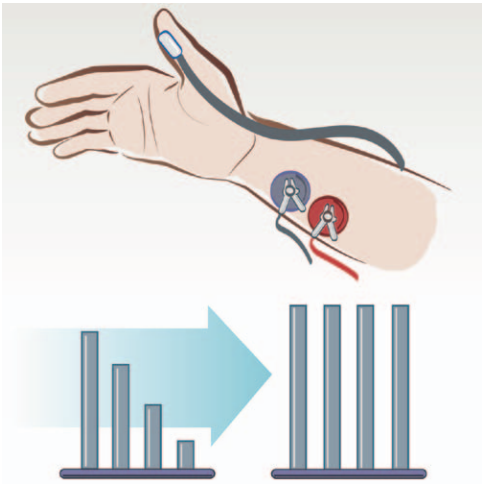
Innovative Disruption in the World of Neuromuscular Blockade

What Is the "State of the Art?"

Mohamed Naguib, M.B., B.Ch., M.Sc., F.C.A.R.C.S.I., M.D., Ken B. Johnson, M.D.

CME This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

SUGAMMADEX represents an innovative disruption in drug technology. The recent approval of sugammadex by the Food and Drug Administration provides us with an opportunity to revisit the "state of the art" and emphasize important nuances in the administration, monitoring, and reversal of neuromuscular blockade. To that end, in this issue of ANESTHESIOLOGY, Brull and Kopman[1] review the status of monitoring and reversal of neuromuscular blockade, highlight persistent concerns with residual neuromuscular block, and address approaches on how to minimize them. This editorial highlights a few of the more important clinical implications of this review to include practice considerations of sugammadex *versus* neostigmine, the importance of monitoring neuromuscular blockade, clinically relevant drug interactions, adverse effects, and the pharmacoeconomics of sugammadex.



"…we encourage the American Society of Anesthesiologists committee on standards and practice parameters to consider adding a monitoring device … anytime a neuromuscular blocking drug is administered."

Why Use Sugammadex When I Can Get by with Neostigmine?

Sugammadex, a modified γ-cyclodextrin, is highly water soluble with a hydrophobic cavity large enough to encapsulate steroidal neuromuscular blocking drugs. The reversal activity of sugammadex is selective for steroidal neuromuscular blocking drugs (rocuronium > vecuronium >> pancuronium). Sugammadex has a little to no affinity for binding to benzylisoquinolinium neuromuscular blockers. The affinity of sugammadex for rocuronium is approximately 4,700 times that of atracurium.[2]

There are many potential applications of sugammadex of interest to anesthesiologists. The main advantages of sugammadex over neostigmine are its predictability and its ability to extend the range of neuromuscular blockade reversal. Reversal of residual competitive neuromuscular blockade by cholinesterase inhibitors has its limitations, as outlined by Drs. Brull and Kopman.[1] Neostigmine provides reversal for minimal, light (shallow), and moderate blockade. Sugammadex extends reversal capability, and in recommended doses of 2 to 16 mg/kg, it is capable of reversing any depth of neuromuscular block induced by rocuronium (from moderate to profound block) to a train-of-four ratio of more than or equal to 0.9 within 3 min. This has been and will continue to be a "game changer" for many patients who suffer from prolonged neuromuscular blockade. Sugammadex is also advantageous in that it does not have any cholinergic side effects that require the coadministration of an anticholinergic agent. However, the administration of sugammadex has been associated with life-threatening bradycardia that may require administration of anticholinergic agents.[3] Hypotension, ST-segment elevation unresponsive to vasopressors and anticholinergic drugs, and even cardiac arrest have been reported after

Image: John Ursino, ImagePower Productions.

Corresponding article on page 173.

Accepted for publication May 23, 2016. From the Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio (M.N.); and Department of Anesthesiology, University of Utah, Salt Lake City, Utah (K.B.J.).

 Anesthesiology 2017; 126:12-5

<zdoi;10.1097/ALN.0000000000001410>

administration of sugammadex.[4] Notably, administration of sugammadex may result in hypersensitivity and anaphylactic reactions, commonly seen within 5 min after administration. Although the incidence of allergic reactions after administration of 2 mg/kg sugammadex appears to be low, in a dedicated hypersensitivity trial (Trial P101), repeated administration of 4 and 16 mg/kg sugammadex was associated with an increased incidence (6.6% and 9.5%, respectively) of hypersensitivity as compared to placebo (1.3%).[4] Nearly 90% of these hypersensitivity reactions were judged to be mild by an adjudication committee.

