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Sugammadex: Past, Present, and Future

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THE PAST

Ever since the introduction of neuromuscular blocking drugs into anesthesia practice, the mechanism by which the paralytic effect is reversed has been imperfect. Traditional muscle relaxant reversal using inhibitors of anticholinesterase is a flawed process for several reasons. The mechanism of reversal is indirect, the efficacy is limited, rapid reversal of deep block is not possible, and undesirable cardiovascular and autonomic responses occur [1].

Reversal acts indirectly via acetylcholinesterase inhibition

Reversal acts indirectly through inhibition of acetylcholinesterase, the enzyme that metabolizes the endogenous neurotransmitter acetylcholine at the neuromuscular junction. After the administration of an anticholinesterase–whether neostigmine, edrophonium, or pyridostigmine–the metabolism of acetylcholine ceases. As a consequence, the concentration of acetylcholine in the neuromuscular junction increases, and opposes the effect of the muscle relaxant. There is no direct effect on the muscle relaxant itself.

Efficacy of reversal is limited and rapid reversal of deep block is not possible

The efficacy of traditional reversal is limited because when the processes of acetylcholine release, diffusion out of the junction, and reuptake reach equilibrium, the concentration of acetylcholine is at its maximum. The maximum concentration of acetylcholine that can be thus achieved is often insufficient to overcome the effect of the muscle relaxant, and ineffective reversal results [1].

In 1990 Magorian and colleagues [2] neatly demonstrated these limitations of neostigmine. In summary, these investigators showed that neostigmine, 70 μg/kg could not rapidly reverse deep (no response to ulnar nerve stimulation) vecuronium-induced block. More interesting was that a second dose of

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neostigmine, 70 μg/kg, given when recovery from the first dose reached 10% had no further effect on recovery. The second dose of neostigmine neither sped nor slowed subsequent recovery. Therefore before sugammadex, there was no way for clinicians to rapidly reverse what was considered profound levels of neuromuscular block, namely no train-of-four (TOF) responses of the thumb to electrical stimulation of the ulnar nerve [1].

Anticholinesterase reversal has adverse effects

The final set of problems with anticholinesterase drugs is that they have widespread undesirable effects at other cholinergic sites. Unopposed muscarinic activity may produce bradycardia, excessive secretions, increased gastrointestinal motility, and bronchospasm [1]. Antimuscarinic drugs (glycopyrrolate, atropine) administered to block these effects may produce the opposing effects to excess, for example, tachycardia. Thus the stage was set for a completely new pharmacologic approach to reversal of neuromuscular block, one that would be completely effective against all levels of block and free of autonomic side effects: in short, a drug such as sugammadex [3].

The standard for adequate reversal has been raised

Another force driving the need for a better mechanism for reversal of neuromuscular block was the redefinition of what constituted an acceptable level of neuromuscular recovery. In the 1970s the concept of the TOF ratio was born and adequate reversal was judged as a TOF ratio of greater than 0.7, because this was associated with adequate vital capacity and inspiratory force [4]. In the late 1990s this dictum was questioned, and current opinion is that subtle but clinically significant effects of muscle relaxants persist unless the TOF ratio is 0.9 or greater and that this should be the new standard [5–8].

As an example, in healthy, nonanesthetized volunteers partially paralyzed with vecuronium and given contrast to swallow, aspiration could occur unless the TOF ratio was at least 0.9 [5,6]. This vulnerability to aspiration was attributable to the disruption of the complex reflex of swallowing (and thus airway protection) induced by even minor degrees of residual block [8]. Another study looked at clinical indices of recovery in healthy volunteers paralyzed with mivacurium [7]. In this study the volunteers felt unsteady when sitting up unless the TOF ratio was 0.9 or more. In addition, diplopia persisted and handgrip strength was reduced even with TOF ratios greater than 0.9. The problem with this new standard for recovery is that it cannot be achieved predictably and reliably with reversal by anticholinesterase administration [9].

