Revista Mexicana de Anestesiología

REVIEW
Vol. 31. No. 2 April-June 2008
pp 139-145

Sugammadex. New alternative for the reversal of neuromuscular relaxation

Raúl Carrillo-Esper, MD;* Rogelio Sánchez-García, MD;** Elsa Elisa Jiménez-Morales, MD***

* Academia Nacional de Medicina. Academia. Mexicana de Cirugía. Coordinator of the Consejo Consultivo del Colegio Mexicano de Anestesiología.
** First Year Resident. Medicine of the Patient in Critical State. Fundación Clínica Médica Sur.
*** First Year Resident. Anesthesiology Fundación Clínica Médica Sur.

Reprints request:
Raúl Carrillo-Esper, MD
Colegio Mexicano de Anestesiología, A.C.
Nueva York No. 32 despacho 803
Col. Nápoles C.P. 03810 Deleg. Benito Juárez
México, D.F.
Tel. 5669-4659, 5669-1457
E-mail: seconcapcma@mail.medinet.net.mx

Received for publication: 13-01-08
Accepted for publication: 05-02-08

SUMMARY

Cyclodextrins are large molecules of various numbers of glucose molecules bound in a ring-like structure. This creates a hydrophilic outer layer with a lipophilic inner core. Sugammadex is a modified cyclodextrin designed to encapsulate aminosteroid nondepolarizing muscle relaxing agents. It has been successfully tested in animals and humans. It has been shown to be well tolerated and effective in humans. Sugammadex binds neuromuscular blocking agents and encapsulates them, making cholinesterase inhibitors unnecesary. Due to its rapid onset of action and relative lack of side effects, this drug promises to change the method of anesthesia delivery. This review summarizes the literature of the drug.

Key words: Cyclodextrins, sugammadex, neuromuscular blockers, rocuronium.

RESUMEN

Las ciclodextrinas son moléculas formadas por varias moléculas de glucosa cuya estructura semeja un anillo, con una capa externa hidrofílica y una porción interna lipofílica, que tridimensionalmente adopta la forma de una dona. El sugammadex es una ciclodextrina modificada diseñada para encapsular agentes relajantes musculares no despolarizantes aminoesteroideos. Ha sido estudiada en modelos animales y estudios clínicos en donde se ha demostrado su efectividad y margen de seguridad. El sugammadex se une al agente bloqueador neuromuscular y lo encapsula, haciendo innecesario el uso de inhibidores de colinesterasa. Por su innovador mecanismo de acción y relativa carencia de efectos colaterales su inclusión en el armamentario terapéutico del anestesiólogo impactará en la práctica cotidiana de la anestesiología. El objetivo de este trabajo es revisar los conceptos actuales sobre el sugammadex.

Palabras clave: *Ciclodextrinas, sugammadex, bloqueadores neuromusculares, rocuronio.*

Sugammadex is a new class of cyclodextrin functioning as encapsulator specific of amino-steroidal muscle relaxants. The discovery of the encapsulation effect of these drugs is the result of the work of Dr. Anton Bom et al. by studying the cyclodextrin molecules as transporter and encapsulator of rocuronium[1,2].

Cyclodextrins are cyclic oligosaccharides with D-glucosyl-alpha-1, 4 rings which can contain 6 (α-cyclodextrins), 7 (β-cyclodextrins) or 8 (β-cyclodextrins) D-glucosyl rings[3]. Their three-dimensional structure consists of a hydrophobic cavity and a hydrophilic exterior due to the presence of polar hydroxyl groups, for which they are water soluble and

biologically stable. For this reason, cyclodextrins have been used and approved by the FDA (Food and Drug Administration) as solvents of different anesthetics such as propofol, midazolam, bupivacaine, and sulfentanyl. γ-cyclodextrins resemble a doughnut where hole is the lipophilic cavity with a diameter of 7.5-8.3Ã[4]. This cavity attracts and binds molecules forming complexes.

