
Hemodynamic Effects of Sugammadex, a Randomized Comparison with Neostigmine-Glycopyrrolate

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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 NMBDs 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 intubation. In view of the potential of sugammadex to reverse even a profound NMB, and its favourable safety profile, this agent may fulfil the criteria of an ideal reversal agent for rocuronium.¹

Introduction:

Sugammadex (designation Org 25969, trade name Bridion) is an agent for reversal of neuromuscular blockade by the agent rocuronium in general anaesthesia. It is the first selective relaxing binding agent (SRBA) and was discovered at the Newhouse research site in Scotland. The scientists who discovered Sugammadex worked for the pharmaceutical company, Organon on January 3, 2008, Schering-Plough submitted a New Drug Application to the US Food and Drug Administration for sugammadex, but the FDA rejected the application on August 2008. It was approved for use in the European Union on July 29, 2008.

Sugammadex is a modified gamma-cyclodextrin, with a lipophilic core and a hydrophilic periphery. This gamma cyclodextrin has been modified from its natural state by placing eight carboxyl thio ether groups at the sixth carbon positions. These extensions extend the cavity size allowing greater encapsulation of the rocuronium molecule. These negatively charged extensions electrostatically bind to the positively charged ammonium group as well as contribute to the aqueous nature of the cyclodextrin. Sugammadex, binding encapsulation of rocuronium is one of the strongest among cyclodextrins and their guest molecules. The rocuronium molecule (a modified steroid) bound within sugammadex, lipophilic core, is rendered unavailable to bind to the acetylcholine receptor at the neuromuscular junction.

The main advantage of sugammadex is reversal of neuromuscular blockade without relying on inhibition of acetylcholinesterase. Therefore, it does not cause the autonomic instability produced by anticholinesterases such as neostigmine, and antimuscarinic agents such as atropine do not need

to be co-administered. Its administration is therefore associated with much greater cardiovascular and autonomic stability than the traditional reversal agents.

In addition, when a fast and short duration of muscle relaxant is required, there has been little choice previously apart from the use of suxamethonium. However, suxamethonium is not ideal, as it has some undesirable side effects, such as anaphylaxis, increasing serum potassium level and other cardiovascular properties. Since, in high doses, rocuronium has a reasonably rapid onset and now can be reversed with sugammadex, it can potentially be used instead.

(Recurarisation), a phenomenon of recurrence of neuromuscular block, may occur where the reversal agents wear off before a neuromuscular blocking drug is completely cleared. This is very unusual with all but the longest acting drugs (such as gallamine, pancurium or tubocurarine). It has been demonstrated to occur only rarely with sugammadex, and only when insufficient doses were administered. The underlying mechanism is thought to be related to redistribution of relaxant after reversal. It may occur for a limited range of sugammadex doses, which are sufficient for complex formation with relaxant in the central compartment, but insufficient for additional relaxant returning to central compartment from peripheral compartments.

Sugammadex also has some affinity for other aminosteroid neuromuscular blocking agents such as Vecuronium and Pancurium. Though sugammadex's affinity for vecuronium is lower than its affinity for rocuronium, reversal of vecuronium is still effective because fewer

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vecuronium molecules are present in vivo for equivalent blockade. Vecuronium is approximately seven times more potent than rocuronium and overall requires fewer molecules to induce blockade. Sugammadex encapsulates with a 1:1 ratio and therefore will adequately reverse vecuronium as there are fewer molecules to bind compared to rocuronium. shallow pancuronium blockade has been successfully reversed in phase III clinical trials.

A study was carried out in Europe looking at its suitability in rapid sequence induction. It found that sugammadex provides a rapid and dose-dependent reversal of neuromuscular blockade induced by high-dose rocuronium.

A Cochrane systemic review on sugammadex has been recently published by Abrishami et al.³ This review article included 18 randomized controlled trials on the efficacy and safety of sugammadex. The trial included a total of 1321 patients. The review concluded that sugammadex was shown to be more effective than placebo (no medication) or neostigmine in reversing muscle relaxation caused by neuromuscular blockade during surgery and is relatively safe. Serious complications occurred in less than 1% of the patients who received sugammadex. The results of this review article need to be confirmed by future trials on larger patient populations.