Reversal adequacy using anticholinesterase drugs is unpredictable

Because the new standard for adequate reversal is a TOF ratio of 0.9 or greater, the question to ask is: can we reliably achieve this level of recovery with current reversal practices? The answer is no. When reversing cisatracurium-induced block, even when 4 twitches are present and 70 μg/kg neostigmine is given, 26% of patients fail to achieve a TOF ratio of 0.9 or

more within 20 minutes [9]. If only one twitch is present when the neostigmine is given, this failure rate rises to 64%. This problem is compounded by the fact that tactile evaluation of the TOF response is very subjective, and the same TOF count can represent a wide range of true neuromuscular block [9]. Fig. 1 shows how any value for tactile TOF count (1–4) can be associated with a wide range of true level of block as measured by a force transducer. For example, at a twitch tension of 12% patients could have a tactile TOF count of 1, 2, 3, or 4 (see Fig. 1).

Discovery of sugammadex

The discovery of sugammadex was serendipitous. Anton Bom, a pharmaceutical chemist with Organon Inc., was performing experiments with rocuronium and needed a drug that would enhance its solubility in the media he was using. He hit on the idea of using cyclodextrins, a group of drugs with a long history in pharmaceutics as solubilizing agents [3,10]. Cyclodextrins are a group of doughnut-shaped sugar molecules consisting of 6 to 8 subunits.

What Bom found was that rocuronium lost its potency when he dissolved it with the cyclodextrin [11]. He could easily have stopped there and moved on to find another solubilizing agent so that he could continue his experiments. Instead he realized that he had a way to "inactivate" rocuronium and thus a radically new mechanism for reversal of neuromuscular block was created. Bom and his group went on to investigate a series of compounds with the purpose of identifying a cyclodextrin that would bind rocuronium with high affinity (ie, irreversibly) [3,10]. Sugammadex (Org 25969) was the compound selected for clinical development. Sugammadex binds

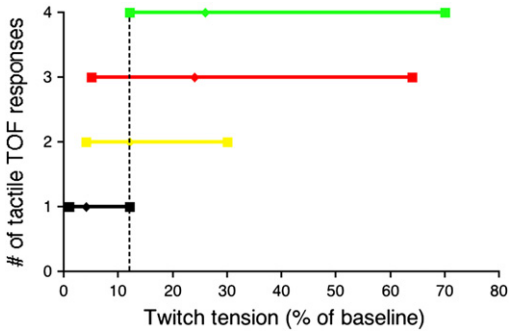

Fig. 1. Twitch tension (X-axis) at which the first, second, third, or fourth tactile response to train-of-four (TOF) stimulation (Y-axis) was detected at the thumb. The poor relationship between tactile count of TOF responses and objective quantitative measurement of neuromuscular block with a force transducer is clear. For example, at a twitch tension or 12% of control, the tactile TOF count felt by the observer in different patients could be 1, 2, 3, or 4. (*Data from* Kirkegaard H, Heier T, Caldwell JE. Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. Anesthesiology 2002;96:45.)

rocuronium 1:1 and essentially decreases the "active" plasma concentration to zero [10,12].

Sugammadex has a lipophilic inner cavity, and the diameter of this cavity is tailored to be an optimal fit for the steroidal nucleus of rocuronium (Fig. 2). In addition, negatively charged hydrophilic carboxyl groups project from the rim of the cyclodextrin molecule [10,12]. These groups, by repelling each other, keep the opening of the cyclodextrin cavity wide, and once the steroidal nucleus is incorporated they close down and lock onto the positively charged quaternary ammonium group of the rocuronium. The rocuronium is thus tightly bound to the cyclodextrin (see Fig. 2).

Sugammadex development pathway

Sugammadex development went along a standard pathway (Fig. 3). In January 2008, the Food and Drug Administration (FDA) took the step of suggesting