Neuromuscular Blockade Monitoring: Why Go Blind When You Can See?

With all the enthusiasm regarding innovation in reversal of neuromuscular blockade, there may be a temptation to minimize or dismiss the use of neuromuscular monitoring. Indeed, if blockade is immediately reversible, why bother with monitoring? We advocate just the opposite. As our understanding of neuromuscular blockade matures, so does our ability to monitor it with higher resolution and make more informed management decisions. Perhaps the most important clinical implication is that of unrecognized residual neuromuscular block. The introduction of sugammadex has produced a hope that residual neuromuscular blockade after rocuronium would be virtually eliminated. Unfortunately, the data[5,6] indicate otherwise! The use of sugammadex is not an excuse to avoid monitoring the depth of blockade for every case when rocuronium or vecuronium is used. A conventional peripheral nerve stimulator (PNS, which requires the clinician to evaluate the evoked response visually or tactilely) would be sufficient to determine which dose is appropriate for a given depth of block. Other clinical implications include reversal agent choice and sugammadex dose. For reversal agent choice, an accurate assessment of neuromuscular blockade is required before selection of neostigmine *versus* sugammadex can be made. When selecting a sugammadex dose, the depth of blockade matters. Deep and profound blocks require larger doses of the drug and have associated cost implications. Accordingly, without formal evaluation of the degree of neuromuscular blockade, residual neuromuscular block is here to stay.

A typical dose of rocuronium (0.6 mg/kg) during opioid–nitrous oxide–oxygen anesthesia has a median onset of 1.8 min and duration of effect of 31 min, although there is substantial variability among patients with the onset of maximum blockade and duration times ranging from 0.6 to 13.0 and 15 to 85 min, respectively.[7] With this range of variability in duration of effect, the rationale for monitoring the depth of blockade is self-evident.

Why is it that anesthesia providers fail to use PNS to guide administration of neuromuscular blockers? Brull and Kopman[1] pointed out that the standard guidelines for neuromuscular monitoring are nonexistent in the United States and that the American Society of Anesthesiologists standards for basic anesthetic monitoring do not include neuromuscular blockade monitoring. We know that the clinical signs of recovery from neuromuscular blockade are insensitive and unreliable,[8] and we encourage the American Society of Anesthesiologists committee on standards and practice parameters to consider adding a monitoring device (whether a PNS or a quantitative monitor that measures and displays the train-of-four ratio in real time) anytime a neuromuscular blocking drug is administered. Why go blind when you can "see"?

What are the obstacles? To put it simply, many anesthesiologists are not convinced that it is beneficial to monitor the degree of neuromuscular blockade to guide clinical management of neuromuscular block. Clinicians may feel confident about their knowledge and experience and believe that they can safely manage neuromuscular blockade without monitoring.[9] Therefore, deviations from these "norms" are unwarranted because the majority of anesthesiologists believe that they have never experienced clinically significant adverse outcomes related to residual neuromuscular block.[10] Evidence, however, contradicts these beliefs.[9]

We recognize that even with a change in standards that recommend neuromuscular blockade monitoring, its impact on the incidence of residual neuromuscular block will be minimal without a change in motivation and attitude enforced by education and implementation strategies.[11] Only by adopting a strategy that could influence the practice of anesthesia providers would one expect to see a turn in the tide. Availability of a monitoring device (conventional or quantitative) *per se* will not result in a reduction in the incidence of residual neuromuscular block without training on the use of these monitors to avoid overzealous administration of neuromuscular blocking agents. What is evident is that effective implementation of educational programs (with feedback) combined with availability and the use of objective neuromuscular monitors can appreciably decrease the incidence of residual neuromuscular block.[12,13] There will always be many practical hurdles to overcome in implementing quantitative monitors given that the currently commercially available quantitative monitors are far from ideal.[13] Although quantitative monitors are superior to PNS, as outlined by Drs. Brull and Kopman,[1] the issue is not which type of device (conventional or quantitative) should be used but how knowledgeable the clinician is who is using the device. A quantitative monitor is no substitute for education and skill.

