

Perioperative Anaphylaxis

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Anesthesia is commonly regarded as a high-risk activity. Many experts acknowledge that “very impressive” safety improvements have been made in this field, leading some investigators to conclude that anesthesia-related mortality has decreased in the previous 2 decades.¹ Nevertheless, anaphylaxis remains a major cause of concern for anesthetists who routinely give many potentially causative agents and who are the medical practitioners most likely to see severe anaphylactic reactions.

Virtually every drug used in anesthesia has been reported to cause a reaction, and no premedication has proven to be able to prevent anaphylactic reactions.² On the other hand, the incidence of anesthetic anaphylaxis can be reduced by preventing second reactions in patients with a history of anaphylaxis. Most patients who have experienced anaphylaxis should be evaluated by a specialist in allergy-immunology.

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Determining the cause of these adverse events and the drug responsible, and adequately communicating those findings, can reduce second reactions.

EPIDEMIOLOGY

Perioperative anaphylactic reactions are potential life-threatening immediate hypersensitivity reactions that are unrelated to the drug’s pharmacologic characteristics and correspond to immune-mediated allergic and nonimmune-mediated so-called “pseudo-allergic or anaphylactoid” reactions.³ They result from the release of pre-formed and newly synthesized mediators from mast cell and basophils.

The reality of the risk of an allergic reaction occurring during anesthesia is established on the basis of the more than 15,000 cases of perioperative hypersensitivity reactions published in the literature during the last 20 years.⁴ Despite increasing awareness about anaphylactic reactions to drugs and compounds used in anesthesia, their incidence remains poorly defined owing to uncertainties over the accuracy and completeness of reporting.

Most reports on the incidence of anaphylaxis originate in France, Australia, New Zealand, the United Kingdom, Thailand, Spain, and Norway. They reflect an active policy of systematic clinical or laboratory investigation of hypersensitivity reactions, or result from the analysis of drug-related adverse event databases. Based on these reports, the estimated incidence of all immune- and nonimmune-mediated immediate anesthetic hypersensitivity reactions was 1 in 5000 to 1 in 13,000 in Australia, 1 in 5000 in Thailand, 1 in 4600 in France, 1 in 1250 to 1 in 5000 in New Zealand, 1 in 3500 in England.^{4–8}

The estimated incidence of immune-mediated reactions was 1 in 10,000 to 1 in 20,000 in Australia,⁹ 1 in 13,000 in France,¹⁰ 1 in 10,263 in Spain,¹¹ 1 in 5500 in Thailand,⁸ and 1 in 1700 to 1 in 20,000 in Norway.¹² In most series, they represent at least 60% of all hypersensitivity reactions observed within the perioperative period.^{11,13–16} Wide variations are reported concerning the expected mortality rate, ranging from 3% to 9%;^{17,18} the overall morbidity is unknown.

CAUSAL AGENTS

The overall distribution of the various causal agents incriminated in anaphylaxis during anesthesia is similar in most reported series. Neuromuscular blocking agents (NMBAs)

Table 1 Substances responsible for IgE-mediated hypersensitivity reactions in France: results from seven consecutive surveys							
	1984–1989 (n = 821)	1990–1991 (n = 813)	1992–1994 (n = 1030)	1994–1996 (n = 734)	1997–1998 (n = 486)	1999–2000 (n = 518)	2001–2002 (n = 502)
Substance (%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
NMBAs	81.0	70.2	59.2	61.6	69.2	58.2	54
Latex	0.5	12.5	19.0	16.6	12.1	16.7	22.3
Hypnotics	11.0	5.6	8.0	5.1	3.7	3.4	0.8
Opioids	3.0	1.7	3.5	2.7	1.4	1.3	2.4
Colloids	0.5	4.6	5.0	3.1	2.7	4.0	2.8
Antibiotics	2.0	2.6	3.1	8.3	8.0	15.1	14.7
Other	2.0	2.8	2.2	2.6	2.9	1.3	3.0
Total	100	100	100	100	100	100	100

represent the most frequently involved substances, with a range of 50% to 70%, followed by latex (12% to 16.7%) and, in recent reports, antibiotics (15%) (**Table 1**).

NEUROMUSCULAR BLOCKING AGENTS

Immune-Mediated Hypersensitivity Reactions

Most hypersensitivity reactions to NMBAs are acute IgE-dependent allergic reactions. Of all the drugs studied so far that elicit immediate allergic reactions, NMBAs demonstrate several intriguing departures from the currently accepted explanations of the mechanisms underlying the allergic immune response to “small” molecules such as drugs and simple chemicals.¹⁹ Until recently, low molecular weight molecules were considered as haptens incapable of inducing the production of drug-specific antibodies by themselves. Consequently, prior covalent binding of the drug or of one of its degradation products to a protein carrier and processing by professional antigen-presenting cells before presentation of peptides on the cell surface in close association with a class I or II histocompatibility molecule were regarded as the initial steps of sensitization. Recent reports have challenged this dogma. At least some muscle relaxants bind loosely to plasma proteins; however, there appears to be no conclusive evidence that covalent conjugation to endogenous proteins to form sensitizing antigenic drug-protein complexes occurs with any of the NMBAs or their degradation products. A possible direct interaction with proteins present on the surface of antigen-presenting cells (class II histocompatibility molecules), as reported for sensitizing metal and some antibiotics, should also be given consideration.²⁰ In this regard, the capacity of dendritic cells, which are considered to be the most powerful antigen-presenting cells, to present NMBA-related epitopes that are recognized by T cells has been demonstrated *in vitro*.²¹

The elicitation of an IgE-mediated reaction is influenced by different immunochemical requirements. In immediate allergic reactions, mast cells and basophils are activated by cross-linking of FcεRI molecules, which is thought to occur by binding of multivalent antigens to the attached molecules. In 1983, Baldo and Fisher demonstrated the role of alcuronium-reactive antibodies in some life-threatening reactions elicited by this NMBA.²² Structure-activity studies designed to explore the molecular basis of the antibody binding have established that quaternary and tertiary ammonium ions were the main component of the allergenic sites on the reactive drugs. Because the structure of NMBAs includes two substituted ammonium ions per molecule, this divalency could explain allergen-induced mediator release in a sensitized subject even in the absence of protein binding.²³ The IgE recognition site of the molecule depends also on the molecular environment of the ammonium ion and on the hydrophobicity and distance to polar groups such as hydroxyls.²⁴ This factor may explain the heterogeneity of the cross-reactivity among patients.