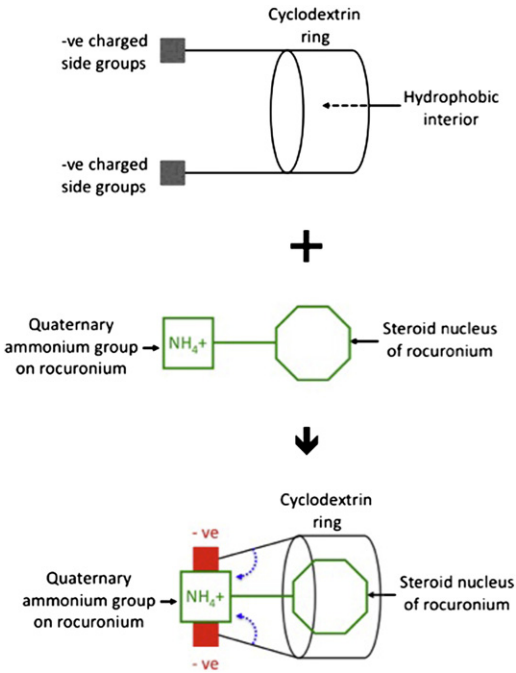

Fig. 2. The interaction of sugammadex and rocuronium. The cyclodextrin has a hydrophobic ring that is conformed optimally to accommodate the steroid nucleus of rocuronium. The ring itself is too small to fit the whole rocuronium molecule, so a method to increase the binding affinity was needed. This increase was accomplished by adding negatively charged side groups, which remain open because of the repulsive force of the negative charges. When a rocuronium molecule enters the cyclodextrin cavity, the negative charge on the side arms is attracted to and locks onto the protruding and positively charged quaternary ammonium group, thus binding the rocuronium with high affinity.

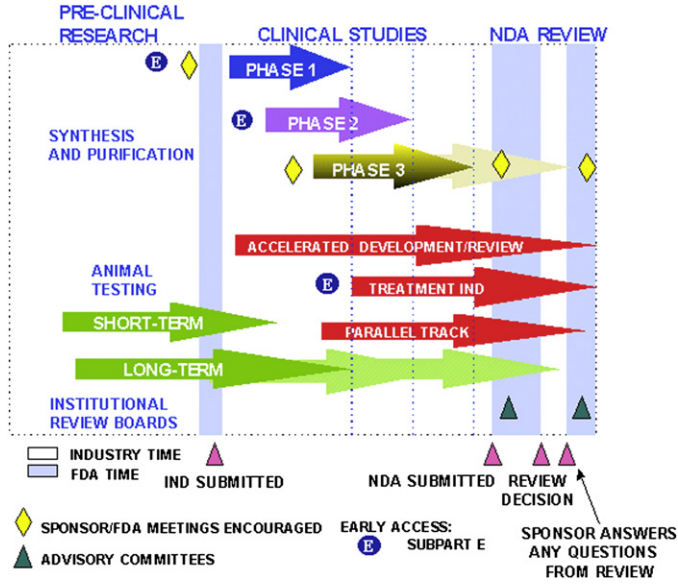

Fig. 3. The development pathway taken by sugammadex when undergoing evaluation by the Food and Drug Administration (FDA). Sugammadex was developed on a parallel track, in that simultaneous studies going on in different countries were used in the submission process to the FDA. At the suggestion of the FDA, sugammadex was placed on a priority (accelerated development) track. At the final expert advisory committee review sugammadex was given a unanimous recommendation for approval. At the final hurdle, the full committee of the FDA, sugammadex was judged ''not approvable'' because of concerns about possible hypersensitivity reactions. To date sugammadex has been approved in 50 countries worldwide, but not by the FDA. IND, investigational new drug; NDA, new drug application. (This figure is in the public domain at the FDA Center for Drug Evaluation and Research.)

priority (accelerated) review status for sugammadex. A Priority Review designation is given to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A Priority Review means that the time it takes the FDA to review a new drug application is reduced. The goal for completing a Priority Review is 6 months. Subsequently, a new drug application (NDA) for sugammadex was submitted to the Advisory Committee on Anesthesia and Life Support, and in March 2008 this committee made a unanimous recommendation to the FDA that sugammadex be approved for marketing. The FDA is not bound by this committee's recommendation, but it usually carries significant weight in the final decision of the FDA.

On June 2, 2008, the European Medicines Agency (EMEA) approved sugammadex for clinical release in Europe while in the United States, the FDA decision was awaited with hopeful anticipation. Much to the surprise of those involved in the development of sugammadex, in August 2008 the FDA issued

a nonapprovable letter for sugammadex. The reasons given by the FDA for not approving sugammadex centered on concerns about possible hypersensitivity reactions in a small number of study subjects. Subsequently the EMEA re-reviewed the data and saw no reason to change their approval of sugammadex. Since then, sugammadex has been approved in more than 50 countries but remains "not approvable" in the United States, to date the only country that has failed to grant approval when requested. Since the start of development of sugammadex Organon was acquired by Schering-Plough, which was in turn taken over by Merck & Co. The new owner seems committed to continue production and promotion of sugammadex.

