Sugammadex: Another Milestone in Clinical Neuromuscular Pharmacology

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Sugammadex is a revolutionary investigational reversal drug currently undergoing Phase III testing whose introduction into clinical practice may change the face of clinical neuromuscular pharmacology. A modified γ-cyclodextrin, sugammadex exerts its effect by forming very tight water-soluble complexes at a 1:1 ratio with steroidal neuromuscular blocking drugs (rocuronium > vecuronium ≫ pancuronium). During rocuronium-induced neuromuscular blockade, the IV administration of sugammadex creates a concentration gradient favoring the movement of rocuronium molecules from the neuromuscular junction back into the plasma, which results in a fast recovery of neuromuscular function. Sugammadex is biologically inactive, does not bind to plasma proteins, and appears to be safe and well tolerated. Additionally, it has no effect on acetylcholinesterase or any receptor system in the body. The compound's efficacy as an antagonist does not appear to rely on renal excretion of the cyclodextrin-relaxant complex. Human and animal studies have demonstrated that sugammadex can reverse very deep neuromuscular blockade induced by rocuronium without muscle weakness. Its future clinical use should decrease the incidence of postoperative muscle weakness, and thus contribute to increased patient safety. Sugammadex will also facilitate the use of rocuronium for rapid sequence induction of anesthesia by providing a faster onset-offset profile than that seen with 1.0 mg/kg succinylcholine. Furthermore, no additional anticholinesterase or anticholinergic drugs would be needed for antagonism of residual neuromuscular blockade, which would mean the end of the cardiovascular and other side effects of these compounds. The clinical use of sugammadex promises to eliminate many of the shortcomings in our current practice with regard to the antagonism of rocuronium and possibly other steroidal neuromuscular blockers.

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Sugammadex is a novel and unique compound designed as an antagonist of rocuronium and possibly other steroidal neuromuscular blockers. This investigational drug is currently in Phase IIIa multicenter trial in the United States, and is likely to be introduced to the market in the future. In this article, I address the unique characteristics of sugammadex and offer a vision for how this drug is likely to change anesthesia practice.

HISTORICAL PERSPECTIVE

The cornerstone of modern neuromuscular pharmacology was laid more than seven decades ago when the chemical theory of the role of acetylcholine in neuromuscular transmission was established by Dale (1,2). The first successful administration of curare to produce surgical relaxation in an anesthetized patient had occurred in 1912, when Arthur Läwen, a German surgeon from Leipzig, used a partially purified preparation of the substance (3). Läwen's findings were subsequently ignored for nearly three decades until January 23, 1942, when Enid Johnson, following Harold Griffith's instructions, administered a total of 5 mL of curare IV to a 20-year-old man who had been anesthetized with cyclopropane *via* a facemask for an appendectomy. The anesthesia lasted for 70 min and was later described as being "nothing less than dramatic" (4). It was without a doubt, a revolutionary step and a milestone that changed anesthetic practice. However, when this technique was initially used, patients were not fully paralyzed, and the pharmacological antagonism of the residual neuromuscular blockade of curare was hardly considered (5). Tracheal intubation and controlled ventilation were also uncommon in routine clinical practice.

The clinical use of neuromuscular blockers in anesthesia has come a long way since then. Since the 1980s, we have witnessed the introduction of many new

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nondepolarizing neuromuscular blocking drugs into clinical practice. In that decade, the two major pharmaceutical competitors (Organon and Burroughs Wellcome) were focused on developing nondepolarizing neuromuscular blockers that would fit the criteria of an "ideal" nondepolarizing blocker (6). Many modern neuromuscular blocking drugs, such as vecuronium, rocuronium, and cisatracurium, were introduced into clinical practice at that time. These new drugs had significant clinical advantages and minimized the side effects associated with older compounds such as *d*-tubocurarine and pancuronium.

Given these strides in anesthetic pharmacology, do any problems remain? Unfortunately, neuromuscular blocking drugs are among the most poorly used drugs in our armamentarium. Reports of residual postoperative weakness, incomplete recovery (7–9), and undesired ventilatory effects (10,11) have continued to appear since 1979. In 2003, for example, Debaene et al. (9) reported a 45% incidence of postoperative residual paralysis in patients arriving in the postanesthesia care unit. A recent survey has indicated that most practitioners do not know what constitutes adequate recovery from neuromuscular blockade (12). The aforementioned problems could be attributed to two main factors. First, most anesthesiologists do not routinely use quantitative neuromuscular function monitors to ensure adequate recovery to a train-of-four (TOF) ratio of 0.9 or more (13,14). Although anesthesiologists are fast to adopt new monitoring technologies, such as capnography, pulse oximetry, and bispectral index monitoring, the same is not true for neuromuscular function monitoring; the reasons for the limited use of such monitoring are unknown. Second, neostigmine has a ceiling effect and, when administered at a deep level of neuromuscular blockade, can result in an inadequate recovery of neuromuscular function (15,16).