Cross-sensitization among the different agents has been reported to be frequent, ranging from 60% to 70% of patients allergic to NMBAs, but it is not constant.^{10,15,16} Indeed, the patterns of cross-reactivity vary considerably among patients. Cross-reactivity to all NMBAs is relatively unusual but seems to be more frequent with aminosteroid NMBAs than with benzylisoquinoline-derived NMBAs.²⁵ In addition to the previously mentioned steric considerations, which could explain why two muscle relaxants do not necessarily behave similarly, further hypotheses have been proposed. In some cases, the antigenic determinant may correspond to the tertiary or quaternary ammonium epitope or extend to the adjacent part of the molecule. The relative affinities of the various muscle relaxants to their corresponding IgEs may also have a role.²⁶

In 15% to 50% of cases, IgE-mediated anaphylaxis to an NMBA has been reported at the first known contact with an NMBA.^{6,13,15,27} This observation suggests a possible cross-reaction with IgE antibodies generated by previous contact with apparently unrelated chemicals. This hypothesis is particularly attractive in cases in which patients react to relatively small and ubiquitous epitopes such as a substituted ammonium group. Indeed, these structures occur widely in many drugs but also in foods, cosmetics, disinfectants, and industrial materials. There would seem to be ample opportunity for sensitive individuals to come into contact with and synthesize IgE antibodies to these unusual, and previously unsuspected, antigenic determinants. Recently, Florvaag and colleagues hypothesized that the striking difference in the rate of allergic reactions to NMBAs, which is more than six times as common in Norway as in Sweden, could be due to differences in preoperative sensitization. They demonstrated a higher prevalence of IgE antibodies to quaternary or tertiary ammonium ion among blood donors and atopic patients from Norway when compared with those from Sweden.²⁸ This study also pointed out that, among common environmental household chemicals with quaternary/tertiary ammonium ions able to bind antibodies, the only difference between Norway and Sweden was in the use of cough mixtures containing pholcodine. The later elaborated finding that pholcodine exposure in sensitized individuals, particularly in patients having experienced an allergic reaction to an NMBA,²⁹ was responsible for a significant increase in specific IgEs to NMBAs led to the hypothesis that pholcodine exposure could lead to IgE sensitization to pholcodine and other quaternary ammonium ions, thereby increasing the risk of allergic reaction to NMBAs. The pholcodine hypothesis is under further investigation in a collaborative study involving several countries across Europe and the United States in an attempt to establish a possible relation between the prevalence of IgE against substituted (quaternary or tertiary) ammonium ions and pholcodine consumption, a parameter that varies considerably between countries (for a more detailed discussion, see the article by Florvaag and Johansson elsewhere in this issue).

Differences regarding the relative risk of allergic reactions between NMBAs have been recognized in large epidemiologic surveys.^{10,12–15,27} In most reports, suxamethonium appears to be more frequently involved, with some differences reflecting variations in anesthetic practices from one country to another.^{12–15,18} In contrast, pancuronium and cis-atracurium are the NMBAs associated with the lowest incidence of anesthetic anaphylaxis in large series.^{13–16} Some controversy has arisen concerning a potential increased prevalence of immediate hypersensitivity reactions to rocuronium. A trend concerning an increased frequency of allergic reactions to rocuronium was initially reported in Norway and France,^{26,30} but not in Australia,³¹ the United Kingdom,³² and the United States.³³ Because of statistical limitations, an analysis of epidemiologic data from Norway was unable to confirm whether rocuronium represented an increased risk.¹² In the same time period, surveys conducted in France by the GERAP (Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques), a network of 40 French allergo-anesthesia outpatient clinics whose aim is to promote the survey of allergic and nonimmune-mediated reactions occurring during anesthesia, seemed to indicate a trend toward an increased risk when the respective market shares of the different NMBAs were taken into account.^{14–16} Further large epidemiologic studies will be necessary to elucidate this problem.

To explain the possible differences observed regarding the risk of allergic reactions with the different NMBAs, it has been suggested that the flexibility of the chain between the ammonium ions as well as the distance between the substituted ammonium ions might be of importance during the elicitation phase of IgE-mediated

reactions.³⁴ Flexible molecules, such as suxamethonium, are considered more potent in stimulating sensitized cells than rigid molecules like pancuronium. This hypothesis would be contradicted if a higher risk of sensitization associated with rocuronium were to be confirmed. Interestingly, in the past, as for rocuronium, alcuronium has been claimed to be associated with a high risk for anaphylaxis. If an increased risk with rocuronium is further confirmed by epidemiologic surveys, propenyl ammonium groups present in both NMBA might be involved in this apparent increased allergenicity. These considerations represent an important issue in the design of an ideal NMBA with a reduced risk of allergic reactions.

Nonimmune-Mediated Hypersensitivity Reactions

The rate of non-IgE-mediated immediate hypersensitivity reactions usually varies between one-fifth and one-third of the reported cases in most large series.^{12,14–16} In a recent report based on spontaneous reporting to the Yellow Card Scheme, the main reporting system for adverse drug reactions in the United Kingdom, nonallergic suspected reactions to NMBA occurred with almost the same frequency as those with an allergic component.¹⁸ Although the precise mechanisms of the non-IgE-mediated reactions remain difficult to establish, they are assumed to result from direct nonspecific mast cell and basophil activation, which causes direct histamine release.³⁵ Reactions resulting from direct histamine release are usually less severe than IgE-mediated reactions,^{15,16} with the exception of a subset of patients who have been considered as “superresponders” to the histamine-releasing effect of NMBA. Histamine release is predominantly found with the use of the benzylisoquinolines d-tubocurarine, atracurium, and mivacurium, and the aminosteroid rapacuronium.³⁶

Recently, severe bronchospasm resulting from the administration of rapacuronium has been reported in children. Increased airway resistance related to rapacuronium administration has been reported in children and adults. It has been suggested that the higher affinity of rapacuronium for M2 versus M3 muscarinic receptors could account for the high incidence of bronchospasm observed in clinical practice.³⁷ As a result of these adverse reactions, rapacuronium has been withdrawn from the market in the United States.

