



Allergy to Local Anesthetics is a Rarity: Review of Diagnostics and Strategies for Clinical Management

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Abstract

Local anesthetics (LA) are commonly used in procedures and in topical agents for pain management. With the increasing use of LA drugs, the management of LA reactions is more frequently encountered in the office and in operating rooms. True allergic reactions involving IgE-mediated reactions and anaphylaxis are rare; they have only been identified in case reports and account for less than 1% of adverse LA reactions. Most reactions are non-allergic or are a result of hypersensitivity to other culprits such as preservatives, excipients, or other exposures. LA reactions that are misclassified as true allergies can lead to unnecessary avoidance of LA drugs or delays in surgical procedures that require their use. A detailed history of prior LA reactions is the first and most crucial step for understanding the nature of the reaction. Reactions that are suspicious for an immediate hypersensitivity reaction can be evaluated with skin prick and intradermal testing with subsequent graded challenge. Reactions that are suspicious for a delayed hypersensitivity reaction can be evaluated with patch testing.

Keywords Local anesthetic · Skin prick testing · Intradermal testing · Challenge · Negative predictive value · False positive rate

Introduction

A Brief History of Use of Local Anesthetic Drugs

The first local anesthetic (LA) was used in 1884 when an Austrian ophthalmologist, Carl Koller, applied a cocaine solution to the human cornea during eye surgery [1, 2]. With time, adverse reactions from cocaine use such as addiction and even death led to a demand for alternative options. Procaine was developed in 1904 followed by other ester LA drugs. Then lidocaine was developed in 1948 followed by new amide LA drugs. LA drugs act as an anesthetic by binding sodium channels in the nerve plasma membrane, blocking action potentials and signal transmission of neuronal networks. The bound LA drug physically obstructs the sodium channel and stabilizes the inactive receptor state [2–5].

LA drugs are commonplace, and lifetime exposure to LA is nearly inevitable. They are used in a variety of settings including surgical, emergency, obstetric, dental, and ophthalmic procedures, regional nerve blocks, subcutaneous analgesia before venipuncture, and in topical creams and gels to treat burns or insect stings. Their ubiquitous use makes it important to understand how adverse drug reactions (ADRs) to LA drugs occur, especially when LA are likely to be necessary in those who have had a history of a LA drug reaction.

Prevalence of Reactions to Local Anesthetics

LA drugs are generally well tolerated with the rate of any ADR ranging from 0.5 to 26% [6, 7]. The literature on ADRs reported by both patients and providers suggests that ADRs are rarely ever allergic. In an open-label prospective study examining ADRs to LA in dentistry, 0.5% of 5018 subjects experienced some ADR; however, none were allergic, hypersensitivity reactions [8]. A questionnaire survey of German dentists found a general incidence of ADRs to be 4.5% in 2731 cases, but less than 1% of reactions were allergic [9]. One survey of patients found a relatively higher rate of ADRs with 47/179 (26%) of participants that self-reported

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a ADR, but similarly none were hypersensitivity reactions [10]. ADRs that were most often reported were dizziness, tachycardia, palpitations, and diaphoresis [6, 9, 10].

Allergic contact dermatitis to LA drugs on the other hand, are more common than IgE-mediated reactions, and their incidence has been reported to be 2–3% [11–14]. Data from the North American Contact Dermatitis Group (NACDG) between 2001 and 2004 shows that 3.4% of 10,061 patients had a positive patch test to at least one LA drug. Data between 2001 and 2014 from NACDG and Mayo Clinic show an incidence of allergic contact dermatitis between 1.3–1.9% for benzocaine and 0.6–1% for lidocaine [12]. A large retrospective study between 2009 and 2013 from the University of British Columbia Contact Dermatitis Clinic looked at 1819 patients who underwent patch testing and found LA drugs to be the culprit in 2.4% of cases [11]. The prevalence of allergic contact dermatitis was rising, and the authors proposed that this may be due to increasing use of LA in over-the-counter products.

