INTRODUCTION

Any substance that patients are exposed to in the perioperative period including drugs, blood products, or environmental antigens such as latex can produce anaphylaxis. Pharmacologic agents also have the potential to produce predictable and unpredictable adverse reactions. The most life-threatening form of an adverse reaction is anaphylaxis, however, the clinical presentation of anaphylaxis may represent different immune and nonimmune responses. There is confusion in the literature about the term anaphylaxis, and multiple terms have been reported to describe the spectrum of reactions. Based on current ideas, anaphylaxis is best defined as a clinical syndrome characterized by acute cardiopulmonary collapse following antigen (also called allergen) exposure. This presentation will define the spectrum of anaphylactic and adverse drug reactions an anesthesiologist may encounter.

ADVERSE DRUG REACTIONS

Adverse drug reactions are common, however, only 6-10% are immunologically mediated. Any drug can induce an immune response, although all drugs can produce adverse reactions. Most serious predictable adverse drug reactions are related to the amount of drug in the body (overdosage), unintended administration route, or known side effects (i.e., opioid related nausea). However, some drugs have direct effects on inflammatory cells (i.e., heparin, histamine releasing agents). Unfortunately, patients often refer to any adverse drug effects as being allergic in nature. Anesthetic drugs can also produce hypotension via different mechanisms (e.g., propofol induced vasodilation) complicating the diagnosis of perioperative adverse drug reactions. Allergic drug reactions are unpredictable and dose-independent (i.e., reactions due to latex allergy from latex gloves).

ALLERGY AND ANAPHYLAXIS

Allergic reactions and anaphylaxis have the same pathophysiologic mechanisms, as both are immune mediated and due to previous exposure to the antigen or a substance of similar structure. Richet and Portier first used the word anaphylaxis (ana -against, prophylaxis - protection) to describe the profound shock and resulting death that sometimes occurred in dogs immediately following a second challenge with a foreign antigen. The term “allergy” was introduced in 1906, but is now often used to describe IgE-mediated allergic disease. The basis of acute allergic reactions including anaphylaxis is the release of inflammatory mediators released by mast cells and basophils when an allergen interacts with membrane-bound IgE.

PATHOPHYSIOLOGY

Anaphylaxis and allergy result from the release of inflammatory mediators including membrane-derived lipids, cytokines, and chemokines. 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 are released including leukotrienes, prostaglandins, and other factors. These inflammatory substances have a critical role in producing acute cardiopulmonary dysfunction, characterized by a symptom complex of bronchospasm and upper airway edema in the respiratory system, vasodilation and increased capillary permeability in the cardiovascular system, and urticaria in the cutaneous system. Cardiovascular collapse during anaphylaxis results from the effects of multiple mediators on the heart and vasculature. The vasodilation seen clinically can result from a spectrum of different mediators that interact with vascular endothelium and/or vascular smooth muscle. Why some individuals develop severe cardiopulmonary dysfunction instead of minor cutaneous reactions is unknown, but may relate to systemic compared to local release of inflammatory mediators. Interestingly, the original description of anaphylaxis from sea anemone toxin represents an IgG-mediated response. IgG mechanisms will be further discussed in protamine reactions that follow.
ANAPHYLACTIC OR ANAPHYLACTOID?
When life-threatening allergic reactions mediated by antibodies or immune mechanisms occur, they are defined as "anaphylaxis." Multiple other terms are used in the literature to describe life threatening reactions that are not immune mediated, but through the years have created major confusion because one cannot distinguish the etiology of reactions based on clinical observation. Much of the confusion about anaphylaxis in the literature is because many older anesthetic agents could directly degranulate mast cells.

