CASE REPORT

Sugammadex reversal of rocuronium-induced neuromuscular blockade in two types of neuromuscular disorders: Myotonic dystrophy and spinal muscular atrophy

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Abstract Neuromuscular disorders like myotonic dystrophy (dystrophia myotonica or Steinert’s disease) and spinal muscular atrophy are associated with perioperative complications related to muscle weakness. These patients have an increased sensitivity to non-depolarising neuromuscular blocking agents, which can lead to postoperative residual curarization (PORC) and its associated respiratory complications. Adequate reversal of neuromuscular blockade is essential to prevent this. Sugammadex is the first selective relaxant binding agent and it reverses rocuronium- and vecuronium-induced neuromuscular block. Two cases are reported in which the patients received sugammadex to reverse a rocuronium-induced neuromuscular block. Reversal of the rocuronium-induced neuromuscular block (NMB) in both cases was fast, effective and without recurarization, and no safety concerns were observed.

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Sugammadex antagoniza el bloqueo neuromuscular provocado por rocuronio en dos tipos de trastornos neuromusculares: distrofia miotónica y atrofia muscular espinal

Resumen Las enfermedades neuromusculares como la distrofia miotónica (o enfermedad de Steinert) y la atrofia muscular espinal se asocian con las complicaciones perioperatorias relacionadas con la debilidad muscular. Estos pacientes presentan una hiper sensibilidad a los bloqueantes neuromusculares no despolarizantes que podría derivar en curarización residual postoperatoria con complicaciones respiratorias. Para evitarlo conviene antagonizar satisfactoriamente el bloqueo neuromuscular (BNM). Sugammadex es el primer relajante selectivo y antagoniza los bloqueos neuromusculares por rocuronio y vecuronio. Se notifican dos casos donde los pacientes recibieron sugammadex para antagonizar un bloqueo neuromuscular.

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Introduction

Myotonic dystrophy, also referred to as dystrophy myotonica or Steinert’s disease (SD) and spinal muscular atrophy (SMA) are progressively disabling neuromuscular disorders which are challenging to the anesthesiologist. SD is an autosomal dominant trinucleotide repeat disorder caused by a mutation on chromosome 19 and affects the gene which codes for myotonic dystrophy protein kinase, a protein expressed in skeletal, smooth and cardiac muscle. This gene defect prevents cells in muscle and other tissues from functioning normally, and leads to muscle weakness, myotonia, cardiac abnormalities and cataracts. SMA is an autosomal recessive deletion of the survival motor neuron (SMN1) gene located on chromosome 5. This results in reduced levels of the SMN protein, leading to degeneration of alpha motor neurons of the spinal cord and resulting in muscle weakness, pulmonary insufficiency, autonomic and bulbar dysfunction and progressive paralysis. Although these diseases have a different etiology, both are associated with an increased incidence of perioperative respiratory and cardiovascular complications, as occurs with neuromuscular disorders in general. Furthermore, postoperative residual curarization (PORC) is a major risk in these patients and therefore reversal of neuromuscular blockade (NMB) is important to prevent PORC. However, reversal with cholinesterase inhibitors, especially in patients with neuromuscular disorders can also cause complications. Sugammadex, a new reversal agent for rocuronium or vecuronium induced NMB, is able to encapsulate the aminosteroid relaxant molecule, resulting in rapid recovery from NMB. Reports of reversal of rocuronium- or vecuronium-induced NMB with sugammadex in patients with neuromuscular disorders are limited. We report two cases in which two patients, one suffering from SD, and the other from SMA received sugammadex to reverse a rocuronium-induced NMB. Neuromuscular management and safety and efficacy of sugammadex in patients with neuromuscular disorders are discussed.

Case 1

A 38-year-old female patient, weight 76 kg, height 165 cm presented for elective laparoscopic cholecystectomy. Her medical history revealed SD diagnosed at the age of 36 years. Three years ago after delivery of her first child, she remained in hospital for two weeks due to a respiratory failure. Ten weeks after discharge she was readmitted to ICU with pneumonia and pericarditis. She was managed without mechanical ventilation and discharged on inhaled salbutamol and antibiotics. One year ago she underwent an uneventful thyroidectomy under general anesthesia without the use of neuromuscular blocking drugs. Her medication consisted of thyroxine 200 μg daily.

On examination she had muscle weakness of the lower limbs, slight slurring of her speech, mild ptosis, weakness of eye and mouth closure. She had weakness of neck flexors, the finger extensors, and the feet distally. She had bilateral percussion myotonia of the abductor pollicis brevis, and poor relaxation of grip on command. No reflexes could be elicited. Blood pressure, ECG and transthoracic cardiac echogram were normal. Respiratory function tests showed a Forced Vital Capacity (FVC) of 52% of predicted and Forced Expiratory Volume in One Second (FEV1) of 42% of predicted. DNA testing of the patient’s leukocyte DNA confirmed SD, and nerve conduction tests showed profuse myotonic discharges and myopathic changes. Laboratory tests showed an elevated creatine kinase of 548 IU l−1 (range 0–192 IU l−1). Full blood count, biochemistry and chest X-ray were normal.

