LUMEN ET VIRTUS

Sugammadex in the reversal of rocuronium-induced anaphylaxis in a pediatric patient: Case report and literature review

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ABSTRACT

INTRODUCTION: Among neuromuscular blockers (NMB), rocuronium is the most notably cited as a cause of anaphylactic reaction. Rocuronium-induced anaphylaxis is a serious and potentially fatal complication, requiring immediate and effective management. The advent of the specific antagonist, sugammadex, has widely spread its use because it reduces the incidence of residual neuromuscular blockade and is indicated in the protocol for the treatment and reversal of refractory anaphylaxis. This study reports an episode of anaphylaxis induced by rocuronium and successfully reversed after administration of sugammadex. CASE REPORT: A 6-year-old child, weighing 30 kg, scheduled for video-assisted thoracoscopy under general anesthesia presented with tachycardia, severe hypotension, and diffuse skin rash after induction of general anesthesia and administration of rocuronium. All therapeutic measures were immediately taken for the treatment of a severe allergic reaction, however there was no clinical improvement, and the patient progressed to sinus bradycardia. At this point, cardiopulmonary resuscitation maneuvers were initiated, and adrenaline was administered, but without satisfactory clinical response. In this context, the possibility of the causative agent being rocuronium was raised. Sugammadex was administered 16mg/kg, and the patient immediately returned to sinus rhythm and later presented a favorable clinical evolution and no sequelae. DISCUSSION: Sugammadex is a molecule that encapsulates rocuronium and removes it from both plasma and neuromuscular junction, and then excretes it inertly in the urine. Some

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authors suggest that sugammadex removes rocuronium molecules from the circulation, whether free or IgE-bound. This mechanism is extremely important, especially in grade III and IV anaphylactic reactions, which can lead to death. In view of the scarcity of publications, this report showed the role of sugammadex in the reversal of rocuronium-induced anaphylaxis, refractory to conventional treatment.

Keywords: Sugammadex, Anaphylaxis, Rocuronium.

INTRODUCTION

Anaphylaxis represents the most severe manifestation of an immediate hypersensitivity reaction, characterized as a potentially fatal response triggered by certain substances, among which anesthetic drugs stand out1. Among the triggering agents, neuromuscular blockers (NMB), such as rocuronium, are notable and are the most common cause of anaphylactic reactions during the perioperative period, being superior to other agents such as latex, colloids, hypnotics, antibiotics, and opioids1.

Rocuronium is a non-depolarizing NMB of intermediate duration and rapid onset of action, widely used to produce intraoperative muscle relaxation and satisfactory mechanical ventilation in the intensive care unit. Its composition is quaternary ammonium ion (QA), a molecule responsible for NMB and also for the allergenic potential of this drug[2]. Sugammadex, a modified cyclodextrin, has stood out due to its specific ability to form a rocuronium-sugammadex complex, offering broad clinical benefits. This interaction provides an agile and predictable reversal of any degree of neuromuscular blockade, in addition to considerably reducing the risk of residual neuromuscular blockade3,4. In addition, it has recently been included in the protocol for the treatment of severe anaphylaxis induced by rocuronium[1].

The aim of this study is to report a case of severe anaphylaxis induced by rocuronium and reversed with the administration of sugammadex in a pediatric patient and to review the literature on this subject.

CASE REPORT

A 6-year-old male child, weighing 30 kg, was being treated for necrotizing pneumonia and pleural effusion in the right hemithorax, with no satisfactory response to clinical therapy, with indication for video-assisted thoracoscopy for pulmonary decortication and pleural drainage. At the pre-anesthetic visit, she did not have other diseases or a history of food or drug allergies. On physical examination, the general condition was good, eupneic, afebrile, acyanotic, anicteric. Respiratory auscultation showed a hypophonetic breath murmur in the right hemithorax. The respiratory rate was 24 rpm and the peripheral oxygen saturation was 99% on room air.

