

Local and General Anesthetics Immediate Hypersensitivity Reactions

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KEYWORDS

• Anesthetics • Allergy • Anaphylaxis • Perioperative • Skin tests

KEY POINTS

- Immediate hypersensitivity reactions can occur with the use of anesthesia and are associated with significant morbidity and mortality.
- Evaluation of anaphylactic reactions in the anesthesia setting can be complex because of the large number of medications administered in the same time frame.
- Neuromuscular blocking agents, antibiotics, and latex are the most common causes of anesthesia-associated allergic reactions, though multiple medications and products may be causative.
- All patients with a history of an anesthesia-related hypersensitivity reaction should have an allergy evaluation to identify the cause.
- Allergy evaluation of an anesthesia-related hypersensitivity reaction may include skin tests, intradermal tests, challenges, in vitro specific-immunoglobulin E testing, or basophil activation test.

Hypersensitivity reactions occurring during anesthesia are rare but can rapidly evolve into life-threatening anaphylaxis, although rapid recognition and treatment of such reactions can prevent much of the morbidity and mortality that would otherwise occur.¹ Unfortunately, screening tests to prevent anaphylaxis during anesthesia are unlikely to have a significant impact on reducing the incidence of these reactions.² This incidence can be reduced by preventing subsequent reactions in patients with a history of anaphylaxis or with major undiagnosed or undocumented adverse events during previous anesthesia.³

It is important for the investigating physician to be aware that the perioperative setting represents a pharmacologically unique situation, during which patients are

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exposed to multiple foreign substances that have the potential to produce a variety of predictable and unpredictable adverse reactions. As a consequence, anesthesiologists are more likely to witness and manage immediate hypersensitivity reactions than other physicians. However, some of the clinical features of anaphylaxis can also be mimicked by other complications of anesthesia, such as hypotension and vasodilation resulting from anesthesia induction, difficulty in tracheal intubation, inadequate depth of anesthesia, hypovolemia, and hemorrhage. Investigation can be challenging, as patients are exposed to many coadministered drugs and agents that have all been associated with anaphylaxis. However, most reactions are accounted for by a relatively small number of agents.⁴

OVERVIEW OF INTRAOPERATIVE ANAPHYLAXIS

Terminology

The surveillance of perioperative anaphylaxis represents a statistical challenge because these reactions are rare, random, and there is no clear relationship between risk and repeated anesthetic use. Another weakness of any review of epidemiologic studies on the subject is the lack of a consensus definition and the heterogeneous use of terms in the literature.

Initially, the term *anaphylaxis* was used only for immunoglobulin E (IgE)-mediated reactions, whereas the term *anaphylactoid* was used for a reaction occurring via a non-IgE-dependent mechanism. However, anesthesiologists usually have little understanding of which drug is actually causing the anaphylactic reaction when several drugs are simultaneously administered as well as of the underlying mechanism.⁵ Therefore, a new definition has been proposed by the European Academy for Allergy and Clinical Immunology whereby all reactions are described as anaphylaxis and subdivided into allergic (IgE or IgG mediated)⁶ or nonallergic anaphylaxis only after diagnostic investigation.⁷

Incidence

Several series from different countries have estimated the incidence of clinical anaphylaxis during anesthesia to be between 1 in 1250 and 10,000.⁸ Despite the reported variations, probably reflecting differences in clinical practice and reporting systems, the proportion of IgE-mediated reactions seems to be relatively similar between countries, ranging from 50% to 60%.^{1,9–15} However, substantial variability regarding the different drugs or agents involved is reported, reactions involving neuromuscular blocking agents (NMBAs) being more frequent in several countries,^{4,10,12,13,16} whereas allergic reactions involving antibiotics or chlorhexidine seem to be more frequent in the United States⁹ and in Denmark,¹⁷ respectively.

Mortality

Despite the fact that these reactions are witnessed and occur in a monitored setting, an unfavorable outcome may occur even when they are appropriately treated. A perioperative mortality rate of 4.76% has been recorded for all causative drugs in Japan¹⁸ and a 4% rate in the United States.¹⁹ According to the Yellow Card Scheme, overall mortality was even higher in the United Kingdom (9%).²⁰ These high rates contrast strongly with the low rate of 0% to 1.4% recently reported for Western Australia (2000–2009).²¹ There are several reasons for high mortality from anaphylactic reactions despite trained staff being present in the operating room and despite short management delays. These reasons include patient frailty caused by the underlying condition prompting surgery, especially emergency surgery; the intrinsic

cardiopulmonary depressive effects of anesthetics; a short reaction time caused by the massive dose of allergen administered intravenously; and a reputedly more severe reaction on administration of drugs, such as NMBA or intravenous antibiotics.²²

Clinical Presentation

Anaphylaxis may occur at any time during anesthesia and may progress slowly or rapidly. The end-organ effects of the variety of mediators resulting from effector cells activation produce the clinical syndrome of anaphylaxis. True allergic reactions require immune-mediated release of mediators. In contrast, other mechanisms can release the vasoactive substances that produce this clinical syndrome. Almost every organ and system may be affected, although patients' medical history may influence both the nature and severity of the clinical symptoms. Asthmatic patients are more likely to have significant bronchospasm,²³ whereas patients with preexisting cardiac disease or those taking β -adrenoceptor blockers are more likely to develop severe hypotension and shock.²⁴

The route of administration and the nature of the allergen will affect the clinical course of the reaction. Ninety percent of reactions appear at anesthesia induction, or at the end of the procedure, within minutes or seconds after the intravenous injection of an offending agent, such as antibiotics, NMBA, aprotinin, or analgesics. However, reactions may be delayed up to 4 hours when a labile blood product is incriminated.²⁵ Reactions resulting from infiltration of dyes^{26,27} or of mucous membrane or skin exposure to latex or disinfectants tends to lead to reactions of slower onset.^{28–30}

