

NEW DRUG SUGAMMADEX: A SELECTIVE RELAXANT BINDING AGENT

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Cyclodextrins are molecules with a hollow, truncated cone shape that possess unique lipophilic and hydrophilic properties. These unique properties enable cyclodextrins to engulf and bind lipophilic molecules while maintaining aqueous solubility. Encapsulation of molecules is the principal action of a new drug class, selective relaxant binding agents, which binds and inactivate aminosteroid nondepolarizing muscle relaxants. Sugammadex is the name of a

modified cyclodextrin currently in phase 3 studies by Organon International (Oss, The Netherlands), and it may hold promise for a new concept in muscle relaxant reversal. Encapsulation rather than competitive antagonism of neuromuscular blockade may be a future modality of anesthetic practice.

Key words: Cyclodextrin, encapsulation, modified cyclodextrin, selective relaxant binding agents, sugammadex.

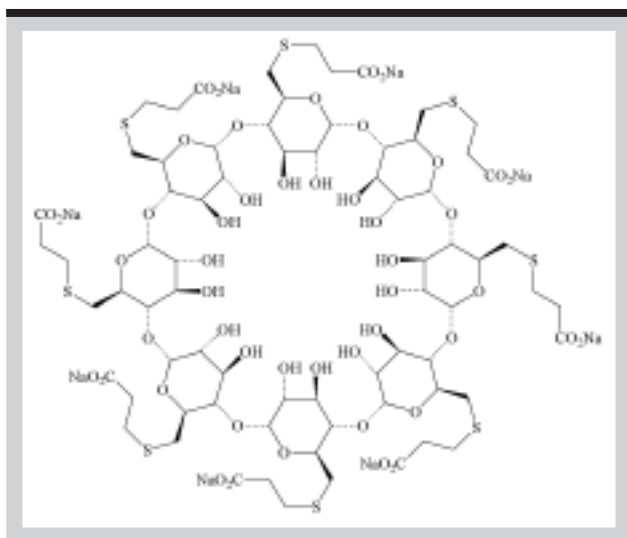
Sugammadex is the first introduction of a new class of drugs called selective relaxant binding agents that encapsulate aminosteroid nondepolarizing muscle relaxants, terminating their effects.¹⁻⁵ The discovery of encapsulation for reversal of aminosteroid muscle relaxants is the result of work done by Anton Bom, a research scientist at Organon International (Oss, The Netherlands) while studying cyclodextrin molecules as a vehicle for rocuronium solubilization.^{1,6,7} Initial study confirmed a high affinity of a modified cyclodextrin, Org 25969, for the rocuronium molecule⁸ (Figure 1). Owing to the discovery of this modified cyclodextrin's high binding affinity for rocuronium, the focus soon changed from in vitro solubilization for drug delivery to in vivo encapsula-

tion for drug extraction. Encapsulation of rocuronium to reverse its muscle relaxant properties became a novel approach to terminating the effects of rocuronium (Figure 2). This new direction of study led to impressive results with Org 25969 in animal and phase 1 and 2 studies. Org 25969, now known as sugammadex, is currently in phase 3 clinical studies with expected initial review and potential availability by 2007.⁹

Animal studies

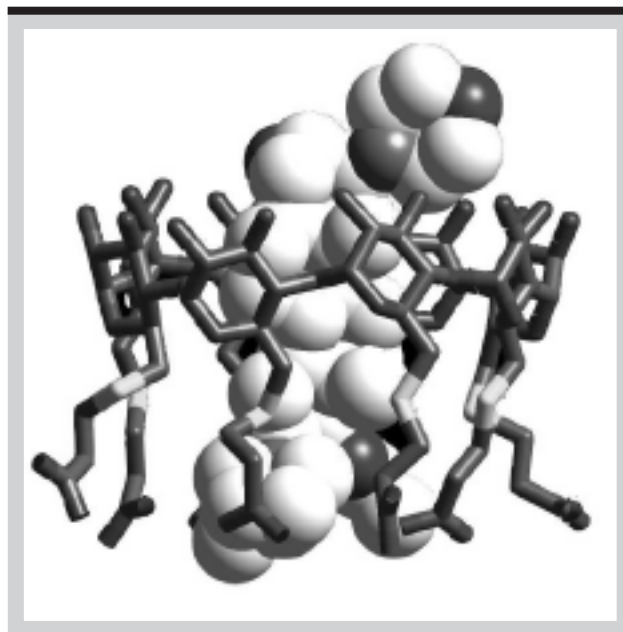
Animal studies evaluated the effectiveness of sugam-