No pre-anesthetic medication was administered. In the operating room, he was monitored with pulse oximetry, cardioscopy and non-invasive blood pressure, whose parameters were: blood pressure (BP) 100x50 mmHg, heart rate (HR) of 130 bpm, oxygen saturation (SpO2) of 99%. No antibiotics were administered in the operating room. After pre-oxygenation, the following were administered for anesthetic induction: 2 mg of midazolam, 150 mcg of fentanyl, 120 mg of propofol and 20 mg of rocuronium. Immediately after the administration of rocuronium, the patient presented flushing in the thoracic region, extending to the abdomen, upper limbs, and face. He was intubated without difficulty and administered 50 mg of hydrocortisone. Immediately afterwards, the patient presented tachycardia (HR 165 bpm) and hypotension (60 x 40 mmHg). The first dose of adrenaline, 1 mcg/kg (30 mcg) and volume expansion (20 ml/kg) were then administered, without success. In this context, 3 consecutive doses of adrenaline were administered, at intervals of approximately 5 minutes, totaling 120 mcg, keeping the patient hypotensive and with diffuse cutaneous rush. The patient progressed with sinus bradycardia, when cardiopulmonary resuscitation maneuvers were immediately initiated and the possibility of rocuronium being the causative agent of the reaction was raised. At this time, the use of sugammadex was suggested, at a dose of 16 mg/kg, and a total of 500 mg was administered. After 02 minutes of sugammadex administration, there was an improvement in the hemodynamic picture, with an increase in HR (160 bpm) and blood pressure (91 x 46 mmHg) and progressive disappearance of the *skin rash*. The surgery was suspended and the patient was sent to the ICU, sedated, hemodynamically stable, without the use of vasoactive drugs. Twenty-four hours later, he was extubated and the clinical treatment was successful. He was discharged from the hospital without sequelae, with a medical report of the incident and referral for investigation by an allergist.

The information collected in this case report fully respected the ethical principles and confidentiality associated with the patient's identity. The disclosure of the collected data was strictly conditioned to obtaining the agreement of the legal representative. After the manifestation of consent, the formalization was carried out by signing the Informed Consent Form and the consent form. This report was approved by the Human Research Ethics Committee (Opinion number: 6.102.709).

DISCUSSION

In a literature review carried out in December 2023 in the *Pubmed and Science Direct* databases, using *rocuronium, sugammadex,* and *anaphylaxis* as keywords, 03 articles of the case report type [2,5,6 were found], but none in a pediatric patient (Table 1). Due to the scarcity of publications, the report presented in this study reinforces the use of sugammadex as a successful therapy in the reversal of rocuronium-induced anaphylaxis.

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction in which mast cells and basophils play an important role through the release of mediators, where the combination of histamine, prostaglandins, and leukotrienes are responsible for increased capillary permeability. These substances are associated with the occurrence of symptoms such as urticaria, erythema, angioedema, systemic arterial hypotension, and bronchospasm1-3. Anaphylaxis during anesthesia is rare. The literature reports a variable incidence of 1 case in every 3,500 to 20,000 anesthesias. The mortality rate ranges from 3% to 9%, and 2% of the survivors have severe cerebral sequelae[7-10].

The drugs most commonly involved as a cause of anaphylaxis during general anesthesia are NMBs, accounting for approximately 65% of cases[9]. Among NMBs, rocuronium has been identified in several studies as the agent most commonly associated with this complication[7-10]. Both in the case described in this study and in others reported in the literature, the patients presented clinical signs and symptoms immediately after the administration of rocuronium2,5,6. The suspicion of this agent as responsible for the reaction and quick and effective decision-making are the fundamental pillars in the successful management of the reaction without sequelae1.

