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CLINICAL INFORMATION

Reversal of neuromuscular block with sugammadex in five heart transplant pediatric recipients

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Abstract Heart transplantation is a frequent procedure in the treatment of end-stage cardiac dysfunction. Therefore, these patient populations will also be more frequent exposed to other more common surgical procedures after their transplantation. Anesthesiologist should be aware in their assessment of these patients, especially regarding some specific issues related to patients with a history of heart transplantation, like reversal of neuromuscular block. Several reports described that cholinesterase inhibitors drugs, like neostigmine, may produce a dose-dependent life-threatening bradycardia in heart transplant recipients while other publication described the safe use of neostigmine. Reversal of neuromuscular block with sugammadex is another possibility, but limited data exists in literature. We describe five cases in which successful reversal of neuromuscular block was performed with sugammadex in heart transplant pediatric recipients without sequale and discuss the reversal of neuromuscular block in this patient population.

PALAVRAS-CHAVE
Rocurônio;
Sugammadex;
Transplante cardíaco;
Reversão do bloqueio neuromuscular

Reversão do bloqueio neuromuscular com sugammadex em cinco receptores pediátricos de transplante cardíaco

Resumo O transplante cardíaco é um procedimento frequente no tratamento da disfunção cardíaca em estágio final. Portanto, essa população de pacientes também será exposta com mais frequência a outros procedimentos cirúrgicos mais comuns após o transplante. Em sua avaliação, o anestesiologista deve ter em mente algumas questões específicas relacionadas à história de transplante cardíaco desses pacientes, tais como a reversão do bloqueio neuromuscular. Vários estudos relataram que os inibidores da colinesterase, como a neostigmina, podem

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produzir uma bradicardia dose-dependente que ameaça a vida em receptores de transplante cardíaco, enquanto um estudo relatou o uso seguro de neostigmina. A reversão do bloqueio neuromuscular com sugammadex é outra possibilidade, mas os dados na literatura são escassos. Descrevemos cinco casos nos quais a reversão bem-sucedida do bloqueio neuromuscular foi realizada com sugammadex em receptores pediátricos de transplante cardíaco sem deixar sequelas e discutimos a reversão do bloqueio neuromuscular nessa população de pacientes.

Introduction

Heart transplantation is a frequent procedure in the treatment of end-stage cardiac dysfunction. Therefore, these patient populations will also be more frequent exposed to other more common surgical procedures after their transplantation. Anesthesiologist should be aware in their assessment of these patients especially regarding some specific issues related to patients with a history of heart transplantation. One of these issues is the reversal of Neuromuscular Block (NMB).[1] Reversal of NMB to prevent Residual Neuromuscular Block (RNMB) and concomitant pulmonary complications, is a challenge in heart transplant recipients.[1–4] Reversal of NMB can be achieved with either cholinesterase inhibitors (in combination with muscarinic antagonists) or sugammadex. Reversal with cholinesterase inhibitors has not only limitations due to its mechanism of action (ineffective against deeper levels of NMB), but is also associated with undesirable cholinergic side-effects. Although a recent retrospective study showed no severe bradycardia, cardiac arrest or deaths after reversal with cholinesterase inhibitors in heart transplant recipients, several reports described that these drugs may produce a dose-dependent life-threatening bradycardia in heart transplant recipients.[5–9] The use of sugammadex in this patient population consists of only two case reports.[10,11] We describe five cases in which reversal of NMB was performed with sugammadex in heart transplant pediatric recipients and discuss the reversal of NMB in this patient population.