LATEX

Allergy to natural rubber latex is the second most common cause of anaphylaxis during anesthesia in the general population. In children who are subjected to numerous operations, particularly those sustaining spina bifida, it is the primary cause of anaphylaxis.^{38–41} The relative frequency of allergy to latex has rapidly increased, rising from 0.5% before 1980 to 20% in France in 2002.¹⁶ Thirty percent of these patients had a history of symptoms suggestive of latex sensitization which could have been detected before the reaction.¹⁶ Nevertheless, a low rate of allergic reactions to latex has been reported in countries where a strategy aimed to reduce latex exposure has been implemented.¹²

ANTIBIOTICS

Antibiotics are commonly administered perioperatively and can cause allergic reactions. A discussion of allergic reactions to antibiotics is beyond the scope of this review; however, their frequency has increased over the last 20 years. Currently, allergy to β -lactams represents 12% to 15% of the perioperative reactions observed in France.^{15,16} Vancomycin, which is increasingly used for prophylaxis, has also been

incriminated in some cases; however, in most cases, the adverse reactions observed are related to the nonimmune-mediated red-man syndrome associated with rapid vancomycin administration.⁴²

HYPNOTICS

Hypnotics commonly used in anesthesia are thiopental, propofol, midazolam, etomidate, ketamine, and inhaled anesthetics. Allergic reactions involving these drugs appear to be relatively rare. The estimated incidence of hypersensitivity reactions with thiopental has been estimated to be 1 in 30,000.⁴³ Most of the generalized reactions are thought to be related to its ability to elicit direct leukocyte histamine release; however, there is evidence for IgE-mediated anaphylactic reactions based on skin tests and specific IgE assays.^{44,45} Recently, thiopental has been involved in less than 1% of allergic reactions in France.¹⁶

Ever since Cremophor EL, used as a solvent for some nonbarbiturate hypnotics, has been avoided, many previously reported hypersensitivity reactions have disappeared. In the last French surveys, reactions to propofol accounted for less than 2.5% of allergic reactions, and reactions to midazolam, etomidate, or ketamine appeared to be rare.^{15,16} No immune-mediated immediate hypersensitivity reaction involving isoflurane, desflurane, or sevoflurane has been reported despite their wide use.

OPIOIDS

Reactions to morphine, codeine phosphate, meperidine, fentanyl, and its derivatives are uncommon. Because of their direct histamine-releasing properties, especially regarding morphine, distinction between anaphylaxis and nonimmune-mediated histamine release is not always easy. Only 12 cases were recorded in the last 2 years of an epidemiologic survey in France, nine of them being related to morphine administration.¹⁶

LOCAL ANESTHETICS

Local anesthetics include amine (lidocaine, mepivacaine, prilocaine, bupivacaine, levobupivacaine, ropivacaine) and ester derivatives of benzoic acid (eg, chloroprocaine, procaine, tetracaine). Allergic reactions to local anesthetics are rare despite their frequent use. It is estimated that less than 1% of all reactions to local anesthetics have an allergic mechanism.^{14,46} Inadvertent intravascular injection leading to excessive blood concentrations of the local anesthetic, or systemic absorption of epinephrine combined with the local anesthetic are by far the most common causes of adverse reactions produced by these drugs. Although severe anaphylactic reactions have been reported with both types of local anesthetics, ester local anesthetics, having the capability of producing metabolites related to para-amino-benzoic acid, are more likely than amide local anesthetics to provoke an allergic reaction. Amide local anesthetics have been involved in less than 0.6% of the perioperative reactions.¹⁶

COLLOIDS

All synthetic colloids used to restore intravascular fluid volume have been shown to produce clinical anaphylaxis. The overall incidence of reactions has been estimated to range from 0.033%⁴⁷ to 0.22%.⁴⁸ Gelatins and dextrans are more frequently incriminated than albumin or hetastarch. Direct release of histamine has been reported with urea-linked gelatin, with antihistamine being efficient for the prevention of these

reactions.⁴⁹ Evidence for IgE-mediated adverse reactions to gelatin have also been reported.⁴⁸ In addition, adverse reactions to urea-linked gelatin (0.852%) seem to be more frequent than with modified fluid gelatin (0.338%),⁴⁸ whereas IgG-mediated adverse reactions to hydroxyethyl starch are less frequent. The rate of adverse reactions has been estimated to be 0.275% for dextrans, 0.099% for albumin, and 0.058% for hydroxyethyl starch solutions.⁴⁸

DYE

Vital dyes have been used for many years in a variety of clinical situations and have long been considered a rare cause of anaphylaxis. This association may be due, in part, to misleading nomenclature.⁵⁰ Patent blue V (also called E131, acid blue 3, disulfine blue) and isosulfan blue (also called patent blue violet or lymphazurine), which belong to the group of triarylmethan dyes and share the same formula, are the most commonly used. A recent literature review that included various names of these dyes revealed an impressive number of case reports of hypersensitivity reactions,⁵¹ and it has been suggested that sensitization occurs using everyday products containing blue dyes. In view of the increasing use of blue dyes for lymphatic mapping for sentinel lymph node biopsy, the incidence of anaphylaxis to these drugs can be expected to increase. The mechanism underlying the allergic reaction to patent blue remains unclear. Both direct mast cell and basophil activation and cross-linking of specific IgE antibodies are possible causative factors. Evidence supporting an IgE-mediated mechanism, at least in some patients, comes from two clinical reports, one demonstrating an immune-mediated mechanism by a passive transfer test⁵² and the second demonstrating the presence of specific IgE detected by an ELISA test.⁵³

Methylene blue has also been shown to be an effective dye for sentinel lymph node localization, with only a limited number of complications reported. Anaphylactic reactions involving methylene blue seem to be rare, perhaps because this small molecule does not bind to plasma proteins, reducing the risk of sensitization via a hapten-protein complex. This dye differs structurally from isosulfan blue and patent blue V; therefore, cross-reactivity is not expected. Nevertheless, several reports of sensitization to both patent blue and methylene blue have been reported.^{54,55} These reports support the systematic investigation of a possible cross-reactivity before the use of an alternate dye. A negative skin test with methylene blue in the case of a hypersensitivity reaction to patent blue V or isosulfan blue might be an argument in favor of using methylene blue for future sentinel lymph node mapping.