Figure 1. Sugammadex molecule



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Figure 2. Rocuronium molecule encased within sugammadex, a modified cyclodextrin



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madex as a reversal agent using mouse, guinea pig, cat, and monkey models. Miller and Bom¹⁰ placed mouse hemidiaphragm preparations with the phrenic nerve intact in an oxygenated buffered bath while electrically stimulated isometric contractions were recorded. A 90% blocking dose of common muscle relaxants was administered and paralysis confirmed, and increasing doses of sugammadex were administered. The return of muscle contraction was measured and timed. The findings indicated that the aminosteroid muscle relaxants rocuronium, rapacurium, vecuronium, and pancuronium were reversed effectively. Rocuronium was the most easily reversed, followed by rapacurium, vecuronium, and pancuronium. The depolarizing muscle relaxant succinylcholine and isoquinolone muscle relaxants atracurium and mivacurium were not reversed. These findings supported the continued *in vivo* animal studies of muscle relaxant reversal by sugammadex.

Anesthetized guinea pigs were given an initial bolus of a muscle relaxant followed by an infusion to assure a steady state of 90% blockade, then it was stopped. Measurement of blockade was conducted at the sciatic nerve. Complete spontaneous recovery was allowed and timed. The procedure to paralyze to 90% blockade was repeated, followed with an intravenous bolus of 1 mg/kg of sugammadex. All steroidal muscle relaxants were reversed in less than 1 minute to 90% train of four (TOF) or greater. The time to recovery of nonsteroidal muscle relaxants after sugammadex injection was not significantly improved.¹¹

Studies using a cat paralyzed after bolus and infusion of rocuronium to 10% of baseline TOF at the tibialis muscle showed rapid recovery. Spontaneous recovery time from 90% blockade was 6.2 minutes. Recovery after sugammadex was 1.3 minutes with no significant hemodynamic changes observed.¹²

The previous studies showed that sugammadex was highly effective in reversing the aminosteroid muscle relaxants rocuronium and vecuronium. Rhesus monkeys were anesthetized intravenously with pentobarbital and ketamine, and baseline TOF was conducted at the thumb using the ulnar nerve. The monkeys then were paralyzed with rocuronium or vecuronium to achieve 90% blockade. Spontaneous recovery was allowed and timed. Again, the paralysis protocol to 90% blockade was repeated and immediately followed by 1 mg/kg of sugammadex intravenously. Time (minutes) to 50%, 75%, and 90% recovery was noted (Table 1). Rapid reversal of both muscle relaxants was found with no hemodynamic changes or appreciated side effects.¹³

The successes of sugammadex binding to aminos-

Table 1. Data summary of sugammadex reversal in anesthetized monkey¹³

TOF ratio	Spontaneous recovery time	Sugammadex, 1 mg/kg, recovery time
Rocuronium		
0.5	7.4	0.5
0.75	10.2	0.9
0.9	14.5	1.9
Vecuronium		
0.5	12.7	1.5
0.75	17.4	2.4
0.9	23.1	4.4

TOF indicates train of four.

