Case Report

Sugammadex to Reverse Neuromuscular Blockade in a Child with a Past History of Cardiac Transplantation

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Abstract

Sugammadex is a novel agent for the reversal of neuromuscular blockade. The speed and efficacy of reversal with sugammadex are significantly faster than acetylcholinesterase inhibitors, such as neostigmine. Sugammadex also has a limited adverse profile when compared with acetylcholinesterase inhibitors, specifically in regard to the incidence of bradycardia. This adverse effect may be particularly relevant in the setting of a heart transplant recipient with a denervated heart. The authors present a case of an 8-year-old child, status postcardiac transplantation, who required anesthetic care for laparoscopy and lysis of intra-abdominal adhesions. Sugammadex was used to reverse neuromuscular blockade and avoid the potential adverse effects of neostigmine. The unique mechanism of action of sugammadex is discussed, previous reports of its use in this unique patient population are reviewed, and its potential benefits compared to traditional acetylcholinesterase inhibitors are presented.

Keywords: *Cardiac transplant, neostigmine, neuromuscular blocking agents, rocuronium, sugammadex, vecuronium*

Introduction

Sugammadex (Bridion®, Merck and Co., Whitehouse Stations, NJ, USA) was approved for clinical use by the United States Food and Drug Administration in December 2015.[1] Its mechanism of action for the reversal of a neuromuscular blockade is entirely different from the commonly used acetylcholinesterase inhibitors such as neostigmine. Sugammadex is a modified γ-cyclodextrin that encapsulates the steroidal neuromuscular blockade agents (rocuronium and vecuronium), resulting in a reduction of the free plasma concentration, thereby terminating neuromuscular blockade.[2] Preliminary data have demonstrated the complete reversal of neuromuscular blockade with limited residual blockade when compared to neostigmine.[3] In addition, in specific clinical scenarios, the parasympathomimetic effects of acetylcholinesterase inhibitors may lead to bradycardia or asystole. The authors present a case of an 8-year-old child, status postcardiac transplantation, who required anesthetic care for laparoscopy and lysis of intra-abdominal adhesions. Sugammadex was used to reverse neuromuscular blockade and avoid the potential adverse effects of neostigmine. The unique mechanism of action of sugammadex is discussed, previous reports of its use in this unique patient population are reviewed, and its potential benefits compared to traditional acetylcholinesterase inhibitors are presented.

Case Report

Institutional Review Board approval for publication is not required for single case reports at Nationwide Children's Hospital (Columbus, Ohio). An 8-year-old, weighing 25.5 kg, male was transferred from an outside hospital with a 3–4-month history of decreased oral intake, abdominal pain, nausea, and abdominal distention. His past medical history was significant for Hirschsprung's disease, constipation, delayed gastric emptying, congenital heart disease (pulmonary atresia) requiring orthotopic heart transplantation, and vesicoureteral reflux. Current medications included tacrolimus (1 mg in the morning and 0.5 mg at bedtime). An echocardiogram, performed before surgery, was unremarkable with no valvular abnormalities and normal left and right ventricular function. An upper gastrointestinal endoscopy performed several days before the surgery revealed

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no evidence of pathology. Preoperative laboratory findings were normal except for a mild elevation of the blood urea nitrogen. Based on the clinical findings, it was decided to perform a gastrocutaneous fistula takedown, diagnostic laparoscopy, and upper endoscopy. After being transported to the operating room, routine American Society of Anesthesiologists' monitors were placed. A modified rapid sequence intubation with cricoid pressure was performed after the administration of propofol (4 mg/kg), fentanyl (2 μg/kg), and rocuronium (0.6 mg/kg). A second dose of rocuronium (0.4 mg/kg) was administered. Maintenance anesthesia was provided by desflurane. No intraoperative complications were reported. Surgical findings included an esophagus with decreased vasculature and mild erythema in distal esophagus. Ulceration was found on the great curvature of the stomach, and biopsies were taken around the ulceration, greater curvature, and antrum. Intraoperative fluids included 400 mL of lactated ringers. Prophylactic antiemetic therapy was provided by dexamethasone (0.15 mg/kg) and ondansetron (0.15 mg/kg). Postoperative analgesia was provided by hydromorphone (0.02 mg/kg). After 2 out of 4 twitches were assessed with train of four, neuromuscular blockade was reversed with sugammadex (2 mg/kg). Within 2–3 min, there was spontaneous movement, and the patient's trachea was extubated in the operating room. He was transported to the postanesthesia care unit. Total anesthesia time was 1 h 39 min. The remainder of the postoperative course was unremarkable except for a slow return of gastrointestinal function and resumption of normal oral intake. The patient was discharged home on postoperative day 8.

