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### ► To cite this version:

Aurélie Gouel-Chéron, Catherine Neukirch, Sylvie Chollet-Martin, Dan Longrois, Pascale Nicaise-Roland, et al.. Grade IV perioperative anaphylaxis to atracurium despite a previous negative skin test. *Journal of Allergy and Clinical Immunology: In Practice*, 2020, 8 (7), pp.2445 - 2447. 10.1016/j.jaip.2020.04.004 . hal-03492356

**HAL Id: hal-03492356**

**<https://hal.science/hal-03492356>**

Submitted on 18 Jul 2022

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

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24 **Reprint request: None.**

25 **Funding sources: None.**

26 **Conflicts of interests: None**

27 **Word count: Title: 12 words. Capsule summary: 36 words. Letter: 1,567 words.**

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

35 In 2011, a 44-year-old male patient was scheduled for aorto-femoral bypass surgery. This patient had  
36 had two previous general anesthetic procedures without complications (unknown protocol), had no  
37 documented allergic or atopic history and was not taking any medication. Two minutes after the  
38 induction performed with etomidate, suxamethonium, remifentanyl and lidocaine, a severe  
39 hypersensitivity reaction (grade III according to the Ring and Messmer classification) characterized by  
40 severe arterial hypotension, bronchospasm and generalized skin rash was observed. Following  
41 administration of epinephrine (600µg total) and salbutamol and fluid resuscitation, he was stabilized,  
42 but the surgery could not be performed. Ten minutes after the reaction, the serum mast cell tryptase  
43 level had increased to 131µg/L (compared to a basal mast cell tryptase level of 5.4µg/L). Six weeks later,  
44 the allergy evaluation resulted in positive skin tests to suxamethonium and all of the aminosteroid  
45 neuromuscular blocking agents tested (vecuronium, pancuronium and rocuronium), but the tests were  
46 negative for benzylisoquinoline neuromuscular blocking agents (mivacurium and atracurium), hypnotics,  
47 opioids, latex and lidocaine<sup>1</sup>. Specific IgE testing (ImmunoCAP, Thermofisher) were negative for  
48 suxamethonium, quaternary ammonium morphine, and latex immediately after the reaction and 6  
49 weeks later. Quaternary ammonium morphine has been used since the 1980s to indirectly measure the  
50 reactivity to quaternary substituted ammonium structures (which is believed to be the major epitope of  
51 neuromuscular blocking agents) and is widely and reliably used in Europe for this purpose, especially for  
52 suxamethonium- and rocuronium-specific IgE detection<sup>2</sup>. The basophil activation test was not  
53 performed. The allergist determined an IgE-mediated reaction to suxamethonium with cross-reactivity  
54 to vecuronium, pancuronium and rocuronium and recommended strict avoidance of suxamethonium  
55 and all aminosteroid neuromuscular blocking agents.

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

67 tested negative by skin test. Five minutes after induction and safely secured tracheal intubation, the  
68 patient had moderate tachycardia, a chest skin rash, arterial hypotension (arterial systolic pressure of  
69 75mmHg) and an end-tidal CO<sub>2</sub> of 17 mmHg. Despite epinephrine bolus injections (300µg), the patient  
70 experienced cardiac arrest two minutes later, requiring 4 minutes of cardiac massage and two  
71 epinephrine bolus doses of 1 mg before spontaneous circulatory activity was recovered under  
72 continuous infusion of epinephrine. Surgery was cancelled, and he was transferred to the intensive care  
73 unit. His condition rapidly deteriorated due to severe limb ischemia, rhabdomyolysis, and general organ  
74 failure, leading to death 2 days later. The biological explorations performed during the acute  
75 hypersensitivity reaction revealed a mast cell tryptase level of 393µg/L. Specific IgE against  
76 succinylcholine was slightly positive (0.13kU/L, detection limit at 0.10), whereas specific IgE against  
77 quaternary ammonium morphine was strongly positive at 11.10kU/L. IgE inhibition tests were positive  
78 for rocuronium (88%), atracurium (67%), suxamethonium (64%) and cisatracurium (58%). Although we  
79 cannot completely rule out the involvement of remifentanyl and lidocaine in this case, the previously  
80 identified allergy, biological findings and perioperative anaphylaxis epidemiology<sup>3</sup> favor a reaction to  
81 atracurium. This patient had known risk factors for both severe and refractory anaphylaxis, including  
82 cardiovascular disease, the medications he was on including beta-blocker, angiotensin-converting  
83 enzyme inhibitors and acetylsalicylic acid<sup>4</sup>, and likely eliciting agent (neuromuscular blocking agent)<sup>5</sup>.  
84 However, this case report highlights the fact that despite adequate biological and allergy testing, the  
85 anesthesiologist in the operating room still faces uncertainty when dealing with a patient with a known  
86 allergy to neuromuscular blocking agents.

