



## Case Report

## Atypical presentation to rocuronium allergy in a 19-year-old female patient

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## ABSTRACT

The danger of anaphylaxis, a rare but life threatening complication of general anesthesia (GA) can be summarized in two: 1. General Anesthesia masks the typical early signs of allergy which can be seen in an awake patient. 2. Anaphylaxis during GA manifests mostly as circulatory/ventilatory failures which can be interpreted as adverse effects of anesthetics or surgery and this can lead to critical delay of effective therapy. A 19-year-old female admitted for posterior spinal fusion and instrumentation (the 5th surgery in patient's life) desaturated seconds after intubation. Cardiopulmonary resuscitation (CPR) was started and the absence of cutaneous signs along with a loud holosystolic murmur were questioned. The patient was promptly resuscitated and allergy to rocuronium was confirmed by intradermal tests 6 weeks later. Factors influencing decision making and potential etiology of the newly heard holosystolic murmur during anaphylaxis are discussed.

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## 1. Introduction

The incidence of anaphylaxis during GA varies between 1:3500 and 1:20,000 cases, the interval cited in the majority of the literature which includes pediatric patients as well [1–4]. Females have a higher propensity with a 3:1 ratio compared to males [5]. About 90% of the time cases develop during induction of anesthesia, and are usually very urgent and serious, with a 3–9% mortality [2]. The variability of the clinical picture and non-anticipation of anaphylaxis, thanks to routine and safe everyday use of rocuronium, both contribute to a clueless life threatening situation in the operating room.

Anaphylaxis is characterized by Type 1 hypersensitivity reaction involving the release of vasomotor substances by Immunoglobulin E (IgE) mediators, which typically occurs within seconds to minutes following the exposure to a susceptible allergen. Typical clinical signs include hypotension, increased airway resistance, as well as the development of a skin rash. The earliest and most sensitive signs of change in a patient's well-being and level of consciousness are missing during GA.

Multiple drugs or agents used in the preoperative period could be responsible for allergy, among which 60% of cases are connected to muscle relaxants, 20% to latexes, 15% to antibiotics, and the remaining 5% to

sleeping pills, colloids, opioids, and others [6]. The risk of anaphylaxis increases with repeated exposure. Among those who have an anaphylactic reaction to neuromuscular blocking agents (NMBA), only 15% have had no previous administration of any type of muscle relaxant [5]. Rocuronium, an aminosteroidal NMBA has been reported to be the most common causative agent of anaphylaxis [7]. Its antigenic determinant is the tertiary ammonium ion [6,7]; frequent harmless use however undermines the risk of developing a serious anaphylactic reaction.

## 2. Case report

A 19-year-old female (154 cm, 41.5 kg, BMI 18.1 kg/m<sup>2</sup>) with congenital thoracolumbar scoliosis, was admitted for posterior spinal fusion and instrumentation. The patient had 4 previous orthopedic surgeries at the ages of 1, 2, 5 and 16 without anesthesiologic complications. She was admitted for one week to the intensive care unit (ICU) after the first surgery due to a pulmonary infection. She was only on calcium carbonate and Ergocalciferol home supplements. The patient did not have any upper respiratory infections, asthma, or known documented allergies present before surgery. Pre-operative laboratory results, chest X-ray, as well as echocardiography were normal. Echocardiography was performed to fulfill the preoperative protocol for this surgery in our institution.

Upon entering the operating suite her vital signs were as follows: heart rate (HR) of 85 beats/min, respiratory rate (RR) of 24 breaths/min, blood pressure (BP) of 129/77 mm Hg, and an oxygen saturation of 100% on room air. Anesthesia was induced through a peripherally

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inserted 22G cannula with 100 mg Propofol, 50 µg Fentanyl and 20 mg of rocuronium. 5 mg of Dexamethasone and 4 mg of Ondasetron were given as antiemetics before induction. Seconds after an uneventful intubation the SpO<sub>2</sub> started to drop progressively. The correct position of the endotracheal tube was reconfirmed with capnography, auscultation and visually with a laryngoscope. No signs of bronchospasm nor lung congestion were present. In spite of intensive bagging with 100% Oxygen, SpO<sub>2</sub> remained below 90% with a tendency to drop. BP measured after induction was 105/60 mm Hg, further updated measurements were not reliable. An arterial line was not available at the time. HR was 85 bpm, and a regular sinus rhythm was maintained on electrocardiogram (ECG). End tidal CO<sub>2</sub> was 20 mm Hg.

