



Anaphylaxis during general anaesthesia: a 10-year survey 1 at the University Hospital of Antwerp

Julie Leysen, Liene De Witte, Chris H Bridts, Didier G Ebo

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Abstract

Anaesthesia-related allergy is a rare but potentially life-threatening condition with serious consequences of diagnostic error. The authors report their experience of a 10-year survey in a Flemish referral centre. Between January 2001 and December 2011, a total of 344 patients who experienced perioperative anaphylaxis were referred to our allergy centre. Allergy was documented on the basis of clinical history, skin tests, measurement of specific immunoglobulin E (sIgE) antibodies and/or basophil activation tests. A total of 344 patients were studied (111 male, 233 female; age ranging from 21 months to 86 years (median 47 years)). Mild reactions, mostly cutaneous, were reported in 110 patients and severe potentially life-threatening reactions in 176 patients. In the remainder 58 patients, severity of the reaction was not reported. An IgE-mediated pathomechanism was documented in 246 cases (72%). Importantly, an IgE-mediated mechanism was not restricted to the severe reactions but also observed in 57% of the mild reactions. The most common offenders were neuromuscular blocking agents (NMBA) (40%), latex (25%), β -lactam antibiotics (12%) and chlorhexidine (9%). In 18 patients (7%) with an IgE-mediated allergy more than 1 causative agent was identified. In 7 patients, an elevated basal tryptase level was diagnosed. In our region, the most frequent causes of anaphylaxis during general anaesthesia are NMBA, particularly rocuronium, latex, antibiotics and chlorhexidine. Given the prevalence of double sensitization it is advocated to test all potential causative agents. Indolent mastocytosis should not be overlooked. Confirmatory testing should not be restricted to patients with severe anaesthesia-related anaphylaxis but also offered to patients with mild (cutaneous) reactions.

Keywords: anaesthesia, anaphylaxis, basophil degranulation test, diagnosis, skin test, immunoassay

INTRODUCTION

Anaesthesia-related anaphylaxis is a rare but potentially life-threatening condition with an estimated median annual incidence of 100.6 per million procedures as reported in a recent French series (1). Based upon skin tests and measurement of specific IgE (sIgE) antibodies, most epidemiological surveys have recognised neuromuscular blocking agents (NMBA), natural rubber latex (NRL) and β -lactam antibiotics as the most common causes of IgE-mediated anaphylaxis during general anaesthesia. However, the reported prevalence varies considerably between different countries (1-6) and controversy has arisen whether we are actually making the correct diagnosis, particularly with respect to allergy from NMBA (7-9) and opioids (10,11). In addition, in some series potential causes such as antiseptics have not been systematically studied (1,5,12,13).

To our knowledge, there are no epidemiological data available on the etiology of anaesthesia-related anaphylaxis in Flanders. Therefore, the primary objective of this survey is to describe characteristics of patients that suffered from presumed anaesthesia-related anaphylaxis. In addition, this study provides the opportunity to briefly summarize on the potentials and shortcomings of the current diagnostic approach.

MATERIALS AND METHOD

This single-centre prospective study

covers 344 consecutive patients referred to the outpatients' clinic of the Immunology – Allergology – Rheumatology Department of the Antwerp University Hospital in Belgium, with perceived allergic reactions related to general anaesthesia between January 2001 and December 2011. The patients were mainly referred from hospitals in three Flemish provinces, i.e. Antwerp (58%), East Flanders (26%) and Limburg (4%). All patients were systematically evaluated by trained physicians and nurses that applied a standardized diagnostic protocol (14).

RECORDING OF MEDICAL HISTORY

To promote correct identification case histories were completed by a thorough revision of anaesthetic notes and fiches provided by the referring physicians (generally the attending anaesthesiologist). Data on demographics, prior allergies, underlying conditions (e.g. atopy, mastocytosis), previous anaesthesia, extent of symptoms, time elapsed between administration of drugs and onset-of-reaction, drugs applied during anaesthesia (not restricted to anaesthetics) and management of the acute reaction were collected. Reactions were classified from grade I to IV according to increasing severity (Table 1) (15,16). Although a recent review of the literature did not give a definite answer to the optimal timing of skin testing after a suspected anaphylactic reaction during anaesthesia (17), like in other surveys, all in vivo and in vitro investigations were postponed until at least 6 weeks after the acute reaction (18-21).

