

Approach to Patients With Suspected Hypersensitivity to Local Anesthetics

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ABSTRACT: Adverse reactions to local anesthetics are relatively common, but true IgE-mediated hypersensitivity is extremely rare. Fortunately, the vast majority of adverse reactions occur via nonimmunologic means, but considerable confusion still exists among providers. We conducted a review of the literature to determine if earlier estimates of IgE-mediated allergy are consistent with current reports and whether current management strategies are consistent with these findings. We identified several confounding variables involved in the evaluation, including the roles of preservatives/additives,

epinephrine, latex, and inadequate testing procedures. These problems may cause significant diagnostic challenges for clinicians. It is in fact much more likely that there is an alternate diagnosis, and in many cases clinicians can begin the evaluation in the office. When local anesthetic allergy is still suspected, the patient should be referred to an allergist for testing to determine if the suspected culprit drug can be safely used, or, if necessary, identify a suitable alternative. **KEY INDEXING TERMS:** Local anesthetic allergy; Drug allergy; Drug hypersensitivity. [*Am J Med Sci* 2007;334(3):190–196.]

Adverse reactions to local anesthetics are relatively common, but true IgE-mediated allergy is extremely rare, estimated to occur in less than 1% of all reported reactions.^{1–3} Dentists and physicians across multiple branches of medicines routinely use local anesthetics. Between 2.5% and 10% of dental patients receiving injected local anesthetics experience some kind of adverse reaction, many of which are reported by the patient as “allergic” in nature.⁴ Fortunately, the vast majority of adverse reactions occur via nonimmunologic means, but considerable confusion still exists among providers. We reviewed the current literature to determine if earlier estimates of IgE-mediated allergy are consistent with current reports and whether current management strategies are consistent with these findings. Using MEDLINE, we identified articles published from October 1994 to October 2004 in the English language that reported an adverse reaction to local anesthetics with allergic-type symptoms and where positive reactions were reported via skin prick-testing and/or intradermal testing via incremental dose

challenge. We also identified articles in which clinical studies were performed to evaluate results of skin prick and incremental dose challenge in patients reporting a history of local anesthetic allergy. We used the following MeSH search headings: local anesthetics, allergy, and hypersensitivity, limited to human and English articles.

Classification of Types of Adverse Reactions to Local Anesthetics

Any patient who presents with a history of an allergic reaction to local anesthetics should be carefully questioned to determine the nature of the reaction. A patient may have been advised that he/she is allergic to one of these drugs without ever receiving a proper evaluation. Differentiating between local anesthetic hypersensitivity and other causes of adverse reactions can be difficult because systemic symptoms such as dyspnea, swelling, and lightheadedness may occur by multiple mechanisms.⁵ There is currently no reliable method to identify or measure serum IgE specific to local anesthetics, so clinicians are dependent on history and skin testing, both of which have shortcomings. Fortunately, the vast majority of adverse reactions to local anesthetics are not immunologically mediated. Such reactions are predominantly the result of anxiety, excessive dosage, rapid absorption, or inadvertent injection into the intravascular compartment.⁶ We present a revised classification of types of adverse reactions that we have found to be clinically helpful (Table 1).

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Table 1. Classification of Types of Adverse Reactions to Local Anesthetics

Local reactions
Local toxic effects
Trauma
Contact dermatitis
Systemic reactions
Psychosomatic (anxiety, vasovagal)
Toxic reactions (CNS, cardiovascular)
Idiosyncratic
Anaphylactoid
Anaphylactic

Modified from Reference 24.

Mechanism of Action of Local Anesthetics and Local Reactions

As an action potential reaches a particular nerve cell, the sodium channels open and sodium ions flood the cell, causing depolarization. The gate that regulates passage of sodium ions is on the cytoplasmic side of the cell, and, when open, is susceptible to the binding of local anesthetics. These compounds keep the channel inactive and block further depolarization; this interruption of conduction is termed conduction block.⁷ Local anesthetics are injected into the subcutaneous tissue where they infiltrate nerve cells but have several known dose-dependent side effects in peripheral tissues notwithstanding systemic toxicity. They cause vasodilatation of surrounding vessels by blocking sympathetic nerves; unfortunately, this can result in more rapid systemic absorption.⁸ At high enough concentrations, local anesthetics are cytotoxic to nerve cells.⁷