So, what is still needed? It is clear that no substantial progress has been made in the area of neuromuscular antagonism. In 2006, neostigmine is still the most common anticholinesterase drug used by anesthesiologists worldwide, despite its undesirable side effects (17). Few studies have attempted to explore the potential of nonclassic reversal drugs. In this regard, suramin, a P_2-purinoceptor antagonist, can reverse nondepolarizing neuromuscular blockade (18–20), but it has serious side effects that render it inapplicable for routine clinical use (21). In contrast, purified human plasma cholinesterase has been shown to be an effective and safe drug in antagonizing mivacurium-induced neuromuscular blockade (22–24). Similarly, cysteine has been shown to reverse the neuromuscular blocking effects of gantacurium (25). Notably, both purified human plasma cholinesterase and cysteine act independently of acetylcholinesterase inhibition.

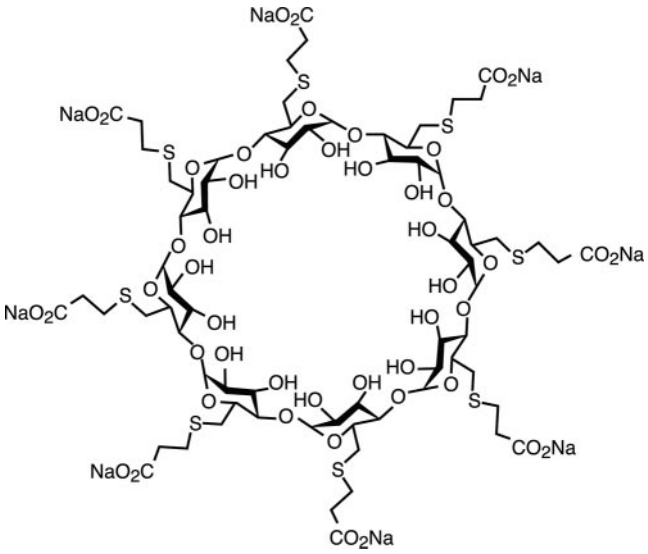

Figure 1. Structure of sugammadex, a synthetic γ-cyclodextrin. The diameters of inner and outer rims of unmodified γ-cyclodextrin are approximately 0.75 and 0.85 nm, respectively. Modifications to the molecule involved adding side chains to extend the cavity to approximately 1.1 nm and adding negatively charged groups at the end of the side chains to enhance binding.

CHEMISTRY OF SUGAMMADEX

Phase IIIa studies are currently underway in the United States and Europe testing a member of a new class of reversal drugs. This drug, sugammadex (ORG 25969), is a modified γ-cyclodextrin (26–29). (**Su** refers to **su**gar and **gammadex** refers to the structural molecule **γ**-cyclo**dex**trin). The three natural unmodified cyclodextrins consist of 6, 7, or 8 cyclic oligosaccharides (i.e., dextrose units joined through 1–4 glycosyl bonds) and are called α-, β-, or γ-cyclodextrin, respectively. Their three-dimensional structures resemble a hollow, truncated cone or a doughnut. The structure has a hydrophobic cavity and a hydrophilic exterior because of the presence of polar hydroxyl groups. Hydrophobic interactions trap the drug into the cyclodextrin cavity (the doughnut hole), resulting in the formation of a water-soluble guest–host complex. For this reason, cyclodextrins have been used as solubilizing agents for many United States Food and Drug Administration-approved drugs (30–32), and have been evaluated as solvents for different anesthetic drugs such as propofol (33,34), midazolam (35), bupivacaine (36), and sufentanil (37).

Although unmodified γ-cyclodextrin has a larger lipophilic cavity than any other cyclodextrin, it is still not deep enough to accommodate the larger rigid structure of the rocuronium molecule. Therefore, the drug was modified by adding eight side chains to extend the cavity to better accommodate the four hydrophobic steroidal rings of rocuronium, and by adding negatively charged carboxyl groups at the end of the side chains to enhance electrostatic binding to the positively charged quaternary nitrogen of rocuronium (Figs. 1 and 2) (26,27). These modifications resulted in a sugammadex

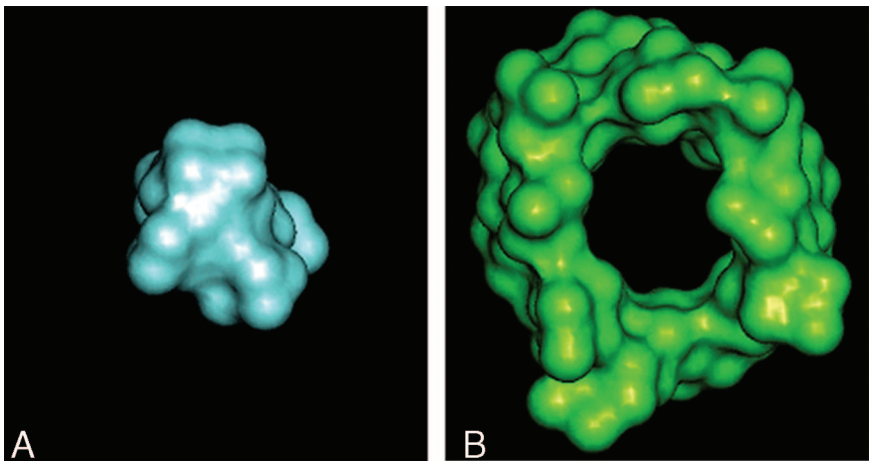

Figure 2. Radiograph crystal structure of a rocuronium molecule (A) and a sugammadex molecule (B). Reproduced from Ref. 38, with permissison from ©Lippincott Williams & Wilkins.

