Anaphylactic reaction to the complex of sugammadex and rocuronium

Introduction

Rocuronium bromide is a nondepolarizing neuromuscular blocking agent with a short onset. It is indicated for *muscle relaxation during surgery and to facilitate tracheal intubation and mechanical ventilation*. Rocuronium acts by competing for cholinergic nicotin receptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine, edrophonium and pyridostigmine [1]. Rocuronium is available as Esmeron® and various generic brands.

Sugammadex is a modified gamma cyclodextrin. It indicated for *the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide*. Sugammadex forms a complex with these neuromuscular blocking agents in plasma reducing the amount of neuromuscular blocking agent available to bind to nicotinic cholinergic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium and vecuronium [2]. Sugammadex is available as Bridion®, Sugagelan® and various generic brands.

Anaphylaxis is an acute, potentially life-threatening, systemic hypersensitivity reaction caused by the sudden release of mast cell mediators. It most often results from immunoglobulin E (IgE) mediated reactions to foods, drugs, and insect stings, but any agent capable of inciting a sudden, systemic degranulation of mast cells can induce it [3].

Reports

In August 2023 the Netherlands Pharmacovigilance Centre Lareb received a case report (NL-LRB-00904426) from a physician of an anaphylactic reaction after administration of rocuronium bromide and sugammadex. The case concerns an 10-20 year old male who received rocuronium bromide at induction of general anaesthesia for surgical evacuation of an epidural hematoma. After surgery sugammadex was administered in order to antagonise muscle relaxation. Two to three minutes after administration of sugammadex a life threatening allergic reaction occurred known as anaphylaxis which presented with severe hypotension, tachycardia and bronchospasm. The anaphylactic reaction was treated with adrenaline, hydrocortisone and clemastine, but there was only a moderate response to the repeated boluses of adrenaline. After 1.5 hours some sort of erythema, but no obvious rash, occurred. Continuous adrenaline administration was needed for over 24 hours. The patient recovered without residual damage. Concomitant medication was: paracetamol, diclofenac, morphine, propofol and sevoflurane.

The patient had never received rocuronium bromide or sugammadex before. Skin prick tests for rocuronium (10mg/ml) and sugammadex, using three different dilutions (1:100 (1mg/ml), 1:10 (10mg/ml) and 1:1 (100mg/ml)), were all negative. For the skin prick test for the sugammadex-rocuronium complex (S-R-Cx) rocuronium 10mg/ml and sugammadex 100mg/ml were mixed 1:1 and histamine was used as a control preparation. The skin prick test for the S-R-Cx was positive. Directly after the anaphylactic reaction tryptase was significantly increased. A few weeks later, tryptase levels were normal, so an immunological disorder was excluded as a cause for increased tryptase levels. No intracutaneous test was performed given the intense anaphylactic reaction and the positive skin prick test.

This report is the only report regarding a hypersensitivity reaction to the S-R-Cx in the Lareb database [4].

Other sources of information

SmPC

In both the SmPCs of rocuronium bromide and sugammadex, hypersensitivity including anaphylactic reactions is described as a possible side effect. Also, hypersensitivity to rocuronium or the bromide-ion, sugammadex or to one of the excipients of the product is described as a contra-indication in section 4.3 of the relevant SmPC [1, 2]. Neither of the SmPCs provides any information about the possibility of hypersensitivity specific to the complex of these two drugs. Nor for hypersensitivity to possible complexes with other substances.

Literature

Several case reports describe an anaphylactic reaction to the S-R-Cx without reactions to sugammadex or rocuronium individually. Table 1 gives an overview of these case reports [5-10].

