A novel neuromuscular blocker binding agent - Sugammadex

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Citation

R Garg, J Dali. *A novel neuromuscular blocker binding agent - Sugammadex*. The Internet Journal of Anesthesiology. 2007 Volume 18 Number 1.

Abstract

A novel approach to reversing neuromuscular blockade is sugammadex (Org 25969). It acts by rapidly encapsulating steroidal NMBDs to form a stable complex at a 1:1 ratio and thus decreasing the free concentration of the drug from the plasma. The encapsulated complex of sugammadex and NMBD are freely filtered by the glomerulus into the urine. The dose-dependency can be readily explained by the need to bind more rocuronium in plasma as blockade becomes deeper. Sugammadex could solve the problems of residual paralysis and failed intuba¬tion. In view of the potential of sugammadex to reverse even a profound NMB, and its favorable safety profile, this agent may fulfill the criteria of an ideal reversal agent for rocuronium. Continued safety and efficacy for this promising agent will be confirmed in future clinical studies.

INTRODUCTION

Steroidal neuromuscular blocking agents (NMBD), such as rocuronium, are widely used in clinical anesthesia and emergency medicine to facilitate tracheal intubation and artificial ventilation [1]. Reversal of neuromuscular blockade is important for the acceleration of patient recovery and prevention of postoperative residual neuromuscular blockade [1,2,3]. Currently, the reversal of neuromuscular blockade is achieved by the administration of acetylcholinesterase inhibitors (neostigmine, edrophonium, or pyridostigmine) [1].

Acetylcholinesterase inhibitors, however, have some problems with their use [4]. Early or “escape” reversal after a short case or an unexpected cannot intubate, cannot-ventilate scenario using neostigmine is limited [4,5]. The inability of cholinesterase inhibitors to reverse a profound nondepolarizing blockade may be one important reason for the unrelenting persistence of succinylcholine in current anesthetic practice, in particular for its two principal indications, relaxation for rapid sequence induction and ultrashort procedures [5]. In addition, acetylcholinesterase inhibitors have effects associated with stimulation of the muscarinic receptors resulting in bradycardia, arrhythmias, increased secretions and contraction of smooth muscle, though these can be counteracted by coadministration of muscarinic antagonists (atropine or glycopyrrolate) [1,4,6,7]. However, muscarinic antagonists also have side effects (blurred vision, dry mouth, and tachycardia) [1].

Few studies have attempted to explore the potential of nonclassic reversal drugs [8]. In this regard, suramin, a P_2-purinoceptor antagonist, can reverse nondepolarizing neuromuscular blockade , but it has serious side effects that render it inapplicable for routine clinical use [8].In contrast, purified human plasma cholinesterase has been shown to be an effective and safe drug in antagonizing mivacurium-induced neuromuscular blockade [8]. Similarly, cysteine has been shown to reverse the neuromuscular blocking effects of gantacurium. Notably, both purified human plasma cholinesterase and cysteine act independently of acetylcholinesterase inhibition [8].

There is thus a clear need for new reversal agents with a rapid onset of action and an improved efficacy and safety profile.and having the capability to reverse neuromuscular blockade effectively, independently of its depth.

SUGGAMADEX

A novel approach to reversing neuromuscular blockade is sugammadex (Org 25969) (Su refers to sugar and gammadex refers to the structural molecule-gammacyclodextrin), a selective relaxant binding agent (SRBD), made up of a ring of eight sugars, to which negatively charged side chains were added for the purpose of binding rocuronium and other steroid-based neuromuscular blocking agents [8,9,10].

MECHANISM OF ACTION

Sugammadex is inert chemically and does not bind to any

receptor. It acts by rapidly encapsulating steroidal NMBDs to form a stable complex at a 1:1 ratio and thus decreasing the free concentration of the drug from the plasma [1,8,10,11,12,16]. 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. 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 [8].

CHEMICAL STRUCTURE

NMBD are quaternary ammonium compounds with at least one charged nitrogen atom. Cyclodextrins have a lipophilic centre but a hydrophilic outer core, attributable to negatively charged ions on their surface. These negatively charged ions on the surface of sugammadex attract the positive charges of the quaternary ammonium relaxant, drawing the drug in to the central core of the cyclodextrin [13]. The binding of the guest molecule into the host cyclodextrin occurs because of van der Waal's forces, hydrophobic and electrostatic interactions. The structure of the cyclodextrin is such that all four hydrophobic rings of the steroidal relaxant fit tightly within the concentric doughnut forming an inclusion complex. This has been confirmed by calorimetry and X-ray crystallography [13]. Such a reaction occurs in the plasma—not at the neuromuscular junction—and the concentration of free rocuronium in the plasma decrease rapidly after sugammadex administration [13].

