Myasthenia gravis is an autoimmune disorder involving the destruction of nicotinic acetylcholine receptors at the neuromuscular junction, and is characterized by weakness and exercise-induced skeletal muscle fatigue. One of the anesthetic-related complications in such patients requiring relaxation (ie. paralysis) during general anesthesia is an increased sensitivity to nondepolarizing neuromuscular blocking drugs (NMBD)\(^1\-3\). Furthermore, the chronic use of acetylcholinesterase inhibitors such as pyridostigmine in these patients may interfere with the dose response relationships and effectiveness of NMBDs and their antagonists\(^4\). Therefore, NMBDs should be given with care (ie. smaller doses) in patients with myasthenia gravis. Even small doses of a NMBD can lead to profound muscle paralysis with a prolonged spontaneous recovery or inadequate reversal by neostigmine\(^4\). A delayed recovery may result in a dangerous postoperative residual paralysis and the need for postoperative mechanical ventilation\(^1\-3\). It is therefore recommended to pharmacologically reverse neuromuscular blockade at the end of surgery to prevent respiratory morbidity and mortality in every patient, especially more vulnerable patients like those with myasthenia gravis\(^5\).

Classically, reversal of NMBDs is performed by administration of acetylcholinesterase inhibitors such as neostigmine. However patients with chronic use of acetylcholinesterase inhibitors may already have an optimal inhibition of this enzyme and therefore reversal with cholinesterase inhibitors is less effective.
Sugammadex, a new drug which reverses rocuronium or vecuronium-induced neuromuscular blockade by encapsulating the NMBD which results in a very rapid recovery from neuromuscular blockade. Sugammadex, a modified g-cyclodextrin has been approved by the European Medicines Agency as therapy for reversal of neuromuscular blockade induced by the steroidal non-depolarizing neuromuscular blocking drugs rocuronium and vecuronium. In clinical anesthesia and emergency medicine sugammadex has been available for almost one year in several European countries and is successfully used to reverse neuromuscular blockade and to eliminate postoperative residual neuromuscular blockage, or partial paralysis induced by these NMBDs.

We describe a case in which a patient received a single dose of sugammadex to reverse a rocuronium-induced profound neuromuscular blockade. The perioperative management, and the safety and efficacy of sugammadex in this myasthenia gravis patient is discussed.

Case Report

A 73 year-old female patient, weight 81 kg, was diagnosed with a malignant tumor of the left breast. Her medical history revealed seronegative myasthenia gravis with ocular signs and symptoms and mild generalized muscle weakness (class I-IIa myasthenia gravis severity classification system by Osserman and Jenkins), diagnosed at the age of 61 years. Eight years earlier the patient underwent an operation for appendectomy under general anesthesia which was complicated by prolonged neuromuscular blockade (NMB) after administration of a single dose (0.6 mg/kg) of the NMBD rocuronium to facilitate endotracheal intubation. After that procedure the patient was admitted to the ICU for postoperative mechanical ventilation.

Eight years later the patient was scheduled for mastectomy and sentinel node procedure under general anesthesia. An ICU bed was available postoperatively if needed. She had a decreased forced vital capacity and decreased maximal forced inspiratory and expiratory flow as measured by pulmonary function tests. Residual volume and total lung capacity were normal. There were no signs of cardiac (or other) pathology. Evaluation of the blood values, including blood chemistry and hematology analysis showed no abnormalities. Her medication, which was oral pyridostigmine 60 mg six times a day, was continued perioperatively.

After obtaining informed consent, the patient agreed that we would study the use of sugammadex in order to determine its rocuronium-binding effectiveness in patients with MG. We agreed to administer a small dose of rocuronium, which would be allowed to recover spontaneously, followed by a second equal dose which we would reverse shortly after its administration. The patient was therefore acting as its own control. Wouldn’t the second dose have a more profound effect?

Neuromuscular function measurement was performed using the TOF-Watch SX (Schering-Plough Ireland Ltd, Dublin, Ireland) monitor. The ulnar nerve was stimulated near the wrist with square wave pulses of 0.2 msec, delivered as train-of-four (TOF) pulses of 2 Hz, at intervals of 15 seconds. The contractions of the adductor pollicis muscle were quantitatively measured using acceleromyography. The data were recorded on a computer (TOFMON 1.2, Schering-Plough Ireland Ltd, Dublin, Ireland). The primary efficacy variable for reversal was defined as the time (recovery time) from the start of the administration of sugammadex, until 90% recovery of the ratio of the fourth (T4) to the first (T1) response in the pulse train. This is the standard of safe recovery as defined in the guidelines for Good Clinical Practice in neuromuscular monitoring.

Premedication consisted of oral paracetamol 1000 mg before anesthesia. On arrival at the operating room, an intravenous (IV) line was inserted. Standard intraoperative monitoring included ECG, non-invasive measurement of arterial blood pressure and pulse oximetry. After the patient breathed 100% oxygen, anesthesia was induced and maintained with continuous IV infusion of propofol (6-12 mg/kg/h) and remifentanil (0.10-0.25 µg/kg/min). Procedures for the setup, calibration, and stabilization of neuromuscular monitoring were performed. The patient then received an IV bolus injection of rocuronium 0.15 mg/kg (total 12.1 mg), which resulted in a profound neuromuscular block. This was followed by endotracheal intubation, and the lungs were ventilated with a mixture of oxygen and air in a ratio of 2:3. After spontaneous recovery (TOF-ratio > 90%) of this profound neuromuscular blockade in about one hour, a second dose of rocuronium 0.15 mg/kg (total 12.1 mg) was given, which again lead to a profound neuromuscular blockade. After reaching profound neuromuscular blockade from this second dose of rocuronium (Fig 1), neuromuscular blockade was reversed by the IV administration of 4.0 mg/kg sugammadex (324 mg). The dose of sugammadex was chosen according to the dose advice in the label regarding the depth of neuromuscular blockade at the time of reversal. The recovery times of both, spontaneous recovery and recovery after reversal with sugammadex were compared.

