Sugammadex: a novel neuromuscular blocker binding agent

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Purpose of review

Sugammadex is a novel drug that binds selected neuromuscular blocking drugs and prevents them from acting at the neuromuscular junction. Due to its rapid onset and relative lack of side effects, this drug promises to change the method of anesthesia delivery. This review summarizes the literature on the drug and addresses some of the potential changes that it may bring.

Recent findings

Currently in phase III clinical trials, sugammadex has been shown to be safe and efficacious in small animal and human study groups and is now undergoing wider clinical testing to secure FDA approval for general use.

Summary

Sugammadex binds neuromuscular blocking drugs and encapsulates them, making cholinesterase inhibitors unnecessary. Its rapid reversal of blockade makes it possible to keep patients profoundly muscle relaxed until drapes come down and it can enable a rapid return to spontaneous ventilation in a 'cannot intubate, cannot ventilate' situation. Costs and date of availability have yet to be determined.

Keywords

cyclodextrin, neuromuscular blockade reversal, sugammadex

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Abbreviation

NMBD neuromuscular blocking drug

0952-7907

Introduction

Sugammadex is a modified cyclodextrin developed by Organon (Oss, the Netherlands) designed to encapsulate aminosteroid nondepolarizing muscle relaxing agents. It was first mentioned in the medical chemical literature in 2002 [1]. Since then, it has been successfully tested in animals [1–7] and humans [8–10,11••]. It has been shown to be well tolerated and effective in humans [10], and the dose response curve has been established [8]. Phase 3a trials have been completed and phase 3b trials are reported to be starting soon. While availability has yet to be officially announced, it is rumored to be in the first quarter of 2008.

Background

Cyclodextrins are large molecules of various numbers (eight in the case of a γ cyclodextrin) of glucose molecules bound in a ring-like structure. This creates a hydrophilic outer layer with a lipophilic inner core. This molecule forms a complex with quaternary ammonium compounds after using its negatively charged molecules to draw in the positively charged nitrogen atom found on rocuronium and other aminosteroid nondepolarizing muscle relaxants. The cyclodextrins are prepared by reacting a thiol with the per-6-bromo-γ-cyclodextrins using thiourea followed by ethanolamine. This forms a host molecule with an internal cavity diameter of 7.5–8.3 Å, which allows accommodation of the large rocuronium molecule [1].

The case for neuromuscular blocker drugs

A review of the need for neuromuscular blocker drugs (NMBDs) may be in order. While intubation can be accomplished by profound anesthesia, NMBDs have been shown to improve intubating conditions. Additionally, the incidence of postoperative hoarseness and vocal cord injury is decreased when NMBDs are used. Subjectively, NMBDs improve surgical exposure, especially during abdominal surgery. Finally, during certain surgeries where even the slightest movement may be detrimental, such as eye or intracranial surgeries, NMBDs can prevent inadvertent damage to tissues [12].

The downside of neuromuscular blocker drugs

While the need for NMBDs has been demonstrated, there are potential detrimental effects as well. The most deadly instance of such effects is a 'cannot ventilate, cannot intubate' situation. Succinylcholine has been the drug of choice for rapid sequence induction for many years due to its rapid onset. Due to its depolarizing effects

and subsequent increase in serum potassium, however, other drugs have been sought to replace it. Rocuronium has been billed as a replacement, with onset nearly as fast as succinylcholine without fasciculation. At 1.2 mg/kg, onset is less than 1 min [13] but recovery of T1 can be greater than 40 min [14]. While the ability to recover from succinylcholine in time to begin spontaneous respirations in a 'cannot intubate, cannot ventilate' situation is theoretically possible, it is not possible if rocuronium is used given this long recovery time. Sugammadex may help return the patient to spontaneous ventilation in these situations.

In everyday use, nondepolarizing agents require reversal agents such as neostigmine, a pseudocholinesterase inhibitor. These reversal agents have their own side effects, such as postoperative nausea and vomiting and bradycardia. This, in turn, requires other agents to counteract these effects such as cholinergic antagonists and antiemetics.

The evidence for sugammadex

Multiple studies in both humans and animals have established the safety and clinical applicability. Below are some of the more recently published data.

Animal studies

The earliest animal work was done by Adam *et al.* in cats [1]. They showed that a rocuronium infusion quickly depressed the twitch height by ~95%. Immediately after stopping the infusion, either saline or sugammadex 1 mg/kg was injected. In the sugammadex group, near-complete recovery took approximately 1.5 min, while recovery in the saline group took 7–8 min [1].

Epemolu *et al.* [5] showed that an infusion of rocuronium in guinea pigs caused muscle relaxation. While the rocuronium infusion continued, infusion of sugammadex was begun. Twitch height quickly returned to normal. They also measured plasma concentrations of both agents. After sugammadex injection, the plasma concentration of both sugammadex and rocuronium increases. This is consistent with the mechanism of action of sugammadex pulling the rocuronium out of the extracellular space and keeping it in the plasma.

The authors of the above study were questioned in a letter to the editor regarding the ability of sugammadex to bind rocuronium on a molar basis. The questioners were able to mathematically reconstruct the number of sugammadex molecules in a given dose of the drug. They showed that on a molar basis, two to four molecules of sugammadex are required to bind each molecule of rocuronium. Since the two molecules bind each other on a one to one basis, this is presumed to be a matter of volume and physical distance necessary to allow them to interact in clinically relevant numbers [15].

In the Rhesus monkey, spontaneous recovery from rocuronium 500 μg/kg took 28 min. Recovery after sugammadex 2.5 mg/kg took 8 min. Differences in the groups were both statistically and clinically significant with an *n* of only 4 per group [3].