Grades	Clinical Signs
I	Cutaneous-mucous signs: erythema, urticaria with or without angioedema
II	Moderate multivisceral signs: cutaneous-mucous signs +/- hypotension +/- tachycardia +/- dyspnea +/- gastrointestinal disturbances
III	Life-threatening mono-or multivisceral signs: cardiovascular collapse, tachycardia, or bradycardia +/- cardiac dysrhythmia +/- bronchospasm +/- cutaneous-mucous signs +/- gastrointestinal disturbances
IV	Cardiac arrest

Table 1. Clinical severity Scale of Immediate Hypersensitivity Reactions as published in (15) and modified by (16).

At the time of confirmatory testing, patients were free of antihistamines and systemic corticosteroids for at least 1 week and 6 weeks, respectively. All patients signed a written informed consent that was approved by the local ethical committee.

SERUM TRYPTASE

Baseline serum tryptase was quantified using the ImmunoCAP tryptase technique (Thermo Fisher Scientific, Uppsala, Sweden). Tryptase levels exceeding 11.4 µg/L were considered positive.

TOTAL AND SPECIFIC IGE

Total IgE and specific IgE (sIgE) antibodies towards NRL, chlorhexidine, ethylene oxide, rocuronium, suxamethonium, morphine, gelatine, rifamycin and the penicillin determinants (penicilloyl G, penicilloyl V, amoxycilloyl, ampicilloyl, cefaclor) were quantified with the ImmunoCAP FEIA sIgE technique (Thermo Fisher Scientific). ImmunoCAP for rocuronium was obtained by experimental prototypes developed for

research use. Decision thresholds were set at 0.35 kUa/L, except for the NMBA rocuronium and suxamethonium for which a drug-specific cut-off of 0.13 kUa/L and 0.11 kUa/L respectively was used (22).

BASOPHIL ACTIVATION TESTS

Flow cytometric analysis of *in vitro* activated basophils is performed as described elsewhere (23). The test includes a negative control (stimulation buffer without any drug), a positive control (anti-IgE) and stimulation with relevant drugs (e.g. NMBA, NRL, chlorhexidine, rifamycin, dyes, antibiotics, etc). Results are expressed as net percentage of CD63 positive basophils.

SKIN TESTS

Skin prick tests (SPT) and intradermal tests (IDT) were performed according to the recommendations of the Société Française d'Anesthésie et de Réanimation (SFAR) (recently summarized in (7)). Briefly, SPT were performed on the ventral part of the forearm and implied histamine 10 mg/mL

(HAL Allergy Benelux BV) as a positive control to assess skin test reactivity, a saline buffer solution as a negative control to exclude dermographism. Administered drugs, potential cross-reactive compounds and safe alternatives are tested (e.g. NMBA, NRL, chlorhexidine (24), analgesics, antibiotics, etc) (14). SPT were read after 15 minutes and considered positive when the wheal reaction exceeded 3 mm. When appropriate, patients with negative SPT had additional IDT. IDT responses were considered positive when the wheal equalled or exceeded 8 mm or had doubled as compared to the injection bleb. Maximal test concentrations for SPT implied the undiluted commercially available solution and for IDT mostly 1/10 of the commercially available solution (7), except for rocuronium that was used in a dilution of 1/200 (25).

RESULTS

To date 344 patients (male: 111 (age range: 5-77 years), female: 233 (age range: 21 months -86 years)), median age 47 years) were evaluated. Mild reactions, mostly cutaneous, were reported in 110 patients (32%) and severe potentially life-threatening reactions in 176 patients (51%). In the remainder 58 patients (17%) no information on the severity of the reaction was provided. A female predominance was observed in both groups (IgE-mediated allergy 67 %; non IgE-mediated allergy 69%).