The clinical diagnosis is presumptive, although essential, because anaphylaxis may progress within minutes to become life threatening. The signs and symptoms differ to some extent from those of anaphylaxis not associated with anesthesia. All early symptoms usually observed in awake patients, such as malaise, pruritus, dizziness, and dyspnea, are absent in anesthetized patients, whereas most individual symptoms of anaphylaxis have a more common cause; diagnosis will often be made only after other likely causes have been excluded. In addition, in mild cases, spontaneous recovery may be observed even in the absence of any specific treatment. Under such circumstances, the lack of a proper diagnosis and appropriate allergy assessment may lead to fatal reexposure.³

Urticaria and angioedema, symptoms highly evocative of the onset of anaphylaxis, may be missed because patients are draped. Moreover, clinical features may occur in isolation, such as a sudden cardiac arrest without any other clinical signs; the absence of cutaneous symptoms does not exclude the diagnosis of anaphylaxis. The attending anesthesiologist can easily misdiagnose hypotension secondary to colloids administered to treat hypotension resulting from sympathetic blockade associated with spinal or epidural anesthesia or from intraoperative hemorrhage.

An acute coronary vasospasm, or Kounis syndrome, resulting from cardiac mast cell activation can also be erroneously attributed to a preexisting coronary artery disease.³¹

Drug Allergy Work-up

The diagnosis of perioperative anaphylaxis begins with a detailed symptom history, and a time frame between the injection of the incriminated drugs and the onset of the reaction is very helpful. The diagnostic strategy is based on laboratory tests performed on samples taken during and shortly after the reaction and on allergy tests carried out days to weeks later, which mainly include skin tests, specific IgE assays, and basophil activation tests. Early tests are mainly designed to determine whether or not

an allergic mechanism is involved, whereas later testing attempts to identify the responsible drug and potential safe alternatives.

None of the available diagnostic tests is absolutely accurate. False-positive test results may cause unnecessary avoidance of a safe drug, whereas false-negative or equivocal results may severely undermine correct secondary prevention. Therefore, in the event of discrepancies between history and skin tests, challenge tests (when possible) and/or in vitro tests must be used to increase the overall sensitivity of the diagnostic procedure.

Tryptase and histamine

Tryptase levels acquired at the time of the reaction can be helpful. Mast cells activated during an IgE-mediated hypersensitivity reaction release proteases such as tryptase as well as stored histamine and newly generated vasoactive mediators. Because in human basophils, tryptase content is 300- to 700-fold less than in mast cells, tryptase levels in serum are used as a marker for systemic mast cell activation. Although it can be marginally elevated in different situations, an increased serum tryptase concentration in an acute setting strongly suggests an allergic mechanism. There is no consensus in the literature as to the cutoff point that should be used to consider a tryptase result as elevated.³² A level greater than $25 \mu\text{g/L}^{-1}$ has been proposed when a single measurement is performed,²⁴ but lower cutoff values ranging between 8.23 and $11.4 \mu\text{g/L}$ have been proposed to increase tryptase sensitivity.³³ However, the use of a cutoff value without taking baseline levels into account is not always appropriate, as baseline levels higher than the cutoff point established can be found in some comorbidities, such as systemic mastocytosis. Therefore, the measurement of basal tryptase is now recommended²⁴; a 2-fold increase compared with the basal level is considered significant.³² Nevertheless, a normal tryptase level does not completely rule out anaphylaxis. Increased tryptase levels in postmortem sera suggest systemic anaphylaxis as a cause of death.³⁴

Histamine measurement at the time of the reaction has also been proposed in the literature. 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; in mild cases, only early measurements may be increased. Histamine has a greater sensitivity than tryptase³² but does not allow to distinguish IgE-mediated from non-IgE-mediated reactions. Histamine assays should not be measured during pregnancy (particularly closer to delivery) and in patients receiving high doses of heparin because of a high rate of false-negative results caused by accelerated histamine degradation.

Skin testing

Skin prick test (SPT) and intradermal test (IDT) with immediate readings are the most commonly used procedures for investigation of immediate hypersensitivity reactions, although their reliability somewhat depends on which class of drug is being tested. The sensitivity of skin tests seems to be moderate to high for immediate hypersensitivity reactions to most perioperative drugs. Several factors may contribute to the variability of skin test results, including the individual's biologic responsiveness, the technique used to perform the test, the reagents (stability, vehicle, allergen concentration, purity), and the method used to grade skin reactions. Therefore, a validated protocol should be used; recent guidelines have been published in an effort to standardize the concentrations to be used (Table 1).^{24,35}

Control tests using saline (negative control) and codeine or histamine (positive control) must accompany skin tests to determine whether or not the skin is able to release

Table 1
Maximal concentrations normally nonreactive for SPT and IDT

Available Agents	SPT		IDT		
	Conc (mg/mL ⁻¹)	Dilution	Cmax (mg/mL ⁻¹)	Dilution	Cmax (mg/mL ⁻¹)
NMBAs					
Atracurium	10.0	1/10	1.0	1/1000	0.01
Cis-atracurium	2.0	Undiluted	2.0	1/100	0.02
Mivacurium	2.0	1/10	0.2	1/1000	0.002
Pancuronium	2.0	Undiluted	2.0	1/10	0.2
Rocuronium	10.0	Undiluted	10.0	1/200	0.05
Vecuronium	4.0	Undiluted	4.0	1/10	0.4
Suxamethonium	50.0	1/5	10.0	1/500	0.1
Hypnotics					
Etomidate	2.0	Undiluted	2.0	1/10	0.2
Midazolam	5.0	Undiluted	5.0	1/10	0.5
Propofol	10.0	Undiluted	10.0	1/10	1.0
Thiopental	25.0	Undiluted	25.0	1/10	2.5
Ketamine	100.0	1/10	10.0	1/100	1.0
Opioids					
Alfentanil	0.5	Undiluted	0.5	1/10	0.05
Fentanyl	0.05	Undiluted	0.05	1/10	0.005
Sufentanil	0.005	Undiluted	0.005	1/10	0.0005
Remifentanil	0.05	Undiluted	0.05	1/10	0.005
Morphine	10.0	1/10	1.0	1/1000	0.01
Local anesthetics					
Bupivacaine	2.5	Undiluted	2.5	1/10	0.25
Lidocaine	10.0	Undiluted	10.0	1/10	1.0
Mepivacaine	10.0	Undiluted	10.0	1/10	1.0
Ropivacaine	2.0	Undiluted	2.0	1/10	0.2

Abbreviations: Cmax, maximal concentration; Conc, concentration.