It has been shown that rocuronium has a high affinity for the modified cyclodextrin molecule called Org 25969 which was called sugammadex (Su refers to sugar, gammadex refers to their γ-cyclodextrin molecular structure). This molecule encapsulates and antagonizes the neuromuscular block induced by rocuronium[5] (Figure 1).

The discovery of this new cyclodextrin led to the development of basic and clinical research protocols to evaluate the properties of encapsulation in order to reverse the effect of non-depolarizing muscle relaxants, especially of rocuronium.

PHARMACOKINETICS AND PHARMACODYNAMICS

Epemolu et al. found that the rapid inactivation of muscle relaxants by Org 25969 was carrying out in the extracellular compartment through a concentration gradient[6].

Sugammadex rapidly decreases the concentration of plasma muscle relaxant, not attached to the neuromuscular receptor, and this allows for establishing a relaxant gradient and flow to the bloodstream, where it is quickly encapsulated. Sugammadex molecules have the ability to penetrate the tissue and form complexes with rocuronium. The formed complex has high affinity, a very low rate of dissociation and it does not interact with the acetylcholine receptor and acetylcholinesterase. The sugammadex's high affinity for vecuronium and rocuronium has been compared with that of other non-steroidal and steroidal molecules such as cortisone, hydrocortisone, aldosterone, atropine and verapamil with which forms complexes, but they are 120 to 700 times weaker because there are no electrostatic interactions with carboxylic groups of their molecules[7].

The sugammadex interaction with other neuromuscular relaxants such as succinylcholine and benzyl-quinoline derivatives (atracurium, cis-atracurium and mivacuronium) and anesthetics such as propofol and sevoflurane is much lower or non-existent with respect to non-depolarizing amino-steroidal muscle relaxants. Cyclodextrins excretion is by kidney within 8 hours after of administration and it goes in parallel to the renal elimination of rocuronium.

Specific studies on the sugammadex action in the presence of abnormalities in renal perfusion and acid-base disturbances have shown that they do not interfere with its activity[8].

ENCAPSULATION BY SUGAMMADEX

The sugammadex's interaction mechanism with rocuronium is through encapsulation via Van der Waals forces and hydrophobic interactions, which keeps the muscle relaxant into the cavity of sugammadex (Figure 2). The binding active site of muscle relaxant is the amino group, which binds thermodynamically with carboxyl groups of the sugammadex molecule, which prevents any other active binding of the two molecules[5].

Although amino-steroidal relaxants are one quarter to one third the size of the cyclodextrins, their encapsulation is incomplete[9].

The modification of cyclodextrins, such as that made with sugammadex, allows to improve encapsulation and binding between both molecules. The modified sites are hydroxyl groups on the second, third and sixth of the carbon atoms of base glucose (Figure 3).

To increase the size of the cavity of cyclodextrins, the molecular structure is altered by replacing every sixth carbon of a carboxyl group by a hydroxyl thioether. (CH2SCH2CH2CO2Na) (Figure 4).

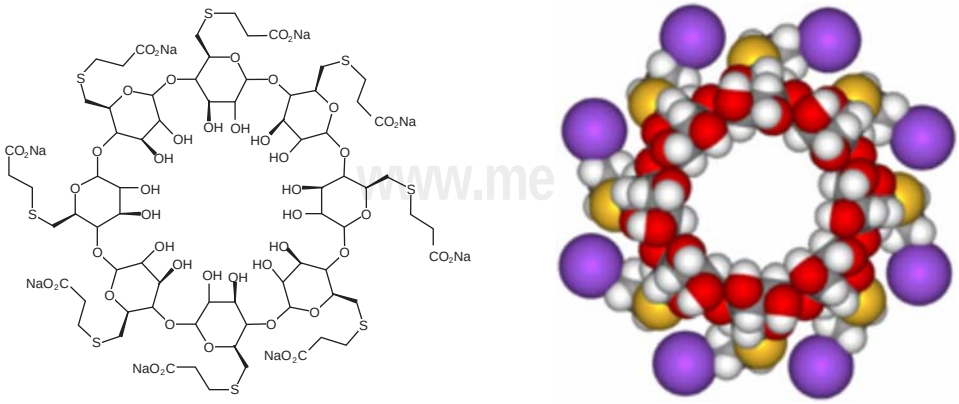

Figure 1. Org 25969 (Sugammadex) structure.