teroid muscle relaxants and rendering them ineffective prompted further analysis of this encapsulation action. Epemolu and others¹⁴ found that the rapid reversal by sugammadex of aminosteroid muscle relaxants is due to the muscle relaxant molecules being drawn out of the extracellular compartment by a reversal of the concentration gradient. Sugammadex rapidly decreases the amount of unbound muscle relaxant molecules in the plasma, and this establishes a net flow of muscle relaxant molecules into the bloodstream where they, too, are quickly bound. Once bound, the new sugammadex-muscle relaxant molecule (host-guest assembly or inclusion complex) becomes unable to exert action at the acetylcholine receptor. The active site of muscle relaxant binding, the ammonium group, is thermodynamically bound to carboxyl groups of the sugammadex molecule and, thus, prevented from any other active binding.⁸

Renal excretion of cyclodextrins is well known. Specific studies of the action of sugammadex in the presence of renal perfusion abnormalities and acid-base disturbances have found continued effectiveness. Bom and others¹⁵ found significantly decreased reversal times for rocuronium-induced neuromuscular block after sugammadex compared with spontaneous recovery in the renal-impaired cat. In this study, cats were anesthetized and deeply paralyzed with 820 µmol/kg (2 x ED 90) of rocuronium confirmed by TOF at the tibialis muscle. Spontaneous recovery of neuromuscular function was timed. Ninety minutes later, both renal arteries of all cats were surgically occluded and the cats re-paralyzed to the previous depth of blockade. Group 1 of the cats was allowed to spontaneously recover, and group 2 received sugammadex, 2,300 nmol/kg. The spontaneous recovery

time of group 1 remained unchanged. The sugammadex group (group 2) recovery time was nearly 10 times faster. The action of sugammadex reversal of deep rocuronium blockade was not affected by cessation of renal blood flow.

Acid-base imbalances also were studied to evaluate possible changes in sugammadex effectiveness.¹⁶ Bom and others¹⁶ anesthetized guinea pigs and paralyzed them with rocuronium to 1/4 TOF recorded at the gastrocnemius muscle. Metabolic acidosis and alkalosis were induced by injection of lactic acid or sodium bicarbonate, and respiratory acidosis and alkalosis was induced by ventilatory changes. Spontaneous baseline recovery times were noted and paralysis repeated. Sugammadex, 1 mg/kg, then was given intravenously to each group. The findings showed rapid and full recovery of neuromuscular blockade within 1 minute after receiving sugammadex compared with spontaneous recovery times of 4 to 9 minutes. These animal studies consistently demonstrated sugammadex effectiveness in reversing the aminosteroid muscle relaxants rocuronium and vecuronium. This reversal was independent of pH and renal perfusion.

Clinical trials

- *Phase 1.* The first documented study of sugammadex in humans was by Gijzenbergh et al¹⁷ in 2002, in which 29 healthy men received placebo or sugammadex in doses ranging from 0.1 to 8.0 mg/kg after rocuronium-induced blockade. There were no untoward effects, and reversal times were quicker than placebo in a dose-related manner. The sugammadex dose of 8.0 mg/kg averaged reversal times of 1 minute, compared with 52 minutes for placebo. This first human exposure to sugammadex indicated effective and fast reversal of rocuronium. The preliminary findings suggested it was safe and well tolerated, which was confirmed by final analysis.¹⁸

- *Phase 2.* Multiple phase 2 studies have been conducted, and the preliminary data have been comparable to animal study findings of dose-related effectiveness and hemodynamic stability. The first introduction of phase 2 findings was May 2005 at the European Society of Anesthesia Congress, Vienna, Austria. Three poster presentations were given (Table 2).

