CME Anaphylaxis During Cardiac Surgery: Implications for Clinicians

Jerrold H. Levy, MD*

N. Franklin Adkinson, Jr., MD†

During surgery, patients are exposed to multiple foreign substances including anesthetic drugs, antibiotics, blood products, heparin, polypeptides (aprotinin, latex, and protamine), and intravascular volume expanders, which have the potential to produce life-threatening allergic reactions termed "anaphylaxis." The hallmark of perioperative anaphylaxis is acute cardiovascular and pulmonary dysfunction. Patients undergoing cardiac surgery have extensive monitoring that permits rapid recognition and treatment when anaphylaxis occurs. Initial, smaller doses of drugs, often called test doses, administered before the therapeutic dose may produce anaphylaxis, and so clinicians need to be prepared to treat reactions if they occur. Institution of cardiopulmonary bypass for hemodynamically unstable patients can be a life-saving maneuver, and should be considered in patients with refractory cardiovascular dysfunction. Arginine vasopressin should also be considered for patients with vasodilatory shock. In this review, we focus on recent concepts in understanding the incidence and management approaches for patients at risk for anaphylaxis in the operating room setting, with an emphasis on cardiac surgical patients.

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During cardiac and noncardiac surgery, patients are exposed to multiple foreign substances including anesthetic drugs, antibiotics, blood products, heparin, polypeptides (aprotinin, latex, and protamine), intravascular volume expanders, and other foreign substances that have the potential to produce life-threatening allergic reactions termed "anaphylaxis." Anesthesiologists are among the few physicians who personally administer parenteral agents, and they need to be able to manage the acute cardiopulmonary dysfunction that may follow. The term anaphylaxis was first coined by Richet and Portier over a century ago (ana—against, phylaxis—protection) to describe the marked shock and resulting death that sometimes occurred in animals immediately after a second challenge with a foreign substance called an antigen.[1] Anaphylaxis is now defined clinically as any severe, systemic allergic reaction of rapid onset, which may cause death or other adverse outcomes. Although classically attributed to immunoglobulin (Ig)E antigen-mediated reactions, it may also be precipitated by IgG-antigen interaction, complement activation, and direct activation, but these distinctions are of marginal utility to the clinician faced with the diagnosis and management of the patient presenting with the clinical syndrome.[2–4] "Anaphylactoid " is a term used to describe reactions that produce a similar clinical picture as anaphylaxis but are not IgE-mediated.[2–4] Currently, if IgE-mediated and non-IgE-mediated mechanisms are a possible cause, the term "anaphylactic" is the preferred term used to describe the reaction rather than anaphylactoid.[2–4]

Anaphylaxis is also an acute, unpredictable adverse drug reaction (ADR).[5,6] Although anaphylactic reactions account for only a small proportion of reported ADRs, they may be associated with substantial morbidity, mortality, and increased health care costs.[7,8] The purpose of this review is to discuss recent and new concepts in understanding the incidence, and management approaches for patients at risk for anaphylaxis in the perioperative setting, with a focus on cardiac surgical patients. The latter group is often exposed to multiple agents, including polypeptides and blood products, and is a unique group of patients that warrant special consideration.

Etiology

Allergic reactions and anaphylaxis have the same pathophysiologic mechanisms; that is, they are both immune-mediated due to prior sensitization. The term "allergy" was introduced in 1906 by von Pirquet, who recognized that in hypersensitivity reactions antigens

From the *Emory University School of Medicine, Atlanta, Georgia; and †Johns Hopkins Asthma & Allergy Center, Division Allergy & Clinical Immunology, Baltimore, Maryland.

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Jerrold H. Levy is a consultant to Bayer, Organon. N. F. Adkinson is a consultant for Bayer.

Address correspondence to Jerrold H. Levy, MD, Emory Hospital, 1364 Clifton Rd., Atlanta, GA 30322.

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Table 1. Mechanisms of Anaphylaxis

Triggering event	IgE-antigen	IgG-antigen	Direct activation	Direct activation
Mechanism	Cellular signaling via phospholipase C	Complement activation and anaphylatoxin generation	Degranulation vascular effects	
Inflammatory cells	Mast cells Basophils	Neutrophils Thromboxane	Cutaneous mast cells	Pharmacologic effects
Mediators	Histamine Tryptase Prostaglandins Leukotrienes Kinins Nitric oxide	Proteases Oxygen free radicals	Histamine ?Tryptase	Direct and indirect pharmacologic effects
Clinical manifestations	Hypotension Vasodilatory shock Bronchospasm Wheezing Urticaria Cardiac arrest	Hypotension Acute pulmonary vasoconstriction Right ventricular failure Cardiac arrest	Hypotension Flushing Urticaria	Hypotension
Dose dependent	No	No	Yes	Yes
Therapy	Volume Catecholamines Antihistamines Corticosteroids Vasopressin CPB for refractory shock	Catecholamines Corticosteroids Therapy for acute right ventricular dysfunction CPB for refractory shock	Slow administration Volume Catecholamines Antihistamines	Treat hypotension

Ig = immunoglobulin; CPB = cardiopulmonary bypass.