Sugammadex was generally well tolerated in clinical trials in surgical patients or healthy volunteers. In pooled analysis, the tolerability, profile of sugammadex was generally similar to that of placebo or neostigmine plus glycopyrrolate. (SU refers to sugar and GAMMADDEX refers to the structural molecule-gammacyclodextrin), a selective relaxant binding agent (SRBA), 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 binding agents.⁴⁻⁶

Sugammadex is inert chemically and does not bind to any receptor. It acts by rapidly encapsulating steroidal NMBAs to form a stable complex at a 1:1 ratio and thus decreasing the free concentration of the drug from the plasma.^{4,6-10} This creates a concentration gradient favouring 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 molecules away from neuromuscular junction back into the plasma.⁴

NMBAD are quaternary ammonium compounds with at least one charged nitrogen atom. Cyclodextrins have a lipophilic center 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.¹¹ The binding of the guest molecule into the host cyclodextrin occurs because of van der Waals forces, hydrophobic and electrostatic interactions. The structure of the cyclodextrin is such that all four hydrophobic rings of the steroidal fit tightly within the concentric doughnut forming an inclusion complex. This has been confirmed calorimetry and X-ray crystallography.¹¹ Such a reaction occurs in the plasma -----not at neuromuscular junction- and the concentration of free rocuronium in the plasma decrease rapidly after sugammadex administration.¹¹

The encapsulated complex of sugammadex and NMBD are freely filtered by the glomerulus into the urine. The plasma clearance is the same as the glomerular filtration rate (120ml/min).¹¹ No dissociation of this K_{it} 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.¹² 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.^{12,13} 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 circulation.¹² Redistributed free rocuronium is largely encapsulated by sugammadex, thus increasing the total rocuronium concentration.

The main advantages of sugammadex is that it 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 arrhythmia. 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.¹⁴

Few adverse effects were reported that were considered related to sugammadex. The common were nausea, vomiting,⁶ and QTc prolongation,^{4,6,12} hypotension,¹³ increased CPK levels,¹⁵ abnormal values for microalbumine, N-acetylglucosaminidase, and/or microglobulineim urine.¹² The other side effects reported includes dry mouth, parosmia, a sensation of changed temperature.⁴ 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 benzylquinolinium 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. There are concerns that cyclodextrins could encapsulate other steroidal drugs and indeed endogenous steroids such as glucocorticoids, sex hormones and aldersterone.¹¹

The role of sugammadex in renal compromised patients has not been studied yet. Recovery from the effects 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 relaxing binding agent in patients with renal dysfunction is unaltered.¹¹

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

Gijsenbergh et al¹⁶ have demonstrated a volume of distribution of approximately 18 L. With the volume distribution at steady state (Vdss) estimated to range from 11 to 14L (0.16-0.20 L/Kg).¹⁷ Sugammadex does not bind to plasma proteins or erythrocytes.^{13,16} It does not produce any metabolite and most of it is excreted in an unchanged form via urine within 24hrs.

An insignificant part is excreted via feces or in expired air (0.02%).¹⁷

In healthy adults, the plasma clearance of sugammadex ranges from 84 to 138 ml/min.¹⁸

It has a low penetration of the blood-brain barrier and a low placenta transfer.¹⁷

Both endogenous and exogenous steroidal molecules have a lower affinity to sugammadex because they lack the positively charged quaternary nitrogen that rocuronium and vecuronium exhibit, enabling tight bounds and thus high affinity with sugammadex. Therefore, the affinity of sugammadex for narcotics and intravenous anaesthetics is negligibly small.⁴

The sugammadex-rocuronium complex is not eliminated by hepatic metabolism; therefore, hepatic impairment does not influence its excretion. However, hepatic failure patients may have higher plasma rocuronium levels.¹⁹

For elderly patients it was found that plasma clearance, Vdss and terminal half-life were homogenous in patients over 75 years with normal renal function (creatinine clearance of >100ml/min) compared with patients of 40 years without renal failure.¹⁷

In paediatric, the variations observed in the plasma of sugammadex are analogous to those seen in adult patients.²⁰

Vdss, plasma clearance and terminal elimination half life increases with age. There is no clinical trials below 2 years.

