

Perioperative Anaphylaxis and the United States Perspective

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Patients are exposed to multiple substances in the perioperative period, including drugs, blood products, and environmental agents (e.g., latex, chlorhexidine). Any of these may trigger an allergic reaction. The most life-threatening allergic reaction is anaphylaxis. Diagnosis of anaphylaxis may be delayed because hypotension and vasodilation are common side effects of many drugs administered in the course of anesthesia, and pruritus, urticaria, and angioedema may be concealed by drapes or may be missed because the patient is draped.

Although any drug or biologic agent can cause anaphylaxis, the literature suggests that antibiotics, blood products, chlorhexidine, neuromuscular blocking drugs (NMBDs), polypeptides (aprotinin, latex, and protamine), and intravascular volume expanders are the most common causes of anaphylaxis in the perioperative period.¹ Most all of these data are from Australia, Europe, the United Kingdom, and New Zealand, where centers have been established to investigate occurrences of perioperative anaphylaxis.^{2–7} In one of the largest reports, perioperative anaphylaxis was evaluated over an 8-year period from 1997 to 2004 in France, on the basis of the combined data of the author and the French Pharmacovigilance system.⁸ Among the 2516 patients with episodes of anaphylaxis, immunoglobulin (Ig)E-mediated reactions occurred in 1816 cases (72.2%). The most common causes for the IgE-mediated events were NMBDs in 58% ($n = 1067$), latex in 19.6% ($n = 316$), and antibiotics in 12.8% ($n = 236$).

Understanding perioperative anaphylaxis is important because of the potential for morbidity and mortality.⁹ However, most estimates of the incidence are based on retrospective data, which may account for variability in the incidence. The risk of perioperative anaphylaxis is

reported as between 1:3500 and 1:20,000, with a mortality rate of 4% and an additional 2% surviving with severe brain damage.^{9,10}

There is very little epidemiologic data from North America about the incidence or agents implicated in perioperative anaphylaxis. A 1990 report from the United States (US) noted that barbiturates were the most likely causative agent for 38% of IgE-mediated anaphylaxis.¹¹ This is important because in many investigations the most frequent agent reported for perioperative IgE-mediated anaphylaxis is NMBDs, and was the focus of an Editorial in this journal in 2004.¹²

In the current study in *Anesthesia & Analgesia*, Gurrieri et al. reviewed the Mayo Clinic Division of Allergic Diseases skin test database between 1992 and 2010 for patients with perioperative anaphylaxis who were tested to medications implicated in the reactions and included 38 patients.¹³ Their data included the history obtained by an allergist, skin test results, and tryptase measurements when available. The authors reported that 40% of the surgical procedures were aborted, and 58% of events resulted in unplanned intensive care unit admissions, suggesting that the allergic responses were clinically severe. Of the 38 patients, 18 were considered IgE-mediated reactions based on skin testing, 6 were non-IgE-mediated anaphylactic reactions as determined by elevated tryptase levels and negative skin testing, and 14 were probable non-IgE-mediated anaphylactic reactions because tryptase levels were normal or not obtained and skin testing was negative. Of the IgE-mediated anaphylactic reactions, antibiotics were the causative agents in half of the patients, and NMBDs were implicated solely as a likely causative agent in only one reaction. The authors noted that causative agents could not be determined in the other half of the patients, and suggested that this placed them at risk of a subsequent reexposure to the same allergen, or conversely unnecessary avoidance of needed medications.¹³

Although this report includes only 38 patients, it illustrates the difficulty studying perioperative anaphylaxis because of its relatively low frequency. The authors identified only one true IgE-mediated reaction to an NMBD, which was a reaction to succinylcholine. Another patient had positive skin tests to 3 agents, including vecuronium, propofol, and cefazolin, making the diagnosis uncertain. Of note, a previous Danish study reported 68 patients who were referred to their center, of which 36 underwent complete investigations with in vitro testing and skin

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testing, and found that only 1 patient tested positive for NMBDs (4.8%, 1 out of 21), whereas chlorhexidine accounted for 19.1% of reactions and antibiotics 14.3%.¹⁴ In the current study, chlorhexidine was tested in only 4% of cases and may account for some of the undiagnosed reactions with elevated tryptase.¹³ This may also account for potentially identifying the causative agent in only half of the reactions. The authors also discuss the importance and controversies of these findings vis-à-vis allergy testing (i.e., skin prick versus intradermal testing) and variability of results based on concentrations used. One useful contribution of the paper is the table of the allergen concentrations used for testing by the Mayo Clinic Allergy Division. This table can be used as a guide for additional evaluations by other clinicians and can be found as their Appendix (see Supplemental Digital Content 1, <http://links.lww.com/AA/A314>).

What can we learn from this report? Antibiotics are the primary cause of perioperative anaphylaxis.^{13,15} Thus, caution must always be exercised when antibiotics are administered. Antibiotics should be started whenever possible 5 to 10 minutes before or after additional agents are to be given to facilitate a diagnosis of anaphylaxis and discover the inciting agent.¹ Furthermore, this investigation supports previous suggestions that the risk of anaphylaxis to NMBDs in the US is less than that in Europe.¹⁴ This ongoing controversy reflects many issues, including the potential for false-positive skin testing, the lack of a consensus on the methods and concentrations of NMBDs for testing, other anesthetic medications that should be included when skin testing, and exposure to certain drugs in other countries that may presentize patients for cross-reactivity to NMBDs.^{16–19} For example, numerous drugs with quaternary ion epitopes are available in Europe, and these may account for the cross-sensitization.¹⁹ The study also suggests that latex reactions are decreasing, an expected finding because this once ubiquitous environmental antigen has been removed from most products used perioperatively.

The authors also found that tryptase levels were not routinely evaluated during allergy testing. Tryptase is a mast cell product, and elevations closely associate to the presence of hypotension during anaphylaxis and indicate mast cell activation.^{10,20–22} For diagnosing anaphylaxis, the positive predictive value of tryptase is reported to be 92.6% and the negative predictive value to be 54.3%.¹⁰ Drugs such as vancomycin that directly release mediators from mast cells will release tryptase.²³ Conversely, IgG-mediated anaphylaxis to protamine, characterized by acute pulmonary hypertension and right ventricular failure, does not elevate tryptase.¹ Despite these limiting factors regarding tryptase, tryptase should be obtained within 2 hours of an allergic reaction, then 24 hours later to help investigate the potential reaction and rule out mastocytosis.

Lastly, the investigators suggest that anesthesiology departments should establish standardized protocols to refer all patients with anaphylactic reactions to the institutional allergy departments. This is a great idea because most anesthesiologists lack the time, expertise, or ability to evaluate patients following anaphylaxis. The authors also suggest that the allergist should test all the agents administered during anesthesia, including medications and occult antigens such as latex and chlorhexidine. In summary,

Gurrieri et al. provide additional insight into the epidemiology of perioperative anaphylaxis in the US and offer a protocol for potential skin testing when evaluating patients with reactions.¹³ The time has come to develop referral centers with allergists interested in working together to test patients following perioperative anaphylaxis, to better understand and prevent this rare but life-threatening complication. ■■

DISCLOSURES

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Contribution: Reviewed manuscript, added additional information and references.

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