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Peri-anesthetic Anaphylaxis

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Anaphylaxis is the umbrella term for an acute reaction defined as a severe, life-threatening, generalized, or systemic hypersensitivity reaction. The immediate treatment of allergic anaphylaxis (allergic anaphylaxis includes both IgE-mediated immunologic reactions and IgG/IgM immunologic-mediated reactions, such as occur in blood transfusion reactions) and nonallergic anaphylaxis (previously referred to as anaphylactoid reactions) are identical, but the subsequent evaluation, testing, and recommendations vary. IgE-mediated anaphylaxis indicates the presence of IgE, specific for the causal agent. A good, general example of IgE-mediated anaphylaxis is an allergic reaction to peanut ingestion. Severe forms of allergic, non-IgE-mediated reactions also can occur, such as with blood transfusion reactions. These are mediated by IgG, IgM, and complement-related immune complexes. In contrast, nonallergic anaphylaxis indicates the lack of a specific antibody or immune response. The exact etiology for nonallergic anaphylaxis is unknown. The potential pathogenic mechanisms of nonallergic anaphylaxis include idiosyncratic events, nonspecific complement activation, activation of humoral proteolytic systems such as the clotting cascade, and direct histamine release (Table 1) [1–3].

In contrast to nonallergic anaphylaxis, the cause of allergic anaphylaxis may be elucidated by specific immune testing of the suspected drug. This testing may include skin testing or in vitro drug-specific testing for IgE. Nonallergic anaphylaxis cannot be explained by testing for specific sensitivity. Distinguishing allergic versus nonallergic anaphylaxis is of some clinical

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Table 1
Agents frequently implicated in peri-anesthetic anaphylaxis and probable mechanisms of adverse reactions

Agent	IgE-mediated mast cell activation	Complement-mediated	Direct mast cell activation
Muscle relaxants d-Tubocurarine Suxamethonium (succinylcholine) Pancuronium Atracurium Vecuronium	+	−	+
Hypnotics–barbiturates Thiopental Methohexital	+	+	+
Nonbarbiturate hypnotics Propofol Althesin	±	+	+
Opioids Morphine Buprenorphine Fentanyl	±	−	+
Plasma expanders Dextran Hydroxyethyl starch	−	+	+
Protamine	+	+	+
Radiocontrast media	−	+	+
Latex	+	−	−

importance. Allergic anaphylaxis, particularly IgE-mediated, often is more severe with subsequent administration of the causal drug. The severity of nonallergic anaphylaxis tends to be similar with repeat administration of the causal drug. Nonallergic anaphylaxis is more likely dose-dependent (ie, lower doses or slower rates of administration may not result in reactions). Specific desensitization may be an option for subsequent treatment with a drug previously causing allergic anaphylaxis, but this is not usually helpful for nonallergic anaphylaxis. A pretreatment regimen may be effective in nonallergic anaphylaxis, such as results with radiocontrast media, but pretreatment is generally of limited value with allergic anaphylaxis. Some drugs, such as protamine or muscle relaxants, may result in both allergic (IgE-mediated) and nonallergic anaphylaxis.

Direct histamine release is common during anesthesia [4]. Physiologic changes resembling anaphylaxis rarely occur following direct histamine release, however. Several observations support this statement. Morphine, a very potent histamine-releasing drug, rarely causes severe systemic reactions. Muscle-relaxing agents that are potent direct histamine-releasing drugs do not result in anaphylaxis more often than agents that are less potent histamine releasers. Bronchospasm, a frequent clinical feature of anaphylaxis, rarely occurs with direct histamine release or experimental histamine infusion

[5,6]. Similar plasma histamine levels occur transiently following exposure to direct histamine-releasing drugs and allergen-specific, IgE-induced histamine release, yet the physiologic effects differ [7]. Anaphylaxis is common in the latter and rare in the former, suggesting that mediators other than histamine are essential for the syndrome of anaphylaxis.

Epidemiology

Anaphylaxis, both allergic and nonallergic, occurs in 1 out of every 3500 to 25,000 general anesthetic administrations, with a mortality rate of up to 6% [8–11]. The wide variability reflects the difficulty in determining the denominator (or total number of anesthesia cases) and the limitations in diagnosing anaphylaxis. The incidence of peri-anesthetic anaphylaxis is increasing, with one Australian source reporting an increased incidence from 1 case per 28,000 general anesthetic administrations in 1970 to 1 case per 5000 general anesthetic administrations in 1981 [11–14]. Muscle relaxants are the most common agents causing anaphylaxis during anesthesia, accounting for 60% to 70% of reactions [15,16].