The clinical diagnosis of reactions elicited by dyes is difficult. Reactions are usually relatively delayed (ie, 30 minutes following injection), long lasting, and justify a prolonged survey in an intensive care unit when prolonged epinephrine administration is necessary.⁵⁴

APROTININ

Aprotinin is a naturally occurring serine protease inhibitor that has found widespread application either by the intravenous route or as a component of biologic sealants because of its ability to decrease blood loss and, as a consequence, transfusion requirements. Anaphylactic reactions are mediated by IgG and IgE antibodies. The risk of anaphylactic reactions has been estimated to range from 0.5% to 5.8% when used intravenously during cardiac surgery; 5 in 100,000 applications are affected when it is used as a biologic sealant.^{56,57} Patients previously treated with this drug present an increased risk, and any new administration should be avoided

for at least 6 months following an initial exposure.⁵⁸ Aprotinin used to reduce blood loss has recently been withdrawn from the market.

OTHER AGENTS

Several cases of allergic reactions to antiseptics have been reported in the literature. They mainly concern allergic reactions to chlorhexidine after insertion of central catheters impregnated with this antiseptic, or after intraurethral use or topical application.⁵⁹ Rare cases of anaphylaxis following topical use of povidone-iodine have been reported.¹⁶

Protamine, whose use to reverse heparin anticoagulation has increased over the last 2 decades, has also been incriminated. Reactions may involve a number of mechanisms including IgE, IgG, and complement. In a recent systematic literature review analyzing 9 retrospective studies and 16 prospective studies, the incidence of anaphylactic reactions was estimated to be 0.19% (retrospective studies) and 0.69% (prospective studies), respectively.⁶⁰

A large number of clinical cases involving many other substances have been published in the literature. These reports underline the importance of a careful and systematic investigation of all substances used during the procedure in the event of perioperative anaphylaxis.

CLINICAL FEATURES

Anaphylaxis is generally an unanticipated reaction. The signs of anaphylaxis occurring during anesthesia differ to some extent from the signs and symptoms that occur during anaphylaxis not associated with anesthesia. All early symptoms usually observed in the awoken patient, such as malaise, pruritus, dizziness, and dyspnea, are absent in the anesthetized patient. In addition, cutaneous signs may be difficult to notice in a completely draped patient, and many signs, such as an increase in heart rate, a decrease in blood pressure, or an increase in airway resistance, may be initially misinterpreted as a result of an interaction between the clinical status of the patient and the drugs administered during the procedure, dose-related site effects of the drugs, or excessively light anesthesia. Reactions may be well established before they are noticed; therefore, vigilance is essential and is the first step toward the diagnosis, successful management, and further investigation of anesthetic anaphylaxis.

The difference between IgE and non-IgE-mediated anaphylactic reactions cannot be made on clinical grounds alone because clinical symptoms and signs can be very similar. Every hypersensitivity reaction occurring during the perioperative period should be investigated to identify the mechanism of the reaction as well as the responsible substance.^{6,61,62} Other differential diagnoses are shown in **Table 2**.

Clinical manifestations show striking variations of intensity in different patients, ranging from mild hypersensitivity reactions to severe anaphylactic shock and death.^{6,13} When a classification based on symptom severity is applied, IgE-mediated reactions are usually more severe than non-IgE-mediated reactions.^{15,16} In addition, for an as yet unexplained reason, IgE-mediated reactions to NMBAs have been shown to be more severe than reactions to other substances like latex in some series.^{14–16}

Anaphylaxis may occur at any time during anesthesia and may progress slowly or rapidly. Ninety percent of reactions appear at anesthesia induction within minutes after the intravenous injection of the offending agent, such as in cases of allergy to an NMBA or antibiotic.^{6,61} If the signs appear later during the maintenance of anesthesia, they suggest an allergy to latex, volume expanders, or dyes. Latex allergy should also be considered when gynecologic procedures are performed. Particles from obstetricians' gloves, which accumulate in the uterus during obstetric

Table 2
Differential diagnosis of anaphylaxis during the perioperative period

All Substances	Succinylcholine
Overdose of vasoreactive substance	Malignant hyperthermia
Asthma	Myotonias and masseter spasm
Arrhythmia	Hyperkalemia
Myocardial infarction	—
Pericardial tamponade	—
Pulmonary edema	—
Pulmonary embolism	—
Tension pneumothorax	—
Venous embolism	—
Sepsis	—
Hereditary angioedema	—
Mastocytosis	—

maneuvers, could suddenly be released into the systemic blood flow following oxytocin injection.¹⁰ Anaphylactic reactions to antibiotics have also been reported following removal of a tourniquet during orthopedic surgery.⁶³

The most commonly reported initial features are pulselessness, difficulty in ventilation, and desaturation.⁹ In the authors' experience, a decreased end-tidal CO₂ is also of diagnostic value. In our most recent series, cutaneous symptoms were observed in 66% to 70% of patients in cases of IgE-mediated reactions, whereas they were present in more than 90% of patients in non-IgE-mediated reactions.^{15,16} On the contrary, cardiovascular collapse and bronchospasm were present in more than 50% and 39% of IgE-mediated reactions but only in 11% and 19% of non-IgE-mediated reactions, respectively.^{15,16} The absence of cutaneous symptoms does not exclude the diagnosis of anaphylaxis. In addition, clinical features may occur in isolation, such as a sudden cardiac arrest without any other clinical signs, as was true in 29 of 491 IgE-mediated reactions in our last published survey.¹⁶ A comparison of the clinical signs observed in IgE-mediated reactions versus non-IgE-mediated reactions based on the results extracted from the French database of the GERAP is detailed in **Table 3**. These results concur with previously published data.^{9,10,13} An anaphylactic

Table 3
Clinical signs observed in IgE-mediated reactions compared with non-IgE-mediated reactions

Clinical Signs	IgE-Mediated Reactions (%)	Non-IgE-Mediated Reactions (%)
Cutaneous symptoms	326 (66.4)	206 (93.6)
Erythema	209	151
Urticaria	101	177
Edema	50	60
Cardiovascular symptoms	386 (78.6)	70 (31.7)
Hypotension	127	50
Cardiovascular collapse	249	12
Cardiac arrest	29	—
Bronchospasm	129 (39.9)	43 (19.5)

reaction restricted to a single clinical symptom (eg, bronchospasm, tachycardia with hypotension) can easily be misdiagnosed because many other pathologic conditions may have an identical clinical presentation. In mild cases restricted to a single symptom, spontaneous recovery may be observed even in the absence of any specific treatment; however, under such circumstances, the lack of a proper diagnosis and appropriate allergy assessment can lead to fatal re-exposure.