(also called allergens) had induced changes in reactivity.[5,6] Over time, the term allergy has changed, and is now frequently used synonymously with IgE-mediated allergic disease.[5,6] The basis of acute allergic reactions, including anaphylaxis, is the release of inflammatory mediators by mast cells and basophils when an allergen interacts with membrane-bound IgE.[5,6] Also, as part of allergic mechanisms, patients may be sensitized to a foreign substance by variable immune responses, including IgG and/or IgE.[5,6,9,10] This is important because multiple inflammatory pathways can trigger anaphylaxis, as noted in Table 1. Mast cell/basophil activation by IgE, complement activation by IgG, and nonimmunologic and direct complement activation can also produce similar clinical responses in the cardiopulmonary system.

Anaphylaxis and allergy classically results from the release of associated mediators, membrane-derived lipids, cytokines, and chemokines when an allergen interacts with IgE that is bound to mast cells or basophils by a high-affinity IgE receptor.[5,6,11] When the offending antigen and IgE bind on the surface of mast cells and basophils, preformed storage granules are released that contain histamine and tryptase. Other membrane-derived lipid mediators, including leukotrienes, prostaglandins, and other factors are also released.[5,6,11] These mediators have a critical role in anaphylaxis and allergy, and form the basis for the clinical responses. It is not known why some individuals develop severe cardiopulmonary dysfunction after reexposure to an antigen instead of minor cutaneous reactions but it may relate to systemic compared with local release of inflammatory mediators.[7,8] Interestingly, the original description of anaphylaxis from sea anemone toxin is an IgG-mediated response.[12] IgG mechanisms will be further discussed in later in this article. The focus of this review is on agents producing anaphylaxis and management strategies.

Clinical Manifestations and Diagnosis

Acute cardiopulmonary dysfunction is the hallmark of anaphylaxis. Intraoperative anaphylaxis often presents with hypotension and cardiac arrest.[3,4,13] Bronchospasm and upper airway edema (angioedema) can also occur. However, many of these manifestations can also be experienced by cardiac surgical patients who have impaired reserve and preexisting biventricular failure. Angioedema can occur after administration of angiotensin converting enzyme inhibitors and from other causes.[14,15] Although cutaneous manifestations may appear intraoperatively, they may be missed, as patients are often covered. Patients may also have life-threatening cardiopulmonary collapse without cutaneous manifestations.[13] Thus, the diagnosis of intraoperative anaphylaxis is problematic in the perioperative period.[16–18]

Airway and respiratory manifestations of intraoperative anaphylaxis include wheezing and increased airway pressures during positive pressure ventilation. Bronchospasm and wheezing can also develop after endotracheal intubation in patients who have asthma, reactive airway disease, or who smoke.[19] Patients with a history of asthma have airway inflammation and reactive airways sensitive to airway manipulation.[20,21]

Bronchospasm is thought to be increased after tracheal intubation in patients with reactive airway disease (asthma) with reported frequencies as high as 30%.[19,22,23]

Cardiovascular manifestations of anaphylaxis include arrhythmias (supraventricular, ventricular, and asystole), hypotension, and cardiac arrest. Patients may also manifest vasodilatory shock (low systemic vascular resistance) and acute pulmonary vasoconstriction with right heart failure. Allergy practice guidelines suggest that, in adults, the diagnosis of anaphylaxis is a systolic blood pressure <90 mm Hg or >30% decrease from baseline after exposure to known allergens.[4] Unfortunately, the cardiovascular changes of anaphylaxis can also have other causes in cardiac surgical patients, often making the clinical diagnosis difficult. In addition, most anesthetics cause vasodilation, hypotension, and potentially cardiopulmonary dysfunction due to direct and indirect effects on sympathoadrenergic responses.[24,25]

The most important consideration in diagnosing anaphylaxis is to suspect a reaction. Acute cardiopulmonary dysfunction after drug or blood product administration is important to consider as a potential anaphylactic reaction.[3,4] Multiple drugs are administered in cardiac surgical patients; however, certain drugs are a greater risk for producing anaphylaxis, as will be discussed.[16–18]

Agents Implicated

Although any molecule can produce anaphylaxis, the drugs typically associated with producing perioperative anaphylaxis include antibiotics, blood products, neuromuscular blocking drugs (NMBDs), polypeptides (aprotinin, latex, and protamine), and intravascular volume expanders.[16] Overall, calculating the incidence of anaphylaxis is difficult because most reporting is retrospective. However, during surgery, the risk of anaphylaxis is reported to be between 1:3500 and 1:20,000, with a mortality rate of 4% and an additional 2% surviving with severe brain damage.[3,4] More recent data suggest the incidence of perioperative anaphylaxis is 1 in 10,000–20,000.[26] Cardiac surgical patients are an increased risk group, because of the multiple blood products, polypeptides, and potential for impaired cardiovascular function.

In cardiac surgery, Levy reported eight reactions in 1743 patients over a 12-mo period for a rate of 0.46%, with no mortality; causative agents were protamine ($n = 4$), vancomycin ($n = 2$), blood, and metocurine.[27] Ford et al. reported 23 patients who developed anaphylaxis during cardiac surgery in Australia. These patients were from a database of 1346 patients investigated for reactions during anesthesia evaluated over a 20-yr period, of which 640 patients had immunologically proven anaphylaxis.[28] Antibiotics ($n = 7$), colloid intravascular volume expanders ($n = 6$), and muscle relaxants ($n = 4$) were most often implicated, as were blood products ($n = 2$), protamine ($n = 3$), and morphine ($n = 1$).[28]

In general surgery, Mertes et al. reported 789 patients evaluated for anaphylaxis in France. Allergic reactions were confirmed in 518 patients (66%) by immunologic testing. NMBDs ($n = 306$, 58.2%), latex ($n = 88$, 16.7%), and antibiotics ($n = 79$, 15.1%) were the agents most commonly reported. NMBDs were most often implicated, with rocuronium ($n = 132$, 43.1%) and succinylcholine ($n = 69$, 22.6%) the drugs most often reported.[18] From Norway, 83 intraoperative reactions were evaluated by case history, tryptase measurements, specific immunoassays, and skin tests; IgE-mediated anaphylaxis was established in 71% of cases, with NMBDs the most frequent allergen (93.2%) followed by latex (3.6%).[29] They estimated the incidence of reactions to NMBDs at 1 of 5200 general anesthetics (95% confidence intervals 1 of 3000 to 1 of 14,000).