Table 1: Overview of case reports with an anaphylactic reaction to the rocuronium-sugammadex-complex only including results of allergy tests and authors' recommendation

Article	**Allergy tests and outcome**	**Recommendation**
Yamaoka et al. [5]	(-) SPT SUG (-) SPT ROC (+) SPT S-R-Cx (-) IDT SUG (+) IDT ROC* (+) IDT ROC undiluted** * Performed directly after IDT SUG, so probably reaction due to formation of the rocuronium-sugammadex-complex ** Considered as false positive	"There may be patients allergic to the rocuronium– sugammadex complex who are considered to be allergic to sugammadex. Should this patient undergo another general anesthesia, sugammadex must not be administered to reverse rocuronium. It might be advisable to avoid rocuronium and sugammadex altogether" "It is important to determine the pathogenesis of anaphylaxis by appropriate examinations to establish optimal risk reduction strategies and to prevent recurrence."
Kim et al. [6]	(-) IDT SUG (-) IDT ROC (+) IDT S-R-Cx	"Anesthesiologists and healthcare providers should be aware of the possibility of anaphylaxis from the sugammadex-rocuronium complex, as well as from sugammadex or rocuronium alone"
Ho et al. [7]	(-) IDT SUG (-) IDT ROC (+) IDT S-R-Cx (+) IDT S-V-Cx	"it is important for anesthesiologists to be aware that anaphylaxis maybe triggered by both free sugammadex and by the sugammadex–rocuronium complex. During the investigation of any anaphylactic event occurring immediately after the administration of sugammadex, it is essential when skin testing to use both the free drug and its complex with rocuronium."
Ebo et al. [8]	(-) SPT ROC (-) SPT SUG (-) IDT ROC (-) IDT SUG (+) IDT S-R-Cx (-) BAT ROC (-) BAT SUG (+) BAT S-R-Cx (+) BAT S-V-Cx (+) BAT S-Pa-Cx (+) BAT S-Pi-Cx	"This case report has several implications. First, it emphasizes that the S-R-Cx could trigger anaphylaxis in patients demonstrating negative ST and BAT to the NMBA and the SRBA. Therefore, the diagnostic exploration of such a patient would not be appropriate if it failed to test for the S-R-Cx."
Lopez-Raigada et al. [9]	(-) SPT ROC (-) SPT SUG (+) SPT S-R-Cx	"When a perioperative allergic reaction happens during awakening, our advice is to

	(-) IDT ROC (-) IDT SUG (-) BAT ROC (-) BAT SUG (+) BAT S-R-Cx	perform skin tests not only with sugammadex and rocuronium separately, but also with a mixture of both, as skin test results could prove negative for the drugs when analyzed separately. In such cases, not testing the drug mixture would lead to a false result, with an unacceptably high risk of severe reactions in subsequent surgical procedures.”
Okuno et al. [10]	(-) SPT ROC (-) SPT SUG (+) SPT S-R-Cx	-

SPT = skin prick test, BAT = Basophil activation test, IDT = intradermal test, ROC = rocuronium, SUG = sugammadex, S-R-Cx = sugammadex-rocuronium complex*, S-V-Cx = sugammadex-vecuronium complex,* S-Pa-Cx = *sugammadex-pancuronium complex, S-Pi-Cx = sugammadex-pipecuronium complex*

Eudravigilance database

On March 1st 2024 the Eudravigilance database of the European Medicines Agency contained 34 reports concerning anaphylactic and anaphylactoid responses (HLT) associated with the use of sugammadex and rocuronium in which the case narrative contained information about a possible reaction to the S-R-Cx. Eleven reports were excluded because the case narrative described that the test for the S-R-Cx was negative, or that it was not investigated or that no conclusion could be drawn. After that, three reports were excluded because a reaction to the S-R-Cx as well as to sugammadex alone was described. Of the 20 reports remaining, 17 were based on literature and three were not, including the Lareb report (NL-LRB-00904426) that has already been described. Appendix 1 contains an overview of the remaining reports, minus the Lareb report.

Prescription data

Table 2: number of patients using rocuronium in the Netherlands [11]

ATC-code	**Drug**	**2018**	**2019**	**2020**	**2021**	**2022**
M03AC09	Rocuronium (Esmeron®)	4,143	4,329	4,932	5,278	5,963

In the GIP database (Drug Information System of the Dutch Health Care Insurance Board) no prescription data is available for sugammadex (ATC-code V03AB35).

