

# Suggamadex: the donut with a bite

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Non-depolarizing muscle relaxants are used much more frequently than in the past, thanks to the fear of complications and side effects (and black-box warning) associated with the use of succinylcholine in children. While the onset time for all relaxants are similar if sufficient doses are administered, the offset time for the non-depolarizing relaxants remains prolonged, particularly at large doses. This has caused fear of the “cannot ventilate, cannot intubate” situation arising in children, a rare but potentially fatal scenario. In the less stressful scenario, timely antagonism of a large dose of relaxant when muscle relaxation is no longer required may be impossible thus needlessly prolonging the anesthetic. Since the steroidal muscle relaxants do not self-destruct and since traditional pharmacologic strategies that antagonize non-depolarizing relaxants cannot restore muscle tone in a timely manner (ie., before hypoxic brain insult sets in), chemists sought to develop a compound that could trap and eliminate the relaxant. This led to the birth of Suggamadex, a unique but vitally important compound that may save lives.

Suggamadex is a  $\gamma$ -cyclodextrin compound, that is a spatially arranged toroid comprised of 8 oligosaccharides. A toroid is a geometric “doughnut” that can rotate around its axis without intersecting the axis (like a wheel on its axle). These compounds are not new, having been discovered in 1891 by Villiers. Although most cyclodextrins are synthetic, enzymatically synthesized from starch, three were discovered in nature by Schardinger, termed Schardinger sugars:  $\alpha$ ,  $\beta$  and  $\gamma$  cyclodextrins. These toroids are very hydrophilic on the outer surface, hence their aqueous solubility, and much less hydrophilic on the inner surface, enabling them to trap hydrophobic and less hydrophilic compounds inside the ring. Cyclodextrins as a class of compounds have found great use in the food (trapping cholesterol removing it from foods), environmental (toxic pesticides, heavy metal) and pharmaceutical industries in the past 2-3 decades. Currently, Organon has developed Suggamadex specifically to irreversibly trap rocuronium (and possibly vecuronium) preventing its binding at the neuromuscular junction and inertly eliminating it. As the free rocuronium concentration decreases, the dissociation of rocuronium from the neuromuscular junction increases and muscle tone is restored.

## $\gamma$ -cyclodextrin

QuickTime™ and a  
decompressor  
are needed to see this picture.

Clinical trials in animals and humans have been progressing with an anticipated release of Sugammadex for clinical use in the first half of 2008. First human studies in 2005 demonstrated that this compound is safe and effective, with few side effects, and eliminated via the kidneys.<sup>1-4</sup> Recurarization has not been detected. Transient side effects were minimal but included hypotension, bradycardia and hiccups.

Recent clinical trials have further defined the clinical utility of Sugammadex in anesthesia. During profound stable neuromuscular block with 0.6 or 1.2 mg/kg rocuronium, the time to TOF 0.9 after Sugammadex was 4-5 minutes at 2 mg/kg and 1-1.5 minutes after 8 mg/kg.<sup>5</sup> In another study in which patients were paralyzed with a single dose of 0.6 mg/kg rocuronium, the time to TOF 0.9 when Sugammadex was given 3 minutes after the rocuronium was 5 minutes after 2 mg/kg and 1.8 minutes after 8 mg/kg.<sup>6</sup> In a comparison of the efficacy of Sugammadex during propofol or sevoflurane anesthesia, 2 mg/kg Sugammadex yielded similar times to recover neuromuscular function (TOF 0.9), 1.8 minutes.<sup>7</sup> In order to prove the clinical effectiveness of Sugammadex, the time to recover TOF during paralysis with rocuronium (twitch height was 6-12%) was compared with Sugammadex, edrophonium and neostigmine.<sup>8</sup> The time to recover TOF 0.9 was 107 seconds after Sugammadex 4 mg/kg versus 331 after edrophonium (1.0 mg/kg) and 1044 after neostigmine (0.07 mg/kg). By 2 minutes after administration of the reversal agent, 75% of those receiving Sugammadex had a TOF 0.9 compared with 0% of those receiving edrophonium and 5% of those receiving neostigmine. To date, no clinical trials with Sugammadex in children have been published.

The introduction of Sugammadex into clinical practice will revolutionize control of neuromuscular blockade. No longer will administration of a neuromuscular blocking agent be considered “burning your bridges” in a subject with a difficult airway.

Furthermore, Sugammadex may extricate patients from a life-threatening airway difficulty in the perioperative period.<sup>9</sup> But we must look beyond this paradigm to appreciate that this pharmacotechnology may be applicable to many other situations in medical practice that heretofore have not been easily managed. Difficult clinical situations such as bupivacaine toxicity, latex anaphylaxis (or any other anaphylaxis) and chronic opioid accumulation may be amenable to stereospecific cyclodextrins that rid the body of these offending compounds with alacrity. I predict that Sugammadex will help the anesthesiologist relax more than the patient when stress levels are rising with a difficult airway in a paralyzed patient. Even more importantly, I predict this class of compounds will solve clinical problems well beyond the neuromuscular junction where solutions to these problems simply do not exist!

#### REFERENCES:

1. de Boer HD, van Egmond J, van de Pol F, et al. Reversal of profound rocuronium neuromuscular blockade by sugammadex in anesthetized rhesus monkeys. *Anesthesiology* 2006;104:718-23
2. de Boer HD, van Egmond J, van de Pol F, et al. Sugammadex, a new reversal agent for neuromuscular block induced by rocuronium in the anaesthetized Rhesus monkey. *Br J Anaesth* 2006;96:473-9
3. Gijzenbergh F, Ramael S, Houwing N, et al. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. *Anesthesiology* 2005;103:695-703
4. Sorgenfrei IF, Norrild K, Larsen PB, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. *Anesthesiology* 2006;104:667-74
5. Groudine SB, Soto R, Lien C. et al. A randomized, dose-finding, phase II study of the selective relaxant binding drug, sugammadex, capable of safely reversing profound rocuronium-induced neuromuscular block. *Anesth Analg* 2007;104:556-62
6. Sparr HJ, Vermeyen KM, Beaufort AM, et al. Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomized multicenter study. *Anesthesiology* 2007;106:935-43
7. Vanacker BF, Vermeyen KM, Struy MRF. Reversal of rocuronium-induced neuromuscular block with the novel drug sugammadex is equally effective under maintenance anesthesia with propofol or sevoflurane. *Anesth Analg* 2007;104:563-8
8. Sacan O, White PF, Tufanogullari B, Klein K. Sugammadex reversal of rocuronium-induced neuromuscular blockade: a comparison with neostigmine-glycopyrrolate and edrophonium-atropine. *Anesth Analg* 2007;104:569-74
9. Lenz A, Hill G, White PF. Emergency use of sugammadex after failure of standard reversal drugs. *Anesth Analg* 2007;104:585-6