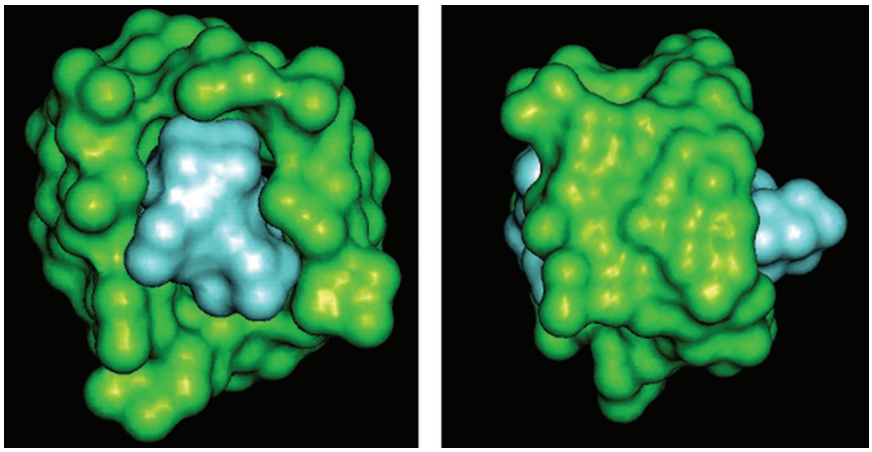

Figure 3. Encapsulation of rocuronium molecule (blue) by a sugammadex molecule (green) at 1:1 ratio. Modified from Ref. 38, with permission from ©Lippincott Williams & Wilkins.

compound that is highly water soluble with a hydrophobic cavity large enough to encapsulate steroidal neuromuscular blocking drugs, especially rocuronium (26–29). The stability of the rocuronium–sugammadex complex is the end result of interplay of intermolecular (van der Waals) forces, including thermodynamic (hydrogen bonds) and hydrophobic interactions (34). The molecular weight of sugammadex sodium salt is 2178.01. Sugammadex is, therefore, the first selective relaxant binding agent (SRBA).

MECHANISM OF ACTION OF SUGAMMADEX

Sugammadex exerts its effect by forming very tight complexes at a 1:1 ratio with steroidal neuromuscular blocking drugs (rocuronium > vecuronium ≫ pancuronium) (Fig. 3) (26–29). The guest–host complex exists in equilibrium with a very high association rate (an association constant of 10^7 M^{-1}) and a very low dissociation rate, so the complex is tight (26).

During rocuronium-induced neuromuscular blockade, the IV administration of sugammadex results in rapid removal of free rocuronium molecules from the plasma. This creates a concentration gradient favoring the movement of the remaining rocuronium molecules from the neuromuscular junction back into the plasma, where they are encapsulated by free sugammadex molecules (38–40). The latter molecules also enter the tissues and form a complex with rocuronium. Therefore, the neuromuscular blockade of rocuronium is terminated rapidly by the diffusion of rocuronium away from the neuromuscular junction back into the plasma (38–44). This results in an increase in the total plasma concentration of rocuronium (both free and bound to sugammadex) (38). Because of the low dissociation rate, no muscle weakness has been reported in available human or animal studies (38–44). Sugammadex, therefore, acts as a binding drug and has no effect on acetylcholinesterase or any receptor system in the body. This eliminates the need for anticholinergic drugs, thus avoiding their undesirable side effects. The findings of sugammadex's reversal of rocuronium-induced neuromuscular blockade have theoretical implications as well (38–44). They disprove the historical hypothesis of Feldman and Tyrrell (45) that reducing the plasma concentration of nondepolarizing neuromuscular blockers does not reverse the neuromuscular blockade.

The compound's efficacy as an antagonist does not appear to rely on renal excretion of the cyclodextrin-relaxant complex (46). Most sugammadex is excreted

unchanged in the urine in the first 8 h (40). Sugammadex also increases the amount of rocuronium excreted unchanged in the urine (40), but a change in acid–base status affects anticholinesterase activity, it appears not to influence the efficacy of sugammadex[1].