The results of the preliminary European studies were later supported by the similar preliminary US findings released in October 2005. Suy and others²³ studied sugammadex reversal of moderate doses of rocuronium and vecuronium in 79 healthy patients ranging in age from 19 to 84 years. Sugammadex, 0.5 to 4.0 mg/kg, was given to the rocuronium-paralyzed group, and 0.5 to 8.0 mg/kg was given to the vecuro-

Table 2. Summary of poster presentations at the European Society of Anesthesia Congress, Vienna, Austria, May 2005

Study 203: Shields et al^{19,20}

Design

- Initial rocuronium dose, 0.6 mg/kg
- Maintenance rocuronium to maintain 2/4 TOF
- Anesthesia duration 2 hours or greater
- Random sugammadex dose, 0.5-6.0 mg/kg

Results

- Dose-related decrease in time to recovery (1.59 min)
- Well tolerated
- No adverse outcomes
- No recurarization

Study 206: Khunl-Brady et al²¹

Design

- 1 mg/kg of rocuronium (profound relaxation)
- 3 or 15 minutes later; placebo or sugammadex, 2.0-16.0 mg/kg

Results

- Profound paralysis reversal, average 2.5 minutes for a dose of 8.0 mg/kg
- No adverse outcomes

Study 210: Vanacker et al²²

Design

- Intravenous intubation bolus rocuronium after propofol induction
- Random sevoflurane or propofol maintenance
- Anesthetic duration 45 minutes or greater
- Reversal with sugammadex, 2.0 mg/kg, at reappearance of 2/4 TOF

Results

- Mean recovery time, 1 min 50 s with propofol
- Mean recovery time, 1 min 48 s with sevoflurane
- No recurarization

TOF indicates train of four.

nium-paralyzed group. Sugammadex was delivered intravenously at 2/4 TOF measured by acceleromyography at the adductor pollicis muscle. Conclusions were that sugammadex reverses rocuronium and vecuronium in a dose-dependent manner. The higher doses of sugammadex reversed both muscle relaxants in well under 2 minutes compared with placebo times of approximately 30 to 48 minutes. Six serious adverse events were observed, which the authors did not relate to sugammadex.

de Boer and others²⁴ studied the efficacy and safety of rocuronium reversal by sugammadex. In their study, 46 healthy patients were anesthetized with propofol, remifentanyl, oxygen, and air and given rocuronium, 1.2 mg/kg. Five minutes later, a placebo or sugammadex in doses ranging from 2.0 to 16.0 mg/kg were delivered intravenously. Data revealed a “dose dependent fast time to recovery of profound rocuronium-induced neuromuscular block.” Safety data indicated sugammadex was well tolerated. Sudden movement after reversal was seen in 2 patients. All patients tolerated sugammadex well, and no signs of recurarization were observed.²⁴

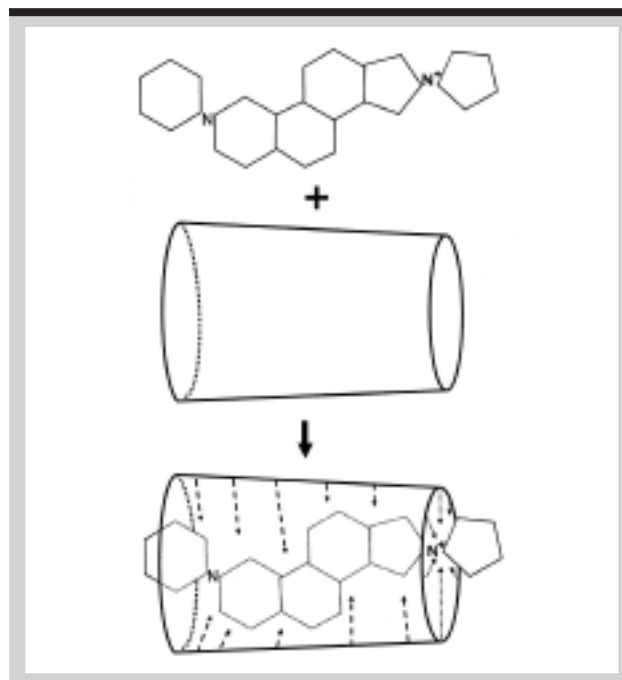
A multicenter study further evaluated high-dose rocuronium recovery after sugammadex. Patients received rocuronium, 1.2 mg/kg, and neuromuscular blockade was confirmed by acceleromyography at the adductor pollicis muscle. Randomly at 3 or 15 minutes after rocuronium administration, a sugammadex dose ranging from 2.0 to 16.0 mg/kg was delivered. Time to recovery was measured and compared with that for placebo. Again, a dose-dependent time to recovery was found with significant decrease in time compared with placebo. At doses of 12.0 mg/kg or higher, sugammadex reversed in 3 minutes or less in 90% of the cases. No recurarization was observed.^{25,26} Sugammadex was described as able to be used safely despite “one event of QT prolongation possibly related to Org 25969.”²⁶