Discussion

Although the time-honored agent for reversal of neuromuscular blockade is acetylcholinesterase inhibitors such as neostigmine, the 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. These may not be prevented by the concomitant administration of an anticholinergic agent (atropine or glycopyrrolate). These concerns may be magnified in the setting of a denervated heart where profound bradycardia or asystole has been reported following the administration of neostigmine. Neostigmine is thought to cause bradycardia following heart transplantation as a result of either variable parasympathetic reinnervation or direct stimulation of nicotinic cholinergic receptors on the postganglionic parasympathetic neurons. This results in the release of acetylcholine from their terminals and subsequent activation of inhibitory cardiac receptors.[4] The cardiac allograft may also develop denervation hypersensitivity of both the postganglionic neurons and the muscarinic myocardial receptors to the cholinergic effects of neostigmine. 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.[5,6]

Regardless of the mechanisms involved, profound bradycardia or asystole has been reported following the administration of neostigmine in heart transplant recipients [Table 1].[7-12] These outcomes have occurred even with the concomitant administration of an anticholinergic agent. In many instances, the bradycardia was unresponsive to atropine. Pharmacological, theoretical, and anecdotal clinical data suggest the potential utility of the novel agent, sugammadex, to reverse neuromuscular blockade and avoid the parasympathomimetic effects of acetylcholinesterase inhibitors. However, till now, there are only four previous reports involving a total of six patients which report the use of sugammadex in patients who have undergone cardiac transplantation.[13-16] In five patients, reversal of neuromuscular blockade with sugammadex was successful without the occurrence of hemodynamic effects including bradycardia. Similar results were noted in our patient, adding further evidence to this anecdotal experience. Although the sample size is limited in number and anecdote, the results are promising for avoiding the potential for bradycardia and asystole with the use of acetylcholinesterase inhibitors for the reversal of neuromuscular blockade in patients who have undergone cardiac transplantation.

Sugammadex reverses neuromuscular blockade directly by encapsulating the neuromuscular blocking agent rather than indirectly, such as acetylcholinesterase inhibitors, by increasing the concentration of acetylcholine at the neuromuscular junction. In addition to having limited muscarinic effects, sugammadex has been shown to be safe and effective in patients with cardiovascular disease with a limited adverse effect profile on hemodynamic function.[2,3,13-16] However, as noted in the package insert, marked bradycardia with the occasional progression to cardiac arrest has been observed within minutes after administration during preclinical trials. No mechanism has been postulated for this response. Administration of an anticholinergic agent (atropine) or a catecholamine (epinephrine), depending on the progression of the heart rate, is recommended if clinically significant bradycardia is observed. Future studies to clearly define the role of this novel agent for reversal of neuromuscular blockade are needed, especially in specific clinical scenarios, such as patient who has undergone cardiac transplantation.

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Conflicts of interest

There are no conflicts of interest.

Table 1: Cardiovascular effects of acetylcholinesterase inhibitors in the transplanted heart

Authors and reference	Clinical cohort	Findings
Backman *et al*.[7]	Case report of a 52-year-old male who was 40 months' status postcardiac transplantation	Following the administration of neostigmine (0.04 mg/kg), the HR decreased from 95 to 75 bpm. HR increased to 90 bpm after the administration of atropine (1.2 mg)
Backman *et al*.[8]	Neostigmine was administered to ASA 1 or 2 patients with normally innervated hearts or to recent (<6 months) and remote (>6 months) cardiac transplantation recipients	Neostigmine produced a dose-dependent decrease in HR in all patients. Control patients were the most sensitive whereas the recently transplanted group was the least sensitive. The response to neostigmine of the remotely transplanted patients was variable. Administration of atropine reversed the neostigmine-induced bradycardia in all the three groups
Beebe *et al*.[9]	Patient 1: a 54-year-old male who was 4 years' status postcardiac transplantation Patient 2: a 63-year-old male who was 8 years' status postcardiac transplantation	Both patients developed bradycardia and asystole following neostigmine. Both patients eventually required transvenous pacemaker placement
Bertolizio *et al*.[10]	Patient 1: a 16-year-old female who was 12 years' status postcardiac transplantation Patient 2: a 16-year-old male who was 3 years' status postcardiac transplantation	Both patients developed severe bradycardia or asystole after the administration of neostigmine which required resuscitation
Bjerke and Mangione[11]	A 67-year-old male who was 11 years' status postcardiac transplantation	Asystole developed after the administration of neostigmine
Sawasdiwipachai *et al*.[12]	A 13-month-old female who was 1 month' status postcardiac transplantation	Following neostigmine, sinus bradycardia progressed to asystole within 2-3 min accompanied by circulatory collapse that was unresponsive to cardiopulmonary resuscitation requiring extracorporeal support

HR: Heart rate, BP: Blood pressure, ASA: American Society of Anesthesiologists

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