Diagnosis

Signs of anaphylaxis include flushing or urticaria, hypotension, difficulty with intubation caused by laryngeal edema, and the requirement of increased ventilatory pressure or the inability to ventilate because of bronchospasm. Diagnosis of peri-anesthesia anaphylaxis may be hampered by the limited ability of the affected subject to describe symptoms of pruritus, shortness of breath, or angioedema. Skin manifestations may be masked by surgical drapes. The early signs often are unrecognized, and cardiovascular collapse may be the sole presentation, occurring in about 50% of cases [17]. Anaphylaxis always should be considered if immediate hypotension develops, with or without bronchospasm, following parenteral administration of a therapeutic agent or the induction of anesthesia [18]. Bradycardia occurs more often with peri-anesthetic anaphylaxis compared with other causes of anaphylaxis [19,20]. For example, 12% to 30% of anaphylaxis cases attributed to muscle relaxants are associated with bradycardia [14,21]. The differential diagnosis of any adverse reaction during or following general anesthesia should include the possibility of an anaphylaxis. The differential diagnosis of peri-anesthetic anaphylaxis includes the conditions listed in Box 1.

Pathophysiology

Four mechanisms may result in the release of mast cell or basophil mediators during anesthesia:

1. Specific IgE on mast cells and basophils cross-linked by allergen (drug)

Box 1. Differential diagnosis of peri-anesthetic anaphylaxis

Asthma
Arrhythmia
Hemorrhage
Hereditary angioedema
Jarish-Herxheimer reaction
Mastocytosis
Myocardial infarction
Overdose of vasoactive drug
Pericardial tamponade
Postextubation stridor
Pulmonary edema
Pulmonary embolus
Sepsis
Tension pneumothorax
Vasovagal reaction
Venous air embolism

2. Complement activation by specific IgG or IgM binding to antigen (drug)
3. Direct activation of humoral proteolytic systems such as complement by way of the alternative pathway, the kinin pathway, or the plasmin systems
4. Direct activation of mast cells or basophils

Examples of agents used in proximity of anesthesia and the mechanisms most often responsible for anaphylaxis are listed in Table 1. Most causal agents may stimulate adverse reactions by more than one mechanism, further adding to the complexity of recognizing and diagnosing this problem.

Neuromuscular blocking agents are the most common cause of peri-anesthetic reactions, followed by latex and antibiotics [15]. The rank order of occurrence is based on reviews of general surgery anesthesia, but specific surgical procedures might differ with respect to likely cause [15,16]. For example, in cardiovascular surgery, anesthesia-induced anaphylaxis is more likely caused by antibiotics, gelatin solutions or protamine allergy rather than muscle relaxants [22]. Table 2 describes one study's findings on the causality incidence, and these causes are reviewed in detail.

Causal agents

Muscle relaxants

Sixty percent to 70% of anaphylaxis cases in the peri-anesthetic period are secondary to muscle relaxants [23,24]. The muscle relaxants are used to facilitate endotracheal intubation or to optimize surgical exposure. Although

Table 2
Agents involved in perioperative anaphylaxis (N = 518) between January 1, 1999, and December 31, 2000 in France

Cause	Rate of reaction
Muscle relaxants	58.2% (n = 306)
Latex	16.7% (n = 88)
Antibiotics	15.1% (n = 79)
Colloids	4.0% (n = 21)
Hypnotics	3.4% (n = 18)
Opioids	1.3% (n = 7)
Other agents (chymopapain, propacetamol, protamine, methylene blue, ethylene oxide)	1.3% (n = 7)

Data from Mertes PM, Laxenaire MC, Alla F. Groupe d'Etudes des Reactions Anaphylactoides Peranesthesiques. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. Anesthesiology 2003:99:536–45.