Adapted from Mertes PM, Malinovsky JM, Jouffroy L, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011;21(6):447; with permission.

histamine and react to it. Immediate reactions (wheal and erythema) are read at 15 to 20 minutes. An SPT is considered positive when the diameter of the wheal is at least equal to half of that produced by the positive control and at least 3 mm larger than the negative control. For IDT, 0.02 to 0.05 mL of solution is injected into the dermis in order to create a postinjection wheal of up to 4 mm in diameter. An IDT is considered positive when the diameter of the wheal is at least twice the injection wheal. Skin tests should be performed 4 to 6 weeks after the reaction. If necessary, they can be performed earlier.³⁶ This practice, however, increases the risk of false-negative results; only positive results are taken into account.³⁷ Early assessment does not replace the one performed after a period of 4 to 6 weeks.²⁴

Specific IgE immunoassays

Allergen-specific IgE immunoassays are also important complementary tests in the diagnosis of perioperative immediate hypersensitivity reactions. Quantification of

drug-specific IgE (slgE) relies on the detection of a drug-carrier-antibody complex. Basically, the drug or the hapten is coupled with a solid phase, which is incubated with the patients' serum. The amount of slgE bound is subsequently detected with a secondary antihuman IgE antibody labeled formerly with a radioisotope radioimmunoassay and nowadays with an enzyme with colorimetric reading (enzyme-linked immunosorbent assay [ELISA]) or with fluorescence reading (FEIA).

The search for specific IgE in serum mainly concerns NMBA, thiopental, latex, β -lactams, chlorhexidine, ethylene oxide, and pholcodine (PHO). These tests can be performed either in conjunction with skin tests or in the event of discrepancies between evocative history and negative skin tests.

Basophil activation test

Historically, activation of basophils was analyzed by the measurement of cysteinyl leukotriene or histamine release *ex vivo*.^{38,39} These techniques are progressively replaced by flow cytometry (*Basophil activation test* [BAT]) used to quantify the shift in expression of basophilic activation markers (CD63 and CD203c) after challenge with a specific allergen using specific antibodies conjugated with a fluorochrome or a dye.⁴⁰

Cellular assays do not allow differentiating between IgE-dependent and IgE-independent basophil activation but might constitute a unique tool in the diagnosis of IgE-independent hypersensitivity reactions. In addition, they may be of particular interest for the diagnosis of IgE-mediated anaphylaxis to compounds that are skin irritant when a specific IgE assay is unavailable. BAT is very useful when skin test results are difficult to interpret (eg, in patients with dermographism; extensive atopic skin lesions; or patients on medication with antihistamine effects, such as antidepressants and antihistamines, which cannot be stopped).²⁴ They also seem complementary to skin testing in the assessment of cross-reactivity between drugs.⁴¹

Challenge tests

Provocation testing represents a gold standard when investigating an immediate hypersensitivity reaction but has limited indications in perianesthetic anaphylaxis because of the pharmacologic effects of anesthetics. These tests can be performed with drugs or agents for which skin tests cannot be conducted or when skin tests are negative (local anesthetics, antibiotics, or, exceptionally, latex) or not validated (NSAIDs). Local anesthetics can be tested by subcutaneously injecting 0.5 to 2.0 mL of undiluted anesthetic solution (without epinephrine). The test is considered negative if no hypersensitivity reaction occurs within 30 minutes after the injection. Oral provocation tests are useful for the diagnosis of β -lactam hypersensitivity when skin tests are negative. These tests should be conducted under strict supervision and only in specialized centers with monitoring and resuscitation facilities.²⁴

GENERAL ANESTHETICS

Neuromuscular Blocking Agents

Immune-mediated reactions

NMBAs represent the class of drugs most commonly implicated in perioperative anaphylaxis, although striking differences can be observed between countries. Reactions are almost exclusively IgE mediated. Delayed allergic reactions have been described on rare occasions and concern only suxamethonium.^{42,43}

In one of the largest reports, perioperative anaphylaxis was evaluated over an 8-year period from 1997 to 2004 using a combined analysis of 3 different French databases. Among the 1816 patients with IgE-mediated reactions, the most common

cause for these allergic events were NMBAs (58%, $n = 1067$).⁴ Reactions have also been reported with a high frequency in Australia and New Zealand,⁴⁴ the United Kingdom,¹⁶ and Norway.¹² They seem to be relatively frequent in Spain, accounting for 37% of the reactions observed,¹⁰ but less frequent in Sweden⁴⁵ and Denmark.¹⁷ Information about the incidence or agents implicated in perioperative anaphylaxis in the United States is very limited. NMBAs have been recently reported to be the offending agent in 11% of cases of perioperative anaphylaxis in a single-center study.⁹

