Original Article

Comprehensive Allergy Evaluation Is Useful in the Subsequent Care of Patients with Drug Hypersensitivity Reactions During Anesthesia

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What is already known about this topic? Much of what is known about drug hypersensitivity reactions (HSRs) during anesthesia comes from registries developed outside the United States. The rate of HSR to specific general anesthetics varies between countries.

What does this article add to our knowledge? We describe the success of a comprehensive evaluation and management plan for patients with HSRs during anesthesia at a large academic center in Boston.

How does this study impact current management guidelines? This study supports a comprehensive evaluation and management plan for patients with HSR during anesthesia, including skin testing and baseline tryptase level, to minimize the risk of subsequent anesthesia even when the cause is not identified.

BACKGROUND: For patients with a history of drug hypersensitivity reaction (HSR) during anesthesia, strategies to minimize risk with subsequent anesthesia are unclear. Identification of the cause of HSR during anesthesia remains challenging.

OBJECTIVE: To determine the success of a comprehensive allergy evaluation and management plan for patients with HSR during anesthesia, including identification of the causative agent and review of outcomes during subsequent anesthesia exposure.

METHODS: We performed chart reviews of patients referred for the evaluation of HSR during anesthesia between 2003 and 2012. Data collection included patient characteristics, signs/symptoms of HSR during anesthesia, and subsequent outcomes. Patients underwent comprehensive allergy evaluation including skin testing for identifying potential culprit agents, and the results were used to provide recommendations for any subsequent anesthesia.

RESULTS: Over the 10-year study period, 73 patients with HSR during anesthesia were referred for further evaluation. Thirteen patients (18%) had positive skin test results to a drug received during anesthesia. One patient with a positive skin test result was diagnosed with mastocytosis. The causative agents identified in these 13 patients included latex, β-lactam antibiotics, neuromuscular blockers, tetracaine, odansetron, and fentanyl. On follow-up, 47 of the 73 patients (64%) subsequently underwent procedures requiring anesthesia. Using our recommendations from evaluation and testing, 45 of these 47 patients (96%) successfully tolerated subsequent anesthesia. The 2 patients who developed recurrent HSR during anesthesia were later diagnosed with mast cell disorders.

CONCLUSIONS: Our comprehensive evaluation and management plan minimizes risk with subsequent anesthesia even when the cause of HSR could not be identified. Baseline tryptase levels may be helpful in this patient population to diagnose mast cell disorders. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:94-100)**

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Drug hypersensitivity reactions (HSRs) during anesthesia are unpredictable and potentially life-threatening immune-mediated events. These HSRs can be classified as IgE-mediated (defined by positive skin test results or serum specific IgE) or non−IgE-mediated (including cytotoxic, immune complex−mediated, cell-mediated, pseudoallergic, and other immunologic reactions).[1] Although the mechanism may differ, the clinical characteristics of both are often indistinguishable.[2] The estimated incidence of HSR during anesthesia is between 1:3,500 and

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Abbreviations used
ACE- angiotensin-converting enzyme
ASA- Aspirin
HSR- Hypersensitivity reaction
IQR- Interquartile range
NSAID- Nonsteroidal antiinflammatory drug

1:20,000.[3-6] Most data on the incidence of HSR come from countries with an active reporting policy (ie, Australia, Denmark, France, New Zealand, Norway, and the United Kingdom); the United States does not have such a policy. Mortality associated with HSRs during anesthesia has been estimated to vary between 3% and 6%.[7]

The complete evaluation of patients who develop adverse drug reactions during general anesthesia remains complex. Patients routinely receive multiple medications in a short period of time, which makes it challenging to identify a culprit drug or drugs on the basis of the timing of administration by review of the medical record alone. Previously published guidelines, based on expert opinion, recommend comprehensive skin testing to agents that are listed in the anesthetic record, in addition to latex and other medications given before the HSR.[8] In the present study, we describe our experience over a 10-year period using a specific evaluation and management plan to identify causative agents and provide recommendations for patients with HSR during anesthesia before subsequent anesthesia.