The time to spontaneous recovery from the first profound rocuronium-induced neuromuscular blockade to a TOF of 0.9 was 36.5 min. The time from the start of the administration of sugammadex after the second dose of rocuronium to recovery of the TOF-ratio to 0.9 was 2.7 min. No changes were observed in arterial blood pressure, heart rate or ECG after administration of the sugammadex dose.

The surgical procedure was uneventful, and at the end of the anesthesia the trachea was extubated. The recovery from anesthesia was also uneventful, and the patient was discharged to the post-operative recovery ward for further observation. There she was monitored until 120 minutes after the administration of sugammadex for signs of possi-
ble residual neuromuscular blockade. No such signs were observed, and the patient was discharged to the ward from which she went home 3 days later.

Discussion

Reversal of rocuronium-induced profound neuromuscular blockade by sugammadex in our patient with myasthenia gravis was faster compared with spontaneous recovery of the same depth of neuromuscular blockade and without signs of residual weakness or neuromuscular blockade. Administration of a small dose of rocuronium was indicated because myasthenia gravis patients are highly sensitive to non-depolarizing NMBDs like rocuronium or vecuronium. Specifically, the ED$_{95}$ for vecuronium in myasthenia gravis patients is 56% of normal, and the neuromuscular blockade is prolonged\textsuperscript{1}. For rocuronium the ED$_{95}$ in myasthenia gravis patients is unknown. Therefore, we decided to give 0.15 mg/kg which is only 25% of the standard dose required for endotracheal intubation in normal patients. Spontaneous recovery of the rocuronium-induced neuromuscular blockade was indeed prolonged, indicating the increased sensibility for rocuronium in myasthenia gravis patients.

Reversal of neuromuscular blockade in myasthenia gravis patients is important for the acceleration of the patient’s recovery and the prevention of postoperative residual weakness and neuromuscular blockade. In patients with myasthenia gravis, spontaneous recovery from neuromuscular blockade is much slower than normal and therefore reversal of neuromuscular blockade is the best strategy to facilitate rapid and complete recovery after surgery\textsuperscript{14,15}.

However, reversal of neuromuscular blockade in myasthenia gravis patients, who are already receiving cholinesterase inhibitor medication, is complicated by variable response and unreliable effect\textsuperscript{14,15}. Moreover, patients with chronic use of acetylcholinesterase inhibitors may already have an optimal inhibition of this enzyme and reversal with these compounds is therefore not possible. Additional doses of cholinesterase inhibitors may even lead to a cholinergic crisis, characterized by muscle weakness, bradycardia, increased secretions and gut motility\textsuperscript{1,4}. Rocuronium-induced neuromuscular block can be reversed by cholinesterase inhibitors such as neostigmine, edrophonium, or pyridostigmine\textsuperscript{50}. However, cholinesterase inhibitors have a number of undesirable side-effects (bradycardia, bronchoconstriction, hypersalivation, abdominal cramps and nausea and vomiting), which can be counteracted by coadministration of muscarinic antagonists (atropine or glycopyrrolate). Importantly, muscarinic antagonists also have side-effects (blurred vision, dry mouth, and tachycardia)\textsuperscript{11}. Furthermore, reversal of neuromuscular block with cholinesterase inhibitors (in combination with muscarinic antagonists) has limitations due to its mechanism of action as this treatment is ineffective against profound neuromuscular block\textsuperscript{12}.

Sugammadex is able to bind the steroidal neuromuscular blocking drug rocuronium or vecuronium, forming a complex\textsuperscript{6}. Encapsulation of the rocuronium molecule by sugammadex results in a rapid decrease in free rocuronium concentration in the plasma, and subsequently also at the nicotinic receptor in the motor endplate. This leads to a rapid reappearance of normal muscle activity. After encapsulation, rocuronium is not available to bind to the nicotinic receptor in the neuromuscular junction, but is excreted in the urine\textsuperscript{13}.

Patients with myasthenia gravis may present for any type of surgery and need to be thoroughly evaluated and prepared preoperatively. Such evaluation includes assessment of respiratory and bulbar function. A reduced forced vital capacity (FVC) and poor bulbar function are strong indicators for the risk that postoperative mechanical ventilation will become necessary\textsuperscript{3}. Furthermore, patients with myasthenia gravis may have cardiac arrhythmias, such as sinus bradycardia and atrial fibrillation\textsuperscript{1,4}. This may evoke complications when in the process of reversing a neuromuscular blockade, atropine is given. Preoperative medical management should also aim at optimal muscle function. Although...
there is controversy whether cholinesterase inhibitor medication should be continued until the time of the operation, if patients are reliant on their cholinesterase inhibitor medication, these patients should probably be continued perioperatively. As sugammadex does not interfere with cholinergic transmission, continuation of cholinesterase inhibitors preoperatively does not affect the efficacy of the reversal of neuromuscular block by sugammadex and therefore optimal muscle function is preserved.

Several publications demonstrated a very fast onset and markedly prolonged duration of action of nondepolarizing NMBDs in patients with myasthenia gravis. Reversal of neuromuscular block by sugammadex will eliminate the risk of residual neuromuscular blockade in such a vulnerable patient population. Reversal of rocuronium-induced profound neuromuscular blockade by sugammadex in our patient with myasthenia gravis was rapid, efficient, and without signs of postoperative residual neuromuscular blockage. Our case suggests that the combination of rocuronium and sugammadex for safe neuromuscular blockade and reversal is beneficial in myasthenia gravis.

BIBLIOGRAFÍA