Cross-reactivity

NMBAs are divalent ammonium compounds that bind to the α -subunit of the acetylcholine receptor at the neuromuscular junction. Structure-activity studies have long established that these substituted ammonium ions were the complementary allergenic sites involved in specific IgE recognition. This finding explains the frequent cross-reactivity between the different NMBAs observed in 60% to 70% of patients allergic to NMBAs identified by skin testing.^{46–54} The patterns of cross-reactivity vary considerably between patients. Cross-reactivity to all NMBAs is unusual but seems to be more frequent when an aminosteroid NMBA is involved in the initial reaction rather than a benzylisoquinoline-derived NMBA.^{1,55} The IgE recognition site of the molecule also depends on the molecular environment of the ammonium ion.^{56,57}

This IgE recognition site and the molecular environment explains the heterogeneity of the cross-reactivity among patients but also part of the differences regarding the relative risk of allergic reactions between NMBAs that have been recognized in large epidemiologic surveys.^{13,58,59} There is a broad consensus to consider succinylcholine as an agent with a high risk of anaphylaxis in the literature, whereas pancuronium and cis-atracurium are the NMBAs associated with the lowest incidence.^{13,60} Regarding the relative risk of anaphylaxis to rocuronium, things are more controversial. An increased frequency of allergic reactions to rocuronium was initially reported in Norway⁶¹ and rapidly confirmed in France.²² Unfortunately, this created controversy. The rapid increase in the rate of rocuronium anaphylaxis in Australia from 1996 to 1999 was assumed to be a result of increased market share,⁶² whereas, based on normalized market-share data provided by the manufacturer for 1996 to 1999 in the United Kingdom, the rate of rocuronium anaphylaxis was considered as similar to that of vecuronium and atracurium.⁶³ Within the same period of time, Bhananker and colleagues⁶⁴ reported a similar rate of reactions to rocuronium and vecuronium in the United States. More recently, this increased risk of allergic reactions has been confirmed in Australia, with a 4-fold increased risk with rocuronium when compared with vecuronium.⁵⁵

Several hypotheses have been provided to explain the apparent increased risk of allergic reactions to succinylcholine and rocuronium. The flexibility of the chain between the ammonium ions and the distance between the substituted ammonium ions might be of importance to favor cross-linking of IgEs bound at the surface of effector cells. Therefore, flexible molecules, such as succinylcholine, are considered more potent in stimulating sensitized cells. Similarly, in the past, alcuronium was claimed to be a high risk for anaphylaxis. Alcuronium and rocuronium share the same propenyl ammonium group in their structure, which might be involved in their increased allergenicity. These considerations represent an important issue in the design of an ideal NMBA with a reduced risk of allergic reactions.

Origin of sensitization to NMBAs

In contrast to the immunologic dogma of previous exposure, a substantial proportion of patients with NMBA IgE-mediated anaphylaxis have never been exposed to a

muscle relaxant before, suggesting that there must be environmental factors that play a role in cross-sensitizing patients against NMBA.⁶⁵ Because compounds containing tertiary and/or quaternary ammonium groups occur widely in the human environment in drugs, cosmetics, and disinfectants, sensitization to NMBA may occur via these sources. Although this hypothesis has long been considered as difficult to prove,⁶⁶ a recent study conducted in hairdressers has demonstrated a significant increase in IgE sensitization to NMBA and quaternary ammonium ion compounds, suggesting that repetitive exposure to quaternary ammonium compounds used in hairdressing is a risk factor for NMBA sensitization.⁶⁷ Another attractive hypothesis arises from the work published by Florvaag and Johansson⁶⁸ who provided repeated evidence for a connection between the consumption of PHO, an opioid antitussive, and IgE-mediated anaphylactic reactions to NMBA. They demonstrated that PHO, which is sold over the counter in many countries, is a strong inducer of an IgE antibody response that leads to sensitization of 20% to 25% of the exposed patients. However, PHO is monovalent for 2 non-cross-reacting epitopes, a quaternary ammonium ion and a non-quaternary ammonium epitope. Thus, PHO itself is not able to induce an allergic reaction in sensitized patients. However, the presence of the PHO-induced IgE to a quaternary ammonium ion will result in a 200- to 300-fold increased risk of anaphylaxis when these patients will be exposed to a bivalent NMBA during a general anesthesia. These results led to the withdrawal of PHO from the Norwegian market, resulting in the decrease of IgEs to quaternary ammonium ions in the population and in the number of reports of allergic reactions to NMBA.⁶⁹ A prospective case control study designed to confirm this possible link between PHO exposure and sensitization to NMBA will start in 2014 in France.

Nevertheless, immediate hypersensitivity reactions involving an NMBA are not always immune mediated. A direct nonspecific mast cell and basophil activation leading to histamine release has been reported with the use of α -tubocurarine, atracurium, mivacurium, and rapacuronium.⁷⁰ There is not always a clear correlation between circulating histamine levels and the resulting symptoms, particularly for bronchospasm.^{71,72} Reactions resulting from direct histamine release are usually less severe than IgE-mediated reactions,^{22,60} with the exception of a subset of patients who have been considered as super-responders to the histamine-releasing effect of NMBA.⁷³

NMBA may also cross-react with nicotinic and muscarinic receptors responsible for actions at the extraneuromuscular junction cholinergic receptors level, causing peripheral autonomic and ganglionic effects. Rapacuronium was responsible for a high incidence of bronchospasm secondary to a higher affinity for M2 versus M3 muscarinic receptors,^{74–76} leading to its withdrawal from the market in the United States.

Allergy testing

Skin tests in association with the clinical history remain the mainstay of the diagnosis of an IgE-mediated reaction (see [Table 1](#)). There has been some controversy concerning the advantages of either SPT or IDT,⁷⁷ and negative SPT should be followed by IDT. Because of the frequent but not systematic cross-reactivity, all available NMBA should be tested using IDT.^{2,13,65,78–81} This testing should help avoid future adverse reactions and provide documented advice for future anesthesia.^{13,79,80,82} However, one should always remember that no diagnostic procedure is devoid of the risk of false-positive or false-negative results. Although rare, some cases of renewed allergic reactions following exposure to an NMBA considered to be safe have been reported in the literature.^{83,84} Therefore, when administering an NMBA to sensitized patients with a negative skin test, one should bear in mind the risk-benefit ratio.