Gender, race or body weight do not affect sugammadex or sugammadex-rocuronium complex clearance.¹⁷

For patients with severe renal impairment it was found that the clearance of sugammadex is reduced in patients with a creatinine clearance below 30ml/min by 17 fold and the elimination half life is increased by 15 fold compared with patients with any renal impairment. Nevertheless, the efficacy of sugammadex is not affected and no block reoccurrence has been observed.²¹

Other studies have not demonstrated a consistency in decreasing the plasma concentration of sugammadex in patients with severe renal impairment or in those needing dialysis.^{4,7} Therefore, it is recommended to avoid its use in such patients.

Considering the dose, it is accepted that in order to reverse shallow block, the suggested dose of sugammadex comes up to 2mg/kg.

Profound NM block demands 4mg/kg. Doses of sugammadex lower than 1mg/kg may lead to rebound of rocuronium, s effect. Higher doses of sugammadex (12-16mg/kg) are used in rescue reversal.

In children and adolescents the 2mg/kg dose is both effective and well tolerated, while, to date data regarding infants are scarce. (Reviews on Recent Clinical Trials, Volume 6, Number 3, September 2011)

Aim of the study:

To compare the hemodynamic effects of sugammadex with that of Neostigmine-Glycopyrrolate

Methods:

20 patients undergoing appendectomy surgery with a standardised sevoflurane-fentanyl-rocuronium-anesthetic technique received either Sugammadex, 4mg/kg i.v (n=10), or neostigmine, 70micro/kg i.v and glycopyrrolate, 14micro/kgi.v (n=10) for

reversal of neuromuscular blockade at 15 min or longer after the last dose of rocuronium. Mean arterial blood pressure and heart rate values were

recorded immediately before and then at 2, 4, 6, and 8 minutes after reversal drug administration.

All the patients were ASA I, males and females aged between 12 and 44 years.

Results:

Ranks

	study or control group	N	Mean Rank	Sum of Ranks
difference between BP1 and BP0	sugammadex	10	6.95	69.50
	neostigmine	10	14.05	140.50
	Total	20		
difference BP2 & BP0	sugammadex	10	7.80	78.00
	neostigmine	10	13.20	132.00
	Total	20		
difference bp3&bp0	sugammadex	10	8.20	82.00
	neostigmine	10	12.80	128.00
	Total	20		
difference bp4&bp0	sugammadex	10	9.90	99.00
	neostigmine	10	11.10	111.00
	Total	20		

Test Statistics^b

	difference between BP1 and BP0	difference BP2 & BP0	difference bp3&bp3	difference bp4&bp0
Mann-Whitney U	14.500	23.000	27.000	44.000
Wilcoxon W	69.500	78.000	82.000	99.000
Z	-2.695	-2.046	-1.744	-.456
Asymp. Sig. (2-tailed)	.007	.041	.081	.649
Exact Sig. [2*(1-tailed Sig.)]	.005 ^a	.043 ^a	.089 ^a	.684 ^a

a. Not corrected for ties.

b. Grouping Variable: study or control group

Ranks

	study or control group	N	Mean Rank	Sum of Ranks
difference of hr1andhr0	sugammadex	10	6.45	64.50
	neostigmine	10	14.55	145.50
	Total	20		
difference hr2and hr0	sugammadex	10	6.70	67.00
	neostigmine	10	14.30	143.00
	Total	20		
difference hr3 and hr0	sugammadex	10	7.50	75.00
	neostigmine	10	13.50	135.00
	Total	20		
difference hr4 and hr0	sugammadex	10	8.60	86.00
	neostigmine	10	12.40	124.00
	Total	20		

Test Statistics^b

	difference of hr1andhr0	difference hr2and hr0	difference hr3 and hr0	difference hr4 and hr0
Mann-Whitney U	9.500	12.000	20.000	31.000
Wilcoxon W	64.500	67.000	75.000	86.000
Z	-3.066	-2.876	-2.272	-1.442
Asymp. Sig. (2-tailed)	.002	.004	.023	.149
Exact Sig. [2*(1-tailed Sig.)]	.001 ^a	.003 ^a	.023 ^a	.165 ^a

a. Not corrected for ties.

b. Grouping Variable: study or control group

The collected data from the 20 patients (10 received neostigmine, and 10 received sugammadex) analyzed by using SPSS software and for comparison between the two drugs, and because of the small sized data, (10 patients in each group) and non-normally distributed data, the statistical test Mann-Whitney U test was used. (non-parametric test).

Regarding the heart rate, as seen on table 1 values, the comparison showed that the heart rate values were significantly higher at min2, min4, and min6, in neostigmine group compared with sugammadex group, P value=.002, .004, .023 respectively.

