

Identifying and Managing Local Anesthetic Allergy in Dermatologic Surgery

RAMIN FATHI, MD, MARC SEROTA, MD, AND MARIAH BROWN, MD

BACKGROUND Local anesthetic (LA) allergy is a concern for dermatologic surgeons given the large number of procedures performed yearly with LAs. Many patients also have anxiety about past or potential anesthesia allergy.

OBJECTIVE This article will review the symptoms of IgE-mediated allergic reactions, the prevalence of IgE-mediated LA allergy, discuss common mimics of LA, and propose a practical approach for diagnostic and therapeutic options for LA allergy for the dermatologic surgeon in practice.

MATERIALS AND METHODS A literature search of Pubmed using keywords "lidocaine," "local anesthetic," "hypersensitivity," and "allergy" was performed.

RESULTS Amide anesthetics result in the most reports of true local anesthetic immediate hypersensitivity.

CONCLUSION True IgE-mediated anaphylaxis to local anesthesia is very rare. Dermatologic surgeons should be aware of the symptoms of anesthetic allergy and its mimickers, as well as how to manage allergic reactions in their clinical practice.

The authors have indicated no significant interest with commercial supporters.

Injectable local anesthetic (LA) agents have been extensively used since the late 19th century and are the most commonly used drugs in everyday dermatologic practice.¹ As a result, LA allergy is an ongoing concern for dermatologic surgeons. The prevalence of true life-threatening reactions to LA is rare and the majority of dermatologic surgeons will not encounter one in the course of their careers. However, fear of past and potential LA allergy remains common, particularly for patients. This article will review the symptoms of IgE-mediated allergic reactions, the prevalence of IgE-mediated LA allergy, discuss common mimics of LA allergy, and propose a practical approach for dermatologic surgeons in identifying and managing LA allergy.

Types of Local Anesthetics

Local anesthetics reversibly interrupt impulse propagation and nerve conduction by interfering with the

influx of sodium ions into nerve cells. Nerve fibers have differing sensitivities to LA depending on their size and degree of myelination. Local anesthetics block pain and temperature sensation before inhibiting pressure and motor function.²

The earliest LA available for medical use was cocaine, which was presented for use in medical and dental procedures in 1884. Cocaine's efficacy as a LA was mitigated by its high potential for addiction, short duration of action, and severe vasoconstrictive effects. In 1905, procaine ("novocaine") was synthesized² and, as it became widely used, "novocaine" became a common term for patients to describe any LA. Allergic reactions to procaine, mainly delayed-type hypersensitivity, were described during the years of peak use. Predominantly, these allergic reactions are believed to be to para-amino benzoic acid, a metabolite of procaine, rather than the LA itself. Starting in the 1950s, amide LAs became commercially available and

Department of Dermatology, University of Colorado School of Medicine, Aurora, Colorado

© 2016 by the American Society for Dermatologic Surgery, Inc. Published by Wolters Kluwer Health, Inc. All rights reserved.
ISSN: 1076-0512 • Dermatol Surg 2016;42:147-156 • DOI: 10.1097/DSS.0000000000000596

by the 1980s, nearly all dentists and physicians had discontinued the use of procaine. Today, the majority of injectable LAs used in clinical practice are of the amide class.

Local anesthetics are broken down into 2 groups based on their chemical structure. Amide anesthetics have an amide linkage and ester anesthetics have an ester linkage. This differing chemical structure impacts how LAs are metabolized and the risk of allergic sensitization. Ester anesthetics are hydrolyzed by plasma pseudo-cholinesterase and then excreted by the kidneys. Amide anesthetics are metabolized by the hepatic microsomal cytochrome P450 enzyme system and subsequently excreted by the kidneys.³

The benzoic acid esters (Group I) include cocaine, benzocaine, procaine, proparacaine, and tetracaine. The amides (Group II) include articaine, bupivacaine, levobupivacaine, dibucaine, etidocaine, lidocaine, mepivacaine, prilocaine, and ropivacaine. A useful way to remember this is that all group “I” agents have only one “I” in their name (e.g., ProcaIne) whereas group “II” agents all have 2 “I”s in their name (e.g., LIIdocaine). This distinction between esters and amides is important, as there have been cases of allergic cross-reactivity among LAs of the same group,⁴⁻⁶ but without sensitivity to agents of the opposite group.⁷ Overall, Group I LAs (esters) are considered more allergic than Group II LAs (amides). Examples of Group I and Group II LAs can be viewed in Table 1.