In some cases, when the clinical history is highly evocative of an allergic reaction to an NMBA but skin tests remain negative, quantification of specific IgE to quaternary ammonium ion will be of high interest to optimize the diagnosis of allergy. Several specific immunoassays have been developed, such as a choline chloride,⁸⁵ a p-aminophenyl phosphoryl choline,⁸⁶ and a morphine-based⁸⁷ and a rocuronium-based assay.⁸⁸ These tests are usually performed several weeks after the reaction but can be carried out at the time of the reaction.^{80,89,90}

Promising results have also been recently provided in the literature by BAT. Although skin tests will remain the first choice for the diagnosis of sensitization to an NMBA and for the study of cross-sensitization, they could be of high interest in cases with negative skin tests and positive sIgE.⁴¹ Indeed, in vitro sensitization to quaternary ammonium structures does not per se indicate the presence of an allergy to NMBAs; a high proportion of subjects with positive IgE assay in the absence of any history of allergic reactions to an NMBA have been reported in the literature.^{45,91} Use of the BAT in the skin test negative, positive IgE assay patient may prevent any unnecessary avoidance of an NMBA.

Hypnotics

Allergic reactions incriminating these drugs are rare.

Reactions were quite frequent with thiopental accounting for 38% of the reactions in the United States.⁹² Their incidence was estimated to be 1:30,000.⁹³ Recently, thiopental was involved in less than 1% of allergic reactions in France, as a result of its decreased use.⁶⁰ Although, most of the reactions were related to the ability of barbiturates to elicit direct leukocyte histamine release, true IgE-mediated anaphylactic reactions confirmed by skin tests and specific IgE assay have been described.^{94,95}

Immediate hypersensitivity reactions may also be observed with propofol. They accounted for 2.5% of allergic reactions in the last French surveys.^{22,60} Diagnosing these reactions may be difficult, and the possibility of false-positive results due to hydrophobic interaction has been reported with IgE immunoassays.⁵⁶ It has been suggested that propofol should be omitted in patients with allergy to eggs or soy because of the presence of lecithins in the propofol vehicle, but this has not been confirmed in daily practice.^{24,96}

Reactions to midazolam, etomidate, or ketamine seem to be really rare^{22,60}; there are no documented cases of inhalational agents causing anaphylaxis.

Opioids

Immediate hypersensitivity reactions caused by opioids are very rare. Morphine, codeine phosphate, or pethidine can induce direct nonspecific skin mast cell activation but not heart or lung mast cell and basophil activation. Therefore, reactions are usually limited to pruritus, urticaria, and mild hypotension; there is significant overreporting of allergy to opiates. However, there are rare reports of IgE antibodies to morphine and codeine being detected in patients with opiate-associated anaphylaxis.⁹⁷ Fentanyl and its derivatives do not induce nonspecific mediator release from mast cells. There is no evidence of cross-reactivity between the different opioid subclasses phenanthrenes (eg, morphine, codeine), phenylpiperidines (alfentanil, fentanyl, remifentanyl, sufentanyl, and meperidine), and diphenylheptanes (methadone and propoxyphene) in the literature⁸²; but cross-reactivity between morphine and codeine is frequent. Morphine cross-reacts strongly with IgE antibodies from patients allergic to NMBAs via the tertiary methylamino group. Although morphine is monovalent and, thus, cannot elicit a clinical reaction in patients allergic to NMBA patients, this cross-reactivity is used in these patients to detect IgE against quaternary ammonium ions.⁵⁴

Allergy to synthetic opioid can be investigated by skin testing (see [Table 1](#)).

The diagnosis of morphine allergy remains more challenging. Skin tests may be helpful; however, because morphine may induce direct histamine release, the maximal concentration recommended for skin testing should not be exceeded. In some cases, when the clinical history does not support the diagnosis of an immediate reaction to morphine, a challenge test can be considered.

LOCAL ANESTHETICS

Background

Local anesthetics stabilize neuronal membranes by inhibiting the ionic movement required for the transmission of neural impulses. Local anesthesia permits the surgeon to perform the surgical procedure in a safe, comfortable fashion for the patient. Local anesthetics are used in dentistry, ophthalmology, minor surgery, endoscopies and obstetrics. They are available in multiple forms including gels, ointments, sprays, solutions and injectable forms. The topical anesthetics seem to be relatively safe. Allergic contact dermatitis and tissue irritation can occur. Patch testing can be used to identify contact sensitivity to a topical local anesthetic. Although benzocaine is often used as a screening agent, when used alone, sensitivity to other topical local anesthetics can be missed, and a -caine mix has been recommended.⁹⁸ This discussion, though, focuses on injected local anesthetics. Local anesthetics have been refined over the years, but adverse reactions still occur. Differentiating between allergic and nonallergic adverse reactions can be difficult because of the overlap of symptoms and lack of availability of documentation of the initial reaction. True allergy to local anesthetics is thought to represent less than 1% of all reactions to local anesthetics.^{99–101}

Types of Local Anesthetics

Local anesthetics may be classified as benzoic acid esters (group 1) or others, primarily amides (group 2) based on the linking chain between the lipophilic aromatic ring and the hydrophilic amine group ([Box 1](#)). Reactions to the benzoic acid esters are thought to be secondary to their metabolism via plasma esterases to para-aminobenzoic acid (PABA). Procaine (Novocain) was one of the commonly used benzoic acid esters. The benzoic acid esters often cross-react with each other but generally do not cross-react with the group 2 agents. The amides, which are not metabolized into the PABA molecule, are less sensitizing and do not generally cross-react with each other. Currently, most local anesthesia is performed using amides. Commonly used amides and their characteristics include the agents listed later.