Drug Interactions That Matter: A Look at Sugammadex

The affinity of sugammadex to bind to corticosteroids is substantially less than that of rocuronium but may have clinical implications.[2] For instance, progestogens and estrogens show some affinity (2 to 22% of that of rocuronium).[14] The administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily dose of oral contraceptive steroids (either combined or progestogen only). The sugammadex package insert states that "Patients using hormonal contraceptives must use an additional, nonhormonal method of contraception for the next 7 days following [sugammadex] administration," and anesthesiologists should take on the responsibility of ensuring that patients are aware of this fact.

The Pharmacoeconomics of Sugammadex

The introduction of sugammadex may present cost challenges. The acquisition cost of sugammadex varies among different healthcare facilities in the United States. The average cost is $90 for a 200-mg vial (personal communication; Mohamed Naguib, M.D., Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio, USA), a price that is comparable to the acquisition cost for neostigmine combined with glycopyrrolate to reverse a moderate block. The cost of sugammadex is greater when higher doses of sugammadex are required for antagonism of a deep or profound neuromuscular blockade.

The economic benefits of using sugammadex (*vs.* neostigmine) are unknown. One necessary step would be to investigate whether the use of sugammadex reduces the time to extubation when compared to neostigmine. This is not oversimplified because prolonged times to extubation limit operating room throughput.[15] No previous work has yet performed this randomized study. The principal confounders to be controlled are known (such as duration of surgical procedure and prone positioning). With consistent neuromuscular monitoring, the incidence of aggressive resuscitative measures such as tracheal intubation becomes small (albeit nonzero),[16] and residual weakness is confounded by opioid effects. Using cost savings per minute when comparing sugammadex to neostigmine reversal time to tracheal extubation *in lieu* of a proper pharmacoeconomic analysis, including accurate modeling of operating rooms time costs, is misleading and inappropriate.[17] An additional factor that might affect the cost of sugammadex is its patent life. U.S. and worldwide sugammadex patents will expire in early 2021.* This may lead to a lower price for generic sugammadex. On the other hand, neostigmine has been generic for decades, and yet its cost in the United States (but not in Europe) has recently skyrocketed as a consequence of the Food and Drug Administration's approach to grandfathered drugs.

Edrophonium: Does It Have a Role?

Given the current issues about the availability and cost of neostigmine, as outlined by Drs. Brull and Kopman,[1] there has been renewed interest in edrophonium to antagonize nondepolarizing neuromuscular blockade. Edrophonium has a fast onset of action, and in doses of 0.5 to 1.0 mg/kg, it can achieve a recovery profile comparable to that of neostigmine. Because of its pharmacokinetic profile, atropine appears to be the anticholinergic of choice to counteract the muscarinic side effects of edrophonium. Currently, the acquisition cost of edrophonium is about one third that of neostigmine at an equipotent dose (personal communication, Mohamed Naguib, M.D., Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio, USA). This may favor edrophonium over neostigmine or sugammadex when considering the cost-effectiveness of each reversal. Although less expensive, edrophonium has a similar side-effect profile and dosing limitations to neostigmine; it cannot be used to reverse deep or profound neuromuscular blockade.

* Based on congruence of information from two Pharma intelligence subscription databases (MedTrack and Evaluate).

In summary, sugammadex represents a novel pharmacologic approach for reversing the neuromuscular blocking effects of rocuronium and vecuronium. It has an attractive pharmacologic profile but can be expensive, especially when reversing deep to profound blocks. It is important to emphasize that the increased versatility of sugammadex does not obviate the need for utilizing at least a PNS, as it is essential for identifying the appropriate dose of sugammadex. Without it, residual neuromuscular blockade will continue to affect patients recovering from anesthesia. As patient advocates, we encourage clinician educators and professional societies to implement educational programs to emphasize the proper use of neuromuscular monitoring devices any time a neuromuscular blocker is used regardless of the reversal agent used.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Naguib: naguibm@ccf.org