When the re-evaluation of the endotracheal tube position, manual ventilation brought no effect, and SpO<sub>2</sub> progressed to drop to ~60%; the anesthesia team, regardless of the patient's regular sinus rhythm called for help and started cardiopulmonary resuscitation (CPR). After few effective chest compressions, the SpO<sub>2</sub> rose to values up to 100%, but would drop again every time the chest compressions were interrupted. BP reading by cuff showed unreliable hypotensive values, peripheral pulses were not palpable, and the carotid pulse was disputable.

Following the administration of vasopressors a remarkable difference between the carotid pulse and radial and femoral pulses was noted, and the necessity to continue CPR was questioned. A loud precordial holosystolic murmur (4/6), new to the preoperative status and examination contributed to our confusion. After approximately 4–6 min of CPR and drug administration, gradual improvement of the SpO<sub>2</sub> and reliable BP readings (90–100/45–50 mm Hg, right arm) were produced. During CPR, hydrocortisone 100 mg, atropine 300 µg, phenylephrine 2 × 50 µg, and epinephrine 7 × 50 µg were given until reaching a stable circulation. An additional 100 mg of hydrocortisone and 25 mg of diphenhydramine were then added. Sugammadex was not given because rocuronium was not confirmed as the triggering agent. Arterial blood gases shortly after CPR were as follows: pH 7.28, CO<sub>2</sub> 5.4, pO<sub>2</sub> 29, Hb 118, Lactate 2.1, HCO<sub>3</sub> 18.8, BE-7.

The surgery was cancelled and the patient was transferred intubated to the ICU after a stable circulation was achieved and the need for vasopressors was no more necessary. She was extubated after a short period of sedation, later fully oriented and without any deficits. The patient and family were informed about the incident and immunology department alerted for allergy workup. Intradermal allergy tests were performed 6 weeks later using saline as negative control and histamine as the positive control. The mean diameter of the measured injection papule was larger than the diameter of the wheal induced by histamine, and consequently the allergic reaction to rocuronium was confirmed. The patient's family was also educated regarding future procedures.

### 3. Discussion

Rocuronium (Esmeron®, in USA Zemuron™) is an excellent muscle relaxant used worldwide. Organon recorded the 100 million landmark use in May 2005, around 11 years after its introduction to clinical practice [8]. NMBAs with Propofol and Fentanyl are probably the most administered drugs in anesthesia induction, with rocuronium and atracurium dominating among NMBAs.

In general, knowledge about the presentation of rocuronium allergy by anesthesiologists seems inadequate. About 70% of patients who experience anaphylactic bronchospasms have accompanying cutaneous signs, such as a rash or flush [9]. We report an atypical presentation of anaphylaxis to rocuronium, as the presence of circulatory collapse was not accompanied by any increased airway resistance or cutaneous signs, and thus doubted by most members of the surgical team.

Rocuronium holds a greater allergic potential compared to Atracurium [10]; they both share the same quaternary ammonium ion that exists in many of the environmental chemicals such as drugs, disinfectants, tooth paste, and shampoo [11]. This along with its frequent use

both make way for prior sensitization of the patient [5,12,13]. The susceptibility to rocuronium-induced anaphylaxis is multifactorial. The higher incidence of anaphylactic reactions to rocuronium in countries like Norway, France, and New Zealand compared to Sweden, Denmark or USA positively correlates with Pholcodine-containing antitussive sale-numbers; Pholcodine, an opioid antitussive was found by Florvaag et al. to dramatically increase IgE in sensitized individuals [14,15].

