

The use of sugammadex in a patient with myasthenia gravis to reverse rocuronium-induced neuromuscular blockade

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Abstract

Myasthenia gravis is an autoimmune disease of the neuromuscular junction with unpredictable response to neuromuscular blocking drugs and an increased risk for postoperative residual neuromuscular blockade. We present a patient with ocular myasthenia scheduled for laparoscopic cholecystectomy and rocuronium-induced neuromuscular block in whom administration of 2.0 mg/kg sugammadex intravenously reversed the neuromuscular blockade to a TOF ratio of 0.91 within 60 sec.

Keywords: myasthenia gravis, rocuronium, sugammadex

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Introduction

Myasthenia gravis is an autoimmune disease of the neuromuscular junction. The autoimmune decrease of acetylcholine receptors in the postsynaptic membrane reduces the synaptic transmission, manifested clinically as muscle weakness and fatigue [1]. The decline in neural acetylcholine release occurs after repeated nerve stimulation and is followed by partial improvement with rest. In these patients, general anaesthesia for abdominal surgery may result in an unpredictable response to neuromuscular blocking drugs. The myasthenic patients are resistant to succinylcholine and sensitive to nondepolarizing muscle relaxants. The reversal of the neuromuscular block with acetylcholinesterase inhibitors may induce a cholinergic crisis and may be influenced by the preoperative chronic therapy with anticholinergic agents [2, 3]. Because of residual muscular blockade, patients often need prolonged postoperative mechanical ventilation.

In recent years, introduction into clinical practice of sugammadex has rendered the use of acetylcholinesterase inhibitors for reversal of the neuromuscular block unnecessary [4, 5]. Sugammadex, a modified gamma cyclodextrin, is specifically designed to encapsulate the steroidal muscle relaxants rocuronium and vecuronium [6]. It compares favourably with neostigmine for reversal of both shallow and profound neuromuscular block [7, 8] and it is not associated with muscarinic side effects, because sugammadex does neither bind to muscarinic receptors, nor increases acetylcholine at the junction. Because of these advantages, sugammadex may be preferred for reversal of rocuronium-induced neuromuscular blockade in myasthenic patients.

We present the case of a patient with myasthenia gravis who underwent a laparoscopic cholecystectomy and who received sugammadex for reversal of rocuronium-induced neuromuscular block.

Case report

A 56 year-old female (height 179 cm, weight 90 kg) was scheduled for laparoscopic cholecystectomy after an episode of acute cholecystitis. Written consent for anaesthesia was obtained and the patient was informed that postoperative respiratory support may be required.

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During the preoperative visit, the patient past medical history included a 26-year history of fatigue and diplopia, which later progressed to ocular symptoms (ptosis). In 1995, she underwent elective hysterectomy under general anaesthesia in another hospital. No data were available about the course of anaesthesia and administered drugs at that time. However, the patient was informed that she had had a prolonged recovery, which necessitated mechanical ventilation for the first 8 hours postoperatively, apparently due to residual paralysis. That same year, she was diagnosed with myasthenia gravis and was started on a regimen of 60 mg pyridostigmine 3 times daily. The anticholinesterase medication was well tolerated and improved her clinical course. However, slight ocular weakness persisted despite therapy. Approximately 3 months prior to her current presentation, the patient underwent elective reconstructive surgery of the right nasogenial region, under general anaesthesia. No muscle relaxants were used that time. Tracheal intubation was performed after induction of general anaesthesia with propofol and sevoflurane. During the anaesthetic, ventilation was assisted mechanically (SIMV). Because the patient did not receive her usual dose of pyridostigmine preoperatively and showed neuromuscular weakness, a dose of 18 µg/kg neostigmine and 6 µg/kg atropine were injected intravenously at the end of surgery. The patient recovered respiratory function and her trachea was extubated after 5 min; the rest of her postoperative course was uneventful.

Two days prior to her current admission, the patient developed acute cholecystitis, manifested by pain, fever and leukocytosis. Ultrasound examination of her abdomen revealed presence of gallstones. After a short preoperative course of antibiotics and parenteral hydration, the patient was scheduled for cholecystectomy.