References

1. Brull SJ, Kopman AF: Current status of neuromuscular reversal and monitoring: Challenges and opportunities. Anesthesiology 2017; 126:173–90
2. Zwiers A, van den Heuvel M, Smeets J, Rutherford S: Assessment of the potential for displacement interactions with sugammadex: A pharmacokinetic-pharmacodynamic modelling approach. Clin Drug Investig 2011; 31:101–11
3. U.S. Food and Drug Administration: FDA approves Bridion to reverse effects of neuromuscular blocking drugs used during surgery: Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477512.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. 2015. Accessed May 11, 2016
4. U.S. Food and Drug Administration Advisory Committee: Sugammadex Injection. NDA 22225: Advisory Committee Briefing Materials. Merck Sharp & Dohme Corporation, 2015. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM470718.pdf. 2015. Accessed May 11, 2016
5. Kotake Y, Ochiai R, Suzuki T, Ogawa S, Takagi S, Ozaki M, Nakatsuka I, Takeda J: Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. Anesth Analg 2013; 117:345–51
6. Batistaki C, Tentes P, Deligiannidi P, Karakosta A, Florou P, Kostopanagiotou G: Residual neuromuscular blockade in a real life clinical setting: Correlation with sugammadex or neostigmine administration. Minerva Anestesiol 2016; 82:550–8
7. U.S. Food and Drug Administration: Rocuronium Package Insert. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/078717s000lbl.pdf. 2008. Accessed May 11, 2016
8. Cammu G, De Witte J, De Veylder J, Byttebier G, Vandeput D, Foubert L, Vandenbroucke G, Deloof T: Postoperative residual paralysis in outpatients *versus* inpatients. Anesth Analg 2006; 102:426–9
9. Naguib M, Brull SJ, Arkes HR: Reasoning of an anomaly: Residual block after sugammadex. Anesth Analg 2013; 117:297–300
10. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ: A survey of current management of neuromuscular block in the United States and Europe. Anesth Analg 2010; 111:110–9

11. Grol R, Grimshaw J: From best evidence to best practice: Effective implementation of change in patients' care. Lancet 2003; 362:1225–30
12. Baillard C, Clec'h C, Catineau J, Salhi F, Gehan G, Cupa M, Samama CM: Postoperative residual neuromuscular block: A survey of management. Br J Anaesth 2005; 95:622–6
13. Todd MM, Hindman BJ, King BJ: The implementation of quantitative electromyographic neuromuscular monitoring in an academic anesthesia department. Anesth Analg 2014; 119:323–31
14. U.S. Food and Drug Administration Advisory Committee: Schering-Plough Sugammadex NDA 22-225: Available at: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4346s1-01-Schering-Plough-corebackup.pdf. 2008. Accessed May 11, 2016
15. Masursky D, Dexter F, Kwakye MO, Smallman B: Measure to quantify the influence of time from end of surgery to tracheal extubation on operating room workflow. Anesth Analg 2012; 115:402–6
16. Bayman EO, Dexter F, Todd MM: Prolonged operative time to extubation is not a useful metric for comparing the performance of individual anesthesia providers. ANESTHESIOLOGY 2016; 124:322–38
17. Epstein RH, Dexter F, Brull SJ: Cohort study of cases with prolonged tracheal extubation times to examine the relationship with duration of workday. Can J Anaesth 2013; 60:1070–6

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Richter's Anchor Pain Expeller: Nondoctor Analgesia from "Doctoring" Chili, Black, and Guinea Peppers

Friedrich Adolf Richter (1846 to 1910) was a German businessman who claimed to have earned an M.D. from the University of Philadelphia, a nonexistent institution. Inside Germany, he flouted the law by peddling his nostrums to consumers by mail order from his company, F. Ad. Richter & Cie, by a nonexistent pharmacy. Featuring the brand's iconic anchor, Richter's advertising to Americans promised pain relief from neuralgia and from "gout, rheumatism, backache, etc." This trade card (*above*) was issued on behalf of the New York branch of Richter's company. In follow-up newspaper testimonials, a New York County Clerk observed that "universal endorsement [implied that the remedy]…must effect the ends claimed." By 1907, analytical pharmacists had determined that nondoctor Richter had created his Anchor Pain Expeller by "doctoring" chili, black, and Guinea peppers with galangal root, astringent rhatany, and the oils of thyme, clove, rosemary, and lavender. Three years later, Richter passed away as one of Germany's ten wealthiest citizens. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.