PHARMACOKINETICS

The encapsulated complex of sugammadex and NMBD are freely filtered by the glomerulus into the urine. The plasma clearance of the complex is the same as the glomerular filtration rate (120 ml/min) [13]. No dissociation of this tightly knit complex occurs in the plasma.

The main difference in the pharmacokinetic profile of sugammadex and rocuronium is that the clearance of sugammadex is approximately three times lower than that of rocuronium [5]. In the absence of sugammadex, rocuronium is eliminated mainly by excretion into bile and feces. In the presence of sugammadex, however, urinary excretion of the rocuronium–sugammadex complex is the major route of elimination of rocuronium [5,7]. Interestingly, shortly after administration of sugammadex, the total plasma concentration of rocuronium increases. This can be explained by redistribution of free rocuronium from the peripheral compartments back to plasma as a result of the decreased free plasma concentration [5]. Redistributed free rocuronium is largely encapsulated by sugammadex, thus increasing the total rocuronium concentration.

SUGGAMADEX AND INVESTIGATION TRIALS

Sacen et al [6] did their study on 60 patients undergoing elective surgery with a desflurane–remifentanil–rocuronium anesthetic technique who received either sugammadex, 4 mg/kg IV, edrophonium, 1 mg/kg IV and atropine, 10 μg/kg IV, or neostigmine, 70 μg/kg IV and glycopyrrolate, 14 μg/kg IV for reversal of neuromuscular blockade at 15 min or longer after the last dose of rocuronium using train-of-four (TOF) responses. They found that although the initial twitch heights (T_1) at the time of reversal were similar in all three groups, the time to achieve TOF ratios of 0.7 and 0.9 were significantly shorter with sugammadex (71 ± 25 and 107 ± 61 s) than edrophonium (202 ±171 and 331 ± 27 s) or neostigmine (625 ± 341 and 1044 ±590 s). All patients in the sugammadex group achieved a TOF ratio of 0.9 ≤5 min after reversal administration compared with none and 5% in the edrophonium and neostigmine groups, respectively. They concluded that Sugammadex, 4 mg/kg IV, more rapidly and effectively reversed residual neuromuscular blockade when compared with neostigmine (70 μg/kg IV) and edrophonium (1 mg/kg IV). In contrast to Sorgenfrei et al. [7], they found no evidence of a hypotensive effect due to sugammadex when it was administered under steady-state anesthetic conditions [6].

In contrast to propofol, sevoflurane enhances the effects of some NMBDs, including rocuronium [10]. Xue et al [14], Kim et al [15] showed that sevoflurane can significantly prolong the duration of action of rocuronium and the time to recovery. These effects are not seen with either propofol or isoflurane. Vanacker et al [10] investigated whether sugammadex, is equally effective at reversing rocuronium-induced neuromuscular block in patients under propofol or sevoflurane anesthesia. After receiving propofol for induction, patients were randomized to propofol (n = 21) or sevoflurane (n = 21). Rocuronium 0.6 mg/kg was administered for tracheal intubation. At reappearance of the second twitch of the TOF ratio, sugammadex 2.0 mg/kg was administered. Mean recovery time for recovery of train-of-four ratio to 0.9 was 1.8 min after both propofol and sevoflurane anesthesia.

