Case Report

Myasthenia gravis and sugammadex: A case report and review of the literature

ABSTRACT

Anesthesia care during surgical procedures in patients with myasthenia gravis (MG) can be challenging, as these patients have increased sensitivity to neuromuscular blocking agents (NMBAs) and may be at high risk for postoperative weakness and respiratory failure. Even intermediate-acting NMBAs may have a prolonged effect resulting in residual weakness after reversal with acetylcholinesterase inhibitors (neostigmine). Sugammadex (Bridion®, Merck and Co, Whithouse Stations, New Jersey) is a novel pharmacologic agent that reverses neuromuscular blockade by encapsulating rocuronium or vecuronium. We report the perioperative management of a 13-year-old adolescent girl with MG undergoing thymectomy. The use of sugammadex for reversal of neuromuscular blockade is discussed and the previous reports regarding its use in patients with MG are reviewed.

Key words: Myasthenia gravis; neuromuscular blockade; rocuronium; sugammadex

Introduction

Myasthenia gravis (MG) is an autoimmune disorder with antibodies directed against the acetylcholine receptor, thereby affecting neuromuscular transmission characterized by muscle weakness. The skeletal muscle weakness progresses with exercise and improves with rest. The prevalence is approximately 20 in 100,000 with women affected twice as often as men. In children, MG presents as either transient neonatal MG or juvenile myasthenia gravis (JMG). Neonatal MG occurs in 20% of infants born to mothers with active MG due to passive trans-placental passage of the antibodies. It presents with hypotonia and poor feeding with a spontaneous resolution by 2–3 months of age.[1] Juvenile MG shares the same pathophysiology as adult MG but generally presents with ocular symptoms as opposed to the generalized skeletal muscle weakness that is seen in adults. The incidence of generalized symptoms varies from 25–75% in JMG.

The management in JMC is different from adults. In children, due to concerns regarding the adverse effects of long-term corticosteroid use including osteoporosis, growth retardation, and immunosuppression-linked malignancies, thymectomy is considered earlier than in adults. Anesthesia care during surgical procedures in patients with MG can be challenging, as these patients

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have increased sensitivity to neuromuscular blocking agents (NMBA) and may be at high risk for postoperative weakness and respiratory failure.[2] We report the perioperative management of a 13-year-old adolescent girl undergoing thymectomy for JMG. The use of sugammadex, a novel agent for reversal of neuromuscular blockade, is discussed and the previous reports regarding its use in patients with MG are reviewed.

Case Report

Publication of this case report followed the regulations of the Institutional Review Board of Nationwide Children's Hospital. A 13-year-old, 78 kg adolescent girl, presented to the emergency department with a 2-month history of symptoms of generalized muscle weakness, which started with intermittent episodes of weakness in the legs. The diagnosis of JMG was confirmed by electromyography and elevated serum acetylcholine receptor antibodies. Initial treatment included pyridostigmine (60 mg by mouth every 4 h) and plasmapheresis on alternate days, which improved her neurologic symptoms. She was scheduled for elective thoracoscopic-assisted thymectomy. The preoperative physical examination was unremarkable. The NIF was -50 cmH2O and the vital capacity was 3300 mL (42 mL/kg). On the day of surgery, the patient was held *nil per os* for 8 h except for her usual morning dose of pyridostigmine. The patient was transported to the operating room and standard American Society of Anesthesiologists monitors were placed. Neuromuscular blockade was monitored using visual observation of the train-of-four (TOF). General anesthesia was induced with fentanyl (100 μg) and propofol (200 mg) followed by neuromuscular blockade with rocuronium (50 mg) to facilitate tracheal intubation. Anesthesia was maintained with desflurane (expired concentration 5–6%) and hydromorphone (total dose of 1 mg administered in increments). Intermittent doses of rocuronium (5 mg) were administered based on the TOF ratio. The surgical procedure, which lasted 120 min, was uneventful. At the completion of the surgical procedure, the patient's TOF count was 0/4, 20 min after the administration of the last dose of rocuronium (5 mg). Sugammadex (300 mg) was administered and within 10 min, a full reversal of residual neuromuscular blockade was demonstrated by return of the TOF to baseline. When the patient was awake with an adequate tidal volume, her trachea was extubated. The patient was transferred to the postoperative anesthesia care unit (PACU) and then admitted to the inpatient ward. The remainder of her postoperative course was unremarkable and she was discharged home on postoperative day 3.