Systemic Reactions

Psychosomatic Responses

Psychosomatic responses are the most common adverse reaction and appear to be more common in dental procedures.⁹ This may be related to the general anxiety some patients have in the dentist's chair. Regardless, anxiety may lead to dyspnea, hyperventilation, and other sympathetic responses, including tachypnea, tachycardia, diaphoresis, and hypertension. Some patients have reported other more nebulous symptoms such as peripheral and/or circumoral paresthesias, which do not occur with true allergic reactions.⁵ Another common event is vasovagal syncope, which is frequently accompanied by bradycardia.^{5,8} In contrast, most patients with systemic allergic reactions have some combination of tachycardia, pruritus, dermal erythema, or urticaria. One large open-label, multicenter study evaluating 5018 participants receiving local anesthetics during dental procedures identified 25 adverse reactions, representing 0.5% of the study population. The authors considered 23 reactions (representing 88%) to be vasovagal and psychogenic reactions.

Symptoms were brief and quickly reversed, but included "anxiety, deep breath, pallor, nausea, confusion." No patients had positive skin testing.¹⁰

Systemic Toxicity

Drug toxicity almost always occurs with inadvertent intravascular injection but can also be seen with excessive dosage or rapid absorption in highly vascular tissues.⁶ Toxicity is directly related to the potency of the local anesthetic chosen, the dose delivered, the rate of plasma uptake, the amount of protein binding, and the site of injection. Once inside the vascular compartment, the onset of symptoms can be extremely rapid and predominantly affects the central nervous and cardiovascular systems.⁷ Central nervous system (CNS) stimulation often occurs initially or with smaller doses, manifesting as light-headedness, talkativeness, restlessness, tremors, shivering, or seizures. CNS depression occurs as serum levels continue to rise, predominantly affecting the medulla and higher nerve centers, leading to drowsiness, coma, or respiratory arrest.⁸ Cardiovascular effects typically occur at significantly higher serum concentrations of the drug. These include depressed myocardial contractility and conduction abnormalities, including QRS-widening, atrioventricular block, and asystole. The combination of depressed myocardial contractility and peripheral vasodilation can lead to shock rather quickly.⁸

Idiosyncratic Reactions

Idiosyncratic reactions are abnormal responses that occur only in susceptible persons and are different from the pharmacologic effects of a drug.¹ The best example for local anesthetics is methemoglobinemia, which has been reported in association with several local anesthetics, including prilocaine, benzocaine, and articaine. There have been more than 50 reported cases, most involving the use of benzocaine in infants and young children.⁷ Metabolites of some local anesthetics oxidize the iron in normal hemoglobin to the ferric state, producing methemoglobin, which cannot carry oxygen. Fetal hemoglobin is more susceptible to oxidation and contains lower levels of circulating reducing substances such as NADH. When the amount of oxidized hemoglobin reaches 4 g/dL, visible cyanosis occurs. Patients with hemoglobinopathies or glucose-6-phosphate dehydrogenase (G6PD) deficiency appear to be at greater risk.⁶ Treatment involves the removal of the causative agent, administration of 100% oxygen, and intravenous methylene blue, an electron acceptor that reduces methemoglobin.⁷

Immunologic Reactions in Drug Allergy

Anaphylaxis refers to type I hypersensitivity reactions (in Gell and Coombs nomenclature) and are the most immediately life-threatening. When anti-

Table 2. Classes of Local Anesthetics Currently Available in the United States

Group I: Benzoic Acid Esters	Group II: Amides	Group III: Miscellaneous
Benzocaine (Americaine, ^c Dermoplast, ^c Lanacaine, ^c Hurricaine, ^c and others)	Articaine (Septocaine ^a)	Dyclonine (Dyclone ^c)
Butamben picrate (Butesin ^c)	Bupivacaine (Marcaine, ^a Sensorcaine ^a)	Pramoxine (Tronothane ^c and others)
Chloroprocaine (Nesacaine ^a)	Dibucaine (Nupercainal ^c)	Ethyl chloride (Chloroethane ^c)
Cocaine ^c	Levobupivacaine (Chirocaine ^a)	
Procaine (Novocaine ^a)	Lidocaine (Xylocaine, ^a Octocaine, ^a Solarcaine, ^b Anestacon, ^b DermaFlex, ^b and others)	
Proparacaine (Alcaine, ^b Opthaine, ^b Oththetic, ^b Fluoracaine ^b)	Mepivacaine (Carbocaine, ^a Polocaine ^a)	
Tetracaine (Pontocaine, ^{a,b,c} Viractin ^c)	Prilocaine (Citanest ^a)	
	Ropivacaine (Naropin ^a)	

^aInjectable preparation.

