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## Allergic reactions in anesthesia

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## Allergic reactions in anesthesia

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### INTRODUCTION

Patients are exposed to multiple foreign substances including latex in the perioperative period. The anesthesiologist also represents one of the few physicians who personally administers a variety of agents including anesthetic drugs, antibiotics, polypeptides (eg, protamine) and blood products, all of which have the potential to produce a variety of predictable and unpredictable adverse reactions. The most life-threatening form of an adverse reaction is anaphylaxis, however, the clinical presentation of reactions assumed to be allergic in origin may in fact represent different immune and nonimmune responses<sup>(1)</sup>. This presentation will define the spectrum of acute life-threatening allergic reactions an anesthesiologist may encounter.

### ADVERSE DRUG REACTIONS

The risk of an adverse drug reaction is an inevitable consequence of drug administration. Up to 30% of medical in-patients may develop some form of an adverse drug reaction during hospitalization<sup>(2)</sup>. Drug reactions can be classified into predictable and unpredictable and include the following characteristics. Predictable adverse drug reactions are often dose-dependent, related to the known pharmacologic actions of the drug, occur in otherwise normal patients and account for approximately 80% of adverse drug effects. Most serious predictable adverse drug reactions are toxic in nature and either directly related to either the amount of drug in the body (overdose), or inadvertent route of administration (i.e., local anesthetic induced seizures). Side effects are the most common adverse drug reactions and are undesirable but often unavoidable pharmacologic actions of the drugs occurring at usual prescribed dosages (i.e., opioid related respiratory depression). Secondary effects are indirect, but not inevitable consequences of the drug's primary pharmacologic action (i.e., drug-mediated histamine release from mast cells). Drug interactions represent important

predictable adverse drug reactions for anesthesiologists. Intravenous opioid administration to a patient who has just received intravenous benzodiazepines or other intravenous sedative/hypnotic drugs produces acute hypotension that results from decreased sympathetic tone. Patients often refer to any adverse drug effects as being allergic in nature. Anesthetic drugs also have the potential to produce direct effects on the cardiovascular system (eg, propofol induced vasodilation) thus complicating the diagnosis of perioperative adverse drug reactions. Unpredictable adverse drug reactions have the following characteristics. They are dose-independent because very small amounts of the antigen including that amount eluted off of latex gloves during latex anaphylaxis can produce life-threatening responses. Unpredictable adverse drug reactions are not related to the drugs' pharmacologic actions, but in the case of allergic reactions, they involve an immunologic response of the patient. Allergic reactions cannot be explained in terms of the normal pharmacology of the drug given in the usual therapeutic doses but is best described as an untoward physiologic event that is mediated by an immunologic reaction<sup>(4)</sup>.

### LIFE-THREATENING ALLERGIC REACTIONS (ANAPHYLAXIS)

Because any parenterally administered agent can cause death from an allergic reaction, anesthesiologists must diagnose and treat the acute cardiopulmonary changes that occur in anaphylaxis, the most severe form of an allergic reaction. Studies suggest approximately one in every 2700 hospitalized patients experiences drug induced anaphylaxis<sup>(5)</sup>. Richet and Portier first used the word anaphylaxis (ana - against, prophylaxis - protection) to describe the profound shock and subsequent death that sometimes occurred in dogs immediately following a second challenge with a foreign antigen<sup>(6)</sup>. When life-threatening allergic reactions mediated by antibodies occur, they are defined as "anaphylactic." When antibodies are not responsible for the re-

action or when we are unable to prove antibody involvement in the reaction, the reaction is called "anaphylactoid"<sup>(7)</sup>. One cannot distinguish between anaphylactic or anaphylactoid reactions on the basis of clinical observation. The spectrum of pathways responsible for anaphylactic or anaphylactoid reactions during the perioperative period will be described.