This new re-arrangement not only increases the size and depth of the cavity but also the area of lipophilic interactions with the rocuronium molecule (Figure 5).

Anionic carboxyl groups provide additional affinity for the rocuronium molecule, especially toward the positively charged amino group[9].

Given the confirmed affinity between sugammadex and rocuronium, Ploeg et al. developed a 3-phases pharmacokinetic and pharmacodynamic model expressing the interaction between sugammadex and rocuronium (Figure 6).

1. Free sugammadex
2. Free rocuronium
3. Sugammadex-rocuronium complex

The Ploeg et al. model was validated to simulate the interactions of sugammadex and rocuronium[10,11].

STUDIES IN ANIMALS

The efficacy of sugammadex as a reverter of muscle relaxation have been confirmed in animal models. Miller and Bom used mouse hemidiaphragm preparations with intact phrenic nerve, in which the isometric contractions produced by electrical stimulation were registered.

Different muscle relaxants (vecuronium, rocuronium, pancuronium, and rapacuronium) were administered until reaching a block 90% of the train of four and confirming paralysis. Subsequently, increasing doses of sugammadex were applied and the time in which the paralysis disappeared was registered.

The findings indicated that the amino-steroidal muscle relaxants such as rocuronium, rapacuronium, vecuronium, and pancuronium were actually reversed. The best effect was observed with rocuronium followed by rapacuronium, vecuronium and pancuronium, respectively. The muscle relaxants succinylcholine, atracurium and mivacurium are not reversed[12].

In the first phase of a model involving Guinea pigs, doses of muscle relaxants were administered via infusion until reaching block 90% of the train of four, monitoring it in the sciatic nerve. Subsequently, spontaneous recovery was allowed and the time in which it occurs was determined. In the second phase, infusion of muscle relaxant was repeated and a 1 mg/kg intravenous bolus of sugammadex was administered, it was observed that all amino-steroidal relaxants were reversed in less than 1 minutes to 90% of the train of four[13].

In another study involving a cat model, it was observed that after induction of paralysis with an initial bolus and continuous infusion of 10% rocuronium using train of four

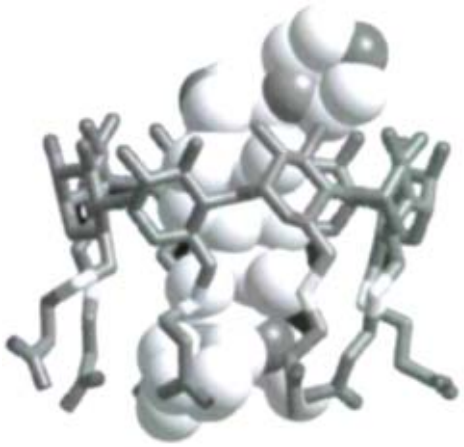

Figure 2. Molecule of rocuronium encapsulated per molecule of sugammadex (Org 25969).