Neuromuscular blocking agents (NMBs) act at the skeletal neuromuscular junction (NMJ) inducing dose-dependent muscle paralysis. The use of NMBs has increased over the years, reflecting awareness of their useful and potential adverse effects3. Rocuronium is an intermediate-acting compound introduced into clinical practice in 1994, depolarizing, which has a rapid onset of action. This rapid onset is due to its low potency and high DE 95 (0.3 mg/kg), which requires a large initial dose, producing a higher concentration of this drug in JNM. Tracheal intubation conditions can be achieved in 90 seconds with a dose of 0.6 mg/kg, providing neuromuscular blockade of approximately 40 minutes. Latency can be reduced to 75 seconds with a dose of 0.9 mg/kg, but provides a longer action time (90 minutes). In this context, these properties make rocuronium the NMB of choice for rapid sequence tracheal intubation. Rocuronium is excreted unchanged by the hepatobiliary and urinary routes. Unlike other steroids, rocuronium can stimulate the release of histamine and, although the mechanism involving NMB-induced anaphylaxis is not fully understood, studies affirm that quaternary ammonium groups, replaced in this class of drugs, play a preponderant role as allergenic determinants, capable of interacting with immunoglobulin E and triggering a hypersensitivity reaction11.

Sugammadex was licensed for reversal of rocuronium- and vecuronium-induced neuromuscular blockade in 2008. In Brazil, this drug received authorization from the National Health Surveillance Agency in 2009. It is a modified γ-cyclodextrin, which binds/encapsulates and renders inactive the molecules of rocuronium and vecuronium, at the neuromuscular junction (NMJ), reversing the NMB. Sugammadex is effective and has shown an excellent safety profile in patients

exposed to the drug. Studies have shown the potential benefit of this reverser in the management of emergency situations or difficulty in accessing the airways12.

Sugammadex binds rapidly to rocuronium and removes it from the neuromuscular junction into the plasma and then into the kidneys, where it is excreted in the urine3,4,12. It is believed that this may be one of the mechanisms that decrease exposure to rocuronium and coupled IgE molecules during the hypersensitivity reaction1. In this context, the literature suggests the use of sugammadex as a potential therapy in cases of rocuronium-induced anaphylaxis. The theory proposed for successful cases of anaphylaxis reversal, such as the one presented in this study, is that Sugammadex inactivates the rocuronium molecule [2,5,6.]

In a literature review, we found the description of only three cases that corroborate the use of sugammadex in the treatment protocol for rocuronium-induced anaphylaxis, as shown in Table 12,4,6. All of them presented a clinical response and favorable outcome, one of them in the induction of general anesthesia for oncological surgery2 and the other in emergency5, showing the potential importance of this agent in the arsenal of drugs in the anesthesiologist's daily practice in reducing morbidity and mortality in the face of unexpected and potentially fatal adverse effects. In all of them, sugammadex was adopted as the last therapeutic alternative to the traditional protocol, since the measures adopted were not satisfactory to reverse the condition. Similar to our case, *McDonnell et al.* reported an adult patient who, after administration of 30 mg of rocuronium, rapidly developed a severe anaphylactic reaction, followed by cardiovascular collapse. After 19 minutes of unsuccessful cardiopulmonary resuscitation, administration of 500 mg sugammadex resulted in restoration of the pulse in just 45 seconds. A skin test performed 4 weeks ago confirmed rocuronium as the causative agent of the reaction6. In this adult patient, also with a severe hypersensitivity reaction, the same dose of sugammadex was administered that we used in our patient, a 30-kg child. Both presented rapid response and reversal of clinical manifestations, which suggests the need for further studies in order to establish the minimum effective dose of sugammadex for the rapid and effective reversal of an anaphylactic reaction induced by rocuronium.