The preoperative blood chemistry, electrocardiogram (ECG) and respiratory function were within normal limits. The severity of myasthenia was determined as class I (ocular myasthenia) as per Osserman and Genkins' classification of myasthenia gravis [9].

Premedication consisted of 10 mg diazepam intramuscularly, and she received her usual dose of pyridostigmine. Anaesthesia was induced with intravenous administration of 2 mg midazolam, 150 µg fentanyl and 250 mg thiopental. Pulse oximetry, electrocardiogram, noninvasive arterial blood pressure and capnography were monitored during anaesthesia. The neuromuscular function was monitored at the adductor pollicis muscle using acceleromyography (TOF-Watch SX, Organon, Dublin, Ireland) and train-of-four mode of stimulation. After forearm immobilization and placement of the electrodes over the ulnar nerve, the TOF-Watch SX was stabilized and calibrated according to published guidelines [10]. A bolus dose of 0.6 mg/kg rocuronium

(54 mg), high dose in such a patient, was injected intravenously, and after 2 min tracheal intubation was performed at a TOF ratio of 0.1. The intubating conditions were excellent. The patient's lungs were ventilated with a mixture of 50/50 oxygen and air and anaesthesia was maintained with sevoflurane 1.2 MAC and 200 µg fentanyl total dose. The neuromuscular block was adequate for the remainder of the laparoscopic surgery, and the end-tidal carbon dioxide (CO₂) was maintained within a range of 38–42 mm Hg. During surgery, the TOF ratio increased gradually to 0.5. After 40 min, the surgery was completed and the inhaled sevoflurane concentration reduced to 0.44 MAC. Return of spontaneous breathing was documented on the monitor, and the TOF ratio at this time was 0.67. Then, 2.0 mg/kg (180 mg dose) sugammadex was administered intravenously and the sevoflurane administration was discontinued. After 30 sec, the TOF ratio increased to 0.81 and to 0.96 after 1 min. The patient became awake, responded to verbal commands and the trachea was extubated after suctioning. In the recovery room for the first 60 min postoperatively, the patient's heart rate, oxygen saturation and level of consciousness were monitored closely. Once she was fully awake and met discharge criteria, the patient was transferred to the ward. She restarted the daily treatment with pyridostigmine, and was discharged from the hospital after two days. No recurrence of neuromuscular blockade or any other complications were reported during her hospitalization. Before discharge, the patient consented for data publication.

Discussion

Our case demonstrates that sugammadex can effect a rapid reversal of relatively high dose rocuronium-induced neuromuscular block in a myasthenic patient who underwent laparoscopic cholecystectomy under sevoflurane maintenance anaesthesia.

Due to reduction in acetylcholinesterase receptors at the neuromuscular junction, myasthenic patients are extremely sensitive to nondepolarizing muscle relaxants. In comparison with responses in normal patients, the potency of atracurium in myasthenic patients is almost double [11]. An increased sensitivity of myasthenic patients was also reported to vecuronium [12]. In fact, it has been reported that the effects of all nondepolarizing agents are more profound and that the duration of block is significantly prolonged in myasthenic patients [3]. The sevoflurane anaesthesia will potentiate this effect.

Both tracheal intubation and the laparoscopic cholecystectomy surgical procedure demand profound muscular relaxation, which we achieved by administering 0.6 mg/kg rocuronium (2xED₉₅) [13]. The

2xED95 dose is the recommended intubating dose in the healthy patient, and would be considered a larger-than usual dose for patients with myasthenia gravis. The resulting intubating conditions were excellent and the abdominal relaxation was adequate for surgery. The relatively high dose of rocuronium and sevoflurane anaesthesia plus myasthenia bring the patient in a situation of a very prolonged relaxation. However two minutes after administration of rocuronium, the TOF ratio was 0.1 and the ratio increased gradually to a value of 0.67 until the end of surgery (45 min), when the patient initiated spontaneous breathing movements.

A similar sensitivity to rocuronium was also reported by Unterbuchner et al [14] in a myasthenic patient. Their patient required almost normal induction dose (43 mg) and repetitive doses (total 108 mg) of rocuronium to achieve and maintain neuromuscular paralysis intraoperatively.