Discussion

Normal neuromuscular transmission results from the release of acetylcholine from the presynaptic nerve terminal, its movement across the synaptic cleft, and binding to the postsynaptic nicotinic receptor on the sarcolemma of the skeletal muscle. Depolarization of the presynaptic axonal membrane opens calcium channels (P channel). The movement of calcium through the channels in the presynaptic membrane results in the movement of synaptic vesicles to and fusion with the membrane. This is followed by the release of acetylcholine into the synaptic cleft. After its release from the synaptic vesicles, acetylcholine diffuses across the synaptic cleft and binds to acetylcholine receptors on the postsynaptic membrane (sarcolemma). This results in depolarization of the sarcolemma, the release of calcium from the sarcoplasmic reticulum, and muscle contraction.

The acetylcholine receptor (nicotinic receptor on the sarcolemma) is a pentameric protein composed of five subunits. There are five possible subunits (alpha, beta, gamma, delta, and epsilon), each of which is encoded by a different gene. The acetylcholine receptor occupies the entire membrane from the outside of the muscle through the cell membrane to the inside and thereby regulates the transmembrane movement of ions. The receptor acts to convert the chemical stimulus (acetylcholine) into an electrical impulse that results in the depolarization of the sarcolemma. The depolarization of the sarcolemma results in the release of calcium from the sarcoplasmic reticulum (SR) and muscle contraction. Cessation of muscle contraction is mediated by the metabolism of acetylcholine by the enzyme acetylcholinesterase, which is present in the synaptic cleft. Once acetylcholine is metabolized, the sarcolemma can repolarize, thereby resetting the muscle for the next round of depolarization. Failure to metabolize acetylcholine that is bound to the receptor results in prolonged depolarization, inability to repolarize the sarcolemma, and cessation of further contraction.

Non-depolarizing NMBAs act as competitive antagonists of acetylcholine at the receptor of the neuromuscular junction. At the completion of the surgical procedure, medications (neostigmine, edrophonium) that inhibit acetylcholinesterase are administered to competitively reverse residual neuromuscular blockade and allow for spontaneous ventilation and tracheal extubation.[3,4] For anticholinesterase inhibitors to be effective in reversing competitive blockade of neuromuscular transmission, the concentration of the NMBA in the synaptic cleft must be relatively low. The reversal of neuromuscular blockade by

acetylcholinesterase inhibitors is likely to be adequate only if there is significant residual neuromuscular function present as demonstrated by TOF stimulation of a peripheral nerve.

Despite the use of appropriate doses of acetylcholinesterase inhibitors, residual neuromuscular blockade may be present in a significant number of patients during the postoperative period.[3,4] This residual neuromuscular blockade may impact not only respiratory function but also upper airway patency, thereby compromising postoperative ventilation and increasing the incidence of critical postoperative respiratory events.[5-7] Although the incidence is lower in children, residual neuromuscular blockade has been noted in 28.1% of pediatric patients with severe residual blockade (TOF ratio ≤ 0.7) present in 6.5%.[8] In addition, although generally thought to potentiate neuromuscular function, neostigmine may actually have a negative impact postoperative respiratory function as it impairs upper airway dilator muscle activity.[9]

Additional issues must be considered in patients with MG. Patients with MG have significant variability in sensitivity to both depolarizing and non-depolarizing NMBAs, even intermediate-acting agents such as atracurium or vecuornium. The enzyme butyrylcholinesterase is inhibited by cholinesterase inhibitors (pydridostigmine), thereby prolonging the duration of action of succinylcholine.[10] When attempting to reverse the residual effect of non-depolarizing NMBAs, neostigmine may not be effective as acetylcholinesterase is already maximally inhibited by pyridostigmine.[11] These factors magnify the potential for postoperative weakness and respiratory failure in patients with MG.