The limitation involved in our report is related to the fact that blood samples were not collected for tryptase measurement, due to difficulties in the institution's laboratory, which is recommended to be done between 1-4 hours after the beginning of the reaction1. As for the confirmation, through skin tests, of the causal agent, we found it unnecessary because the facts made it evident that rocuronium was the causative agent. In this context, we can conclude that despite the scarcity of publications, this study showed the importance of sugammadex in the reversal of anaphylaxis induced by rocuronium, refractory to conventional treatment. Further studies are needed to establish the dose necessary for the reversal of anaphylaxis, because sugammadex is a high-cost drug.

Table 1 - Report of cases of sugammadex use in the reversal of rocuronium-induced anaphylaxis.

Age	Gender	Clinical manifestations	Surgery	Anesthetic technique	Complications	Reference
62 years old	Female	Urticarial erythema and moderate hypotension	Mastectomy	Overall balanced	Favorable outcome; Surgical schedule maintained	https://doi.org/10.1016/j.jclinane.2011.04.015
62 years old	Female	Erythematous plaques; hypotension and desaturation	Hematoma extradural	Overall balanced	Favorable outcome; Surgical schedule maintained	https://doi.org/10.1016/S0034-7094(12)70152-6
33 years old	Female	Desaturation, High peak pressure, PCR in pulseless electrical activity.	Diagnostic laparoscopy	Overall balanced	CPR maneuvers; administration of sugammadex; The patient was transferred to the ICU, extubated 30 minutes later without sequelae.	https://doi.org/10.1093/bja/aeq366

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Informed Consent Form (TALE)

TERMO DE ASSENTIMENTO LIVRE E ESCLARECIDO (TALE) - *modelo* Para crianças e adolescentes (maiores que **seis anos** e menores de **18 anos**) e para **legalmente incapaz**.

Eu, João Paulo Costa Fernandes convido você a participar do estudo SUGAMADEX NA REVERSÃO DA ANAFILAXIA POR ROCURÔNIO EM PACIENTE PEDIÁTRICO: RELATO DE CASO. Informamos que seu pai/mãe ou responsável legal permitiu. Pretendemos Relatar um caso de anafilaxia induzida por rocurônio e revertida com sugamadex em um paciente pediátrico no Hospital da Restauração. Gostaríamos muito de contar com você, mas você não é obrigado a participar e não tem problema se desistir. A coleta dos dados foi feita no Hospital da Restauração – Recife/Pernambuco, onde o participante Rosivaldo Felix dos Santos Desenvolveu uma anafilaxia ao rocurônio e revertemos com o uso do sugamadex. Caso aconteça algo errado, você, seus pais ou responsáveis poderá nos procurar pelos contatos que estão no final do texto. A sua autorização para divulgação do relato de caso é importante para que a informação possa ser disseminada e possa ajudar outras pessoas. As suas informações ficarão sob sigilo, ninguém saberá que você está participou desse relato; não falaremos a outras pessoas, nem daremos a estranhos as informações que você nos der. O relato de caso será publicado, mas sem identificar (dados pessoais, vídeos, imagens e áudios de gravações) do paciente.

CONSENTIMENTO PÓS-INFORMADO

Eu Josefa Maria Felix aceito compartilhar meus dados para o relato de caso: SUGAMADEX NA REVERSÃO DA ANAFILAXIA POR ROCURÔNIO EM PACIENTE PEDIÁTRICO: RELATO DE CASO. Entendi as coisas ruins e as coisas boas que podem acontecer. Entendi que posso dizer "sim" e participar, mas que, a qualquer momento, posso dizer "não" e desistir e que ninguém vai ficar com raiva/chateado comigo. Os pesquisadores esclareceram minhas dúvidas e conversaram com os meus pais/responsável legal. Recebi uma cópia deste termo de assentimento, li e quero/concordo em participar da pesquisa/estudo.

Recife-PE, 21 de março de 2023.