The overall risk of anaphylaxis depends on patient exposure to different agents. Perioperatively, the cardiac surgery patient receives specific foreign substances, including antibiotics, blood products, heparin, NMBDs, protamine, and potentially aprotinin. This high acuity patient is different from the one undergoing a simple outpatient procedure. This discussion will focus on proteins and drugs most often implicated in cardiac surgical patients, and review updated recommendations regarding patient management.

Antibiotics

Antibiotics are routinely administered in surgical patients and include a cephalosporin or vancomycin. Estimates of the prevalence of antibiotic allergy vary widely, and often these patients present with cutaneous manifestations.[7] The incidence of anaphylaxis with penicillins is low, occurring in 0.004%–0.015%, but this widely quoted reference is old.[30] Data on anaphylaxis due to cephalosporins suggest that it is uncommon, occurring from 0.0001% to 0.1%.[31] The risk of anaphylactic reactions to vancomycin are rare, but this antibiotic is a potent histamine-releasing drug that can cause severe hypotension and flushing.[32,33]

One perplexing problem is how to manage the patient with a history of penicillin allergy when the surgeon requests cephalosporin administration. Some consider that cross-reactivity to cephalosporins among penicillin-allergic patients is high, and suggest choosing another drug. This clinical practice most likely evolved from case reports from 40 yr ago[34] of anaphylaxis after first-generation cephalosporins together with *in vitro* and skin testing, which showed extensive cross-reactivity between penicillins and first-generation cephalosporins. However, the clinical relevance of this *in vitro* cross-reactivity was never demonstrated.[34] More recent publications document the risk of acute cephalosporin reactions among patients with positive penicillin skin tests as about 4.4%, compared with

0.6% among patients with negative penicillin skin tests.[33] Anaphylactic reactors were selectively omitted from these open studies. Further, an allergic reaction to a cephalosporin may occur independently of prior penicillin sensitization. In the United Kingdom from 1992 to 1997, first-generation cephalosporins were responsible for half of the fatal anaphylactic reactions to antibiotics, and half of these patients had histories of penicillin allergy.[35] One authority has concluded that most patients who have a history of penicillin allergy will tolerate cephalosporins, but that indiscriminate administration cannot be recommended, especially for patients who have had serious acute reactions to any β lactam antibiotic.[7] Penicillin skin testing, when available, can be useful in identifying the 85% of patients with histories of penicillin allergy who no longer have (or never had) IgE antibodies to major and minor determinants, and are therefore at negligible risk of cephalosporin reactions. For the remaining patients who are skin test positive, gradual escalation of the first dose of a cephalosporin under careful observation will further mitigate against uncommon but potentially serious acute reactions.

If a patient's penicillin allergy history is consistent with anaphylaxis and penicillin skin testing is unavailable, then cephalosporins should be used with caution, with graded dose escalation of the first dose. A patient who has experienced an allergic reaction to a specific cephalosporin should probably not receive that cephalosporin again. The risk of an acute reaction when a different cephalosporin is administered appears to be low, but systemic evaluations of reaction risks when administering other cephalosporins or β lactam antibiotics to patients with IgE antibodies to a particular cephalosporin are not available. Unfortunately, patient histories are often unreliable in this circumstance.

Blood Products

Blood product administration exposes patients to both humoral and cellular antigens that can cause anaphylactic and other immune-mediated adverse events, including anaphylaxis, transfusion-associated acute lung injury (TRALI), and acute hemolytic transfusion reactions.[36–39] In 1613 adverse transfusion reactions evaluated in one center over 9 yr, allergic transfusion reactions accounted for 17% (273 of 1613) of the transfusion reactions. Severe allergic reactions (considered anaphylaxis) were observed in 21 patients (7.7% of allergic reactions, or 1.3% of all transfusion reactions).[26] Of note (9.5%) patients did not have skin manifestations. Allergic transfusion reactions were estimated to occur in approximately 1 in 4124 blood components transfused, or 1 in 2338 transfusion episodes.[35]

Transfusion-related adverse events occur often, and serious adverse events are estimated to occur in 0.1% of red cell and 0.04% of platelet transfusions.[40] Transfusion-associated respiratory distress can be related to fluid overload, allergic reactions, or TRALI. Estimated rates of TRALI range from 1 in 432 to 1 in 88,000 transfused platelet units and 1 in 4000 to 1 in 557,000 transfused red blood cell units.[41] This variability reflects the difficulty diagnosing and the underreporting that likely occurs. Hemolytic transfusion reactions can be immediate and life-threatening or delayed with minimal clinical consequences (e.g., serologic conversion).[36] Current estimates suggest that the wrong unit of blood is administered 1 in 14,000 (range, 1 in 12,000 to 1 in 19,000 U) of which transfusion of 1 in 33,000 to 1 in 100,000 U involves ABO incompatibility.[40,42] Catastrophic, acute hemolytic reactions occur in every 33,000–500,000 U transfused; however, they can be fatal in 2%–6% of cases and account for at least 16 deaths every year (i.e., 1 in 800,000 U transfused) in the United States and can present with shock.[42–45]