Sugammadex is reported to be effective and well tolerated in

healthy volunteers and surgical patients at doses up to 16.0 mg/kg [11] . Additionally, sugammadex at doses of 2.0–4.0 mg/kg has been shown to safely reverse moderate neuromuscular block induced by rocuronium in a dose-dependent manner. Groudine et al [11] enrolled 50 patients into a Phase II dose-finding study of the efficacy and safety of sugammadex. Subjects, anesthetized with nitrous oxide and propofol, were randomized to one of two doses of rocuronium (0.6 or 1.2 mg/kg) and to one of five doses of sugammadex (0.5, 1.0, 2.0, 4.0 or 8.0 mg/kg). Sugammadex was administered during profound block when neuromuscular monitoring demonstrated a posttetanic count of one or two. They concluded that the mean time to recovery decreased with increasing doses. Sugammadex doses of1.0 mg/kg did not bind sufficient rocuronium to rapidly reverse a profound NMB. Doses ≥2 mg/kg of sugammadex consistently resulted in a TOF ratio ≥0.9 in 15 min or less. Increasing the dose from this level resulted in faster reversal [11] .This may indicate that sugammadexat doses of 0.5–1.0 mg/kg does not reliably bind sufficient rocuronium to produce complete reversal of the NMBD[17]. A molecule of sugammadex (molecular weight 2178) is approximately 3.6 times heavier than a molecule of rocuronium (molecular weight 610) [11] . This would suggest that a dose of 1.8 mg/kg of sugammadex would be required bind all the rocuronium in a 0.5 mg/kg dose [11] .

Boer et al [1] investigated the efficacy and safety of sugammadex in reversing rocuronium-induced profound neuromuscular blockade at 5 min in 45 patients. Anesthesia was induced and maintained with propofol and an opioid. Profound neuromuscular blockade was induced with 1.2 mg/kg rocuronium bromide. Sugammadex (2.0, 4.0, 8.0, 12.0, or 16.0 mg/kg) or placebo (0.9% saline) was then administered 5 min after the administration of rocuronium. They concluded that increasing doses of sugammadex reduced the mean recovery time from 122 min (spontaneous recovery) to less than 2 min in a dose-dependent manner. This study showed that, compared with spontaneous recovery, sugammadex produces rapid and effective reversal of profound rocuronium-induced neuromuscular blockade, without signs of residual or recurrence of neuromuscular blockade. Increasing the dose of sugammadex up to 16 mg/kg reduced the mean recovery time to a TOF ratio of 0.9 from 122.1 min (spontaneous recovery to less than 2 min). A clear dose– response relation between the time from start of administration of sugammadex and recovery of the TOF ratio to 0.9 was seen [1] .

Suy et al [16] explored the dose–response relation of sugammadex rocuronium (0.60 mg/kg) and vecuronium (0.1 mg/kg) in 80 patients. Compared with placebo, sugammadex produced dose-dependent decreases in mean time to recovery for all train-of-four ratios in the rocuronium and vecuronium groups. The mean time for recovery of the TOF ratio to 0.9 in the rocuronium group was 31.8 min after placebo compared with 3.7 and 1.1 min after 0.5 and 4.0 mg/kg sugammadex, respectively. The mean time for recovery of the train-of-four ratio to 0.9 in the vecuronium group was 48.8 min after placebo, compared with 2.5 and 1.4 min after 1.0 and 8.0 mg/kg sugammadex, respectively. They concluded sugammadex rapidly reversed rocuronium- or vecuronium-induced neuromuscular block at reappearance of the second muscle twitch. A dose–response relation was observed with sugammadex for reversal of both rocuronium- and vecuronium-induced neuromuscular block.

Sorgenfrei [7] investigated 27 subjects, randomized to receive placebo or sugammadex (0.5, 1.0, 2.0, 3.0, or 4.0 mg/kg) for reversal of 0.6 mg/kg rocuronium– induced neuromuscular block. Anesthesia was induced and maintained using intravenous fentanyl and propofol.. Sugammadex or placebo was administered at reappearance of T_2 of the TOF. Sugammadex decreased 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. Doses of sugammadex of 2.0 mg/kg or greater reversed rocuronium induced neuromuscular block within 3 min. A median of 59–77% of sugammadex was excreted unchanged in the urine within 16 hr, mostly in the first 8hr. Sugammadex increased the proportion of the rocuronium dose excreted unchanged in the urine (from a median of 19% in the placebo group to 53% in the 4.0-mg/kg group within 16 h). No evidence of recurarization was observed in any patient. They concluded that at doses of 2.0 mg/kg or greater, sugammadex safely reversed 0.6 mg/kg rocuronium–induced neuromuscular block in a dose-dependent manner. Sugammadex enhanced renal excretion of rocuronium and was excreted unchanged by the kidneys.

While sugammadex appears to be superior and an outstanding SRBA, the case report by Eleveld et al. [17] reminds us that all drugs have a dose–response type of pharmacology. They administered a very small dose of sugammadex (0.5 mg/kg) for a rocuronium neuromuscular block (0.9 mg/kg). Although reversal was initially successful, the neuromuscular block partially reappeared [18] .

