Original Article

Antibiotics Are the Most Commonly Identified Cause of Perioperative Hypersensitivity Reactions

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What is already known about this topic? Current knowledge of drug hypersensitivity reactions (HSRs) during anesthesia comes from retrospective studies. The most commonly implicated drugs causing perioperative HSRs vary between countries.

What does this article add to our knowledge? We describe a successful referral and treatment plan for patients with HSRs during anesthesia in a Boston teaching hospital.

How does this study impact current management guidelines? The most commonly identified cause of perioperative HSRs was antibiotics. Allergists should evaluate patients with HSRs during anesthesia to minimize risk with subsequent anesthesia.

BACKGROUND: Hypersensitivity reactions (HSRs) during the perioperative period are unpredictable and can be life threatening. Prospective studies for the evaluation of perioperative HSRs are lacking, and data on causative agents vary between different studies.

OBJECTIVE: The objective of this study was to prospectively determine the success of a comprehensive allergy evaluation plan for patients with HSRs during anesthesia, including identification of a causative agent and outcomes during subsequent anesthesia exposure.

METHODS: All patients referred for a perioperative HSR between November 2013 and March 2015, from a Boston teaching hospital, were evaluated using a standardized protocol with skin testing (ST) within 6 months of HSR. Comprehensive allergy evaluation included collection of patient information, including characteristics of HSR during anesthesia. We reviewed the results of ST and/or test doses for all potential causative medications Event-related tryptase levels were reviewed when available.

RESULTS: Over 17 months, 25 patients completed the comprehensive allergy evaluation. Fifty-two percent (13 of 25) were female with a median age of 52 (interquartile range 43-66) years. The most frequently observed HSR systems were cutaneous (68%), cardiovascular (64%), and pulmonary (24%). A culprit drug, defined as a positive ST, was identified in 36% (9 of 25) of patients. The most common agent identified was cefazolin (6 of 9). After our comprehensive evaluation and management plan, 7 (7 of 8, 88%) patients tolerated subsequent anesthesia.

CONCLUSIONS: Cefazolin was the most commonly identified cause of a perioperative HSR in our study population. Skin testing patients within 6 months of a perioperative HSR may improve the odds of finding a positive result. Tolerance of subsequent anesthesia is generally achieved in patients undergoing our comprehensive evaluation. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: *Drug; Allergy; Hypersensitivity; Reaction; Anesthesia; Perioperative; Anaphylaxis; Tryptase; Cefazolin*

Perioperative hypersensitivity reactions (HSRs) have been estimated to occur in 1:3500 to 1:20,000 procedures, with a mortality rate of up to 9%.[1] However, newer prospective data suggest that this incidence may be as high as 1 in 385

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Abbreviations used
HSR(s)- Hypersensitivity reaction(s)
IgE- Immunoglobulin E
NMBAs- Neuromuscular blocking agents
PCN- Penicillin

operations.[2] Several drugs are often administered simultaneously during general anesthesia, making identification of the causative agent(s) difficult. Identification of the culprit agent of a perioperative HSR is crucial to avoid re-exposure and prevent subsequent untoward outcomes.

Guidelines recommend comprehensive skin testing to chlorhexidine, all preoperative medications listed in the anesthetic record that were given before the HSR, and specific immunoglobulin E (IgE) testing to latex.[3] The literature suggests that there is a geographic difference in the most frequently identified cause of perioperative HSRs. Studies from Europe have implicated neuromuscular blocking agents (NMBAs),[4,5] whereas studies from the United States (US)[6-8] more commonly implicate antibiotics as the cause of perioperative HSRs.

A recent retrospective study described a 10-year period utilizing a specific evaluation and management plan to identify causative agents and provide recommendations for patients with HSRs during anesthesia that require subsequent anesthesia.[6] Limitations of this study were the absence of antibiotic skin testing in some patients due to the lack of skin testing reagents and the prolonged and variable length of time from perioperative HSRs to skin testing, which may have led to a higher rate of false-negative skin testing.[9,10] Decreased availablity of β-lactam testing may explain the low rate of a positive skin test on evaluation (13 of 73 patients, or 18%) and antibiotics as the causal agent (3 of 13 patients, or 23%).