- *Phase 3.* Currently underway are studies that explore the efficacy of sugammadex in a variety of clinical settings and patients. There are at least 10 studies underway in the phase 3 clinical trials of sugammadex covering a wide range of pathophysiological states and clinical scenarios.⁹

Sugammadex encapsulation

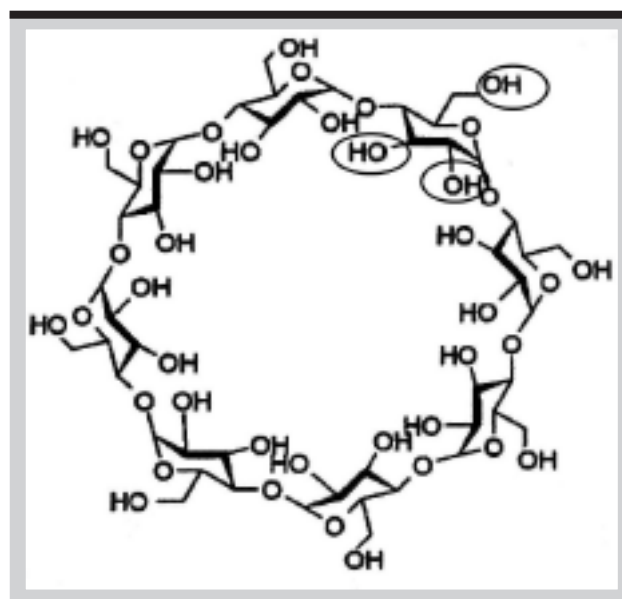
Sugammadex binding of steroidal muscle relaxants is by encapsulation, along with van der Waals and hydrophobic interactions, which hold the muscle relaxant molecule in place (Figure 3). Although steroids are one fourth to one third the size of cyclodextrins, full encapsulation of steroidal muscle relaxants by cyclodextrins is incomplete.²⁷ Modification of cyclodextrins allows for improved encapsulation and binding. The modification sites are the hydroxyl groups on the second, third, and sixth carbon atoms of the base glucose molecules (Figure 4). To increase the cavity size of the γ -cyclodextrin, Bom¹ replaced each sixth carbon hydroxyl group with a carboxyl thioether ($\text{CH}_2\text{SCH}_2\text{CH}_2\text{CO}_2\text{Na}$) (Figure 5). This arrangement increased not only the cavity depth but also the lipophilic interaction area with the

Figure 3. Cyclodextrin encapsulation process of rocuronium



Dashed arrows represent hydrophobic, thermodynamic attractions. Arrows at the positively charged ammonium of rocuronium represent electrostatic interaction with the negatively charged carboxyl groups of the sugammadex cyclodextrin.