For blood pressure comparison, the values were higher significantly in min2 and min4 only for neostigmine than for sugammadex, P values=.007 and .041 respectively.

As can be seen, there were minimal effects on heart rate and mean arterial blood pressure following sugammadex administration compared to neostigmine-glycopyrrolate. 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.

Discussion:

Evaluation of changes in vital signs during the study do suggest, however, that sugammadex may be associated with fewer hemodynamic effects compared with neostigmine-glycopyrrolate.

A study done by Russo R²² included 50 patients (mean age 40-70 years), homogenous for age and ethnicity, were included. Every patient has been undergoing general anaesthesia using Ramifentanyl, propofol, and Sevoflurane. At the end of surgery, all patients were treated with sugammadex 4mg/kg administered 15 min after the last dose of muscle relaxant. The mean arterial pressure and heart rate values were recorded immediately before and 30 min after administration of sugammadex. In all patients, there were no serious changes in heart rate and blood pressure at 5, 10, and 30 min after the reversal of the block.

A study done by Karin S Khuent-Brady²³ were patients aged $\geq$ 18 years, ASA I-III and scheduled for a surgical procedure under sevoflurane/opioid anaesthesia. At the end of surgery, patients were randomized to receive either sugammadex (2 mg/kg) or neostigmine (50 micro/kg) plus glycopyrrolate (10micro/kg) i.v.

Mean values for systolic and diastolic blood pressure and heart rate from the screening visit to the post anaesthetic were similar in both treatment groups. Higher mean diastolic pressure at 2min post dose with neostigmine (64 vs 59 mm Hg) and a faster heart rate with neostigmine at 2min (74 vs 61 bpm) and 5min postdose (70 vs 62) compared with sugammadex were observed.

Shields et al¹⁴ studied 30 patients anaesthetized patients who received rocuronium 0.6mg/kg as an initial dose followed by increments to maintain a deep block. Patients received their randomly assigned dose of 0.5, 1.0, 2.0, 4.0, or 6.0mg/kg of sugammadex. He found that there were minimal effects on heart rate and arterial pressure following sugammadex administration.

Ozlem Sacan²⁴ studied 60 patients undergoing elective surgery with a standardized desflurane-remifentanyl-rocuronium anaesthetic technique received either sugammadex, 4mg/kg i.v (n=20), edrophonium, 1mg/kg i.v and atropine, 10micro/kg i.v (n=20), or neostigmine, 70micro/kg i.v and

glycopyrrolate, 14micro/kg i.v(n=20) for reversal of neuromuscular blockade at 15 min or longer after the last dose of rocuronium. He found, that compared to sugammadex, use of neostigmine-glycopyrrolate, for reversal was associated with significantly higher HR values at 2 and 5 min after reversal drug administration.

A study was carried out by Dahl V²⁵ regarding the safety and efficacy of sugammadex for the reversal of rocuronium-induced neuromuscular blockade in cardiac patients undergoing noncardiac surgery. An overall, 116 patients (New York Association class II-III) were randomized and received sugammadex 2.0mg/kg(n=38), sugammadex 4.0mg/kg(n=38) or placebo(n=40) for reversal.

Safety variables included heart rate, blood pressure, and electrocardiogram characters including QT(QTcFridericia and QTcBazett) interval. There were no significant differences in terms of QT(Fridericia) interval. Blood pressure and heart rate decreased after initiation of anaesthesia and remained stable in all groups up to 10 min after

administration of study drug. Blood pressure was significantly higher ($P<0.05$) in both sugammadex dose groups compared with placebo at 30 min. The decrease in heart rate from baseline (prestudy drug) was significantly greater in the 2.0 mg/kg sugammadex group at 2 and 5 min, and, for both sugammadex groups, the increase at 30 min was greater compared to placebo.

In our study we found that neostigmine-glycopyrrolate group showed heart rate was significantly higher at 2, 4 and 6 min post dose than sugammadex group ($P<0.05$). on the other hand Blood pressure was significantly higher in neostigmine-glycopyrrolate group at 2 and 4 min only postdose than sugammadex group ($P<0.05$).

Conclusion:

The findings indicate that sugammadex can be given for the reversal of rocuronium-induced neuromuscular blockade without significant variations in heart rate and blood pressure, in comparison to neostigmine-glycopyrrolate.

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