^bOphthalmic preparation.

^cTopical preparation.

gen binds to preformed IgE antibodies on the surface of mast cells in sufficient quantities to cross-link 2 or more antibodies, a signal is transmitted into the cell that causes degranulation.¹¹ This process releases potent intracellular inflammatory mediators including histamine, leukotrienes, cytokines, and proteases.¹² The result is a constellation of symptoms including pruritus, urticaria, bronchospasm, hypotension, and/or angioedema, usually within minutes of exposure to the causative agent.⁵ When this is initiated via IgE-mediated mechanisms, it is known as an anaphylactic reaction. Mast cell degranulation may occur via non-IgE-mediated mechanisms as well, producing the same symptoms. These reactions are termed anaphylactoid reactions.¹³ Drugs that are thought to cause mast cell degranulation via anaphylactoid mechanisms include some opiates, muscle relaxants, vancomycin, and iodinated radiographic contrast media.¹⁴

In contrast, type IV hypersensitivity reactions are delayed-type reactions. These reactions are not mediated by antibody but primarily occur by T-lymphocyte-mediated mechanisms. With skin exposure to the offending agent, antigen is processed by antigen-presenting Langerhans cells, which interact with sensitized T-helper lymphocytes and stimulate cytotoxic T-lymphocytes to produce inflammatory mediators. This ultimately leads to symptoms within 12 to 48 hours of exposure in sensitized patients. The most common clinical manifestation is contact dermatitis, presenting as dermal erythema, pruritus, papules, and vesicles; chronic exposure leads to lichenification and excoriation.¹⁴ Allergic contact dermatitis, a type IV reaction, is widely recognized as the most common immunologic reaction to local anesthetics.¹⁵ Aside from local anesthetics, multiple transdermal drugs, topical antimicrobials, sulfonamides, and other *para*-amino (PABA)-containing compounds are recognized causes of contact dermatitis. Evaluation with radioallergosorbent testing (RAST), skin testing, or provocative dose challenge is not indicated, as these evaluate IgE mechanisms

of disease. Contact dermatitis is evaluated clinically through the use of patch testing, where the offending agent is applied via an occlusive dressing and removed after 48 to 96 hours. Appearance of a similar rash, when coupled with the patient's history of exposure, confirm the diagnosis.¹⁶

Special Problems with Local Anesthetic Allergy

Cross-Reactivity

Local anesthetics are composed of an aromatic ring connected to a tertiary amine via an amide- or ester-bonded intermediate chain. They are classified as amides or esters on the basis of this bond⁷ (Table 2). The vast majority of reported allergic reactions in the literature have been to ester-bonded agents, which are derivatives of PABA, a known allergen. This allergenicity has led to the near-exclusive use of the newer amide-bonded agents in clinical situations. Cross-reactivity does occur among members of the ester class in contact dermatitis as demonstrated by patch testing. Amide-bonded local anesthetics are not immunologically cross-reactive with their ester-bonded cousins.⁸ Amides generally are not thought to be cross-reactive with other amides on the basis of published data from both patch testing and skin prick with incremental dose challenge. However, there have been a few recent case reports suggesting cross-reactivity among amides as well. One case reported in the literature described a 33-year-old woman in whom urticaria and shortness of breath developed while she was undergoing spinal anesthesia with lidocaine. She subsequently reacted to both lidocaine and procaine during her skin testing.¹⁷ More studies are needed to fully evaluate this question.