Anaphylaxis requires immediate management, including removal of the offending agent, securing the airway, correction of hypoxia, intravascular fluid supplementation, administration of sympathomimetics, and others [16]. Anaphylactic signs occur quite nonspecifically during anesthesia, just after induction when fluctuations of circulatory/ventilation parameters are rather typical. Furthermore, desaturation right after intubation evokes attributing the endotracheal tube as the reason behind ventilatory difficulties. This indeed can lead to detrimental delay in proper management. Guttormsen explains the Triple A approach for managing intraoperative anaphylaxis: Be Alert, Aggressive, and Adrenaline with fluids [14]. Despite case reports around the world, awareness about NMBAs allergy seems to be inadequate among anesthesiologists; who tend to overlook allergy as the reason behind circulatory/ventilatory collapse especially during induction. To act is crucial and lifesaving, irrespective of a confusing clinical picture such as the one in our case; CPR was initiated and the patient's hypoxia recovered promptly. In terms of fluid resuscitation, recommend doses are commonly known yet standard ampules with numbers differing in tens or hundreds can be confusing in urgent and stressful situations, risking dangerous or even fatal mistakes of over/underdosing. Although available, Sugammadex was not administered during management of the demonstrated case because allergy to rocuronium was not considered. The team reacted promptly yet unspecifically. The use of Sugammadex however, remains questionable especially when allergy to Sugammadex itself has also been reported [17,18]. It is known that Sugammadex does not fully encapsulate the molecule of rocuronium and therefore, may continue to induce anaphylaxis. Nonetheless, its use during anaphylaxis should remain in the arsenal of anesthesiologists as demonstrated by the literature [19,20].

The newly appeared loud holosystolic murmur (4/6) during circulatory collapse along with the discrepancy between normal sinus rhythm, and profound desaturation were the most puzzling in our case. The circulatory collapse was neither accompanied by increased airway resistance, nor cutaneous signs, and thus anaphylaxis was doubted during CPR and by some surgeons even after skin tests confirmed the allergy. The results have answered all doubts, but the question about the murmur remained. There was no valvular failure on the preoperative echocardiography, and the murmur was unanimously confirmed during hypotension with every auscultation. It had disappeared after the recovery of circulation. We hypothesize the possibility of some kind of physiological murmur in the absence of an anatomical substrate.

In 2007, Aveniros et al. described a new form of functional mitral regurgitation as the reason behind heart failure with normal ejection fraction and in the absence of coronary artery stenosis or left ventricular remodeling [21]. The same picture; a transient severe functional regurgitation due to sudden tenting of the mitral leaflets with a circular mitral annulus resulting in a total absence of leaflet coaptation, documented by transesophageal echocardiography, was reported by Labbe et al. [22]. The onset can be spontaneous, triggered by methylergonovine injection, respiratory distress, or transient myocardial ischemia around the anterolateral papillary muscle due to coronary spasm and/or microvascular dysfunction [21,23–25].

The anatomy of the mitral valve in particular highlights this rare phenomenon. The mitral valve has a single papillary muscle for each leaflet compared to the multiple, widely separated papillary muscles of the tricuspid valve. Any dysfunction of a relatively small area, especially by an 'eclipsed' suboptimal condition can lead to tethering of the valve tendineae, and severe regurgitation. Despite prompt resuscitation, our patient underwent severe hypotension and rapid volume

fluctuations which likely precipitated an abnormal anterolateral systolic leaflet motion, and incomplete closure with subsequent regurgitation. This rare and confusing motion of the valve leaflets is of particular concern due to the possibility of abruptly transforming into clinically significant failure resulting in pulmonary edema [23].

#### 4. Conclusion

Although the potential of rocuronium (Esmeron®, Zemuron™) to cause allergic reactions is known, awareness among anesthesiologists remains insufficient. The risk of allergy grows with repeated use and with preconditioning by environmental chemicals containing the quaternary ammonium ion. A variable clinical picture with symptoms seen during routine induction of GA contribute to a missed diagnosis. Aggressive approach, resuscitation and properly dosed Sugammadex are keys to success. An eclipsed mitral valve, a transient physiological dangerous form of MR was the probable culprit for the systolic murmur and circulatory collapse in our case. Cardiac alterations on echocardiography are indeed not compulsory for functional regurgitation and can result from subtle ischemic alterations responsible for leaflet discoordination [21]. Such patients should be closely monitored, and adequately managed especially under lethal settings. Timely recognition besides prevention is crucial to prevent delays, the wait to analyze unreliable values in hope of spontaneous recovery could have detrimental sequelae.

#### Disclosure of conflict of interest

None.

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