At the end of the diagnostic workup, a diagnosis of an IgE-mediated allergy was established in 246 cases (72%),

whereas the remaining 98 cases (28%) were considered as non IgE-mediated allergy (amongst them only 3 were probably related to non-selective inhibition of COX1/2 by non-steroidal anti-inflammatory drugs). Importantly, the pathomechanism was unpredictable by the severity of the reaction. As shown in figure 1, an IgE-mediated mechanism was demonstrable in 84% of cases with severe grade III-IV reactions, but, importantly, also in 57 % of patients with mild grade I-II reactions.

Figure 2 displays the most prevalent causes of IgE-mediated anaphylaxis in relationship to the severity of the anaphylactic reaction. NMBA, NRL, antibiotics (mostly beta-lactam antibiotics) and chlorhexidine were observed to be the most important causal agents. Rocuronium accounted for 74% (n=65) of NMBA-related anaphylaxis in these cases. Very infrequent causative agents (<5% of IgE mediated allergy in the study) are for example oxytocine, geloplasma, povidon iodine, ethylene oxide and solumedrol.

In general, diagnosis of a NMBA allergy relied upon skin testing and measurement of sIgE antibodies, except for example 3 cases (2 rocuronium, 1 atracurium) that needed an additional BAT because of negative sIgE and skin test investigations. By no means the causal agent could be distinguished on the basis of clinical symptoms alone, although anaphylaxis from NMBA tended to be more severe with profound hypotension and bronchospasm within 5 minutes after

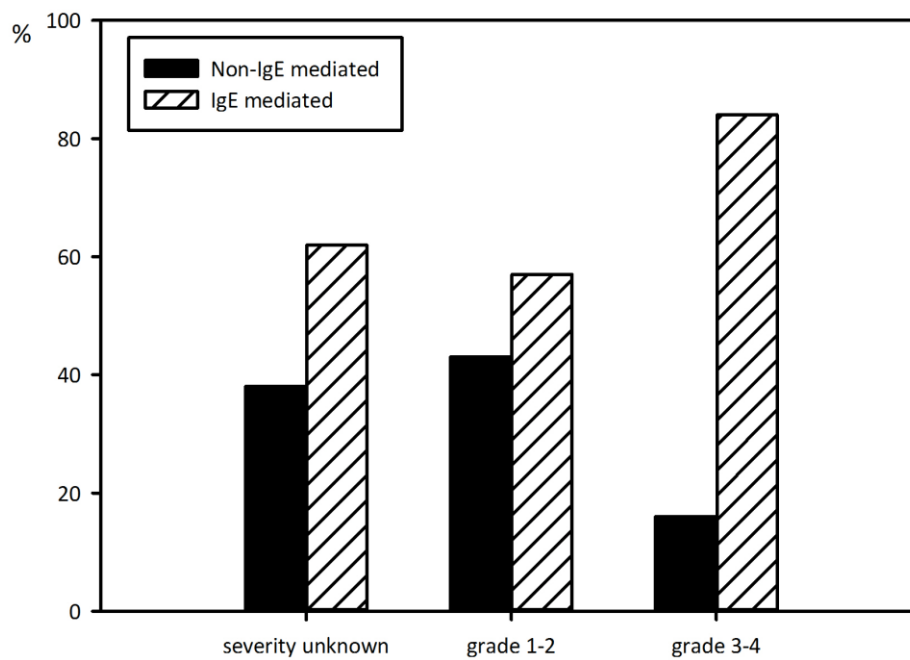


Figure 1: Percentage of IgE-mediated and non IgE-mediated hypersensitivity in relation to the severity of perioperative anaphylaxis