### PATHOPHYSIOLOGY

Antigen binding to IgE antibodies initiates anaphylaxis. Prior exposure to the antigen or to a substance of similar structure is required to produce sensitization, although an allergic history may be unknown to the patient. On reexposure, the binding of the antigen to bridge two immunospecific IgE antibodies located on the surfaces of mast cells and basophils liberates a complex series of inflammatory molecules that produce acute cardiopulmonary dysfunction<sup>(1,8,9)</sup>. The liberated mediators produce 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<sup>(1)</sup>. Cardiovascular collapse during anaphylaxis results from the effects of multiple mediators on the heart and peripheral vasculature<sup>(1,8)</sup>. The vasodilation seen clinically can result from a spectrum of different mediators that interact with vascular endothelium and/or vascular smooth muscle<sup>(1,2)</sup>.

### RECOGNITION OF ANAPHYLAXIS

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 of anaphylaxis, but the onset may be delayed 2-20 minutes<sup>(10)</sup>. Individuals vary greatly in the

manifestations and course of anaphylaxis. A spectrum of reactions exist, ranging from minor clinical changes to acute cardiopulmonary collapse, leading to death<sup>(1)</sup> (Table I). The enigma of anaphylaxis is the unpredictability of occurrence, the severity of the attack, and the lack of a prior allergic history<sup>(1)</sup>.

### NON-IGE MEDIATED REACTIONS

Other immunologic and nonimmunologic mechanisms liberate many of the mediators previously discussed independent of IgE, creating a clinical syndrome identical to anaphylaxis. Specific pathways important in producing the same spectrum of clinical manifestations will be considered.

### POLYMORPHONUCLEAR LEUKOCYTE ACTIVATION

Polymorphonuclear leukocyte (neutrophil) activation can occur following complement activation by immunologic (antibody mediated: IgM, IgG-antigen activation) or non-immunologic (heparin-protamine, endotoxin) pathways. Complement fragments of C3 and C5 (C3a and C5a) are called anaphylatoxins because they release histamine from mast cells and basophils, contract smooth muscle, and increase capillary permeability. In addition, C5a interacts with specific high-affinity receptors on white blood cells and platelets, initiating leukocyte chemotaxis, aggregation, and activation<sup>(14)</sup>. 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). Antibodies of the IgG class directed against antigenic determinants or granulocyte surfaces can also produce leukocyte aggregation<sup>(15)</sup>. These antibodies are

**Table I.** Recognition of anaphylaxis during anesthesia.

Systems	Symptoms	Signs
Respiratory	Dyspnea, chest discomfort	Coughing, wheezing, sneezing, laryngeal edema, decreased pulmonary compliance, fulminant pulmonary edema, acute respiratory distress
Cardiovascular	Dizziness, malaise, retrosternal oppression	Disorientation, diaphoresis, loss of consciousness, hypotension, tachycardia, dysrhythmias, decreased systemic vascular resistance, cardiac arrest, pulmonary hypertension
Cutaneous	Itching, burning	Urticaria (hives), flushing, periorbital edema, perioral edema

From Levy JH: Anaphylactic Reactions in Anesthesia and Intensive Care. Stoneham, Butterworth-Heinemann, 1992.

called leukoagglutinins. Investigators have implicated polymorphonuclear leukocyte activation in producing the clinical manifestations of transfusion reactions<sup>(15)</sup>, pulmonary vasoconstriction following protamine reactions<sup>(16)</sup>, and transfusion related acute lung injury (TRALI)<sup>(17)</sup>.

### NONIMMUNOLOGIC RELEASE OF HISTAMINE

Many diverse molecular structures of different agents administered during the perioperative period degranulate mast cells to release histamine in a dose-dependent, nonimmunologic fashion<sup>(18-21)</sup>. Intravenous administration of morphine, atracurium, or vancomycin can release histamine, producing vasodilation and urticaria along the vein of administration<sup>(18)</sup>. 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<sup>(1)</sup>. The newer neuromuscular blocking agents (e.g., rocuronium and cisatracurium) are devoid of histamine releasing effects<sup>(22)</sup>. The mechanisms involved in nonimmunologic histamine release are not well understood but appear to represent degranulation of mast cells but not basophils. A spectrum of different molecular structures release histamine in man, and the mechanisms involved are not well understood.