THE PRESENT

Before its clinical release we knew that sugammadex, unlike neostigmine, worked well against all degrees of block [13], was unaffected by the use of vapor anesthesia [14], and was free of cardiovascular effects [15]. We knew also that part of its effectiveness was because it inactivated not only the rocuronium in the circulation, but diffused into the neuromuscular junction and inactivated the rocuronium in the area of the acetylcholine receptors themselves [16]. Since its release, sugammadex has been used in a much wider variety of patients than was possible in the clinical trials, and our knowledge of its utility has grown commensurately. As suggested by the clinical trials, it has proved to be effective at reversing all degrees of rocuronium-induced block [17–19].

The difference in efficacy between sugammadex and neostigmine is most noticeable when reversing deep block. Fig. 4 shows a comparison of sugammadex and neostigmine given when only 2 posttetanic twitches are present. Recovery to a TOF ratio of 0.9 or greater was less than 3 minutes in the patient who received sugammadex (4 mg/kg) and greater than 60 minutes in the patient who received neostigmine (70 μg/kg) [20]. Since its widespread release, sugammadex has shown itself effective in a wide variety of clinical situations that were not specifically studied during its development phase.

Sugammadex in specific patient groups

We now know that sugammadex works well both in the elderly [21,22] and in children [23]. It is both efficacious and safe in patients with renal failure [24] or severe cardiac disease [25], and has little effect on the QTc interval [26]. Patients having electroconvulsive therapy require paralysis of rapid onset and short duration, for which succinylcholine has traditionally been the drug of choice. The combination of paralysis with rocuronium and reversal with sugammadex provides both fast onset and rapid recovery, and works well for these patients [27,28]. Rapid reversal of block can be useful in other situations also; for example, sugammadex can rapidly reverse rocuronium during spine surgery to allow for intraoperative neurophysiological monitoring [29].

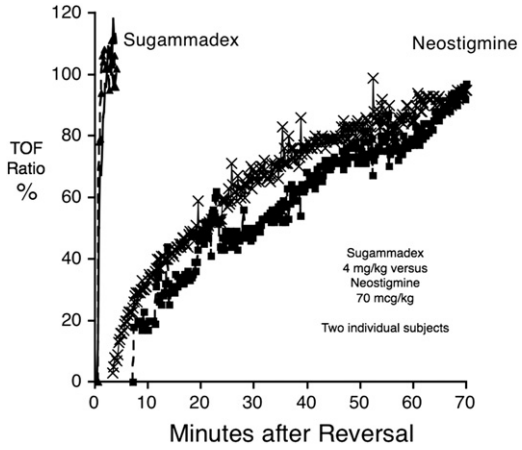

Fig. 4. The response in two patients given reversal when there was one posttetanic response. One patient received sugammadex, 4 mg/kg and recovered to a TOF ratio of 0.9 within 3 minutes. The other patient received neostigmine, 70 μg/kg, and took well over an hour to reach a similar level of recovery. This example illustrates that maintaining deep block with rocuronium until the end of the surgical procedure is feasible only if sugammadex is available. (*Data from* Jones RK, Caldwell JE, Brull SJ, et al. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. Anesthesiology 2008;109:816.)

Sugammadex in patients with neuromuscular disease

Patients with myasthenia gravis are exquisitely sensitive to nondepolarizing blocking drugs, and are at significant risk of inadequate reversal. Sugammadex works very effectively to rapidly restore neuromuscular function in patients with myasthenia gravis paralyzed with rocuronium [30,31]. Response of patients with neuromuscular disease can be difficult to predict, and block difficult to reverse. Because sugammadex results in almost immediate elimination of free and, hence, active rocuronium, the patient is restored to the baseline (prerelaxant) state. This approach has proved useful in the management of patients with myotonic dystrophy [32] and transverse myelitis [33].

Rapid reversal after high-dose rocuronium

Clinicians have always had some degree of trepidation when administering large doses of rocuronium for rapid sequence intubation (RSI), because the patient would remain paralyzed for a considerable length of time and would not recover spontaneous ventilation soon enough to prevent desaturation if their airway could not be managed adequately [34,35]. The availability of sugammadex offers some degree of comfort in the RSI situation. Even high-dose (1.2 mg/kg) rocuronium can be reversed within a few minutes with 16 mg/kg of sugammadex [13]. This treatment does not guarantee recovery of

spontaneous ventilation in the "cannot intubate, cannot ventilate" situation, but it will guarantee rapid recovery of neuromuscular function, which can only be to the patient's benefit [36–38]. Such rapid recovery from neuromuscular block was not possible before the introduction of sugammadex, not even with succinylcholine [39].

