



HAL
open science

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

Aurélie Gouel-Chéron, Catherine Neukirch, Sylvie Chollet-Martin, Dan Longrois, Pascale Nicaise-Roland, Luc de Chaisemartin

► **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-03492356v1>

Submitted on 18 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

3 **Authors**

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

6 1 – Anesthesiology and critical care medicine department, DMU PARABOL, Bichat hospital, AP-HP, Paris
7 University, Paris, France.

8 2 – Antibody in Therapy and Pathology, Pasteur Institute, UMR 1222 INSERM, Paris, France.

9 3 – Biostatistics Research Branch, Division of Clinical Research, National Institute of Allergy and
10 Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.

11 4 – Pulmonology department, Bichat hospital, AP-HP, Paris University, Paris, France.

12 5 – INSERM1152, DHU FIRE, Paris University, Paris, France.

13 6 – Immunology department, UF autoimmunity and hypersensitivity, DMU BIOGEM, Bichat hospital, AP-
14 HP, Paris University, Paris, France.

15 7 – Cytokines, Chemokines, and Immunopathology, INSERM UMR S996, Paris-Saclay University,
16 Châtenay-Malabry, France.

17 **Corresponding author**

18 Aurélie Gouel-Chéron

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

20 48 rue Henri Huchard, 75018 Paris, France

21 Phone number: 00-33-140258355.

22 Fax number: 00-33-140256309

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

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 lidocaine¹. 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 detection². 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 CO₂ 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 epidemiology³ 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 acid⁴, and likely eliciting agent (neuromuscular blocking agent)⁵.
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 recommendations¹. 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%⁶ 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 result⁷. 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 anesthesia⁸. 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 anesthesia⁶. 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 review⁹. However, some specialized
106 centers have recently started to implement low-dose provocation tests of anesthetic agents⁹. 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 test⁸. 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.

149 **References**

- 150 1. Garvey LH, Ebo DG, Mertes P-M, Dewachter P, Garcez T, Kopac P, et al. An EAACI position paper on
151 the investigation of perioperative immediate hypersensitivity reactions. *Allergy*. 2019;74:1872–84.
- 152 2. Takazawa T, Sabato V, Ebo DG. In vitro diagnostic tests for perioperative hypersensitivity, a
153 narrative review: potential, limitations, and perspectives. *Br J Anaesth*. 2019;123:e117–25.
- 154 3. Tacquard C, Collange O, Gomis P, Malinovsky JM, Petitpain N, Demoly P, et al. Anaesthetic
155 hypersensitivity reactions in France between 2011 and 2012: the 10th GERAP epidemiologic survey.
156 *Acta Anaesthesiol Scand*. 2017;61:290–9.
- 157 4. Simons FER, Arduzzo LRF, Bilò MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy
158 Organization Guidelines for the Assessment and Management of Anaphylaxis. *World Allergy Organ
159 J*. 2011;4:13–37.
- 160 5. Francuzik W, Dölle-Bierke S, Knop M, Scherer Hofmeier K, Cichocka-Jarosz E, García BE, et al.
161 Refractory Anaphylaxis: Data From the European Anaphylaxis Registry. *Front Immunol*.
162 2019;10:2482.
- 163 6. Miller J, Clough SB, Pollard RC, Misbah SA. Outcome of repeat anaesthesia after investigation for
164 perioperative anaphylaxis. *Br J Anaesth*. 2018;120:1195–201.
- 165 7. Chiriac AM, Tacquard C, Fadhel NB, Pellerin C, Malinovsky JM, Mertes PM, et al. Safety of
166 subsequent general anaesthesia in patients allergic to neuromuscular blocking agents: value of
167 allergy skin testing. *Br J Anaesth*. 2018;120:1437–40.
- 168 8. Garvey LH, Ebo DG, Krøigaard M, Savic S, Clarke R, Cooke P, et al. The use of drug provocation
169 testing in the investigation of suspected immediate perioperative allergic reactions: current status.
170 *Br J Anaesth*. 2019;123:e126–34.
- 171 9. Garvey LH, Dewachter P, Hepner DL, Mertes PM, Voltolini S, Clarke R, et al. Management of
172 suspected immediate perioperative allergic reactions: an international overview and consensus
173 recommendations. *Br J Anaesth*. 2019;123:e50–64.