

Perioperative Hypersensitivity Reactions: Time for Collaboration



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The investigation of suspected perioperative hypersensitivity (POH) is one of the most complicated undertakings in drug allergy. Multiple simultaneous exposures to different drugs, many of which are very potent and unfamiliar to allergists, combined with the relative rare occurrence of these events, means that experts in this field have called for POH to be investigated in highly specialized centers.^{1,2} In this issue, Banerji et al³ report on 118 patients who underwent allergy evaluation for suspected POH at the Massachusetts General Hospital in the period 2003 to 2017. The authors have previously published data and this publication combines previous datasets with more recent data. Only very few other publications on perioperative allergy have come from the United States and the authors call for evidence-based guidelines in the United States to improve evaluation of POH reactions including recommendations for subsequent anesthesia.³ In other parts of the world, a lot of work has been done over the years to produce guidelines at national,^{4,5} European,¹ and international levels²; this should provide a good starting point for producing guidelines in the United States.

The aims of investigation are to elucidate the mechanism of the reaction and to identify a culprit or an alternative plausible mechanism, so that recommendations for safe future anesthesia can be made. Banerji et al³ report a rate of 8% of patients with recurrence of allergic reactions during subsequent anesthesia. This is higher than in European centers, and the authors suggest that this calls for improvements in the procedure. In Europe, where perioperative allergy investigation has been systematically performed in some countries for 20 to 30 years many pitfalls have been identified and solved. Therefore, recommendations from recent European and international guidelines may help form the basis for optimizing protocols in the United States.

Tryptase is very useful in the perioperative setting owing to the multiple nonallergic differential diagnoses related to patient comorbidity or anesthetic and surgical technique. Tryptase must be taken at the right time and collaboration with anesthesiologists is necessary to ensure samples are taken in the acute setting and referrals sent. Banerji et al³ highlight the importance of comparison with a baseline tryptase sample. This improves diagnostic sensitivity and may reveal elevated baseline serum tryptase, warranting further investigations for hereditary alpha-tryptasemia or mast cell disorders such as systemic mastocytosis.

When deciding which drugs to investigate, all drugs and other substances the patient was exposed to should be identified.¹ Several nonanesthetic drugs are important perioperative allergens such as latex, disinfectants (eg, chlorhexidine), sterilizing agents (eg, ethylene oxide), and blue dyes (eg, patent blue) used for sentinel lymph node procedures in cancer surgery.⁶ In recent guidelines, it is suggested that all patients with suspected POH should be tested for allergy to disinfectants (chlorhexidine) and latex from *Hevea brasiliensis*.¹ The diagnostics of latex allergy is based primarily on skin prick tests, which can be supported by specific immunoglobulin E (IgE) including molecular diagnostics. Specific IgE to latex can be elevated owing to *H. brasiliensis* 8 (profilin) in patients with grass or birch pollen sensitization, and latex allergy should not be diagnosed on an elevated specific IgE result alone.⁷ Routine testing with chlorhexidine is advocated in recent guidelines, and centers carrying out routine testing consistently report a rate of around 9% of reactions attributed to chlorhexidine.⁶ In centers in which such routine testing is not in place, cases may be missed leading to reexposure and renewed reactions during subsequent anesthesia or other invasive procedures. Banerji et al³ did not routinely test for chlorhexidine early on, and they consider that an overlooked chlorhexidine allergy may be the cause in one, or more, of the patients who had reactions during subsequent anesthesia. This is an important take-home message. When no cause is found on initial investigations, excipients (eg, polyethylene glycol, mannitol, and carboxymethylcellulose) should be considered because these are ingredients in gels, sprays, bone cements, and other exposures not always documented.⁸

Once a decision is made on which drugs to investigate, it is important that investigations are standardized. Skin testing (skin prick testing and intradermal testing) have long been the reference standard in POH investigation. Many of the drugs used on the perioperative setting are unfamiliar to allergists, and it is imperative that information from existing up-to-date guidelines on nonirritant concentrations is used for skin testing.¹ False-positive testing may lead to a dismissal of the real culprit. Banerji et al³ mention this in relation to a patient who had a positive skin test to a quinolone, which was avoided during subsequent anesthesia, but the patient still had an allergic

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reaction, potentially due to another overlooked allergen. Reactions to two allergens have also been described, and therefore, planned investigations should be continued even if a culprit is identified.¹

A large proportion of patients with POH experience severe reactions fulfilling the criteria for anaphylaxis, sometimes even with cardiac arrest. In such patients, *in vitro* tests carrying no risk to the patient could be performed before skin testing. Specific IgE tests are available for latex and chlorhexidine (ThermoFisher, Uppsala, Sweden) and to some penicillins. Basophil activation tests and basophil histamine release tests are used in some specialized centers.⁷

When all tests are negative, but the suspicion of hypersensitivity is high, Banerji et al³ recommend that the case should be reassessed, including looking for potentially overlooked culprits. This is best done by communicating with the attending anesthesiologists or other personnel present at the initial reaction. In some cases, a nonallergic explanation for the symptoms might become a realistic alternative after discussing the case with an anesthesiologist.⁸

If all tests are negative and specific agents are still suspected, drug provocation test or graded challenge may be warranted.⁹ This is not routinely recommended in guidelines on POH investigation but may be indicated in specific cases. Carrying out such provocations should only be done in close collaboration between the allergist and anesthesiologist and only after other tests have proven negative.^{1,9}

Historically, POH investigation was initiated in France, Australia, and the United Kingdom.⁸ In Australia, a national network of anesthesiologists, the Australian and New Zealand Anaesthetic Allergy Group (ANZAAG), exists and investigations are mainly carried out by anesthesiologists.⁵ In France, a national network, Groupe d'Étude des Réactions Anaphylactoïdes Pér opératoires (GERAP), has been in place for many years with collaboration between anesthesiologists and allergists.⁴ In a small country like Denmark, it has been possible to establish one national reference center with total integration and collaboration between anesthesiologists and allergists.⁹ In 2018, the National Audit project 6 in the United Kingdom made a case for collaboration between anesthesiologists and allergists.¹⁰ In many European countries, POH has mainly been investigated by allergists, but the 2019 European Academy of Allergy and Clinical Immunology (EAACI) position paper on the investigation of POH has called for collaboration among specialties.¹ Lastly, in 2019, a series of

papers was published by an international group of experts in POH from several specialties, the International Suspected Perioperative Allergic Reaction (ISPAR) group, which is now open for members from all relevant specialties and countries.² Until now, only a few series have been published from the United States and as suggested by Banerji et al,³ there is a need for guidelines in the United States to improve the evaluation of these patients and give recommendations for subsequent anesthesia. We hope that, in preparing such guidelines, our American colleagues will look toward Europe and Australia/New Zealand and the large body of knowledge available from those and other regions of the world. We welcome and encourage further collaborations across specialties, locally, nationally, and internationally.

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