A special case of RSI is in women having general anesthesia for cesarean section. Succinylcholine has traditionally been the neuromuscular blocking drug used to facilitate rapid tracheal intubation in these patients. Opinion is now shifting toward the use of rocuronium in this situation [40]. A short series of 7 cases showed that while rocuronium, 0.6 mg/kg was sufficient for rapid tracheal intubation, it resulted in significant residual block at the end of the procedure. In all patients the residual paralysis was rapidly reversed with sugammadex, 2 mg/kg [41].

Sugammadex and adverse events

There have been few serious adverse events reported for sugammadex. In one study with 13 volunteers, 96 mg/kg was administered [42], which is 48 times the normal clinical dose and 6 times the maximum clinical dose. One of the volunteers experienced symptoms suggestive of hypersensitivity. A Cochrane meta-analysis found no evidence of a higher rate of adverse events than with placebo [18,43]. To date there has been only one report of a patient who had an apparent allergic reaction to sugammadex, 3.2 mg/kg [44]. An interesting twist on allergic responses is that sugammadex may be useful in the treatment of rocuronium-induced anaphylaxis [45,46].

Given its record of efficacy and safety, one would expect that sugammadex would have replaced neostigmine for routine reversal of rocuronium-induced block. Unfortunately this has not happened, for one overwhelming reason: the price. It appears that the company made a strategic marketing decision to go for a high profit margin on a low volume of sales. This approach has severely limited the use of sugammadex. In Australia, the cost of sugammadex is approximately $1 per milligram. In the United Kingdom, RSI with rocuronium, 1.2 mg/kg followed by sugammadex, 16 mg/kg is 170 times more expensive than using succinylcholine. Because of the high cost, most countries where sugammadex is approved have restricted its use. A quote from the Scottish Medicines Consortium (SMC) illustrates the point: "Sugammadex is not recommended for the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults, children and adolescents as the manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC." A cost-effectiveness analysis suggests that sugammadex can be justified only for use in specialized or emergency situations [47,48].

Because of its high cost, a 200-mg vial costs 78 euros in Germany, 58 pounds in the United Kingdom, and 200 dollars in Australia. Some clinicians have even advocated using very small doses of sugammadex, 0.22 mg/kg, in combination with neostigmine to reverse shallow degrees of residual

block [49]. This approach minimizes cost but introduces other potential problems such as using a single-dose vial for multiple patients, and use of several drugs instead of one. There is no doubt that the cost of sugammadex is prohibitive and prevents its more widespread use. Perhaps this situation might change if and when sugammadex becomes a generic drug. The next section outlines the author's personal predictions for what the future might hold if the cost of sugammadex is decreased to a point where it becomes the routine drug for reversal.

THE FUTURE

There are two major questions hanging over the future of sugammadex. One relates to its use in the United States and whether the FDA will eventually approve the drug. The other is what will happen with the pricing of the drug in those countries where it can be used.

The FDA and sugammadex

The reason given by the FDA for not approving sugammadex was concern about possible hypersensitivity reactions. It is unclear what, if anything, will persuade the FDA to change its opinion and approve the drug. The use of sugammadex around the world has not raised any red flags regarding adverse events. In the United States, a study specifically looking at hypersensitivity, the "Sugam-madex Hypersensitivity Study (Study P06042)," ClinicalTrials.Gov identifier NCT00988065, has been completed and results are awaited. It is hoped that the FDA will be persuaded to approve sugammadex, and the only concern then will be how the drug is priced.

Sugammadex and cost

If Merck & Co. replicates its current international pricing policy in the United States, sugammadex will cost about $100 for a 200-mg vial [48,49], which is approximately 25 times the cost of reversal with neostigmine and glycopyrrolate [50]. Because the recommended dose for routine reversal when there are 1 or 2 TOF responses is 2 mg/kg, the 200-mg vial will be sufficient for one patient only. Can a cost-benefit case be made for sugammadex at this price?

