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Sugammadex and recurarization in an infant

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Keypoints

1. Sugammadex is a novel pharmacologic agent, which reverses neuromuscular blockade by encapsulating rocuronium or vecuronium, thereby providing rapid and complete recovery of neuromuscular function even in the presence of profound neuromuscular blockade.

2. When compared to acetylcholinesterase inhibitors (neostigmine), sugammadex is able to more effectively reverse deep blockade, has a more rapid onset, and a lower incidence of residual neuromuscular blockade.

3. Recurarization refers to the clinical scenario where reversal of neuromuscular blockade appears adequate and the patient appears strong, but develops weakness. Despite the demonstrated efficacy of sugammadex, the potential for recurarization exists.

4. Dosing of sugammadex should be guided by train-of-four monitoring whenever this is clinically feasible as several of the case reports of recurarization following reversal with sugammadex appear to be related to inadequate sugammadex dosing.

5. An explanation of the exact mechanisms or pharmacodynamics responsible for recurarization requires further investigation.

Abstract

Sugammadex is a novel pharmacologic agent, which reverses neuromuscular blockade via a mechanism that differs completely from acetylcholinesterase inhibitors such as neostigmine. By encapsulating rocuronium or vecuronium, sugammadex provides rapid and complete recovery of neuromuscular function even when there is profound neuromuscular blockade. In general, clinical trials and experience with sugammadex have demonstrated its superiority over acetylcholinesterase inhibitors. Although generally effective, there may be the potential for recurrence of neuromuscular blockade despite effective reversal. We present a 4-month old infant who developed recurarization after the administration of sugammadex to reverse neuromuscular blockade. Previous reports of this adverse effect are reviewed, mechanisms discussed, and strategies to limits its incidence presented.

Keywords

Sugammadex, residual paralysis, neuromuscular blockade, recurarization

Introduction

Sugammadex (Bridion®, Merck & Co, Whithouse Stations, New Jersey) is a novel non-competitive agent for the reversal of steroidal neuromuscular agents (NMBAs), which was approved for clinical use in December 2015 by the United States Food & Drug Administration

(FDA).[1,2] It differs from neostigmine and other acetyl-cholinesterase inhibitors in that its novel mechanism of action provides prompt and complete recovery even with profound neuromuscular blockade. Sugammadex has been shown to provide more rapid and more effective reversal of neuromuscular blockade when compared with acetylcholinesterase inhibitors such as neostigmine.[3-7] Although generally effective, there may be the potential for recurrence of neuromuscular blockade despite effective reversal. We present a 4-month old infant who developed recurarization after the use of sugammadex to reverse neuromuscular blockade. Previous reports of this adverse effect are reviewed, mechanisms discussed, and strategies to limits its incidence presented.

Case report

Preparation of this case report followed the guidelines of the Institutional Review of Nationwide Children's Hospital (Columbus, Ohio). A 4-month old, 2.6 kg infant presented for exploratory laparotomy, lysis of intestinal adhesions, liver biopsy, and small bowel anastomosis. Past medical and surgical history included necrotizing enterocolitis status post bowel resection and stoma placement, bronchopulmonary dysplasia with an oxygen requirement of 0.1 liters/minute, and direct hyperbilirubinemia. The patient had no known allergies. Medications included ursodiol 26 mg enterally three times a day. Physical examination was non-contributary and her vital signs were unremarkable. The patient was assigned an American Society of Anesthesiologists' (ASA) physical classification 3. The patient was transported to the operating room and standard ASA monitor were placed. Hypothermia was prevented by the use of underbody forced air warmer and overhead warming lights. Anesthesia was induced with propofol (4 mg/kg) and endotracheal intubation facilitated by the administration of rocuronium (1.1 mg/kg). Following anesthetic induction and endotracheal intubation, a caudal epidural catheter was placed and threaded to the low thoracic region. Per our usual routine, the catheter was dosed with a combination of chloroprocaine and clonidine followed by a continuous

infusion to supplement intraoperative anesthesia. Anesthesia was maintained with sevoflurane (0.3% - 2.7%) and subsequent doses of rocuronium (2 mg, 5 mg, 2 mg, and 2 mg) were administered 38 minutes, 78 minutes, 128 minutes, and 147 minutes after anesthetic induction, respectively. The surgical procedure lasted approximately 4 hours and 10 minutes. At the completion of the surgical procedure, residual neuromuscular blockade was reversed with sugammadex (4 mg/kg). The patient was awake during tracheal extubation with adequate spontaneous respiration and tidal volume, moving all 4 extremities. The oropharynx was suctioned and adequate protective airway reflexes were present with a cough and grimace. After tracheal extubation, the patient was transported to the post-anesthesia care unit (PACU) with adequate spontaneous ventilation. Approximately 26 minutes after the PACU hand-off, the anesthesia team was called to the patient's bedside for oxygen desaturation (oxygen saturation of 80%) and lack of effective respiratory effort. Upon arrival, the nursing staff was providing bag-valve-mask ventilation. The patient was unresponsive to tactile stimulation. A second dose of sugammadex (4 mg/kg) was administered and was promptly followed by the patient opening their eyes, increased depth and rate of respirations, movement of all four extremities, and crying. The anesthesia team remained with the patient for the next 30-45 minutes until the patient was transferred to the neonatal intensive care unit (NICU). The remainder of the postoperative course was unremarkable.