Further studies in Rhesus monkeys compared the ability of sugammadex to reverse the effects of rocuronium to the ability of sugammadex to reverse the effects of either mivacurium or atracurium. An infusion of rocuronium, mivacurium, or atracurium was titrated to 10% of baseline twitch height. After stopping the infusion, sugammadex was given in a dose of 1 mg/kg to all groups. Recovery in the rocuronium/sugammadex group took 1.7 min compared with spontaneous recovery from rocuronium, which took 14.4 min. Sugammadex had no effect on the recovery from mivacurium or atracurium [4].

de Boer *et al.* [2] elegantly designed a study on the half life of sugammadex in the Rhesus monkey. They first administered rocuronium 100 μg/kg and measured the depression of the first twitch height, which was found to be 93% compared with baseline. They then administered sugammadex 1 mg/kg and injected rocuronium after several different time periods and measured the effects. Fifteen minutes after sugammadex injection, rocuronium 100 μg/kg resulted in a 17% twitch height; after 30 min it was 49%, and finally after 60 min it was found to return to 79%. They concluded that the effective half life of sugammadex was 30 min.

Using liquid chromatography and mass spectrometry, Epemolu *et al.* [7] were able to show that the injection of rocuronium influenced the pharmacokinetics of sugammadex, and that the injection of sugammadex influenced the pharmacokinetics of rocuronium, as measured in guinea-pig urine. This is presumed to be due to the ability of sugammadex to chelate rocuronium.

Human studies

The first reports of sugammadex being used in a human population are from 2005.

Gijsenbergh *et al.* [10] used healthy male humans to test the safety and efficacy of the drug. They were able to show that side effects due to sugammadex were mostly mild and limited in duration. The most severe side effect was a period of paresthesia found in one patient receiving the highest dose of sugammadex (8 mg/kg), which resolved over a period of 7 days. The onset of this reaction, however, was the day after the administration of sugammadex, calling into question the causation. Other side effects included taste perversion, sense of temperature change, and a sense of abnormal smell. Efficacy was shown by giving rocuronium 0.6 mg/kg and administering sugammadex at different doses or placebo, both 3 min

after the rocuronium dose. Patients receiving placebo required between 36 and 64 min to recover. Those receiving clinical doses of rocuronium required between 1 and 13 min to recover to the same degree. As was expected, those receiving the highest doses of sugammadex recovered the most quickly. With the dosing regimen shown by Gijsenbergh *et al.* 4 min after an intubating dose of rocuronium, and only 1 min after sugammadex, patients had almost complete recovery from their blockade.

More recent work in humans was completed by Shields *et al.* [9]. Their study involved 30 healthy male volunteers given rocuronium 0.6 mg/kg. They monitored twitches and, at the return of T2, were given sugammadex at one of five doses or placebo. They demonstrated that the clinical dose range to sugammadex was between 2 and 4 mg/kg, although they were able to demonstrate significant differences between sugammadex groups and placebo groups at a dose range between 0.5 and 6 mg/kg. Shortest time to recovery was the 4 mg/kg dose and was 1.04 min. No evidence of recurarization was found and, again, side effects were mild and short lived.

In a very similar study, Sorgenfrei *et al.* [8] studied sugammadex in various escalating doses after spontaneous return to T2 twitch, after an intubating dose of 0.6 mg/kg of rocuronium. They showed that the median recovery time was 1.1 min in the group receiving 4 mg/kg sugammadex. Only one serious adverse event was reported in this group, which was hypotension. This finding was confounded, however, by the fact that the patient was given propofol and fentanyl between the sugammadex dose and the hypotensive event.

Suy *et al.* [11••] recruited healthy volunteers who were administered rocuronium (0.6 mg/kg) or vecuronium (1.0 mg/kg) and then given sugammadex in various doses after the return of the second twitch. Recovery took 1.1 min after sugammadex (4.0 mg/kg) in the rocuronium group and 1.4 min after sugammadex (8.0 mg/kg) in the vecuronium group.

Recently, Bettelli [16] discussed the need for neuromuscular blocking agents in ambulatory surgery settings. Her conclusions were that nearly all these agents, both depolarizing and nondepolarizing, have disadvantages, and the ideal agent has yet to be discovered. Succinylcholine has the advantage of rapid onset time, but has many side effects that have been covered extensively in the literature and are well known to the practitioner [17]. It is still widely used despite extensive research into finding agents to overcome its shortcomings. Neuromuscular blocking agents often are too potent to have rapid onset time, but when given in sufficient doses to overcome this, have a time action profile that is too long to work in the ambulatory setting. Given the ability of sugammadex to overcome many of the shortcomings inherent in rocuronium, however, this combination may soon become the technique of choice in this unique setting [16].

In a recent meta-analysis, succinylcholine was shown to be superior to high-dose rocuronium for providing excellent intubating conditions and avoiding unacceptable intubating conditions in emergency airway settings [18•]. In burn victims, however, or patients with high serum potassium levels, or those with abnormal pseudocholinesterase, succinylcholine may be contraindicated. In situations where a return to spontaneous ventilation should remain an option, rocuronium followed by sugammadex may be the best choice.

Conclusion

In conclusion, sugammadex is a novel drug currently under FDA testing for use as a reversal agent for rocuronium and other neuromuscular blocking agents. It has been shown to be safe in humans at doses up to 8 mg/kg, and to have no serious side effects in the small studies conducted thus far. In certain settings, such as outpatient surgery and emergency airway situations, sugammadex provides the practitioner with a previously unavailable tool and can improve patient safety. Pricing and availability have yet to be officially announced by the manufacturers of sugammadex.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 390).

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