Lidocaine is considered the prototype for amide local anesthetics. It is characterized by a rapid onset of action and intermediate duration of efficacy. It is metabolized by the liver and excreted by the kidneys with 10% unchanged and 80% as metabolites.

Mepivacaine has a reasonably rapid onset and medium duration of action. It is metabolized by the liver. Higher-concentration (4%) mepivacaine causes slight vasoconstriction providing it with a longer duration of action.

Prilocaine is a secondary amide that is metabolized in both liver and kidneys. Therefore, liver and renal diseases may change prilocaine kinetics. Methemoglobinemia may be a side effect when large doses are used and should be avoided in patients with sickle cell anemia, chronic anemia, and hypoxia and in patients taking high doses of acetaminophen or phenacetin.

Articaine is an amide with unique structures including a thiophene ring that enhances its lipid solubility and an additional ester group allowing hydrolysis in the

Box 1**Commonly used local anesthetics**

Group 1 (esters)

Benzocaine

Butamben picrate

Cocaine

Procaine (Novocain)

Tetracaine (Pontocaine)

Group 2 (primarily amides)

Short acting

Lidocaine (Xylocaine)

Medium acting

Mepivacaine (Carbocaine, Polocaine)

Prilocaine (Citanest)

Articaine (also contains ester group)

Lidocaine with epinephrine

Long acting

Bupivacaine (Marcaine)

plasma as well as in the liver. This structure allows for less systemic toxicity, especially with repeated doses.¹⁰²

Bupivacaine is 4 times more potent than lidocaine, mepivacaine, and prilocaine and has a longer duration of action than lidocaine. It is often administered when long-term pain control is needed, such as extraction of impacted third molars or surgical wound sites.¹⁰³ This agent has potential higher cardiotoxicity and should be used with caution in patients taking β -blockers or digoxin.

Epinephrine (1:100,000) may be added to a local anesthetic to cause vasoconstriction, resulting in an increased duration of action and less systemic absorption of the local anesthetic. The adverse effect associated with a local anesthetic is often secondary to the systemic absorption of epinephrine. It may cause palpitations, tachycardia, arrhythmia, hypertension, tremor, headache, and anxiety.

Adverse Reactions

Adverse reactions to local anesthetics that mimic allergy can have numerous causes, including anxiety (needle phobia, panic attacks, vasovagal syncope), intravascular administration of local anesthetic, intravascular absorption of epinephrine, overdosage of local anesthetic, toxic levels caused by a lack of metabolism, and intolerance. When evaluating patients with a reported allergy to a local anesthetic, it is imperative to obtain a detailed history of the reaction and when possible to include the following:

1. Type of procedure performed at time of reaction
2. Timing of administration of local anesthetic in relation to symptom development
3. Complete review of systems of the reaction
4. Type, amount, and concentration of the local anesthetic used
5. Whether the local anesthetic contained epinephrine
6. Patients' medical history, particularly kidney, liver, cardiac, and psychiatric history

This information coupled with a basic knowledge of the commonly used local anesthetics will help determine whether the reaction is likely allergic in nature or secondary to another cause. Although the focus here is on the local anesthetics, it is also important to note other concomitant agents or exposures, particularly antibiotics, NSAIDs, and latex.

Large Clinical Studies

A recent literature review of local anesthetic reactions identified 23 case series involving 2978 patients.¹⁰¹ Twenty-nine of these patients had true IgE mediated reactions to local anesthetics resulting in a prevalence of 0.97%. The number of patients in the case series ranged from 20 to 386. There was significant variability in the protocols used for the investigations. Most investigators used a combination of skin tests and challenges to confirm (or rule out) the diagnosis and find alternative agents. Most studies used recommended vasoconstrictor-free (epinephrine) preparations with and without preservatives for testing and subsequent use. The local anesthetic involved in the initial reaction was often not used in the skin testing or challenge evaluation. In a review of 135 cases with alleged allergic reactions to local anesthetics, 83 cases (61%) did not include challenge to the culprit local anesthetic.¹⁰⁴ In an analysis of 197 reported episodes in 177 patients, challenge tests with an alternative agents were performed in the first 54 patients, though the remainder of the patients was challenged with the suspected local anesthetic.¹⁰⁵ In 236 patients evaluated by SPT and IDT, followed by subcutaneous challenge, none was tested or challenged with the suspected local anesthetic but rather to a different one. In this group, 22% of the patients reported initial symptoms compatible with immediate hypersensitivity, 11% with local swelling at the injection site, 27% described nonspecific symptoms, 15% delayed reactions, and 25% were referred because they were atopic but had no history of adverse reactions to local anesthetics.¹⁰⁶ Although negative challenge to an unrelated local anesthetic is valuable/beneficial clinically in that it provides a treatment option, the risk of underestimating the true incidence of hypersensitivity to local anesthetics in these populations exists.

The type of patients studied could also impact the results of testing. Given that true local anesthetic allergy is rare, studying large number of patients without symptoms suggestive of an immediate hypersensitivity will further dilute the percentage of true positive test results. Harboe and colleagues¹⁰⁴ noted a considerable overlap in manifestations between test-positive and test-negative groups, though itch, urticaria, and documented hypotension (as opposed to local rash, palpitations, feeling of narrow throat, or feeling faint) were reported most/more frequently in cases with positive tests.

