Sugammadex: A neuromuscular blockade agent encapsulator

Victoria Yepes Hurtado BSN, RN

Abstract

Sugammadex sodium, a modified γ-cyclodextrin, represents a new class of drugs effective at reversing non-depolarizing muscle relaxants rocuronium and vecuronium. The cylindrical, basket-like structure encapsulates neuromuscular blocking agents which results in rapid reversal of paralysis within three minutes. The current literature was reviewed to analyze the clinical implications and considerations with its administration.

Keywords: cyclodextrin, encapsulation, selective relaxant binding agent, sugammadex, supramolecular

Sugammadex sodium, a modified γ-cyclodextrin and a pioneer of its kind, represents a new class of drugs effective at reversing the non-depolarizing muscle relaxants rocuronium and vecuronium.[1] In order to induce paralysis, non-depolarizing neuromuscular blocking agents (NMBAs) compete with acetylcholine (ACh) for the cholinergic receptors at the motor end-plate of the neuromuscular junction. Traditional reversal of non-depolarizing NMBAs consists of either spontaneous recovery or administration of neostigmine, an anticholinesterase that indirectly reverses the block by increasing the amount of ACh in the neuromuscular junction. Several limitations exist with neostigmine such as time-sensitive administration of the reversal, which must be given no sooner than visualization of two-out-of-four twitches on the train-of four. Inconsistent, variable outcomes occur with neostigmine, related to time- and dose-dependent requirements of administration, which results in incomplete reversal. Neostigmine is unable to reverse deep neuromuscular blockade (NMB) and unable to inactivate free circulating NMBA from binding to ACh receptors to prevent recurarization. In addition, glycopyrrolate or atropine is usually administered concurrently with neostigmine to counteract the adverse effects associated with neostigmine use alone. The adverse effects of atropine and glycopyrrolate are related to muscarinic antagonism and cause dry mouth, urinary retention, and tachycardia, the latter of which can negatively affect the hemodynamic status in patients with cardiac disease. Conversely, sugammadex provides a new alternative for reversal that negates many of the risks associated with neostigmine and muscarinic antagonist administration.

Corresponding author: **Victoria Yepes Hurtado**
Contact Information: vyepeshurtado@gmail.com
DOI: 10.12746/swrccc.v5i20.407

Chemical structure

The fundamental properties of cyclodextrins consist of a cylindrical, basket-like shape with a lipophilic cavity and hydrophilic exterior, which produces a water-soluble complex that transports lipophilic molecules within its core (Figure).[2,3] Sugammadex's name gives light to its chemical structure, *su* denoting sugar and *gammadex* representing gamma-cyclodextrin, the basic structural molecule.[2] The original γ-cyclodextrin is unable to accommodate the full size of the NMBA, but modifying the γ-cyclodextrin by extending the molecule with eight hydroxyl side chains enables

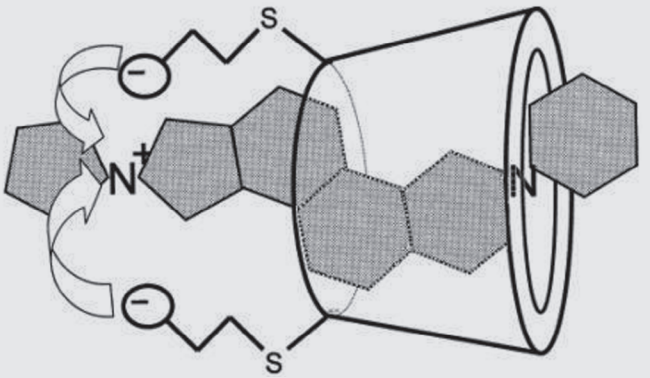

Figure The sugammadex-NMBA complex. For simplification only two of the eight hydroxyl side chains are shown. From https://en.wikipedia.org/wiki/Sugammadex. Accessed 6-1-2017

sugammadex to encapsulate the entire aminosteroid NMBA. The addition of terminal negatively charged carboxyl groups inhibits the side chains from collapsing into the core and creates an electrostatic bond with the positively charged aminosteroid quaternary groups, which entraps the NMBA within the cyclodextrin cavity at a 1:1 ratio.[2-5] The "host-guest complex" is achieved by electrostatic bonds and van der Waals' interactions, creating a stable supramolecule that binds to vecuronium and rocuronium at an association-disassociation rate of 10,000,000:1 and 25,000,000:1, respectively.[2,3,6-9] Therefore, sugammadex binds 25 million times more rocuronium than it releases; it has a 2.5-times greater affinity for rocuronium than vecuronium.

