JPPT | Case Report

Bradycardia in a Pediatric Heart Transplant Recipient: Is It the Sugammadex?

Adele King, MD; Aymen Naguib, MD; and Joseph D. Tobias, MD

Sugammadex is a novel pharmacologic agent that is used to selectively reverse the effects of the neuromuscular blocking agents rocuronium and vecuronium. Various advantages have been reported when comparing its reversal of neuromuscular blockade to that achieved with acetylcholinesterase inhibitors (neostigmine). In heart transplant recipients, bradycardia may occur following the administration of acetylcholinesterase inhibitors, due to the denervation of the heart. Theoretically, the combination of rocuronium and sugammadex could be advantageous in this clinical scenario to avoid the potential bradycardia resulting from neostigmine administration. We present a 10-year-old male who developed profound bradycardia immediately following the administration of intravenous sugammadex. The options for reversal of neuromuscular blockade in heart transplant recipients is discussed, previous reports of bradycardia following sugammadex are presented, and the role of sugammadex in the bradycardia in our patient is reviewed.

ABBREVIATIONS BP, blood pressure; HR, heart rate; RR, respiratory rate

KEYWORDS bradycardia; neuromuscular blockade; pediatric; sugammadex

J Pediatr Pharmacol Ther 2017;22(5):378–381

DOI: 10.5863/1551-6776-22.5.378

Introduction

Neuromuscular blocking agents are a key component of intraoperative care. They are frequently administered to facilitate endotracheal intubation, provide immobility, and maintain relaxation of the skeletal musculature for surgical procedures. Following the surgical procedure, medications (neostigmine, edrophonium) that inhibit acetylcholinesterase are used to increase the concentration of acetylcholine at the neuromuscular junction and competitively reverse residual neuromuscular blockade, thereby allowing spontaneous ventilation and tracheal extubation.[1] Sugammadex (Bridion, Merck & Co, Whitehouse Station, NJ) is a novel pharmacologic agent with a unique mechanism of action for the reversal of neuromuscular blockade.[2] The reader is referred to Tobias[2] for a review of its use in the pediatric population.

Sugammadex encapsulates rocuronium or vecuronium, eliminating the active compound from the circulation and thereby providing rapid and complete recovery even with profound or complete neuromuscular blockade. Sugammadex provides more effective and complete reversal of neuromuscular blockade than neostigmine, and with a lower adverse effect profile.[3,4] In heart transplant recipients, it has been suggested that sugammadex be considered for reversal of neuromuscular blockade in order to avoid the potential for bradycardia resulting from neostigmine administration in the setting of a denervated heart.[5–7] We present a 10-year-old male who developed profound bradycardia immediately following the administration of intravenous sugammadex. The options for reversal of neuromuscular blockade in heart transplant recipients is discussed, previous reports of bradycardia following sugammadex are presented, and the role of sugammadex in the bradycardia in our patient is reviewed.

Case Report

Institutional Review Board approval is not required for the publication of individual case reports at Nationwide Children's Hospital (Columbus, OH). A 10-year-old, 21-kg male presented for hemodynamic cardiac catheterization and endomyocardial biopsy as part of ongoing surveillance for heart transplant rejection. The patient had received a heart transplant in 2006 because of a dilated cardiomyopathy, and in 2009 he had his first episode of rejection, requiring the administration of corticosteroids. Since then, he had been under scheduled surveillance with endomyocardial biopsy to assess for transplant rejection. Two months prior to this admission, the biopsies showed moderate cellular rejection, requiring the administration of corticosteroids and an increase in tacrolimus dose. Hemodynamic evaluation at that time showed worsening cardiac index, which had decreased from 3.5 to 2.7 L/min/m^2, and increased left atrial and left ventricular end-diastolic pressure with normal pulmonary vascular resistance and normal pulmonary artery pressure. Additional past medical history was significant for epilepsy, which was currently well controlled, requiring no anticonvulsant medica-