Case report

Case 1

A 14 years-old female patient (47 kg), was diagnosed with cholecystitis for which laparoscopic cholecystectomy under general anesthesia was indicated. The patient had a history of hypertrophic cardiomyopathy since she was 3 month of age. Two months prior to the laparoscopic cholecystectomy she underwent a successful cardiac transplantation. After preoxygenation, anesthesia was induced with sevoflurane and fentanyl 5 $\mu g.kg^{-1}$. This was followed by endotracheal intubation and the lungs were ventilated with oxygen and air (ratio 2:3). Anesthesia was maintained with propofol continuously i.v. and intravenous opioids. Hereafter, Neuromuscular Monitoring (NM Monitoring) was performed using the TOF-Watch® SX (Schering-Plough Ireland Ltd., Dublin, Ireland) by measuring the effect of stimulation of the ulnar nerve on the activity of the adductor pollicis muscle. After the procedures for the set-up, calibration, and stabilization of NM monitoring, according to the good clinical research practice in pharmacodynamic studies of NMB agents, rocuronium 0.9 $mg.kg^{-1}$ was administered.[12] NM monitoring continued until recovery to a TOF-Ratio (TOFR) to 0.9. The data were recorded on a laptop computer using the TOFMON 2.5 monitoring program (NV Organon, Oss, The Netherlands). The primary efficacy variable was defined as the time from the start of the administration of sugammadex, to recovery of the (TOFR) to 0.9. Additional rocuronium doses of 0.3 $mg.kg^{-1}$ were administered (total dose 56.4 mg). At the end of the procedure NM monitoring showed a reappearance of T_2, indicating moderate NMB. Reversal of rocuronium-induced NMB was performed with sugammadex 2.0 $mg.kg^{-1}$ (94 mg) according to the recommended dose. After 1 minute and 45 seconds the TOFR recovered to 0.90 (Fig. 1-I). No clinical relevant changes from baseline were observed in blood pressure, heart rate or ECG after the sugammadex dose. The trachea was extubated and the patient was fully awake discharged to the PACU. The patient's recovery from anesthesia was uneventful and no signs of RNMB or recurarization were observed. Surgery was uneventful.

Case 2

A 9 years-old male patient (26.1 kg) was diagnosed with cholecystitis for which laparoscopic cholecystectomy under general anesthesia was indicated. The patient had a history of hypoplastic ventricular chambers and underwent a successful cardiac transplantation 3 years prior. The patient was planned for surgery under general anesthesia. Anesthesia strategy, NM monitoring and primary end points were identical as in Case 1, except for the initial dose of rocuronium which was in this patient 0.6 $mg.kg^{-1}$ and repeat doses of rocuronium 0.3 $mg.kg^{-1}$ (total dose 31.3 mg). At the end of the procedure NM monitoring showed 2 Post Tetanic Counts (PTC), indicating deep NMB. Reversal of rocuronium-induced NMB was performed with sugammadex 4.0 $mg.kg^{-1}$ (104.4 mg) according to the recommended dose. After 1 minute and 45 seconds the TOFR recovered to 0.90 (Fig. 1-II). No clinical relevant changes from baseline were observed in blood pressure, heart rate or ECG after the sugammadex dose. The trachea was extubated and the patient was fully awake discharged to the PACU. The patient's recovery from anesthesia was uneventful and no signs of RNMB or recurarization were observed. Surgery was uneventful.

