

EDITORIAL

Dilemmas of allergy diagnosis in perioperative anaphylaxis

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Drugs are the most common elicitors of fatal anaphylaxis in adults (1). The majority of these events as well as a significant proportion of less severe anaphylactic reactions is caused by drugs and substances associated with general anaesthesia (1, 2). Neuromuscular blocking agents (NMBA), latex, antibiotics, induction agents and opiates are the most common substances incriminated in perioperative anaphylaxis (2–5). Because of highly efficient avoidance strategies, the prevalence of anaphylaxis to latex declined during the last years and is now considerably less than would be suggested by the presence of specific IgE (sIgE) or positive skin tests (6). Instead, increasingly other elicitors of anaphylaxis have been reported in the perioperative setting (2, 7, 8).

Previous reactors carry a highly increased risk for renewed reactions and thus require an allergy workup to find the best strategy in order to avoid future episodes associated with anaesthesia (6, 9). However, allergy diagnosis in this area still faces several obstacles:

First, it remains difficult to determine the exact mechanism of these reactions, which would be important for the development of reliable test protocols. Skin tests, the most important test method for drug anaphylaxis, may at higher concentrations be positive even in tolerant controls, particularly when testing NMBAs, which has been interpreted as a sign for a nonallergic mechanism [e.g. direct histamine release (HR)] (9, 10). On the other hand, large skin test reactions are typical for previous reactors and sIgE to quaternary ammonium substances, such as the NMBA suxamethonium, has been demonstrated (9). Thus, it is believed that about 60–70% of immediate hypersensitivity reactions to anaesthetics are, in fact, mediated by IgE (9). In some European countries, the prevalence of NMBA anaphylaxis was also associated with the availability and use of pholcodine, a potentially sensitizing antitussive agent with similar structure to morphine and NMBAs, which was able to induce sIgE antibodies cross-reacting with suxamethonium (11). Unfortunately, however, the sensitivity of the presence of sIgE to drugs, such as suxamethonium and pholcodine for the prediction of anaphylaxis, appears to be rather low and its specificity is not well determined.

Second, reports on culprit drugs and substances responsible for perioperative anaphylaxis as determined by skin test positivity differ between different regions in Europe, which may lead to confusion (2, 3, 11). This may be the result of differences in anaesthetic procedures and used substances, genetic backgrounds as well as of skin test methods. Whereas skin tests are performed and interpreted in Europe predominantly according to the standards of the European Network on Drug Allergy (ENDA), the Anesthetic/Allergologic Network in France has interpreted their skin test results and

determined nonreactive drug concentrations by their own standard, probably leading to different results (9, 12).

Third and most important, uncertainty prevails as the gold standard of allergy diagnosis, the provocation test, is not performed for the majority of perioperative anaphylactic reactions (13). It is normally not justified to induce general anaesthesia including intubation for test purposes and/or the risk for the patient having experienced a severe reaction is often judged to be too high for a drug provocation test. When tolerability of subsequent anaesthesia is used as read-out, allergy diagnosis appears to be highly efficient and reaction rates are very low (9). Nevertheless, the influence of confounders, such as choice of anaesthesia using different less-reactive compounds or premedication, cannot be estimated. Without provocation test, the causal relationship as well as sensitivity and specificity for skin tests, sIgEs and cellular tests cannot be reliably determined.

Fourth, hidden and less well-known substances may cause perioperative anaphylaxis, and education of allergists about these allergic compounds is warranted. Chlorhexidine, blue dyes, macrogol, carboxymethylcellulose and ethylene dioxide have increasingly been reported as elicitors of anaphylaxis, with chlorhexidine being a most relevant in this setting (7–9).

Perioperative anaphylaxis to chlorhexidine is often severe and easily overlooked (3). Chlorhexidine is a widely used disinfectant in the hospital as well as in the private health care. In the perioperative setting, the risk for severe reactions appears to be highly increased (14). The mechanism appears to be IgE mediated, and determination of sIgE, skin tests [skin prick test (SPT) and intradermal test (IDT)] as well as cellular tests, such as the basophil HR test, has been used to confirm sensitization to this compound in patients with suspected chlorhexidine allergy (14).

In the study by Opstrup et al (7) in this issue of Allergy, of 343 patients with perioperative anaphylaxis evaluated by the Danish Anaesthesia Allergy Center (DAAC) during the last years, 32 patients had at least one positive allergy test (of those mentioned above) for chlorhexidine. Without a validated provocation test, confirmation of the diagnosis 'chlorhexidine allergy' is difficult and based on an evaluative interpretation of the history together with available test results. To follow a scientific approach, a model of at least two different positive diagnostic tests in combination with a compatible history has been chosen. This definition has previously also been applied for rocuronium allergy.

All tests were performed within a 6 months timeframe after the reaction, as longer intervals may lead to declined diagnostic test reactivity. This model works best, if the tests would be equally reliable. In total, 22 patients fulfilled the criteria of ≥ 2 positive diagnostic tests. The highest

concordance between the tests was between sIgE and the SPT, which were positive in 22 of 22 and 21 of 22 patients. The authors recommend a combination of both tests as the minimum when diagnosing chlorhexidine allergy. HR and IDT showed a lower estimated sensitivity, but excellent specificity of 99–100%. In the ten patients with only one positive diagnostic test, results were reported to be just above the cut-off value rendering the causal association questionable, but not impossible.

The present study demonstrates how difficult it is to confirm allergy in the perioperative setting without a provocation test as gold standard (13). Sensitivity and specificity can only be estimated against an available ('silver') standard, for example two concordant positive test results. Other centres should confirm the results and conclusions drawn in this study using the same methodology, best in a multicentre study.

It also shows that there are situations in allergology, where a black-and-white picture cannot be drawn by available tests. Here, we have to revert to our virtues: a critical interpretation of available results in combination with an accurate record of events including information on drug administration. Critical interpretation may become more important than primary test

results. Expertise on clinical symptoms, differential diagnoses and test characteristics are required for this task. In the complex field of perioperative anaphylaxis without a gold standard of diagnosis available, investigation in major knowledgeable allergy expert centres and close cooperation between allergists (evaluation and critical interpretation of test results) and anaesthetists (record of events, drugs given and differential diagnoses), for example, as practiced in the DAAC and centres in France is highly recommended. This should lead to a better recognition of causative drugs and should avoid serious consequences of diagnostic error.

Author contribution

Knut Brockow is the sole contributor.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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