In this study, we describe the application of a comprehensive management plan for perioperative HSRs prospectively over a 17-month period, including skin testing to all possible causative agents within 6 months of HSR, and assessing patients' tolerability of subsequent anesthesia, when indicated.

METHODS

Study design

We performed a prospective cohort study of all patients at Massachusetts General Hospital who were referred to Allergy and/or Immunology for a perioperative HSR between November 2013 and March 2015. These patients were evaluated using a standardized protocol.[6]

Patients were identified based on referral information provided by a central patient scheduler. Patients who had an HSR during induction or maintenance of anesthesia, or during the immediate postoperative recovery period, were included.

Patients were excluded if they were below the age of 18 at the time of evaluation, declined participation in the comprehensive evaluation, or did not complete the recommended comprehensive evaluation. The study was approved by the Partners Healthcare Institutional Review Board.

Comprehensive allergy evaluation

All patients referred to the Allergy and/or Immunology Unit for a perioperative HSR underwent evaluation involving a detailed review of the HSR obtained from the patient's perioperative medical records. The review included anesthesia records, nursing records, operative and procedural reports, and consultation notes of the Allergy and/or Immunology Unit, when applicable. Patient information, including age, sex, atopic history, history of prior drug allergy, medications at the time of the surgery, history of previous surgery, serum-specific IgE to latex, and serum tryptase levels (when available), was recorded. Documentation of perioperative organ system involvement was also recorded and included cutaneous, oropharyngeal, pulmonary, cardiovascular, gastrointestinal, or other system involvement. HSR severity was determined following an established grading scale (I-IV) with a grade of IV representing cardiac and/or respiratory arrest to classify the perioperative HSR (Table I).[3]

TABLE I. Severity of hypersensitivity reactions during anesthesia

Grade	Symptoms
I	Cutaneous signs: urticaria, angioedema, and generalized erythema
II	Measurable but not life-threatening symptoms: cutaneous signs, hypotension (defined as a decrease of more than 30% in blood pressure with tachycardia), and respiratory symptoms (cough, difficulty with mechanical ventilation)
III	Life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, and severe bronchospasm
IV	Cardiac and/or respiratory arrest

Adapted from Ring J, Messmer K. Lancet 1977;1:466-9 and Mertes PM, Malinovsky JM, Jouffroy L; Working Group of the SFAR and SFA, Aberer W, Terreehorst I, et al. J Investig Allergol Clin Immunol 2011;21:442-53.

Formal collaboration was established between the Allergy and/or Immunology Unit and the Department of Anesthesia at our institution to capture cases of a perioperative HSR. Initial steps included meetings with the Department of Anesthesia's Quality Assurance Chair and lead nurse coordinator to discuss our cohort project and development of a referral checklist to ensure the best possible patient outcomes. We subsequently arranged a case-based presentation at the Department of Anesthesia's Mortality and Morbidity conference, to discuss commonly encountered drug allergy issues in the perioperative setting including associated HSRs. We encouraged sending serum total tryptase within 4 hours for any suspicion of a perioperative HSR and outpatient referral to Allergy. To ensure the vigilant capture of all possible or probable perioperative HSRs, we maintained weekly communication with the Anesthesia Department's Quality Assurance team during the study period.

Skin testing was performed between 4 weeks and 6 months of the perioperative HSR to minimize false-negative results.[11] Intradermal and/or skin prick testing was performed to all agents received before the HSR with published nonirritating skin testing concentrations. Inhalational agents, which have not been demonstrated to cause HSRs and to which no standardized skin testing exists, were not skin tested. Skin testing during allergy evaluation was performed with nonirritating skin testing concentrations, and appropriately positive (histamine 6 mg/mL) and negative (saline) controls (Table II). A positive skin prick reaction, suggesting an IgE-mediated cause, was considered if the diameter of the wheal was at least 3 mm larger than that induced by the negative control. If the skin prick test was negative, increasing concentrations of intradermal skin testing was performed, when available. A positive intradermal skin test reaction was considered if the diameter of the wheal had an increase of more than 3 mm compared with the saline wheal, and had an associated erythematous flare.

Laboratory evaluation of patients including total baseline tryptase level (if perioperative tryptase value during the HSR was elevated or