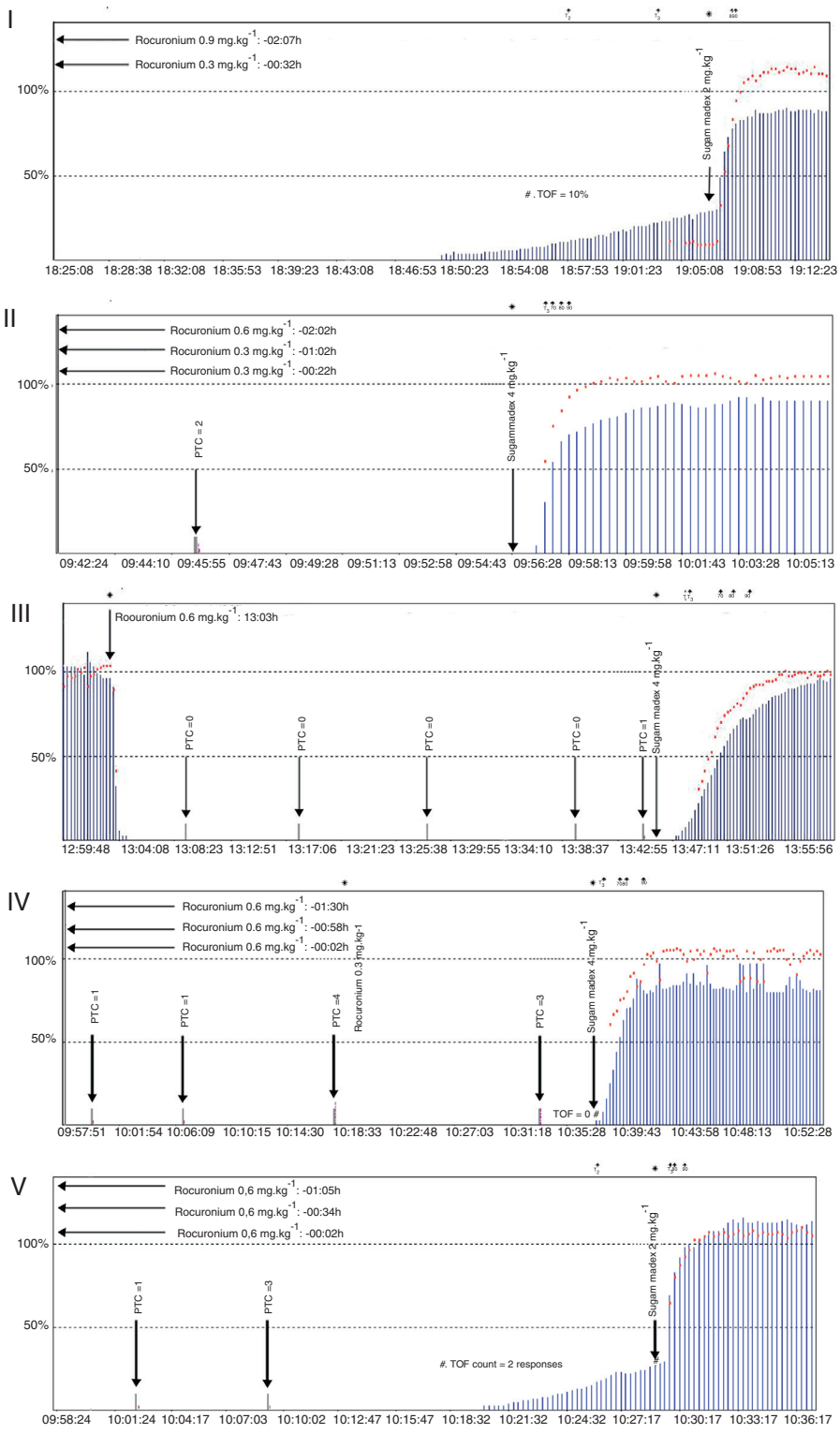

Figure 1 (I–V) TOF-Watch SX tracings of the first twitch height (blue vertical lines) and TOF ratio (red dots) and the different time points at which rocuronium and sugammadex were administered.

Case 3

A 7 years-old male patient 13.1 kg was diagnosed with gastric lymphoma for which stem cells collection was planned under general anesthesia. The patient had a history of hypertrophic cardiomyopathy since he was 1 year-old. Eleven months prior to this procedure he underwent a successful cardiac transplantation.

Anesthesia strategy, NM monitoring and primary end points were identical as in Case 2. Total dose of rocuronium

administered was 7.9 mg. At the end of the procedure NM monitoring showed 1 PTC, indicating deep NMB. Reversal of rocuronium-induced NMB was performed with sugammadex 4.0 mg.kg^{-1} (52.4 mg) according to the recommended dose. After 7 minutes and 15 seconds the TOFR recovered to 0.90 (Fig. 1-III). No clinical relevant changes from baseline were observed in blood pressure, heart rate and ECG after the sugammadex dose. The trachea was extubated and the patient was fully awake discharged to the PACU. The patient's recovery from anesthesia was uneventful and no signs of residual NMB or recurarization were observed. Surgery was uneventful.

