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CASE REPORTS / CASE SERIES

Reversal of a rocuronium-induced grade IV anaphylaxis via early injection of a large dose of sugammadex

Neutralisation d'une réaction anaphylactique de grade IV induite par le rocuronium grâce à l'injection précoce d'une dose importante de sugammadex

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Abstract

Aim *To report rapid recovery from grade IV rocuronium-induced anaphylaxis with a large dose of sugammadex administered early after the onset of symptoms.*

Clinical features *A 22-yr-old female without relevant medical history developed an anaphylactic reaction within three minutes of rocuronium injection at induction of anesthesia for a routine cholecystectomy. During the first six minutes, she was unresponsive to usual treatment and her condition evolved to a grade IV anaphylaxis reaction despite a cumulated dose of epinephrine 0.7 mg. Sugammadex 14 mg·kg^{-1}, injected six minutes after rocuronium, resulted in total resolution of all manifestations of anaphylaxis within three minutes. The patient was discharged from hospital the next day. Allergy investigations confirmed rocuronium as the cause of anaphylaxis.*

Conclusion *Very early administration of a large dose of sugammadex may be an effective treatment for rocuronium-induced anaphylaxis.*

Résumé

Objectif *Rapporter le rétablissement rapide d'une patiente suite à une réaction anaphylactique de grade IV induite par le rocuronium grâce à l'administration rapide d'une dose importante de sugammadex après la manifestation des symptômes.*

Éléments cliniques *Une femme de 22 ans sans antécédents médicaux pertinents a manifesté une réaction anaphylactique dans les trois minutes suivant une injection de rocuronium à l'induction de l'anesthésie pour une cholécystectomie de routine. Au cours des six premières minutes, elle n'a pas réagi au traitement conventionnel et son état a évolué jusqu'à une réaction anaphylactique de grade IV, malgré une dose cumulée de 0,7 mg d'épinéphrine. L'injection de 14 mg·kg^{-1} de sugammadex six minutes après le rocuronium a permis la résolution totale de toutes les manifestations d'anaphylaxie en trois minutes. La patiente a reçu son congé de l'hôpital le lendemain. Des examens d'allergie ont confirmé que le rocuronium était la cause de la réaction anaphylactique.*

Conclusion *L'administration très rapide d'une dose importante de sugammadex pourrait constituer un traitement efficace des réactions anaphylactiques induites par le rocuronium.*

Anaphylaxis is a rare complication of anesthesia (estimated incidence 1/13,000) that can be severe and life threatening.[1] In more than 58% of cases, the causal agent is a neuromuscular blocking agent, and the specific drugs most frequently involved are succinylcholine and rocuronium.[1,2] Several case reports in the literature

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describe a possible reversal of the signs and symptoms of rocuronium-induced anaphylaxis by the injection of sugammadex.[3-9] The pathophysiology of the attenuation of this phenomenon remains uncertain; however, in most cases described, there was a relatively long interval between the first symptom and injection of sugammadex, which was administered only after failure of standard treatment (14-60 min). Moreover, the doses of sugammadex varied widely (range 3.4-18 $mg{\cdot}kg^{-1}$), with relatively low doses being administered; only one case in seven received a dose $> 10\ mg{\cdot}kg^{-1}$.

We report a recent case of rapid recovery from the hemodynamic signs of rocuronium-induced anaphylactic shock with a very early injection of a large dose of sugammadex (only four minutes from first symptom to sugammadex injection).

Case report

A 22-yr-old female patient was scheduled for an elective laparoscopic cholecystectomy. She was overweight (height, 170 cm; weight, 87 kg; body mass index, $30\ kg{\cdot}m^{-2}$), an active smoker, and had already undergone two anesthetics for an exploratory laparoscopy and the insertion of an intra-uterine contraceptive device. No adverse events had occurred during these procedures. As a premedication, the patient received hydroxyzine 100 mg *po* the evening and the morning before surgery. No prophylactic antibiotic was administered. Induction of anesthesia consisted of sufentanil 10 µg ($0.12\ \mu g{\cdot}kg^{-1}$), ketamine 20 mg ($0.23\ mg{\cdot}kg^{-1}$), and propofol 200 mg ($2.3\ mg{\cdot}kg^{-1}$), followed by rocuronium 50 mg ($0.57\ mg{\cdot}kg^{-1}$). Tracheal intubation was performed within two minutes after rocuronium injection.