After obtaining informed consent from the patient she was scheduled for laparoscopic cholecystectomy under general anesthesia. The neuromuscular function was monitored quantitatively with train-of-four (TOF) stimulation of the ulnar nerve using the neuromuscular transmission module (M-NMT, Datex-Ohmeda, Helsinki, Finland). The primary efficacy variable for reversal was defined as the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9.

Premedication consisted of oral esomeprazole 40 mg before anesthesia. An intravenous line was inserted on arrival in the operating room. Standard intraoperative monitoring included pulse oximetry, ECG, non-invasive blood pressure (NIBP), radial arterial line, continuous capnography, temperature, inspired/expired oxygen concentration, State entropy (SE) and response entropy (RE). Intravenous fluids were warmed through a coil and the patient was kept normothermic by using warmed intravenous fluids and a warming blanket. The patient was preoxygenated for 5 min, cricoid pressure was applied and anesthesia was induced and maintained with propofol Target Controlled Infusion (TCI, range 3–6 μg ml−1) and remifentanil TCI (range 2–5 ng ml−1).

Procedures for the set-up, calibration, and stabilization of neuromuscular monitoring were performed. The patient then received rocuronium 35 mg IV (0.47 mg kg−1). This was followed by endotracheal intubation, under excellent intubation conditions, within 80 s (at TOF 3) and the lungs were ventilated with a mixture of oxygen and air at a ratio of 2:3. The time that elapsed from the injection of rocuronium to a maximal NMB (TOF 0) was 220 s. Additional analgesia was provided with paracetamol 1000 mg IV, parecoxib 40 mg IV, and infiltration of the surgical incision with bupivacaine 0.5% and cefotaxime 2 g IV was also administered. Surgery was uneventful and the duration of anesthesia was 65 min. At the end of the procedure neuromuscular monitoring showed
recovery of the second twitch (T2) of the TOF, indicating shallow NMB. Reversal of rocuronium-induced NMB was performed by administration of sugammadex 2.7 mg kg\(^{-1}\) (one ampoule of 200 mg). The recovery time from a shallow rocuronium-induced NMB (return of T2) to TOF ratio of 0.9 was 5 min. No change in heart rate or blood pressure occurred with the administration of sugammadex. When the patient was awake and responding to commands she was placed in the left lateral position, the trachea was extubated and she was transferred to the intensive care ward for monitoring of respiratory and cardiac status. No signs of residual NMB or recarization were observed. The patient was discharged home from ICU on the third morning after the operation.

Case 2

A 61-year-old female patient, weight 40 kg, height 162 cm presented for elective combined approach tympanoplasty. Her medical history revealed SMA diagnosed at the age of 51 years, and chronic obstructive pulmonary disease Gold class II. Nightly continuous positive airway pressure ventilation was started two years ago. She underwent two uneventful identical operations 6 and 9 years ago, under general anesthesia without the use of neuromuscular blocking drugs. Her medication consisted of a diotroplum bromide inhaler. On examination she had muscle weakness of the upper and lower limbs, and difficulties in swallowing. Blood pressure, ECG and transthoracic cardiac echogram were normal. Respiratory function tests showed a FVC 65% of predicted, FEV1 66% of predicted and 59% Forced expiratory flow (FEF 50%) 52% of predicted. X-ray of the chest showed no abnormalities. Arterial blood gas evaluation showed a \(P_\text{a}O_2\) of 10.2 kPa, \(P_\text{a}CO_2\) of 6.7 kPa and an \(O_2\) saturation of 92% without oxygen.

After obtaining informed consent for the surgical procedure, she was scheduled for combined approach tympanoplasty under general anesthesia. The neuromuscular function was monitored quantitatively using train-of-four (TOF) stimulation of the ulnar nerve using a TOF-Watch\-Sx (Merck, New Jersey, USA). The primary efficacy variable for reversal was defined as the time from the start of the administration of sugammadex to recovery of the TOF ratio to 0.9.

Premedication consisted of oral paracetamol 1000 mg before anesthesia. On arrival in the operating room, an intravenous line was inserted. Standard intraoperative monitoring included pulse oximetry, ECG, NIBP, radial arterial line, continuous capnography, temperature and inspired/expired oxygen concentration. After pre-oxygenation, anesthesia was induced and maintained with continuous IV infusion of propofol (8−12 mg kg\(^{-1}\) h\(^{-1}\)) and remifentanil (0.05−0.20 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)). Procedures for the set-up, calibration, and stabilization of neuromuscular monitoring were performed. The patient then received rocuronium 40 mg IV (1.0 mg kg\(^{-1}\)). This was followed by endotracheal intubation (at TOF 0) and the lungs were ventilated with a mixture of oxygen and air in a ratio of 2:3. The time elapsed from the injection of rocuronium to a maximal NMB was 65 s.