Testing to Local Anesthetics

IgE-mediated reactions to local anesthetics, particularly amides, are rare. Evaluation consists of SPT, IDT, and challenges. McClimon and colleagues¹⁰⁷ studied the predictive value of skin testing in the diagnosis of local anesthetic allergy. In their study of 178 patients, the negative predictive value was 97%, using undiluted preserved local anesthetic solution without epinephrine for SPT, 1:100 dilution for IDT, and subsequent challenge with 0.1 mL, 0.5 mL, and 1.0 mL of undiluted local anesthetic solution. Of the 227 skin tests performed, 220 were negative and 7 were positive. Based on the study criteria, 6 of the 220 patients had positive challenges that were confined to local skin reactions. Three of the patients with positive IDT subsequently had negative challenges to the same agent. This finding is similar to the overall finding of Bhole and colleagues¹⁰¹ who noticed an overall higher positive rate with IDT when compared with positive reactions as determined by challenge tests. The evaluation of 28 patients

with histories of reaction to local anesthetics, elicited positive SPT in 4 patients and positive IDT (at 1:10 dilution) in 10. Subsequent challenge, though, was negative for all.¹⁰⁸ Multiple skin test–positive results to local anesthetics are rarely seen among skin test–positive patients, only one in the McClimon and colleagues¹⁰⁷ study. In the large studies, patients were often tested only to a single nonculprit local anesthetic. Gonzalez-Delgado and colleagues¹⁰⁹ demonstrated the clinical utility of skin testing in a man with a clinical history of reaction to mepivacaine with positive skin test reactions to mepivacaine, lidocaine, and ropivacaine but negative reaction to bupivacaine. Bupivacaine was subsequently tolerated in a double-blind placebo-controlled challenge.

Only 3 cases of in vitro–specific IgE to local anesthetics have been reported in the literature.^{110–112} In one instance, the patient had a history highly suggestive of an immediate hypersensitivity reaction to mepivacaine. Intradermal skin testing at 1:100 dilution was positive to mepivacaine and bupivacaine and positive to lidocaine at 1:10 dilution. Skin testing to prilocaine was negative. Mepivacaine induced the strongest inhibition of IgE binding, followed by bupivacaine, lidocaine, and prilocaine, respectively. The significantly weaker inhibition with prilocaine was clinically relevant and confirmed the negative skin test, as the patient subsequently used it for dental procedures without complication.¹¹¹ Stahl and colleagues¹¹² reported a patient with immediate hypersensitivity reaction to lidocaine followed one week later by another immediate hypersensitivity reaction to an unknown local anesthetic, resulting in another immediate hypersensitivity reaction. Subsequent skin testing was positive to tetracaine and challenges positive to lidocaine and articaine. ELISA testing showed parallel curves to both amides and esters, but the esters did not correlate with the amides. Inhibition study demonstrated possible cross-reactivity between tetracaine and articaine but not between tetracaine and mepivacaine, likely because of the dual amide and ester group found on articaine. This case was the first case demonstrating specific IgE to both amides and esters in the same patient.

Allergy to local anesthetics may be caused by methylparaben, paraben, or metabisulfite used as preservatives. Although preservative-free local anesthetics exist, they may not be easy to obtain. Methylparaben, a preservative commonly found in foods and cosmetics, is used as a preservative in multiuse local anesthetics. In 1984, the Food and Drug Administration mandated its removal from single-dose local anesthetic cartridges. Reactions to methylparaben in local anesthetics have been reported.¹¹³ Sulfites are antioxidants used to stabilize epinephrine in local anesthetic solutions. They are not typically used when the local anesthetic does not contain epinephrine. Sulfites have been involved in non-IgE-mediated hypersensitivity reactions, particularly in patients with asthma. Because testing is very inconsistent, it is difficult to know the role sulfites may play in reactions attributed to a local anesthetic preparation.

These findings have raised the question of the most efficient way to evaluate local anesthetic allergy. Multiple skin tests at various dilutions and progressive multistep challenges can be time consuming and painful for patients. Based on recent data, proposals that came forth using preservative-containing, non-epinephrine-containing local anesthetics include the following:

1. SPT and IDT (concentrations not defined), if negative, a single subcutaneous challenge (as opposed to incremental); if positive, then skin test and challenge to an unrelated local anesthetic¹⁰¹
2. SPT, if negative, IDT with 0.04 mL of 1:100 dilution, if negative, 1 mL subcutaneous challenge; if skin test result positive, retest with pure local anesthetic solution without methylparaben or other preservative¹¹⁴

3. SPT, if negative, IDT with 1:100 dilution, if negative, subcutaneous challenge with 1:10 dilution 0.1 mL, followed by undiluted 0.1 mL, followed by undiluted 1.0 mL¹⁰⁴

Whether to test the culprit local anesthetic or an alternative agent will depend on the expected future need of the specific local anesthetic, but testing the initial offending drug is favored in order to make a definite diagnosis. Based on their different properties, a specific local anesthetic may be preferable.

OTHER SUBSTANCES IMPLICATED IN THE SETTING OF ANESTHESIA

Antibiotics

Antibiotics are often administered in the anesthesia setting. The percentage of allergic reactions during anesthesia secondary to antibiotics varies depending on the study and particularly the reporting country. The Groupe d'Etudes des Reactions Anaphylactoides Peranesthesiques, a network of 40 French allergeo-anesthesia outpatient clinics whose aim is to survey reactions during anesthesia, noted an increase in percentage of antibiotics responsible for anaphylaxis during anesthesia in France from 2% in 1984 to 1989 to 18% in 2005 to 2007.¹¹ In these studies, NMBAs continue to be the most common cause, though decreasing from 81% in 1984 to 1989 to 47% in 2005 to 2007. This finding contrasts with 2 recent reports from tertiary care centers in North America in which antibiotics were the most commonly identified cause of anaphylaxis in the anesthesia setting accounting for 50% and 47% of reactions.^{9,115} Similarly in Spain, Lobera and colleagues¹⁰ reported antibiotics accounting for 44% of allergic reactions during anesthesia. Penicillins and cephalosporins account for most anesthesia-related anaphylactic reactions secondary to antibiotics. Vancomycin and quinolones have also been incriminated in some cases, but it can be difficult to distinguish vancomycin allergy from the basophil degranulation causing the red-man syndrome. Although quinolones can be involved based on timing or subsequent challenge, there is no standardized skin test or specific IgE assay available for quinolones.