IgE-mediated hypersensitivity reactions to LA are estimated to account for less than 1% of reported ADRs. Bhole et al. performed a systematic review and found 23 cases in 2978 patients (0.97%) with suspected LA allergy [15]. The rarity of reports of IgE-mediated reactions to LA drugs underscores that many immediate-type ADRs to LA can be explained by another culprit, including non-allergic causes, additives/excipients, or other perioperative exposures [16–19].

Pharmacology of Local Anesthetics

LA drugs have 3 structural groups: a lipophilic aromatic group that penetrates lipid-rich membranes, an amine group for hydrophilicity, and an intermediate chain linkage that distinguishes the two major classes of LA, benzoic acid esters and amides (Fig. 1). Esters are degraded by plasma cholinesterases into a metabolite called *p*-aminobenzoic acid (PABA), a known allergen present in cosmetics, lotions, and sunscreen. Amides are metabolized by the liver and do not form PABA metabolites. Therefore, allergic reactions to esters have more commonly been reported than to amides, which explain why in clinical practice amides are typically preferred.

LA preparations may contain excipients that have been identified as allergens such as hyaluronidase, antioxidants (i.e., sodium bisulfite and metabisulfite), or preservatives (i.e., methylparaben and ethylenediaminetetraacetic acid) [20–22]. Historically, some reactions to amides have been attributed to methylparaben, which was added to multiple dose vials. Methylparaben is metabolized to compounds similar to PABA and can cause anaphylactoid reactions. Consequently, the Food and Drug Administration has mandated its removal from dental cartridges and epidurals [23]. Methylparaben is not found in single-dose vials.

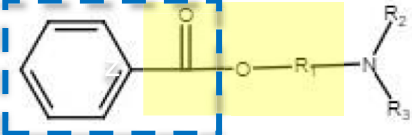
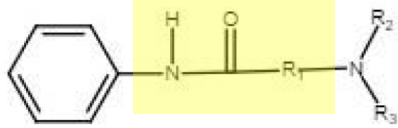
Group I: Benzoic acid esters 	Group II: Amides 
Benzocaine Chlorprocaine Cocaine Procaine Proparacaine Propoxycaine Tetracaine	Articaine (thiophene aromatic ring) Bupivacaine Dibucaine Etidocaine Lidocaine Levobupivacaine Mepivacaine Prilocaine Ropivacaine

Fig. 1 Local anesthetic (LA) classes. The major classification of LA is based on the intermediate chain linkage between the aromatic ring and amine group highlighted in yellow. The two classifications are benzoic acid esters, which can be metabolized into *p*-aminobenzoic

acid (PABA), a known allergen (outlined in blue), and amides. Common LA are classified into ester and amide groups as there is known cross-reactivity among esters in delayed hypersensitivity reactions that can be avoided by switching classes

Local Anesthetic Reactions

Immediate Hypersensitivity Reactions

Confirmed immediate hypersensitivity reactions to LA exposure have been limited to case reports of anaphylaxis or anaphylactoid reactions with positive skin prick or intradermal testing as shown in Table 1. The typical clinical presentation of an immediate hypersensitivity includes symptoms such as generalized urticaria, hypotension, bronchospasm, angioedema, and/or anaphylaxis within seconds to minutes after exposure. Cross-reactivity for immediate hypersensitivity reactions to LA has not been well established. Based on our review of cases with limited testing, there is no clear pattern of cross-reactivity within and between ester or amide LA classes (Table 1). Patients with reactions and positive testing to an ester were not consistently tested to other esters but most tolerated lidocaine (an amide). Patients with reactions and positive testing to an amide had inconsistent testing and tolerance of esters and other amides. However, skin testing was often able to identify an alternative LA that patients tolerated.

The mechanism of LA immediate hypersensitivity reactions has not been clearly identified. Specific IgE to LA have not been demonstrated [19]. Since LA are too small to be antigenic (low molecular weight of 200–300 DA), LA drug immunogenicity is thought to be via sensitization of a hapten–carrier complex [23] (Fig. 2). The LA drug or one of its metabolites acts as a hapten binding to an endogenous or exogenous peptide to form a complex that functions as an allergen. For esters, PABA may be the culprit. Other haptens and hapten–carrier conjugates may exist but have not yet been identified. Other mechanisms of drug-dependent but non-antigen-mediated drug hypersensitivity may also result in LA drug reactions [24], including the “p-i stimulation” concept in which the drug directly binds to immune receptors such as HLA or T cell receptors and “pseudo-allergy” wherein the drug binds receptors and stimulates inflammatory pathways such as complement activation and antibody-independent mast cell and basophil degranulation [25–28] (Fig. 2). These inflammatory mechanisms present similarly to IgE-mediated reaction and exhibit symptoms such as urticaria, erythema, bronchospasm, angioedema, or anaphylaxis.