VASODILATORY SHOCK AND ANAPHYLAXIS
Vasodilatory shock occurs in anaphylaxis due to multiple mechanisms that include: excessive activation of vasodilators that increase nitric oxide synthesis to activate soluble guanylate cyclase and increase cGMP, and increased prostacyclin synthesis that activates soluble adenylate cyclase and produces cAMP. Collectively, this produces vasodilation and shock. (1,8) Nitric oxide and metabolic acidosis from shock also activate vascular potassium channels to cause persistent vasodilation despite catecholamine therapy. (10) Other mediators that are released by non IgE mechanisms may also produce shock by different mechanisms (e.g., protamine induced acute pulmonary vasoconstriction) and heparin will be discussed in non IgE mediated reactions. (1)

RECOGNITION OF ANAPHYLAXIS
Because any parenterally administered agent can cause death from anaphylaxis, anesthesiologists must diagnose and treat the acute cardiopulmonary changes that can occur. Studies from Europe suggest that perioperative drug induced anaphylaxis may be increasing. The onset and severity of the reaction relate to the mediator's specific end organ effects. Antigenic challenge in a sensitized individual usually produces immediate clinical manifestations, but the onset may be delayed 2-20 minutes. (3,6,9) The manifestations and course of anaphylaxis are variable, ranging from minor clinical changes including urticaria to cardiopulmonary collapse including severe bronchospasm, vasodilatory shock, and pulmonary vascular injury in certain cases, leading to death. (1) The enigma of anaphylaxis is the unpredictability of occurrence, the severity of the attack, and the lack of a prior allergic history. (1)

NON-IgE MEDIATED REACTIONS
Other immunologic and nonimmunologic mechanisms release inflammatory mediators independent of IgE, creating a clinical syndrome identical with anaphylaxis. (11-17) Polymorphonuclear leukocyte (neutrophil) activation can occur following complement activation by immunologic (antibody mediated: IgM, IgG-antigen activation) or non-immunologic (heparin, protamine, endotoxin, cardiopulmonary bypass) pathways. (11-14) Complement fragments of C3 and C5 (C3a and C5a) release histamine from mast cells and basophils, contract smooth muscle, and increase capillary permeability. In addition, C5a binds receptors on neutrophils and platelets, causing chemotaxis, aggregation, and activation. (13) Aggregated leukocytes embolize to various organs producing microvascular occlusion and liberation of inflammatory products including oxygen-free radicals, lysosomal enzymes and arachidonic acid metabolites (i.e. prostaglandins and leukotrienes). IgG antibodies directed against antigenic determinants or granulocyte surfaces can also activate leukocytes, and are thought to be responsible for the clinical manifestations of transfusion reactions (15), pulmonary vasoconstriction following protamine reactions, and transfusion related acute lung injury (TRALI). (17)

HEPARIN, HIT, AND KININ GENERATION
Following heparin administration, IgG antibody formation is common. These antibodies bind heparin-PF4 complexes on the platelet surface to form immune complexes that activate platelets to promote thrombin formation and thrombosis. (11) This is the clinical manifestation of heparin induced thrombocytopenia (HIT). Approximately 7-50% of heparin-treated patients generate heparin-PF4 antibodies. (11) However, recent reports regarding allergic reactions to heparin from China were due to an oversulfated chondroitin sulfate contaminant that directly activated the kinin-kallikrein pathway to generate bradykinin, a potent vasoactive mediator. In addition, this contaminant induced generation of C3a and C5a. (14) Angiotensin converting enzyme inhibitors also may potentially increase bradykinin levels, and this is the mechanism of vasodilation, angioedema, and cough that can occur with their use.
ANGIOEDEMA

Angioedema is the rapid swelling of skin, mucosa, and submucosal tissues most commonly produced by allergic reactions, but also by ACE inhibitors as noted above. Oral, laryngeal, and pharyngeal swelling can occur with acute airway compromise requiring urgent airway control. There are also inherited qualitative and quantitative deficiencies of the complement C1 esterase inhibitor (C1-INH) called hereditary angioedema (HAE). Patients with HAE also have recurrent episodes of gastrointestinal manifestations of the disease. Bradykinin plays a critical role in angioedema as previously noted. Therapy of attacks includes symptomatic management and C1-INH from C1-INH concentrates. Patients with this history and documented HAE need short-term prophylaxis before surgery or dental treatment because tissue injury activates complement to increase C1-INH levels and also antifibrinolytics that inhibit plasmin mediated activation. New therapies are also being studied in this life threatening disease. (16) A C1-INH concentrate (Cinryze™) is currently FDA-approved indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).

