BJA

British Journal of Anaesthesia, ■ (■): 1–4 (2018)

CORRESPONDENCE

Safety of subsequent general anaesthesia in patients allergic to neuromuscular blocking agents: value of allergy skin testing

A. M. Chiriac[1,2], C. Tacquard[3], N. B. Fadhel[1], C. Pellerin[4], J. M. Malinovsky[5], P. M. Mertes[3,*] and P. Demoly[1,2]

[1]Montpellier, France, [2]Paris, France, [3]Strasbourg, France, [4]Bordeaux, France and [5]Reims, France

*Corresponding author E-mail: paul-michel.mertes@chru-strasbourg.fr

Editor—Allergy to neuromuscular blocking agents (NMBA) is the leading cause of perioperative anaphylaxis in France. In the last GERAP survey (*Groupe d'Etude des Réactions Anaphylactiques Peroperatoires*), proved NMBA allergy accounted for 60.6% of the immediate hypersensitivity reactions in the perioperative setting (302 patients explored between 2011 and 2012).[1] Immunoglobulin E-mediated reactions to NMBAs have also been reported with a high frequency in other parts of Europe (UK, Norway, Belgium, and Spain) and in Australia and New Zealand.[2]

When confronted with patients allergic to NMBA, anaesthetists are bound to avoid all NMBAs. It is generally accepted that allergy skin testing is the method of choice to identify the culprit NMBA, possible cross-reactivities with other NMBAs and potential safe alternatives.[3] However, only a few reports (biased by small numbers of included patients) have tackled the issue of the negative predictive value (NPV) of NMBA skin testing in patients allergic to at least one NMBA.[4–9] As control trials are not realistic, follow-up surveys in real life should assess tolerance of a negative skin tested NMBA in subsequent general anaesthesia. Although the NPV is high in most reports, reactions to negative skin tested NMBAs have been reported.[5–7]

Between 2011 and 2016, a multicentre follow-up survey of NMBA allergic patients was conducted in four centres in France (Bordeaux, Montpellier, Strasbourg, and Reims). All diagnostic procedures for NMBA allergy followed the recommendations of the *Société Française d'Anesthésie Réanimation*, endorsed by the Drug Allergy Interest Group/European Network of Drug Allergy of the European Academy of Allergy and Clinical Immunology.[3] The diagnosis of allergy to NMBA was based on a compatible clinical history, positive skin test, and exclusion of other potential allergens. When allergy to an NMBA was diagnosed, cross-reactivity was assessed to other NMBAs. Initial reactions (referred to as index reactions) were graded according to severity (Supplementary Fig. 1).[1] Patients with positive skin testing to at least one NMBA were contacted and questioned about subsequent general anaesthesia. All patients included in this study gave their consent to participate in the survey, and to have the records of their subsequent general anaesthesia exposures retrieved and analysed. The study received approval from local Ethics Committees.

Of the 148 patients allergic to NMBA, 118 were successfully contacted (rate of response, 79.7%). Of the 92 patients undergoing a subsequent general anaesthetic procedure, only 25 (27.2%) received another NMBA (Fig. 1). The characteristics of these 25 patients are presented in Table 1. Female patients were predominant (15 patients, 60%). Mean age was 47.9 yr (range, 15–70) and half were tested within 4 months after the index reaction (inter-quartile range Q25–75:2–204). Most index reactions (84%) were severe, life-threatening events (16 Grade III and five Grade IV reactions), and positivity for the culprit agent occurred in skin prick testing in 19 patients (76%). In 100% of patients, the NMBA responsible for the index reaction was skin test positive: suxamethonium in 20 patients (80%), rocuronium and atracurium in three (12%) and two (8%) patients, respectively. Cross-reactivity was systematically assessed (with three to seven NMBA tested/patient), and was found in 10 patients (40% of patients). The most frequently re-injected NMBA was cis-atracurium (16 administrations in 15 patients, 60%), followed by atracurium (five patients, 24%) and rocuronium (four patients, 16%).

Two patients (8%, Patients 5 and 11, Table 1) reacted with anaphylaxis upon re-exposure to a negative skin tested NMBA. Patient 5 underwent a new general anaesthesia within 2 months after the initial allergy work-up that had proved allergy to suxamethonium (with cross-reactivity to vecuronium, but not to rocuronium). She received rocuronium and reacted