TRALI is an important life-threatening acute hypersensitivity response to blood. Patients present with acute respiratory failure, bilateral pulmonary edema, hypoxemia, and hypotension[46] and manifest with interstitial and alveolar infiltrates. The onset after the transfusion is within 1–6 h, and usually within 1–2 h.[36,46,47] The mortality rate from TRALI ranges from 5% to 25%. Although most patients recover within 72 h, death is due to acute respiratory failure. Autopsy specimens have demonstrated pulmonary findings, including widespread leukocyte infiltration with interstitial and intraalveolar pulmonary edema, hyaline membrane formation, and destruction of the normal lung parenchyma.[46] TRALI may be significantly under diagnosed and confused with other potential problems in a multiply transfused, critically ill cardiac surgical patient. It can develop after any blood component transfusion, although fresh frozen plasma and platelets are most commonly implicated.[46] Although various mechanisms for TRALI are reported, current thinking considers it to be an immune-mediated event in which the pathologic antibodies are typically from the donor rather than the recipient. These antibodies include HLA-specific agglutinins or leukoagglutinins in the plasma of the donors of implicated blood components.[46] The exact frequency of TRALI is unknown; however, Food and Drug Administration (FDA) data suggest that it is the third most common cause of transfusion-associated deaths, accounting for 9% of reported cases.[46] Multiple immune and nonimmune mechanisms have been implicated in its pathophysiology, including the potential need for an initial priming event for a reaction to occur.

Heparin

Unfractionated heparin is commonly used in cardiac surgical patients. After heparin administration, IgG antibody formation is common. IgG antibodies are formed that bind heparin–PF4 complexes on the

platelet surface to form immune complexes. The platelets in turn are activated by the Fc domain of the IgG in the immune complexes. Activated platelets release microparticles that promote thrombin formation and thrombosis.[48] This is the clinical manifestation of heparin-induced thrombocytopenia (HIT). Approximately 7%–50% of heparin-treated patients generate heparin–PF4 antibodies.[49] Anaphylactic reactions to heparin can occur but, based on the antigenicity of heparin, are surprisingly infrequent.[50–57] IgG may be an important mechanism for anaphylaxis in these patients, and may explain the combined occurrence of HIT and hypersensitivity.[51] TRALI and HIT share many similar characteristics in their pathophysiologic mechanisms.

NMBDs

In recent years, NMBDs, especially steroid-derived drugs, have been reported as potential causative drugs of anaphylactic reactions during anesthesia. NMBDs have unique structural characteristics as antigens. Most nonpeptide drugs are small molecular weight compounds of <1000 Da that require binding to host proteins (haptenization) to become antigens.[58] NMBDs are highly charged biquarternary molecules that can function as complete antigens.[59] Anaphylaxis to NMBDs is rare in North America but has been reported more often in Europe. Although suggestions have been made that this is due to under-reporting, the severity of anaphylaxis and its tendency to produce adverse outcomes make this unlikely.[60] Analysis of adverse drug events reported to the United States FDA in the United States did not indicate a difference in risk of anaphylaxis with rocuronium versus vecuronium.[61] One way to explain this divergent perspective is to understand how the diagnosis is made. Steroid-derived drugs induce positive weal and flare responses independent of mast cell degranulation after intradermal injection,[62,63] which is likely due to a direct effect on the cutaneous vasculature.[64] In volunteers, 50% and 40% of the subjects had a positive skin reaction to prick testing with undiluted rocuronium and vecuronium, respectively.[64] Therefore, as prick tests are often used for authenticating NMBDs as causative, anaphylaxis estimates attributed to these drugs may be inflated.

Polypeptides

Aprotinin

Aprotinin is a bovine-derived broad spectrum protease inhibitor administered for its blood-sparing effects. It is a protein with a molecular weight of 6512 Da infused after anesthesia induction, but is also present in some topically applied fibrin glue preparations, as listed in Table 2. The risk of anaphylaxis is reported as 2.7% in reexposed patients from several studies.[65–68]

Beierlein et al. reviewed literature from 1963 to 2003 and noted 124 cases of aprotinin-induced anaphylaxis reported in 61 publications with 11 deaths.[65] The reexposure interval was <3 mo in 72% (38 of 53 patients). Dietrich et al. reported adverse reactions after reexposure in cardiac surgery between 1988 and 1995.[66] There were 248 reexposures to aprotinin in 240 patients: 101 adult and 147 pediatric cases with a reexposure time of 344 days (interquartile range, 1039). They noted seven reactions to aprotinin (2.8% incidence). Reexposure <6 mo had a higher incidence of adverse reactions (5 of 111–4.5% vs 2 of 137–1.5%, $P < 0.05$), and two patients reacted to a 10,000 KIU test dose. Jacquiss et al. reported a retrospective review of aprotinin reactions in children undergoing cardiac surgery ($n = 865$) that included 681 first exposures, 150 second exposures, and 34 third or more exposures.[69] Reactions were classified as mild (generalized cutaneous erythema) or severe (unexplained cardiopulmonary instability after aprotinin exposure), occurring in 7 of 681 first exposures (1.0%; 2 minor, 5 severe) and 2 of 150 s exposures (1.3%—both severe). In third or more exposures, there was one reaction (2.9%; severe). Skin testing had a negative predictive value of 98.9% and a positive predictive value of 20%. Antiaprotinin IgE was undetectable in 7 of 8 reactor cases tested. No adverse sequelae were attributed to aprotinin reaction.