The patient developed a skin rash immediately after tracheal intubation, noninvasive blood pressure measurements were unobtainable, and her heart rate increased to 165 $beats{\cdot}min^{-1}$. Simultaneously, end-tidal CO_2 ($EtCO_2$) decreased markedly. No bronchospasm was detected on auscultation and airway pressure was normal. The initial treatment consisted of ventilation with 100% oxygen, fluid loading with hydroxyethyl starch 500 mL, and repeated epinephrine boluses of 100 µg and 200 µg (total 700 µg). In spite of all these endeavours, the patient's blood pressure measurement was still unobtainable. The patient's condition deteriorated to a grade IV anaphylaxis ($EtCO_2 = 1$ mmHg). A bolus of sugammadex 1,200 mg ($13.8\ mg{\cdot}kg^{-1}$, the total dose immediately available in the operating theatre) was administered six minutes after the onset of symptoms. Within one minute, a complete recovery of hemodynamic parameters was observed, and within three minutes, the patient's skin rash disappeared. The time course of acute events, as retrieved from an electronic database, is summarized in Table 1. The procedure was cancelled and the patient was allowed to emerge from anesthesia. The tracheal tube was removed 29 min after the appearance of the first signs of anaphylaxis. The patient stayed in hospital for 24 hr and was discharged the next morning.

Laboratory results obtained from blood samples drawn 30 min after the beginning of the anaphylactic reaction showed a blood histamine level at 62.1 $\mu Mol{\cdot}L^{-1}$ (Normal $< 10\ \mu Mol{\cdot}L^{-1}$), a tryptase level at 53.9 $\mu g{\cdot}L^{-1}$ (Normal $< 11.4\ \mu g{\cdot}L^{-1}$). The fixation level of quaternary ammonium-specific immunoglobulin E (IgE) (Fluoro enzymo immuno assay, Gueant's technique, Nancy, France) was at 31.2% (positive value $> 2\%$) with an inhibition percentage of 95.98% for rocuronium (positive value $> 15\%$). The patient was referred for an allergo-anesthesia consultation six weeks later. She missed the first appointment but was seen eight months later before a new procedure was planned. The test results excluded all other drugs used for anesthesia and latex as potential causes of anaphylaxis. The skin prick tests were negative for propofol, sufentanil, and ketamine. There was a very strong skin reaction on the test for rocuronium (1/10,000 dilution), whereas no reaction was induced from all other neuromuscular blockers at dilutions up to 1/100 (suxamethonium, vecuronium, atracurium) and 1/10 (cisatracurium). The cholecystectomy was rescheduled 13 months after the event. General anesthesia was induced with propofol, sufentanil, and cisatracurium and maintained with sevoflurane: there were no complications.

Discussion

This case report shows resolution of grade IV anaphylactic shock due to rocuronium soon after administration of a large dose of sugammadex (approximately 14 $mg{\cdot}kg^{-1}$).

The present case report supports the findings of several previous reports suggesting the possibility of using sugammadex to reverse signs of anaphylactic shock induced by steroid neuromuscular blocking agents. Previous case reports described recovery from a grade II anaphylaxis reaction responsive to catecholamine[3-6] or, as presented here, a complete reversal of grade IV anaphylactic shock resistant to well-conducted resuscitation measures and catecholamine administration.[7-9] In all cases, a sugammadex injection was followed by a rapid hemodynamic improvement, usually within two minutes. The case with the lowest dose of sugammadex was resolved in ten minutes.[8] Nevertheless, although all case outcomes were positive, it is important to remain cautious given that negative case reports are published less frequently than

Table 1 Time course of events

Time (min)	−3	0	+2	+3	+4	+5	+6	+7	+9	+19	+23
Event		Rocuronium injection	Tracheal Intubation				Sugammadex injection				
Erythema			beginning	generalized, intense	generalized, intense	generalized, intense	generalized, intense	decreasing	disappearing	disappeared	none
Arterial blood pressure (mmHg)	131/73	92/35	61/39	non measurable	non measurable	non measurable	non measurable	110/60	120/65	129/72	135/78
Heart rate (beats·min^{-1})	100	110	145	165	168	170	168	142	120	98	99
End-tidal PCO_2 (mmHg)	Not measured	Not measured	35	32	12	1	1	28	35	36	36
Treatments			Hydroxyethyl starch 500 mL	epinephrine 100 µg	epinephrine 200 µg	epinephrine 200 µg	epinephrine 200 µg sugammadex 1,200 mg Lactated Ringer's 500 mL	methylprednisolone 120 mg			extubation

Data were obtained from the automatic IT records from the anesthesia ventilator machine and the patient monitor. Rocuronium was injected at zero minute. Tracheal intubation was performed between 0 and +2 min. Sugammadex was given at six minutes

positive cases. Randomized controlled trials are lacking, which, for obvious reasons, would be very difficult to organize.