NONIMMUNOLOGIC RELEASE OF HISTAMINE

Many diverse molecular structures administered during the perioperative period degranulate mast cells to release histamine in a dose-dependent, nonimmunologic fashion. (18-21) Intravenous administration of morphine, atracurium, or vancomycin can release histamine, producing vasodilation and urticaria along the vein of administration. (18) Although the cardiovascular effects of histamine release can be treated effectively with intravascular volume administration and/or catecholamines, the responses in different individuals may vary. (1) The newer neuromuscular blocking agents (e.g., rocuronium and cisatracurium) lack histamine releasing effects but can produce direct vasodilation and false-positive cutaneous responses that can confuse allergy testing and interpretation. (22,23) The mechanisms involved in nonimmunologic histamine release represent degranulation of mast cells but not basophils by cellular activation and stimulation of phospholipase activity in mast cells. (19)

TREATMENT PLAN

Most anesthetic drugs and agents administered perioperatively have been reported to produce anaphylaxis. (1) Therefore, a plan for treating anaphylactic reactions must be established before the event. (1) Airway maintenance, 100% oxygen administration, intravascular volume expansion, and epinephrine are essential to treat the hypotension and hypoxia that results from vasodilation, increased capillary permeability, and bronchospasm. (6-9,24-28) Table 2 lists a protocol for management of anaphylaxis during general anesthesia, with representative doses for a 70-kilogram adult. Therapy must be titrated to desired effects with careful monitoring. The route of administration of epinephrine and the dose depends on the patient's condition. (1) Rapid and timely intervention with common sense must be used to treat anaphylaxis effectively. (27) Reactions may be protracted with persistent hypotension, pulmonary hypertension and right ventricular dysfunction, lower respiratory obstruction, or laryngeal obstruction that persist 5 to 32 hours despite vigorous therapy. (24) Novel therapeutic approaches for shock and/or right ventricular failure are currently under investigation. (28-30) During general anesthesia patients may have altered sympathoadrenergic responses to acute anaphylactic shock. In addition, the patient during spinal or epidural anesthesia may be partially sympathectomized, needing earlier intervention with even larger doses of epinephrine and other catecholamines. (27) Additional hemodynamic monitoring including radial and pulmonary artery catheterization may be needed when hypotension persists despite therapeutic interventions as listed. When available, the use of transesophageal echocardiography in an intubated patient can be useful in diagnosing the cause of acute or persistent cardiovascular dysfunction. (28) Following anaphylaxis, patients should be carefully monitored for 24 hours as they may develop recurrence of manifestations following successful treatment and covered with corticosteroids for the acute event. (1) Based on the efficacy of vasopressin in vasodilatory shock, it should also be considered in therapy of anaphylactic shock not responding to therapy (8,29).

Table 2. **Management of anaphylaxis**

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<th>Initial therapy</th>
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<tr>
<td>1. STOP ADMINISTRATION OF ANTIGEN</td>
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<td>2. MAINTAIN AIRWAY WITH 100% OXYGEN</td>
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<td>3. DISCONTINUE ALL ANESTHETIC AGENTS</td>
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<td>4. START INTRAVASCULAR VOLUME EXPANSION</td>
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<td>5. GIVE EPINEPHRINE (5-10 mcg IV initial bolus with hypotension, titrate as needed; 0.1 to 0.5 mcg IV with cardiovascular collapse)</td>
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Secondary treatment

1. **ANTIHISTAMINES** (0.5-1 mg/kg diphenhydramine)
2. **CATECHOLAMINE INFUSIONS** (starting doses: epinephrine 5-10 mcg/min. norepinephrine 5-10 mcg/min, as an infusion, titrated to desired effects)
3. **BRONCHODILATORS** (inhaled albuterol or terbutaline with bronchospasm)
4. **CORTICOSTEROIDS** (0.25-1 g hydrocortisone; alternately 1-2 g methylprednisolone)
5. **AIRWAY EVALUATION** (prior to extubation)
6. **PERSISTENT HYPOTENSION**: Consider vasopressin; Consider additional hemodynamic evaluation potentially with echocardiography