Table 2. Aprotinin Containing Tissue Sealants/Fibrin Glues

Tisseel® (US)
Boheal (Japan)
Beriplast (Europe, South America)
Hemaseel (Canada)
Tissucol, TachoComb (Europe)

Scheule et al. evaluated aprotinin-specific antibodies preoperatively in patients scheduled for cardiac surgery.[70] Sera of 520 consecutive patients were collected preoperatively and screened retrospectively for aprotinin-specific IgG using an enzyme-linked immunosorbent assay. Positive sera were also analyzed for aprotinin-specific IgA (enzyme-linked immunosorbent assay) and IgE (fluorescence enzyme immunoassay). The histories of all patients were reviewed with a focus on aprotinin preexposure. Of 520 patients, 22 (4%) had specific IgG, and 3 patients had a documented aprotinin preexposure suggesting exposure from tissue sealants. Of 448 patients receiving aprotinin intraoperatively, 15 had preformed antibodies. The only patient presenting with severe anaphylaxis was positive for both IgG and IgE, and had had a recent exposure within 3 mo.

Dietrich et al. evaluated 121 cases of aprotinin reexposure in cardiac surgery in a prospective observational study.[67] Antiaprotinin IgG and IgE antibody levels were measured pre- and postoperatively. Preoperative antibodies to aprotinin were detected as IgG in 18 patients and IgE in 9 patients.[67] The three patients experiencing an anaphylactic reaction after aprotinin exposure had the highest preoperative IgG concentrations ($P < 0.05$), whereas preoperative IgE measurements were increased in 2 of 3 reactive patients, but also in three nonreacting patients. This

finding suggests that quantitation of IgG to aprotinin may identify patients at risk for aprotinin reexposure. IgG also increases with IgE, reported in other studies of anaphylaxis to protamine, and IgG is easier to measure. Also, data from Scheule et al.[70] and Dietrich et al.[67] suggest that exposure history alone may not be useful to identify patients at risk for protamine reactions because occult sensitization may occur, perhaps via fibrin glue exposure.

Also of importance is that an aprotinin test dose may also cause anaphylaxis.[67] After 248 aprotinin reexposures there were seven reactions; four had received test doses, and two showed no response to the test dose, but developed anaphylaxis during the initial loading dose.[66] Additional reports note that 3 of 121 patients developed anaphylaxis after aprotinin reexposure, and 2 of 3 patients did not react to the test dose, but both developed anaphylaxis within 5 min after the initial loading dose.[67] The three patients had also been pretreated for anaphylaxis with antihistamines and corticosteroids, therapy that may have modified the onset of the reactions.[67] Thus, even after an uneventful test dose, an anaphylactic reaction can occur. The updated aprotinin injection United States package insert (12/06) notes that fatal reactions have occurred with an initial (test) dose, as well as with any of the components of the dose regimen and in situations where the initial (test) dose was tolerated.

Thus, the risk for anaphylaxis is increased in patients with prior aprotinin exposure, and a history of exposure should be determined before aprotinin administration. The risk for a fatal reaction appears to be greater on reexposure within 12 mo. Also, test doses and initial loading doses should only be performed when the conditions for rapid cannulation are present with reexposure. On November 5, 2007, the marketing of aprotinin was suspended pending the review of a Canadian study. This information can be found at the FDA website www.fda.gov/cder/drug/infopage/aprotinin/default.htm.

Latex

Latex is another important cause of perioperative anaphylaxis. Latex anaphylaxis appears to have reached a plateau, perhaps due to decreased presence of latex and surgical products and labeling warnings about the presence of latex in medical products enforced by the FDA.[3,4] Latex allergy should be considered in patients who develop intraoperative anaphylaxis after surgical intervention without another identifiable cause.[71] Latex (rubber) hypersensitivity is a significant medical problem, and certain groups are at higher risk of reaction. These include health care workers, children with spina bifida and genitourinary abnormalities, workers with occupational exposure to latex, and others, as listed in Table 3.[2,71]

Table 3. Patients at Risk for Latex Allergy

Allergy to bananas, avocados, kiwis, mangoes, stone fruits (stone fruits include cherries, plums, apricots, nectarines, and peaches)
Chronic care (latex-based products)
Spina bifida with multiple operations
Intraoperative anaphylaxis with undetermined etiology
Repeated surgical procedures (>9)
Intolerance to latex-based products
Health care workers

Protamine

Protamine sulfate is a polypeptide with molecular weights ranging from 4500 to 5000 Da that is used to reverse heparin anticoagulation and retard the absorption of insulin, often as neutral protamine Hagedorn (NPH). The polypeptide is extracted from salmon milt in a protein purification process. Protamine is a series of arginine-rich basic proteins (also called histones) in fish cell nuclei that provide structural integrity to chromatin.[72] The basic guanidine groups of arginine allow it to bind to the acidic heparin molecule to reverse its activity.[73]

Protamine can produce multiple adverse reactions after IV administration, including rash, urticaria, bronchospasm, pulmonary hypertension, or systemic hypotension leading at times to cardiovascular collapse and death. Multiple mechanisms for protamine reactions have been suggested and the literature is confusing regarding its adverse hemodynamic effects and description of reactions. The direct myocardial effects of protamine in humans are variable.[74–76] Although the rate of administration has been suggested to cause protamine reactions, this is also variable, occurring with bolus administration. However, more than 60% of North American clinical practices administer this drug over 5–10 min.[77]