The almost normal sensitivity to nondepolarizing neuromuscular blocking drugs may be explained by a mild form of the disease of our patient, restricted to eye muscles. However, there are *in vitro* studies on muscle biopsy samples taken from such patients, which indicate that the disease is present also in other muscles, though subclinically [15]; thus, pharmacological reversal of neuromuscular blockade is compulsory. In our patient, despite recovery of spontaneous breathing and a TOF ratio 0.67 at the end of surgery, the neuromuscular block was reversed with 2.0 mg/kg sugammadex.

For many years, a TOF ratio of 0.7 was considered sufficient for adequate recovery and to exclude postoperative residual paralysis ("curarization"). However, residual neuromuscular blockade continues to be observed commonly in the postanaesthesia care unit. Despite the use of intermediate-acting neuromuscular blocking agents, and the use of pharmacologic antagonism with neostigmine, an inadequate neuromuscular recovery was observed in a significant number (47%) of patients on arrival to the postanaesthesia care unit [16]. Incomplete recovery of the neuromuscular function contributes to adverse respiratory events [17] and to delayed recovery and discharge. Our patient's history revealed a history of prolonged recovery after general anaesthesia for hysterectomy, possibly due to a residual neuromuscular block after a conventional pharmacologic reversal with neostigmine. In fact, it is entirely possible that our patient may have exhibited the same slow and delayed recovery of neuromuscular function at the current surgery. Since we elected to antagonize her rocuronium-induced block once the TOF was 0.67, we are unable to document that the return of the rest of her neuromuscular function to at least 0.9 would not have been markedly delayed. Based on her previous history of prolonged postoperative

weakness, however, such an assumption would be reasonable. It is now generally accepted that for a complete recovery of a non-depolarizing neuromuscular block, a TOF ratio ≥ 0.90 should be obtained [18] and sugammadex is the agent of choice.

The results of a COCRANE systematic review of 18 randomized controlled trials (n = 1,321 patients) suggest that in comparison to placebo or neostigmine, sugammadex can more rapidly reverse rocuronium-induced neuromuscular block [19]. The optimal dosage depends on the depth of block at the time of reversal. The recommended dose of sugammadex to be administered at reappearance of the second twitch (T₂) of the train-of-four is 2 mg/kg sugammadex.

There are a few data concerning the dose and efficacy of sugammadex in patients with myasthenia gravis. In two case reports [14, 20] published recently, a dose of 2 mg/kg of sugammadex was used. TOF ratio of 0.90 and 1.0 were obtained within 120 sec [14], and 240 sec [20]. In our patient, administration of the same dose of sugammadex was followed by a more rapid reversal, as TOF ratio of 0.91 from a TOF of 0.67 was obtained within 60 sec. The difference in speed of the recovery in our patient compared with the previous reports can be attributed to a more advanced stage of disease (II_a) in the other published reports, and to the different timing of administration: at TOF ratio 0.48 [14] and 0.23 [20] versus a starting TOF ratio in 0.67 in our patient.

In conclusion, we report here our experience with rapid and reliable reversal of rocuronium-induced block by sugammadex in a patient with myasthenia gravis. Despite a previous history of prolonged recovery and need for mechanical ventilation after general anaesthesia and muscle paralysis with a nondepolarizing agent, our patient recovered to a TOF of 0.91 within one minute of sugammadex administration. Our case report suggests that in patients who are sensitive to nondepolarizing relaxant effects (such as patients with myasthenia gravis), the use of rocuronium for muscle relaxation and pharmacologic reversal with sugammadex may be the preferred technique.

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Utilizarea sugamadexului pentru antagonizarea blocului neuromuscular indus de rocuronium la un pacient cu miastenia gravis

Rezumat

Miastenia gravis este o boală autoimună a joncțiunii neuromusculare caracterizată printr-un răspuns impredictibil la acțiunea relaxantelor musculare și un risc postoperator crescut de bloc neuromuscular rezidual. Prezentăm cazul unui pacient cu miastenie forma oculară, supus colecistectomiei laparoscopice, cu un bloc neuromuscular moderat după administrare de rocuronium la care injectarea i.v. de 0,2 mg/kg sugamadex a produs în 60 sec antagonizarea blocului neuromuscular la o valoare a TOF de 0,91.

Cuvinte cheie: miastenia gravis, rocuronium, sugamadex