Figure 4. Natural γ cyclodextrin showing available modification sites



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rocuronium molecule (Figure 6). The anionic carboxyl groups lining the rim provided additional electrostatic affinity for the rocuronium molecule at the positively charged ammonium group. The carboxyl

Figure 5. Sugammadex molecule

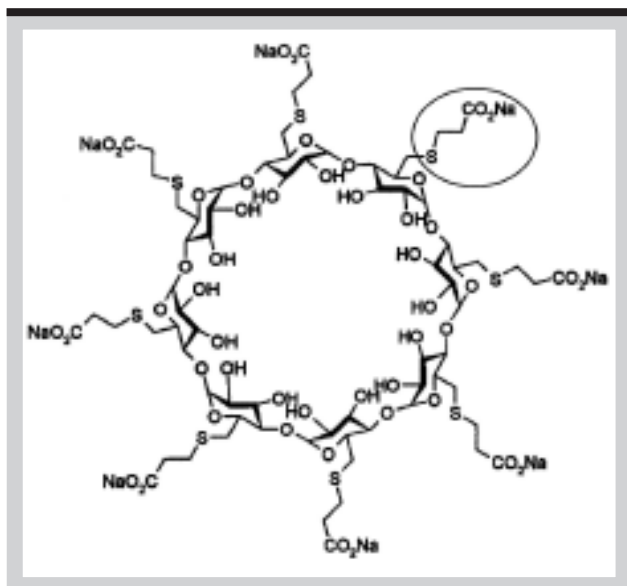
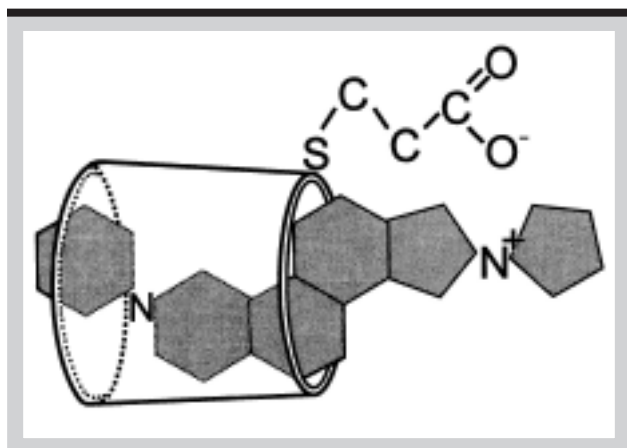


Figure 6. Encapsulation of rocuronium showing carboxyl thioether extension of cyclodextrin



Note: Eight carboxyl thioether extensions are present on the sugammadex molecule; only 1 is shown.

groups also promoted excellent aqueous solubility.⁶ The binding of rocuronium by sugammadex is so strong it has been reported to be one of the most stable cyclodextrin complexes ever studied ($K_a 1.8 \times 10^7 M^{-1}$).^{5,6,28} With the high affinity confirmed, Ploeger and others^{29,30} developed a pharmacokinetic and pharmacodynamic model that expressed the action of sugammadex and rocuronium as dynamic in 3 states: free sugammadex, free rocuronium, and bound sugammadex-rocuronium complex. Ploeger et al^{29,30} formulated a dynamic pharmacokinetic/pharmacodynamic interaction model that was validated to accurately simulate the interactions of sugammadex

and rocuronium. It also was concluded that this model may assist in dose scheduling.^{29,30} The rapid action of sugammadex reversal is due to the drawing out of rocuronium from the extracellular compartment into the plasma, where it is quickly bound.¹⁴ The high affinity of sugammadex for rocuronium accounts for this reversal of the concentration gradient and explains the speed and effectiveness of reversal with this new drug.

The high selectivity of sugammadex for rocuronium and vecuronium and lower selectivity for pancuronium has been compared with other lipophilic molecules. The sugammadex interaction with other anesthetic drugs is much lower than with the aminosteroid nondepolarizing muscle relaxants. Cortisone, hydrocortisone, and aldosterone formed complexes with sugammadex but were more than 100 times weaker. It was concluded that the weaker attractions for these biologic steroids is due to no electrostatic interactions with the molecule's carboxyl groups.⁶

Anesthesia practice may have an opportunity to not only reverse rocuronium and vecuronium more effectively but also eliminate serious side effects related to cholinesterase inhibitors and anticholinergics. The multiple side effects associated with cholinesterase inhibitors and anticholinergics have not been found with sugammadex. Sugammadex has consistently been well tolerated in animal and human studies. The clinical studies to date also have shown the ability of sugammadex to reverse even profound blockade, which cholinesterase inhibitors are unable to do. Improved surgical relaxation conditions may be maintained until the last moments of surgery and then fully reversed.