Classification of Reactions

Adverse reactions related to LA can broadly be defined first as either local or systemic. Further, systemic reactions can then be classified as either IgE-mediated allergic reactions, non-IgE-mediated allergic reactions, or nonallergic adverse reactions. This distinction is critical in the evaluation and management of a patient with a suspected LA allergy (or any other allergy). Immediate hypersensitivity (Type I) is mediated by mast cells and basophils. When a specific antigen binds mast cell-bound IgE, degranulation of preformed mediators (histamine, serotonin, prostaglandins, leukotrienes, and platelet-activating factor)

TABLE 1. A List of Ester and Amide Local Anesthetics

<i>Benzoic Esters</i>	<i>Amides</i>
Procaine (Novocaine)*	Bupivacaine (Marcaine, Exparel)*
Proparacaine (Alcaine, Opthetic, Paracain)	Articaine (Septocaine, Zorcaline)*
Benzocaine (Americaine, Lanocaine)	Lidocaine (Xylocaine, Lidoderm)*
Chlorprocaine (Nesacaine)*	Mepivacaine (Carbocaine)*
Tetracaine (Protocaine)	Prilocaine (Citanest)
Cocaine	Levobupivacaine (Chirocaine)*
	Ropivacaine (Naropin)*
	Etidocaine (Duranest)
	Dibucaine (Nupercainal)
Common trade names are included in parentheses. ^{8,9}	
*Anesthetics that are locally injectable.	

occurs. This cascade of events can lead to enhanced vascular permeability, bronchoconstriction, and induction of an inflammatory reaction¹⁰ that clinically manifests as anaphylaxis.

Non-IgE mediated allergic reactions include Type IV hypersensitivity reactions (contact allergy). A retrospective chart review of 1,819 patients found that true Type IV hypersensitivity prevalence to LA has been rising with benzocaine (45%), lidocaine (32%), and dibucaine (23%) as the most common allergens.¹¹ Nonallergic adverse reactions include dose-related toxic effects, trauma related to the surgery itself, epinephrine reactions, and vasovagal syncope. Table 2 summarizes the differences between the commonly reported adverse reactions to LAs.

Local Reactions

Local reactions associated with anesthetic delivery are typically due to injection technique or local effects of epinephrine. Trauma from needle insertion can rarely cause tenderness, bruising, or even hematoma formation. There is also a theoretical risk of nerve damage from injection, although this complication is quite uncommon and is usually associated with peripheral

TABLE 2. A List of Common Reactions Seen With Local Anesthetics and Their Characteristics¹²⁻¹⁷

	<i>Anaphylaxis</i>	<i>Delayed Type Hypersensitivity</i>	<i>Vasovagal Response</i>	<i>Epinephrine Reaction</i>	<i>Toxic Effect of Anesthesia</i>	<i>Trauma</i>
Time course	Reaction within minutes up to 1 h after exposure	Reaction within 72 h after exposure	Any time before, during, or after procedure	Reaction typically within minutes	After high doses of local anesthetic	Hours following procedure
Symptoms	Wheal and flare, itching, hives, angioedema, cough, wheezing, hypotension, diarrhea	Eczematous dermatitis corresponding to area of contact with allergen	Lightheadedness, nausea, diaphoresis, tinnitus, visual disturbance, confusion, pallor, bradycardia, hypotension	Tachycardia, hypertension, palpitations, malaise, lightheadedness, flushing	Early: Lightheadedness, visual disturbance; Late: CNS depression, convulsions, muscle twitching, respiratory depression, loss of consciousness, cardiovascular collapse	Swelling limited to surgical site or areas of dependent drainage
Treatment	Administer 0.3–0.5 mg IM epinephrine, basic life support, transport to acute care facility (911)	Topical steroids	Assume a supine position with legs raised	Supportive. Nonselective beta-blockers (rarely)	Treat systemic symptoms (e.g., seizures with diazepam). Transport to acute care facility (911)	Reassurance, pain control
Pattern	Occurs every time patient is exposed to drug	Occurs every time patient is exposed to drug or preservative	Occurs in different settings but with the same or similar stimuli (pain, sight of blood, etc.)	Higher risk in patients who take propranolol or tricyclic antidepressants, or have a medical history of hyperthyroidism, severe hypertension, or pheochromocytoma	Singular event corresponding to very high doses of LA	No history of systemic symptoms. No itching
Testing	Positive skin prick and/or intradermal testing	Positive patch testing	Clinical history. Tilt table for orthostatic cause. Cardiology evaluation for syncope or concern for arrhythmia	Clinical medical history and drug history	None	None

TABLE 2. (Continued)