rocuronium and succinylcholine were the most frequently incriminated muscle relaxants in a French study [15], the causation frequency of the putative drugs varies according to the relative amount of each muscle relaxant used in each location [24]. Succinylcholine anaphylaxis may be disproportionately frequent, because the molecular flexibility of this agent facilitates cross-linking of specific IgE bound on the surface of mast cells and basophils. Most of the muscle relaxants cause direct release of mast cell histamine without the requirement for specific antibody; however, life-threatening reactions usually are IgE-mediated [25]. The tertiary or quaternary ammonium group, common to all muscle relaxants, is likely the immunodominant determinant recognized by the IgE [26]. The antigenicity of the shared ammonium structures may be responsible for cross-reactivity among the muscle relaxants. Cross-reactivity occurs most consistently between pancuronium and vecuronium [27]. Cross-reactions also may occur with other classes of pharmaceuticals, based upon in vitro inhibition of specific IgE binding to the muscle relaxants. These drugs include:

Acetylcholine
Choline
Morphine
Neostigmine
Pentolinium
Procaine
Promethazine

Cross-inhibition suggests that previous exposure to these nonanesthetic drugs may sensitize individuals to muscle-relaxing agents, resulting in reactions among subjects without prior anesthesia [28]. Three out of four cases of anaphylaxis to muscle relaxants occur in females, suggesting cross-reactivity with ammonium compounds in personal care products [23]. Skin testing may be useful to determine the safest alternative for subsequent anesthesia

following a suspected reaction, recognizing that nonimmunologic reactions are not identified by this diagnostic method (Table 3) [29,30]. Skin testing is not recommended for preanesthetic screening of subjects without a history of suspected reactions [31].

Latex

Natural rubber latex sensitivity is the second most common cause of perioperative anaphylaxis in some series [22]. Latex allergy may develop from multiple medical and nonmedical sources. Thus, the absence of a history of reactions or prior anesthesia should not eliminate the suspicion of latex causality. The prevalence of latex allergy increased in the later part of the 20th century. Latex allergy accounted for approximately 10% of anaphylaxis cases during surgery in 1996 [32], and by 2000, latex caused more than 16% of perioperative anaphylaxis cases [33]. The increase in latex hypersensitivity is probably multifactorial, partially related to the demand for latex gloves with increased HIV awareness and increased use of latex products in general [32,34]. Nonmedical latex exposure occurs from contact with balloons, gloves, condoms, toys, and other domestic articles made of latex. Although the incidence of latex allergy has increased over the last 20 years, it appears to have reached a plateau largely because of increased awareness, a decreased use of latex products, and new label warnings about the presence of latex in medical products [17].

Individuals at high risk for latex allergy include health care workers and patients who have spina bifida, urogenital abnormalities, and multiple prior surgeries (Box 2) [35]. The prevalence of latex hypersensitivity in the general population ranges from 0.8% to 6.5% [36]. In nurses working in the operating room, the prevalence is approximately 11%, and in patients requiring

Table 3
Skin testing concentrations for anesthetic agents

Medication	Intradermal skin test concentration (mg/mL)
Alcuronium	0.005[a]
Methohexital	0.1[b]
Metocurine	0.002[b]
Pancuronium	0.002[a,b]
Succinylcholine	0.02[b], 0.05[a]
Thioamyl	0.1[b]
Thiopental	0.20[b]
Tubocurarine	0.0003[b], 0.001[a]
Rocuronium	0.01[a]
Vecuronium	0.004[a]

[a] *Data from* Moscicki RA, Sockin SM, Corsello BF, et al. Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. J Allergy Clin Immunol 1990; 86:325–32.

[b] *Data from* Rose M, Fisher M. Rocuronium. High risk for anaphylaxis? Br J Anaesth 2001; 86:678–82.

Box 2. Groups at risk for anaphylaxis to latex

Chronic bladder care
Neural tube defects
Spinal bifida
Myelomeningocele
Spina cord trauma
Urogenital malformations
Neurogenic bladder
Health care workers (greatest for operating room)
Patients with multiple surgical procedures
Atopic individuals

Data from Lieberman P. Anaphylactic reactions during surgical and medical procedures. J Allergy Clin Immunol 2002;110:S64–9.

repeated bladder care, it is as high as 72% [37,38]. Anaphylaxis caused by latex is more likely to be delayed or to occur later during the procedure compared with muscle relaxants or induction agents [23]. Latex- containing articles potentially used for anesthesia or surgery are listed in Box 3. Latex gloves and catheters are the most common sources of significant exposure. Articles such as diaphragms, valves, syringes, and tubing are not likely to cause symptoms because of the limited amount of latex allergen in these products.