In addition to improved reversal of aminosteroid nondepolarizing muscle relaxants, the ability of sugammadex to rapidly reverse rocuronium after doses of 1.2 mg/kg may enable safer rapid-sequence intubation by avoiding succinylcholine and its side effects and the possible "can't intubate, can't ventilate" scenario associated with nondepolarizing muscle relaxants. Postoperative residual paralysis is unlikely after sugammadex reversal, and sugammadex may be considered as a rescue drug for patients experiencing incomplete reversal from cholinesterase inhibitors.

Deliberate re paralysis after sugammadex reversal remains possible because of the low affinity of this modified cyclodextrin for cis-atracurium and mivacurium.³¹ Sugammadex reversal of steroidal nondepolarizing muscle relaxants will not preclude continuing with nonsteroidal, nondepolarizing-induced paralysis.

Sugammadex also may have benefit in critical care

settings when weaning trials of prolonged mechanically ventilated patients are initiated. Assurance of no residual paralysis may enable healthcare personnel to better evaluate success or failure when attempting to wean and extubate patients who have received aminosteroid muscle relaxants. These and other potential benefits of sugammadex encapsulation instead of cholinesterase competitive antagonism need to be explored further. The findings of the clinical trials previously described have been promising, and after further study, approval from the US Food and Drug Administration may be likely. Sugammadex has been enthusiastically called “unique” and “novel” in its approach to muscle relaxant reversal and is poised to herald a new class of drug, the selective relaxant binding agents. Sugammadex (Org 25969) is recognized in the US Adopted Name and World Health Organization International Nonproprietary Name classifications. Organon International has expressed through media and Web releases a potential market date as early as 2007 or 2008. Anesthesia providers are likely to find the growing safety and efficacy profile of sugammadex of great benefit to the anesthetic management of their patients.