Cammu et al [12] investigated the single i.v. doses of sugammadex 16, 20, or 32 mg/ kg administered simultaneously with 1.2 mg/kg rocuronium or 0.1 mg/kg vecuronium to 12 anaesthetized (with propofol/remifentanil) and non-anaesthetized healthy volunteers. They found, rocuronium/ vecuronium plasma concentrations declined faster than those of sugammadex. They concluded that single-dose administration of sugammadex 16, 20, or 32 mg/kg in combination with rocuronium 1.2 mg/kg or vecuronium 0.1 mg/ kg was well tolerated with no clinical evidence of residual neuromuscular block, confirming that these combinations can safely be administered simultaneously to non-anaesthetized subjects.

Shields et al [4] studied 30 anaesthetized patients who received rocuronium 0.6 mg/kg as an initial dose followed by increments to maintain a deep block at a level of <10 post-tetanic counts recorded every 6 min. At recovery of T_2, following at least 2 h of neuromuscular block, patients received their randomly assigned dose of 0.5, 1.0, 2.0, 4.0 or 6.0 mg/ kg of sugammadex. The results showed a dose-related decrease in the average time taken to attain a TOF ratio of 0.9 from 6:49 min with the 0.5 mg/ kg dose to 1:22 with the 4.0 mg/ kg dose.They concluded that sugammadex effectively reversed a deep and prolonged neuromuscular block induced by rocuronium and recommended the effective reversal dose to be 2–4 mg/ kg.

Sparr et al [5] evaluated sugammadex for reversal of profound rocuronium-induced neuromuscular blockade in 98 patients, randomized to receive sugammadex (1, 2, 4, 6, or 8 mg/kg) or placebo at 3, 5, or 15 min after 0.6 mg/kg rocuronium. They found that the mean time to recovery of the TOF ratio to 0.9 after dosing at 3, 5, and 15 min decreased from 52.1, 51.7, and 35.6 min, respectively, after administration of placebo to 1.8, 1.5, and 1.4 min, respectively, after 8 mg/kg sugammadex. The median cumulative excretion of rocuronium in the urine over 24 h was 26% in the placebo group and increased to 58–74% after 4–8 mg/kg sugammadex. The mean plasma clearances of sugammadex and rocuronium were 0.084 and 0.26 l/min, respectively. They concluded that sugammadex safely reversed profound neuromuscular blockade induced by 0.6 mg/kg rocuronium in a dose-dependent manner. Sugammadex enhanced the renal excretion of rocuronium, and its clearance is approximately one third that of rocuronium.

Hunter et al [13] mentioned that aminosteroid agents other than rocuronium do not interact as tightly with sugammadex, but animal and human studies suggest that if larger doses of the cyclodextrin (at least 4 mg/kg) are given when T_2 has reappeared, vecuronium can be adequately antagonized. At this early stage, it does seem that sugammadex would need to be given in even larger doses to be efficacious in reversing pancuronium [13] . In contrast, and importantly, sugammadex does not antagonize residual block induced by the benzylisoquinolinium relaxants such as atracurium and mivacurium because of more bulky benzylisoquinolinium structures [13] .

DOSE

The dose-dependency can be readily explained by the need to bind more rocuronium in plasma as blockade becomes deeper. Thus, even after the introduction of sugammadex, neuromuscular monitoring will be useful, allowing the right dose to be chosen. The alternative would be to give a large sugammadex dose for all cases, a more expensive course of action than monitoring [9] .

The other question that needs to be answered relates to the possibility of re-paralysis. If the dose of sugammadex given is just enough to capture most of the rocuronium in plasma, then there will be sufficient movement of rocuronium away from the neuromuscular junction down the concentration gradient of free drug into plasma. This may produce full return of neuromuscular function. However, with time, more rocuronium molecules will be transferred from peripheral tissue into plasma, and there will no longer be enough free sugammadex molecules available [9] . The free rocuronium will then have access to the neuromuscular junction, where blockade can ensue. Another issue which needs to be tested is to administer sugammadex in divided doses: a first injection to achieve immediate recovery, and a second to make sure there is no recurarization [9] . The tendency to adopt a “one dose fits all” approach for both rocuronium and sugammadex is likely to become expensive and contrary to the patient's best interests.