In most cases, after adequate treatment, clinical signs regress within an hour without sequelae. In some cases, bronchospasm can be particularly severe and resistant to treatment, with a risk of cerebral anoxia or death. Treatment mainly depends on early adrenaline administration and volume expansion. Adrenaline administration should be tailored to the severity of symptoms (Table 4) (ie, initial dose of 10 to 20 µg intravenously in grade II reactions and 100 to 200 µg in grade III reactions, repeated every 1 to 2 minutes as necessary).² Rapid but goal-oriented administration of adrenaline is mandatory to ensure treatment efficacy but also to minimize potential side effects of treatment.¹⁶ Prolonged inotropic support may also be required in some patients. Moreover, prior treatment with beta blockers is a potential risk factor explaining an absence of tachycardia as well as resistance of arterial hypotension to adrenaline.⁶⁴ In cases resistant to adrenaline, the use of vasoactive drugs such as noradrenaline, glucagons, or even vasopressin or vasopressin analogues has been advocated.

POPULATION AT RISK

The potential severity of anaphylaxis during anesthesia underscores the interest of developing a rational approach to reduce its incidence by identifying potential risk factors before surgery. Although several risk factors occur more frequently in patients with anaphylaxis during anesthesia, their prevalence in the general population is such that few would benefit in terms of preoperative screening for a potential sensitization toward anesthetics.⁶⁵

Recently, recommendations have been proposed concerning the identification of a population at risk for perioperative anaphylaxis who would benefit from preoperative investigation.² Indeed, false-negative results or false-positive results of preoperative investigation could have disastrous consequences in regard to anesthesia by leading to a change to a maladapted anesthesia technique. Patients at risk have been defined as follows:

Patients who are allergic to one of the drugs or products likely to be administered or used during the anesthesia procedure and for whom the diagnosis has been established by a previous allergy investigation

Table 4 Grade of severity for quantification of immediate hypersensitivity reactions	
Grade	Symptoms
I	Cutaneous signs: generalized erythma, urticaria, angioedema
II	Measurable but not life-threatening symptoms Cutaneous signs, hypotension, tachycardia Respiratory disturbance: cough, difficulty to inflate
III	Life-threatening symptoms: collapse, tachycardia or bradycardia, arrhythmias, bronchospasm
IV	Cardiac and/or respiratory arrest

Patients who have shown clinical signs suggesting an allergic reaction during a previous anesthesia

Patients who have presented with the clinical manifestations of allergy when exposed to latex, regardless of the circumstances in which this occurred

Children who have had multiple operations, especially those with spina bifida, because of the high frequency of sensitization to latex and the high incidence of anaphylactic shock caused by latex in such patients

Patients who have experienced clinical manifestations of allergy to avocado, kiwi, banana, chestnut, and buckwheat because of the high frequency of cross-reactivity with latex

In contrast, according to this recommendation, patients who are allergic to a drug or other product that is not likely to be used during the course of the anesthesia or who are atopic (eg, those with asthma or hay fever) should not be considered at risk for perioperative anaphylaxis.² Other recommendations consider patients with a history of hay fever, rhinitis, asthma, or eczema (atopy) as being at risk for latex allergy.⁶⁶

INVESTIGATION OF AN ALLERGIC REACTION

Any suspected hypersensitivity reaction during anesthesia must be extensively investigated using combined perioperative and postoperative testing to confirm the nature of the reaction, to identify the responsible drug, to detect possible cross-reactivity in cases of anaphylaxis to an NMBA, and to provide recommendations for future anesthetic procedures.^{2,67} Although serious attempts have been made to standardize and validate in vitro and in vivo techniques for the diagnosis of drug allergy,^{2,65,67–69} none of the available diagnostic tests demonstrate absolute accuracy. False-positive test results may merely cause an inconvenience (unnecessary avoidance of a safe drug), whereas false-negative or equivocal results may be extremely dangerous and severely undermine correct secondary prevention. The problem in the assessment of the reliability of tests is that, when a single diagnostic test is negative, it is impossible to determine whether it is a false-negative test or whether the patient is tolerant to the tested agent unless the agent is administered. Whenever possible, confirmation of the incriminated allergen should be based on immunologic assessment using more than one test. In the event of discrepancies between different tests, an alternative compound that was completely negative in tests is advocated.

The diagnostic strategy is based on a detailed history including concurrent morbidity, previous anesthetic history, and any known allergies, and a combination of investigations performed both immediately and days to weeks later. Biologic investigations include mediator release assays at the time of the reaction,⁷⁰ quantification of specific IgE immediately or 6 weeks later,^{70,71} skin tests,⁶⁸ and other biologic assays such as histamine release tests or basophil activation assays.^{69,72} Early tests are essentially designed to determine whether an immunologic mechanism is involved. Delayed skin tests attempt to identify the responsible drug.

HISTAMINE AND TRYPTASE

During an IgE-mediated reaction, basophils and mast cells are activated and then degranulate and release mediators in intracellular fluids. These mediators can be measured in the patient's serum and have proved to be useful for the diagnosis of anaphylaxis during anesthesia.^{15,62,70,73,74} Histamine concentrations are maximal almost immediately and decrease thereafter with a half-life of about 20 minutes; therefore, circulating levels should be assayed within the first hour of a reaction, and, in mild

cases, only the early measurements may be increased.⁷³ Histamine assay should be avoided during pregnancy (particularly near term) and in patients receiving high doses of heparin because of a high rate of false negativity due to accelerated histamine degradation. When increased, histamine circulating levels confirm basophil cell activation which can result from direct or IgE-mediated activation. In our most recent study, the sensitivity of this test for the diagnosis of anaphylaxis was estimated to be 75%, the specificity 51%, the positive predictive value 75%, and the negative predictive value 51%. Urinary methylhistamine assays are no longer available.