	Anaphylaxis	Delayed Type Hypersensitivity	Vasovagal Response	Epinephrine Reaction	Toxic Effect of Anesthesia	Trauma
Management	Avoidance of known agent. Use of agent from opposite class or an agent demonstrated to be safe on skin prick/intradermal testing	Avoidance of known agent. Use of agent from opposite class or an agent demonstrated to be safe on patch testing	Avoid stimuli known to cause reaction. Ensure patient has eaten and is well hydrated before procedure	Reassurance or avoidance in high risk individuals	Use appropriate doses of LA based on weight based dosing and consideration of impaired excretion	Observation
Cause	Preformed IgE antibodies	T-cell mediated	Emotional or orthostatic stress, pain	Direct effect of adrenergic stimulation	Direct effect of LA	Direct trauma to tissue

nerve blocks. Epinephrine is added to LA to assist with hemostasis and prolong the duration of local anesthesia. The most common dilutions of epinephrine in use in LA today are 1:100,000 and 1:200,000.¹⁸ Use of epinephrine in LA causes a local tissue reaction consisting of tissue blanching that resolves spontaneously. Epinephrine has historically been implicated as causing tissue necrosis because of vasoconstriction of end arteries, particularly of the digits. However, currently, LA with epinephrine is believed to be safe for use in all anatomic locations for local anesthesia and digital blocks.¹⁹ Proper injection technique and adequate selection of patients (absence of thrombotic conditions, vasospastic conditions, or uncontrolled hypertension) should be considered.

The safety of using epinephrine in LA is supported by data in the literature on accidental finger sticks with epinephrine auto-injector pens for treatment of anaphylaxis. Auto-injector pens contain epinephrine at 1:1,000 dilution i.e., 100 times the strength of epinephrine in most LAs. A study examining finger injections with high-dose epinephrine auto-injectors found no instances of necrosis or skin loss, but neuropraxia lasting as long as 10 weeks and reperfusion pain were documented.¹⁹ Patients who underwent treatment were most frequently treated with local injections of phentolamine 0.5 mg/mL. Phentolamine is a reversible, nonselective, alpha-adrenergic antagonist that is used to counteract severe peripheral vasoconstriction secondary to epinephrine.²⁰

Systemic Reactions

Anaphylaxis, a systemic, immediate hypersensitivity, is defined as one of 3 scenarios: (1) The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following; respiratory compromise, or reduced blood pressure or symptoms of end-organ dysfunction. (2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient; involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms, and/or persistent gastrointestinal symptoms. (3) Reduced blood pressure after exposure to a known

allergen.²¹ Although these definitions are useful for the practicing allergist, these definitions can be simplified for surgeons who treat these reactions uncommonly. The authors suggest remembering that systemic hypersensitivity (anaphylaxis) involves 2 or more organ systems, or any evidence of respiratory or cardiovascular compromise.²² The clinical symptoms of IgE-mediated reactions are described in more detail below.

Multiple studies have described LA hypersensitivity as confirmed by skin testing in the literature,¹² although the overall number of patients described is low. Bhole and colleagues²³ reviewed the English language literature from 1950 to 2011 to determine the overall prevalence of LA allergy. They identified 23 case series involving 2,978 patients and found that 29 of these patients had true IgE-mediated allergy to LA (0.97%). Of note, 22/29 (75%) of the reactions were due to an amide allergy, which the authors felt was related to the overall prevalence of the use of amides today rather than enhanced allergenicity of amides versus esters.¹³ The authors also identified 31 individual case reports involving 34 patients with 21 proven cases of LA hypersensitivity. Similarly, Batinac and colleagues¹ found that 3/331 patients with reported LA adverse reactions (0.91%) had a true LA hypersensitivity, whereas the remaining patients were found to have non-IgE mechanisms of reactions. The only IgE-mediated reactions were to bupivacaine. Harboe and colleagues²⁴ reviewed 135 cases of suspected hypersensitivity and found 2 patients with true hypersensitivity to articaine-epinephrine and tetracaine-epinephrine. Fuzier and colleagues found an immediate hypersensitivity to lidocaine or mepivacaine in 11 out of 16 suspected patients.²⁵ Interestingly, they reported 6 patients as having cross-reactivity of hypersensitivity among amide anesthetics with intradermal testing. One study of 38 suspected cases found 2 patients with positive intradermal testing to lidocaine.²⁶ Amsler and colleagues²⁵ demonstrated only 1 patient out of 199 with reported lidocaine intolerance to have true lidocaine hypersensitivity. Two case reports also discussed immediate hypersensitivity to mepivacaine, levobupivacaine, and ropivacaine.^{4,27}

Overall, the rate of true IgE-mediated allergy to LA in high risk populations (patients reporting an LA allergy) was found to be around 1%. Therefore, the true prevalence of LA allergy in the general population should be assumed to be significantly lower.