**PRETREATMENT FOR ALLERGIC REACTIONS**

Hypersensitivity reactions are more likely to occur in patients with a history of allergy, atopy, or asthma. However, this does not make it mandatory to pretreat these patients with antihistamines and/or corticosteroid because there is no data in the literature to suggest that pretreatment is effective for true anaphylactic reactions. Most of the literature on pretreatment is from studies evaluating patients with previous radiocontrast media reactions that are non-immunologic mechanisms. Although attempts to pretreat patients for anaphylaxis to latex are growing in clinical practice, there is no data to support this as an effective preventative measure. In fact, pretreatment may lull physicians into a false sense of security. Further, even when large doses of corticosteroids have been administered, life threatening anaphylactic reactions have occurred.(1,25)

**MANAGEMENT OF THE ALLERGIC PATIENT**

Patients presenting with an allergic history need to be carefully evaluated. Patients may report allergy when the reaction was a predictable adverse drug reaction. However, for practical and medico-legal purposes, that class of drug should be avoided if possible when the history is consistent with an allergic reaction, and preservative free alternatives should be chosen. The problem occurs whenever multiple drugs are simultaneously administered or when patients present with muscle relaxant reactions because of the risk of cross reactivity to the biquaternary ammonium ions in the molecule. In this situation, skin testing may be required to see what the patient is can safely be administered.(1)

**EPIDEMIOLOGY OF ANAPHYLAXIS: 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.(28) 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.(28) More recent data suggest the incidence of perioperative anaphylaxis is 1 in 10,000–20,000.(28) Patients undergoing major surgery are an increased risk group, because of the multiple blood products, polypeptides, and potential for impaired cardiovascular function. Mertes reported an epidemiological study from 99-01 of 789 reactions diagnosed by clinical history, skin tests, and/or specific IgE in 518 cases (66%) and nonimmune reactions in 271 cases (34%).(31) The most common causes were NMBAs (58.2%), latex (16.7%), and antibiotics (15.1%), of which rocuronium (43%) and succinylcholine (22.6%) were the most common NMBAs reported. The positive predictive value of tryptase for the diagnosis of anaphylaxis in their study was 92.6%; the negative predictive value was 54.3%. The agents most often implicated will be discussed.

**LATEX ALLERGY**

Latex represents an environmental agent often associated as a cause of perioperative anaphylaxis. Health care workers, children with spina bifida and urogenital abnormalities, and certain food allergies have also been recognized as individuals at increased risk for anaphylaxis to latex.(31-36) Brown reported a 24% incidence of irritant or contact dermatitis and a 12.5% incidence of latex-specific IgE positivity in Anesthesiologists.(34) Of this group, 10% were clinically asymptomatic although IgE positive. A history of atopy was also a significant risk factor for latex sensitization. Brown suggests these individuals are in their early stages of sensitization and perhaps, by avoiding latex exposure, their progression to symptomatic disease can be prevented.(34)
Patients allergic to both tropical fruits (e.g., bananas, avocados, and kiwis) and stone fruits have also been reported to have antibodies that cross-react with latex.(35-37) Multiple attempts are being made to reduce latex exposure to both healthcare workers and patients. If latex allergy occurs, then strict avoidance of latex from gloves and other sources needs to be considered, following recommendations as reported by Holzman.(33) Because latex is such a widespread environmental antigen, this represents a daunting task.

