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Grade IV perioperative anaphylaxis to atracurium despite a previous negative skin test.

Authors

Aurélie Gouel-Chéron MD, PhD ^{1,2,3}, Catherine Neukirch MD ^{4,5}, Sylvie Chollet-Martin PharmD, PhD ^{6,7},
Dan Longrois MD, PhD ¹, Pascale Nicaise-Roland PharmD, PhD ^{5,6}, Luc de Chaisemartin PharmD, PhD ^{2,6,7}

1 – Anesthesiology and critical care medicine department, DMU PARABOL, Bichat hospital, AP-HP, Paris University, Paris, France.

2 – Antibody in Therapy and Pathology, Pasteur Institute, UMR 1222 INSERM, Paris, France.

3 – Biostatistics Research Branch, Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.

4 – Pulmonology department, Bichat hospital, AP-HP, Paris University, Paris, France.

5 – INSERM1152, DHU FIRE, Paris University, Paris, France.

6 – Immunology department, UF autoimmunity and hypersensitivity, DMU BIOGEM, Bichat hospital, AP-HP, Paris University, Paris, France.

7 – Cytokines, Chemokines, and Immunopathology, INSERM UMR S996, Paris-Saclay University, Châtenay-Malabry, France.

Corresponding author

Aurélie Gouel-Chéron

Département d'Anesthésie-Réanimation, Hôpital Bichat – Claude Bernard

48 rue Henri Huchard, 75018 Paris, France

Phone number: 00-33-140258355.

Fax number: 00-33-140256309

23 E-mail address: aurelie.gouel@aphp.fr

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28 Clinical Implications:

29 A patient developed anaphylactic shock after atracurium injection despite a negative skin test 8 years
30 before. We discuss the possible mechanisms underlying this observation and suggest that uncertainty
31 might be addressed by performing low-dose provocation tests.

32 Keywords

33 Allergy, Anesthesia, Anaphylaxis, Drug provocation test, Guidelines, Hypersensitivity reaction,
34 Neuromuscular blocking agent, Skin test

In 2011, a 44-year-old male patient was scheduled for aorto-femoral bypass surgery. This patient had had two previous general anesthetic procedures without complications (unknown protocol), had no documented allergic or atopic history and was not taking any medication. Two minutes after the induction performed with etomidate, suxamethonium, remifentanyl and lidocaine, a severe hypersensitivity reaction (grade III according to the Ring and Messmer classification) characterized by severe arterial hypotension, bronchospasm and generalized skin rash was observed. Following administration of epinephrine (600µg total) and salbutamol and fluid resuscitation, he was stabilized, but the surgery could not be performed. Ten minutes after the reaction, the serum mast cell tryptase level had increased to 131µg/L (compared to a basal mast cell tryptase level of 5.4µg/L). Six weeks later, the allergy evaluation resulted in positive skin tests to suxamethonium and all of the aminosteroid neuromuscular blocking agents tested (vecuronium, pancuronium and rocuronium), but the tests were negative for benzylisoquinoline neuromuscular blocking agents (mivacurium and atracurium), hypnotics, opioids, latex and lidocaine¹. Specific IgE testing (ImmunoCAP, ThermoFisher) were negative for suxamethonium, quaternary ammonium morphine, and latex immediately after the reaction and 6 weeks later. Quaternary ammonium morphine has been used since the 1980s to indirectly measure the reactivity to quaternary substituted ammonium structures (which is believed to be the major epitope of neuromuscular blocking agents) and is widely and reliably used in Europe for this purpose, especially for suxamethonium- and rocuronium-specific IgE detection². The basophil activation test was not performed. The allergist determined an IgE-mediated reaction to suxamethonium with cross-reactivity to vecuronium, pancuronium and rocuronium and recommended strict avoidance of suxamethonium and all aminosteroid neuromuscular blocking agents.

Eight years later, with no other documented anesthetic procedures, the patient was hospitalized again for acute limb ischemia (grade III) requiring thrombolysis. As the surgery was urgent, there was no time to perform a new allergy evaluation. Due to acid reflux, the anesthesiologist chose to use endotracheal tube to secure airway rather than laryngeal mask. Previous preanesthetic evaluations had documented difficulty with intubation (grade IV according to the Mallampati classification), requiring a neuromuscular blocking agent for anesthesia induction according to the French guidelines. The anesthesia protocol included etomidate, remifentanyl and atracurium because they all tested negative in the first allergy evaluation (8 years before), in which only aminosteroid NMBA tested positive, and because cross-reactivity is more common among neuromuscular blocking agents of the same chemical family as they share similar chemical structures. Indeed, in patients with known allergy to neuromuscular blocking agents, it is recommended to use alternatives from another chemical family and

tested negative by skin test. Five minutes after induction and safely secured tracheal intubation, the patient had moderate tachycardia, a chest skin rash, arterial hypotension (arterial systolic pressure of 75mmHg) and an end-tidal CO₂ of 17 mmHg. Despite epinephrine bolus injections (300µg), the patient experienced cardiac arrest two minutes later, requiring 4 minutes of cardiac massage and two epinephrine bolus doses of 1 mg before spontaneous circulatory activity was recovered under continuous infusion of epinephrine. Surgery was cancelled, and he was transferred to the intensive care unit. His condition rapidly deteriorated due to severe limb ischemia, rhabdomyolysis, and general organ failure, leading to death 2 days later. The biological explorations performed during the acute hypersensitivity reaction revealed a mast cell tryptase level of 393µg/L. Specific IgE against succinylcholine was slightly positive (0.13kU/L, detection limit at 0.10), whereas specific IgE against quaternary ammonium morphine was strongly positive at 11.10kU/L. IgE inhibition tests were positive for rocuronium (88%), atracurium (67%), suxamethonium (64%) and cisatracurium (58%). Although we cannot completely rule out the involvement of remifentanyl and lidocaine in this case, the previously identified allergy, biological findings and perioperative anaphylaxis epidemiology³ favor a reaction to atracurium. This patient had known risk factors for both severe and refractory anaphylaxis, including cardiovascular disease, the medications he was on including beta-blocker, angiotensin-converting enzyme inhibitors and acetylsalicylic acid⁴, and likely eliciting agent (neuromuscular blocking agent)⁵. However, this case report highlights the fact that despite adequate biological and allergy testing, the anesthesiologist in the operating room still faces uncertainty when dealing with a patient with a known allergy to neuromuscular blocking agents.