Mechanism of action

Neuromuscular blockade reversal is dependent on decreasing the plasma free concentration of rocuronium or vecuronium. Upon injection, sugammadex begins encasing the circulating NMBA, resulting in a concentration gradient. This rapid decrease in circulating concentration causes the paralyzing agent to migrate out of the neuromuscular junction, back into the bloodstream where it is inactive by the formation of the host-guest complex. Unlike neostigmine, reversal is successful even with profound neuromuscular blockage while remaining chemically inert, consequently preventing receptor interactions or interference with enzyme activity, biosynthesis, or voltage-gated ion channels.[1-3,5,10-14]

Interactions

Theoretically, there is a possibility that sugammadex could bind to other drugs, leading to the displacement of the non-depolarizing NMBA and causing recurarization, or bind to other medications, such as oral contraceptives, and reduce their efficacy.[10,11,15,16] However, its affinity for rocuronium is at least 700 times greater than its affinity for other drugs, making this unlikely. An exception to this involves hormonal contraceptives. *In vitro* binding studies have shown that sugammadex may encapsulate progestogen, which reduces the efficacy of hormonal contraceptives considered equivalent to missing dose(s) of an estrogen or progestogen contraceptive.[17] Due to this possibility, women using hormonal contraceptives should be advised to use additional birth control methods for seven days post sugammadex administration.[17]

Dosing

Sugammadex dosing is based on total body weight. It has been suggested that in obese patients dosing based on lean body weight using gender and height can produce complete reversal while minimizing the high costs associated with sugammadex administration. However, utilizing lean body weight can cause under dosing of sugammadex, which can result in incomplete reversal of NMB and subsequent respiratory failure potentiated by obstructive apnea associated with obesity. Therefore, at this time standard dosing continues to be based on weight and train of four twitches as outlined in the Table.

Train-of-four	Post-tetanic count	Sugammadex dose
2/4	-	2 mg/kg
0/4	1-2	4 mg/kg

Metabolism

Hepatic metabolism is responsible for rocuronium and vecuronium clearance; renal clearance regulates the sugammadex-NMBA complex elimination.[10,18-24] In healthy kidneys with a glomerular filtration rate (GFR) of 75-120 ml/min, 70% of the dose is excreted in six hours, and 80-90% in 24 hours.[21,25,26] In renal failure, with GFR <30ml/min, only 29% of the dose administered is cleared by 72 hours.[24] The use of high-flux dialysis removes the bound sugammadex, but at this time sugammadex administration is not recommended for patients with severe renal dysfunction.[16,18,23,24]

Clinical applications

Sugammadex has many advantages when compared to the administration of neostigmine or no reversal agent at all. On average, dose-dependent intravenous administration of sugammadex results in full reversal of NMB within three minutes, even in circumstances of deep neuromuscular block, and avoids the possibility of recurarization.[3,27] This makes it a possible rescue strategy in "can't intubate, can't ventilate" scenarios to recover spontaneous ventilation and airway tone. However, analysis of the cause of inability to intubate as well as correct timing of sugammadex administration must be considered. If the inability to intubate is due to airway swelling related to traumatic injury, such as after multiple intubation attempts, or due to angioedema from anaphylaxis, sugammadex administration is unlikely to restore a patent airway.[28,29] With traditional reversal using neostigmine, residual blockade is a common occurrence and can lead to adverse outcomes.[30,31] The use of sugammadex as a rescue during residual paralysis prevents negative sequelae associated with prolonged intubation or extubation after incomplete cholinesterase inhibitor reversal.[5,32-34] After sugammadex administration, if reinduction of neuromuscular blockade is required, NMB can be achieved with isoquinoline NMBAs or succinylcholine at standard dosing.[5] Rocuronium can be re-administered five minutes after receiving sugammadex, but a slower onset and duration time should be expected due to the remaining sugammadex in circulation.[35-37]

Special populations

Sugammadex administration is especially advantageous in special patient populations, including patients with severe pulmonary diseases, cardiac diseases, hepatic dysfunction, or morbid obesity, and patients with neuromuscular diseases, particularly myasthenia gravis.