Skin testing with latex is the most sensitive method to detect latex allergy, but a commercial, standardized testing reagent is not available [39]. A standardized in vitro assay is US Food and Drug Administration (FDA) approved but has a lower sensitivity than skin testing, ranging from 73% to 93% [16,40].

Latex exposure should be limited as much as possible once sensitivity is demonstrated. Ideally, latex-safe operative suites should be available. If a latex-safe suite is not an option, scheduling the anesthesia or interventional procedure as the first case of the day and avoiding latex products as much as possible is an option [41]. None of the anesthesia or surgical team should use latex gloves. Contact with blood pressure cuffs or tourniquets should be limited by wrapping the arm with gauze or other protectants. Premedication regimens, usually including corticosteroids and combination antihistamines, may lessen the severity but not prevent latex reactions [42,43].

Antibiotics

Antibiotics frequently are administered before, during, or immediately after anesthesia and surgery. Allergic reactions to antibiotics, particularly anaphylaxis, may present during the peri-anesthetic period. The most commonly implicated antibiotics resulting in reactions are β-lactam antibiotics and vancomycin [44].

Box 3. Latex-containing articles potentially used for anesthesia or surgery

Adhesive tape
Airway masks
Ambu-bag
Anesthesia bags and tubing
Self- adhesive bandages
Blood pressure cuffs
Bulb syringes
Catheter leg bag straps
Catheters
Condoms
Indwelling
Straight
Elastic bandages
Electrode pads
Endotracheal tubes
Gloves, sterile and exam
Intravenous bags, ports, infusion sets
Penrose drains
Rubber pads
Stethoscope tubing
Suction catheters
Syringes
Tourniquets

Allergic reactions occur in 0.015% to 0.04% of penicillin-treated subjects, and approximately 0.001% of subjects treated with parenteral penicillin develop anaphylaxis [45,46]. Intravenous penicillin administration results in the most severe forms of anaphylaxis. Lack of a prior reaction is not completely reassuring, as most serious and fatal reactions occur in individuals without a history of penicillin allergy. Penicillin skin testing is validated by laboratory studies, clinical science, and experience [39,47]. The sensitivity of penicillin skin testing is approximately 97% if aqueous penicillin and penicillin major determinant are used [47]. Major determinant is a product of in vivo metabolism and comprises the largest component of metabolites, resulting in the designation major determinant. Percutaneous testing followed by intracutaneous testing with concentrations of up to 3 mg/mL for aqueous penicillin and 6×10^{-5} M/L for major determinant, when available, are recommended to exclude penicillin allergy [47–49]. In vitro testing for penicillin-specific IgE is available, but its sensitivity and specificity are less than skin testing. The penicillin major determinant Pre-Pen, previously manufactured by Hollister-Stier Laboratories, is not available commercially. The development of a commercial

penicillin major determinant product is in progress. Besides the current lack of major determinant, there has never been a commercially available minor determinant. Minor determinant is a metabolic product with lower concentration than major determinant. The lack of minor determinant is an impediment, as sensitivity to minor determinant is associated with the most severe anaphylaxis. Skin testing with penicillin derivatives or cephalosporins is not as well studied but is used clinically. Maximum testing concentrations of 1 to 3 mg/mL have been suggested. Monobactams, such as aztreonam, do not cross-react immunologically with penicillin and may be used in penicillin allergic subjects. Desensitization protocols are available to facilitate use of β-lactam antibiotics in subjects with documented or suspected allergy and a critical need for treatment with β-lactams.

Vancomycin is a glycopeptide antibiotic selectively used for treatment of resistant organisms and for use in individuals who have penicillin allergy. Administration, especially rapid, may result in life-threatening non-IgE-mediated anaphylaxis [50–52]. Both direct histamine release and direct myocardial depression partially explain this phenomenon [53]. These nonimmunologic reactions to vancomycin can be reduced or eliminated by administering this drug as a dilute solution, dissolved in at least 200 mL, and infused over a 2 hour period or longer. IgE-mediated anaphylaxis to vancomycin is much less common than other reactions [54]. Skin testing with a concentration of 0.15 mg/mL or less has been reported, but the reliability of this testing is less secure than with penicillin [54]. Skin testing may have some value in distinguishing rate-related adverse events from anaphylaxis.