If the benefit is so great that cost is not an issue then a case can certainly be made. The cost of sugammadex can be justified in cases where no other form of reversal is available. An example would be rapid reversal of rocuronium or vecuronium to restore spontaneous ventilation when airway control cannot be established, the so-called rescue reversal [38,47,51]. Another example might be treating the respiratory failure that occurs when drugs such as magnesium are given in the setting of residual neuromuscular block in the postanesthesia care unit [52]. In a similar vein, sugammadex cost can also be justified if it allows patients to avoid admission to an intensive care unit. For example, a patent whose trachea would remain intubated because of inadequate reversal of block with neostigmine might be given sugammadex and be extubated, and have a less morbid postoperative course [53]. These situations, however,

represent only a small fraction of clinical practice. Can sugammadex be justified in more routine practice?

To justify its increased cost, sugammadex would have to decrease expenses in some other area. The single most effective way to decrease cost is to save operating-room time. Whether or not sugammadex can be justified will depend on the cost of the time saved, and how much time can be saved. The cost per minute of operating-room time in the United States is somewhere between $15 and $20 per minute [54]. In theory, if the use of sugammadex reduces operating-room time by 5 minutes it might have paid for itself. For routine reversal from 2 TOF responses, sugammadex produces recovery of TOF ratio = 0.9 in 1.5 minutes versus 18.6 minutes for neostigmine. On the surface this looks like it should justify the cost of sugammadex; however, this is not the whole story.

Most clinicians do not measure the TOF ratio, and extubation is based on clinical criteria. Studies show that the TOF ratio is less than 0.7 when the trachea is extubated at the end of surgery, and in this situation the time advantage of sugammadex over neostigmine is significantly decreased [55]. In addition, tracheal extubation would need to be the rate-limiting step in the time taken to leave the operating room, which usually is not the case. Finally, the full cost of the decreased time would have to be saved, and this is not a realistic expectation [48,56]. If sugammadex is released in the United States with a pricing structure similar to that for other countries, it will be difficult to justify its routine use with simply a cost-benefit analysis.

Justifying sugammadex: quality and safety

There is another argument to justify the use of sugammadex, and that is on the basis of quality and safety. An irreducible incidence of residual neuromuscular block is an inevitable consequence of a reversal strategy based on anticholinesterase drugs [57]. This residual block is not benign, and has measurable adverse effects on the airway and other muscle groups [5–7]. Residual neuromuscular block per se is associated with adverse patient outcomes [5,58,59]. There is even evidence that recovery to a TOF ratio to the new minimum standard of 0.9 leaves patients with measurable impairment of muscle function [60]. The only way to eliminate residual block after administration of rocuronium (or vecuronium) is with sugammadex. It is very difficult to quantify hard cost savings by the elimination of residual block. However, if we assume that it is possible for the use of sugammadex to become routine, then what effect might that have on our practice?

We can maintain profound block until the end of the procedure

Rocuronium will allow profound block to be maintained until the very end of the surgical procedure. Because until now it has been impossible to rapidly reverse deep block, it is a common clinical situation for the surgeon to be requesting a deeper level of muscle relaxation and the anesthesia provider being reluctant to provide this in case reversal proves difficult. There is validity to both sides of the argument. This situation in theory should no longer be

a problem because greater doses of rocuronium can be administered and a deeper level of block maintained throughout the procedure. For anesthesia providers, this will require some changes in practice and relearning their techniques of drug administration.

Because of the deeper level of block, parameters for monitoring will also have to change. Because there are no clinically available methods to monitor the diaphragm, clinicians who use nerve stimulators will need to become familiar with using the posttetanic count at the adductor pollicis [61]. However, many anesthesia providers do not use a nerve stimulator and their drug administration has been guided by their experience, clinical acumen, and familiarity with the surgeon's practice [62]. To run deeper levels of block without using a nerve stimulator will require relearning their drug-dosing paradigms.

Sugammadex will allow precise control of rocuronium duration

Sugammadex will allow the duration of action of rocuronium to be precisely tailored to match the clinical needs of any procedure, short or long. An example might be short procedures that require tracheal intubation. Previous possible approaches were to intubate without using a muscle relaxant [63–65], to use succinylcholine, or a small dose, 0.3 to 0.5 mg/kg, of rocuronium [66,67]. Intubating without a relaxant was able to be performed effectively, particularly with propofol and short-acting potent opioids, but it carried the consequence of increased incidences of hypotension and tracheal injury [68]. Succinylcholine's many side effects made clinicians wary of its use, and in pediatrics it should not be used for routine intubation. Finally, intubation assisted with small doses of rocuronium could result in diminished quality of intubation, and still require pharmacologic reversal [66,67]. With sugammadex, a standard intubating dose of rocuronium can be used, and its effects rapidly reversed even if the procedure lasts only a few minutes [13,69].