Intraoperative facial nerve monitoring was applied by the surgeon and since NMB interferes with this monitoring, NMB was reversed 17 min after the administration of rocuronium. At that time neuromuscular monitoring showed TOF of 0 and a post-tetanic count (PTC) of 1, indicating profound NMB. Reversal of rocuronium-induced NMB was performed by administration of sugammadex 160 mg (4.0 mg kg\(^{-1}\)). The recovery time from a profound rocuronium-induced NMB (1 PTC) to TOF ratio of 0.9 was 2.8 min. No change in heart rate or blood pressure occurred with the administration of sugammadex. Surgery was uneventful and the duration of anesthesia was 118 min. The patient’s trachea was extubated and she was transferred to the intensive care ward for further monitoring. No signs of residual NMB or recarization were observed. Post-operative analgesia was provided with morphine, regular paracetamol and diclofenac. She was discharged home from ICU on the third morning postoperatively.

Discussion

Both patients required rapid intubation to protect the airway, and in our opinion administration of rocuronium was indicated. Rocuronium has a rapid onset of NMB and is safe to use in neuromuscular disorders.\textsuperscript{13−17} A rapid onset of NMB was observed in both patients. Furthermore, the surgical procedure of the patient with SD also required relaxation. However, we realized that NMB was only necessary for intubation in the patient with SMA. In this specific surgical procedure intraoperative facial nerve monitoring was used to prevent iatrogenic damage of the facial nerve due to surgery. However, intraoperative facial nerve monitoring precludes the application of NMB. Therefore we decided to use rocuronium, due to its rapid onset in protecting the airway, and sugammadex for fast and efficient reversal of the rocuronium-induced NMB to facilitate facial nerve monitoring. Propofol and remifentanil were used in both cases, as these agents have minimal interaction with neuromuscular function. Recovery from these agents is rapid, even in patients with neuromuscular disorders. The onset time of rocuronium used in both cases was fast. Reversal of the rocuronium-induced NMB in both cases was fast, effective and without recarization. The time to recovery from a shallow rocuronium-induced NMB (recovery of T2) to a TOF ratio of 0.9 was 5 min and from a profound rocuronium-induced NMB (PTC 1) to TOF ratio of 0.9 was 2.8 min in the patient with SD and SMA, respectively. No clinically relevant changes from baseline were observed after administration of sugammadex. In the first case 2.7 mg kg\(^{-1}\) sugammadex was administered, which was 0.7 mg/kg higher than recommended. We were aware that the correct dose should be 2.0 mg kg\(^{-1}\) according to the results of monitoring, but for this case one ampoule was administered, resulting in a slightly higher dose of 2.7 mg kg\(^{-1}\). Neuromuscular disorders, including SD and SMA, have abnormal responses to anesthetic agents and these patients in particular have an increased sensitivity to non-depolarising NMB agents (NMBAs).\textsuperscript{14−16} Depolarizing NMBAs are contraindicated because of the risk of hyperkalemia, rhabdomyolysis, or even cardiac arrest.\textsuperscript{17−19} Administration of non-depolarizing NMBAs in neuromuscular disorders is
accompanied with a prolonged spontaneous recovery even after a single dose. Delayed recovery may result in a dangerous PORC and related morbidity and mortality. Reversal of NMB is thus important for rapid reversal of NMB, prevention of PORC, and the best strategy to facilitate rapid and complete recovery after surgery. Rocuronium-induced NMB can be reversed with cholinesterase inhibitors. However, cholinesterase inhibitor induced reversal of NMB has limitations due to its mechanism of action. Reversal with cholinesterase inhibitors is slow, unpredictable, and is therefore unreliable. Furthermore, the reversal with cholinesterase inhibitors (in combination with muscarinic antagonists) is associated with undesirable cholinergic side effects and may be contraindicated in SD as it can lead to muscle spasm.

Sugammadex is able to bind to the steroidal NMB agents rocuronium or vecuronium, forming a complex. After encapsulation rocuronium is not available to bind to the nicotinic receptor in the neuromuscular junction. This promotes liberation of acetylcholine receptors and results in a fast recovery from NMB, without recurarization, given in the recommended dose.

Besides the choice of an appropriate NMBA and adequate reversal of that NMBA, neuromuscular management in patients with neuromuscular disorders should include NM monitoring. Objective (quantitative) NM monitoring should be used in all patients with neuromuscular disorders receiving NMBA not only to define the depth of NMB during and at the end of surgery, but also to judge the adequacy of the reversal of that NMB.

Reversal of rocuronium-induced NMB by sugammadex in our cases was rapid, effective and without recurarization. These findings together with the previously published cases on the reversal of rocuronium-induced NMB with sugammadex in patients with neuromuscular disorders suggest that the combination of rocuronium and sugammadex can replace previous strategies in neuromuscular management in patients with neuromuscular disorders. Rocuronium can be used for a rapid onset of NMB and sugammadex can provide a rapid and safe reversal thereby reducing the risk of PORC. This needs to be confirmed with additional cases or clinical studies.

Conflict of interest

Dr Paul Stewart received honoraria from Schering Plough Pty Ltd and was a member of their Medical Advisory Board in 2009. Drs Paul Stewart and Stephanie Phillips received an unrestricted educational grant from MSD 2011. Dr de Boer is member of the Global Advisory Board of MSD.

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References