Colloid plasma expanders

Dextran and hydroxyethyl starch (HES), large molecular-weight polysaccharides, may be used as a nonblood, high-oncotic fluid replacement during surgery. These agents infrequently are associated with adverse reactions and anaphylaxis, most likely caused by complement activation. Estimates of reaction rates are 0.008% to 0.08% for dextran and 0.08% for HES [23,55]. Specific antibodies can be detected for dextran or HES, but their clinical significance is unknown [55–57]. Confirmation of dextran or HES as the cause of an adverse reaction is limited by the absence of accurate serologic or skin tests. Skin test reactivity to undiluted solutions has been described but is of unknown significance [23].

Case reports in the medical literature also describe systemic reactions to albumin [27]. Details concerning the mechanism of the adverse effects are not available.

Hypnotic induction agents

Intravenous drugs used for anesthetic induction are the third to fifth most common cause of peri-anesthetic anaphylaxis, depending on the study.

More than 290 cases of anaphylaxis are reported in the literature from the use of barbiturates, especially thiopental; however, the reaction rate with barbiturates is only 1:25,000, with the reported occurrence of reactions reflecting the common use of these compounds [25]. Women are three times more likely to react to thiopental than men [23,31]. Most of the adverse reactions with barbiturates, particularly thiopental, are caused by specific IgE antibody, although direct histamine-releasing activity also occurs [1,23,58]. The importance of immunologic cross-reactivity is unknown [29,59,60]. Skin testing may be clinically useful, but testing drug concentrations must be less than the concentrations that result in irritation (see Table 3).

Propofol is a nonbarbiturate induction agent that is potentially useful if sensitivity to barbiturates is a concern [61]. Specific IgE against propofol may occur; however, most adverse reactions to propofol are nonimmunologic [62–64]. Although skin testing may be positive, results do not predict anaphylaxis. Propofol may stimulate histamine release directly, and this effect may be greater when administered with muscle relaxants [65].

Opioids

Narcotics used in anesthesia are common causes of flushing and urticaria following intravenous administration. The risk of anaphylaxis, in contrast, is very rare [23,31,66,67]. Reducing the rate of opioid administration usually limits the severity of these reactions. Dermal mast cells express opioid receptors that stimulate histamine release following narcotic binding. Other populations of mast cells do not express this receptor. Cutaneous flushing and hives often occur after intravenous morphine, but with rare exception, the amount of histamine release does not result in hypotension or bronchospasm [67]. Fentanyl does not stimulate histamine release directly by way of the mast cell opioid receptor [1,19,68].

Reports of allergic anaphylaxis to morphine and fentanyl are in the medical literature [23,69]. Skin testing, with a 1:100,000 dilution of a therapeutic morphine concentration, has been suggested to avoid direct histamine release resulting in a positive test [39]. This precaution would not be as great a concern with fentanyl, because this agent does not result in direct histamine release [27,64]. Predictive value of skin testing with morphine has not been validated. If morphine is needed following a previous suspected reaction, one authority suggests test dosing or challenging with morphine, beginning at 0.1 mg and doubling every 15 minutes until a 4 mg dose is attained [39].

Protamine

Intravenous protamine, an agent used to reverse heparin anticoagulation, may cause allergic and nonallergic anaphylaxis. Nonallergic anaphylaxis with protamine is characterized by increases in pulmonary blood pressure. The potential pathophysiologic mechanisms are numerous and varied [70–77]. A case control study (multivariate odds ratio [95% confidence

interval]) showed that previous neutral protamine Hagedorn insulin use (8.18 [2.08, 32.2]), fish allergy (24.5 [1.24, 482.3]), and other medication allergy (2.97 [1.25, 7.07]) are independent risk factors for anaphylaxis [73]. Estimates are that up to 39% of cardiopulmonary bypass patients have one or more of these risk factors. Allergy to fish has not been shown conclusively to be associated with protamine allergy [78,79]. Other literature suggests that previous vasectomy and the rate of protamine infusion are also risk factors, but epidemiologic confirmation is lacking [76]. Skin prick tests and specific IgE have not been demonstrated to be clinically useful in the diagnosis of hypersensitivity to protamine. Alternative agents may be used for heparin reversal, but these agents are not readily available. Pretreatment regimens with corticosteroids and antihistamines have been recommended, but no studies confirm efficacy [75].

