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Case report

Coma resulting from a grade IV anaphylactic reaction to atracurium

Coma secondaire à une réaction anaphylactique de grade IV sous atracurium

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Abstract

We report a grade IV anaphylactic reaction to atracurium. A 51-year-old woman was scheduled for an elective laparoscopic fibroidectomy. Her past medical history was negative for allergies, previous anaphylactic or anaphylactoid reactions, and acute or chronic diseases and she had no current symptoms. Atracurium injection evoked an immediate respiratory arrest and neck edema, hindering intubation. An emergency tracheotomy was performed, resulting in significant hemorrhage, shock and hypoxic coma. The diagnosis of anaphylaxis to atracurium was confirmed by an allergy investigation. This case report stresses the fact that acutely severe anaphylactic reactions can occur without typical skin or cardiac symptoms. Furthermore, low risk patients with a bland medical history are never exempt from the risk of anaphylactic shock, even with a designated low-risk agent of sensitization.

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Mots clés : Anaphylaxie ; Anesthésie ; Curares ; Atracurium

1. Introduction

The mortality from perioperative anaphylaxis has been quoted in a range between 3 and 9% [1]. The most recent studies report 4.1% mortality due to neuromuscular blocking agents [2]. Anaphylactic and anaphylactoid intraoperative anesthetic reactions occur with various incidences depending on the country, with an estimated frequency between 1/1000 to 1/20 000 [3–5]. The exact incidence remains underestimated as reactions are underreported. Independently from the regional differences, muscle relaxants are found to be the most common cause for severe anaphylactic responses [6–8]: two European studies

(observation period 2 and 6 years) reported NMBA as culprit agent in 58.2 and 93.2% of the cases (followed by latex allergy with 3.6 and 16.7%) [7,9]. A study conducted in France (data from 2005–2007) identified an IgE-mediated reaction in 63% and non-IgE-mediated in 37%. In keeping with previous findings, neuromuscular blocking agents (NMBA) were the leading cause of anaphylaxis (47.4%), followed by latex (20%), and antibiotics (18.1%) [10]. Among the NMBA, suxamethonium and rocuronium have mostly been described as the underlying agent (60.6%), whereas cis- and atracurium showed the lowest frequency (5.9%) [3,10]. Recent literature shows atracurium being involved in non-IgE-mediated reactions in relation with its direct histamine releasing properties [3]. It has been also incriminated in IgE-mediated reactions in large epidemiological surveys showing no differences regarding symptoms severity between the different NMBA [11,12].

We report a severe, life-threatening anaphylactic reaction after induction of atracurium, resulting in a coma following an emergency tracheotomy and partial thyroidectomy. Our patient

Abbreviations: NMBA, Neuromuscular Blocking Agents; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists physical status classification system; IDT, Intradermal testing.

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was asymptomatic and had a bland post medical history. From the onset of the anaphylactic reaction, mechanical ventilation was impossible. Immediate therapy according to the anaphylaxis guidelines was applied, without success. Complications of the emergency tracheotomy lead to a significant blood loss and prolonged hypoxia for 2 h. Postoperatively, atracurium was later identified as the culprit agent, using prick-test and intradermal testing.

2. History

A 51-year-old female was scheduled for an elective laparoscopic excision of asymptomatic uterine fibroids. The patient was in excellent physical state (ECOG 0, ASA 1, 90 kg, BMI 26 m/l²), without comorbidities, without a history of allergies or allergic predispositions, with an uneventful past medical history, no regular medication or substance misuse. General history and the physical examination were unremarkable. Mallampati score was III. Premedication with clonidine was given.