Delayed Hypersensitivity Reactions to Local Anesthetics

Delayed hypersensitivity reactions are the most commonly described immunologic reactions to LA drugs, although they are still uncommon [23, 30]. The typical clinical

presentation of a delayed hypersensitivity reaction is localized erythema, induration, edema, and pruritus several hours to days later. An eczematous rash may also be present. Additional delayed type IV LA drug reactions have been described in case reports, including a rare case of lidocaine-induced erythema nodosum and erythema multiforme [31]. Other severe delayed hypersensitivity reactions such as SJS, AGEP, or DRESS syndrome have not been described in the literature in association with LA use. For delayed hypersensitivity reactions, cross-reactivity has been identified among esters due to PABA [29]. Cross-reactivity among amides is less consistent. Some authors have suggested that there may be additional cross-reactivity between LA drugs that have a meta-xylene aromatic ring, which is found in lidocaine, mepivacaine, and bupivacaine [32, 33]. A possible alternative in this scenario would be articaine which contains a thiophene ring instead of a meta-xylene ring. However, there are instances of both negative cross-reactivity testing of alternate amides with meta-xylene rings [13] and positive testing of articaine and amides with meta-xylene rings [34]. There is no evidence for cross-reactivity between ester and amides. Positive patch testing is not associated with positive SPT or IDT, and patients are considered low risk for anaphylaxis [35].

Non-allergic Reactions

The typical clinical presentation of a non-allergic response to LA is diaphoresis, dizziness, paresthesias, or vasovagal syncope accompanied by bradycardia. Differentiating between allergic and non-allergic ADRs can be difficult because both can present similarly with lightheadedness, nausea, dyspnea, hypotension, or syncope. Not all adverse reactions to LA have a clear pathophysiology, and many may be idiosyncratic. The most frequently reported non-allergic causes associated with LA are toxicity, vasovagal reactions, anxiety, and adverse effects of the vasoconstrictors commonly compounded with LA. Vasoconstrictors like epinephrine can cause anxiety, palpitations, headaches and even cardiotoxic effects when absorbed systemically (i.e., hypertension, arrhythmia). Local anesthetic systemic toxicity can also occur with large doses or intravascular injection. Classic presentations of systemic toxicity start with unopposed central nervous system excitation including agitation, auditory changes, and metallic taste, followed by seizures, then drowsiness, coma, or respiratory arrest along with cardiac depression (i.e., bradycardia, arrhythmia, and hypotension) [20, 38, 39]. Typical submucosal or subcutaneous administration does not result in toxic serum levels [40]. Since esters are metabolized by cholinesterase, patients with pseudocholinesterase deficiency are at increased risk for toxic effects to ester LA.

Table 1 Case reports of immediate hypersensitivity reactions to local anesthetics with testing