Incomplete Allergens

Complete allergens typically have a molecular weight of 10 to 20 kDa and are able to generate production of IgE antibodies independently. Examples include common airway allergens such as pollen

and dust mites as well as high-molecular-weight drugs such as insulin and heparin.^{14,18} Local anesthetics have a much lower molecular weight of 200 to 300 Da, making them incomplete allergens, as is the case with β -lactam antibiotics and phenytoin.⁹ Incomplete antigens are known as haptens and must bind to host cells or carrier proteins such as albumin to elicit an allergic response.¹⁸ The haptenate (hapten-protein complex) is then recognized as foreign and able to elicit an immunogenic response.¹⁴ This has not been shown to occur with local anesthetics.

Epinephrine

Another possible cause of adverse symptoms is the epinephrine added to some agents, which can be systemically absorbed, causing flushing, palpitations, anxiety, and headache.⁶ Vasoconstrictors such as epinephrine are frequently added to local anesthetic preparations to decrease systemic absorption. This lowers peak plasma concentrations and slows the time to produce peak tissue levels and the cumulative effect reduces the potential for toxicity.⁶ Epinephrine counteracts the intrinsic vasodilatory properties of local anesthetics, prolonging the anesthetic effects. However, side effects produced by the epinephrine such as hypertension, tachycardia, cardiac arrhythmias, and myocardial ischemia can occur in some individuals.⁷ Additionally, similar symptoms may be secondary to the release of endogenous catecholamines as a response to pain/anxiety.⁵ One study showed no significant hemodynamic response to lidocaine with epinephrine in dental procedures, despite significant elevations in plasma levels of epinephrine above baseline, in healthy young men.¹⁹ Effects in other populations, specifically patients with known cardiovascular disease, have not been widely studied. It has been generally thought that the epinephrine in local anesthetic preparations is not of sufficient dose to cause significant hemodynamic changes in most patients⁵ but could potentially cause symptoms in susceptible persons.

Preservatives

Another variable in the consideration of reactions to local anesthetics is the role of preservatives. Many preparations of local anesthetics (articaine, lidocaine, mepivacaine, prilocaine, and bupivacaine), are available with preservatives in multidose vials. Articaine is only available with preservatives in the United States. Preservatives are more commonly found in multidose vials, which are more frequently used by emergency room physicians and some dentists.

Parabens

Historically, most commercially available local anesthetics contained parabens (typically methylparaben), which is a bacteriostatic agent related in

structure to the benzoic acid ester local anesthetics.⁵ Reports demonstrated delayed hypersensitivity to parabens in the late 1970s, and since that time more local anesthetics have become available without parabens.²⁰ However, many local anesthetics are still available with methylparaben because it increases shelf life of the drug, and as such many reactions (and positive skin tests) probably are secondary to this additive. One recent prospective, double-blinded study performed intravenous injections into an arm with a proximal tourniquet in place (not currently recommended), using 0.5% prilocaine solutions with and without methylparaben.²¹ Seventeen percent of patients who received methylparaben-containing preparations reacted with acute localized erythema and swelling compared with 4% of patients who received prilocaine alone. Subsequent intradermal testing for both methylparaben and prilocaine were negative in all patients. The author hypothesized that methylparaben induced an anaphylactoid release of vasoactive substances and that IgE-mediated effects were excluded by negative intradermal testing.²¹ Parabens are not present in single-use dental cartridges or vials but are found in many multidose vials.²²

Sulfites

Sulfites, typically bisulfite or metabisulfite, are antioxidants used to stabilize vasoconstrictors such as epinephrine in local anesthetic preparations.²³ They are found in multidose vials of articaine, bupivacaine, lidocaine, mepivacaine, and prilocaine. Because these preparations contain both vasoconstrictors and sulfites, it is difficult to ascribe causation of reactions to the local anesthetic or one specific additive. Studies have shown contradictory evidence, with multiple case reports demonstrating sulfite-associated reactions with symptoms of urticaria, angioedema, seizure, asthma, and death in sensitive persons.²⁴ Inhaled metabisulfite induces decreases in FEV₁ among asthmatics and even in some nonasthmatic patients. One hypothesis is that the breakdown product sulfur dioxide is released in the airway and affects sensory nerve endings, leading to bronchoconstriction, similar to the actions of bradykinin.²⁵ These data would appear to indicate that metabisulfite induces mast cell degranulation via non-IgE dependent mechanisms.