ADVANTAGES

Sugammadex could solve the problems of residual paralysis and failed intubation [9] . If rocuronium is given at induction of anesthesia and the airway cannot be secured, prompt restoration of normal neuromuscular function could be achieved with the appropriate dose of sugammadex [9] . If large doses of rocuronium can be given, the surgeons may be presented with better surgical conditions with a more intense neuromuscular block, and reversal can still be accomplished, because sugammadex appears to be more reliable than

neostigmine [18] . When sugammadex becomes available, concerns about reversal of blockade at the end of a case will be diminished. Therefore, anesthesiologists may be tempted to give larger doses of rocuronium than they do now with a benefit of better intubating conditions, less delay between induction and laryngoscopy, less desaturation, less airway trauma, better surgical conditions, fewer respiratory problems at emergence, less residual paralysis.

Moreover, there were minimal effects on heart rate and arterial pressure following sugammadex administration [4] . As the drug does not act via the nicotinic receptors or by influencing the liberation or metabolism of acetylcholinesterase, there are no muscarinic side-effects associated with its use. Such effects are responsible for the side-effects observed with the use of anticholinesterase agents requiring the concomitant use of anticholinergic drugs. The anticholinergic drugs, in particular atropine, may produce undesirable tachycardia and/or arrhythmias. The absence of cardiovascular and other muscarinic effects during the process of reversal will be of great advantage in patients with cardiovascular and respiratory disease [4] .

OTHER USES

Sugammadex has been used for rescue agent in a patient of renal failure who had residual neuromuscular blockade after the use of neostigmine and had acute respiratory distress [19] .

CONCERNS

However, there are some dangers. There could be a greater incidence of awareness, because total absence of movement may mask insufficient anesthesia and analgesia [9] . Also, the problem of managing the airway after sugammadex has been given, for instance if a repeat procedure needs to be performed, is not settled [9] . Perhaps there will be a role for succinylcholine after all.

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. Further, the use of rapid-sequence induction with rocuronium can be facilitated by the presence of sugammadex. Nevertheless, studies are needed to address the role of sugammadex as a”rescue” reversal drug in patients with unanticipated difficult airways who received rocuronium.

ADVERSE EFFECTS

Few adverse effects were reported that were considered related to sugammadex. The common were nausea, vomiting [10] and QTc prolongation [5,8,10,13] , hypotension [7] , increasesd CPK levels [18] , abnormal values for microalbumin, N-acetyl-glucosaminidase, and/or microglobulin in urine [5] . The other side effects reported includes dry mouth, parosmia, a sensation of a changed temperature [8] .

QTc prolongation was attributed to sevoflurane, propofol, morphine used in these studies [10,12,13] but needs further evaluation. The other issue includes signs characteristic of insufficient depth of anesthesia, such as an increase in Bispectral Index, grimacing, moving, sucking on the tube, and coughing [5,7] . Theoretically, the anesthetic state might also be changed due to capture of fentanyl and/or propofol by sugammadex. This mechanism, however, is unlikely, because the affinity of sugammadex for narcotics and intravenous anesthetics is negligibly small. These effects may also be due to sudden reversal of neuromuscular block after administration of sugammadex combined with a surgical stimulus at a time of insufficient depth of anesthesia [5,7] . The hypotension may have been related to administration of propofol and fentanyl, rather than to sugammadex [7] .

EFFECT ON OTHER DRUGS

Sugammadex is ineffective against succinylcholine and benzylisoquinolinium neuromuscular blockers, such as mivacurium, atracurium, and cisatracurium, 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. 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.There are concerns that cyclodextrins could encapsulate other steroidal drugs and indeed endogenous steroids such as glucocorticoids, sex hormones and aldosterone [13] .

STATUS IN RENAL DYSFUNCTION

The role of sugammadex in renal compromised patient has not been studied yet. Recovery from the effect of an i.v. bolus dose of any drug occurs by redistribution, not

elimination. This is thought to be the reason why the effect of this selective relaxant binding agent in patients with renal dysfunction is unaltered [13]. Much work is still required, however, in this vulnerable patient group.

PREGNANCY AND DRUG

No study for safety profile in pregnant and lactating females has been reported till yet.

CONCLUSION

In view of the potential of sugammadex to reverse even a profound NMB, and its favorable safety profile, this agent may fulfill the criteria of an ideal reversal agent for rocuronium. Continued safety and efficacy for this promising agent will be confirmed in future clinical studies.

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