Drug	Reaction	Testing	SPT	IDT	Challenge	Ref
Esters						
Procaine	Immediate generalized reaction	<u>Esters</u>	Neg	Pos 1:10,000	-	[36]
		Procaine	Neg	Neg 1:10	Tolerated	
		<u>Amides</u>	Neg	Pos 1:10,000	-	
		Lidocaine				
Mepivacaine						
Procaine	Local swelling	<u>Esters</u>	Pos	-	-	[36]
		Procaine	Pos	Neg 1:10	Tolerated	
		<u>Amides</u>	Equiv	-	-	
		Lidocaine				
Mepivacaine						
Procaine	Nonspecific systemic symptoms	<u>Esters</u>	Equiv	Saline control pos so not	-	[36]
		Procaine	Neg	able to interpret	Tolerated	
		<u>Amides</u>	Equiv		-	
		Lidocaine				
Mepivacaine						
Procaine	Nonspecific systemic symptoms	<u>Esters</u>	Neg	Equiv 1:100	-	[36]
		Procaine	Neg	Neg 1:10	Tolerated	
		<u>Amides</u>	Neg	Pos 1:10,000	-	
		Lidocaine				
Mepivacaine						
Benzocaine	Burning and mouth tingling; chest pain, vomiting, lightheadedness, respiratory distress, and loss of consciousness	<u>Esters</u>	Neg	Pos 1:1,000,000	-	[79]
		Benzocaine	Neg	Neg 1:1	-	
		<u>Amides</u>	Neg	Pos 1:1	-	
		Lidocaine				
Prilocaine						
Tetracaine	Nasal congestion, rhinorrhea, facial rash, fever	<u>Esters</u>	Neg	Pos 1:10,000	Reaction	[16]
		Tetracaine	-	Neg	Tolerated	
		<u>Amides</u>				
		Lidocaine				
Unknown LA	Rash, facial angioedema	<u>Esters</u>	Neg	Pos 1:10	-	[80]
		Tetracaine	Neg	Pos 1:1	-	
		Proparacaine	Neg	Neg	Tolerated	
		<u>Amides</u>				
Lidocaine						
Amides						
Lidocaine EMLA	Anaphylaxis Large local urticaria	<u>Esters</u>	Neg	Neg	Tolerated	[81]
		Procaine	Pos	-	-	
		<u>Amides</u>	Pos	-	-	
		Bupivacaine	Pos	-	-	
		Lidocaine	Neg	Pos 1:100	Reaction	
		Mepivacaine				
Ropivacaine						
Lidocaine	Erythematous pruritic plaques; eyelid and lip swelling	<u>Amides</u>	Neg	Pos	-	[82]
Lidocaine						
Mepivacaine	Itching and generalized urticaria	<u>Amides</u>	Neg	Neg 1:100	Tolerated	[83]
		Bupivacaine	Pos	Pos 1:100	-	
		Mepivacaine	Neg	Neg 1:100	Tolerated	
		Levobupivacaine	Pos	Pos 1:100	-	
		Lidocaine	Pos	Pos 1:100	-	
		Ropivacaine				
Mepivacaine	Pruritus, erythema and swelling of the hands and feet, vomiting, syncope	<u>Amides</u>	-	Pos 1:100	-	[84]
		Bupivacaine	-	Pos 1:10	-	
		Lidocaine	-	Pos 1:100	-	
		Mepivacaine	-	Neg 1:100	Tolerated	
		Prilocaine				

Table 1 (continued)