Tryptase reaches a peak in the patient's serum 30 minutes after the first clinical manifestations. Its half-life is 90 minutes. The levels usually decrease over time, but in some cases, elevated levels can still be detected for up to 6 hours or more after the onset of anaphylaxis.⁷⁰ Basophils and mast cells highly differ in the amount of tryptase contained in their granules; mast cells contain high tryptase levels (12–35 pg/cell) and basophils very low levels (<0.05 pg/cell). Although elevated tryptase levels can be observed in different situations, an elevated tryptase concentration greater than 25 $\mu\text{g.L}^{-1}$ is usually regarded as specific for mast cell activation and differentiates between an IgE-mediated and alternative effector cell activation.^{70,72} The absence of increased serum tryptase does not rule out an allergic reaction.⁷² In our last series, using tryptase measurements for the diagnosis of anaphylaxis, the sensitivity was estimated at 64%, specificity at 89.3%, positive predictive value at 92.6%, and negative predictive value at 54.3%.¹⁵

SPECIFIC IgE ASSAY

In vitro tests are available to detect the presence of serum-specific IgE antibodies. Baldo and Fisher were the first to demonstrate that drug-reactive IgEs were involved in anaphylactic reactions using NMBAs coupled to epoxy Sepharose in a radioimmunoassay.⁷⁵ The detection of antidrug-specific IgE assays in serum is performed by a sandwich-type immunoassay in which the serum IgE is first adsorbed to a reactive phase and subsequently quantified via the binding of an anti-IgE tracer. The reactive phase is prepared by covalently coupling a drug derivative to a solid phase such as nitrocellulose membrane or a polymer.

IgE binding to different NMBAs bound to solid phases and competitive inhibition assays with several muscle relaxants, other drugs, and chemicals including morphine demonstrate a cross-reactivity of specific IgE.^{22,75,76} Nevertheless, some patients do not react with all NMBAs, showing that the substituted ammonium ion is not always the only part of the epitope. Gueant and colleagues⁷⁷ improved a radioimmunoassay method for detecting NMBA-specific IgE in serum using a quaternary ammonium compound coupled to Sepharose (QAS-RIA). The sensitivity of this test was estimated at 88%. An inhibition step in the presence of 130 nmol of soluble drug is performed, and in most cases, the highest inhibition is observed with the incriminated drug (83.3%). Guilloux and colleagues⁷⁸ have developed a radioimmunoassay test by coupling p-aminophenyl phosphoryl choline on agarose (PAPPC-RIA). P-aminophenyl phosphoryl choline contains a larger choline derivative (quaternary ammonium ion), including a secondary ammonium group, an aromatic ring, and a phosphate group. Both methods were found to have similar sensitivity and specificity. Recently, Fisher and Baldo⁷⁶ supported the use of a morphine-based immunoassay for the detection of specific IgE to ammonium ions in the sera of sensitized subjects. More recently, Ebo and colleagues⁷⁹ investigated the diagnostic value of quantification of IgE by the ImmunoCAP method (Phadia AB, Uppsala, Sweden) in the diagnosis of rocuronium allergy. They also studied whether IgE inhibition tests can predict clinical

cross-reactivity between NMBA. They concluded that the rocuronium ImmunoCAP constitutes a reliable technique to diagnose rocuronium allergy provided an assay-specific decision threshold is applied, because these assays reach a sensitivity of more than 85% and absolute specificity.

Specific IgEs against thiopental, morphine, phenoperidine, and propofol have also been detected in the serum of sensitized patients using IgE radioimmunoassays.^{80,81} The presence of hydrophobic IgE reacting nonspecifically with propofol has been reported.⁸² With respect to latex, a radioallergosorbent test is available. Although it is considered to be less sensitive than the skin prick test, a 92.8% sensitivity has been reported.⁸³

These findings have recently led to limiting the indications for specific IgE assays to the diagnosis of anaphylaxis to NMBA, thiopental, and latex.² These tests are usually performed several weeks after the reaction but also can be performed at the time of the reaction.^{2,70,71}

SKIN TESTING

In most reports, skin tests in association with history remain the mainstay of the diagnosis of an IgE-mediated reaction. Intradermal skin or prick tests are usually performed 4 to 6 weeks after a reaction, because, before 4 weeks, the intracellular stocks of histamine and other mediators are still lower than normal.⁸⁴ Skin tests to NMBA may remain positive for years later. Ideally, testing should be performed by a professional experienced in performing and interpreting tests with anesthetic agents (Table 5).²

Prick tests and intradermal reactions with dilutions of commercially available drug preparations are advised. Although highly reliable, skin tests are not infallible.⁸⁵ Standardized procedures and dilutions must be precisely defined for each agent tested to avoid false-positive results. Control tests using saline (negative control) and codeine (positive control) must accompany skin tests to determine whether the skin is apt to release histamine and react to it.

A certain degree of controversy remains as to the maximal concentrations to be used when sensitization to NMBA is investigated.^{86,87} Detailed recommendations for skin and intradermal test dilutions of anesthetic drugs including NMBA have been proposed by the SFAR and the French Society of Allergology (Société Française d'Allergologie et d'Immunologie Clinique) (Table 5).² The accuracy of these recommended maximal concentrations has been confirmed in a prospective study conducted in 120 healthy volunteers tested with all NMBA available at increasing concentration both on the anterior part of the forearm and the back. Results were similar on both injection sites.⁶⁸ Skin tests are interpreted after 15 to 20 minutes. A prick test is considered positive when the diameter of the wheal is at least equal to half of that produced by the positive control test and at least 3 mm greater than the negative control. Intradermal tests are considered positive when the diameter of the wheal is twice or more the diameter of the injection wheal.

