Current Knowledge and Management of Hypersensitivity to Perioperative Drugs and Radiocontrast Media

Karen S. Hsu Blatman, MD[a], and David L. Hepner, MD, MPH[b] *Chestnut Hill and Boston, Mass*

Perioperative anaphylaxis is an iatrogenic clinical condition, most often after anesthetic induction. Several mechanisms are implicated, including IgE- and non−IgE-mediated mechanisms. Perioperative anaphylaxis tends to be severe and has a higher mortality rate than anaphylaxis in other settings. This is partly due to factors that impair early recognition of anaphylaxis. Neuromuscular blocking agents, latex containing products, and antibiotics are the most common etiology. Chlorhexidine and dyes are increasingly culprits. The newest emerging cause is sugammadex, which is used for reversal of the effects of steroidal neuromusclar agents, such as rocuronium. Latex-induced allergy is becoming less common than in the 1980s due to primary and secondary prevention measures. Serum tryptase levels during the time of anaphylaxis and skin testing to suspected agents as an outpatient are necessary to confirm the diagnosis. Management includes epinephrine and aggressive fluid therapy. With radiocontrast media allergy, patients with a history of immediate hypersensitivity reactions to radiocontrast media should receive steroid and antihistamine premedication before re-exposure. Because IgE-mediated anaphylaxis to radiocontrast media is rare, there is a universal consensus that routinely skin testing all patients with a past reaction is not effective. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:587-92)

Key words: *Perioperative; Anaphylaxis; Anesthesia; Tryptase; Latex; Antibiotics; Beta-lactam; Cephalosporin; Chlorhexidine; Neuromuscular blocking agents; Skin test; Radiocontrast media; Gadolinium*

Perioperative anaphylaxis is a clinical condition with a presentation that ranges from mild symptoms to multiorgan failure with cardiac arrest and bronchospasm to hypotension. Recognition of perioperative anaphylaxis may be complicated by known effects produced by intravenous or inhalational anesthetic agents, the inability of an anesthetized patient to communicate early symptoms, and coverage of the patient by surgical drapes. Often the surgery or procedure is aborted, so diagnosing an etiology is crucial for the patient. In addition, trying to figure out the etiology may be difficult because the patient is receiving multiple medications at the same time.

EPIDEMIOLOGY OF PERIOPERATIVE ANAPHYLAXIS

The incidence of anaphylaxis during general anesthesia is approximately 1:2,000 to 1:20,000 from different countries.[1-8] The variability in estimates of incidence and prevalence reflects difficulties in determining the total number of anesthesia cases. Perioperative anaphylaxis occurs equally in girls and boys. It is more common in adult women compared with men. The proportion of IgE-mediated allergic reactions seems to be similar between countries, around 60% of all allergic reactions. The best data about perioperative anaphylaxis are from a series of multicenter French surveys, which began in the 1990s.[3] In the United States, preoperative antibiotics is the most common cause of perioperative anaphylaxis, accounting for 50% of IgE-mediated reactions,[8] compared with France, where it makes up only 12% to 15% of cases.[3] Beta-lactam antibiotics (penicillin and cephalosporins) cause IgE-mediated reactions.[8] A small study at Massachusetts General Hospital found cefazolin to be the most frequent cause of perioperative hypersensitivity reactions.[9] Most vancomycin reactions are non−IgE-mediated reactions and are related to the rate of infusion.[10]

In France, the leading causes of perioperative anaphylaxis are neuromuscular blocking agents (NMBAs) (almost 70%), followed by latex and antibiotics (used for antimicrobial prophylaxis).[3] It has been hypothesized that the increased incidence of immediate hypersensitivity in women would be due to a possible cross-sensitization with quaternary ammonium ion-containing compounds such as cosmetics and other personal care products.[3] However, this hypothesis is not yet confirmed. NMBAs can also cause nonspecific mast cell release.[11] A new anaphylactoid mast cell receptor MrgprB2 has been discovered that is responsible for reactions to NMBAs carrying tetrahydroisoquinoline motifs such as atracurium. Patients presenting anaphylaxis during anesthesia with negative skin testing may present direct mast cell activation through this newly discovered receptor.[12]

ETIOLOGIES OF PERIOPERATIVE ANAPHYLAXIS

Penicillins and cephalosporins account for most perioperative cases of anaphylaxis in the United States.[8,9,13] Those patients with IgE-mediated allergy to penicillins may be reactive to the

[a]Division of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Chestnut Hill, Mass
[b]Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass
No funding was received for this work.
Conflicts of interest: K. S. Hsu Blatman is employed by the Brigham and Women's Hospital. D. L. Hepner serves as an editor for UpToDate.
Received for publication November 7, 2016; revised February 16, 2017; accepted for publication March 21, 2017.
Corresponding author: Karen S. Hsu Blatman, MD, Division of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 850 Boylston Street, Suite 540, Chestnut Hill, MA 02467. E-mail: khsublatman@partners.org.
2213-2198

http://dx.doi.org/10.1016/j.jaip.2017.03.016

Abbreviation used
NMBA- Neuromuscular blocking agent

beta-lactam ring structure that is common to all penicillins, except in the case of amoxicillin, where the likely culprit is the side chain. In the United States, most penicillin-allergic patients are sensitive to the beta-lactam core. It has been stated that the risk of cephalosporin cross-sensitivity in penicillin-allergic patients may be as high as 10%.[14] One of the reasons why the actual risk may be lower is that cephalosporins produced before 1980 were known to have been contaminated with trace amounts of penicillin. Furthermore, most of the reactions are rashes that are non-IgE-mediated. Another reason for the lower risk of cross-reactivity is that only first-generation cephalosporins share a similar structural side chain with penicillin.[15]