3. Anesthesia

Induction of anesthesia started with 40 mg/10 s propofol infusion, 20 µg sufentanil, and 3 mg midazolam, followed by 50 mg atracurium. Immediately after the administration of atracurium, a significant neck and facial edema occurred, independent breathing arrested within a minute and cyanosis occurred. Patient's blood pressure (BP) was at 100/60 mmHg. Three attempts at tracheal intubation were made, however they were unsuccessful due to pharyngeal edema, rendering the epiglottis and glottis invisible. We hypothesized a severe allergic reaction grade IV with a massive bronchospasm and edema. Antiallergic medication was given (adrenaline i.v., methylprednisolone 40 mg i.v., hydrocortisone 100 mg i.v.) without response. Oxygen saturation was rapidly decreasing, reaching levels of 58%. In order to start mechanical ventilation, an emergency tracheotomy was performed by an experienced surgeon (no ENT doctor was available for tracheostomy). Due to an incision in the thyroid cartilage, a severe bleeding hindered an insertion of intratracheal tube. An operative tracheotomy was imperative to insert a tracheal tube (diameter 6.5 mm) and commence the mechanical ventilation. However, ventilation was barely (tidal volume < 200 ml) possible, demanding high pressures of Ppeak ~ 40 mbar. The hypoxia improved slightly (SO₂ 75–80%). The bleeding following the tracheotomy still did not cease, causing a significant blood loss. The patient became increasingly cardiovascularly unstable, becoming hypotensive (BP 80/50 mmHg), making adrenaline and dopamine infusions imperative (a total of 1 mg and 600 mg respectively over 2 hours) to maintain the circulation. The oxygen saturation fluctuated between 60–80% during the operation period, while the acrocyanosis persisted. Since the source of hemorrhage could not be found, a partial left thyroidectomy was performed. The total blood loss was 2.5 l during the operation.

4. Postoperative course

Postoperatively, the oxygen saturation of patient gradually rose to 90%. The patient was transferred to the surgical intensive care unit (SICU), where she presented with a GCS 2 (reaction to pain-grimace). The eyelid edema persisted, conjunctival chemosis was noticed, the pupils were symmetrical, middle wide and promptly reactive to light. The cyanosis resolved. Mechanical ventilation via an intratracheal tube was continued, assuring oxygen saturations of 89–96% with tidal volume ~ 450 ml and Ppeak ~ 40 mbar. Babinski and Grinaud reflexes were not inducible. Head CT was normal.

Differential diagnoses of arrhythmia, pulmonary embolism, tension pneumothorax, angioedema, intracranial pathology and mastocytosis were investigated and excluded.

The further recovery was surprising, with the patient regaining a GCS12 on day 4. Mechanical ventilation was required for 10 days in total. Supportive hyperbaric oxygen therapy was initiated: according to the Chinese protocol of 40 dives in a hard, high pressure cabin (totally 10 days, 2 h each day). Initially, neurological deficits in form of an intentional tremor, accompanied by a partial left hemiparesis, were present. These resolved fully and the patient was discharged on the 23rd postoperative day.

A skin prick test with atracurium besylate (50 mg/ml) diluted 1:10 000 was performed 3 days after the anaphylactic reaction and was positive (erythema, immediate local reaction); negative and positive controls were also performed. In the intradermal tests with 0.02 ml of atracurium at dilutions of 1:10 000, we found a positive skin response (wheal diameter > 8 mm, induration and erythema). Intradermal tests to propofol, fentanyl, midazolam and sufentanil were all negative. Intradermal test with cisatracurium and rocuronium were positive, suggesting a cross-reactivity of these agents. Intradermal tests with suxamethonium and vecuronium were negative, suggesting that these agents could be used for further anesthesia. A RAST assay of IgEs against the quaternary ammonium groups is not available in our institution.

5. Discussion

Anaphylaxis is a potentially fatal clinical condition with multiorgan involvement [13]. The European Academy of Allergy and Clinical Immunology proposed to define anaphylaxis as “a severe, life-threatening, generalized or systemic hypersensitivity reaction”. In 1977, Ring and Messmer suggested a severity grading scale, according to the clinical manifestation (Table 1). In the guidelines, epinephrine given early is the most important intervention. Adjunctive treatments include fluid therapy, H1 and H2 histamine receptor antagonists, corticosteroids, and bronchodilators.

Muscle relaxants have been known to potentially lead to severe immune-mediated adverse reactions, including anaphylaxis and anaphylactoid reactions. Both anaphylaxis, which is the most severe immune-mediated reaction, as well as anaphylactoid reaction require a rapid diagnosis and appropriate management. Guidelines and recommendation have been established since the perioperative anaphylaxis mortality rate is

Table 1
Severity grading of anaphylactic reactions according to Ring and Meßmer (Lancet, 1977).

