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### **INTRODUCTION**

Patients are exposed to multiple foreign substances in the perioperative period from parenteral exposure (drugs, blood products, contrast agents) or environmental exposure (latex). The anesthesiologist also represents one of the few physicians who personally administers a variety of agents including anesthetic drugs, antibiotics, polypeptides, 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.(1) This presentation will define the spectrum of anaphylactic and adverse drug reactions an anesthesiologist may encounter.

#### ADVERSE DRUG REACTIONS

Drug reactions can be classified into predictable and unpredictable.(2) Predictable adverse drug reactions are 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 (overdosage), or inadvertent route of administration. 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 nausea). Secondary effects are indirect consequences of the drug's primary pharmacologic action (i.e., drug-mediated histamine release from mast cells). Drug interactions also 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) complicating the diagnosis of perioperative adverse drug reactions. Unpredictable adverse drug reactions 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, usually are not related to the drugs' pharmacologic actions, and in the case of allergic reactions, they involve an immunologic response of the patient. Allergic reactions are best described as an untoward physiologic event that is mediated by an immunologic reaction.(1)

# 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.(5) 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.(6) When life-threatening allergic reactions mediated by antibodies occur, they are defined as "anaphylactic." When antibodies are not responsible for the reaction or when we are unable to prove antibody involvement in the reaction, the reaction is called "anaphylactoid."(7) 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.

# 125 Page 2

# PATHOPHYSIOLOGY OF ANAPHYLAXIS

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.(1.8.9) 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 cutaneus system.(1) Cardiovascular collapse during anaphylaxis results from the effects of multiple mediators on the heart and peripheral vasculature.(1.8) The vasodilation seen clinically can result from a spectrum of different mediators that interact with vascular endothelium and/or vascular smooth muscle.(1,2)

# VASODILATORY SHOCK AND ANAPHYLAXIS

Vasodilatory shock occurs in anaphylaxis in part due to the inappropriate activation of vasodilator mechanisms including unregulated nitric oxide synthesis that activates soluble guanylate cyclase and generates cGMP, and prostacylcin synthesis that activates soluble adenylate cyclase and generating cAMP, both causing dephosphorylation of myosin and hence vasorelaxation. (1,10) In addition, nitric oxide synthesis and metabolic acidosis activate the potassium channels in the plasma membrane of vascular smooth muscle. The resulting vascular hyperpolarization prevents calcium from entering the cell. Hence, hypotension and vasodilatation persist, despite catecholamine therapy.(10) Other mediators that are released by non IgE mechanisms may also produce shock by different mechanisms (eg, protamine induced acute pulmonary vasoconstriction) will be discussed in non IgE mediated reactions.(1)

### **RECOGNITION OF ANAPHYLAXIS**

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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.(10) 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.(1)(Table 1) The enigma of anaphylaxis is the unpredictability of occurrence, the severity of the attack, and the lack of a prior allergic history.(1)

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

#### Table 1. RECOGNITION OF ANAPHYLAXIS DURING ANESTHESIA CVA DTOMO

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

#### 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. Polymorphonuclear leukocyte (neutrophil)

#### <u>125</u> Page 3

activation can occur following complement activation by immunologic (antibody mediated: IgM, IgG-antigen activation) or non-immunologic (heparin-protamine, endotoxin, cardiopulmonary bypass) 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.(14) 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.(15) These antibodies are called leukoagglutinins. Investigators have implicated polymorphonuclear leukocyte activation in producing the clinical manifestations of transfusion reactions,(15) pulmonary vasoconstriction following protamine reactions,(16) and transfusion related acute lung injury (TRALI).(17) Studies have examined the potential of C5a inhibition by monoclonal antibodies (pexelizumab) to prevent the adverse effects of complement generation.

### 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.(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) are devoid of 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 are not well understood but appear to represent degranulation of mast cells but not basophils. A spectrum of different molecular structures release histamine via cellular activation and stimulation of phospholipase activity in mast cells. (19)

### TREATMENT PLAN

Most anesthetic drugs and agents administered perioperatively have been reported in the literature to produce anaphylactic and anaphylactoid reactions.(1) Therefore, a plan for the treatment of anaphylactic or anaphylactoid 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.(23) Table 2 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 lifethreatening 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.(24) 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 larvngeal obstruction that persist 5 to 32 hours despite vigorous therapy (24-26) Novel therapeutic approaches for anaphylactic 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, requiring earlier intervention with even larger doses of epinephrine and other catecholamines.(27) Additional hemodynamic monitoring including radial and pulmonary artery catheterization 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

# <u>125</u>

Page 4

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.(1) Based on the efficacy of vasopressin in vasodilatory shock, it should also be considered in therapy of anaphylactic shock not responding to therapy (9,29).

# Table 2. 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
- 5. GIVE EPINEPHRINE (5-10 mcg 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 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. SODIUM BICARBONATE (0.5-1 mEq/kg with persistent hypotension/ acidosis)
- 6. AIRWAY EVALUATION (prior to extubation)

# Persistent hypotension: Consider vasopressin

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

# 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.(1,25)

# 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 biquarternary ammonium ions in the molecule. In this situation, skin testing may be required to see what the patient is truly safely be administered.(1)

<u>125</u> Page 5

### AGENTS IMPLICATED IN ANAPHYLAXIS

Many agents administered in the perioperative period have the potential to produce allergic reactions upon reexposure. However, the agents most often reported to cause a perioperative anaphylactic reaction are antibiotics, blood products, latex (rubber), muscle relaxants, and polypeptides (protamine or aprotinin).

#### 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.(31-37) 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 bananas, avocados, and kiwis 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.(38) 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.(1)

## 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. (39-42) Epidemiological data from France suggest that NMBAs are responsible for 62–81% of reactions, depending on the time period evaluated. (41,42) Succinylcholine was previously the NMBA most reported; however, in 1996, atracurium and vecuronium had similar incidences to succinylcholine.

We have reported previously that aminosteroidal compounds in addition to benzylisoquinoline-derived agents produce positive weal and flare responses when injected intradermally.(20,23). Estimates of anaphylactic/anaphylactoid reactions in anesthesia vary, but data suggests that that false-positive skin tests overestimate the incidence of rocuronium-induced anaphylactic reactions. The differences noted in the incidence of reactions may reflect the potential for false-positive weal and flare responses. NMBAs can also produce direct vasodilation by multiple mechanisms, which include calcium channel block. The false-positive skin tests that were reported to be biopsy-negative for mast cell degranulation clearly confound the interpretation of 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.

#### **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

# 125

Page 6

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. (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 via multiple mechanisms, and blood products have a greater potential for allergic reactions compared to protamine.(1) 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.(42,43)

SUGGESTED WEB SITES: Anaphylaxisweb.com, Bronchospasm.com

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# 125

Page 7

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