EFFECT OF SUGAMMADEX ON OTHER DRUGS

Sugammadex is ineffective against succinylcholine and benzylisoquinolinium neuromuscular blockers, such as mivacurium, atracurium, and cisatracurium (44), because it cannot form inclusion complexes with these drugs. Therefore, if neuromuscular blockade must be re-established after using sugammadex, succinylcholine or one of the benzylisoquinolinium neuromuscular blockers should be considered. Under these conditions, what would be the potency of cisatracurium and succinylcholine? Sugammadex binds at a 1:1 ratio to rocuronium and vecuronium, but for effective reversal, all rocuronium or vecuronium molecules do not have to be complexed with sugammadex. The margin of safety of the neuromuscular transmission is such that only 20%–25% of postsynaptic receptors need to be free for transmission to occur (47). Therefore, sugammadex only has to reduce the occupation of these receptors from 100% to 70% to obtain complete reversal. After induction of neuromuscular blockade with rocuronium and complete reversal with sugammadex in anesthetized guinea pigs, the administration of cisatracurium caused a more intense neuromuscular blockade with a faster than normal onset (48). Kopman et al. (49) also demonstrated that the ED_{50} of mivacurium was 56% less if calculated after full recovery from mivacurium-induced neuromuscular blockade than after the initial blockade. When succinylcholine rather than cisatracurium was administered, complete blockade could also be induced; however, its onset was delayed in the guinea pig (48). Pretreatment with nondepolarizing neuromuscular blockers had a marked antagonistic effect on the development of the subsequent depolarizing blockade produced by succinylcholine (50).

The interaction of sugammadex with other molecules has been tested with isothermal titration microcalorimetry. This technique measures the heat production when two molecules form a complex. The ability of sugammadex to form complexes with other steroidal and nonsteroidal compounds, such as cortisone, atropine, and verapamil, is probably clinically insignificant and is approximately 120–700 times less than that of rocuronium (51). Steroidal molecules form complexes with sugammadex, but with a much lower affinity, because the high affinity of sugammadex for rocuronium and vecuronium is caused by the interaction between the negatively charged carboxyethyl side chains of sugammadex and the positively charged quaternary nitrogen of rocuronium and vecuronium. As endogenous steroidal hormones and steroidal drugs lack the quaternary nitrogen of the steroidal blockers, they show a much lower affinity. Furthermore, steroidal hormones are also bound tightly to specific protein carriers; for example, the sex hormones are bound with very high affinity to globulin.

The possible effects of the sugammadex-induced improved solubility of propofol, midazolam, and bupivacaine on the pharmacodynamics/pharmacokinetics of these compounds have not yet been studied.

ANIMAL STUDIES

All animal studies have thus far demonstrated that sugammadex is effective in antagonizing rocuronium-induced neuromuscular blockade without any significant effects on arterial blood pressure or heart rate (39,42–44). In one study that used anesthetized guinea pigs, rocuronium was infused for 1 h to maintain a steady state 90% neuromuscular blockade (39). After 30 min, a concomitant infusion of sugammadex at a rate of 50 $nmol \cdot kg^{-1} \cdot min^{-1}$ resulted in rapid reversal of the neuromuscular blockade. An average twitch recovery of approximately 80%, 90%, and 100% occurred 10, 20, and 30 min, respectively, after the start of the sugammadex infusion (39). This was accompanied by an increase in the total plasma concentration of rocuronium (free and that encapsulated by sugammadex). In contrast, the plasma concentration of rocuronium and the depth of neuromuscular blockade remained unchanged in saline-treated animals. In clinical practice, the antagonism of residual neuromuscular blockade is normally attempted after discontinuing infusion of neuromuscular blockers. The ability of sugammadex to antagonize the neuromuscular blockade despite concomitant infusion of rocuronium points out its unique characteristics. The study design also explains the prolonged recovery times noted (39).

VOLUNTEERS AND CLINICAL STUDIES

The effectiveness of sugammadex is dose dependent. In male volunteers, the administration of 8 mg/kg sugammadex 3 min after the administration of 0.6 mg/kg rocuronium resulted in the recovery of the TOF ratio to 0.9 within 2 min (38). Decreasing the dose of sugammadex to 4 mg/kg resulted in a recovery of the TOF ratio to 0.9 in <4 min (38). In one study, different doses of sugammadex or placebo were administered to surgical patients anesthetized with total IV anesthesia who had received 0.6 mg/kg rocuronium at the reappearance of the second twitch of the TOF response (40). Sugammadex decreased the median recovery time in a dose-dependent manner from 21.0 min in the placebo group to 1.1 min in the group receiving 4.0 mg/kg sugammadex. The authors of this study concluded that doses of 2.0–4.0 mg/kg of

[1] Bom A, Mason R, McIndewar I. Org 25060 causes rapid reversal of rocuronium-induced neuromuscular block, independent of acid-base status [abstract]. Anesthesiology 2002;97:A1009.