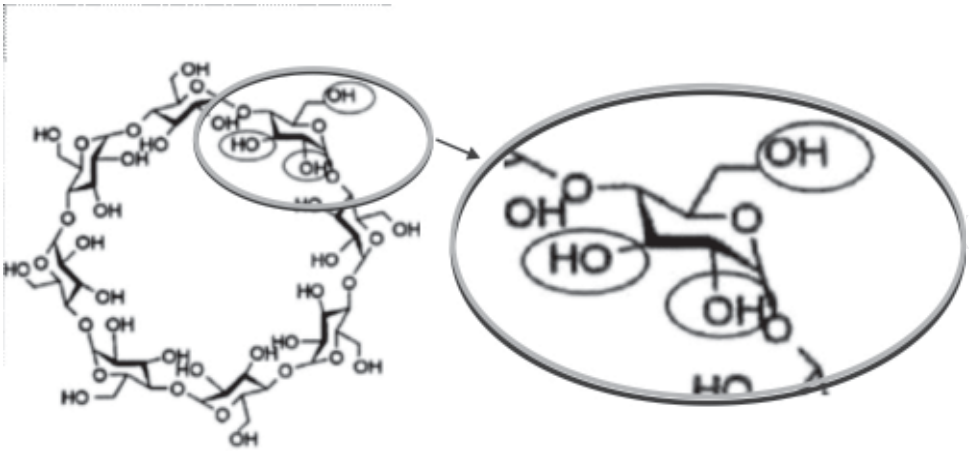

Figure 3. Gamma cyclodextrin in natural form, in showing the hydroxyl groups that can be modified.

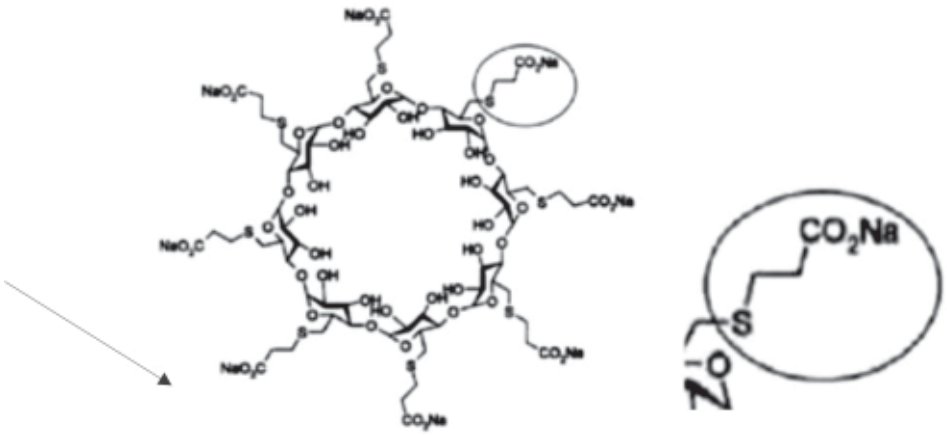

Figure 4. Cyclodextrin molecule where it has been replaced every sixth carbon of a hydroxyl group by a carboxy tioether group to obtain sugammadex.

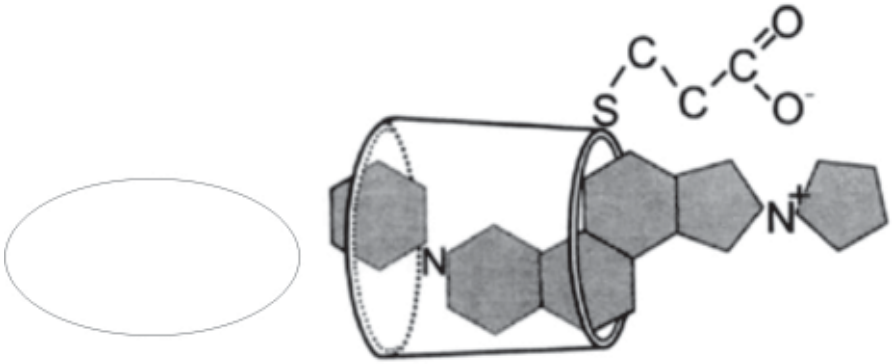

Figure 5. Encapsulation of the rocuronium by a molecule of sugammadex, where the carboxil extention is observed to tioether of the cyclodextrin.