Discussion

For anticholinesterase inhibitors such as neostigmine to be effective in reversing competitive blockade of neuromuscular transmission, there must be residual neuromuscular function with a low concentration of the NMBA in the synaptic cleft. Even with significant residual neuromuscular function and appropriate dosing of acetylcholinesterase inhibitors, residual blockade may still be present leading to the compromise of postoperative respiratory function thereby placing the patient at risk for

postoperative respiratory insufficiency.[8-10] The presence of this residual neuromuscular may result in an increased incidence of critical respiratory events including pneumonia in the adult population.[8] The more rapid and more complete reversal of residual neuromuscular blockade has been demonstrated to be one of the advantages when comparing sugammadex to acetylcholinesterase inhibitors.

Despite the general efficacy of sugammadex, whenever neuromuscular blockade is reversed, the potential for recurarization exists. Recurarization refers to the clinical scenario where reversal of neuromuscular blockade appears adequate and the patient initially appears strong, but then later during the immediate postoperative period develops weakness. Albeit rare, anecdotal reports have demonstrated the potential for this phenomenon even with sugammadex.[11-17]

However, on closer examination of some of these reports, the neuromuscular weakness were the result of inadequate dosing of sugammadex without TOF monitoring thereby leaving a paucity of reports where reversal with sugammadex was demonstrated to be effective (TOF ≥ 0.9) and then followed by apparent recurrence of neuromuscular blockade and impending respiratory failure (Table 1).[11-13]

Inadequate sugammadex dosing with only 0.5 mg/kg is reported in at least two of these reports, both of which noted fading of the TOF response after initial recovery.[15,18] Iwasaki et al reported a 19-month-old female infant undergoing elective surgery for cleft lip repair.[18] Neuromuscular monitoring was performed at the adductor pollicis muscle after the induction of anesthesia prior to the administration of rocuronium. The total dose of rocuronium during the surgery was 0.9 mg/kg. Neuromuscular block was reversed with 0.5 mg/kg sugammadex when one post-tetanic response on the TOF was noted. Twitch responses after sugammadex administration showed a temporary decrease after its initial recovery. Twitch responses recovered to their control value after 4 mg/kg of sugammadex.

Author and reference	Demographic data	Clinical summary
Carollo DS et al.[11]	Pediatric patient after a cardiac catheterization procedure.	Intraoperative neuromuscular blockade was achieved with 2 doses of rocuronium. Blockade reversed with sugammadex. Postoperatively, the patient developed respiratory failure and a decline in the TOF response. The patient fully recovered after receiving a second dose of sugammadex.
Le Corre F et al.[12]	54-year-old, 115 kg woman for laparoscopic repair of abdominal dehiscence.	General anesthesia with a total of 170 mg rocuronium for a 170-minute procedure. Two twitches of the TOF were present and sugammadex (1.74 mg/kg) was administered resulting in TOF of 0.9. Ten minutes after tracheal extubation, reintubation was required for respiratory failure. Another dose of sugammadex (200 mg) was administered and the patient's trachea was extubated.
Lorinc AN et al.[13]	4 pediatric patients (age 2 days, 3 weeks, 5 months, 11 years)	Three of the patients had recovery of neuromuscular function as demonstrated by the TOF and received sugammadex, but developed recurrence or persistent weakness requiring a second dose of sugammadex (2 patients) or neostigmine (1 patient). The final patient had no twitches on the TOF, received 4.88 mg/kg of sugammadex followed by a second dose without full reversal. Reversal was accomplished with neostigmine.

The current literature and manufacturer recommendations outline dosing based on the TOF response. Sugammadex (2 mg/kg) is recommended when there are ≥ 2 twitches of the TOF and 4 mg/kg if there are 1-2 posttetanic twitches.[14] The maximum dose of 16 mg/kg is recommended for reversal immediately following an intubating dose of rocuronium (1.2 mg/kg) when there is no recovery noted on the TOF. Despite these recommendations, TOF is not universally applied in the operating room, which may impact sugammadex dosing.[19-22] As illustrated by our patient, this may be true, especially in neonates and infants, where TOF monitoring may be problematic due to technical challenges with current monitors as well as limited access to the patient. The newer generation of TOF monitors that use electromyography rather than acceleromyography may offer clinical

advantages with monitoring residual neuromuscular blockade.[23,24]

Even with appropriate TOF monitoring and sugammadex dosing based on recommended guidelines, there remains anecdotal reports of recurrence of neuromuscular blockade. Given the high affinity for sugammadex and rocuronium, dissociation of the complex is an unlikely explanation. Other factors that may potentiate neuromuscular blockade including medications or hypothermia were not identified in our patient or other case reports. Although the differential for postoperative respiratory insufficiency in infants remains broad, no other causes were identified in our patient and there was a prompt clinical response following the second dose of sugammadex. The exact mechanisms behind this phenomenon remain speculative. These concerns may be especially relevant in neonates and infants due to the prematurity of neuromuscular junction development with an increased sensitivity to non-depolarizing neuromuscular blocking agents. To date, the majority of events have occurred within 60 minutes of reversal with sugammadex leading some authors to suggest ongoing monitoring for at least 1 hour following the administration of sugammadex.

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