Severe life-threatening cardiovascular dysfunction in humans after protamine administration is consistent with anaphylaxis, although multiple reactions have been described, including myocardial depression,[78] cardiac arrest,[79] bronchospasm,[80] pulmonary hypertension,[81,82] pulmonary edema with loss of capillary membrane integrity,[83–85] and vasodilatory shock.[86] Patients at risk for protamine reactions are those who have been sensitized from prior exposure. Patients who receive protamine containing insulins, including NPH insulin, are at the greatest risk. Stewart et al. reported in 1984 that 4 of 15 NPH diabetics (27%) had anaphylaxis after protamine reversal of heparin after cardiac catheterization.[87] We reported an incidence of 0.6% (1 of 160) to 2% (1 of 50) in NPH insulin-dependent diabetics undergoing cardiac surgery, a rate 10–30 times more than other patients from 4796 patients evaluated.[81,86]

Another group suggested to be at increased risk for protamine reactions are men who have undergone vasectomies, because they may develop antibodies to sperm.[88–90] The testis and sperm are immunologically isolated organs. After vasectomy, the blood–testis barrier exposes the tissues, and 55%–73% of men with vasectomies develop antibodies to sperm antigens[88,91,92] of this group, 20%–33% develop autoantibodies

against protamine.[93] Protamine reactions in vasectomized men have been reported.[94] We did not observe any clinical reactions in a prospective evaluation of 16 vasectomized patients undergoing cardiac surgery with protamine reversal of heparin, but these are small numbers.[86]

Fish-allergic patients are thought to be at a theoretical risk for protamine reactions. Protamine is produced from salmon or other fish testes; however, patients who eat fish consume fish muscle and not testes. Evidence supporting the increased risk for protamine reactions in fish-allergic patients is limited to case reports.[95,96] We did not observe any clinical reactions to protamine in six patients studied over a 3-yr period, who had a history of fish allergy, but these numbers are small.[86] However, patients with multiple allergies may be at risk for hypersensitivity to other agents, and fish allergy or shellfish allergy may reflect their hypersensitivity status and not cross-reactivity to protamine.

Previous exposure to IV protamine in vascular or cardiac procedures may increase the risk of a reaction on subsequent protamine administration. This may explain variability in the incidence of reactions reported in different studies.[97] Weiler et al. reported an incidence of 10.7% of protamine reactions in 243 patients after cardiopulmonary bypass (CPB) and noted prior protamine exposure from insulin or prior surgery were risk factors.[97]

The mechanisms by which acute protamine reactions occur are variable, because protein antigens may produce multiple immunologic and nonimmunologic responses. Studies have implicated direct mast cell activation, complement activation, and antibody formation as the pathophysiology of protamine reactions, as previously reviewed. Protamine can degranulate human cutaneous mast cells *in vitro* to release histamine; however, this occurs at concentrations not achieved clinically.[98] Studies using human basophils and human lung mast cells have not demonstrated significant histamine release from protamine or protamine–heparin complexes.[81,99]

Protamine can also activate the complement system by different mechanisms. When protamine binds heparin, a polyanionic–polycationic complex is formed that activates complement generating the anaphylatoxins C3a and C5a.[100,101] Morel et al. reported transient neutrophil sequestration in the pulmonary vasculature after rapid protamine administration, a mechanism that may be responsible for some of the hypotensive reactions observed with bolus administration.[102] However, there is conflicting evidence regarding the adverse hemodynamic effects of protamine in humans, especially with rapid administration.[103]

Pulmonary vasoconstriction, also called "catastrophic pulmonary vasoconstriction," has been reported.[81,82,104] This type of reaction is mediated by complement activation. However, this occurs by protamine–heparin interaction,[100,105] or through protamine and complement fixing and antiprotamine IgG antibody interaction.[82,106] The pulmonary hypertension results from C5a-mediated thromboxane generation.[102,104,107] Protamine may also inhibit the action of plasma carboxypeptidase N, which cleaves the C-terminal arginine residue from the complement anaphylatoxins and bradykinin, converting them to their less active des arg metabolites.[108] Pulmonary vasoconstriction occurs as an occasional idiosyncratic reaction in humans. If protamine–heparin activation of the complement cascade were the primary mechanism for hypotension or pulmonary hypertension, then the incidence of reactions should be more frequent. Although multiple pathways can be activated after protamine administration, life-threatening reactions are relatively rare.[81,86] The only explanation of the predictably unpredictable nature of protamine reactions is that severe life-threatening reactions are IgG- or IgE-mediated events.

Protamine-specific IgG antibodies cause protamine reactions most likely by activating complement.[106,109] Weiss et al. reported that in NPH diabetics the presence of antiprotamine IgE antibody was a significant risk factor for acute protamine reactions, as was the presence of antiprotamine IgG. In patients without previous exposure to protamine–insulin injections, antiprotamine IgG antibody was also a risk factor for protamine reactions; thus, previous exposure may explain their sensitization.[82]

Although left-sided protamine administration has been suggested to avoid pulmonary effects, intraaortic injection of protamine may also cause hemodynamic instability.[110] Particulate matter formed by the protamine–heparin complex not filtered in the lung may, theoretically, embolize to the coronary and cerebral circulation. Furthermore, cardiovascular dysfunction occurs even with left atrial administration when the lung is initially bypassed.[111] If the patient has an immunospecific antibody to protamine, administration anywhere in the body can produce anaphylaxis.