Mechanism

Sugammadex encapsulates the steroid backbone of rocuronium in its cavity leading to formation of the S-R-Cx. It is reported that the complex differs in drug solubility, delivery, distribution, or stability compared to the two individual drugs. This suggests possible structural and chemical alterations to both rocuronium and sugammadex, which may create specific S-R-Cx antigens. These antigens could cause allergic reactions to the complex even when allergic reactions do not occur to sugammadex or rocuronium alone [6] .

Ebo et al. mentions the possibility of an allergic reaction to the S-R-Cx due to shape alterations of the carboxyethyl side chains attached at the primary rim of sugammadex. In their tests IgE antibodies recognised not only the S-R-Cx but also complexes of sugammadex with other steroidal neuromuscular blocking agents suggesting cross-reactivity [8].

Discussion and conclusion

Hypersensitivity, including anaphylactic reactions, is described as an adverse drug reaction in the SmPCs of both rocuronium and sugammadex. Both SmPC texts indicate that the use of the product is contraindicated in case of hypersensitivity to one of the components of the product. However, neither SmPC text describes the possibility of hypersensitivity to the complex of both drugs: the sugammadex-rocuronium complex (S-R-Cx). Lareb received a case in which there was a hypersensitivity reaction to

the S-R-Cx and not to the individual drugs. In literature similar case-reports can be found as well as case reports mentioning a reaction to both the S-R-Cx and sugammadex alone [12]. An allergic reaction to only the complex and not the individual drugs is plausible as specific antigens for the complex can exist. And might also exist for complexes formed by sugammadex with other steroidal neuromuscular blocking agents.

The reporter of the Lareb case states that the focus of routine testing is primarily on the individual drugs rocuronium bromide and sugammadex and not on the complex of both drugs.
Healthcare professionals, especially anaesthesiologists, should be aware of the possibility of hypersensitivity to the S-R-Cx and allergy tests for the complex as well as the individual drugs should be carried out. Therefore attention for hypersensitivity to the S-R-Cx is warranted.

References

1. *Dutch SmPC of Esmeron®. version date* 19-12-2022; Available from: https://www.geneesmiddeleninformatiebank.nl/smpc/h16946_smpc.pdf.
2. *Dutch SmPC of Bridion®. version date* ?; Available from: https://www.ema.europa.eu/nl/documents/product-information/bridion-epar-product-information_nl.pdf.
3. Campbell R. *Anaphylaxis: Acute diagnosis*. In UpToDate, Connor RF (Ed), Wolters Kluwer. Accessed [8-3-2024] Available from: https://www.uptodate.com/
4. *Netherlands Pharmacovigilance Centre Lareb Database* (access date: February 2024)
5. Yamaoka, M., et al., *A suspected case of rocuronium-sugammadex complex-induced anaphylactic shock after cesarean section.* J Anesth, 2017. **31**(1): p. 148-151.
6. Kim, G.H., et al., *Anaphylactic shock after sugammadex administration, induced by formation of a sugammadex-rocuronium complex -a case report.* Korean J Anesthesiol, 2019. **72**(5): p. 495-499.
7. Ho, G., et al., *The First Case Report of Anaphylaxis Caused by the Inclusion Complex of Rocuronium and Sugammadex.* A A Case Rep, 2016. **7**(9): p. 190-192.
8. Ebo, D.G., et al., *Anaphylaxis to sugammadex-rocuronium inclusion complex: An IgE-mediated reaction due to allergenic changes at the sugammadex primary rim.* J Allergy Clin Immunol Pract, 2020. **8**(4): p. 1410-1415 e3.
9. Lopez-Raigada, A., et al., *Severe Perioperative Anaphylaxis due to Allergy to the Sugammadex-Rocuronium Complex.* J Investig Allergol Clin Immunol, 2022. **32**(2): p. 163-164.
10. Okuno, A., et al., *A suspected case of coronary vasospasm induced by anaphylactic shock caused by rocuronium-sugammadex complex.* J Clin Anesth, 2018. **48**: p. 7.
11. *GIPdatabase - Drug Information System of the Dutch Health Care Insurance Board*. 29-02-2024.
12. Zecic, F., et al., *Sugammadex-induced anaphylactic reaction: A systematic review.* J Anaesthesiol Clin Pharmacol, 2022. **38**(3): p. 360-370.