Any drug administered during the perioperative period should be considered as a potential cause.⁶¹ In addition, because of the frequent but not systematic cross-reactivity observed with muscle relaxants, all available NMBA should be tested.^{2,13,64,72} In most cases, patients allergic to one muscle relaxant can be given another agent chosen on the basis of skin test screening. In our experience, we suggest that the concentration of muscle relaxant used for skin testing be increased to a dilution of 10^{-1} of the commercially available substance tested to reduce false-negative results. Furthermore, we recommend leukocyte histamine release or

Table 5 Concentrations of anesthetic agents normally nonreactive in practice of skin tests					
Available Agents		Prick Tests		Intradermal Tests	
INN	Concentration (mg · mL ⁻¹)	Dilution	Maximal Concentration (mg · mL ⁻¹)	Dilution	Maximal Concentration (μg · mL ⁻¹)
Atracurium	10	1/10	1	1/1000	10
Cis-atracurium	2	Undiluted	2	1/100	20
Mivacurium	2	Undiluted	0.2	1/1000	2
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium	10	Undiluted	10	1/100	100
Suxamethonium	50	1/5	10	1/500	100
Vecuronium	4	Undiluted	4	1/10	400
Etomidate	2	Undiluted	2	1/10	200
Midazolam	5	Undiluted	5	1/10	500
Propofol	10	Undiluted	10	1/10	1000
Thiopental	25	Undiluted	25	1/10	2500
Alfentanil	0.5	Undiluted	0.5	1/10	50
Fentanyl	0.05	Undiluted	0.05	1/10	5
Morphine	10	1/10	1	1/1000	10
Remifentanil	0.05	Undiluted	0.05	1/10	5
Sufentanil	0.005	Undiluted	0.005	1/10	0.5
Bupivacaine	2.5	Undiluted	2.5	1/10	250
Lidocaine	10	Undiluted	10	1/10	1000
Mepivacaine	10	Undiluted	10	1/10	1000
Ropivacaine	2	Undiluted	2	1/10	200

Abbreviation: INN, International Nonproprietary Name.

Data from Mertes PM, Laxenaire MC. [Anaphylactic and anaphylactoid reactions occurring during anaesthesia in France: seventh epidemiologic survey (January 2001–December 2002)]. *Ann Fr Anesth Reanim* 2004;23(12):1133–43 [in French].

basophil activation testing of the muscle relaxant selected on the basis of a negative skin test to ensure an absence of an in vitro basophil activation release. This testing should help avoid future adverse reactions and provide documented advice for the future administration of anesthesia.^{2,13} No diagnostic procedure can be devoid of false-positive or false-negative results. Although rare, some cases have been reported of renewed allergic reactions following exposure to an NMBA considered to be safe.^{85,88} When administering an NMBA to a sensitized patient with a negative skin test, one should bear in mind the risk-benefit ratio. In addition, any new muscle relaxant should be routinely tested in patients known to be allergic to this class of agents to detect possible cross-reactivity.²

The estimated sensitivity of skin tests for muscle relaxants is approximately 94% to 97%.⁸⁹ The sensitivity for other substances varies. It is good for synthetic gelatins and β-lactams but poor for barbiturates, opioids, and benzodiazepines.¹³ There has been some controversy concerning the advantages of prick versus intradermal testing. Studies comparing both techniques show little differences between them;^{90,91} however, reliability over time concerning prick testing has not been assessed, and the reliability of prick tests alone in the individual patient has been questioned by some authorities.⁹² Consequently, prick testing is advised for the diagnosis of the

muscle relaxant responsible for an anaphylactic reaction, but intradermal testing should be preferred when investigating cross-reaction.⁹³ Latex sensitization must be investigated by prick tests using two different commercial extracts.⁹⁴ Both prick and intradermal tests have been proposed in the literature for the diagnosis of sensitization to blue dyes; however, false-negative prick tests have been occasionally reported in the literature. These reports strongly suggest favoring intradermal tests using up to a 1:100 dilution for the diagnosis of sensitization to blue dyes in patients with a history of a possible immediate hypersensitivity reaction to dyes.⁵⁴

MEDIATOR RELEASE TESTS

Basophil Activation Evaluation by Secreted Mediator Assays

Allergen-induced mediator release tests quantify mediators released during effector cell degranulation, mainly peripheral blood basophils, following stimulation with specific antigen. There are two categories of mediator release tests: histamine release tests and sulphidoleukotriene release tests (cellular allergen stimulation test). Mata and colleagues⁹⁵ evaluated in vitro leukocyte histamine release tests for the diagnosis of allergy to muscle relaxant drugs in 40 patients and a control group of 44 subjects with negative leukocyte histamine release. The tests were positive in 65% of the allergic patients, for a threshold corresponding to specificity at 100%. The concordance between the leukocyte histamine release test and QAS-RIA was 64%.^{95,96} Despite good specificity, the diagnostic application of these tests remains limited because of the heavy experimental conditions and insufficient sensitivity; therefore, they are not used as routine diagnostic tests.² They could be useful when cross-reactivity among muscle relaxants is investigated with a view to future anesthesia in sensitized patients. Similarly, reports concerning the monitoring of serotonin,⁹⁷ eosinophil cationic protein,⁹⁸ or LTC₄⁹⁹ release have also been published; however, these assays cannot be recommended in routine clinical practice at the present time.

Flow Cytometry

The basis of flow-assisted allergy diagnosis relies on quantification of shifts in the expression of basophilic activation markers after challenge with a specific allergen using specific antibodies conjugated with a fluorochrome or dye. Activated basophils not only secrete quantifiable bioactive mediators but also up-regulate the expression of different markers which can be detected efficiently by flow cytometry using specific monoclonal antibodies.^{69,100–103} Currently, the most commonly used antibody in allergy diagnosis is anti-CD63 and, to a lesser extent, anti-CD203c. This technique has been clinically validated for several classical IgE-mediated allergies, including indoor and outdoor inhalant allergies, primary and secondary food allergies, natural rubber latex allergy, Hymenoptera venom allergy, and some drug allergies.⁶⁹ Although it does not allow differentiating between IgE-dependent and IgE-independent basophil activation, it is anticipated that it might constitute a unique tool in the diagnosis of IgE-independent hypersensitivity reactions as well as the diagnosis of IgE-mediated anaphylaxis when a specific IgE assay is unavailable.^{69,104} Several methodologic issues remain to be addressed, including realization of the test on whole blood or isolated basophils, the need for preactivation with IL-3, the choice of appropriate dose for different allergens, positive and negative controls, characterization and activation markers, and the appropriate diagnostic threshold for different allergens.⁶⁹ Nevertheless, once fully validated, the basophil activation test using flow cytometry will probably represent an interesting diagnostic tool for NMBA anaphylaxis and cross-sensitization studies.