Two objectives motivated our decision to administer a large dose of sugammadex: 1) to reverse neuromuscular blockade (and thus stop anesthesia and its unwanted hemodynamic effects) and 2) to obtain the potential direct beneficial effects of sugammadex. The mechanism of reversal of rocuronium-induced anaphylactic shock is debated. The triggering event leading to anaphylactic shock is the binding of quaternary ammonium allergens to specific membrane IgEs. This provokes mast cell degranulation and the release of mediators, the most important of which is histamine (type I immediate hypersensitivity reaction). When this type of reaction occurs, removal of the causing allergen is recommended.[10] Sugammadex is a cyclodextrin with high binding affinity for steroid-type neuromuscular blocking agents. The main hypothesis for the effect of sugammadex on anaphylactic shock, which is offered as the explanation in case reports of hemodynamic recovery, is that sugammadex is also able to encapsulate quaternary ammonium allergens. This makes the binding and blocking of the IgE allergen impossible at the onset of histamine release, which occurs early in the course of an anaphylactic reaction.[8] Nevertheless, the ability of sugammadex to alter the course of a fully developed anaphylactic reaction solely by removal of the trigger allergen remains a matter of debate. In a report by Clarke *et al*., patients known to be allergic to rocuronium had no skin reactions when exposed to a mixture of rocuronium and sugammadex.[11] They also reported that administering sugammadex after exposure to rocuronium reduces the skin reaction without stopping it completely. Leysen *et al.* show that adding sugammadex to a solution of rocuronium-activated basophils does not reverse the activation, even at high doses.[12] The key may be early administration of a large dose of sugammadex, thus stopping the anaphylactic cascade before it is self-enhanced.

The present report is a novel case of early administration of a large dose of sugammadex (14 mg·kg^{-1}, six minutes after the rocuronium injection and four minutes after the first manifestations) without waiting for the hypothetic efficacy of standard management (Table 2). Interestingly, early treatment allowed a very rapid recovery. The effectiveness and rapidity of using sugammadex to reverse the signs of anaphylaxis lead us to think that the effectiveness of sugammadex depends on rapid administration. Nevertheless, caution must be used because sugammadex can also lead to anaphylaxis: two cases of sugammadex-induced anaphylaxis have been reported.[13,14]

Table 2 Previous case reports with duration of resuscitation before sugammadex injection, and sugammadex dosage

First author[reference]	Surgical procedure	Rocuronium dose $mg \cdot kg^{-1}$	Severity of anaphylaxis	Initial therapy	Response to epinephrine	Time from first symptom to sugammadex	Sugammadex dose	Surgery performed or cancelled	Improvement after sugammadex
Pedersen[8]	Intracranial Tumour	unknown	Grade III	Phenylephrine 0.5 mg Epinephrine 40 µg Clemastine 2 mg Methylprednisolone 80 mg	No	45 min	3.4 $mg \cdot kg^{-1}$	yes	Within 10 min
Raft[6]	Umbilical Hernia	0.45 $mg \cdot kg^{-1}$	Grade III	Epinephrine 1,000 µg	No	18 min	18 $mg \cdot kg^{-1}$	cancelled	Began within seconds, stable hemodynamics after 2 min
McDonnell[5]	Laparoscopy (infertility)	0.39 $mg \cdot kg^{-1}$	Grade IV	Epinephrine 4,000 µg	No	19 min	6.5 $mg \cdot kg^{-1}$	cancelled	Within 2 min
Badaoui[7]	Laparoscopy (rectal tumour)	0.65 $mg \cdot kg^{-1}$	Grade III	Epinephrine 6,000 µg	Incomplete	20 min	13 $mg \cdot kg^{-1}$	cancelled	Within 5 min
Motamed[9]	Vertebral Cementoplasty	0.6 $mg \cdot kg^{-1}$	Grade III	Ephedrine 6 mg Epinephrine 200 µg	Transient and limited	14 min	4 $mg \cdot kg^{-1}$	cancelled	Within 2 min
Kawano[3]	Radical Mastectomy	0.45 $mg \cdot kg^{-1}$	Grade II	Ephedrine 4 mg	No	30 min	4.5 $mg \cdot kg^{-1}$	performed	« shortly afterwards »
Funnell[4]	Laparoscopic Cholecystectomy	0.64 $mg \cdot kg^{-1}$	Grade III	Hydrocortisone 200 mg Chlorpheniramine 10 mg Epinephrine infusion 0.17 $\mu g \cdot kg^{-1} \cdot min^{-1}$ + boluses	No	60 min	5 $mg \cdot kg^{-1}$	cancelled	Within 2.5 min