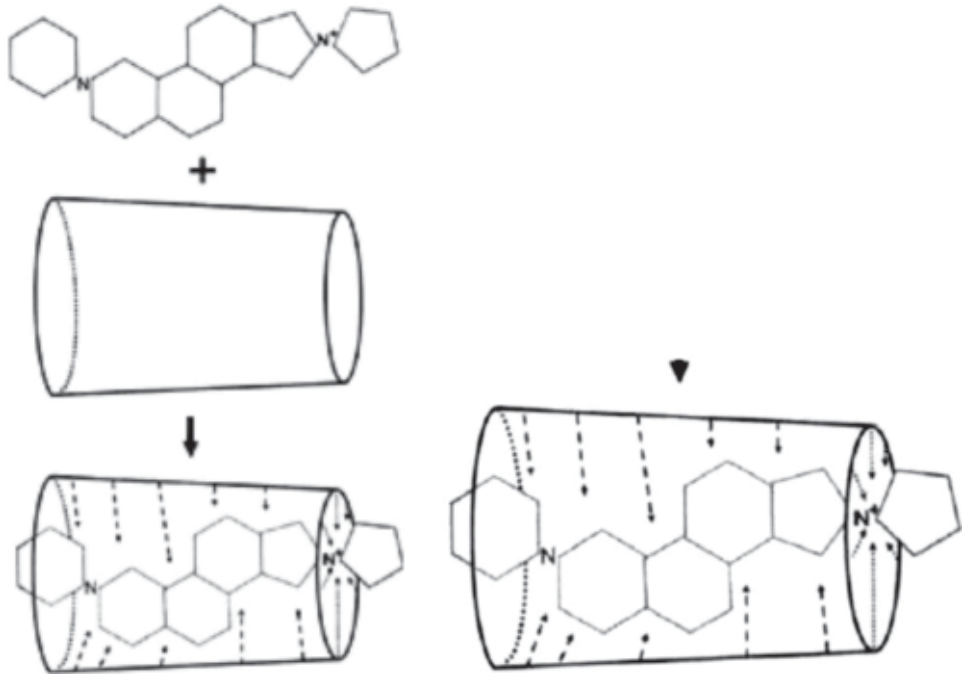

Figure 6. The broken arrows represent hydrophobic and thermodynamic attractions. The arrows pointing towars the ammonium group rocuronium represent electrostatic interactions with the carboxyl group of the cyclodextrin sugammadex.

in the tibial nerve to monitor relaxation, 90 % spontaneous recovery from block was of 6.2 minutes, and after the infusion of sugammadex was of 1.3 minutes without significant hemodynamic effects[14].

A study involving Rhesus monkeys which received intravenous anesthesia with pentobarbital and ketamine, baseline train of four was performed in cubital nerve, paralysis was induced with rocuronium or vecuronium until reaching block 90%. In a first phase spontaneous recovery was monitored and in the second phase it was recorded after 1 mg/kg sugammadex, by considering the 50%, 75% and 90% recovery from the train of four. The results of this study are shown in Table I. Speed with which reversal of muscle relaxation occurs with sugammadex was a relevant information[15].

De Boer et al. used 2 groups of cats as experimental model, they were anesthetized and then paralyzed with 820 µmol/kg of rocuronium, monitoring the relaxation with train-of-four in the tibial nerve. Ninety minutes later, both renal arteries were occluded. Spontaneous recovery time was recorded in group 1 and recovery time after administration of sugammadex at a 2,300 nmol/kg dose was recorded in group 2. There were no changes in the spontaneous recovery from muscle relaxation in group 1. It was observed that the paralysis was reverted 10 times faster in group 2. In this way the results of this study showed that the effect of sugammadex is not modified to exclude blood flow and renal function[16].

Bom and Miller conducted a study to evaluate whether the acid-base disturbances cause changes in the activity of sugammadex. For this reason, they carried out a protocol in which Guinea pigs were anesthetized and paralyzed with rocuronium until reaching 25% of the train of four, recording it in the gastrocnemius muscle. Subsequently, alkalosis and metabolic acidosis were induced by injecting lactic acid and sodium bicarbonate respectively, and respiratory disorders (acidosis and alkalosis) were induced by modifying mechanical ventilation. Initially spontaneous recovery from muscle relaxation was recorded, then 1 mg/kg sugammadex was administered intravenously to each group. The results showed a rapid and complete recovery from neuromuscular block after receiving sugammadex as compared to spontaneous recovery was taking from 4 to 9 minutes. This study demonstrated the effectiveness of sugammadex regardless of acid-base state[17].