Latex Allergy

Another potential cause of reported allergy to local anesthetics is latex antigen. Latex found in gloves or rubber dams used during dental procedures can cause contact dermatitis, the most common manifestation of latex allergy. However, there have been some reports suggesting latex as the cause of immediate hypersensitivity reactions as well.²⁶ In such situations, latex antigen found in the plunger at the end of the cartridge of dental prepa-

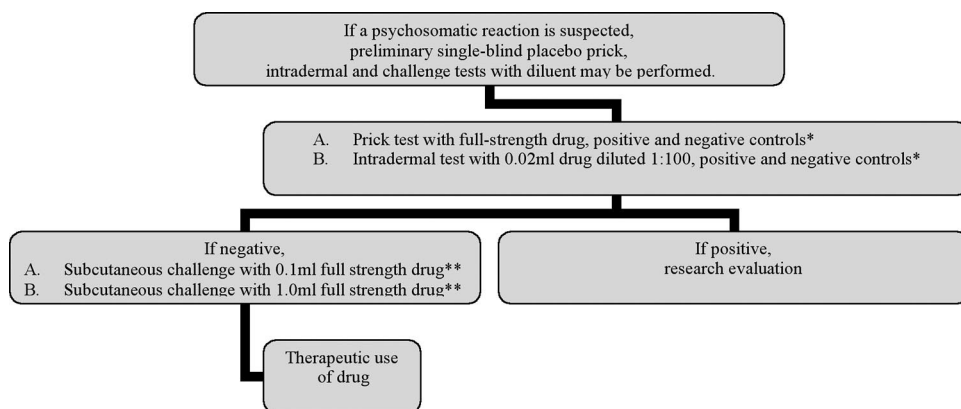


Figure 1. Algorithm for management of suspected local anesthetic allergy. *Using saline as negative control; **challenge at 15-minute intervals.

rations or the vial enclosures covering multidose vials are possible culprits. One prospective study tested intradermal responses in participants with history of latex allergy when exposed to a saline/albumin solution encased with a latex vial enclosure. Five subjects had a positive reaction when exposed to solution from a punctured vial enclosure and 2 subjects reacted positively when the vial enclosure was removed intact. The authors theorize that latex antigen is released into the solution when the needle penetrates the enclosure and may be released into the solution even if the enclosure is intact.²⁷ Single-use dental cartridges appear to be relatively safe in latex-sensitive individuals.²⁶

Management of Patients with Suspected Allergy to Local Anesthetics

When a patient presents to the office after the event and gives a history of an untoward reaction to a local anesthetic, the first step is to obtain a careful history. Past medical records should be reviewed in an attempt to identify the agent and the concentration under which it was used. The time interval between administration and the onset of symptoms and the specific symptoms reported should also be queried. If obtainable, this information will allow discrimination between psychosomatic, vasomotor, and allergic reactions. This may require talking directly with the healthcare professional who administered the drug. When the history does not allow discrimination between allergic versus nonallergic mechanisms for a reaction to a particular drug, referral to an allergist is indicated. With delayed or cutaneous symptoms indicating type IV hypersensitivity/contact dermatitis, patch testing is indicated. For immediate symptoms that may indicate anaphylactic mechanisms, the recommendation is to perform skin prick and intradermal testing. With these methods, an allergist may be able to reassure the physician/dentist and the patient that the drug may be safely used or identify a suitable alternative drug.

The process used by allergists to identify an agent

for future use involves skin prick/intradermal testing followed by a subcutaneous provocative dose challenge. The recommended protocol is presented in algorithmic form (Figure 1) and is generally accepted on the basis of published experience.^{5,28,29} The preparation used should not contain a preservative or vasoconstrictor to minimize false-positives. Epinephrine may inhibit potential wheal-and-flare reactions, contributing to false-negative skin tests, or, conversely, may directly provoke symptoms.³⁰ Amides are used in this process to prevent the possibility of cross-sensitivity that exists with esters. If there is suspicion of psychosomatic response, the single-blinded injection of normal saline should be performed before skin testing. If skin testing is negative, one can proceed to the provocative dose challenge, which should always be performed to confirm the drug is safe to use clinically.⁵ The challenge is best performed 24 to 48 hours after skin testing to confirm that there is no delayed reaction from testing, particularly if history suggests delayed onset of symptoms. If the intradermal skin test is positive, another agent should be chosen and the procedure started over.²⁹ A negative provocative dose challenge suggests that the drug is safe.