Most true allergic reactions to local anesthetics are actually Type IV reactions, also known as delayed hypersensitivity (DTH) reactions. Both amide and esters can cause this reaction. The clinical symptoms of delayed hypersensitivity are similar to the induration seen with purified protein derivative placement. Although the anesthetic itself can rarely cause DTH, most commonly the allergic culprit is preservatives such as parabens and sulfites. Esters have been more commonly implicated to cause DTH, a factor contributing to their decrease in use.²⁸

Mimickers of Local Anesthetic Allergy

Vasovagal Response

Anxiety, fear of needles, or the pain of injection are just a few common clinical scenarios that can precipitate a vasovagal response.²⁹ Increased parasympathetic tone leads to lightheadedness, diaphoresis, nausea, bradycardia, and hypotension.³⁰ In severe cases, this reaction can progress to syncope. In cases of vasovagal reaction, reassurance, a cool towel on the forehead, and placing the patient in Trendelenburg can alleviate the symptoms. For vasovagal reactions not responding to these measures, atropine 0.4 mg delivered subcutaneously has been recommended.¹⁴ If patients have a history of anxiety or vasovagal reactions before procedures, preoperative oral sedation can be considered.

Epinephrine Reaction

Even the low concentrations of epinephrine in LAs can result in systemic effects. The adrenergic effects of epinephrine can result in palpitations, flushing, and malaise which patients may find quite distressing.⁴ The tachycardia seen in an epinephrine reaction may be confused with that seen in an anaphylactic reaction, but blood pressure tends to be elevated with epinephrine and lowered with

anaphylaxis. Many commonly used drugs can hypothetically alter the natural physiologic effects of epinephrine; making a drug history important when administering LAs with epinephrine. For example, patients who take propranolol could have severe hypertension as a result of unopposed alpha-adrenergic activation. Tricyclic antidepressants block the reuptake of serotonin and norepinephrine, and may potentiate the effects of epinephrine, leading to rapid heart rate, abnormal heart rhythms, and an increase in blood pressure. These complications are uncommon, but emphasize the need to be aware of potential drug interactions.³¹ Finally, epinephrine should be avoided in patients who have a medical history of uncontrolled hyperthyroidism, severe hypertension, or pheochromocytoma.^{18,32} Epinephrine effects resolve spontaneously and usually do not require treatment. If needed, first line treatment includes a nonselective beta-blocker.^{33,34}

Toxic Effect of Anesthesia

When local anesthetics exceed the dosage maximum or their excretion is impaired, life-threatening systemic toxicity can occur. Lidocaine is the most commonly used LA in dermatologic practice and has a maximum dose of 4.5 mg/kg without epinephrine and 7.0 mg/kg with epinephrine in adults.³⁵ When lidocaine dosage exceeds these values, central nervous system and cardiovascular toxicity can ensue. Fortunately, in routine skin surgery, these doses are rarely exceeded.³⁶ Central nervous system toxicity can initially manifest as drowsiness, circumoral or lingual paresthesia and then progress to tinnitus, nystagmus, ataxia, hallucinations, twitching, restlessness, and finally seizures, coma, or apnea.³ Cardiovascular effects are a manifestation of sodium-channel blockage on cardiomyocytes leading to decreased contractility. These cardiac signs usually do not manifest until after central nervous system findings. With increasing toxic levels of lidocaine, there is progressive cardiovascular deterioration with hypotension secondary to decreased contractility, followed by bradycardia, and then respiratory depression. Bupivacaine toxicity can manifest initially as ventricular fibrillation.^{15,37} The first step when toxicity is suspected is to halt all anesthetic delivery, to focus on maintaining airway and

oxygenation, and contact emergency services for transfer to a higher level of care.