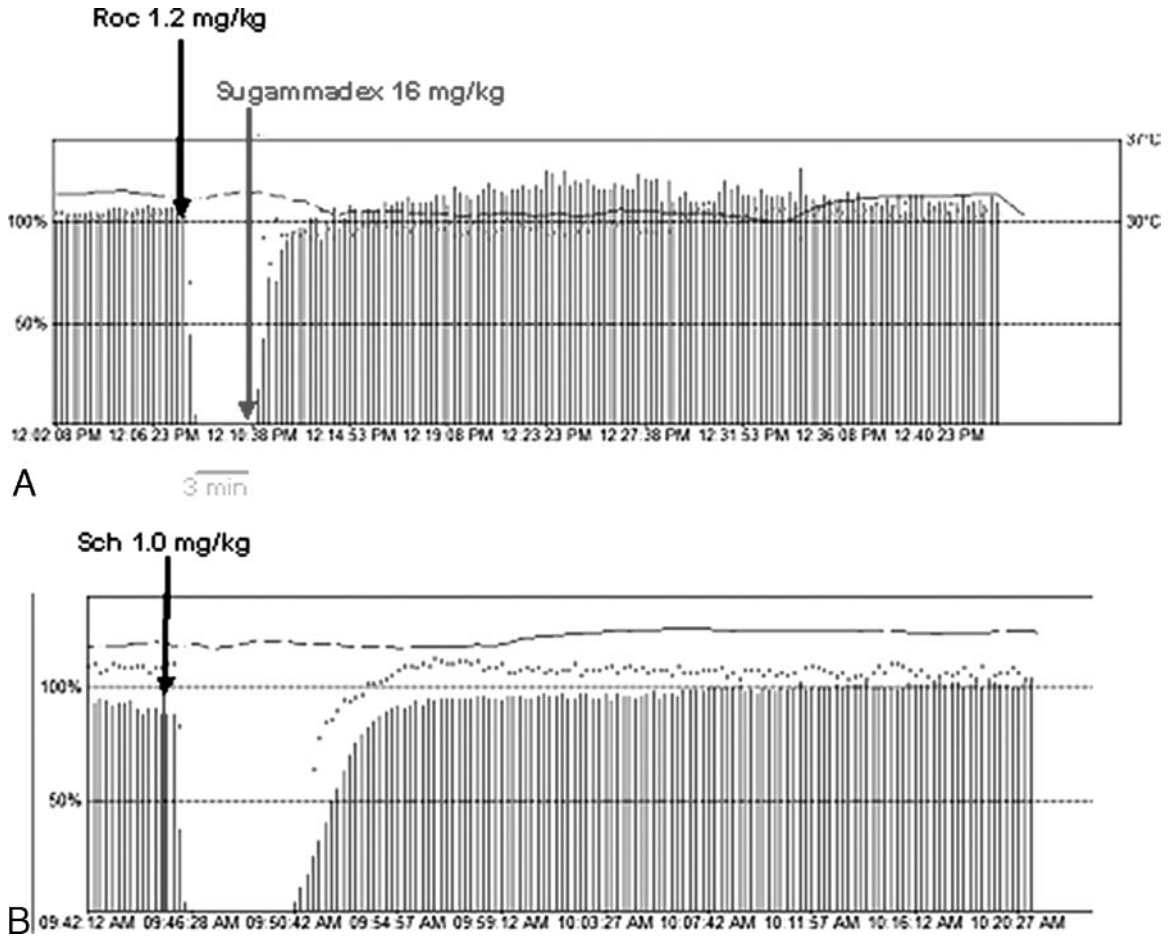

Figure 4. Panel A shows the recovery of the twitch height and train-of-four (TOF) ratio after administration of 1.2 mg/kg rocuronium followed 3 min later by 16 mg/kg sugammadex, both given IV. Recovery to a first twitch height (T1) of 90% and a TOF ratio of 0.94 occurred 110 s later. The onset-offset time with this sequence (i.e., the time from the end of the injection of rocuronium to a T1 recovery to 90%) was 4 min 47 s. Panel B shows the effects of administering 1.0 mg/kg succinylcholine (Sch) with spontaneous recovery to a T1 of 90% occurring after 9 min and 23 s.

sugammadex reversed rocuronium-induced neuromuscular blockade within 3 min (40). In another study, deep neuromuscular blockade (posttetanic count of <10) was maintained for at least 2 h in patients anesthetized with propofol–nitrous oxide–opioid anesthesia (41). After the spontaneous recovery of the second twitch of the TOF, different doses of sugammadex were administered; increasing the sugammadex dose from 0.5 to 4.0 mg/kg shortened the average recovery time to a TOF of 0.9 from 6.8 min (range, 4.8–11.4 min) to 1.4 min (range 0.95–2.3 min), respectively (41). Unexpectedly, the recovery time was longer (2.6 min [range 1.3–3.9 min]) with a 6.0 mg/kg dose (41). The reason for this deviation is unclear, but the reversal still occurred in <3 min, on average.