**NEUROMUSCULAR BLOCKING AGENTS**

Neuromuscular blocking agents (NMBAs) have several unique molecular features that make them potential allergens. All neuromuscular blocking drugs are functionally divalent and are thus capable of cross-linking cell-surface IgE and initiating mediator release from mast cells and basophils without binding or haptenizing to larger carrier molecules.(1) NMBAs have also been implicated in epidemiological studies of anesthetic drug-induced anaphylaxis. (38-40) Epidemiological data from France suggest that NMBAs are responsible for 62–81% of reactions, depending on the time period evaluated. (31,38) Rocuronium is currently the NMA most reported from France. We and others have reported previously that aminosteroidal compounds as well as benzylisoquinoline-derived agents produce positive weal and flare responses when injected intradermally.(19,22,42) Estimates of anaphylactic reactions in anesthesia vary, but data suggests that false-positive skin tests may overestimate the incidence of rocuronium-induced anaphylactic reactions.(19,22,41,42) The differences noted in the incidence of reactions may reflect the potential for false-positive weal and flare responses. (41,42) NMBAs can also produce direct vasodilation by multiple mechanisms, which include calcium channel blockade. The false-positive skin tests that were reported to be biopsy-negative for mast cell degranulation clearly confound interpreting skin tests in patients who have had life-threatening cardiopulmonary collapse. Dilute solutions of NMBAs need to be used when skin testing for potential allergic reactions to these agents. However, the exact concentration that should be used is unclear. Since skin-testing procedures are important in evaluating potential drug allergies, the threshold for direct vasodilating and false-positive effects must be determined whenever subjects are skin-tested for a particular drug.

**POLYPEPTIDES AND BLOOD PRODUCTS**

Polypeptides are larger molecular weight molecules that pose greater potential to be antigenic, and include aprotinin, latex, and protamine. Diabetic patients receiving protamine containing insulin as neutral protamine Hagedorn (NPH) or protamine insulin have a 10-30 fold increased risk for anaphylactic reactions to protamine when used for heparin reversal, with an absolute risk of 0.6-2% in this patient population. (25-26) Because protamine is often administered concomitantly with blood products, protamine is often implicated as the causative agent in adverse reactions, especially in cardiac surgical patients. Platelet and other allogeneic blood transfusions can produce a series of adverse reactions by multiple mechanisms, and blood products have a greater potential for allergic reactions including TRALI.(15) Although antigen avoidance is one of the most important considerations in preventing anaphylaxis, this is not always possible, especially with certain agents where alternatives are not available. Protamine is an important example of where alternatives are under investigation, but not currently available. Aprotinin, a bovine derived, ~6512 dalton molecular weight protein used to reduce bleeding, has had anaphylactic reactions following reexposure for cardiac surgery. (43) A history of prior exposure should be determined before aprotinin administration. Current recommendations are not to reexpose patients within 12 months, although the drug is currently removed from marketing.

**EVALUATING THE PATIENT FOLLOWING ANAPHYLAXIS**

A detailed history is one of the most important considerations to evaluate a patient following anaphylaxis, determining what agents were administered, and what the temporal sequence was.(44) Also, after resuscitation collect a red top tube (serum) for mast cell tryptase, preferably within 1-2 hours of the reaction, and then repeat 24 hours later. Serum can also be collected postmortem, which may be important for you medicolegally. Most hospital laboratories will need to send this test to a reference laboratory. If tryptase is positive, sending the patient for an allergy consultation may be useful if the temporal sequence is confusing, and the agent responsible needs further investigation. Often, a positive mast cell tryptase usually represents an IgE mediated reaction (i.e., anaphylaxis) but vancomycin and other histamine releasers can also increase tryptase.(19) Negative mast cell tryptase tests are rarely associated with positive skin tests and antibody tests. IgG reactions due to protamine, or blood products are unlikely to increase tryptase. Few laboratory based tests are available for determining immunologic testing, so skin testing is required if better differentiation of the agent responsible is required.
CONCLUSIONS

Anaphylaxis represents an important potential problem for anesthesiologists and an important cause of life threatening events. Clinicians must be able to recognize and treat these life threatening events if they occur. Clinicians should remember that test doses may produce anaphylaxis. There are few in vitro tests available to assess patients at high risk for reexposure anaphylaxis. Anaphylactic reactions represent a continuing challenge, but rapid diagnosis and treatment are important in preventing adverse clinical outcomes.

SUGGESTED WEB SITES: AnaphylaxisWeb.com, FDA.gov

REFERENCES