Diagnosing and Treating Anaphylaxis

Knowledge of how to recognize and treat allergic reactions is critical for dermatologic surgeons. Although these reactions remain rare, anaphylaxis is an acutely life-threatening emergency that requires awareness of symptoms and a knowledge of appropriate treatment to avoid morbidity and mortality. When a patient develops allergic symptoms, a crucial decision point is to quickly determine whether or not it is a local or systemic reaction (anaphylaxis). A local reaction consists of hives or angioedema alone without laryngeal involvement and can be treated with antihistamines and close observation. Anaphylaxis, a potentially fatal systemic hypersensitivity, has varied presentations, but respiratory and cardiac compromise are the most concerning. Although urticaria and angioedema are the most commonly seen manifestations of anaphylaxis, their presentation may be delayed, especially if anaphylaxis is rapidly progressive.³⁸ Nausea, vomiting, and diarrhea may be seen in anaphylaxis, but this is more common with ingestions and should not be relied upon as a clinical finding in this setting. Patients with respiratory compromise will report a subjective feeling of shortness of breath and may have cough or wheezing. Cardiovascular effects include hypotension with a reactive tachycardia, although in rare cases there may be bradycardia as well. Anaphylaxis usually develops within minutes of exposure to the offending antigen, although there are late reactions (greater than 30 minutes after exposure). Theoretically, patients with anaphylaxis had an initial sensitization to the product of concern, however, cross-reactivity may occur and result in anaphylaxis on initial exposure. Epinephrine should immediately be given for anaphylaxis and the threshold for administration should be low. In true anaphylaxis, treatment with diphenhydramine or another antihistamine with observation is inappropriate.

Although it is impractical to fully discuss the treatment of anaphylaxis, there are several key points regarding the treatment of anaphylaxis in the office setting.

Dermatologic surgeons should have epinephrine available in their offices for treatment of anaphylaxis of any cause. If anaphylaxis is suspected, intramuscular (IM) epinephrine is the treatment of choice. There is no convincing data that epinephrine use during anaphylaxis causes significant morbidity or mortality. There is also no scenario when a patient is believed to be in anaphylaxis where the use of epinephrine is contraindicated.²¹ Conversely, delayed administration of epinephrine is a commonly associated factor with morbidity and mortality.^{39,40} The recommended dosing for an adult is 0.3 to 0.5 mg (this typically equals the same volume: 0.3–0.5 mL of a 1 mg/mL solution) of a 1:1,000 solution delivered IM to the lateral aspect of the vastus lateralis muscle. The patient or provider should insert the auto-injector or syringe with an IM needle into the upper outer thigh to theoretically avoid the larger vessels of the medial thigh. This injection may be repeated every 5 minutes as needed. For a child, the recommended dosing is 0.01 mg/kg up to the adult dose of 0.5 mg. Commercially available auto injectors deliver a preset dose of epinephrine. For adults this is 0.3 mg and for children it is 0.15 mg. When a child reaches 25 kg, an adult dose should be given. Commercially available auto injectors are typically given as a 2-pack and these are designed to remain together. The second injector is designed to be given should the first injection not fully relieve symptoms or should the reaction continue or worsen beyond the duration of action of the first injection. The 2-pack should never be divided.^{21,22,39,41}

Testing Procedures

Allergy testing for adverse reactions to LAs suspected to be allergic in origin is divided into immediate hypersensitivity testing (skin prick or intradermal testing) and delayed hypersensitivity testing (patch testing). Skin prick testing consists of percutaneous delivery of an allergen using one of several commercially available percutaneous skin prick devices. Intradermal testing is delivered using a needle into the dermis of the skin, similar to placing a purified protein derivative. For both tests, a local reaction, indicated by a wheal or flare (redness and swelling), would be considered a positive test. Systemic reactions to skin prick or intradermal testing are very rare. The general

approach is to perform testing by delivering the lowest dose of LA to the patient and observing for reaction (beginning with skin prick) and then increasing either the concentration, volume, or both, until it has been determined that the patient can tolerate the LA. If a patient tolerates skin prick testing, they should progress to intradermal testing. McClimon and colleagues⁴² found the negative predictive value for skin prick and intradermal testing to be 97%. Also, 98% of patients receiving local anesthetics in the clinical setting after passing intradermal testing tolerated the medications. Another study reported 10/13 patients with positive skin prick testing to preservative- and additive-free local anesthetic to have a negative subcutaneous challenge. The other 3 patients tolerated another local anesthetic in the same class with no reaction.⁴³ The subcutaneous challenge is similar to the intradermal test, but it uses an undiluted concentration of the medication. If a patient undergoes intradermal testing to an LA without a local reaction, that medication can be considered safe to use in dermatologic surgery.