### TREATMENT PLAN

Most anesthetic drugs and agents administered perioperatively have been reported in the literature to produce ana-

phylactic and anaphylactoid reactions<sup>(1)</sup>. Therefore, a plan for the treatment of anaphylactic or anaphylactoid reactions must be established before the event<sup>(1)</sup>. 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<sup>(23)</sup>. Table II lists a protocol for management of anaphylaxis during general anesthesia, with representative doses for a 70-kilogram adult. The treatment plan is the same for life-threatening anaphylactic or anaphylactoid reactions. Therapy must be titrated to desired effects with careful monitoring. Severe reactions require aggressive therapy. The route of administration of epinephrine and the dose depends upon the patient's condition<sup>(24)</sup>. Rapid and timely intervention with common sense must be utilized to treat anaphylaxis effectively. 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<sup>(24-26)</sup>. Novel therapeutic approaches for anaphylactic shock and/or right ventricular failure are currently under investigation<sup>(28-30)</sup>.

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, requiring earlier intervention with even larger doses of epinephrine and other catecholamines<sup>(27)</sup>. Additional hemodynamic monitoring including radial and pulmonary artery cath-

**Table II.** Management of anaphylaxis

#### Initial therapy.

1. Stop administration of antigen
2. Maintain airway with 100% oxygen
3. Discontinue all anesthetic agents
4. Start intravascular volume expansion (2-4 liters of crystalloid with hypotension)
5. Give epinephrine (5-10 µg IV initial bolus with hypotension, titrate as needed; 0.1 to 0.5 mg IV with cardiovascular collapse)

#### Secondary treatment

1. Antihistamines (0.5-1 mg/kg diphenhydramine)
2. Catecholamine infusions (starting doses: epinephrine 5-10 µg/min. norepinephrine 5-10 µg/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. Sodium bicarbonate (0.5-1 mEq/kg with persistent hypotension/acidosis)
6. Airway evaluation (prior to extubation)

From Levy JH: Anaphylactic Reactions in Anesthesia and Intensive Care. Stoneham, Butterworth-Heinemann, 2nd edition, 1992.

terization may be required when hypotension persists despite therapeutic interventions as listed. When available, the use of transesophageal echocardiography in an intubated patient can be extremely useful in diagnosing the cause of acute or persistent cardiovascular dysfunction. All patients following anaphylactic reaction should be admitted to an intensive care unit for 24 hours of monitoring as they may develop recurrence of manifestations following successful treatment<sup>(1)</sup>.

## MANAGEMENT OF THE ALLERGIC PATIENT

Patients presenting with an allergic history need to be carefully evaluated. Often, patients will complain of allergy when in fact the reaction was a predictable adverse drug reaction. However, for practical and medico-legal purposes, that class of drug should be avoided when the history or records are 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 truly safely be administered<sup>(1)</sup>.

## LATEX ALLERGY

For the anesthesiologist, latex represents an environmental agent often implicated as an important 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<sup>(31-37)</sup>. Brown reported a 24% incidence of irritant or contact dermatitis and a 12.5% incidence of latex-specific IgE positivity in Anesthesiologists<sup>(34)</sup>. 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<sup>(34)</sup>. Patients allergic to bananas, avocados, and kiwis have also been reported to have antibodies that cross react with latex<sup>(35-37)</sup>. 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<sup>(38)</sup>. Because latex is such a ubiquitous environmental antigen, this represents a daunting task. Despite the recognition of latex anaphylaxis, multiple other agents including

antibiotics, induction agents, muscle relaxants, non steroidal anti-inflammatory drugs, protamine, colloid volume expanders, and blood products represent additional etiologic agents often responsible for anaphylaxis in surgical patients<sup>(1)</sup>.

## PRETREATMENT FOR ALLERGIC REACTIONS

The anesthesia literature suggests life-threatening 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 corticosteroids 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<sup>(1,25)</sup>.

## PROTAMINE ALLERGY

Certain groups of patients may also be at an increased risk for allergic reactions to specific drugs. 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. Despite the greater risk of protamine reactions in NPH insulin dependent diabetics, the actual incidence of anaphylaxis to protamine is only 0.6-2% in this patient population<sup>(25-26)</sup>. 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 via multiple mechanisms, and blood products have a greater potential for allergic reactions compared to protamine<sup>(1)</sup>. 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<sup>(39,40)</sup>.

SELECTED WEB SITES: AnaphylaxisWeb.com, Anaphylacticreactions.com, Bronchospasm.com

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