Benzodiazepines

Reactions to benzodiazepines are exceedingly rare; however, because of frequent use perioperatively, one survey reported benzodiazepines were the sixth most common cause of anaphylaxis during anesthesia [80]. No studies are available to verify the mechanism of clinical adverse reactions. Specific IgE has not been detected by skin tests or in vitro tests [81,82]. One in vitro study reported histamine release from lung mast cells by diazepam and from basophils and mast cells by midazolam [1].

Local anesthetics

Local anesthetic agents readily induce cell-mediated immunologic reactions when applied topically to the skin, but humoral immune responses are rare [70]. Adverse effects from local anesthetics are not uncommon, but immunologically mediated reactions following parenteral administration are very unusual. The usual cause of a local anesthetic reaction is a vasovagal response, anxiety, toxic complications, or an idiosyncratic reaction. Toxic effects usually result from inadvertent systemic, high-dose administration of local anesthetic preparations. Systemic toxicity includes central nervous system stimulation or suppression and cardiac suppression with peripheral vasodilation.

Proving a pathophysiologic immune response following an adverse local anesthetic event is often difficult or inconclusive. Both immediate, wheal-and-flare skin testing, and delayed-type hypersensitivity patch testing have been used for diagnosis. Positive patch tests occur more commonly with the para-aminobenzoic ester local anesthetics compared with the amide class (Table 4) [16]. Cross-reactions among the members of the para-aminobenzoic ester group occur with delayed-type hypersensitivity patch testing. The clinical relevance of delayed hypersensitivity to the adverse effects of injected, as opposed to topically applied, local anesthetics is unknown and unlikely to be significant.

Table 4
Local anesthetics

Para-aminobenzoic acid esters	Amides
Benzocaine	Bupivicaine (Marcaine)
Butacaine (Butyn)	Dibucaine (Nupercaine)
Butethamine (Monocaine)	Dyclonine (Dyclone)
Chlorprocaine (Nesacaine)	Lidocaine (Xylocaine)
Procaine (Novocain)	Mepivicaine (Carbovocaine)
Tetracaine (Pontocaine)	Oxethazaine (Oxaine)
	Phenacaine (Holocaine)
	Pramoxine (Tronothane)
	Prilocaine (Citonest)

Data from Thong BY, Yeow-Chan. Anaphylaxis during surgical and interventional procedures. Ann Allergy Asthma Immunol 2004;92:619–28.

Determining which local anesthetic should be used with a history of an adverse reaction is based on details of the history and diagnostic testing. Generally an alternative anesthetic is considered despite the knowledge that the likely cause of a previous reaction is toxic or idiosyncratic. The former type of reaction likely would not occur with subsequent administration using standard techniques. An amide class anesthetic usually would be the choice following a reaction with a para-aminobenzoic ester. Percutaneous testing, followed by intradermal testing, usually is performed with one or more local anesthetics. Dilutions of the anesthetics may be considered for the initial testing if the history is highly suggestive of anaphylaxis. Ideally, anesthetic agents with and without preservatives are used to determine if preservative sensitivity, rather than anesthetic allergy, is responsible for the reaction. Subcutaneous injections of increasing dosages of the anesthetic agent, 0.1 to 0.5 mL, may be administered to verify that reactions are not dose-dependent. Local anesthetics without epinephrine are preferable if the history is suggestive of an anxiety response.

Almost invariably, a local anesthetic can be identified as safe to permit procedures with minimal pain. Knowledge that anaphylaxis is extraordinarily rare facilitates reassurance of the patient after testing and progressive dose challenge.

Other potential causes of anaphylaxis

Various other potential causes or mimics of anaphylaxis during the peri-anesthetic period are listed in Box 4.