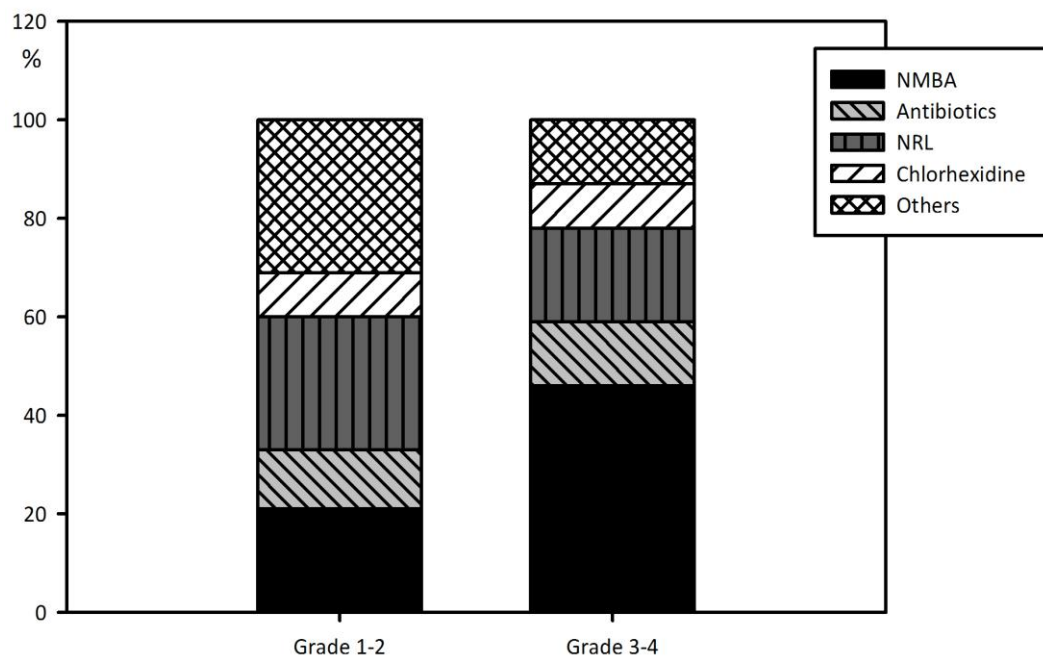


Figure 2: Causal agents in perioperative IgE-mediated allergy in relation to the severity of the reaction

administration. None of the patients suffered from anaphylaxis during previous anaesthesia or demonstrated an overt drug allergy. Importantly, multi-sensitisation, most frequently to 2 compounds, was demonstrable in 18 cases (7%) and generally involved latex and β -lactam antibiotics. With respect to rocuronium allergy, the BAT was confirmed to be complementary to skin tests in identifying safe alternatives and cross-reactivity between the aminosteroids rocuronium and vecuronium. Actually 14 rocuronium allergic patients were also double positive in skin test and BAT for vecuronium, 14 demonstrated a positive skin test and negative BAT for vecuronium, *vice versa*, 8 demonstrated a negative skin test and positive BAT to vecuronium. In contrast, no rocuronium allergic patients were double positive in skin test and BAT for the benzylisoquinolines atracurium/cisatracurium, 13 patients demonstrated a positive skin test and negative BAT for atracurium/cisatracurium or *vice versa*, a negative skin test and positive BAT for atracurium/cisatracurium.

Immediate tryptase levels (sampled within 2 hours after acute reaction) were available in only 42 cases (12%) and were raised in 35 patients. In all severe grade III and IV reactions with an elevated immediate tryptase level (n=17), an IgE mediated mechanism was documented. However, a normal tryptase did not rule out IgE-mediated allergy, as in 4 of the 5 patients with a normal immediate tryptase level and a grade III or IV reaction, an IgE mediated cause for the reaction could be identified as well. Seven patients had an

elevated baseline tryptase (11,5 - 32,2 $\mu\text{g/L}$) indicative for an indolent mastocytosis.

DISCUSSION

Correct management of anaesthesia-related anaphylaxis requires a multidisciplinary approach with prompt recognition and treatment of the acute event and identification of the offending agent(s) and strict secondary prevention with absolute avoidance of the implicated compound(s). However, diagnosis of anaesthesia-related anaphylaxis is not always straightforward and too easily overlooked. Alternatively, some conditions such as allergy to NMBA, latex and particularly opioids might be over-diagnosed. First, anaesthesia-related anaphylaxis is rare and physicians are not always familiar with the most important causes. Second, anaphylaxis falls apart into i) allergic anaphylaxis that is driven by an immunologic mechanism and is generally IgE-mediated and ii) non-allergic anaphylaxis that results from non-specific mediator release or alternative mechanisms such as non-selective COX inhibition (26). Third, diagnostic tests are not always readily available, poorly validated, do not demonstrate absolute reliability (22,27-29) or as already exemplified in the introductory paragraph, have been subject of controversy (7-10). Forth, a broad spectrum of drugs and related agents can elicit anaphylaxis and causes might differ from country to country (1-5,12). Finally, the problem is compounded due to inadvertent or simultaneous administration

of various compounds. To our knowledge this study constitutes the first epidemiologic survey on anaesthesia-related anaphylaxis in Flanders.

