Sugammadex

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January 14, 2016

Unmet Need

- An unmet need exists in anesthesia for a neuromuscular blockade (NMB) reversal agent that acts quickly, with minimal side effects, and with low risk for residual or recurrent paralysis following surgery.
- Currently, reversal of NMB is achieved via the use of acetylcholinesterase inhibitors (AChEIs), which increase the availability of acetylcholine at the neuromuscular junction and reverse NMB, however these agents do not affect the metabolism or elimination of neuromuscular blocking agents (NMBAs) themselves.

This educational activity is supported by an educational grant from Merck.

Current State

- At Maximal inhibition of acetylcholinesterase activity (deep NMB) neuronal release of acetylcholine becomes the rate limiting step in further restoration of muscle function, limiting the efficacy that can be achieved with AChEIs.
- Because of their indirect mechanism of action (MOA), AChEIs cannot reverse deep NMB, therefore, deep NMB cannot be maintained to the end of the surgical procedure. AChEIs also have unwanted side effects related to increased cholinergic activity.
- To help ameliorate these, anti-muscarinics, such as atropine or glycopyrrolate, are usually co-administered with AChEIs, but this practice leads to additional side effects.
- Finally, AChEIs are associated with risk for recurrence of NMB or post-operative residual paralysis.

Disclosure

- I have received Consulting Fees and have been awarded a Research Grant from Merck.

Background

- On 11-Mar-2008, Sugammadex was discussed at the Anesthetics and Life Support Advisory Committee .
- The committee voted with a positive vote (10/0) in favor of the safety and efficacy of sugammadex, the issue of potential for hypersensitivity was not fully discussed.
- Subsequently, the FDA issued a Not Approvable letter, citing two clinical issues that needed to be further addressed:
  - 1) The potential for repeated sugammadex administration to increase risk of potential hypersensitivity reactions, and
  - 2) The potential for sugammadex to affect coagulation and/or bleeding risk.

Background

- Merck conducted three dedicated trials to address these two issues, and resubmitted the NDA in December 2012.
- The FDA in 2012 then issued a Complete Response letter indicating that the potential of hypersensitivity upon repeated dosing had not been adequately addressed due to issues associated with conduct of the clinical hypersensitivity trial, including incomplete maintenance of the blind, and deficiencies in study monitoring and documentation falling short of clinical trial standards.
- The NDA was resubmitted in October 2014 with a new hypersensitivity trial (Trial P101) and following review, the FDA issued a second Complete Response letter where the FDA asked for a number of sensitivity analyses in several patient subgroups in Trial P101.
- The NDA resubmission in June 2015 included these sensitivity analyses.

Indication

- FDA Approved Indication:
  - BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery.
- Dosage Forms:
  - 200 mg/2 mL (100 mg/mL) in a single-dose vial for bolus injection
  - 500 mg/5 mL (100 mg/mL) in a single-dose vial for bolus injection

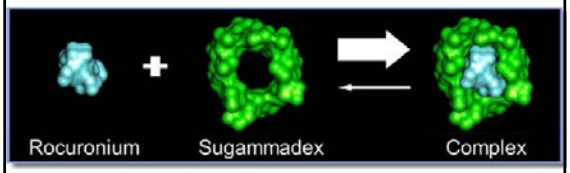
Sugammadex

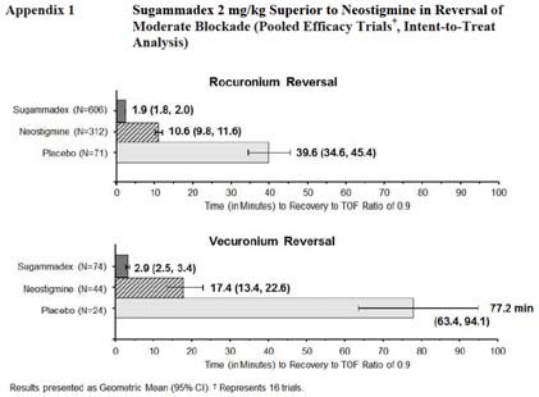
- A modified cyclodextrin and a novel selective relaxant binding agent (SRBA), which has been developed to reverse any depth of NMB including deep NMB, induced by the NMBAs rocuronium or vecuronium bromide.
- Sugammadex acts by forming high affinity complexes with rocuronium or vecuronium, which prevents the complexed NMBAs from binding to nicotinic receptors in the neuromuscular junction, thus reversing NMB.
- Sugammadex does NOT cross the blood-brain-barrier and does not stimulate the cholinergic nervous system, thus avoiding the unwanted autonomic nervous system side effects associated with neostigmine and similar drugs, thereby negating the need for concurrent administration of antimuscarinic drugs in an attempt to counteract AChEI-related side effects.