Discussion

The recommended algorithm for treatment of patients with possible local anesthetic allergy has undergone some modification in recent years. Recent literature has raised questions about the efficacy of skin testing because the prevalence of false-positives is as high as 10% to 36% of subjects.^{2,31} These may occur in patients with no previous local anesthetic reactions, especially when high concentrations of undiluted local anesthetics are injected intradermally.³² This probably is due to an irritant effect of the local anesthetic. False-positive reactions can be minimized by using saline controls and by using the 1:100 concentration of local anesthetic in the initial intradermal phase of skin testing.

Some protocols call for a lengthy intradermal phase in which escalating concentrations of local anesthetic are given after negative skin prick testing. Because of false-positives, more recent publications have recommended eliminating the skin testing component altogether. Wasserfallen and Frei² performed provocative dose challenge in patients with positive skin tests. They found that all patients were able to tolerate either the tested amide local anesthetic or another drug of the same class. The authors suggested omitting testing with undiluted local anesthetic during the intradermal phase and only using diluted local anesthetic intradermally if the patient had reacted to all tested local anesthetic agents by skin prick testing. As such, we recommend intradermal testing with local anesthetic diluted to 1:100 only. Additionally, we prefer an abbreviated subcutaneous provocative dose challenge using volumes of 0.1 mL and 1 mL, respectively, of undiluted local anesthetic to ensure the patient will be able to tolerate the full strength of the drug. There will be some false-positives with this approach. False-positives, that is, wheal and flare reactions at the injection site, falsely suggest the presence of IgE antibody to local anesthetics. They probably reflect direct triggering of inflammatory mediator release from dermal mast cells by high osmolar local anesthetic solutions. A patient with true IgE-mediated allergy to local anesthetics is so rare as to be reportable.

In the rare case of a positive skin prick test with full strength local anesthetic or 1:100 drug injected intradermally, we do not recommend proceeding to provocative dose challenge, unless under controlled research conditions. The safe course of action is to perform skin testing with another amide local anesthetic so that a suitable drug can be found. A positive skin test does not necessarily confirm allergy to the tested drug. The gold standard for diagnosis of any drug allergy is a positive provocative dose challenge and the demonstration of drug-specific IgE,³³ which has not yet been identified for local anesthetics, as previously stated.

Two recent studies support the utility of provocative dose challenge in the management of purported local anesthetic allergy. In one study, 236 patients with histories of either adverse reaction to drugs, anaphylactic reactions, food allergy, or atopy but no history of reactions to local anesthetics underwent skin prick testing and provocative dose challenges. Multiple local anesthetics of the amide class were used with epinephrine, methylparaben, and metabisulfite. The authors chose to use vasoconstrictors and/or preservatives in the preparation because of the frequent use of these additives in preparations clinically. They found no patient with a reaction to either skin prick or intradermal testing, which was confirmed with provocative dose challenge. Since most dentists use local anesthetics that contain per-

servatives and/or epinephrine, they recommend performing studies with such additives.³⁴

Another study was performed in 198 individuals with either a history of previous adverse reaction to local anesthetics, a family history of atopy, or without any history of allergy-related problem. Using a combination of skin prick testing and intradermal challenge among 72 patients with histories of adverse reactions to local anesthetics, they reported 9 patients with immediate reactions to latex, 5 patients with immediate reactions to parabens, and no patients with immediate reactions to mepivacaine.³⁵

Conclusion

This review supports the opinion that type I hypersensitivity (IgE-mediated) reactions to local anesthetic agents are extremely rare. The reported cases in the literature are difficult to objectively analyze and may represent true allergy, false-positives, or anaphylactoid reactions in sensitive persons. In the latter individuals, local anesthetics may be capable of initiating mast cell degranulation, which leads to symptoms and physical signs that mimic an IgE-mediated allergic reaction. When local anesthetic allergy is suspected, referral to an allergist for skin testing and provocative dose challenge is appropriate. The allergist may be able to confirm the suspected culprit drug can be safely used, or if necessary, identify a suitable alternative.

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