Patch testing is indicated when allergic contact dermatitis (delayed type hypersensitivity) is suspected.⁴⁴ Commercially available patch testing kits in North America include a “caine mix,” which includes benzocaine, tetracaine, and dibucaine. Patch testing to individual LAs or their components can also be considered.⁴⁵

Approach to a Patient With “LA Allergy”

The surgeon should initially take a thorough history, focusing on the nature of the reaction. Pertinent information includes agents administered to the patient, quantity administered, route given, the presence of preservatives, presence of vasoconstrictors, type of symptoms and signs experienced, time course, concomitant medications, medical history, and preceding episodes. Based on that history there are 3 potential scenarios to consider:

The Surgeon Feels the History Is Not an IgE-Mediated Reaction

This scenario would include when a patient’s symptoms are completely consistent with one of the mimics of allergic reaction discussed in Table 2. This

scenario would also include when the history is so remote that the patient is at no greater risk than the general population. Commonly encountered scenarios include when the patient was “told they were allergic since they were a child” or states a non-physiologic reason such as “my sibling had a reaction so I must be allergic too.” In this scenario, no additional testing or precautions beyond that used for any other patient needs to be done. If the patient or physician needs reassurance, a saline-controlled intradermal or subcutaneous challenge can be quickly and easily performed in the office (See Table 3 for step-by-step instructions). A non-IgE-mediated reaction will be the most common scenario encountered.

The Surgeon Feels the History Is Questionable for an IgE-Mediated Reaction

In this scenario, the surgeon can consider allergy testing before the scheduled procedure. If a delay is practical, the patient should be referred to an allergist for skin prick and intradermal testing. The surgeon should send the patient with samples of the suspected prior allergen (if available) and 2 options for LA that the surgeon would be comfortable using (ideally one from each class of LA). These should not include epinephrine, as this can give a false negative test.^{46–48}

If the procedure is urgent and delaying the procedure is not feasible, the surgeon should attempt to identify the specific agent that caused the initial reaction. The surgeon may then perform testing before the procedure using an alternate LA. We recommend a skin prick test using an alternative LA (preferably from the opposite class of the suspected causative LA). If skin prick materials are not readily available, a graded intradermal challenge using the alternate LA with a saline control can be quickly and easily performed in the office (See Table 3 for step-by-step instructions). Alternatives to local anesthetics include using injections of 0.9% saline with benzyl alcohol preservative, diphenhydramine, or using general anesthesia.^{3,49} These approaches may expose the patient to either increased risk or pain and are likely unnecessary if evaluation of a history of LA adverse reaction is adequately assessed.

TABLE 3. A Step-By-Step Guide to the Intradermal Challenge for Local Anesthetic^{46–48}

Step 1. Choose the location: typically performed on the volar forearm as opposed to the back, which is commonly used in skin prick testing. The back is more reactive, but the forearm is more convenient for tourniquet placement in the event of a systemic reaction.

Step 2. Clean the area with an alcohol wipe, and inject a 2–3 mm bleb of a 1:1,000 dilution of an LA from the opposite class* as the suspected allergen (usually 0.02–0.05 mL) superficially in the skin. All test sites should be marked and placed 2–2.5 cm apart to avoid overlapping reactions for allergen identification. Correct technique dictates a positive control (0.10 mg/mL of histamine base) and a negative control (normal saline) for comparison. Note potential false negatives if there is no histamine available.

Step 3. Evaluate wheal size (raised bump) and flare (surrounding erythema) size at 15–20 minutes and record as the longest diameter of the wheal. To be deemed positive, the allergen-induced wheal or flare must be at least 3 mm greater in diameter than the negative control used. If 1:1,000 is read as negative, test an increased concentration of injectable 1:100 before the test is deemed negative. A subcutaneous challenge can then be performed in low-risk individuals. This is similar to the intradermal challenge, but performed with an undiluted concentration of LA.

A false negative skin test can occur in patients who have taken antihistamines or a drug with antihistaminic properties (e.g., tricyclic antidepressants). Depending on the medication, specific pharmacologic agents should be stopped anywhere from 2 to 11 d before skin testing. Topical corticosteroids can alter the reading of a skin test for greater than 3 wk. After anaphylaxis, skin testing should be delayed for at least 4 wk, as testing may yield a false negative result to the allergen that actually caused the episode.

A false positive skin test can occur in patients with dermatographism, experienced by 2%–5% of the population. This reaction can be easily delineated using the negative control of normal saline injection.

If the patient has a systemic reaction during testing, assess for anaphylaxis and consider placing a tourniquet on the arm that was tested to limit systemic drug dispersion.

*Whereas most protocols call for testing of an opposite class of local anesthetic, it is the authors' opinion that a drug in the same class can be used for testing, as the chance of cross-reactivity is hypothetical but low.

The Surgeon Feels the History Is Probable for IgE-Mediated Reaction

All attempts should be made to hold the procedure until the patient is formally evaluated by an allergist. If

the procedure is urgent and there is a known allergy, an LA from the opposite class from that of the causative LA should be used. If it is unknown if the patient has a true allergy, consider the risks and benefits of alternative methods of anesthesia.