Currently, as a part of a multicenter study, we are comparing the speed of recovery from 1.2 mg/kg rocuronium followed 3 min later by 16 mg/kg sugammadex with that of spontaneous recovery from 1.0 mg/kg succinylcholine in surgical patients. Our initial results are very encouraging with respect to the antagonism of this profound level of rocuronium-induced neuromuscular blockade and indicate that the total duration from administration of rocuronium until a TOF ratio recovery to more than 0.9 is shorter than the time needed for spontaneous recovery from 1.0 mg/kg succinylcholine-induced blockade to a similar degree of recovery (Fig. 4).

SIDE EFFECTS

Sugammadex is biologically inactive, does not bind to plasma proteins, and appears to be safe and well tolerated (38,40,50). The safety of sugammadex has been assessed in the phase I and II studies (in a total of 86 subjects). In one study, sugammadex was administered to awake volunteers who had received no neuromuscular blocking drugs (38). The most frequently reported side effects have been hypotension (three subjects), coughing (three subjects), movement (three subjects), nausea (three subjects), vomiting (three subjects), dry mouth (four subjects), parosmia (an abnormal smell) (two subjects), a sensation of a changed temperature (three subjects), and abnormal levels of *N*-acetylglucosaminidase in the urine (five subjects) (38,40,41). In one study, prolongation of the corrected QT interval was noted in five subjects who received placebo and in three subjects who received sugammadex (38).

FUTURE APPLICATIONS AND CHALLENGES

What can we look forward to? Does the introduction of sugammadex herald the elimination of many of the shortcomings in our clinical practice with regard to antagonism of neuromuscular blockers? The deep levels of neuromuscular blockade induced by rocuronium (and possibly by vecuronium, although there is no clinical evidence for the latter drug yet) can be promptly antagonized with appropriate doses of sugammadex. This should make surgical care much easier and safer: Surgeons should no longer encounter inadequate muscle relaxation, and anesthesiologists should no more encounter patients whose neuromuscular blockade is hard to reverse at the end of surgery. The introduction of sugammadex into clinical practice would thus contribute to both increased patient safety and improved surgical conditions. One expects to see no more patients either being held in the operating room because the antagonism of residual neuromuscular blockade is incomplete, or being transferred to postoperative care units with residual neuromuscular blockade. Additionally, no anticholinesterase or anticholinergic drugs would be needed for the antagonism of residual neuromuscular blockade, which would mean the end of the cardiovascular and other side effects of these compounds (17). The postoperative nausea and vomiting associated with the use of these compounds should also be eliminated (52). Will sugammadex replace neostigmine as an antagonist for rocuronium-induced neuromuscular blockade? Kopman (53) rightly believes that this will ". . . depend at least in part on economic considerations." Although concerns have been raised about the acquisition cost of new drugs (54), the economic evaluations are complex, and not simply defined by the acquisition cost (55). In the final analysis, improvements in inpatient outcome must have a dollar value that offsets the cost of the drug (56).

Do we still need to use neuromuscular function monitoring with sugammadex? Without knowing the depth of the rocuronium-induced neuromuscular blockade, it would be difficult to know the dose of sugammadex needed. Perhaps conventional nerve stimulators would be sufficient to determine the presence or absence of the twitch response, and the appropriate dose of sugammadex could be administered accordingly. In such circumstances, objective neuromuscular monitoring would no longer be needed.

Further, the use of rapid-sequence induction with rocuronium can be facilitated by the presence of sugammadex. The previously described sequence of 1.2 mg/kg rocuronium followed 3 min later by 16 mg/kg sugammadex seems to provide a faster onset-offset profile than that seen with 1.0 mg/kg succinylcholine. If the rocuronium induction/sugammadex reversal paradigm achieves the reliability of succinylcholine, will this mark the end of years of effort directed toward developing a nondepolarizing version of succinylcholine? Why would one ever give succinylcholine if one could give rocuronium and achieve reversal more quickly than the succinylcholine would wear off? Before these questions can be answered, however, we must know whether the rocuronium-sugammadex sequence will be safer than succinylcholine? In this regard, studies using succinylcholine have indicated that the risk of desaturation in the immediate postinduction period is much greater than initially recognized in "cannot intubate, cannot ventilate" situations (57,58). Nevertheless, studies are needed to address the role of sugammadex as a "rescue" reversal drug in patients with unanticipated difficult airways who received rocuronium. For now, succinylcholine is expected to remain on the hospital formulary, but its clinical use will most likely become limited to reparalyzing patients who have already received sugammadex.

The introduction of propofol almost two decades ago changed anesthetic practice (34). Nothing since then, however, has had the same effect. Unquestionably, the introduction of sugammadex is an important breakthrough, and one that is likely to change the face of clinical neuromuscular pharmacology. This molecule is specifically suited to rocuronium and vecuronium, and its future clinical use should decrease the incidence of postoperative muscle weakness caused by these drugs and facilitate the use of rocuronium for rapid sequence induction of anesthesia. For now, however, we still need benzylisoquinolinium neuromuscular blockers in our practice, so the residual postoperative muscle weakness caused by this class of drugs is likely to continue unless objective neuromuscular function monitors are routinely used, or until a molecule capable of binding to benzylisoquinolinium neuromuscular blockers is discovered.