Table I. Recovery time (minutes) in spontaneous form and subsequent to administration of sugammadex. (Modified of *Eur J Anaesthesiol* 2001;18:100).

Train of four	Spontaneous recovery time	Recovery time after sugammadex 1 mg/kg
Rocuronium	Minutes	Minutes
0.50	7.4	0.5
0.75	10.2	0.9
0.90	14.5	1.9
Vecuronium		
0.50	12.7	1.5
0.75	17.4	2.4
0.90	23.1	4.4

CLINICAL STUDIES

Phase I

The first documented study on sugammadex in humans was published by Gijsenbergh et al.[18] in 2002. This study included 29 healthy subjects which were divided into two groups to receive placebo or sugammadex at doses ranging from 0.8 to 8 mg/kg after the relaxation with rocuronium. There were no adverse effects in the sugammadex group and time to reverse the effect of relaxation was faster than with placebo. The sugammadex at 0.8 mg/kg doses reversed the relaxing effect in 1 minutes as compared to 52 minutes of placebo. This study allowed to evaluate the effectiveness, safety and tolerance of sugammadex in healthy subjects[19].

Phase II

The results of phase II studies have been consistent with those performed in animals in regard to dose- effectiveness and hemodynamic stability. The first studies and results are shown in Table II.

These results were confirmed by Suy et al using a protocol including 79 healthy individuals between 19 and 84 years assigned to three groups, the first group received rocuronium and subsequently sugammadex at doses from 0.5 mg/kg to 4.0 mg/kg, the second group received vecuronium and sugammadex at doses from 0.5 to 8.0 mg/kg, and the third group received placebo. The sugammadex was administered intravenously when the relaxation response was 50% of the train of four. The results concluded that sugammadex reversed the relaxation induced by rocuronium and vecuronium in a dose-dependent manner. The highest dose of sugammadex (8 mg/kg) reversed both relaxants in less than 2 minutes in comparison with 30 to 48 minutes of placebo[24].

De Boer et al. developed a protocol for the purpose of confirming the efficacy and safety of rocuronium reversal by sugammadex, in which included 46 healthy subjects who were anesthetized with propofol, remifentanil and oxygen, then rocuronium at 1.2 mg/kg dose was administered and

Table II. Clinical tests Phase II with sugammadex.

Shields[20,21]
Design
Initial dose of rocuronium 0.6 mg/kg
Rocuronium was instilled to keep train of four 2/4
Duration of anesthesia 2 hours or more
Random dose of sugammadex 0.5-6.0 mg/kg.
Results
Recovery time related to dose (1.59 minutes)
Well tolerated
Without adverse effects
Without recurarization
Khunt-Brady[22]
Design
Rocuronium 1 mg/kg (deep relaxation)
3 to 15 minutes later, placebo or sugammadex 2-16 mg/kg
Results
Deep paralysis reversion, average 2.5 minutes with dose of 8 mg/kg
without adverse effects
Vanacker[23]
Design
Intravenous bolus of rocuronium after induction with propofol
Maintenance with sevoflurane or propofol in random form
Reversion with sugammadex, 2.0 mg/kg until reapperance of 2/4 of the train of four
Results
Average recovery time of 1 minute 50 seconds with propofol
Average recovery time of 1 minute 48 seconds with sevoflurane
Not submitted recurarization.

five minutes after sugammadex at 2 to 16 mg/kg dose or placebo was administered intravenously.