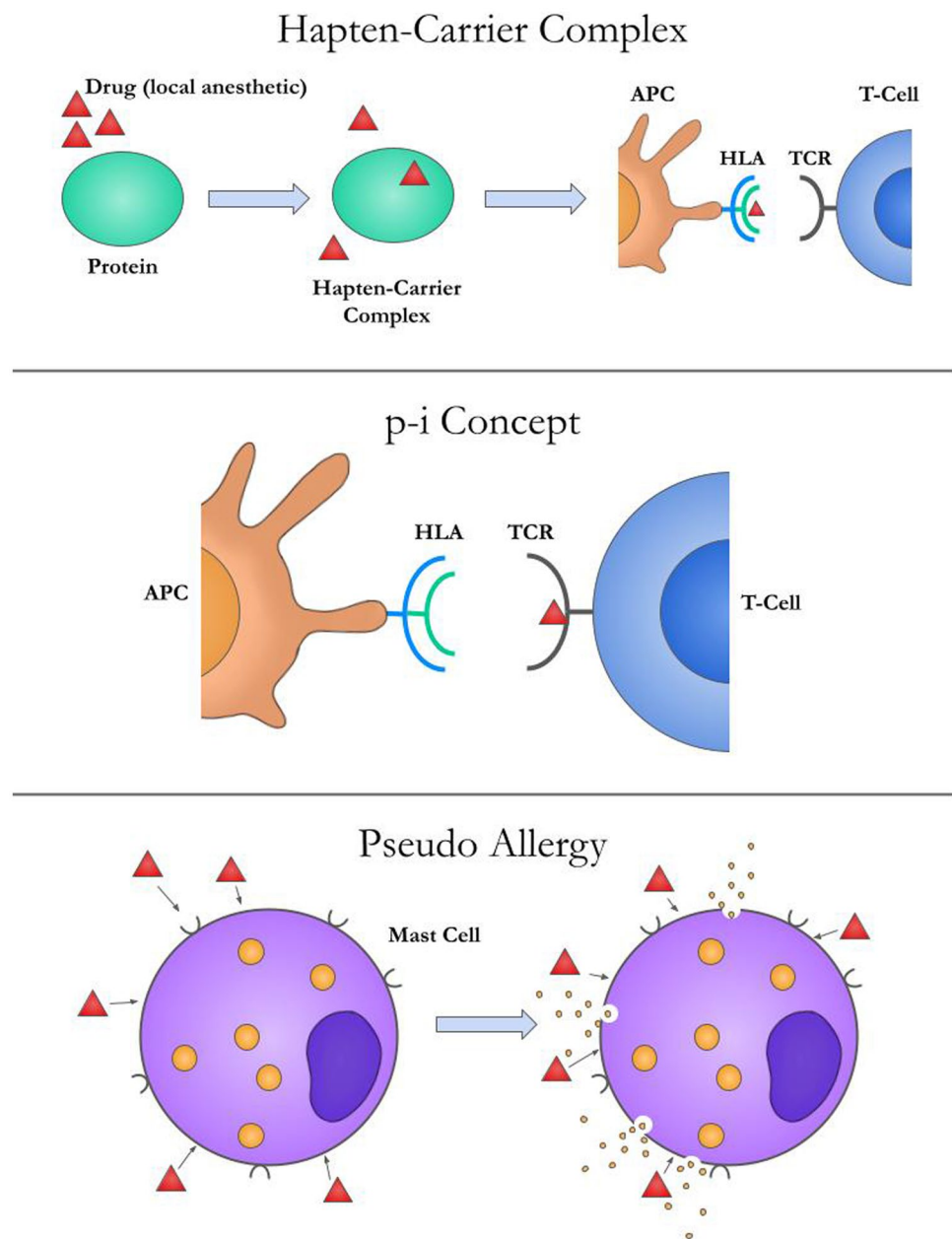
Drug	Reaction	Testing	SPT	IDT	Challenge	Ref
Mepivacaine Lidocaine	Immediate generalized reaction	<u>Esters</u> Procaine <u>Amides</u> Lidocaine Mepivacaine	Equiv Equiv Equiv	Equiv 1:100 Neg 1:100 Pos 1:100	- Tolerated -	[43]
Unknown	Pruritus, generalized urticaria	<u>Esters</u> Procaine <u>Amides</u> Bupivacaine Lidocaine Mepivacaine	Neg Neg Neg Neg	Neg Pos 1:100 Pos 1:100 Pos 1:100	Tolerated - Reaction Reaction	[85]
Bupivacaine Lidocaine	Pruritic skin rash, tongue edema, bronchospasm	<u>Amides</u> Bupivacaine Lidocaine Mepivacaine Procaine	Pos Pos Neg Pos	Systemic rx with SPT so not done	Systemic reaction with SPT so not done	[86]
Levobupivacaine Ropivacaine	Levobupivacaine: cognitive dysfunction, seizure, cutaneous flushing, tachycardia, hypotension Ropivacaine: facial erythema, hypotension	<u>Amides</u> Articaine Levobupivacaine Lidocaine Ropivacaine	Neg Pos Neg Pos	- - - -	- - - -	[87]
Lidocaine	Reaction 1: generalized body swelling, itching, and urticaria, drowsiness with hypotension Reaction 2: generalized urticaria and respiratory compromise	<u>Amides</u> Articaine Lidocaine	Neg Pos	Neg 1:1 -	Tolerated -	[88]
Lidocaine	Dizziness, systemic urticaria	<u>Esters</u> Procaine <u>Amides</u> Articaine Bupivacaine Levobupivacaine Lidocaine Mepivacaine Ropivacaine	Neg Pos Neg Neg Pos Neg Pos	Neg - Neg - Pos Neg -	Tolerated - - Tolerated - - -	[89]
Lidocaine, benoxinate, bupivacaine	Lidocaine: urticaria, throat fullness, dyspnea, confusion, and fatigue Benoxinate: shortness of breath, dysphagia, and increased sputum production Bupivacaine: pruritus, dysphagia, heart palpitations, chest tightness, shortness of breath	<u>Amides</u> Benoxinate Bupivacaine Lidocaine Mepivacaine Prilocaine	Pos Neg Neg Neg Neg	Systemic reaction Neg 1:1 Pos 1:1 Pos 1:100 Pos 1:1	Tolerated bupivacaine initially but developed delayed reaction and underwent desensitization, which was tolerated	[77]
Articaine	Urticaria and hypotension	<u>Esters</u> Procaine <u>Amides</u> Articaine Mepivacaine Prilocaine	- - - -	Neg 1:10 Pos 1:10 Pos 1:10 Neg 1:10	Tolerated - Tolerated Tolerated	[47]