Some of these causes are reviewed in other articles in this issue. Some, such as chymopapain, are used rarely. Blood transfusion reactions may be hemolytic reactions with complement activation or antibody specific for IgA in nonwashed packed red blood cells or whole blood collected from

Box 4. Other potential causes or mimics of peri-anesthetic anaphylaxis

Aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs)
Bisulfites or other medication preservatives
Blood transfusion reaction
Incompatibility
Immune reaction to IgA
Chlorhexidine
Chymopapain sensitivity (used for herniated disc surgery)
Ethylene oxide (used for sterilization)
Insulin
Hypersensitivity reaction
Isosulphan blue dye (used for sentinel lymph node biopsy)
Methylmethacrylate (bone cement)
Radiocontrast reaction
Streptokinase or urokinase

a subject with normal IgA. IgA antibodies occur in IgA-deficient subjects and may be an IgE isotype.

Approach to patients with peri-anesthetic anaphylaxis

The management of anaphylaxis in proximity to anesthesia is similar to anaphylaxis in other situations. The diagnosis is challenging because of the multiple drugs administered, concurrently or sequentially, and the effects of anesthesia itself. Serum complement assays may be valuable if complement activation is suspected. An elevated serum tryptase level 1 to 6 hours after suspected anaphylaxis suggests mast cell degranulation and supports the diagnosis of anaphylaxis in the presence of a typical history and clinical findings [83–85]. Additional diagnostic testing for the agent responsible for mast cell degranulation, usually by measuring specific IgE, would be advisable if the serum tryptase were elevated. A negative tryptase result, however, does not exclude anaphylaxis.

Final testing for specific IgE to a suspected causal agent is not recommended until several weeks after the initial reaction. This recommendation is based on the precedent of other hypersensitivities in which transient decreases in measurable allergen-specific IgE occur after anaphylaxis. Skin tests may be difficult to interpret with agents used during anesthesia, because many drugs cause direct mast cell histamine release in the absence of specific IgE. Nonetheless, skin testing has been shown to be valuable in evaluating anaphylaxis to barbiturates, chymopapain, streptokinase, penicillin, insulin, and latex. Suggested concentrations of anesthetic agents for use in skin

testing are listed in Table 3 [29,30]. In vitro testing for specific IgE has been reported for muscle relaxants, thiopental, morphine, propofol, and latex. Latex in vitro testing is recommended because of an available standardized assay, and there is patient risk when using nonstandardized latex skin-testing reagents. Skin testing may be necessary with a strong suspicion of latex allergy and negative in vitro results.

Prevention of peri-anesthetic anaphylaxis

The prevention of peri-anesthetic anaphylaxis is an elusive ideal because of the rare occurrence of reactions, multiple pathophysiologic mechanisms (many of which are undefined), the limited ability to test for sensitization, and the limited ability to define the risk of recurrence. A careful medical history that focuses on previous adverse reactions is most important [75]. Any previous medication reaction nonspecifically increases the possibility of adverse reactions, and multiple previous medication reactions pose a greater risk. Atopic individuals may be at increased risk because of either increased occurrence of reactions or, more often, an increased severity of reactions. Asthma therapy should stabilize optimal lung function and minimize bronchial hyper-reactivity, if possible, before anesthesia. β-Blocker therapy and possibly angiotensin-converting enzyme (ACE) inhibitor therapy are potential risk factors that ideally should be avoided or limited. Previous anesthetic-associated reactions should be evaluated thoroughly, with specific testing if indicated. IgA-deficient subjects should receive washed red blood cells and not whole blood to avoid exposure to exogenous IgA. Intraoperative antibiotics should be administered slowly with careful hemodynamic monitoring. Drugs with histamine-releasing properties (eg, morphine, d-tubocurarine, vancomycin, quaternary muscle relaxants) should be administered as slowly as possible, particularly in subjects with asthma or cardiopulmonary disease. Pretreatment regimens, as used for radiocontrast nonallergic anaphylaxis, have not been proven to prevent peri-anesthetic reactions, but pretreatment may reduce the severity of such reactions if a non-IgE-mediated mechanism is suspected.

Summary

Peri-anesthetic anaphylaxis, mediated by immunologic, nonimmunologic, or undefined mechanisms, is becoming more common, probably because of more frequent use of anesthesia and the increasing complexity of used drugs. Recognition and immediate treatment are particularly important, because anesthetized subjects are at greater risk for adverse outcomes caused by the physiologic effects of anesthesia. Vigilance for the signs of anaphylaxis and consideration of risk factors, with possible modification of the agents used, likely will reduce the morbidity and mortality associated with these reactions.

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