The current classification of protamine reactions widely quoted is by defining reactions based on their clinical sequelae.[112] This description is problematic because anaphylaxis, an antibody-mediated response, can occur with both IgE and IgG antibodies. Table 1 summarizes different mechanisms of anaphylaxis/protamine reactions based on pathophysiologic mechanisms.

Intravascular Volume Expanders

Although all available colloid intravascular volume expanders carry the risk of anaphylaxis, the incidences are low. Ring and Messmer reported, in 1977, a multicenter prospective trial and noted 69 reactions in 200,906 infusions of colloid intravascular volume substitutes.[113] The frequency of severe reactions (shock, cardiac and/or respiratory arrest) was 0.003% for

plasma–protein solutions, 0.006% for hydroxyethyl starch, 0.008% for dextran, and 0.038% for gelatin solutions.[113] Laxenaire et al. prospectively evaluated patients in France between June 1991 and October 1992 by asking clinicians to report a data sheet for patients given a plasma substitute, whether or not there was an incident.[114] In 19,593 patients, 48.1% were given gelatins, 26.7% hydroxyethyl starch, 15.7% albumin, and 9.5% dextrans.[114] There were 43 reactions for a frequency of 0.219%, or 1 of 456 patients. The frequency was 0.345% for gelatins, 0.273% for dextrans, 0.099% for albumin, and 0.058% for hydroxyethyl starch.[114] However, only 20% were life-threatening (grades III and IV). Gelatins are not approved for use in North America.

Test Doses, Pretreatment, and Anaphylaxis

Test doses are often administered before giving the full therapeutic dose to test for a reaction. Test doses are used empirically in clinical practice, and may cause anaphylaxis. The test dose alerts the clinician that an anaphylactic reaction can occur and reminds them to consider this when giving an antigen in question. When a test dose is administered, clinicians are often monitoring patients for acute cardiopulmonary dysfunction, which is the hallmark of anaphylaxis.[16] However, nonreactive test doses can be followed by anaphylaxis after full-dose administration, as previously reviewed with aprotinin.[66,67] Why this occurs is not clear, but it may relate to delayed immunologic responses. Further, the speed of administration is important in drugs that are know histamine releasers, but not for anaphylaxis, since small doses may trigger reactions.

Patients pretreated for anaphylaxis with antihistamines and corticosteroids can still have anaphylaxis.[67,81] Most studies concerning pretreatment protocols are derived from radiocontrast media reactions that are not immunologically mediated.[115] Pretreatment using hapten inhibition when the specific antigen has been defined has been reported with dextrans, but this is a unique situation.[116] A summary of recommendations regarding test doses and pretreatment is listed in Table 4.

Table 4. Guidelines for Managing Potential Drug Reexposures

1. Patients with a history of penicillin or other allergy need to be carefully questioned regarding the authenticity of this information. Often, the history is more consistent with an adverse drug reaction that may not be immunologically mediated including vomiting, diarrhea, or an unrelated or delayed rash.
2. Determining drug allergy on clinical history alone can be misleading. However, patients with known anaphylaxis to specific agents should not receive those agents again, except via a desensitization protocol.
3. Most patients who have a history of penicillin allergy will tolerate cephalosporins. However indiscriminate administration cannot be recommended, especially for patients who have had serious acute reactions. If a patient has a history of reactions to penicillin or beta lactam antibiotics that was not likely immunoglobulin (Ig)E-mediated it is reasonable to administer a cephalosporin. For skin test positive patients and patients with anaphylactic histories, graded escalation of the first dose under direct observation is warranted.
4. Initial (test) doses may produce anaphylaxis, thus clinicians must be cautious during a reexposure. Test doses of foreign proteins should be administered IV at least 10 min before the initial loading dose.
5. In patients with known previous exposure to aprotinin, the initial loading dose should be given just prior to cannulation; test doses may cause anaphylaxis and if administered should be given just prior to cannulation.
6. The "pump prime" dose of aprotinin should not be added until the initial test dose and initial loading doses of aprotinin are completed.
7. Current recommendations include not reexposing patients to aprotinin within 12 months of prior exposure, without careful risk/benefit analysis.

Therapy

Airway maintenance with 100% oxygen, intravascular volume expansion, and epinephrine are important for treating the hypotension and hypoxemia associated with vasodilation, increased capillary permeability, and bronchospasm in anaphylaxis.[117] Table 5 lists a representative protocol for management of perioperative anaphylaxis. Most guidelines, including the American Heart Association for the treatment of anaphylaxis, discuss IM epinephrine, an issue not relevant in acute cardiovascular collapse.[118] Cardiac anesthesiologists are well prepared to diagnose and treat acute cardiopulmonary dysfunction that occurs in anaphylaxis as they routinely perform transesophageal echocardiography and administer pharmacologic support.