tions. Food allergies included milk, egg, soy protein, and aspartame. There was no previous history of bradycardia or arrhythmias. Current medications included tacrolimus (0.6 mg by mouth twice daily), sirolimus (0.5 mg alternating with 1 mg by mouth every morning), and ondansetron (8 mg by mouth as needed). Physical examination was unremarkable, with a blood pressure (BP) of 89/53 mm Hg, heart rate (HR) of 94 beats/min (sinus), respiratory rate (RR) of 24 breaths/min, and room air oxygenation saturation of 100%. Echocardiography a month ago revealed moderate right and left atrial dilation with normal biventricular function. Oral midazolam (10 mg) was administered prior to transport to the cardiac catheterization suite, where full American Society of Anesthesiologists monitoring was placed, including continuous electrocardiography and pulse oximetry, intermittent non-invasive blood pressure, end-tidal carbon dioxide, and body temperature. Anesthesia was induced with the inhalation of incremental concentrations of sevoflurane in oxygen and nitrous. Following the induction of anesthesia, intravenous access was secured and neuromuscular blockade was achieved with rocuronium (1 mg/kg), followed by endotracheal intubation with a 5.5-mm cuffed endotracheal tube. Maintenance anesthesia was achieved with isoflurane (inspired concentration of 0.2%–0.4%) in air and oxygen, fentanyl (2 mcg/kg), and a dexmedetomidine infusion at 0.5 mcg/kg/hr to prevent emergence delirium, which had occurred previously. Arterial access was gained by the pediatric cardiologist. Vital signs were stable, with the BP ranging from 84 to 100/52 to 56 and an HR ranging from 80 to 120 beats/min. Serum electrolytes were unremarkable (serum sodium 141 mEq/L, potassium 3.4 mEq/L, and ionized calcium 1.25 mmol/L). The procedure time for the cardiac catheterization and endomyocardial biopsy was 1 hour 30 minutes. At the completion of the procedure, acetaminophen was administered intravenously for postprocedure analgesia, and ondansetron (0.15 mg/kg) was administered for prophylaxis of postoperative nausea and vomiting. The patient was spontaneously ventilating, with 3 twitches present on the train-of-four. Train-of-four monitoring is used intraoperatively to assess recovery from neuromuscular blockade. This involves the use of an electrical stimulus administered twice a second (2 Hz) for 2 seconds to deliver a series of 4 stimuli, hence the term *train-of-four*. Residual neuromuscular blockade and the need for reversal are indicated by the absence of 4 twitches in response to these stimuli. Sugammadex was administered to reverse residual neuromuscular blockade. Thirty seconds after the administration of sugammadex (2 mg/kg), bradycardia developed, with a rapid decrease in HR from 102 to 26 beats/min. The end-tidal carbon dioxide decreased to 10 mm Hg, peripheral pulses were weak, and the BP was 60/20 mm Hg. Epinephrine (2 mcg/kg) was administered, and chest compressions were initiated for 10 to 15 seconds. Following the single dose of epinephrine, the HR increased to 160 beats/min and the BP to 120 to 130/70 to 90 mm Hg. Echocardiography revealed no pericardial effusion seen or any other anatomic concerns. The patient's trachea was subsequently extubated, and he was transferred to the pediatric cardiothoracic intensive care unit for further monitoring. He was discharged home the next day.

Discussion

Since the 1950s, the reversal of neuromuscular blockade has been achieved by the administration of acetylcholinesterase inhibitors. However, the excessive accumulation of acetylcholine at sites away from the neuromuscular junction may result in the expected adverse effect profile of bradycardia, bronchospasm, hypersalivation, increased gastrointestinal motility, nausea, and vomiting.[8] The concerns regarding bradycardia or asystole may be magnified following cardiac transplantation with a denervated heart.[6,7] The mechanism of action by which neostigmine is thought to cause bradycardia following heart transplantation is due to variable parasympathetic re-innervation and/or direct stimulation of nicotinic cholinergic receptors on the postganglionic parasympathetic neurons. This results in the release of acetylcholine from their terminals and the subsequent activation of inhibitory cardiac receptors.[6] The cardiac allograft may also develop denervation hypersensitivity of both the postganglionic neurons and the muscarinic myocardial receptors to the cholinergic effects of neostigmine.[7] These factors combined with intrinsic allograft sinoatrial node dysfunction may produce severe dysfunction or sinus arrest after acetylcholinesterase inhibitors are administered to heart transplant recipients.[5]

In comparison with anticholinesterase inhibitors, sugammadex does not influence cholinergic conduction and does not have muscarinic effects.[9] Gomez-Rios and Lopez[5] reported the use of sugammadex to reverse neuromuscular blockade in 2 cardiac transplant patients, one of whom was a child. The first patient was a 66-year-old adult who received sugammadex (4 mg/kg) to reverse neuromuscular blockade after a thyroidectomy. The second patient was a 9-year-old who received sugammadex (2 mg/kg) for reversal of neuromuscular blockade after a tonsillectomy. No clinically significant changes were observed in the vital signs after the administration of sugammadex in either patient. Following this experience, the authors suggested the use of sugammadex for reversal of neuromuscular blockade in cardiac transplant recipients to avoid the concerns of the effects of anticholinergic agents and acetylcholinesterase inhibitors on the denervated heart. Additionally, 3 further studies have reported experience without complications with the use of sugammadex in cardiac transplant recipients.[10–12]