Latex

Latex is typically cited as one of the top 3 causes of anaphylaxis during anesthesia. IgE-mediated latex allergy has been well documented with recognized risk groups, including children undergoing numerous procedures, particularly those with spina bifida; adults requiring multiple procedures; health care workers; and individuals with a food allergy to latex fruits. Investigation of latex allergy is performed in the United States using latex glove extracts, though the latex protein content is not standardized, whereas in Europe, commercial extracts with excellent sensitivity are available. Specific IgE to latex (including IgE to specific latex components: Hev b1, b3, b6, b7, b8, b9, b10, b11) is also commercially available. Latex as the cause of anesthesia-related allergy has increased in France from 0.5% (in 1984–1989) to 20.0% in 2005 to 2007.¹¹ Identification of patients at risk and strategies to reduce latex exposure both environmentally (eg, latex-free gloves and equipment) and in the surgical setting have resulted in decreased reactions secondary to latex in other areas.^{9,104}

NSAIDs

NSAIDs have been increasingly used in postsurgical and postprocedural settings. They are given orally or by injection. The types of reaction can vary from isolated cutaneous or respiratory symptoms to anaphylaxis. In the very rare setting of IgE-mediated NSAID anaphylaxis, patients often only react to one NSAID. Unfortunately, the mechanism is not always clear; both IgE-mediated and non-IgE-mediated reactions occur. Skin testing is not reliable. The basophil activation test on blood basophils shows

potential, though more studies are needed.¹¹⁶ When exploring NSAIDs hypersensitivity, drug provocation test is particularly useful.

Chlorhexidine

Chlorhexidine is a standard skin antiseptic and disinfectant. It is widely used in medical, procedural, and surgical settings. Sensitization to chlorhexidine can occur from home products, such as mouthwash, toothpaste, dressings, ointments, and over-the-counter disinfectant solutions. Systemic allergic reactions ranging from widespread urticaria to anaphylactic shock have been reported to chlorhexidine via topical skin application, ophthalmic wash solution, chlorhexidine bath, coated central venous catheter, and urethral gels. The largest group reported so far (including 12 allergic patients) sheds some light on the potential risk factors for chlorhexidine sensitization.²⁸ Most of the patients were male with a median age of 64 years, with nearly half of the reactions occurring during urologic surgeries or procedures. During these procedures, chlorhexidine exposure is enhanced by absorption through mucosal surfaces (urethra, bladder) and skin (incision, epidural), especially if the chlorhexidine is not dry before the initiation of the procedure. Chlorhexidine skin testing has been shown to be predictive of allergic sensitivity to chlorhexidine and to correlate with in vitro chlorhexidine sIgE testing.¹¹⁷

Dyes

Dyes have become increasingly recognized as a cause of allergic or anaphylactic reactions in the anesthesia setting. The triarylmethane dyes, patent blue V and isosulfan blue, share a similar structure and are commonly used for lymphatic mapping. It is thought exposure to blue dye in cosmetics and other everyday products contributes to sensitization. The mechanism of reaction to the dye is unclear, both direct mast cell and/or basophil activation and specific IgE sensitization have been described. Methylene blue, a smaller molecule, which differs structurally from the triarylmethane dyes, has also been associated with reactions. Sensitization to both patent blue and methylene blue has been reported.²⁶ Reactions to dyes are often delayed, occurring 30 minutes after injection, and can be prolonged. Although the mechanism is not always clear, the drug allergy work-up includes SPT and IDT. These tests can help identify the cause of a reaction and, in conjunction with negative testing, may identify a safe dye alternative.

Colloids

Colloids have rarely been implicated in anesthesia-related anaphylaxis. The incidence has been estimated to range from 0.03% to 0.22%.¹¹⁸ Gelatins and dextrans are more commonly associated with reactions than albumin and hetastarch. Skin tests can be performed to identify IgE-mediated reaction to gelatin and hydroxyethyl starch. Specific IgE assays to gelatin can also be used.

Aprotinin

Aprotinin, a serine protease inhibitor, is used to prevent bleeding. It has been administered in intravenous form and as a component of biologic sealants. In 2007, the intravenous drug was withdrawn from the market. Currently, it is part of the fibrin glue combined with human coagulation factors used to aid hemostasis and sealing of tissue wounds. Prevalence of reactions to aprotinin is higher in patients with a history of previous exposure. A reexposure interval less than 6 months could be considered a relative contraindication to fibrin glue application.¹¹⁹ SPT and IDT (up to 1:10 dilution) can be used for diagnosis.

Prevention

Preventive testing of patients to the most common elicitors of anesthesia-related anaphylaxis is not justified by current evidence. The primary risk factor is a history of a hypersensitivity reaction with previous anesthesia or a known allergy to one or more medications or products likely to be administered during the procedure. Unless already documented, all patients with such history should have a comprehensive evaluation, including skin testing and/or specific IgE testing and drug provocation tests to the potential culprit anesthetic agents and related compounds, before further administration of anesthetics. A strategy should be used to avoid these medications and those that are cross-reactive. Patients who are atopic, those with asthma or allergic rhinitis, or those who have a medication allergy to a drug not likely to be used during the course of anesthesia or procedure are not considered to be at a significantly increased risk for a hypersensitivity reaction.

For those with latex sensitivity, a latex-free environment should be available. Many centers have set up latex-free operating rooms and procedural areas. This set-up requires coordination among the surgical, medical, and anesthetic teams.

The role of pretreatment with H1-receptor antagonists and corticosteroids is not well defined. These medications may help decrease non-IgE histamine-mediated reactions. However, they do not reliably prevent IgE-mediated reactions. Avoidance of the allergen is the only true way to prevent an anaphylactic reaction.

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