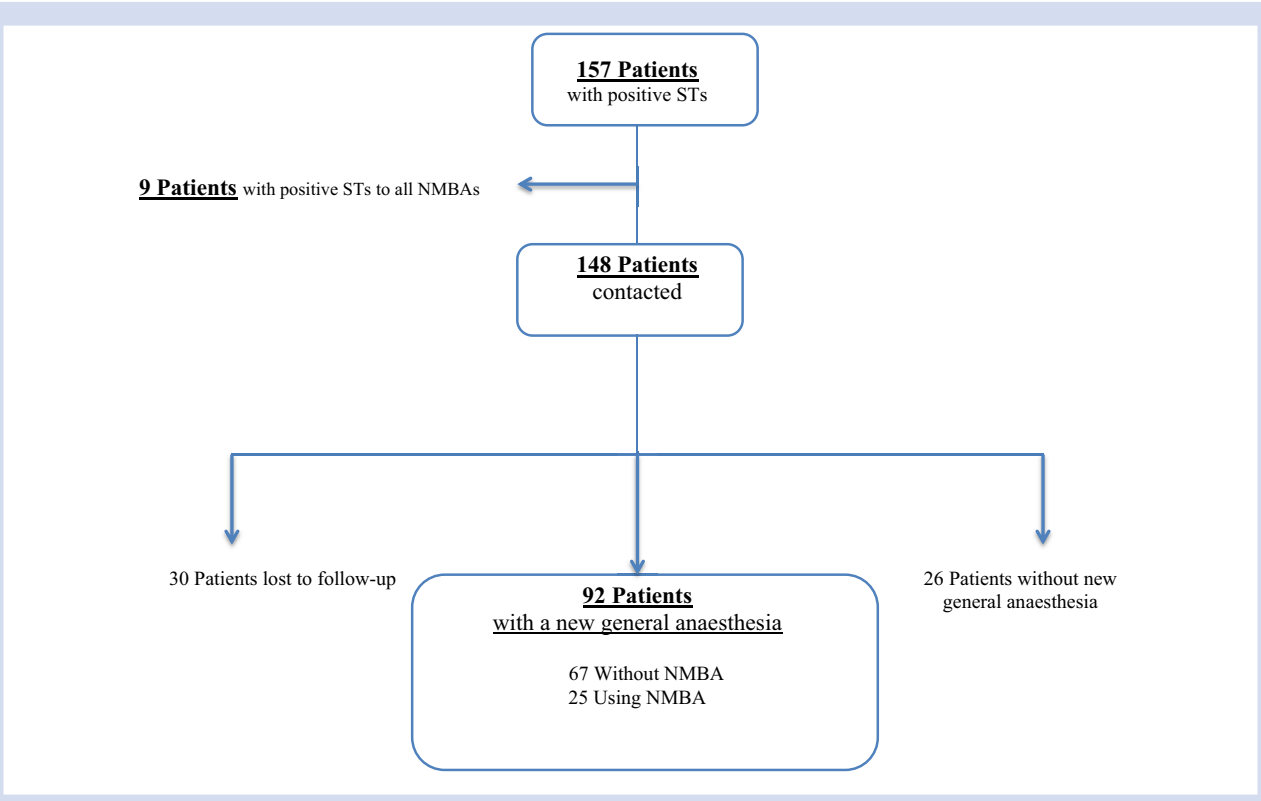

Fig 1. Flow chart of the study. NMBA, neuromuscular blocking agent; ST, skin test.

with generalised cutaneous erythema, hypotension (75/35 mm Hg), and tachycardia. Tryptase during the reaction was 5.1 μg litre^{-1} (basal tryptase not measured). The reaction was antagonised with ephedrine, methylprednisolone, and dexchlorpheniramine. Upon the second evaluation (performed 9 months after the second reaction), she exhibited positive skin testing to rocuronium and was considered allergic to this NMBA. The reaction presented by Patient 11 was interpreted as probable non-specific histamine-release. This patient reacted with severe bronchospasm, followed by cardiovascular collapse, after administration of two negative skin tested NMBAs, rocuronium and cis-atracurium. The reaction was antagonised with salbutamol, ephedrine, and i.v. fluids. The tryptase (perioperative at 30 min and 1 h after the episode: 5.7 μg litre^{-1} and 2.5 μg litre^{-1}, respectively, with baseline 4.8 μg litre^{-1}) did not support an allergic aetiology. Subsequent evaluation indicated underlying bronchial hyperreactivity and negative drug allergy evaluation for all involved drugs.

The NPV of skin tests to NMBA in our study is 96% (95% confidence interval: 88.3–99.9%) when considering only one reactor. These results confirm previous findings regarding the value of skin testing in NMBA allergy.[4–6,8,9] The high NPV in our series could also be related to preferential use (60%) of cis-atracurium for subsequent general anaesthesia procedures. Recently, Tacquard and colleagues[1] showed a lower estimated risk of cis-atracurium-related allergic reactions, compared with both suxamethonium and rocuronium, when their respective market share is taken into account (0.4/100 000 vials compared with 13.8 and 13.3/100 000 vials, respectively). Most of the patients presented in this survey suffered from severe life-threatening index reactions, in accordance with literature data on NMBA allergy; all the more reason for these results to be valuable.

Like others,[5–7] we have found that in a minority of patients, allergic reactions can occur despite initial negative skin testing. Two hypotheses arise: false negative skin tests at first evaluation or re-sensitisation. Neither can be confirmed or ruled out. Therefore, vigilance is mandatory and strict indications of NMBA usage in an NMBA allergic patient should be followed. Validation of negative skin testing for NMBA by a drug provocation test, which is considered to be the 'gold standard allergy test' for most drugs, is not considered as such for NMBA because of the pharmacological effects of these drugs and the unfavourable risk-benefit ratio for conducting such tests.[3] In order to evaluate tolerance of a therapeutic dose of a negative skin test NMBA, a full therapeutic dose should be administered, and this cannot occur in the absence of general anaesthesia. Whether or not provocation tests to NMBA can be performed within a clear frame established by research studies remains to be discussed.

Cross-reactivity might have been underestimated in our study, because all commercially available NMBA were not systematically tested, either because of retirement from the French market (e.g. pancuronium) or low use in daily clinical practice (e.g. vecuronium, mivacurium). However, estimation of cross-reactivity was not the purpose of this paper.

Current strategies to reduce overall mortality and morbidity of perioperative anaphylaxis rely on the knowledge and vigilance of the attending clinicians. This survey sums up to present (scarce) knowledge regarding the safety of negative skin tested NMBAs in NMBA-allergic patients.