Patients with significant pulmonary disease and respiratory dysfunction are at a higher risk for negative outcomes, such as prolonged mechanical ventilation, atelectasis, and exacerbation of chronic lung disease, related to residual NMB and side effects of cholinesterase inhibitor reversal agents administration. The use of sugammadex supports respiratory mechanics, allows greater recovery of muscle strength, and promotes more successful and timely extubations.[5,13]

Sugammadex administration in patients with cardiac disease does not produce hemodynamic instability or arrhythmias as cholinesterase inhibitors and anticholinergics can. In patients with heart failure, reversal of NMB occurs safely without altering hemodynamics but with slightly longer recovery times. This occurrence is due to decreased cardiac output and slower circulation times, which lead to delayed distribution of sugammadex.[5,11,38] Furthermore, neostigmine is contraindicated in patients with cardiac conduction abnormalities, such as Brugada syndrome or prolonged QT intervals, as it may precipitate heart block, ventricular fibrillation, or torsades de pointes. However, sugammadex is safe and effective in these patients.[39-41]

Patients with liver disease have longer blockade recovery times, even after administration of neostigmine, due to slower hepatic metabolism of rocuronium or vecuronium.[42] The encapsulation by sugammadex alters the excretion of rocuronium or vecuronium to a liver-independent, renal pathway and allows safe administration in patients with hepatic dysfunction.

In obese patients, delayed recovery from NMB after neostigmine administration is related to paralytic overdosing based on actual body weight and subsequent residual paralysis, which causes increased airway collapsibility and impaired breathing mechanics.[43]

Administration of sugammadex dosed on actual body weight eliminates the variability associated with neostigmine and allows complete reversal with optimal neuromuscular function.

The area of greatest potential benefit with the use of sugammadex is in patients with muscular and neuromuscular diseases, particularly myasthenia gravis. Patients with these diseases have multiple challenges, including preexisting muscle weakness and fatigability, altered sensitivity toward NMBA, concurrent cholinesterase inhibitor use, and existing comorbidities, such as chronic obstructive pulmonary disease, bronchiectasis, and basal atelectasis. Full return of baseline motor function is paramount for these patients to prevent prolonged mechanical ventilation, which could further compromise lung and muscle function. Reversal consisting of a train of four ratio of 0.9 may not be adequate for these patients who require the addition 10% function to adequately ventilate spontaneously. Sugammadex administration negates the potential for residual paralysis and allows quick and reliable restoration of their preoperative state.[5] Reversal using neostigmine in these patients poses a risk of cholinergic crisis, due to cholinesterase inhibitor administration for reversal coupled with concurrent oral cholinesterase inhibitor use. This risk can be avoided with sugammadex administration.[5,44-49]

Future implications

Supramolecular chemistry utilizing encapsulation methods will continue to contribute to the development of neuromuscular blockade agent reversals. A medication of interest is calabadion 2, a nanocontainer capable of reversing steroidal and benzylisoquinoline NMBAs, the latter of which sugammadex cannot encapsulate.[14,50] This medication is an acyclic cucurbit[n]uril molecule suitable for binding to the hydrophobic steroidal NMBA due to its barrel-shaped cavity formed by a central glycoluril tetramer with four sulfonate groups which promote cation binding and water solubility.[51] After testing in rats, it was found that calabadion 2 was able to rapidly reverse vecuronium, rocuronium, and cisatracurium, even with profound neuromuscular blockade in a dose-dependent manner.[52] Compared to sugammadex, calabadion 2 has a superior binding affinity to rocuronium and is 89 times stronger.[52] Due to the broad-spectrum reversal, other studies have shown calabadion 2 also encapsulates etomidate and ketamine, potentially making it an ideal antagonist for both general anesthetics and neuromuscular blockade.[53]

Conclusions

Although sugammadex is a relatively new drug in the United States market, its use among clinicians will continue to increase as the advantages over traditional methods are realized. Therefore, thorough understanding of the mechanism of action, pharmacokinetics, pharmacodynamics, and benefits of use in special patient populations is essential for all levels of providers, regardless of their scope of practice.

Sugammadex is the first representative of a new class of drugs designed to selectively reverse steroidal neuromuscular agents by encapsulation. The host-guest complex provides a unique method of inactivating NMBAs rocuronium and vecuronium with minimal adverse effects, unlike the traditional methods depending on a spontaneous recovery or indirect reversal with cholinesterase inhibitors. Sugammadex rapidly and predictively reverses all levels of NMB and can be used in multiple patient categories with a limited number of contraindications. Supramolecular chemistry will continue the development of muscle-relaxant binding agents using drug inactivation by encapsulation with calabadion 2, a prospective drug likely to enter clinical practice.

Article citation: Yepes Hurtado V. Sugammadex: a neuromuscular blockade agent encapsulator. The Southwest Respiratory and Critical Care Chronicles 2017;5(20):44-49.
From: University Medical Center, Lubbock, TX.
Submitted: 4/30/2017
Accepted: 7/4/2017
Reviewer: John Wasnick MD
Conflicts of interest: none

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