This signal has been raised on May 16, 2024. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl

1.1. Appendix

Table 2: Eudravigilance cases – excluding the Lareb case (NL-LRB-00904426 = EU-EC-10016353891

Report number	WWUCID	Literature source	Test results
Spontaneous reports			
EU-EC-10003036340	BE-009507513-1812BEL003496		(+) S-R-Cx* * kind of test not specified
EU-EC-10006838821	JP-MSD-M2020-19541		(+) SPT S-R-Cx
Literature reports not already described in signal			
EU-EC-10004715617	JP-MSD-1910JPN002420J	Sasakawa et al. P2-017 Perioperative management of a patient diagnosed with anaphylaxis induced by sugammadex–rocuronium complex. The Journal of Japan Society for Clinical Anesthesia. The 39th Annual Meeting. 2019;39:S319	(-) SPT ROC (-) SPT SUG (+) SPT S-R-Cx (-) IDT ROC (-) IDT SUG (+) IDT S-R-Cx
EU-EC-10014060560	JP-MSD-2203JPN001849J	Mukai et al. [A Case of Anaphylaxis Caused by Sugammadex Rocuronium Complex]. The 490th Japanese Dermatological Association Osaka Local Meeting Mukai et al. [3 A case of anaphylaxis due to Sugammadex Rocuronium Complex]. Skin Research/The 490th Osaka Regional Meeting of Japanese Dermatological Associ. 2022;21(3):251 Murota et al. [P5-05 A case of anaphylaxis due to rocuronium-sugammadex inclusion complex]. The 27th Annual Meeting of the Japanese Society of Pediatric Anesthesiology. 131	(-) ST ROC** (-) ST SUG** (+) IDT S-R-Cx ** Type of skin test (ST) not specified
Literature reports already described in signal			
EU-EC-12438964	JP-FRESENIUS KABI-FK201706076	Yamaoka et al. [5]	
EU-EC-12784482	AU-EMA-20170929-pagraharip-121406002	Ho et al. [7]	
EU-EC-12784503	AU-EMA-20170224-mshettyp-133107835	Ho et al. [7]	
EU-EC-10000721908	JP-009507513-1409JPN010124	Yamaoka et al. [5]	

EU-EC-10004840843	KR-PFIZER INC-2019468522	Kim et al. [6]	
EU-EC-10005567736	KR-009507513-1910KOR010819	Kim et al. [6]	
EU-EC-10006029131	BE-BBM-202000396	Ebo et al. [8]	
EU-EC-10007214877	ES-FRESENIUS KABI-FK202013353	Lopez-Raigada et al. [9]	
EU-EC-10007238854	ES-BBM-202001235	Lopez-Raigada et al. [9]	
EU-EC-10007339385	ES-009507513-2012ESP004111	Lopez-Raigada et al. [9]	
EU-EC-10011419523	KR-SUN PHARMACEUTICAL INDUSTRIES LTD-2019R1-231461	Kim et al. [6]	
EU-EC-10012444724	ES-STADA-248623	Lopez-Raigada et al. [9]	
EU-EC-10012450169	JP-MSD-1709JPN000608J	Okuno et al. [10]	
EU-EC-10013065330	ES-FreseniusKabi-FK202209961	Lopez-Raigada et al. [9]	
EU-EC-10013116661	ES-009507513-2107ESP008847	Lopez-Raigada et al. [9]	

SPT = skin prick test, IDT = intradermal test, ROC = rocuronium, SUG = sugammadex, S-R-Cx = *sugammadex-rocuronium complex*