Conclusion

Patient-reported “allergy” to local anesthetics is a commonly encountered problem in dermatologic surgery. Most often, the patient does not have a true allergy, but rather an adverse reaction to the medication itself or to the process of receiving the medication. True IgE-mediated hypersensitivity to LA is exceedingly rare, and physicians and patients can be reassured that this complication is unlikely to occur. A good history from the patient can help delineate if there is valid suspicion for a true hypersensitivity reaction. When in doubt, one can refer the patient to an allergist for IgE hypersensitivity testing or perform in-office intradermal testing. Dermatologic surgeons should be comfortable identifying anesthetic allergy and its mimickers, as well as managing these complications. Epinephrine should be available in the dermatologic surgeon’s office and practitioners should not hesitate to immediately treat anaphylaxis should it occur in response to LA or another allergen while the patient is under their care.

References

- Batinac T, Sotosek Tokmadzic V, Peharda V, Brajac I. Adverse reactions and alleged allergy to local anesthetics: analysis of 331 patients. *J Dermatol* 2013;40:522–7.
- Ruetsch YA, Boni T, Borgeat A. From cocaine to ropivacaine: the history of local anesthetic drugs. *Curr Top Med Chem* 2001;1:175–82.
- Wolverton SE. Comprehensive dermatologic drug Therapy (3rd ed). Saunders E, editor. Edinburgh: Elsevier Saunders; 2013.
- Calderon AL, Diot N, Benatir F, Christin F, et al. Immediate allergic cross-reactivity to levobupivacaine and ropivacaine. *Anaesthesia* 2013; 68:203–5.
- Gonzalez-Delgado P, Anton R, Soriano V, Zapater P, et al. Cross-reactivity among amide-type local anesthetics in a case of allergy to mepivacaine. *J Investig Allergol Clin Immunol* 2006;16:311–3.
- Cuesta-Herranz J, de las Heras M, Fernandez M, Lluch M, et al. Allergic reaction caused by local anesthetic agents belonging to the amide group. *J Allergy Clin Immunol* 1997;99:427–8.
- Morais-Almeida M, Gaspar A, Marinho S, Rosado-Pinto J. Allergy to local anesthetics of the amide group with tolerance to procaine. *Allergy* 2003;58:827–8.
- Grekin RC, Auletta MJ. Local anesthesia in dermatologic surgery. *J Am Acad Dermatol* 1988;19:599–614.
- Covino BG. Local anesthesia. 1. *N Engl J Med* 1972;286:975–83.
- Abraham SN, Arock M. Mast cells and basophils in innate immunity. *Semin Immunol* 1998;10:373–81.
- To D, Kossintseva I, de Gannes G. Lidocaine contact allergy is becoming more prevalent. *Dermatol Surg* 2014;40:1367–72.
- Berkun Y, Ben-Zvi A, Levy Y, Galili D, et al. Evaluation of adverse reactions to local anesthetics: experience with 236 patients. *Ann Allergy Asthma Immunol* 2003;91:342–5.
- Wildsmith JA, Mason A, McKinnon RP, Rae SM. Alleged allergy to local anaesthetic drugs. *Br Dent J* 1998;184:507–10.
- Fisher DA. Treatment of vasovagal reactions. *J Am Acad Dermatol* 1998;38(2 Pt 1):287–8.
- McCaughey W. Adverse effects of local anaesthetics. *Drug Safety* 1992; 7:178–89.
- Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. *J Allergy Clin Immunol* 1996;97:933–7.
- deShazo RD, Nelson HS. An approach to the patient with a history of local anesthetic hypersensitivity: experience with 90 patients. *J Allergy Clin Immunol* 1979;63:387–94.
- Krunic AL, Wang LC, Soltani K, Weitzul S, et al. Digital anesthesia with epinephrine: an old myth revisited. *J Am Acad Dermatol* 2004;51:755–9.
- Fitzcharles-Bowe C, Denkler K, Lalonde D. Finger injection with high-dose (1:1,000) epinephrine: does it cause finger necrosis and should it be treated? *Hand (N Y)* 2007;2:5–11.
- Denkler K. A comprehensive review of epinephrine in the finger: to do or not to do. *Plast Reconstr Surg* 2001;108:114–24.
- Joint Task Force on Practice P, American Academy of Allergy A, Immunology, American College of Allergy A, Joint Council of Allergy A. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115(3 Suppl 2):S483–523.
- Simons FE. Anaphylaxis: recent advances in assessment and treatment. *J Allergy Clin Immunol* 2009;124:625–36; quiz 37–8.
- Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. *Br J Anaesth* 2012;108:903–11.
- Harboe T, Guttormsen AB, Aarebrot S, Dybendal T, et al. Suspected allergy to local anaesthetics: follow-up in 135 cases. *Acta Anaesthesiol Scand* 2010;54:536–42.
- Amsler E, Flahault A, Mathelier-Fusade P, Aractingi S. Evaluation of re-challenge in patients with suspected lidocaine allergy. *Dermatology* 2004;208:109–11.
- Jacobsen RB, Borch JE, Bindselev-Jensen C. Hypersensitivity to local anaesthetics. *Allergy* 2005;60:262–4.
- Sharma V, Harper NJ, Garcez T, Arkwright PD. Allergic reaction to mepivacaine in a child. *Br J Anaesth* 2013;110:1059–60.
- Mackley CL, Marks JG Jr, Anderson BE. Delayed-type hypersensitivity to lidocaine. *Arch Dermatol* 2003;139:343–6.
- Tetzlaff JE. The pharmacology of local anesthetics. *Anesthesiol Clin North America* 2000;18:217–33, v.
- Faccenda KA, Finucane BT. Complications of regional anaesthesia Incidence and prevention. *Drug Saf* 2001;24:413–42.
- Goulet JP, Perusse R, Turcotte JY. Contraindications to vasoconstrictors in dentistry: Part III. Pharmacologic interactions. *Oral Surg Oral Med Oral Pathol* 1992;74:692–7.
- Berbaum MW, Bredle DL, Futamura W. Absence of significant adverse effects from low-dose subcutaneous epinephrine in dermatologic procedures. *Arch Dermatol* 1997;133:1318–9.