In most surveys, IgE-mediated reactions represent up to 60% of all anaesthesia-related hypersensitivity reactions (1,2,5,30,31). Thanks to a systematic evaluation by standardized questionnaire (available from the Website of the Society of Anesthesia and Reanimation (SARB): <http://www.sarb.be/nl/algemeen/allergie/index.htm>) and application of quantification of sIgE antibodies, skin tests and basophil activation tests (BAT), an IgE-mediated pathomechanism was demonstrable in almost three-quarters of our cases. Surprisingly, this figure does not exceed the findings of the French epidemiological survey on 2516 patients (1) that did not routinely investigate all potential causative agents and did not apply basophil activation tests (1,13). The exact explanation for this observation remains elusive but could relate to an overestimation of some offenders in the French studies. For example, in another French survey reported by Dong *et al* (13) 13 patients with anaesthesia-related anaphylaxis were diagnosed as allergic towards morphine based upon skin tests and/or measurement of sIgE. However, as repeatedly discussed elsewhere it is rare that the presence of sIgE antibodies to morphine is associated with clinical allergy and it is highly unlikely that skin test is of any use to diagnose allergy to this compound because morphine, as codeine, is a potent histamine releaser from cutaneous mast cells (10,11,32). Moreover,

sIgE antibodies to morphine have been demonstrated in about 1 (22) to 10% (33) of the sera obtained from patients with classical inhalant allergies, probably as a result of non-specific binding to the solid phase (22). Actually, correct diagnosis of an IgE-mediated allergy to morphine and structurally closely related agents such as codeine probably needs additional basophil activation experiments. Basophils, in contrast to cutaneous mast cells, do not release histamine in response to these opioids. Alternatively, no cases of chlorhexidine allergy have been reported in over 3500 patients described in the French series (1,13).

Like in other surveys, we observed a female predominance and found that neither the clinical manifestations nor the acute serum tryptase level measured during the allergic reaction allows to predict whether the reaction was IgE-mediated or not (1,30).

It is shown that an IgE mediated mechanism can be demonstrated in 84% of patients presenting with severe reactions but, most importantly, also in over half of patients presenting with mild reactions. Therefore, confirmatory testing should by no means be restricted to the more severe cases but be offered to all patients that suffered from a presumed anaphylactic reaction. It cannot be excluded that the mild reactions only represent the top of the iceberg and that these patients might be at risk for future life-threatening anaphylaxis (31,34). Furthermore, we recommend that all patients that suffered from perioperative anaphylaxis should be thoroughly

investigated for the eventuality of mastocytosis (35), as for patients with mastocytosis, general anaesthesia appears to be a procedure associated with risk of mast cell degranulation and special precautions should be considered (36).

Because the causative agents can only correctly be identified in cases of IgE-mediated reactions, most of the discussion regarding the implicated compounds focuses on allergic anaphylaxis. In our series, the drugs and related agents most frequently implicated are curarising NMBA, alongside NRL, β -lactam antibiotics (particularly amoxicillin and cephazolin) and chlorhexidine, which is greatly in parallel with other surveys (1-3,13). Like in other series (2,5) the predominant offending curare was rocuronium that accounts for over three quarters of reported NMBA-related allergy in our population. The exact explanation(s) for this high prevalence of rocuronium allergy in some geographical regions remain(s) obscure but certainly exceeds the rocuronium market share of 46 % in Flanders (data from Merck & Co, Merck Corporate Office, Whitehouse Station, NJ 08889, United States). It is also unlikely that rocuronium anaphylaxis in our survey is overestimated due to inappropriate irritating skin test dilutions (8,9) or false-positive sIgE results (22), as the majority (70%) of our patients had their diagnosis of rocuronium allergy established by 2 or 3 confirmatory tests (i.e. measurement of sIgE, skin tests and basophil activation tests) as described elsewhere (29). Whether this high prevalence of rocuronium allergy in our region relates to the use of the

antitussive pholcodine (37) remains to be established, but none of the patients had a history of anaphylaxis to this cough suppressant.