The results showed a shorter recovery time from neuromuscular relaxation induced by rocuronium after sugammadex's administration of a dose-dependent manner and there was no recurarization in any case[25]. In a multicenter study, the effectiveness of rapid sequence intubation was compared between succinilcholine at 1 mg/kg doses and rocuronium at 1.2 mg/kg doses followed by sugammadex at 16 mg/kg doses three minutes later. The rapid sequence intubation with rocuronium-sugammadex offered better intubation conditions with a rapid recovery[26].

Side effects associated to sugammadex that have been reported in these studies are: hypotension, cough, nausea, vomiting, dry mouth, parosmia, prolonged QT and elevated levels of N-acetyl glucosaminidase in urine[27,28].

Phase III

Studies are being conducted currently to evaluate the efficacy and safety of sugammadex in a wide variety of patients and clinical settings, still no results have been obtained from this studies[29].

CONCLUSION

Cyclodextrins are donut-shaped complex molecules which have the capacity to be solvents and encapsulation medium of drugs. Sugammadex is a cyclodextrin modified by replacing every sixth carbon from the hydroxyl group by a carboxyl thioether which has the ability to encapsulate amino-steroidal neuromuscular relaxants with particular affinity for rocuronium.

Experimental studies in animals and Phase I, II and III clinical studies have proved its efficacy and safety margin as reverter of profound neuromuscular relaxation and as part of a new technique of rapid sequence intubation based sugammadex-rocuronium. Doses ranging from 0.5 to 16 mg/kg have been used in various clinical assays, but the standard dose is from 4 to 8 mg/kg. The availability of this new molecule will broaden the range of the therapeutic armamentarium of the anesthesiologist, which naturally will impact on safety and quality of the daily practice of anesthesiology.

REFERENCES

1. Bom A, Cameron K, Clark JK. Chemical chelation as a novel method of NMB reversal: discovery of Org 25969 [abstract). Eur J Anesthesiol 200l;18:99.
2. Bom A, Bradley M, Camuron K. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic-host. Angew Chemv Int Ed Engl 2002;41:266-270.
3. Alvarez GJA. Muscle reluxants: novelties and future development. Anaesthesiologie and Reanimation 2002;12:95-98.
4. Adam M, Bennetl DJ, Bon A. Cyciodextrin-derived host molecules as reversal agents for the neuromuscular blocker rocuronium bromide: synthesis and structure-activity. J Med Chem 2002;45:1806-1816.
5. Tarver GJ, Grove SJA, Buehanan K. 2-0-Substituted cyclodextrins as reversal agents for the neuromuscular blocker rocuronium bromide. Bioorg Med Chem 2002;10:1819-1827.
6. Epemolu O, Bom A, Hope F, Mason R. Reversal of neuromuscular blockade and simultaneous increase in plasma rocuronium