This exquisite control of the duration of rocuronium has even more implications. Rapid reversal of the effect of rocuronium can be achieved in the scenario of difficulty with airway management and tracheal intubation [13], and may enable rapid return of spontaneous respiration, so-called rescue reversal [51]. It can also make irrelevant the increased variability in the duration of action of rocuronium seen in circumstances such as administration of large doses, organ dysfunction, and treatment of the elderly and the severely obese [70]. Rocuronium will essentially become a drug whose clinical duration and effect can be titrated to exactly match the clinical need. Such facility with control of neuromuscular block has not been available previously.

Benefits of avoiding anticholinesterase reversal

Acetylcholinesterase inhibitors have actions not only at the nicotinic but also at the muscarinic receptors [71]. The unopposed action of neostigmine, for example, would result in severe bradycardia, copious secretions, increased

gastrointestinal motility, and bronchospasm [72]. Consequently a drug with antimuscarinic effects, usually atropine or glycopyrrolate, must accompany anticholinesterase drugs.

Even when accompanied by an antimuscarinic drug, neostigmine can result in severe bradycardia in patients with autonomic dysfunction [73], and a case of coronary artery vasospasm provoked by neostigmine has been reported [74]. The antimuscarinic drugs atropine and glycopyrrolate result in impaired parasympathetic control of heart rate with decreased baroreflex sensitivity and high-frequency variability in heart rate [75,76]. It is not always possible to balance exactly the muscarinic effects of the anticholinesterase and the dose of atropine or glycopyrrolate. As a result, changes in heart rate commonly occur with reversal [77–79]. Clinicians who might omit pharmacologic reversal because of these potential adverse effects may now be comfortable reversing the rocuronium effect with sugammadex.

Other concerns with the use of neostigmine, such as possible increase in the rate of postoperative nausea and vomiting [80] or breakdown of colonic anastomoses [81], will no longer be issues with sugammadex.

Will we still need muscle relaxants other than rocuronium?

With sugammadex the duration of rocuronium action can be tailored to any clinical situation and its rapid and complete reversal guaranteed. Does this suggest that a case be made for eliminating the use of other relaxants? It is certainly cost-advantageous for a pharmacy to decrease the number of drugs on its formulary. So what drugs might we eliminate?

The first to consider for elimination is vecuronium. Because sugammadex is less efficacious with vecuronium than rocuronium, and vecuronium has an active metabolite, there seems very little reason to keep vecuronium [82,83]. Second, the benefits of the rocuronium/sugammadex combination do not exist with the benzylisoquinolinium relaxants atracurium, cisatracurium, and mivacurium. Should the availability of sugammadex lead to the decreased use of these drugs? This question is difficult to answer, and will depend on factors such as why the clinician uses the other drug in the first place. Is it because of perceived problems with rocuronium such as variability of duration, or concern over possible severe allergic reactions? Sugammadex can remove the former objection to rocuronium, but not the latter.

Before sugammadex, cisatracurium had an advantage over rocuronium in that it had a less variable duration of action [70,84], and its recovery was less affected by impaired organ function. The availability of sugammadex will eliminate these advantages. In a direct comparison, reversal with sugammadex-rocuronium was almost 5 times faster than with the cisatracurium-neostigmine combination, 1.9 versus 9.0 minutes [85]. There is one situation in which it may be necessary to retain the availability of cisatracurium. If, after reversal of rocuronium with sugammadex, a patient needs to be urgently reintubated, then cisatracurium can be used because is not affected by sugammadex.

Mivacurium is still in common use in some countries, mostly because of its short duration of action [86,87]. However, even with its short duration of action mivacurium can have a high incidence (about 10%) of residual block unless its action is pharmacologically reversed [88]. In comparison, rocuronium already has faster onset than mivacurium, and with the use of sugammadex it can be made to have a short duration of action, thus to be free of residual block and the adverse effects of anticholinesterase reversal. Potentially, therefore, with the exception of cisatracurium for urgent reintubation, benzylisoquinolinium drugs could be eliminated from clinical use.

Will we still need succinylcholine?