Grade ^a	Skin	Gastrointestinal	Respiratory	Cardiovascular
I	Pruritus Flush Urticaria Angioedema	–	–	–
II	Pruritus Flush Urticaria Angioedema	Nausea Cramps	Rhinorrhoea Hoarseness Dyspnoea	Tachycardia (> 20/min) RR changes (> 20 mmHg syst) Arrhythmia
III	Pruritus Flush Urticaria Angioedema	Vomitus Defecation	Laryngeal edema Bronchospasm Cyanosis	Shock
IV	Pruritus Flush Urticaria Angioedema	Vomitus	Respiratory arrest	Cardiac arrest

^a Grade depends on the worst manifestation present.

as high as 3–9% with reported 4.1% NMBA caused mortality [2].

Furthermore, the postemergent correct identification of the causative compound(s) and safe alternatives is a complex task, which still very often is ignored or forgotten. However, allergologic diagnostics is crucial in order to prevent recurrences. It is recommended that all patients with suspected perioperative anaphylaxis be referred for testing. Prevention is critical to avoid mortality and morbidity, as there are no preemptive therapeutic strategies and since NMBAs often show cross-reactivity, which is not predictable by drug structure.

The identification of the causative drug can be performed using either a skin-prick (PT), intradermal (IDT), or serologic testing. The overall concordance of PT and IDT is 97%. IDT have to be carried out for the search of the cross sensitization (occurring in 84% of patients, 16% react to all muscle relaxants). The further use of muscle relaxants selected by negative IDTs has been proved to be safe [14].

In our case, a low-risk agent evoked an adverse anaphylactic reaction. The history did not reveal any obvious risk factors for sensitization. It is commonly known that patients without any previous adverse events to muscle relaxants are not exempt from risk of anaphylactic shock, thus the anesthesia team should always be alert and take immediate actions if an adverse reaction occurs. We acted according to the guidelines, administering adrenaline and steroids. Inhaled betamimetics were not administrable due to the bronchospasm and the necessity of immediate airway management. Since the patient was obese, with a short neck, and the anaphylactic edema was significant, thus we were unable to identify the landmarks for a less invasive cricothyrotomy (cricoid membranes). Furthermore, the patient was obviously in need of mechanical ventilation. In our institution, only a tracheostoma can be connected to a ventilator and tracheotomy is performed more often. These factors motivated more for a more radical procedure of tracheotomy in the emergency situation under given conditions.

Appropriate alert and monitoring while applying neuromuscular blocking agents is not only essential for the anesthesia, but also for a variety of further clinical situations, where muscle relaxants are implemented (for example emergency intubation,

acute respiratory distress syndrome, status asthmaticus, elevated intracranial and intra-abdominal pressure, therapeutic hypothermia). The development of ultra short NMBAs with a rapid onset of effect and possible immediate option for reversal is ongoing [15].

Recently, a triad of clinical, biological and allergologic evidence has been suggested in order to make a correct etiological diagnosis of an anaphylactic reaction due to NMBAs [16]. In our case, the first component – the clinical history – was negative. Biological in vivo and in vitro tests (tryptase, histamine, NMBA specific IgE assay) form the second component of the triad. Skin tests are considered the gold standard with intradermal testing showing most reliable sensitivities.

The here presented case differs from the majority the previously published incidents in the clinical course of perianaesthetic anaphylaxis. Our patient developed a rapid facial and neck edema, combined with a bronchospasm, without a cardiovascular depression or a skin rash as initial symptom. In this Grade IV anaphylactic reaction, characterized by the impossibility of intubation and thus controlled ventilation, followed by an emergency tracheotomy with unexpected hemorrhage and ensuing hypoxic brain injury and coma, atracurium was suspected and subsequently proven to be the offending agent. Specific IgE concentration determination is to be performed at external institution.

In summary, perianaesthesia anaphylaxis to NMBAs is a serious, potentially lethal, allergic reaction with rapid onset. Diagnosis of anaphylaxis is currently based on established clinical criteria, but it should be stressed that skin manifestations are not mandatory, and their absence is considered a risk factor for severe anaphylactic reaction. After anaphylaxis, allergologic assessment is essential to identify the culprit agent and to prevent recurrences.

6. Author's contribution

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E.B. and C.Q. contributed equally to the case and manuscript.
E.B., C.Q., X.G., A.T. finalised the writing up of the manuscript.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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