The most striking observation in this case is the occurrence of severe anaphylaxis in response to a neuromuscular blocking agent previously found to produce a negative result by a skin test. Indeed, skin testing is a cornerstone of allergy evaluation following a perioperative acute hypersensitivity reaction. The evaluations performed in this case after the first reaction were consistent with the international recommendations¹. Some authors have performed follow-up studies of patients with positive neuromuscular blocking agent testing results, focusing on the subsequent use of neuromuscular blocking agents during anesthetic procedures. In these studies, the neuromuscular blocking agent used was chosen based on a negative skin test result, sometimes in combination with a negative basophil-activation test result. Even if no death is reported, anaphylactic reactions occur in 4%⁶ to 7.5% of cases, which has been attributed to inadequate communication about the potential culprits, skin testing that is performed with inadequate drug dilutions, or a false negative skin test result⁷. In light of these studies, it has been recommended that despite previous documentation of IgE-mediated neuromuscular blocking

agent allergies, neuromuscular blocking agents producing a negative skin testing result can be safely injected during subsequent anesthesia⁸. However, some authors also suggest that patients with a severe initial reaction and a positive skin test to one or more neuromuscular blocking agents should have new intradermal testing performed before subsequent anesthesia⁶. Although drug provocation tests are considered the gold standard in drug allergy diagnosis, they are not recommended for the assessment of acute hypersensitivity reactions to neuromuscular blocking agents because of the pharmacological properties of these drugs, as recently described in an extensive review⁹. However, some specialized centers have recently started to implement low-dose provocation tests of anesthetic agents⁹. Explicitly, low-dose provocation tests (3-4 steps with a 10-fold increase leading to a maximum dose of 1/10 of the therapeutic dose performed in an intensive care setting) could identify safe neuromuscular blocking agent alternatives after a negative skin test⁸. While the safety of this approach remains to be carefully evaluated with explicit and validated protocols, in high-risk situations such as the one presented here, the benefits might outweigh the risks. To date, no study has shown that the absence of a reaction to 1/10 of the full dose safely excludes the possibility of an acute hypersensitivity reaction to a full dose of the same agent. However, we believe that patients with neuromuscular blocking agent cross-reactivities identified by skin tests and/or basophil activation tests would benefit from this procedure to identify safe alternatives before subsequent re-exposure. We have since started to implement this strategy in our center. In practice, it is always recommended to use an agent from the other chemical family with a negative skin test. If the dose provocation test is performed and positive, the total eviction of the tested agent is mandatory. Cis-atracurium is an accepted alternative option, because of its low cross-reactivity and the rare incidence of anaphylaxis to this molecule.

The other striking observation in this case is the evolution of the IgE positivity profile, leading us to wonder if the initial negative reaction was only due to a lack of sensitivity or if the repertoire of recognized neuromuscular blocking agents might have also evolved over time. It is not clear what could explain such a dramatic increase in specific IgE in the absence of neuromuscular blocking agent re-exposure. Little is known about the pathophysiology of neuromuscular blocking agent sensitization, and the sensitization potential of neuromuscular blocking agents themselves is not established. For 60% of patients with an acute hypersensitivity reaction to a neuromuscular blocking agent in the operating room, no previous exposure could be found. This leads to the question of whether the atracurium reaction observed in this case could be attributed to a new allergy or to cross-reactivity due to the patient's prior identified allergy to suxamethonium. In patients with preexisting anti- neuromuscular blocking agent antibodies, exposure to pholcodine has been shown to increase neuromuscular blocking

agent-specific IgE concentrations, but it is unclear whether such exposure can also expand the repertoires of the neuromuscular blocking agents recognized by the antibodies. Indeed, pholcodine exposure does not sensitize patients to all molecules containing quaternary ammonium ions, and the neuromuscular blocking agent-specific antibody cross-reactivity profile differs widely in patients. In this case, we could neither assess pholcodine exposure nor exposure to other quaternary ammonium molecules that might have triggered sensitization.

This case report additionally raises the question of whether subsequent allergic evaluation is required for patients with a previously identified allergy. Because of the uncertainty surrounding the sensitization mechanism, no firm answer to this question can be provided yet. Furthermore, the inadequate/low number of allergy specialists and the restricted timeline before surgery can make it difficult to organize and implement such an evaluation. This emphasizes the urgent need for more allergy specialists, especially considering the continuous increase in allergy incidence.

To the best of our knowledge, this is the first case of grade IV anaphylactic shock reported after negative skin testing. This case report highlights the urgent need for a better understanding of the pathophysiology of neuromuscular blocking agent sensitization and advocates for additional testing (including basophil-activation testing, additional skin testing and drug provocation testing) prior to re-exposure of patients with a previous history of severe neuromuscular blocking agent anaphylaxis and neuromuscular blocking agent cross-reactivities.

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