33. Weinberg GL. Treatment of local anesthetic systemic toxicity (LAST). *Reg Anesth Pain Med* 2010;35:188–93.
34. Mulroy MF, Hejtmanek MR. Prevention of local anesthetic systemic toxicity. *Reg Anesth Pain Med* 2010;35:177–80.
35. Lie RL, Vermeer BJ, Edelbroek PM. Severe lidocaine intoxication by cutaneous absorption. *J Am Acad Dermatol* 1990;23(5 Pt 2):1026–8.
36. Klein JA, Kassardjian N. Lidocaine toxicity with tumescent liposuction. A case report of probable drug interactions. *Dermatol Surg* 1997;23:1169–74.
37. Reiz S, Nath S. Cardiotoxicity of local anaesthetic agents. *Br J Anaesth* 1986;58:736–46.
38. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010;126:477–80.e1–42.
39. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy* 2000;30:1144–50.
40. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380–4.
41. Chiu CY, Lin TY, Hsia SH, Lai SH, et al. Systemic anaphylaxis following local lidocaine administration during a dental procedure. *Pediatr Emerg Care* 2004;20:178–80.
42. McClimon B, Rank M, Li J. The predictive value of skin testing in the diagnosis of local anesthetic allergy. *Allergy Asthma Proc* 2011;32:95–8.
43. Troise C, Voltolini S, Minale P, Modena P, et al. Management of patients at risk for adverse reactions to local anesthetics: analysis of 386 cases. *J Investig Allergol Clin Immunol* 1998;8:172–5.
44. Gonzalez-Rodriguez AJ, Gutierrez-Paredes EM, Revert Fernandez A, Jorda-Cuevas E. Allergic contact dermatitis to benzocaine: the importance of concomitant positive patch test results. *Actas Dermosifiliogr* 2013;104:156–8.
45. Brinca A, Cabral R, Goncalo M. Contact allergy to local anaesthetics—value of patch testing with a caine mix in the baseline series. *Contact Dermatitis* 2013;68:156–62.
46. Tomoyasu Y, Mukae K, Suda M, Hayashi T, et al. Allergic reactions to local anesthetics in dental patients: analysis of intracutaneous and challenge tests. *Open Dent J* 2011;5:146–9.
47. Hamilton RG. Clinical laboratory assessment of immediate-type hypersensitivity. *J Allergy Clin Immunol* 2010;125(2 Suppl 2):S284–96.
48. Wohrl S, Vigl K, Stingl G. Patients with drug reactions—is it worth testing? *Allergy* 2006;61:928–34.
49. Jolliffe VM, Sinclair RD. Excision biopsy in a patient with suspected local anaesthetic allergy: use of 0.9% saline with benzyl alcohol as local anaesthesia. *Clin Exp Dermatol* 2012;37:862–4.

Address correspondence and reprint requests to:
 Mariah Brown, MD, Department of Dermatology,
 University of Colorado School of Medicine, Mail Stop
 F703 1665 North Aurora Ct, Aurora, CO 80045, or
 e-mail: mariah.brown@ucdenver.edu