Conclusion

A series of case reports have been published detailing the effectiveness of sugammadex in reversing rocuronium-induced anaphylactic shock. The pathophysiology of this action remains unclear. A well-conducted blind comparison trial, impossible for ethical reasons, would be necessary to confirm this hypothesis. In the absence of scientific proof, the use of sugammadex should be limited to the most severe cases of rocuronium-induced anaphylaxis after failure of well-conducted initial management. Nonetheless, very early administration (within five minutes of the first symptoms) of a high dose of sugammadex (> 10 mg·kg^{-1}) should be considered as a possible key component of effective case management.

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References

1. *Dong SW, Mertes PM, Petitpain N, Hasdenteufel F, Malinovsky JM; GERAP.* Hypersensitivity reactions during anesthesia. Results from the ninth French survey (2005-2007). Minerva Anestesiol 2012; 78: 868-78.
2. *Sadleir PH, Clarke RC, Bunning DL, Platt PR.* Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. Br J Anaesth 2013; 110: 981-7.
3. *Kawano T, Tamura T, Hamaguchi M, Yatabe T, Yamashita K, Yokoyama M.* Successful management of rocuronium-induced anaphylactic reactions with sugammadex: a case report. J Clin Anesth 2012; 24: 62-4.
4. *Funnell AE, Griffiths J, Hodzovic I.* A further case of rocuronium-induced anaphylaxis treated with sugammadex. Br J Anaesth 2011; 107: 275-6.
5. *McDonnell NJ, Pavy TJ, Green LK, Platt PR.* Sugammadex in the management of rocuronium-induced anaphylaxis. Br J Anaesth 2011; 106: 199-201.
6. *Raft J, Leclercq M, Longrois D, Meistelman C.* Fast recovery of haemodynamic and ventilatory functions after sugammadex bolus following rocuronium-induced anaphylactic shock refractory to conventional treatment (French). Ann Fr Anesth Reanim 2012; 31: 158-61.
7. *Badaoui R, Popov I, Dupont H.* A case of rocuronium-induced anaphylactic shock, improved by sugammadex (French). Can J Anesth 2012; 59: 909-10.
8. *Pedersen NA, Findsen L, Olsen SK.* Should sugammadex be used for the treatment of anaphylaxia induced by rocuronium? American Society of Anesthesia 2010: A539 (abstract). Available from URL: http://www.asaabstracts.com/strands/asaabstracts/abstractList.htm;jsessionid=51E7E9DD8C30935D82DB080633E7D8D5?year=2010&index=13 (accessed January 2014).
9. *Motamed C, Baguenard P, Bourgain JL.* Possible mitigation of rocuronium-induced anaphylaxis after administration of sugammadex. J Anaesthesiol Clin Pharmacol 2012; 28: 127-8.
10. *Mertes PM, Malinovsky JM, Jouffroy L; Working Group of the SFAR and SFA, Aberer W, Terreehorst I, Brockow K, Demoly P; ENDA; EAACI Interest Group on Drug Allergy.* Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol 2011; 11: 442-53.
11. *Clarke RC, Sadleir PH, Platt PR.* The role of sugammadex in the development and modification of allergic response to rocuronium: evidence from cutaneous model. Anaesthesia 2012; 67: 266-73.
12. *Leysen J, Bridts CH, De Clerck LS, Ebo DG.* Rocuronium-induced anaphylaxis is probably not mitigated by sugammadex: evidence from an in vitro experiment. Anaesthesia 2011; 66: 526-7.
13. *Menendez-Ozcoidi L, Ortiz-Gomez JR, Olaguibel-Ribero JM, Salvador-Bravo MJ.* Allergy to low dose sugammadex. Anaesthesia 2011; 66: 217-9.
14. *Tokuwaka J, Takahashi S, Tanaka M.* Anaphylaxis after sugammadex administration. Can J Anesth 2013; 60: 733-4.