To answer this question requires that we define why succinylcholine is necessary in the first place. To begin, succinylcholine is unique in having a fast onset and short duration of action. Second, no other relaxant provides better conditions for tracheal intubation, although rocuronium in large doses (1.2 mg/kg) is almost as good [89,90]. Finally, succinylcholine dosing is flexible and there is little penalty in terms of prolonged duration for using increased doses. Because of these attributes, succinylcholine has been used for RSI, intubation for short procedures, intubation for longer procedures whereby no further relaxation is required, and intubation in patients for whom dose calculations for rocuronium are difficult, for example, the morbidly obese [91].

The advent of sugammadex has rendered succinylcholine redundant for essentially all of these situations. For RSI, a large dose of rocuronium can be used with similar quality of intubation as succinylcholine [90], and without risk of prolonged duration [13,69]. Procedures, either short or long, requiring paralysis just for tracheal intubation are amenable to use of rocuronium [69,92]. It is difficult to see where succinylcholine will be needed except in one circumstance, the same as already described for cisatracurium, that is, reintubation after reversal with sugammadex. In conclusion, succinylcholine will continue to have a place, but one that is much diminished where rocuronium and sugammadex are used.

Implications of sugammadex for neuromuscular function monitoring

There are two principal indications for neuromuscular monitoring: one is to guide intraoperative dosing of relaxant, the second is to assess adequacy of reversal. For the first, where monitoring is used, the tactile TOF count at the adductor pollicis has been standard practice for many years. However, if sugammadex promotes the use of deeper levels of block, the TOF response is an inadequate monitoring modality for monitoring of this deeper block [61].

Compared with the adductor pollicis, the diaphragm and larynx require a plasma concentration 1.6 to 1.8 times higher to achieve the same level of block [93–95]. This concentration of relaxant will completely abolish the TOF responses at the thumb, so the posttetanic count (PTC) will need to be used [61]. This stimulation modality is available on all modern nerve stimulators for operating-room use, and allows the clinician to monitor the depth of block required for paralysis of the diaphragm and larynx. The PTC can also

guide sugammadex administration at the end of the procedure. If only 1 or 2 posttetanic responses are present, the appropriate dose of sugammadex is 4 mg/kg [20,96].

Despite the many recommendations by experts that encourage the use clinical neuromuscular monitoring, evidence that it is of benefit in decreasing residual paralysis is lacking [97]. Monitoring can only reliably document adequate recovery if it measures and displays the TOF ratio. Clinical assessment of TOF ratio, tetanic fade, or even double-burst fade does not have the sensitivity to reliably detect TOF of below 0.7, much less below 0.9 [98].

Quantitative measurement of TOF ratio using acceleromyography (AMG) is clinically available [98], and can detect even minor degrees of residual block. Unfortunately, detecting the block does not mean that it can be reversed. If the patient already has had a full dose of anticholinesterase then no more can be done to accelerate recovery [2]. How will sugammadex alter neuromuscular monitoring? The answer is that the cost of the drug will possibly drive monitoring at the end of the case to determine the minimum dose that can be given to achieve an acceptable degree of recovery, for example, TOF ratio = 1.0 [48,50,56,99,100].

Sugammadex dosing recommendations

The recommendations for dosing sugammadex are 2 mg/kg at 2 TOF responses, 4 mg/kg for a level of 2 posttetanic responses, and 16 mg/kg for immediate reversal of a large dose of rocuronium (Table 1). If the drug is very expensive, clinicians may start to titrate their dosing against the TOF recovery on the AMG and stop administration when the TOF ratio is 1.0. In doing this they need to keep in mind that if underdosed, sugammadex will not be effective [101]. Alternatively, if cost is not an issue, clinicians will simply administer a large dose, confident in the drugs affect, and not monitor reversal at all. Sugammadex could conceivably eliminate the need for monitoring of reversal in patients receiving rocuronium [102].

Table 1
Dose recommendations and estimated cost of sugammadex in different clinical reversal scenarios

Scenario	Sugammadex dose (mg/kg)	Number of vials (200 mg) (for 80 kg patient)	Estimated cost in US$ (50 cents/mg)
PTC = 1 or 2	16	7	700
PTC = 1 or 2	4	2	200
TOF count = 1 or 2	2	1	100
TOF count = 4	1	1 (0.5)	50[a]
TOF ratio ≥0.5	0.22	1 (0.2)	20[a]

Abbreviations: PTC, posttetanic count; TOF, train-of-four.
[a]Cost estimate is for contents of one 200-mg vial of sugammadex divided up between several patients.

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