Vasopressin is also an important therapeutic approach for vasodilatory shock associated with anaphylaxis,[119] an event that is complex, and thought to be due to the multiple activation of vasodilator mechanisms and the inability of α adrenergic mechanisms to compensate.[119] Excessive nitric oxide synthesis, by activating soluble guanylate cyclase, causes dephosphorylation of myosin and, hence, vasorelaxation. In addition, nitric oxide synthesis and metabolic acidosis activate the potassium channels (K_{ATP} and K_{Ca}) in vascular smooth muscle.[119] The resulting hyperpolarization of the membrane prevents norepinephrine-induced vasoconstriction, causing hypotension and vasodilatation despite high doses of catecholamines.[119] Although the pressor response to vasopressin may be due to different mechanisms, its ability to block K_{ATP} channels in vascular smooth muscle and interfere with multiple signaling pathways are important contributors.[119,120] Reports have suggested vasopressin's efficacy in case reports and experimental models of anaphylactic shock.[121–123] Although there are case reports using methylene blue for the treatment of anaphylactic shock, this selective nitric oxide synthetase inhibitor blocks only one of the many pathways for causing vasodilatory shock, and has not been shown to be consistently effective.[120,124]

Table 5. Management of Anaphylaxis

If acute hypotension develops, intravascular volume administration, and adrenergic drugs are the cornerstones of therapy. Critical therapies are as follows:

Initial therapy

1. Maintain airway maintenance with 100% oxygen.
2. Initiate intravascular volume expansion. Near-fatal anaphylaxis produces profound vasodilation that significantly increases intravascular capacity and producing hypovolemia. Massive intravascular volume replacement is needed. Additional intravascular volume administration should be considered based on monitoring and echocardiography if available.
3. Administer IV epinephrine, and titrate to restore arterial blood pressure. Patient refractory to epinephrine, consider norepinephrine or vasopressin.
4. Vasopressin administration in patients with refractory hypotension or vasodilatory shock. In patients with arterial blood pressures consider starting at doses of 1–2 units. In patients with cardiac arrest, 40 units are part of Advanced Cardiac Life Support guidelines.
5. Asystole/Pulseless Electrical Activity: Cardiac surgical patients should all have pacing capabilities, and ventricular, atrial, or atrioventricular pacing used.

Secondary therapy

6. Consider antihistamines. There are little data about the value of antihistamines administration but H1 and H2 blockers are reasonable.
7. Corticosteroids should be considered as they may have value in the early hours of any post-resuscitation period.
8. Treat bronchospasm with β2 agonists by inhalation via the endotracheal tube using terbutaline or albuterol.
9. Reassess ventilatory mode to be sure appropriate inspiratory/expiratory ratios for patients. Patients may develop bronchospasm and need longer exhalation times.
10. Treat right ventricular dysfunction that can ensue after protamine and transfusion reactions associated with pulmonary vasoconstriction, using pulmonary vasodilators (milrinone, inhaled nitric oxide, inhaled prostacyclin) if arterial blood pressure stable.
11. Consider reinitiating cardiopulmonary bypass in patients with refractory shock or cardiac arrest.

Right ventricular dysfunction due to acute pulmonary hypertension can also be associated with protamine reactions, and TRALI. Therapeutic interventions reported to be effective in these reactions are pulmonary vasodilators, including inhaled nitric oxide, inhaled prostacyclin, and milrinone, and potentially mechanical support (e.g., intraaortic balloon pump). In patients with refractory shock and hypotension, reheparinization and reinstitution of CPB should be considered. Ford et al. noted most anaphylactic reactions occurred before the start of CPB, and in patients with refractory hypotension, rapid placement onto CPB was life-saving.[28]

Evaluation of Patients After Anaphylaxis

Evaluating a patient after anaphylaxis involves initial and secondary considerations. The first consideration is to obtain a blood sample for serum tryptase, a mast cell mediator that may be increased in IgE-mediated reactions, and that correlates with histamine release.[125] A blood sample should be measured for tryptase within 2 h of the reaction and repeated at 24 h to demonstrate a return to normal values.[125] Mast cell tryptase can also be released by drugs like vancomycin, and may be negative in the case of patients who have IgG antibodies causing reactions.[33] Plasma histamine levels require blood specimens to be processed immediately to prevent spontaneous basophil histamine release and artifactually elevated histamine levels.[125] Also, measuring histamine in plasma is not diagnostic; rather, tryptase has replaced histamine as the mediator to measure. There appear to be minimal effects of CPB on tryptase release.[126,127] However, patients with mastocytosis and abnormal proliferation of mast cells may have elevated tryptase levels.[128]

Few *in vitro* tests are available to measure immunospecific antibodies for drugs administered perioperatively and, therefore, most of the data reported for evaluating patients after perioperative anaphylaxis includes skin testing.[129] Skin testing has been reported by multiple investigators and includes prick and intradermal administration of antigens in question.[129,130] Anesthesiologists should consider consulting an allergist to help them evaluate patients after reactions.

CONCLUSIONS

Anaphylaxis is a continuing problem for anesthesiologists and an important cause of life-threatening ADRs.[131] Potential guidelines for prevention of anaphylaxis or management for reexposure are listed in Table 4. Education regarding prevention, recognition, evaluation, and reporting is important. In cardiac surgery, the ability to rapidly establish CPB and institute mechanical support is important to manage acute cardiovascular collapse—therapies that can be life-saving. Clinicians should remember that test doses may produce anaphylaxis. *In vitro* testing, including antibody tests, is being developed to assess patients at high risk for reexposure anaphylaxis, and will help clinicians make decisions regarding reexposure. We still do not know the ideal therapy for these reactions. Fortunately, cardiac surgical patients are managed by physicians skilled in the rapid diagnosis and management of acute cardiovascular dysfunction. Anaphylactic reactions are a continuing challenge, but developing diagnostic testing to prevent reactions, as well as rapid diagnosis and treatment, are important in preventing adverse clinical outcomes.

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