Despite these previous reports, we noted profound bradycardia that was temporally related to the admin-

istration of sugammadex. Although our online review of the published literature did not reveal previous reports of bradycardia following sugammadex administration in a heart transplant recipient, bradycardia has been noted following the use of sugammadex to reverse neuromuscular blockade. Furthermore, the product package insert states that marked bradycardia with the occasional progression to cardiac arrest has been observed within minutes after administration. No mechanism has been postulated for this response. Bilgi et al[13] reported a sinusoidal bradycardia resistant to atropine in a 56-year-old, 77-kg adult man without associated comorbidities who was undergoing ureterorenoscopy. At the completion of the surgical procedure sugammadex (200 mg) was administered intravenously. Two minutes later, bradycardia with an HR of 35 beats/min was noted. Osaka et al[14] reported on a 21-year-old woman who developed Wenckebach-type atrioventricular block following the administration of sugammadex (200 mg). Other effects of sugammadex on cardiac conduction include a potential to prolong the QTc interval.[15] In a prospective evaluation of the efficacy of sugammadex in reversing neuromuscular blockade, 176 adult patients anesthetized with propofol were randomly assigned to receive sugammadex (2, 4, 8, 12, or 16 mg/kg) or placebo at 3 or 15 minutes after rocuronium (1 or 1.2 mg/kg) during propofol anesthesia. Although there was prolongation of the QTc interval in 9 patients, this was considered to be related to sugammadex in only 1 patient.

In our patient, the causal relationship between sugammadex and bradycardia is not possible to prove definitely. The patient had no previous history of bradycardia or arrhythmia and pharmacodynamically, sugammadex does not have direct cholinergic effects on the denervated heart. As noted previously, although bradycardia has been reported following the administration of sugammadex, no definitive mechanism has been postulated. Also of note in our patient was the concomitant administration of dexmedetomidine. Although generally safe and effective, bradycardia is a recognized central sympatholytic effect of dexmedetomidine.[16] Furthermore, it has been suggested that dexmedetomidine may augment the negative chronotropic effects of other medications (digoxin, β-adrenergic antagonists, propofol).[17] Given the elimination half-life, the duration of the infusion, and the time of its discontinuation, the plasma concentration of dexmedetomidine would likely be within the therapeutic range at the time that sugammadex was administered. As such, we cannot exclusively rule out that dexmedetomidine played a role in the bradycardia noted in our patient.

In summary, we report the temporal association of profound bradycardia following the administration of sugammadex to a pediatric heart transplant recipient. When evaluating the relationship of the sugammadex to the adverse reaction, bradycardia, using the Naranjo ADR scale, the relationship was graded as a possible reaction with a score of 3 on a 1 to 10 scale.[18] It has been previously suggested that sugammadex be used for the reversal of neuromuscular blockade in this patient population in order to avoid the cholinergic effects of neostigmine on the denervated heart. Although a definitive mechanism has not been proposed, close patient monitoring is recommended to detect potential heart rate changes following the administration of sugammadex. Given the expected lack of response to anticholinergic agents in the denervated heart, the administration of epinephrine (1–2 mcg/kg) is recommended. Given that loss of spontaneous circulation had not occurred, our practice is to use smaller doses of epinephrine (1–2 mcg/kg) to treat bradycardia, rather than the full resuscitation dose (10 mcg/kg or 0.01 mg/kg). In our clinical experience, we have found that the smaller dose generally treats the bradycardia and avoids the arrhythmogenic effects of a larger dose. In addition to epinephrine, closed chest compressions should be initiated based on Pediatric Advanced Life Support guidelines.

ARTICLE INFORMATION

Affiliations Department of Anesthesiology & Pain Medicine (AK, AN, JDT), Nationwide Children's Hospital, Columbus, Ohio, Department of Anesthesiology & Pain Medicine (AN, JDT), The Ohio State University College of Medicine, Columbus, Ohio, and Department of Pediatrics (JDT), The Ohio State University College of Medicine, Columbus, Ohio

Correspondence Adele King, MD;
Adele.king@Nationwidechildrens.org

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

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