METHODS

Study design

We performed a chart review of all patients 18 years or older at Massachusetts General Hospital who were referred to the Allergy/Immunology Unit for the evaluation of HSR during anesthesia between January 1, 2003, and December 31, 2012.

Patients were identified using the *International Classification of Diseases, ninth revision* billing codes 995.27 (Other drug allergy), 995.0 (Other anaphylactic reaction), and in-office procedure code 95010 (percutaneous testing to drug, biologic, or venom). Patients who had an HSR during induction or maintenance of anesthesia, or during the immediate postoperative recovery period, were reviewed.

The Wilcoxon rank-sum test was used to calculate the difference in median time to skin testing. The institutional review board approved the study.

Comprehensive allergy evaluation

All patients referred to the Allergy/Immunology Unit underwent comprehensive allergy evaluation, including a detailed review of the HSR obtained from medical records. All anesthesia records, nursing records, operative and procedural reports, and consultation notes of the Allergy/Immunology Unit were reviewed in detail. Patients' demographic characteristics including age, sex, history of atopy, history of drug allergy, medications at the time of the surgery, history of surgery, serum specific IgE to latex, and serum tryptase levels (where available) were recorded. Organ system involvement was also documented with particular attention to cutaneous, oropharyngeal, pulmonary, cardiovascular, gastrointestinal, or other systems. The severity of each reaction was documented using a published grading scale to classify HSR during anesthesia (Table I).[8]

Skin testing was performed at least 4 weeks after the initial HSR as previously described.[9] Skin prick and intradermal testing were performed to all available agents listed in the anesthetic record and received immediately before the HSR, with the exception of inhalational agents that have not been previously demonstrated to cause HSR. Previously validated, nonirritating skin testing concentrations were used during allergy evaluation (Table II). Appropriate positive (histamine 6 mg/mL) and negative (saline) controls were also included. A skin prick reaction was considered positive if the maximum diameter of the wheal was at least 3 mm larger than that induced by the negative control. Intradermal skin testing at increasing concentrations was also performed if the skin prick reaction was negative. An intradermal test result was considered

TABLE I. Severity of hypersensitivity reactions during anesthesia

Grade	Symptoms
I	Cutaneous signs: urticaria, angioedema, 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), respiratory symptoms (cough, difficulty with mechanical ventilation)
III	Life-threatening symptoms: cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm
IV	Cardiac and/or respiratory arrest

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TABLE II. Skin testing reagents

Medication	Concentration (mg/mL)	SPT	ID Dilution
Succinylcholine[10,11]	50	Undiluted	1:1,000
Cisatracurium[10,11]	2	Undiluted	1:1,000 1:100
Rocuronium[10,11]	10	Undiluted	1:1,000 1:100
Atracurium[10,11]	10	Undiluted	1:1,000
Pancuronium[10,11]	2	Undiluted	1:1,000 1:100 1:10
Midazolam[10,11]	5	Undiluted	1:20 1:10
Ketamine[10,11]	10	Undiluted	1:40
Propofol[10-12]	10	Undiluted	1:1,000 1:100 1:10
Etomidate[11]	2	Undiluted	1:1,000 1:100 1:10
Fentanyl[11]	0.05	Undiluted	1:10,000 1:1,000 1:100 1:10
Lidocaine 1%[11,13,14]	1%	Undiluted	1:100
Bupivacaine 0.25%[11,13,14]	0.25%	Undiluted	1:100
Tetracaine 1%[13,14]	1%	Undiluted	1:100
Chlorhexidine gluconate 0.5%[15]	1.2	Undiluted	1:2,500
Odansetron[16,17]	2	Undiluted	1:100
Cefazolin[18]	330	1:10	1:100 1:10

ID, Intradermal testing; *SPT*, skin prick testing.