Sugammadex: A Comprehensive Review of the Published Human Science, Including Renal Studies

Kelsey Martin, MD.
CA3 Resident,
Indiana University
School of Medicine
Department of Anesthesia
Article Abstract


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Partownavid P¹, Romito BT, Ching W, Berry AA, Barkulis CT, Nguyen KP, Jahr JS.

Author information

Abstract

Although neuromuscular block (NMB) allows immobility for airway management and surgical exposure, termination of its effect is limited by and associated with side effects of acetylcholinesterase inhibitors. Sugammadex is a selective relaxant binding agent that has been shown to reverse deep NMB, even when administered 3 minutes following a 1.2 mg/kg dose of rocuronium. This novel drug is a modified gamma cyclodextrin, that through encapsulation process terminates the effects of rocuronium and vecuronium (aminosteroid muscle relaxants), and enables the anesthesiologists rapidly to reverse profound NMB induced by rocuronium or vecuronium, in a "can't ventilate, can't intubate" crisis. In this review, data from published phase 1, 2, and 3 clinical trials are reviewed and presented. In addition, clinical trials on special patient populations (patients with pulmonary disease and renal insufficiency) are evaluated. Each article reviewed will conclude with a discussion of relevance, focus on adverse event profile, and clinical usefulness.

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Safety, tolerability, efficacy, and ideal dosing of sugammadex.

Coughing, movement during anesthesia, mild-to-moderate hypotension, headache, nausea, and injection site irritation were the main adverse reactions noted.

Primary efficacy endpoint was generally a train of four of 0.9 by acceleromyograph. Not surprisingly, the studies demonstrated a significant decrease in T4/T1 recovery time with sugammadex as compared to placebo. A study (Groudine et al) designed to assess the safety and efficacy of sugammadex for the reversal of profound neuromuscular blockade (post-tetanic count of one or two) found that in patients who received 0.6 mg/kg of rocuronium, the mean time to recovery of TOF ratio to 0.9 decreased from an average of 44.2 minutes with 0.5 mg/kg of sugammadex to 1.5 minutes with 8 mg/kg of sugammadex.

Therefore, they concluded that sugammadex doses of 4-8 mg/kg safely and quickly reversed profound NMB but lower doses (0.5-1 mg/kg) can result in incomplete reversal.
**HIGHER DOSES** of sugammadex (16 mg/kg, 32 mg/kg) were also studied and demonstrated a similar side effect profile to smaller doses. Puhringer et al demonstrated a plateau in recovery time following sugammadex reversal of a 1.2 mg/kg rocuronium dose which occurred at sugammadex doses greater than or equal to 8 mg/kg.

![Plateau in recovery time](image_url)
Later studies incorporated volatile anesthetics (as opposed to the TIVA of prior studies) and the effectiveness of sugammadex was unaffected.

Duvaldestin et al found a plateau effect in sugammadex doses greater than 4 mg/kg and again demonstrated suboptimal reversal with 0.5-1 mg/kg.

Another study by Purhinger et al found a slightly faster reversal of rocuronium than vecuronium which they attributed to the increased affinity of sugammadex for rocuronium, leading to faster complex formation and shorter recovery times. Times to TOF 0.9 in that study for rocuronium were 96.3 minutes with placebo and 1.5 minutes with sugammadex compared to vecuronium reversal times of 79 minutes after placebo and 3 minutes after sugammadex.
Comparing its reversal to that of the standard reversal drug, neostigmine

**FIGURE 5.** Time to recovery of the TOF ratio to 0.9 from profound rocuronium-induced NMB after administration of sugammadex or neostigmine (intent-to-treat population, imputed data, n = 74). Adapted from Jones et al. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Flockton et al compared sugammadex reversal of rocuronium-induced NMB with neostigmine reversal of cisatracurium-induced NMB and reported that the sugammadex reversal was significantly faster. Further studies supported this finding.

Examples of recovery profiles for vecuronium 0.1 mg/kg after administration of (A) sugammadex 4 mg/kg or (B) neostigmine 70 µg/kg at a target of 1–2 PTC. Bars represent first twitch ($T_1$) values (twitch height %) and dots represent the TOF ratio. PTC, post-tetanic counts. Adapted from Lemmens et al.14 Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
An interesting study by Lee et al compared 16 mg/kg of sugammadex given 3 minutes after 1.2 mg/kg of rocuronium for reversal of profound NMB to that of spontaneous recovery from block induced by 1 mg/kg of succinylcholine.

The mean time of recovery of T1 to 90% was significantly faster with rocuronium/sugammadex at 6.2 minutes compared with succinylcholine recovery of 10.9 minutes.

Rex et al studied continuous rocuronium infusion (7 mcg/kg/min to maintain NMB depth of zero response to TOF) reversal by sugammadex and concluded that a single dose of sugammadex 4 mg/kg administered after appearance of T1 of 3%-10% is well-tolerated and effective reversal.
Safety of sugammadex

**ELDERLY PATIENTS**

Results showed that recovery time of TOF to 0.9 after sugammadex was *slightly slower in elderly patients* versus adult patients (3.6 vs. 2.3 minutes). Side effects possibly related to sugammadex that were seen in the elderly included *tachycardia, pyrexia, dizziness, oliguria, and procedural hypotension*. Although sugammadex has decreased clearance in the elderly, *no dose adjustment was found to be necessary*.

**PULMONARY DISEASE**

study included in this review article dealt with patients with a history of asthma, COPD, bronchitis, or tobacco use. The author concluded that the occurrence of *bronchospasm* in 2.6% of patients in this study suggests that physicians be prepared for this event when administering sugammadex to patients with underlying pulmonary disease. However, it should be noted that the study did not include a nonsugammadex group with which to compare rates of bronchospasm.
RENAL DISEASE

In the absence of sugammadex, rocuronium excretion is primarily through the bile. In the presence of sugammadex, urinary excretion of the rocuronium-sugammadex complex is the primary elimination route. Some early studies indicated the possibility of renal tubular or glomerular damage with use of sugammadex. This prompted further studies into patients with renal disease. Reversal efficacy and blood/urine levels of sugammadex following administration were studied in patients with a wide spectrum of renal function (normal controls to dialysis-dependent patients). The difference in reversal speed with standard dosing was not statistically significant in the renal impairment vs control groups. However, the drug was retained for a longer period in renal failure patients and the author concluded that larger studies on the pharmacokinetics of sugammadex in this patient population would be needed. Another study noted that after the reversal of rocuronium-induced NMB in renal failure patients, the recovery of TOF ratio to 0.9 is significantly faster than T1 recovery to 90%. Therefore, after reversal with sugammadex in these patients, the TOF ratio as the only measurement for adequate reversal of NMB may not always be reliable and twitch height has to be taken into account as well.