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Neuromuscular block reversal with sugammadex in type 2 diabetic patients

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ABSTRACT

Background: There are very few studies on the pharmacodynamics of neuromuscular blockers in diabetic patients.
Objective: To analyze neuromuscular block reversal with sugammadex in type 2 diabetics compared with non-diabetic individuals, following rocuronium administration at usual doses.
Patients and methods: Prospective observational study. A total of 67 patients [33 diagnosed with type 2 diabetes (T2DM group) and 34 non-diabetics (control group)] were enrolled. Muscle relaxation was induced with rocuronium at usual doses (0.6 mg/kg plus maintenance boluses of 0.15 mg/kg), and neuromuscular block was monitored through the surgical procedure. At the end of the operation, upon return of the second response (T2) to the train of four (TOF), sugammadex was administered at a dose of 2 mg/kg. *Primary endpoint*: time from sugammadex administration to TOF ratio ≥ 0.9 (T2-TOF90) and TOF ratio ≥ 0.7 (T2-TOF70). *Secondary endpoints*: onset time, time to return of the first response (T1) to the TOF.
Results: No statistically significant differences ($p=0.797$) in reversal with sugammadex (T2-TOF90) were recorded between T2DM group and control group (162.73 versus 156.32 s). Likewise, there were no differences in the remaining pharmacodynamic variables analyzed (onset time, reappearance of T1 and T2-TOF70).
Conclusion: Sugammadex reversal at usual doses in diabetic patients shows no differences versus general population. This drug is therefore useful for preventing residual neuromuscular block in the diabetic population.

1. Introduction

There are very few studies on the pharmacodynamics of neuromuscular blockers (NMBs) in diabetic patients. Lawrence[1] found peroneal, cubital and radial nerve conduction velocity to be slower in diabetic patients than in healthy individuals, even in the absence of diabetic neuropathy. Saitoh's experiments[2,3] were based on the work by Lawrence, and demonstrated significant prolongation of the neuromuscular function recovery parameters after the administration of vecuronium. Likewise, Alper[2] and Topal[3] found recovery to be delayed in diabetic patients when rocuronium was used. On the other hand, the risk of residual neuromuscular block, expressed by $DURTOF_{70}$ and $DURTOF_{90}$ (time to recovery of TOF ratio

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≥ 0.7 and TOF ratio ≥ 0.9 from the administration of a single dose of 0.6 mg/kg of rocuronium or 0.1 mg/kg of vecuronium), is greater in patients with diabetes mellitus.[4,5] Saitoh[6] found neostigmine reversal of block induced by vecuronium to be slower in diabetic patients than in a control group. Sugammadex is a recent selective neuromuscular reversal agent. It acts by encapsulating aminosteroids such as rocuronium or vecuronium.[7] However, no studies have examined whether there are differences in the reversal with sugammadex in diabetic patients. Sugammadex is approved for use in Europe but not in the United States. The US Food and Drug Administration (FDA) has not approved sugammadex because of its concern over reports of allergic reactions.

Considering the all of the above, the main hypothesis of the study stated that the reversal with sugammadex in diabetic patients could be prolonged compared to non-diabetics. Time to reach a TOF ratio ≥ 0.9 after the administration of sugammadex was the primary outcome variable. Sugammadex was injected at the time of apparition of the second response of the train-of-four (T2-TOF90).

2. Patients and methods

2.1. Study design

The study is a prospective observational study of sugammadex reversal of neuromuscular block induced by rocuronium in a group of diabetic patients (T2DM group) versus a group of non-diabetic patients (control group).

The study was approved by the Ethics Committee of San Pedro Hospital in Logroño (Spain) (code ARM-SUG-2013-01). The study was classified by the Spanish Medicines Agency (AEMPS) as a post-marketing prospective observational study. All patients gave their consent to participation, after receiving a detailed explanation of the study.

2.2. Patients

The present study involved patients with and without T2DM that were enrolled when scheduled for surgery under general anesthesia . The T2DM group was limited to patients with type 2 diabetes without diagnosed diabetic neuropathy or neurological symptoms. Patients with allergy to sugammadex or rocuronium were excluded, as were those diagnosed with diseases that alter neuromuscular blocker response (e.g., Guillain–Barré syndrome, Duchenne type muscle dystrophies, etc.), and patients receiving treatment with drugs capable of altering neuromuscular transmission or neuromuscular blocker response (e.g., antiseizure drugs, certain antibiotics, etc.). Patients with suspected difficult airway (Mallampati class III and IV, thyromental distance < 6.5 cm, oral aperture < 3.5 cm) were also excluded. In relation to kidney function, patients with serum creatinine > 1.5 mg/dl or creatinine clearance according to the Cockroft–Gault formula of < 60 ml/min/1.73 m^2 were excluded. Lastly, we excluded individuals with GPT or GOT enzyme values > 42 IU/l or a body mass index (BMI) of < 18.5 kg/m^2 or > 30 kg/m^2.

2.3. Study endpoints

The primary endpoint was the evaluation of T2-TOF90, which is the time from sugammadex administration (2 mg/kg) to the recovery of TOF ratio ≥ 0.9. Sugammadex was administered after return of the second response (T2) to the train of four (TOF). When a TOF ratio ≥ 0.9 is reached, it is considered that there is no residual block, and therefore the patient can be safely awakened. This is the reversal protocol most commonly used in routine clinical practice, and is also the most widely investigated approach. The time from sugammadex administration to the return of TOF ratio ≥ 0.7 (T2-TOF70) was also determined. Other pharmacodynamic variables of neuromuscular block unrelated to reversal were also recorded, such as the onset time or latency period (T1 = 0) and time to return of the first response (T1) to the TOF.

2.4. Intervention

In the preanesthesia room, all patients received intravenous midazolam at a dose of 10–20 μg/kg. Monitoring was carried out as usual in the operating room, with electrocardiography, noninvasive arterial pressure recording, pulse oximetry, bispectral index (BIS), capnography and expiratory gas analysis. Anesthesia was induced with intravenous bolus doses of fentanyl (1–2 μg/kg) and propofol (2–2.5 mg/kg). Following induction, and after preparation and calibration of neuromuscular block monitoring (as detailed below), we administered 0.6 mg/kg of rocuronium as a bolus dose over 5 seconds. Once the first response to the TOF was 0 (T1 = 0), orotracheal intubation was carried out via direct laryngoscopy. The rocuronium maintenance dose during surgery was 0.15 mg/kg. It was administrated when the first twitch of TOF stimulation (T1) recovered to 25% of control value. With the patient intubated, anesthesia was maintained using sevoflurane in air/oxygen to secure $FiO_2 = 0.4$ and an end-expiratory sevoflurane concentration (EtSev) of 1.5% with a BIS of 40–60. Ventilation was adjusted to maintain end-expiratory CO_2 concentrations ($EtCO_2$) of 30–35 mmHg. Patient thermal protection was afforded by hot air blankets, monitoring skin temperature to avoid reductions to under 32 °C. Fentanyl boluses (50–100 μg) were administered when the heart rate or arterial pressure values increased by over 15% with respect to baseline. In turn, an increase in fluid therapy, atropine or ephedrine was used when the heart rate or arterial pressure decreased by over 15% with respect to baseline. At the end of the operation, upon return of the second response (T2) to the TOF, sugammadex was administered at a dose of 2 mg/kg. Monitoring of TOF was continued until reaching a TOF ratio of $\geq$ 0.9 between the fourth and first response.

2.5. Monitoring of neuromuscular block

Following the induction of anesthesia, the monitoring of neuromuscular function was started by percutaneous