Historically, latex accounted for approximately 20% of perioperative anaphylaxis cases.[3] The incidence of latex allergy has decreased because of primary prevention measures such as the use of powder-free latex gloves and nonlatex surgical material (such as drains and catheters) in the operating room. Reactions to latex tend to occur later in the procedure, usually more than 30 minutes after the start of the procedure or at the time of maximal glove contact with mucosa. Latex allergy is more likely in subjects with repeated exposure to latex gloves or catheters, including health care workers, and in children with spina bifida.[16] If a patient has a latex allergy, it is recommended that the procedure be performed as the first case, when the levels of latex aeroallergens are the lowest. Secondary prevention would also include providing a latex-free room during surgery.[17,18]

Chlorhexidine is a topical antiseptic and surgical scrub that is increasingly noted in the literature to cause allergic reactions, making up to 5% to 10% of IgE-mediated perioperative anaphylaxis.[19-21] Increased exposure has probably contributed to greater sensitization and the emergence of IgE-mediated anaphylaxis. Antiseptic solutions applied to surgical fields are the most common exposure, but it is important to consider other types of exposure, such as chlorhexidine-impregnated central venous catheter tips.

Dyes also have been implicated. Isosulfan blue and methylene blue have been used to identify sentinel lymph nodes.[22,23] Isosulfan blue has a warning in the package insert of a risk of anaphylaxis of 1% to 3%. Reactions are usually delayed, and are long lasting.

One of the newest emerging triggers of perioperative anaphylaxis includes sugammadex, which is a reversal agent for aminosteroid NMBAs.[24] This agent was approved by the US Food and Drug Administration in December 2015. Anaphylaxis presents at the end of the case, when sugammadex is used for reversal. The first reports came from Japan, where it has been used for many years. Sugammadex has a higher affinity for rocuronium than vecuronium, and no affinity for succinylcholine.[25] There are case reports of anaphylaxis caused by sugammadex alone, and reports of patients reacting to a sugammadex-rocuronium complex.[25,26] Interestingly, patients may be allergic to a sugammadex-rocuronium complex, but not to each agent alone. Anaphylaxis can happen on first exposure due to environmental sensitization by prior exposure to foods or pharmaceuticals containing cyclodextrins.[24,26] The estimated incidence is 29 per 1,000,000 population and the mechanism is IgE mediated.[24] Sugammadex anaphylaxis leads to an increase in the serum tryptase and there is no commercial IgE assay.

Anaphylaxis to sedative-hypnotic drugs such as barbiturates and propofol and opioids are rarely reported. Typically, opioids cause limited cutaneous reactions due to histamine release.[27] Intravenous barbiturates used to be widely used in anesthesia. Most reactions by barbiturates are IgE mediated, although direct mast cell activation has also been described.[28]

Propofol, a nonbarbiturate medication, is the induction agent most widely used in the United States. Propofol was initially solubilized in Cremophor (polyethoxylated castor oil), a vehicle that may cause non—IgE-mediated anaphylaxis.[29] The vehicle was then changed to a soybean oil emulsion with egg. Although allergies to egg or soy are listed as a possible contraindication to use, most egg and soy allergic subjects can tolerate propofol.[30,31] That is because the refined soy oil, which is present in propofol, is safe for people with soy allergy because the allergenic proteins are removed. Although patients allergic to eggs demonstrate immediate hypersensitivity reactions to egg white proteins, propofol's egg lecithin is from the egg yolk.[15]

Benzodiazepines are nonbarbiturate sedatives and induction agents. Allergic reactions to benzodiazepines are extremely rare.[13]

Both ionic and nonionic radiocontrast media can be responsible for immediate reactions. Direct histamine release is the most common mechanism for the radiocontrast media reactions, as well as complement activation. It is typically not IgE mediated, although there is increasing literature of some immediate reactions being caused by an IgE-mediated mechanism.[32,33] Since the introduction of nonionic radiocontrast media, immediate adverse reactions have decreased.[34,35] Anaphylaxis to gadolinium-based chelates used in magnetic resonance imaging may also occur, although less frequently than radiocontrast media.[36] Despite common misperceptions, radiocontrast media reactions are not related to shellfish allergies.[37] In addition, there is no cross-reactivity between povidone iodine and iodinated contrast agents, as the cause of the allergy is not the iodine.[15]

Other medications and agents can also be implicated in perioperative anaphylaxis. These agents include nonsteroidal anti-inflammatory drugs,[38] gelatin,[39] and blood tranfusions.[40] Local anesthetic reactions are rare and most are nonimmunologic in origin. Most reported reactions are due to intravenous injection or systemic absorption of local anesthetic or epinephrine. Immunologic reactions to local anesthetic are more likely to be a type IV cell-mediated reaction (delayed hypersensitivity) than a type I IgE-mediated reaction.[41,42] Type I IgE-mediated reactions to local anesthetics are due to the para-aminobenzoic acid metabolite from esters (eg, procaine) or the preservative methylparaben. There is no cross-reactivity among amide (eg, lidocaine or bupivacaine) and ester local anesthetics, and cross-reactivity is more common among esters than between amides. Most local anesthesia is performed with amides. Skin test has a 97% negative predictive value.[43]

CLINICAL PRESENTATION OF PERIOPERATIVE ANAPHYLAXIS

Perioperative anaphylaxis usually occurs within minutes of anesthetic induction. Cardiovascular and respiratory compromise are the hallmarks of perioperative anaphylaxis.[44] Cardiovascular collapse may be the first detected manifestation in up to 50% of the cases.[13] Cutaneous symptoms may be absent or may not be