Table 1 (continued)

Drug	Reaction	Testing	SPT	IDT	Challenge	Ref
Articaine	Urticaria, angioedema, tachycardia	Esters	-	Neg 1:10	Tolerated	[47]
		Procaine	-	Pos 1:10	-	
		Amides	-	Pos 1:10	-	
		Articaine	-	Pos 1:10	-	
		Mepivacaine Prilocaine	-	-	-	
Lidocaine	Delayed urticaria and angioedema	Amides	Neg	Pos 1:1	-	[90]
		Lidocaine	-	-	-	

SPT skin prick testing, IDT intradermal testing, Pos positive, Neg negative, Equiv equivocal

Fig. 2 Mechanisms of local anesthetic (LA)-induced hypersensitivity reactions. In the hapten-carrier complex model, LA is a hapten that binds to a carrier. The hapten-carrier complex is displayed by antigen-presenting cells (APC) on human leukocyte antigen (HLA) to activate T cells via the T cell receptor (TCR). In the p-i stimulation concept, LA directly binds to HLA or TCR to activate T cells, which is thought to explain certain drug reactions associated with specific HLA alleles. In the pseudo-allergy model, LA directly binds to mast cells causing degranulation



Additionally, there are other uncommon adverse reactions seen with LA. Purpuric lesions have been reported with the use of EMLA cream, a eutectic mixture of 1:1 prilocaine and lidocaine, and are hypothesized to be a result of direct toxicity of LA to blood vessels [41]. Methemoglobinemia, which causes cyanosis from dysfunctional oxygen binding and delivery to tissues, has also been described with benzocaine, prilocaine, lidocaine, and articaine [20, 42, 43]. This is more common in infants and young children or older adults, as well as people with hemoglobinopathies or glucose-6-phosphate dehydrogenase (G6PD) deficiency [20].

Diagnosing a Local Anesthetic Allergy

Clinical History

A clinical history is key to classifying the type of adverse reaction to LA. Similar to other drug allergies, we recommend eliciting the following details:

- (a) What were the properties of the LA drug (name and structural classification, dose, and route given)?
- (b) What symptoms occurred and what body systems were involved?
- (c) What was the timing of reaction onset and resolution?
- (d) What treatment was given and was there an appropriate response?
- (e) Was a tryptase sent, and if so, was it elevated?
- (f) Was there exposure to other drugs or substances (including epinephrine and preservatives in LA)?
- (g) Is there any history of other LA use or other procedures received?
- (h) Does the patient have any personal or family history of atopy?
- (i) Have LA drugs been tolerated since?