Alternatively, the short-acting NMBA, mivacurium, has been suggested as a suitable agent to allow for neuromuscular blockade to facilitate endotracheal intubation and yet have effects that rapidly dissipate without residual neuromuscular blockade.[12-14] However, the supply of mivacurium has been variable in recent years and it is not uniformly available on hospital formularies. Endotracheal intubation can also be facilitated by inhalational or intravenous anesthetic agents without the need for NMBAs.[15-17]

Sugammadex (Bridion®, Merck and Co, Whithouse Stations, New Jersey) is a novel pharmacologic agent, which was approved for clinical use in adults in December 2015 by the United States Food and Drug Administration (FDA). It reverses neuromuscular blockade with a mechanism that differs completely from acetylcholinesterase inhibitors, by encapsulating rocuronium or vecuronium. Although not specifically approved by the FDA for use in pediatric patients, there is significant literature describing its safe and effective use in infants and children with the suggestion that it offers the same advantages over neostigmine as those reported in adults.[18-22]

Systematic searches of PubMed® and Google were conducted using the search terms sugammadex and myasthenia gravis (August 2019) to identify articles from the English language regarding the use of sugammadex in patients with myasthenia gravis. The abstracts from the publications were reviewed and those pertaining to the current subject matter were included for further review. In addition, the reference lists of these publications were reviewed to ensure that all reports regarding the use of sugammadex in patients with MG had been identified. This review revealed only one case report in the English language describing the use of sugammadex in a pediatric-aged patient with MG.[23] The reported described the use of sugammadex to reverse neuromuscular blockade induced by rocuronium in a neonate with transient neonatal MG following surgical repair of pyloric stenosis.[23] In addition to this single report in a pediatric patient, other anecdotal reports were identified in adults [Table 1]. These cases demonstrate the effective reversal of neuromuscular blockade by sugammadex in patients with MG. Neuromuscular blockade was induced by rocuronium in all of the cases except for one (reference 27 where the patient received vecuronium). Reversal was accomplished with sugammadex in doses ranging from 2–4 mg/kg.

While the majority of cases have demonstrated the effective use of sugammadex to reverse neuromuscular blockade in patients with MG, failures have also been reported [Table 2].[37-40] Failure occurred despite large or repeated doses of sugammadex (total dose up to 16 mg/kg). These cases did not seem to relate only to the severity of illness as two of the patients had mild clinical symptoms and were undergoing elective surgical procedures. All 4 of the patients were chronically treated with pyridigostigmine, which is common practice in adults with MG. Of note, all four of the patients improved when a cholinesterase inhibitor (either neostigmine or pyridostigmine) was administered after sugammadex.

One of the challenges of anesthesia care in patients with MG is the management of NMBAs. In many circumstances, NMBAs can be avoided or lower doses used to accomplish endotracheal intubation. In our patient, the initial dose of rocuronium was 50 mg or approximately 0.6 mg/kg. Although it is possible that a lower dose (5–10 mg) may have been effective or endotracheal intubation accomplished without an NMBA, the availability of sugammadex expands the clinical options for patients with underlying neuromuscular

Table 1: Reports of the successful use of sugammadex in patients with myasthenia gravis

