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CASE REPORT

Bradycardia in a pediatric population after sugammadex administration: case series

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Abstract Sugammadex is a distinctive neuromuscular reversal drug that acts by encapsulating the neuromuscular relaxant molecule and dislodging it from its site of action. Sugammadex has been approved for pediatric patients over 2 years of age. Although arrhythmias have been reported, there is no report of adverse effects in healthy children, such as severe bradycardia requiring intervention. We report two cases of severe bradycardia immediately after the administration of sugammadex in healthy children. Our aim is to alert to the occurrence of one of the most severe adverse effects of sugammadex, in the healthy pediatric population as well.

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Introduction

Sugammadex is a modified γ -cyclodextrin, regularly used to effectively reverse the neuromuscular blockade induced by rocuronium and vecuronium.¹ Sugammadex acts by encapsulating rocuronium or vecuronium molecules, dislodging them from the neuromuscular junction and, consequently, reversing neuromuscular blockade. Since the inception of sugammadex in clinical practice, mild and transient adverse effects have been described, and severe adverse effects such as bradycardia followed by cardiac arrest have been reported in adults. Arrhythmias (3rd degree atrioventricular block, QT interval prolongation, persistent bradycardia, coronary vasospasm),

hypersensitivity and anaphylaxis are among the most prominent severe side effects reported.¹⁻³

In the pediatric population, sugammadex has been approved for patients above 2 years of age, and there are already some studies focusing on the adverse effects of sugammadex in pediatric patients. In most cases, severe bradycardia occurred in patients presenting cardiac comorbidities.⁴ Conversely, we describe two case reports of healthy pediatric patients in which, despite complying with drug administration recommendations, severe bradycardia was diagnosed and reversed only after treatment with atropine.

Case reports

Informed consent for publication was obtained from the parents.

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Case 1

Three-year-old female patient, weighing 17 kg, ASA (American Society of Anesthesiologists) physical status I, scheduled for cleft lip and palate repair.

After standard ASA monitoring (pulse oximetry, noninvasive blood pressure, continuous ECG, temperature, and capnography), train-of-four neuromuscular blockade monitoring, bispectral index and urinary output, general anesthesia was induced with intravenous administration of fentanyl 3 mcg.kg⁻¹, propofol 3 mg.kg⁻¹, and rocuronium 0.6 mg.kg⁻¹. Amoxicillin and clavulanic acid (30 mg.kg⁻¹ intravenously) were administered as antibiotic prophylaxis. Dexamethasone (0.15 mg.kg⁻¹ intravenously) was administered to prevent nausea and vomiting, and ketorolac (0.5 mg.kg⁻¹ intravenously) was administered as a multimodal analgesia component. Anesthesia was maintained with a mixture of oxygen and sevoflurane. Boluses of fentanyl (10 mcg) and rocuronium (3 mg) were administered 70 minutes after anesthesia induction. Before wound closure, the remaining multimodal analgesia components (paracetamol 260 mg and tramadol 35 mg both intravenously) and ondansetron 1.7 mg were administered intravenously. The surgery lasted circa 3 hours, was uneventful, and the patient remained hemodynamically stable (Heart Rate [HR] between 103 and 121 beats per minute (bpm) and Mean Arterial Pressure [MAP] between 60 and 62 mmHg). After observing a train-of-four ratio below 0.9, 34 mg (2 mg.kg⁻¹) of sugammadex was administered intravenously in the following dilution: 100 mg diluted in 10 mL of saline (10 mg.mL⁻¹). Immediately after administration, marked bradycardia of 53 bpm (Fig. 1), without hemodynamic consequences was observed, and was reversed after the administration of 0.35 mg of atropine. The trachea was extubated uneventfully. The patient was sent to the Postanesthetic Care Unit (PACU) and was discharged after criteria were met, without any complications registered.

Case 2

Six-year-old male patient, weighing 21 kg, ASA I scheduled for ureter cystoscopy. Standard ASA monitoring (pulse oximetry, non-invasive blood pressure, continuous electrocardiogram, temperature, and capnography), train-of-four neuromuscular blockade monitoring, bispectral index, and urine output was followed. General anesthesia was induced with intravenous administration of fentanyl 2 mcg.kg⁻¹, propofol 3 mg.kg⁻¹ and rocuronium 0.6 mg.kg⁻¹. The patient developed an

episode of bronchospasm with oxygen desaturation and bradycardia (Fig. 2), that was treated with manual ventilation, sevoflurane, inhaled salbutamol plus ipratropium bromide and intravenous hydrocortisone. Anesthesia was maintained with a mixture of oxygen and sevoflurane. Approximately 20 minutes before the end of surgery, paracetamol (320 mg) and ketorolac (10 mg) were administered intravenously for post-operative analgesia. Ondansetron (2 mg) was administered intravenously for nausea and vomiting prophylaxis. The surgery was uneventful with the patient hemodynamically stable (MAP 67–70 mmHg and HR 90–106 bpm). After observing train-of-four ratio below 0.9, 42 mg of sugammadex IV (2 mg.kg⁻¹) in the following dilution were administered: 100 mg diluted in 10 mL of saline (10 mg.mL⁻¹). After the administration, bradycardia (55 bpm) with hemodynamic changes (PAM ~ 50 mmHg) was observed and reverted after the administration of 0.45 mg of atropine (Fig. 2). Minutes after resolution, and 90 minutes after the event, blood was drawn for measuring tryptase (both resulted negative). Extubation was uneventful and the patient remained at the PACU until discharge criteria were met, uneventful and without other adverse effects associated with sugammadex.