REFERENCES

- Bom A, Cameron K, Clark JK, et al. Chemical chelation as a novel method of NMB reversal: discovery of Org 25969 [abstract]. *Eur J Anaesthesiol.* 2001;18(suppl):99.
- Booij LHDG, de Boer HD, van Egmond J. Reversal agents for non-depolarizing neuromuscular blockade: reasons for and development of a new concept. *Semin Anesth Perioper Med Pain.* 2002;21:92-98.
- Alvarez Gomez JA. Muscle relaxants: novelties and future development. *Anesthesiologie und Reanimation (German).* 2002;12:95-98.
- Adam JM, Bennett DJ, Bom A, et al. Cyclodextrin-derived host molecules as reversal agents for the neuromuscular blocker rocuronium bromide: synthesis and structure-activity relationships. *J Med Chem.* 2002;45:1806-1816.
- Bom A, Bradley M, Cameron K, et al. A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew Chem Int Ed Engl.* 2002;41:266-270.
- Zhang MQ. Drug specific cyclodextrins: the future of rapid neuromuscular block reversal? *Drugs Future.* 2003;28:347-354.
- Puhringer FK, Rex C, Renner M, Friemel T, Baur P. Cyclodextrine: a new concept for rapid antagonization of deep neuromuscular block. *Journal für Anästhesie und Intensivbehandlung (German).* 2004;11:97-98.
- Tarver GJ, Grove SJA, Buchanan K, et al. 2-O-Substituted cyclodextrins as reversal agents for the neuromuscular blocker rocuronium bromide. *Bioorg Med Chem.* 2002;10:1819-1827.
- Organon International. Organon reports positive results from phase II studies with novel agent to reverse muscle relaxation in anesthesia [press release]. Available at: http://www.organon.com/news/press_releases/2005_05_31_organon_reports_positive_results_from_phase_ii_studies_with_novel_agent_to_reverse_muscle_relaxation_in_anesthesia.asp. Accessed May 26, 2005.
- Miller S, Bom AH. Org 25969 causes selective reversal of neuromuscular blockade induced by steroidal NMBs in the mouse hemidiaphragm preparation [abstract]. *Eur J Anaesthesiol.* 2001;18(suppl 23):100.
- 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(suppl 23):100.
- Hope F, Bom A. Org 25969 reverses rocuronium-induced neuromuscular blockade in the cat without important hemodynamic effects [abstract]. *Eur J Anaesthesiol.* 2001;18(suppl 23):100.
- van Egmond J, van de Pol F, Booij L, Bom A. Neuromuscular blockade induced by steroidal NMBs can be rapidly reversed by Org 25969 in the anaesthetized monkey [abstract]. *Eur J Anaesthesiol.* 2001;18(suppl 23):100.
- 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;99:632-637.
- de Boer HD, van Egmond J, van de Pol F, Bom A, Booij LH. Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized rhesus monkeys. *Anesthesiology.* 2006;104:718-723.
- Bom A, Mason R, McIndewar I. Org 25969 causes rapid reversal of rocuronium-induced neuromuscular block, independent of acid-base status [abstract]. *Anesthesiology.* 2002:A-1009.
- Gijsenbergh F, Ramael S, De Bruyn S, Reitbergen H, van Iersal T. Preliminary assessment of Org 25969 as a reversal agent for rocuronium in healthy male volunteers [abstract]. *Anesthesiology.* 2002; 96:A1008.
- Gijsenbergh F, Ramael S, Houwing N, van Iersal T. First human exposure of Org 25969: a novel agent to reverse the action of rocuronium bromide. *Anesthesiology.* 2005;103:695-703.
- Shields M, Giovannelli M, Moppett I, Mahajan RP, Mirakhor RK. Deep neuromuscular block with Org 25969. Poster presented at the European Society of Anesthesia Congress; May 2005; Vienna, Austria.
- Shields M, Giovannelli R, Mirakhor RK, Moppett I, 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.
- Khunl-Brady K, Rex C, Kjaer 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.
- Vanacker B, Vermeyen K, Struys MRF, et al. 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.
- 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.
- de Boer H, Marcus M, Schouten P, 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.
- Groudine SB, Soto R, Ehlers M, Roberts K, El-Mohtar K. Reversal from deep neuromuscular blockade with Org 25969. Poster presented at the American Society of Anesthesiologists Annual Meeting; October 2005; Atlanta, Ga.
- Rex C, Khuenl-Brady K, Sielenkaemper A, Kjaer CC, Puhringer FK. Reversal of high-dose rocuronium (1.2 mg/kg) with Org 25969. Poster presented at the American Society of Anesthesiologists meeting; October 2005; Atlanta, Ga.
- Cameron S, Fielding L. NMR diffusion coefficient study of steroid-cyclodextrin complexes. *Magn Reson Chem.* 2002;40:S106-S109.

28. Rekharsky MV, Inoue Y. Complexation thermodynamics of cyclodextrins. *Chem Rev*. 1998;98:1875-1917.
29. Ploeger BA, Ruigt G, Danhof M. Pk/pd modeling of reversal of neuromuscular blockade by a chemically optimised cyclodextrin [abstract]. *Clin Pharmacol Ther*. 2004;75:80.
30. Ploeger B, Houwing H, Bom A, van Iersel T, Zollinger D, Danhof M. The reversal of rocuronium-induced neuromuscular block by the cyclodextrin Org 25969: model development and validation. Poster presented at the Annual Meeting of the Population Approach Group in Europe; June 2004; Upsala, Sweden.
31. Bom AH, Thomson K. The potency and efficacy of non-steroidal blocking agents is not reduced when administered after reversal of

rocuronium-induced neuromuscular block by Org 25969 [abstract]. *Anesthesiology*. 2004;101:A1144.

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