Rosival Felix dos Santos — Assinatura do menor

João Paulo C. Fernandes — Assinatura do pesquisador responsável

Em caso de dúvidas com respeito aos aspectos éticos desta pesquisa, você poderá consultar: Pesquisador(a) Responsável: João Paulo Costa Fernandes ou o Comitê de Ética em Pesquisa Envolvendo Seres Humanos do Hospital da Restauração no endereço: (Avenida da Agamenon Magalhães s/n – 5º Andar - Derby, Recife-PE, CEP: 25.010-040 Tel.: (81) 3181.5603 – e-mail: eticaempesquisahr@gmail.com), ou também a Comissão Nacional de Ética em Pesquisa-CONEP pelo endereço: (SRTV 701, Via W 5 Norte, lote D - Edifício PO 700, 3º andar – Asa Norte CEP: 70719-040, Brasília – DF Tel.: (61) 3315.5878).

CONSOLIDATED OPINION OF THE ETHICS COMMITTEE

HOSPITAL DA RESTAURAÇÃO - PE

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: SUGAMADEX NA REVERSÃO DA ANAFILAXIA POR ROCURÔNIO EM PACIENTE PEDIÁTRICO:
RELATO DE CASO

Pesquisador: JOAO PAULO COSTA FERNANDES

Área Temática:

Versão: 1

CAAE: 69553323.8.0000.5198

Instituição Proponente: Hospital da Restauração - PE

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 6.102.709

Apresentação do Projeto:

Trata-se de um relato de caso cujo tema é: SUGAMADEX NA REVERSÃO DA ANAFILAXIA POR ROCURÔNIO EM PACIENTE PEDIÁTRICO. Pesquisador Principal: Residente de Anestesiologia JOÃO PAULO COSTA FERNANDES, orientadores: Prof. Dra. Jane Auxiliadora Amorim/ Dr. Armando Moreira Mendes Filho. Segue a Apresentação:

Em uma anestesia realizada em um paciente masculino, 06 anos no Hospital da Restauração - Recife/PE. O paciente apresentou um quadro de hipotensão, taquicardia, eritema em região de tronco e face logo após a administração de rocurônio. Aventada a hipótese que o quadro de anafilaxia foi desencadeado pelo rocurônio, foi decidido utilizar o sugamadex por apresentar características químicas que reverte os efeitos do rocurônio, medida essa tomada após seguir o protocolo para resgate de anafilaxia padronizada, no qual não tinha se mostrado eficaz. O objetivo do trabalho é relatar esse acontecido por apresentar poucos relatos sobre esse tema nas plataformas de estudos.

Objetivo da Pesquisa:

Objetivo Primário:

Relatar um caso de anafilaxia induzida por rocurônio e revertida com sugamadex em um paciente pediátrico no Hospital da Restauração.

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Continuação do Parecer: 6.102.709

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_2106929.pdf	11/05/2023 16:15:44		Aceito
Outros	Lattesjoaopaulo.pdf	11/05/2023 16:15:14	JOAO PAULO COSTA	Aceito
Projeto Detalhado / Brochura Investigador	projetoJP.docx	10/05/2023 23:05:59	JOAO PAULO COSTA FERNANDES	Aceito
Cronograma	CRONOGRAMA.docx	10/05/2023 23:05:20	JOAO PAULO COSTA	Aceito
Outros	Cartadeapresentaccao.pdf	09/05/2023 17:26:16	JOAO PAULO COSTA	Aceito
Outros	LattesArmando.pdf	09/05/2023 17:16:41	JOAO PAULO COSTA	Aceito
Outros	LattesJane.pdf	09/05/2023 17:16:21	JOAO PAULO COSTA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TALE.pdf	09/05/2023 17:05:34	JOAO PAULO COSTA FERNANDES	Aceito
Outros	termodeconfidenciabilidade.pdf	09/05/2023 16:57:25	JOAO PAULO COSTA	Aceito
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Folha de Rosto	Folha_de_rosto_assinada.pdf	09/05/2023 16:49:29	JOAO PAULO COSTA	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

RECIFE, 06 de Junho de 2023

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