Reference	Patient demographics	Findings
Kondo *et al*.[24]	79-year-old, 59 kg woman for aortic arch replacement.	Neuromuscular blockade successfully reversed with sugammadex (200 mg).
Casarroti *et al*.[25]	Two patients: 48-year-old man for emergency laparotomy for sigmoid perforation and a 71-year-old woman with hematemesis for upper endoscopy.	Neuromuscular blockade successfully reversed with sugammadex (4 mg/kg).
Sunger Ulke *et al*.[26]	Case series of 10 patients for thoracoscopic-assisted thymectomy.	Neuromuscular blockade successfully reversed with sugammadex (2 mg/kg) in all 10 patients.
Rudzka-Nowak and Piechota[27]	85-year-old man for abdominal surgery.	Neuromuscular blockade successfully reversed with sugammadex (3 mg/kg).
De Boer *et al*.[28]	Two patients (unspecified demographics) for short surgical procedures.	Neuromuscular blockade successfully reversed with sugammadex (4 mg/kg)
Petrun *et al*.[29]	40-year-old woman for laparoscopic cholecystectomy.	Neuromuscular blockade successfully reversed with sugammadex (2 mg/kg).
Unterbuchner *et al*.[30]	72-year-old man for radical prostatectomy.	Neuromuscular blockade successfully reversed with sugammadex (2 mg/kg).
Soyoral *et al*.[31]	28-year-old parturient for cesarian section.	Neuromuscular blockade successfully reversed with sugammadex (2 mg/kg).
Kim and Kim[32]	56-year-old man for nasal surgery.	Neuromuscular blockade successfully reversed with sugammadex (4 mg/kg)
Shah and Dharmarajan[33]	87-year-old man for emergency exploratory laparotomy.	Neuromuscular blockade successfully reversed with sugammadex (4 mg/kg)
Jakubiak *et al*.[34]	38-year-old morbidly obese woman (160 kg) for elective laparoscopic gastric banding.	Neuromuscular blockade successfully reversed with sugammadex (200 mg)
Argiriadou *et al*.[35]	31-year-old obese woman (95 kg) for thymectomy.	Neuromuscular blockade successfully reversed with sugammadex (2 mg/kg)
Puhringer *et al*.[36]	Series of 7 patients for cesarian section.	Neuromuscular blockade successfully reversed with sugammadex (2-4 mg/kg)

Table 2: Reports of failures of sugammadex in patients with myasthenia gravis

Reference	Patient demographics	Findings
Fernandes *et al*.[37]	27-year-old, 110 kg woman for laparoscopic cholecystectomy	Failure of reversal of neuromuscular blockade with sugammadex (800 mg).
Garcia *et al*.[38]	35-year-old, 80 kg woman for cesarian section.	Failure of reversal of neuromuscular blockade with sugammadex (200 mg).
Kiss *et al*.[39]	25-year-old woman for thymectomy.	Persistently low train-of-four (TOF) ratio despite sugammadex (16 mg/kg).
Sugi *et al*.[40]	26-year-old woman for thymectomy.	Sugammadex (total dose 4 mg/kg) failed to restore TOF to ≥0.55. Neostigmine (30 μg/kg) resulted in successful recovery of TOF.

weakness. Prior to its availability, reversal of the effects of the NMBA regardless of the dose was problematic with the potential for residual neuromuscular blockade to result in postoperative weakness and respiratory failure. Sugammadex is a novel pharmacologic agent that reverses neuromuscular blockade by encapsulating rocuronium or vecuronium. In general, its effects are more complete than cholinesterase inhibitors with a limited chance of residual neuromuscular blockade even in healthy patients. The majority of the literature has demonstrated the potential utility of this agent in patients with MG. However, anecdotal reports emphasize the difficulties of caring for such patients as failures have been reported. Of note, reversal of neuromuscular blockade was eventually achieved with the use of a cholinesterase inhibitor (neostigmine or pyridostigmine) in addition to sugammadex. Anesthesia care during surgical procedures in patients with MG can be challenging, as these patients have increased sensitivity to NMBAs and may be at high risk for postoperative weakness and respiratory failure.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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