Case 4

A 13 years-old male patient 39.8 kg was diagnosed with cholecystitis for which laparoscopic cholecystectomy under general anesthesia was indicated. The patient had a history of hypertrophic cardiomyopathy and underwent a successful cardiac transplantation 4 years prior. Anesthesia strategy, NM monitoring and primary end points were identical as in Case 2. Total dose of rocuronium administered was 71.6 mg. At the end of the procedure NM monitoring showed 3 PTC, indicating deep NMB. Reversal of rocuronium-induced NMB was performed with sugammadex 4.0 mg.kg^{-1} (159.2 mg) according to the recommended dose. After 3 minutes and 45 seconds the TOFR recovered to 0.90 (Fig. 1-IV). No clinical relevant changes from baseline were observed in blood pressure, heart rate or ECG after the sugammadex dose. The trachea was extubated and the patient was fully awake discharged to the PACU. The patient's recovery from anesthesia was uneventful and no signs of residual NMB or recurarization were observed. Surgery was uneventful.

Case 5

A 2.5 years-old female patient, 37 kg, was diagnosed with pneumoperitoneum for which exploratory laparotomy under general anesthesia was indicated. The patient had a history of dilated cardiomyopathy and underwent a successful cardiac transplantation 11 months prior. Anesthesia strategy, neuromuscular monitoring and primary end point were identical as in Case 2. Total dose of rocuronium administered was 20.5 mg. At the end of the procedure NM monitoring showed a reappearance of T_2, indicating moderate NMB. Reversal of rocuronium-induced NMB was performed with sugammadex 2.0 mg.kg^{-1} (22.8 mg) according to the recommended dose. After 2 minutes the TOFR recovered to 0.90 (Fig. 1-V). No clinical relevant changes from baseline were observed in blood pressure, heart rate or ECG after the sugammadex dose. The trachea was extubated and the patient was fully awake discharged to the PACU. The patient's recovery from anesthesia was uneventful and no signs of residual NMB or recurarization were observed. Surgery was uneventful.

Discussion

All five pediatric patients (2.5–14 y) showed a mean recovery time to TOFR to 0.9 in 255 s and 112 s for deep NMB and moderate NMB respectively. Reversal times were in line with other patient populations. There was no difference from the baseline regarding heart rate, blood pressure or ECG after the administration of sugammadex. Moreover, no other sequale like hypersensitivity were seen. Reversal of NMB in heart transplanted recipients with sugammadex is reported in one pediatric patient and two adult patients only.[10,11] These patients showed similar recovery times. Reversal of NMB in heart transplant recipients can be achieved by either cholinesterase inhibitors or sugammadex. Reversal with cholinesterase inhibitors is associated with a dose-dependent induced bradycardia and asystole in patients who underwent heart transplantation, both in recent and remote transplanted patients.[6,9,13] However, in a recent retrospective study in 118 anesthetic procedures in heart transplant recipients the safety of reversal of NMB with cholinesterase inhibitors showed no subsequent deaths or cardiac arrest and heart rates were not decreased statistically significant.[5] Sugammadex unlike cholinesterase inhibitors reverses a rocuronium-induced neuromuscular block rapid and complete and without the well-known undesirable side effects associated with the use of cholinesterase inhibitors.[1,4] This has been explained by the differential mechanism of action because, unlike cholinesterase inhibitors, sugammadex does not interfere with other receptor systems, in particular cholinergic transmission (cholinesterase, nicotinic receptors or muscarinic receptors).[1] Furthermore, the administration of sugammadex, even in high doses, did not influence QTc intervals and blood pressure and was well tolerated in patients with cardiovascular disease.[14–16] Therefore to avoid potential cardiovascular side effects associated with the administration of cholinergic inhibitors in heart transplant recipients, sugammadex might be a good alternative with the prospects of a fast and complete reversal of NMB, no cardiovascular side-effects and the prevention of RNMB.

Ethics

The institutional ethical committee was consulted for approval of publication of the data. As only patients' charts (as individual cases) were retrieved from the hospital archives and no clinical interventions were undertaken, ethical approval was not needed.

Conflicts of interest

RVC and HDDB have provided lectures about sugammadex sponsored by the pharmaceutical company Merck Sharp & Dome. MLAT has no conflict of interest declared.

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