Discussion

The purpose of these case reports is to alert to the occurrence of one of the most concerning adverse effects associated with sugammadex, severe bradycardia in the healthy pediatric population. There have been cases reported of profound bradycardia culminating in asystole in adults, thus bradycardia is well recognized as a potential adverse effect of sugammadex by the manufacturer.² However, despite the time relationship between sugammadex and bradycardia, no specific pharmacological or physiological mechanism of action has been suggested or established.³ Thus, the only recommendation is to inject sugammadex quickly (10 seconds) and in a single bolus. In addition, in the case of the pediatric population, the manufacturer recommends diluting sugammadex up to 10 mg.mL⁻¹ to enhance the accuracy of the dose administered.²

Moreover, large-scale studies focusing on this issue are scarce and virtually non-existent in the pediatric population. In 2020, Alsuehmani et al.⁴ reported a study that included 221 children in which sugammadex was administered for neuromuscular blockade reversal. Bradycardia was registered in 18 patients, of whom 7 presented cardiac

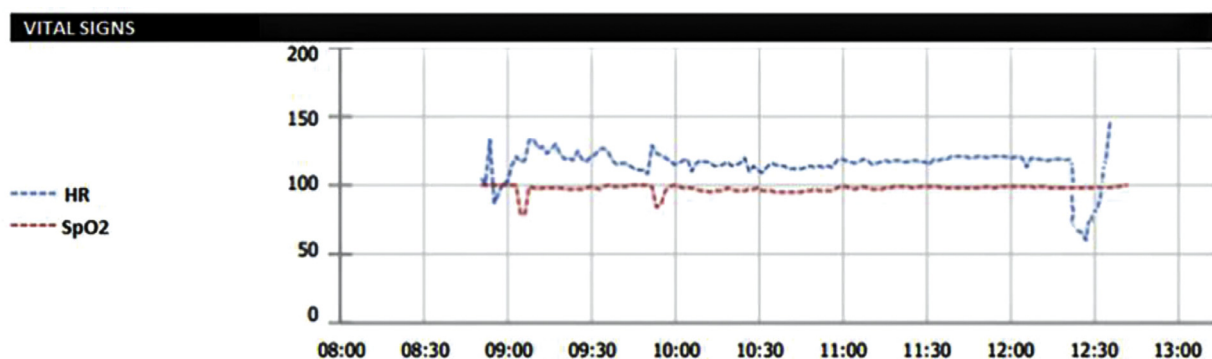


Figure 1 HR and Peripheral Oxygen Saturation (SpO₂) during the intraoperative period.

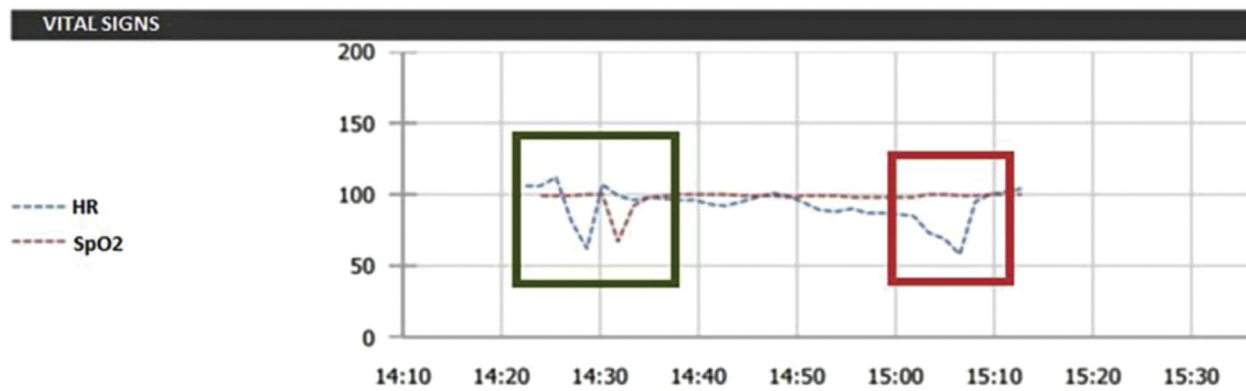


Figure 2 HR and SpO₂ during the intraoperative period. The black square represents bronchospasm at induction, and the red square represents bradycardia after administration of sugammadex.

comorbidities. None of the patients required pharmacological treatment to reverse bradycardia and no clinically significant changes in blood pressure were observed. However, this adverse effect may not always resolve spontaneously, and it may require pharmacological treatment to avoid it evolving to severe arrhythmia or cardiac arrest.

In addition to this adverse effect, anaphylaxis following sugammadex administration has also been described,³ so in Case 2, given the simultaneous hypotension, anaphylaxis was cogitated as a differential diagnosis, and therefore serum tryptase was measured. As serum tryptase levels were negligible (in both samples) and hemodynamic instability reversed after atropine administration, we excluded the diagnosis of anaphylaxis.

Hence, in the absence of further studies on bradycardia in the healthy pediatric population, the clinical report of these cases is an important and valuable source of information. The adverse effect described in these two patients was reported to the manufacturer, and also to the National Medicine and Health Product Authority (INFARMED), the agency responsible for pharmacovigilance in Portugal.

Conclusion

Even when administered at the appropriate dose and according to the manufacturer's recommendations, sugammadex can effectively cause severe bradycardia associated with hemodynamic instability in healthy children, and that may not easily reverse without adequate pharmacological

treatment. Therefore, more studies are required in this specific population.

Learning points

Bradycardia is a well-known adverse effect of sugammadex administration.

More studies focusing on this adverse effect in the pediatric population are required.

Conflicts of interest

The authors declare no conflicts of interest.

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