

Intraoperative and Procedure-Related Anaphylaxis

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Whether from intravenous medications, other therapeutic agents, topical antiseptics, irrigation solutions, diagnostic aids, blood products, or latex, intraoperative anaphylaxis is iatrogenic and may be life threatening or fatal. Its onset is unexpected, and often, the full dosage of the causative agent such as a neuromuscular blocking agent or an antibiotic has been administered by the time there is the precipitous drop in blood pressure or sudden difficulty in maintaining effective ventilation. In a landmark study published in 1986, Fisher described 227 patients evaluated for anesthesia-associated anaphylaxis, 205 of whom experienced cardiovascular collapse, defined as systolic blood pressure <40 mm Hg.¹ There were 7 (3.1%) fatalities. The most frequent electrocardiographic finding was supraventricular tachycardia (SVT), but some patients had SVT with ST elevation, SVT then ventricular fibrillation, or bradycardia preceding the SVT.¹ The presence of bradycardia during intraoperative anaphylactic shock is infrequent and occurs in the absence of beta-adrenergic blockers.² Using serial measurements of hemoglobin and recording the volume of colloid and crystalloid solutions infused, Fisher reported that there was a 35% loss of plasma from the blood volume "within 10 minutes."¹ The central venous pressure was low in all 37 patients without known cardiac disease, whereas it was elevated in 9 of 11 patients with cardiac disease.¹ The cardiac patients still required sufficient fluid administration during resuscitation. There were 6 patients who had a balloon catheter in situ at the time of the anaphylactic shock, and the pulmonary artery pressures "rose initially and fell over 10 minutes."¹ Thus, in patients with underlying cardiac disease who experience intraoperative anaphylactic shock, there is the deleterious combination of acutely elevated pulmonary artery pressure and low central venous pressure. Patients without cardiac disease also could have this dangerous combination from acute severe bronchoconstriction along with low systemic vascular resistance. Alternatively, intraoperative anaphylaxis can present with sudden hypotension and require recognition and immediate resuscitation. Fisher concluded that "adrenaline is the

drug of first choice in management and that colloid solutions are preferable to crystalloid solutions in volume replacement."¹ Almost 30 years later, adrenaline (epinephrine) remains the drug of first choice, but in critically ill patients, there are comparable results with either colloid or crystalloid solutions.³

As with all forms of anaphylaxis, prompt recognition and early treatment with epinephrine is essential.^{4,5} Even when that is accomplished, there can be a fatality. Nevertheless, the literature on fatalities from anaphylaxis is replete with examples of delays in both diagnosis and administration of epinephrine including in 6 of 7 fatal cases in the Fisher series.¹ With quick recognition and effective resuscitation, the anesthesiologist can protect most patients from an iatrogenic death. The surgeon faces an emergency in that there is an open surgical field, and the procedure may have to be aborted. In spinal surgery, the patient may be in the prone position when anaphylactic shock and bronchoconstriction appear unexpectedly.

In performing the consultation on a patient who has experienced intraoperative or procedure-related anaphylaxis, the allergist-immunologist can demonstrate superior medical knowledge and diagnostic acumen. Indeed, the initial differential diagnosis can include planning for and ruling in or out hypersensitivity to neuromuscular blocking agents, antibiotics (often, cephalosporins, penicillins, or vancomycin administered intravenously or aminoglycosides or bacitracin applied directly to the wound), the induction/hypnotic/amnestic agent, propofol, and fentanyl or other opioid analgesic.⁵ Besides reviewing the circumstances of a previous intraoperative or procedure-related anaphylactic event and the patient's history of drug, food, and latex allergy, the consultation may involve identifying if the patient has unrecognized indolent systemic mastocytosis,⁶ undiagnosed dermatographism, spontaneously occurring urticaria, unexplained pruritus or frank prurigo nodularis, latex allergy, insufficiently controlled eczema, or episodes of transient flushing. The differential diagnosis of intraoperative or procedure-related anaphylaxis can extend to radiographic contrast material (which is a clear solution), dyes which are employed as mapping agents,^{7,8} blood products, protamine,⁹ and hemostatic agents.^{10,11}

In this issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Joel Hartman and Phil Lieberman provide a comprehensive case-based discussion of perioperative anaphylaxis in our Difficult Cases feature (p. 142). In addition, 4 reports expand the literature of intraoperative anaphylaxis. Paulos Viegas and colleagues describe a penicillin-allergic patient who received cefazolin, but antibiotics and other possible suspects were excluded as causes of anaphylaxis.⁷ The authors concluded that patent blue dye was etiologic based on positive skin tests and exclusion of multiple other potential causes by skin testing and challenge.⁷ Agarwal and colleagues report a 9-year-old boy with kyphosis who underwent spinal surgery and experienced pulseless anaphylactic shock from bovine gelatin, which was injected intraosseously with thrombin as a hemostatic agent.¹⁰ This case exemplifies the need for system-wide improvement to provide

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optimal and safe patient care. The patient had experienced a less severe anaphylactic reaction during spinal surgery 8 years previously during which it was determined that the same branded gelatin-thrombin product was used. Furthermore, the boy had experienced anaphylaxis during administration of MMR and varicella vaccines, both of which contain gelatin.¹² There was a history of a facial rash after eating beef, but that gelatin was etiologic was identified after survival of truly, life-threatening intraoperative anaphylaxis and with the allergy-immunology consultation. The third report focuses on the importance of antibiotics as attributable causes of intraoperative anaphylaxis.¹³ In that series of 30 patients, the presentation was cardiac arrest in 7 (23%) patients. From a practical standpoint, when considering beta-lactam antibiotics as potential causes of intraoperative anaphylaxis, it is most informative to test with highly sensitive skin tests such as major and minor determinants of penicillin.¹⁴ If prick and intradermal tests are negative, the very high negative predictive value helps exclude beta-lactam allergy according to the acronym SNOOUT (a high SeNsitivity test rules OUT). And if the testing is positive, the provisional diagnosis of beta-lactam allergy is confirmed. (It is my hope that commercially available minor determinants of penicillin will become a reality so as to facilitate more precise and easily obtained diagnoses.) In their absence, one can skin test with available reagents and perform a challenge but with added risk that skin testing may be insensitive or that the challenge may cause anaphylaxis.

From a retrospective review over 10 years, the results from a comprehensive allergy-immunology evaluation of 73 patients were reported in the fourth paper in this issue.¹⁵ Based on assessments from the consultation, lab testing, and skin testing, 45 of 47 (96%) patients underwent subsequent uneventful anesthesia. The authors noted that the 2 patients who had a repeat anesthetic hypersensitivity reactions were found to have mast cell disorders based on serum tryptase >11.4 ng/mL.¹⁵

The incidence of intraoperative or procedure-related anaphylaxis has been estimated to be from 1:4000 to 1:25,000.⁵ Based on the 8-year survey in France, the median serum tryptase was 45 ng/mL (range 1-1020) in IgE-mediated anaphylaxis contrasted with 6 ng/mL (range 1-106) for non-IgE-mediated reactions, whereas atopy and asthma were not different between groups.¹⁶ Cardiovascular collapse was reported in 54.9% of IgE-mediated versus 10.6% of non-IgE-mediated anaphylaxis. The list of possible etiologic agents continues to grow, and the diagnostic testing and medical decision making are complicated. Comparable to management of asthma in the patients who are undergoing elective surgery, the allergist-immunologist can provide the

expert advice to improve patient care *in anticipation* of anesthesia and thereby minimize avoidable errors, patient harm and deaths. Thus, there can be improved quality and safety of health care at the patient and system level.

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