An important finding from our survey relates to chlorhexidine. As already addressed, this popular antiseptic seems to be frequently overlooked as a potential offender for (severe) anaesthesia related anaphylaxis (1,5,13). In our survey an IgE-mediated chlorhexidine allergy was documented in 22 of the patients (9%). Actually in a Danish survey, chlorhexidine was the most important cause of perioperative anaphylaxis and accounted for 9% of the cases (4). Moreover, as this antiseptic might be hidden in various products (24,38) such as soaps, shampoos, mouth rinses, tooth paste, topical drugs, lubricants and jellies, central venous catheters, sponges and topical skin dressings, unnoticed exposure is common and not reported in the anaesthetic report. Therefore, the diagnostic exploration of anaesthesia-related anaphylaxis cannot be considered complete when it did not include confirmatory testing for this antiseptic (39). Note that a history of contact dermatitis to chlorhexidine may be a forerunner of anaphylactic shock to chlorhexidine (40).

Our study results also reveals that 7% of the patients demonstrate double or multiple sensitizations. This underlines the importance of systematic investigation of all potential causal and cross-reactive compounds, even when a potential cause has already been identified.

As already exemplified, the diagnostic algorithm of a perioperative anaphylaxis generally starts with a thorough revision of the anaesthetic record and skin testing complemented with quantification of sIgE. Although these confirmatory tests can provide useful information, they do not demonstrate an absolute predictive value and their results are not always unequivocal. For example, caution should be called upon interpretation of positive sIgE results, as it emerges that an isolated positive sIgE (27,29) or skin test (10,41) result frequently does not constitute the absolute proof of allergy (42). In these cases, particularly where there exists a discrepancy between history, skin test and IgE results, or when conventional tests remain negative, additional tests, might help to establish correct diagnosis. In this respect, for years we added the BAT to our diagnostic instrumentation. The technique, that more closely mirrors the clinical situation, relies upon a flow-assisted quantification of the appearance or up-regulation of particular basophil activation markers and seems promising in drug allergy (43). In this study, the BAT technique was used routinely to diagnose allergy to NMBA (14) and in individual cases when diagnosis was dubious due to contradictive skin test and sIgE results (e.g. NRL allergy) or when no definite proof for an IgE mediated was obtained by more traditional confirmatory tests. Providing a detailed overview of all the individual results is far beyond the scope of this manuscript. Most important

observations were that BAT served as a unique test to curare allergy in 3 patients without other diagnostic proof. BAT also helped to elucidate on the clinical relevance of positive sIgE to NRL and rocuronium in patients with negative skin tests. Some of these data have been published elsewhere (29,44). Furthermore, the BAT proved clearly complementary to skin tests in the assessment of cross-reactivity between NMBA (45) that all share a substituted ammonium group as main allergenic determinant (32).

CONCLUSION

This is the first Flemish epidemiologic study on anaphylaxis during general anaesthesia. It confirms that perioperative anaphylaxis exhibits distinct clinical characteristics from mild to very severe reactions and that IgE mediated allergy is not restricted to the most severe cases. The most common causes of anaesthesia-related anaphylaxis were NMBA (particularly rocuronium), latex, β -lactam antibiotics and chlorhexidine. The possibility of multiple sensitizations should not be overlooked. Therefore it is mandatory to test all drugs and related compounds the patient was exposed to. For the time being, we believe that the use of standardized anesthetic notes and combined employment of skin testing and measurement of sIgE (if available) is the most efficient and reliable strategy to correctly diagnose IgE-mediated anaesthesia-related allergy. In cases with equivocal sIgE and skin test results, additional tests, such as the BAT, might be

needed to establish correct diagnosis and identify alternatives for safe future anaesthesia.

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