concentration after the intravenous infusion of the novel reversal agent Org 25969. Anesthesiology 2003:632-637.
7. Zhang MQ. Drug specific cyclodextrins: the future of rapid neuromuscular block reversal. Drugs Future 2003;28:347-354.
8. Bom A, Mason R, Mclndewar L. Org 25969 causes rapid reversal of rocuronium-induced neuromuscular block, independent of acid-base status (abstract) Anesthesiology 2002:A-1009.
9. Fielding S, Cameron L. MRI diffusion coefficient study of steroid cyclodextrin complexes. Magn Reson Chem 2002;40:S106-S109.
10. Ploeger BA, Ruigt G, Danhol M. Pk/pd modeling of reversal of neuromuscular blockade by a chemically optimized cyclodextrin (abstract). Clin Pharmacol Ther 2004;75:80.
11. Ploeger BA, Houwiiig H, Bom A, van Lersel T, Zollinger D, Danliof M. The reversal of rucuronium-induced neuromuscular block by the cyclodextrin Org 25069: model development and validation. Poster presented at the Annual Meeting of the Population Approach Group in Europe; June 2004,Upsala, Sweden.
12. Miller S, Bom AH. Org 25969 causes selective reversal of neuromuscular blockade induced by steroidal NMBs in the mouse hemidiaphragm preparation (abstract). Eur J Anesthesiol 2001;18:100.
13. Mason R, Bom A. Org 25969 causes selective reversal of neuromuscular block induced by steroidal NMBs in anaesthetized Guinea pigs (abstract). Eur J Anaesthesiol 2001;18:100.
14. Hope F, Bom A. Org 25969 reverses rocuronium-induced neuromuscular blockade in the cat without important hemodynamic effects (abstract). Eur J Anesthesiol 2001:18:100.
15. Van Fgmont IJ, van de Pol F, Booij L, Bom A. Neuromuscular blockade induced by steroidal NMBs can be rapidly reversed by Org 23969 in anaesthetized monkey and cats (abstract). Eur J Anaesthesiol 2001;18:100.
16. De Boer HD, Van Egmond J. Reversal of profound rocuronium neuromuscular blockade by sugammadex. Anesthesiology 2003;99:632-637.
17. Miller S, Bom AH. Org 25969 causes selective reversal of neuromuscular blockade induced by steroidal NMBs in ihe mouse hemidiaphragm preparation (abstract). Eur J Anesthesiol 2001;18:100.
18. Gijsenbergh F, Ramael S, De Bruyn S, Reilbergen H, van Lersal T. Preliminar assessment of Org 25969 as a reversal agent for rocuronium in heatlhy male volunteers (abstract). Anesthesiology 2002:A1008.
19. Gijsenbergh F, Ramael S, Houwing N, van Lersel T. First human exposure to Org 25969: a novel agent to reverse the action of rocuronium bromide. Anesthesiology 2005;103:695-703.
20. Shields M, Giovannelli M, Moppett L, Mahajan RR, Mirakhur RK. Deep neuromuscular block with Org 25969. Poster presented at the European Society of Anesthesia Congress; May 2005; Vienna, Austria.
21. Shields M, Giovannelli R, Mirakhur RK, Moppeu L, Adams J, Hermens Y. Org 25969 (sugammadex), a selective relaxant binding agent for the antagonism of prolonged rocuronium-induced neuromuscular block. Br J Anaesth 2006;96:36-43.
22. Khunl-Brady K, Rex C, Kjacr CC, Larsen PB, Prins ME, Puhringer F. Reversal of high dose rocuronium with Org 25969, Poster presented at the European Society of Anesthesia Congress: May 2005; Vienna. Austria.
23. Vanacker B, Vermeyen K, Struys MRF. Reversal by Org 25969 is not affected by sevoflurane when compared with propofol. Poster presented at the European Society of Anesthesia Congress; May 2005; Vienna, Austria.
24. Suy K, Morias K, Hans P, Heeringa M, Denmeyer I. Fast, effective and safe reversal of rocuronium and vecuronium-induced moderate neuromuscular block by the selective relaxant binding agent Org 25969, Poster presented at the American Society of Anesthesiologists Annual Meeting; October 2005; Atlanta, Ga.
25. de Boer H, Marcus M, Schouten I, Heeringa M. Reversal of rocuronium-induced (1.2 mg/kg) neuromuscular block by Org 25969: a multi-center dose finding and safety study. Poster presented at the American Society of Anesthesiologists. Annual Meeting; October 2005; Atlanta, Ga.
26. Naguib M. Sugammadex: Another milestone in clinical neuromuscular pharmacology. Anesth Analg 2007;104: 575-581.
27. Sorgenfrei IIF, Norrild K, Larsen PB. Reversal of profound rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. Anesthesiology 2006;104:667-674.
28. Shields M, Giovanenelli M, Mirakhur RK. Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium induced neuromuscular block. Br J Anaesth 2006;96:201-206.
29. Organon International, Organon reports positive results from phase III studies with novel agent to reverse muscle relaxation in anesthesia (press release) Available at http://www.organon.com/news/press_release /2005_05_31_organon_reports_positive_results_from_phase_II_studies_with_novel_agent_o_reverse_muscle_relaxation_in_anesthesia.asp. Accessed May 26, 2005.