Dosing and Administration

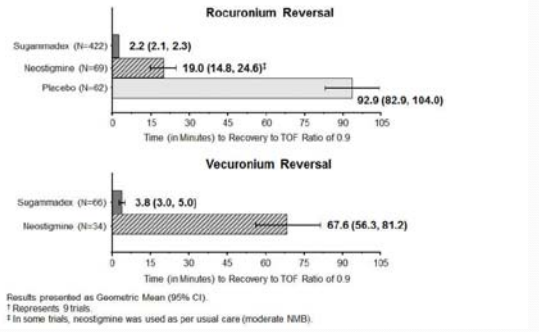
- Administered as a single bolus injection.
- **Monitor for twitch responses** to determine the timing and dose for BRIDION administration.
- For rocuronium and vecuronium:
  - **4 mg/kg** is recommended if spontaneous recovery of the twitch response has reached **1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation.**
  - **2 mg/kg** is recommended if spontaneous recovery has reached the reappearance of the **second twitch in response to TOF stimulation**.
- For rocuronium only:
  - **16 mg/kg** is recommended if there is a clinical need to reverse neuromuscular blockade soon (approximately **3 minutes**) after administration of a single dose of **1.2 mg/kg of rocuronium**

Structure - Cyclodextrin





Appendix 2 **Sugammadex 4 mg/kg Superior to Neostigmine in Reversal of Deep Blockade (Pooled Efficacy Trials*, Intent-to-Treat Analysis)**



Results presented as Geometric Mean (95% CI).
† Represents 9 trials.
‡ In some trials, neostigmine was used as per usual care (moderate NMB).

Specific Populations

- Pediatrics: Safety and effectiveness of BRIDION have not been established in patients ≤ 17 years of age.
- Severe Renal Impairment: Not recommended

Caution

- **Contraindication:** Known hypersensitivity to sugammadex or any of its components.
- **Anaphylaxis:** Anaphylaxis has occurred in 0.3% of healthy volunteers. Observe patients for an appropriate period of time after administration.
- **Marked Bradycardia:** Cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after administration. Monitor for hemodynamic changes and administer anticholinergic agents such as atropine if clinically significant bradycardia is observed.
- **Respiratory Function Monitoring:** Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored and the ability to maintain a patent airway is assured. Should neuromuscular blockade persist after BRIDION or recur following extubation, take appropriate steps to provide adequate ventilation.
- **Waiting Times for Re-Administration of Neuromuscular Blocking Agent:** If re-administration of a neuromuscular blocking agent is required after reversal with BRIDION, waiting times should be based on the dose of BRIDION, and the renal function of the patient. Consider use of a nonsteroidal neuromuscular blocking agent.

Improvements over Current Standard of Care

- Only sugammadex can reverse deep NMB induced by rocuronium or vecuronium.
- Compared with spontaneous reversal of the effects of the depolarizing NMBA succinylcholine (with short duration of action currently used for rapid sequence induction), the data demonstrate that sugammadex 16 mg/kg resulted in significantly faster and more reliable reversal of rocuronium-induced NMB when given three minutes after the administration of rocuronium 1.2 mg/kg, providing the potential to reduce anoxia and poor outcomes when urgent or emergent reversal of rocuronium-induced NMB is required.
- Residual NMB and recurrence of NMB following reversal were infrequent with the use of sugammadex at recommended doses as compared to usual care, implying reduced risk for complications post-operatively.

Drug Interactions

- Toremifene (Antiestrogen Therapy): Recovery could be delayed in patients using toremifene.
- Hormonal contraceptives: Patients using hormonal contraceptives must use an additional, non-hormonal method of contraception for the next 7 days following BRIDION administration.

Safety and Tolerability

- Safety and tolerability were assessed in data from 56 clinical trials in which IV sugammadex was administered, comprising 5999 exposures in 4453 unique adult subjects. Within these 56 trials, two pooled datasets were defined:
  - Pooled Phase 1-3 dataset (42 of the 56 clinical trials): surgical subjects or healthy subjects receiving IV sugammadex with anesthesia and/or NMBA. Two subsets were defined from the Pooled Phase 1-3 data set for head-to-head comparisons between sugammadex and placebo or neostigmine, respectively.
  - Pooled Phase 1 dataset (14 of the 56 clinical trials): subjects receiving IV sugammadex without anesthesia or NMBAs.
- Experience informing safety is also available from routine clinical use, as sugammadex is currently approved and marketed in more than 50 countries worldwide, with approximately 11.5 million patients exposed as of 31-Mar-2015.