Challenge Tests

Indications for these tests are limited. They are restricted to local anesthetics, β -lactams, and latex.¹⁰⁵ They should only be performed in the situation of negative skin tests. Local anesthetics can be tested by subcutaneously injecting 0.5 to 2 mL of undiluted anesthetic solution (without epinephrine). The test is considered negative if no any adverse reaction occurs within 30 minutes after injection.¹⁰⁶

PREVENTION**Primary Prevention**

Prevention of anaphylaxis has two major objectives: (1) preventing the sensitization of a patient to a particular allergen, or (2) preventing the occurrence of an anaphylactic reaction to a reintroduced allergen in a presensitized patient. In this regard, prevention of latex allergy in spina bifida or multioperated children by primary prevention, which consists of avoiding latex during medical and surgical care of these patients, has been found to be very effective.¹⁰⁷ Similarly, the wearing of powderless, low-latex-allergen gloves by health care workers has been proposed as a possible means to reduce the levels of latex aeroallergen in the operating room and the rate of sensitization to latex in health care workers.

Secondary Prevention

Avoidance of causal agent

Prevention of anaphylactic reactions relies mainly on accurate documentation of previous reactions and avoidance of the incriminated drug. During the preanesthetic consultation, a detailed history should be taken with special emphasis on atopy, drug allergy, and allergy to latex and tropical fruits. The use of a specific questionnaire is particularly helpful.^{64,105}

Latex-sensitive patients should be managed by complete avoidance of potential latex exposure.^{105,108} This avoidance is most easily achieved if a comprehensive institutional policy exists. Patient care must be carefully coordinated among all professionals, including pre- and postoperative nursing and operating teams. Whenever possible, the patient should be scheduled for elective surgery as the first case of the day to reduce exposure to aerosolized latex particles. Warnings identifying a risk for latex allergy should be posted inside and outside the operating room and in perioperative care areas, and the patient should wear a medical alert bracelet or necklace. A checklist of recommendations should accompany the patient throughout his or her hospital stay. In addition, a list of readily available non-latex alternatives should be established in collaboration with the facility's central supply service and should be prominently displayed in patient care locations.

Steroids and Antihistamines

Pretreatment with corticosteroids or histamine receptor antagonists, by either H₁ or H₁ and H₂ receptor antagonists, remains controversial. It has been proposed as an efficient way to reduce anaphylaxis due to chymopapaine administration.¹⁰⁹ Prophylaxis has also been found to reduce the severity but not the overall incidence of adverse reactions to dye.¹¹⁰

Pretreatment with H₁ and H₂ receptor antagonists has been found to reduce histamine-mediated adverse effects in various studies.^{42,49} Antihistamine administration was effective in reducing the adverse effects of nonimmune histamine release following muscle relaxant, gelatin,⁴⁹ or vancomycin⁴² administration.

Histamine detected during alarming immune-mediated reactions is merely a marker of the co-release of more dangerous mediators. Allergic reactions to anesthetic drugs have been documented in several epidemiologic surveys even when H₁ and H₂ receptor antagonists and steroids were applied preoperatively.^{14–16} No evidence of beneficial effects of the prophylactic administration of corticosteroids in allergic reactions to anesthetic drugs have been shown. Many authorities believe that pretreatment with corticosteroids, antihistamines, or both does not reliably prevent immune-mediated reactions.⁹²

Monovalent Hapten Inhibition

Monovalent hapten inhibition with hapten dextran has been shown to significantly reduce but not completely abolish adverse reactions to dextran.¹¹¹ The use of monovalent haptens, which can occupy antibody sites without bridging specific IgE fixed on sensitized cells, has also been proposed for muscle relaxants. In this respect, any molecule presenting a substituted tertiary or quaternary ammonium ion could be considered as a potential monovalent hapten. Although choline and tiemonium were initially used, clinical tolerance of the highest doses was poor. As a result, the concentrations obtained were too low to be effective.²³ Moneret-Vautrin and colleagues¹¹² demonstrated inhibition of skin mast-cell reactivity to muscle relaxants by mixing them with the monovalent haptens cytidylcholine and ethamsylate. Furthermore, they obtained an inhibition of leukocyte histamine release for up to 3 hours following the infusion of these monovalent haptens in patients allergic to muscle relaxants. Morphine, with its high affinity to reactive muscle relaxant antibodies, has also been proposed as a possible preventive hapten;¹³ however, large doses of morphine would be necessary, and H₁ and H₂ receptor antagonists would be required to counteract the cardiovascular effects of such high doses. This possibility has not yet been evaluated, and prevention of NMBA-induced anaphylaxis by monovalent haptens cannot be recommended at present in standard clinical practice.²

SUMMARY

Perioperative anaphylaxis remains a significant adverse event during anesthesia that remains underestimated because it is underreported. NMBAs, latex, and antibiotics are the most frequently involved drugs, but any drug used during the perioperative period might be involved. Because no premedication can effectively prevent an allergic reaction, any suspected hypersensitivity reaction must be investigated to confirm the anaphylaxis and to identify the eliciting drug. Patients must be fully informed about the investigations and advised to provide a detailed report before future anesthesia. The wearing of a warning bracelet or possession of a warning card is mandatory.

With the exception of high-risk patients, systematic preoperative screening for sensitization against anesthetic drugs is not justified at this time. A thorough pre-anesthetic history is the most important tool for screening at-risk subjects. Particular attention must be paid to patients who have already experienced such a reaction during anesthesia, those alleging an allergy to muscle relaxants, or those at risk of latex sensitization. In these patients, the choice of the safest possible anesthetic agents should be based on the result of a rigorously performed allergologic assessment.

In view of the relative complexity of allergy investigation, an active policy to identify patients at risk and to provide all necessary support from providing expert advice to anesthesiologists and allergologists to the constitution of allergeo-anesthesia centers should be promoted.

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