REFERENCES

1. Dale HH. Chemical transmission of the effects of nerve impulses. Br Med J 1934;1:835–41.
2. Dale HH, Feldberg W, Vogt M. Release of acetylcholine at voluntary nerve endings. J Physiol 1936;86:353–80.
3. Läwen A. Über die Verbindung der Lokalanästhesie mit der Narkose, über hohe Extraduralanästhesie und epidurale Injektionen anästhesierender Lösungen bei tabischen Magenkrisen. Beitr klin Chir 1912;80:168–80.
4. Bodman RI, Gillies D. Harold Griffith: The evolution of modern anaesthesia. 1st ed. Toronto: Hannah Institute and Dundurn Press, 1992.
5. Prescott F, Organe G, Rothbotham S. Tubocurarine chloride as an adjunct to anaesthesia. Lancet 1946;2:80–4.
6. Savarese JJ, Kitz RJ. Does clinical anesthesia need new neuromuscular blocking agents? Anesthesiology 1975;42:236–9.
7. Viby-Mogensen J, Jorgensen BC, Ording H. Residual curarization in the recovery room. Anesthesiology 1979;50:539–41.
8. Kim KS, Lew SH, Cho HY, Cheong MA. Residual paralysis induced by either vecuronium or rocuronium after reversal with pyridostigmine. Anesth Analg 2002;95:1656–60.
9. 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.