Sugammadex - Tolerability

- In clinical studies, the use of sugammadex was generally safe and well tolerated.
- No clinically important differences were observed between sugammadex and placebo in the Pooled Phase 1-3 datasets for the incidence of AEs, SAEs, AEs with severe intensity, deaths, or discontinuation due to AEs.
- The **most commonly reported AEs were primarily related to the surgical process and/or general anesthesia in both groups** (e.g., procedural pain, nausea, wound complication), and evidence did not suggest increased frequency or severity of AEs with increased dose (2 mg/kg, 4 mg/kg and 16 mg/kg).
- **No clinically relevant effects of sugammadex were observed for laboratory or vital signs** in Phase 1 subjects who were not anesthetized and who did not receive an NMBA.
- In subjects who received an NMBA in the Pooled Phase 1-3 trials, observed changes in vital signs were consistent with those expected in a population of surgical subjects.
- Infrequent reports of potential hypersensitivity reactions prompted a request from the FDA for further characterization of these AEs prior to approving sugammadex.

Trial 101 Outcomes

- 4 mg/kg and 16 mg/kg sugammadex were associated with a higher incidence (6.6% and 9.5%, respectively) of hypersensitivity as compared to placebo (1.3%).
- 91% of hypersensitivity reactions were mild (as judged by the adjudication committee), started within minutes after dose administration, and resolved spontaneously within minutes to hours of onset of symptoms.
- Three cases required treatment, all in the 16 mg/kg treatment arm, and all responded quickly to antihistamine and/or corticosteroid, and no cases required treatment with epinephrine.
- There was one case adjudicated as anaphylaxis that was mild in severity (sneezing, nasal congestion, conjunctival edema, urticaria, and swelling of the uvula, and a transient decrease in peak expiratory flow to ~30% below baseline, that responded to treatment with antihistamine and corticosteroid).
  - This case, in which the subject displayed no signs of hypotension, occurred in the 16 mg/kg arm after the subject's first dose of sugammadex.
- **No cases of anaphylaxis were observed in the 4 mg/kg or placebo arms.**
- **There was no increase in the frequency or severity of hypersensitivity with repeated administration of sugammadex**, providing evidence that sensitization and hence increased clinical risk does not occur with repeated administration of sugammadex.

Severe Events

- Extensive post-marketing safety experience of sugammadex in approximately 11.5 million patients has confirmed the potential for hypersensitivity reactions in exposed patients.
- Rare cases of bradycardia have been reported in the postmarketing environment that appear to be responsive to usual anticholinergic therapy.

Hypersensitivity – Mechanism of Action

- Based on the measurement of serum tryptase, the evidence did not suggest mast cell degranulation in any of the adjudicated cases of hypersensitivity and anaphylaxis.
- Specific IgE antibody development was not detected.
- In Trial P06042, skin testing was also employed, as well as serum and urine biomarkers for the complement pathway, the contact system, endothelial and neutrophil activation, and ex-vivo measurements of histamine release from basophils.
- Based on the totality of the mechanistic and clinical data, the events of hypersensitivity, including anaphylaxis, are not consistent with Type 1 immune-mediated (IgE) hypersensitivity and the mechanism of hypersensitivity to sugammadex is undetermined.

Dedicated Hypersentivity Trial (Trial 101)

- Trial P101 was a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the incidence of hypersensitivity after repeated single-dose administrations of sugammadex.
- In this trial, 375 healthy awake subjects, who did not receive NMBAs or anesthetics, were randomized to treatment with three successive single doses (separated by approximately five weeks to allow potential sensitization to develop) of one of the following treatments in a 2:2:1 ratio: 4 mg/kg sugammadex, 16 mg/kg sugammadex, or placebo, respectively.
- Aim of the trial was to understand whether repeated administration of sugammadex was associated with increasing risk for hypersensitivity and anaphylaxis.
- For this reason, the trial was designed to maximize the likelihood of detecting all hypersensitivity events, irrespective of their immediate clinical significance, and used an intensive case-finding methodology to elicit signs and symptoms consistent with a hypersensitivity reaction.

Conclusions

- Sugammadex is a new drug developed for reversal of NMB induced by either rocuronium or vecuronium, and has been studied for reversal of moderate or deep NMB at doses of 2 or 4 mg/kg, respectively.
- Sugammadex acts rapidly and completely to reverse NMB of any depth.
- Because of its effectiveness at reversing NMB, sugammadex allows anesthesiologists to maintain deep NMB until the end of the procedure, as necessary, to improve surgical conditions and safety by ensuring more complete muscle relaxation and preventing unwanted patient movement.
- The rapidity and completeness of NMB reversal after sugammadex administration also reduces the risk of recurrent or residual NMB post-operatively.
- Because residual block has been associated with post-operative respiratory complication, this is an important potential safety advantage over current practice.

Recommendations

- Approve Sugammadex (200 and 500 mg vials) for MH System Formulary
- Mandate that all areas where Sugammadex/General Anesthesia may be provided, Train of Four Twitch Monitors be installed and maintained
- Require Assessment and Documentation of TOF by all Anesthesia Providers prior to Administration of Sugammadex (to reduce under/over dosing).

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