87 The most striking observation in this case is the occurrence of severe anaphylaxis in response to a  
88 neuromuscular blocking agent previously found to produce a negative result by a skin test. Indeed, skin  
89 testing is a cornerstone of allergy evaluation following a perioperative acute hypersensitivity reaction.  
90 The evaluations performed in this case after the first reaction were consistent with the international  
91 recommendations<sup>1</sup>. Some authors have performed follow-up studies of patients with positive  
92 neuromuscular blocking agent testing results, focusing on the subsequent use of neuromuscular  
93 blocking agents during anesthetic procedures. In these studies, the neuromuscular blocking agent used  
94 was chosen based on a negative skin test result, sometimes in combination with a negative basophil-  
95 activation test result. Even if no death is reported, anaphylactic reactions occur in 4%<sup>6</sup> to 7.5% of cases,  
96 which has been attributed to inadequate communication about the potential culprits, skin testing that is  
97 performed with inadequate drug dilutions, or a false negative skin test result<sup>7</sup>. In light of these studies, it  
98 has been recommended that despite previous documentation of IgE-mediated neuromuscular blocking

99 agent allergies, neuromuscular blocking agents producing a negative skin testing result can be safely  
100 injected during subsequent anesthesia<sup>8</sup>. However, some authors also suggest that patients with a severe  
101 initial reaction and a positive skin test to one or more neuromuscular blocking agents should have new  
102 intradermal testing performed before subsequent anesthesia<sup>6</sup>. Although drug provocation tests are  
103 considered the gold standard in drug allergy diagnosis, they are not recommended for the assessment of  
104 acute hypersensitivity reactions to neuromuscular blocking agents because of the pharmacological  
105 properties of these drugs, as recently described in an extensive review<sup>9</sup>. However, some specialized  
106 centers have recently started to implement low-dose provocation tests of anesthetic agents<sup>9</sup>. Explicitly,  
107 low-dose provocation tests (3-4 steps with a 10-fold increase leading to a maximum dose of 1/10 of the  
108 therapeutic dose performed in an intensive care setting) could identify safe neuromuscular blocking  
109 agent alternatives after a negative skin test<sup>8</sup>. While the safety of this approach remains to be carefully  
110 evaluated with explicit and validated protocols, in high-risk situations such as the one presented here,  
111 the benefits might outweigh the risks. To date, no study has shown that the absence of a reaction to  
112 1/10 of the full dose safely excludes the possibility of an acute hypersensitivity reaction to a full dose of  
113 the same agent. However, we believe that patients with neuromuscular blocking agent cross-reactivities  
114 identified by skin tests and/or basophil activation tests would benefit from this procedure to identify  
115 safe alternatives before subsequent re-exposure. We have since started to implement this strategy in  
116 our center. In practice, it is always recommended to use an agent from the other chemical family with a  
117 negative skin test. If the dose provocation test is performed and positive, the total eviction of the tested  
118 agent is mandatory. Cis-atracurium is an accepted alternative option, because of its low cross-reactivity  
119 and the rare incidence of anaphylaxis to this molecule.

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

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

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

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



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