10. Eriksson LI. Reduced hypoxic chemosensitivity in partially paralysed man. A new property of muscle relaxants? Acta Anaesthesiol Scand 1996;40:520–3.
11. Eriksson LI. The effects of residual neuromuscular blockade and volatile anesthetics on the control of ventilation. Anesth Analg 1999;89:243–51.
12. Sorgenfrei IF, Viby-Mogensen J, Swiatek FA. [Does evidence lead to a change in clinical practice? Danish anaesthetists' and nurse anesthetists' clinical practice and knowledge of postoperative residual curarization]. Ugeskr Laeger 2005;167:3878–82.
13. Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. Anesthesiology 1997;86:765–71.
14. Eriksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. Anesthesiology 2003;98:1037–9.
15. Bartkowski RR. Incomplete reversal of pancuronium neuromuscular blockade by neostigmine, pyridostigmine, and edrophonium. Anesth Analg 1987;66:594–8.
16. Beemer GH, Bjorksten AR, Dawson PJ, et al. Determinants of the reversal time of competitive neuromuscular block by anticholinesterases. Br J Anaesth 1991;66:469–75.
17. Suresh D, Carter JA, Whitehead JP, et al. Cardiovascular changes at antagonism of atracurium. Effects of different doses of premixed neostigmine and glycopyrronium in a ratio of 5:1. Anaesthesia 1991;46:877–80.
18. Henning RH, Nelemans A, Houwertjes M, Agoston S. Reversal by suramin of neuromuscular block produced by pancuronium in the anaesthetized rat. Br J Pharmacol 1993;108:717–20.
19. Henning RH, Nelemans A, Scaf AH, et al. Suramin reverses non-depolarizing neuromuscular blockade in rat diaphragm. Eur J Pharmacol 1992;216:73–9.
20. Henning RH, Rowan EG, Braga MF, et al. The prejunctional inhibitory effect of suramin on neuromuscular transmission *in vitro*. Eur J Pharmacol 1996;301:91–7.
21. Kaur M, Reed E, Sartor O, et al. Suramin's development: what did we learn? Invest New Drugs 2002;20:209–19.
22. Naguib M, el-Gammal M, Daoud W, et al. Human plasma cholinesterase for antagonism of prolonged mivacurium-induced neuromuscular blockade. Anesthesiology 1995;82:1288–92.
23. Naguib M, Daoud W, el-Gammal M, et al. Enzymatic antagonism of mivacurium-induced neuromuscular blockade by human plasma cholinesterase. Anesthesiology 1995;83:694–701.
24. Naguib M, Selim M, Bakhamees HS, et al. Enzymatic versus pharmacologic antagonism of profound mivacurium-induced neuromuscular blockade. Anesthesiology 1996;84:1051–9.
25. Belmont MR, Horochiwsky Z, Eliazo RF, Savarese JJ. Reversal of AV430A with cysteine in Rhesus monkeys [abstract]. Anesthesiology 2004;101:A1180.
26. 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;41:266–70.
27. Adam JM, Bennett DJ, Bom A, et al. 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.
28. Tarver GJ, Grove SJ, Buchanan K, et al. 2-O-substituted cyclodextrins as reversal agents for the neuromuscular blocker rocuronium bromide. Bioorg Med Chem 2002;10:1819–27.
29. Cameron KS, Clark JK, Cooper A, et al. Modified 4:3403–6.
30. Thompson DO. Cyclodextrins–enabling excipients: their present and future use in pharmaceuticals. Crit Rev Ther Drug Carrier Syst 1997;14:1–104.
31. Davis ME, Brewster ME. Cyclodextrin-based pharmaceutics: past, present and future. Nat Rev Drug Discov 2004;3:1023–35.
32. Munro IC, Newberne PM, Young VR, Bar A. Safety assessment of γ-cyclodextrin. Regul Toxical Pharmacol 2004;39:3–13.
33. Egan TD, Kern SE, Johnson KB, Pace NL. The pharmacokinetics and pharmacodynamics of propofol in a modified cyclodextrin formulation (Captisol) versus propofol in a lipid formulation (Diprivan): an electroencephalographic and hemodynamic study in a porcine model. Anesth Analg 2003;97:72–9.
34. Baker MT, Naguib M. Propofol: the challenges of formulation. Anesthesiology 2005;103:860–76.
35. Gudmundsdottir H, Sigurjonsdottir JF, Masson M, et al. Intranasal administration of midazolam in a cyclodextrin based formulation: bioavailability and clinical evaluation in humans. Pharmazie 2001;56:963–6.
36. Estebe JP, Ecoffey C, Dollo G, et al. Bupivacaine pharmacokinetics and motor blockade following epidural administration of the bupivacaine-sulphobutylether 7–19:308–10.
37. Meert TF, Mesens J, Verheyen P, Noorduin H. Hydroxypropyl-9:399–409.
38. 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.
39. 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.
40. Sorgenfrei IF, Norrild K, Larsen PB, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. Anesthesiology 2006;104:667–74.
41. Shields M, Giovannelli M, Mirakhur RK, et al. Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block. Br J Anaesth 2006;96:36–43.
42. de Boer HD, van Egmond J, van de Pol F, et al. Chemical encapsulation of rocuronium by synthetic cyclodextrin derivatives: reversal of neuromuscular block in anaesthetized Rhesus monkeys. Br J Anaesth 2006;96:201–6.
43. de Boer HD, van Egmond J, van de Pol F, et al. Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized Rhesus monkeys. Anesthesiology 2006;104:718–23.
44. de Boer HD, van Egmond J, van de Pol F, et al. Sugammadex, a new reversal agent for neuromuscular block induced by rocuronium in the anaesthetized Rhesus monkey. Br J Anaesth 2006;96:473–9.
45. Feldman SA, Tyrrell MF. A new theory of the termination of action of the muscle relaxants. Proc R Soc Med 1970;63:692–5.
46. Bom A, van Egmond J, Hope F, van de Pol F. Rapid reversal of rocuronium-induced neuromuscular block by Org 25969 is independent of renal perfusion [abstract]. Anesthesiology 2003;99:A1158.
47. Paton WD, Waud DR. The margin of safety of neuromuscular transmission. J Physiol 1967;191:59–90.
48. Bom A, Hope F. Neuromuscular block induced by rocuronium and reversed by the encapsulating agent Org 25969 can be re-established using the non-steroidal neuromuscular blockers succinylcholine and cis-atracurium [abstract]. Eur J Anaesthiol 2005;22 (Suppl S34):A457.
49. Kopman AF, Mallhi MU, Neuman GG, Justo MD. Re-establishment of paralysis using mivacurium following apparent full recovery from mivacurium-induced neuromuscular block. Anaesthesia 1996;51:41–4.
50. Naguib M, Abdulatif M, Selim M, al-Ghamdi A. Dose-response studies of the interaction between mivacurium and suxamethonium. Br J Anaesth 1995;74:26–30.
51. Zhang MQ. Drug-specific cyclodextrins: the future of rapid neuromuscular block reversal? Drugs Future 2003;28:347–54.
52. King MJ, Milazkiewicz R, Carli F, Deacock AR. Influence of neostigmine on postoperative vomiting. Br J Anaesth 1988; 61:403–6.
53. Kopman AF. Sugammadex: a revolutionary approach to neuromuscular antagonism. Anesthesiology 2006;104:631–3.
54. Philip BK. Practical cost-effective choices: ambulatory general anesthesia. J Clin Anesth 1995;7:606–13.
55. White PF, Watcha MF. Pharmacoeconomics in anaesthesia: what are the issues? Eur J Anaesthesiol Suppl 2001;23:10–15.
56. Souetre EJ, Qing W, Hardens M. Methodological approaches to pharmaco-economics. Fundam Clin Pharmacol 1994;8:101–7.
57. Hayes AH, Breslin DS, Mirakhur RK, et al. Frequency of haemoglobin desaturation with the use of succinylcholine during rapid sequence induction of anaesthesia. Acta Anaesthesiol Scand 2001;45:746–9.
58. Naguib M, Samarkandi AH, Abdullah K, et al. Succinylcholine dosage and apnea-induced hemoglobin desaturation in patients. Anesthesiology 2005;102:35–40.