There is higher suspicion for an immediate hypersensitivity reaction if there is:

- Cutaneous or mucosal involvement with associated pruritis
- Reaction within 30 min (up to 2 h) of administration
- Persistent symptoms or that worsen until treatment (as opposed to non-allergic reactions which spontaneously resolve within minutes)
- Response to antihistamines, bronchodilators, steroids, and epinephrine
- Elevated tryptase level

Protocol for Skin Prick Testing and Graded Challenge

When the history raises concerns for an immediate hypersensitivity reaction to LA, clinicians should refer the patient to an allergist who can evaluate the patient and consider skin testing and graded challenge. There have been many different versions of SPT, IDT, and challenge testing protocols that have been published. Most protocols utilize skin testing with graded challenge for diagnosis of immediate hypersensitivity reactions to LA and identification of alternative LA that may be tolerated. No commercial serologic testing is available.

Choice of Reagent Testing may be limited by formulations available for clinical use. Testing is not recommended with formulations containing vasoconstrictors such as epinephrine as they may mask a wheal and flare [44]. Ideally, testing would also be done with a preservative-free formulation. However, since these may not be available for clinical use, providers may choose to test with the formulation that will be used in practice. In these instances, if testing is positive, additional testing for preservative-free formulations may be considered.

The suspect LA should be tested as well as other clinically relevant LA to determine safe alternatives. Lidocaine is often included in testing since it is commonly available. The concentration of the LA drugs used also varies between protocols. Some studies specify using a 1% concentration (i.e., 10 mg/mL) for most LA drugs except for bupivacaine [19, 36, 45, 46]. For bupivacaine, lower concentrations such as 0.5% or 0.25% have generally been used. Several publications have outlined the maximum concentrations of each LA used [17, 47–49]. The European Network on Drug Allergy/European Academy of Allergy and Clinical Immunology Drug Allergy Interest Group published a position paper on skin test concentrations for the evaluation of drug hypersensitivity reactions which did not specify LA drug concentrations but did recommend undiluted LA for SPT and 1:10 dilution LA for IDT [44]. Nonirritating concentrations of LA drugs for SPT and IDT that have been studied are outlined in Table 2.

SPT. The standard approach is to use undiluted SPT. A few SPT protocols have started with lower dilutions, most often a 1:100 dilution [13, 45, 50–52]. Skin testing should include a positive (histamine) and negative (saline) control. A positive test is considered a wheal 3 mm or larger than the negative control after 20 min.

IDT. The standard approach is to perform IDT to a maximum dilution of 1:10 or 1:100 if SPT was negative. Experts do not recommend undiluted LA because it can

Table 2 Nonirritating concentrations of local anesthetics for testing

Drug	Commercially available US concentrations (mg/mL)	Concentration (mg/mL)	Maximum SPT dilution	Maximum IDT dilution	Maximum challenge dose (mL)
Articaine	40 (4%)	10 [48] 40 [47]	Undiluted	1:10 ^f 1:100 ^g	1 ^a 1.5 [47] 2 ^b
Bupivacaine	2.5 (0.25%) 5 (0.5%) 7.5 (0.75%) Preservative and epinephrine-free available	2.5 ^c 5 ^d			1 ^a 2 ^b
Lidocaine	5 (0.5%) 10 (1%) 20 (2%) Preservative and epinephrine-free available	10 ^e 20 [47]			1 ^a 2 ^b
Mepivacaine	10 (1%) 15 (1.5%) 20 (2%) 30 (3%) Preservative and epinephrine-free available	10 ^c			1 ^a 2 ^b 4 [47]
Prilocaine	Not available in the USA	20 [48] 30 [47]			1 ^a 1.5 [47] 2 ^b
Ropivacaine	2 (0.2%) 5 (0.5%) 7.5 (0.75%) 10 (1%) Preservative and epinephrine-free available	2 [29, 49] 7.5 [47]			1 ^a 2 ^b 10 [47]

^a[7, 13, 16, 29, 36, 55–57]^c[17, 29, 47, 49]^d[7, 18, 46, 48]^e[29, 48, 49]^f[13, 17, 19, 31, 42, 43, 46, 47, 54, 56, 91, 92]^g[7, 18, 22, 33, 50, 52, 56]

cause false positive IDT in healthy controls [52, 53] and patients [45, 52, 54]. The expert groups generally recommend a maximum IDT of 1:10, but some allergists favor using a maximum IDT of 1:100 since false positives have been identified in a number of patients with 1:10 IDT [17, 36, 45], whereas false positives with healthy volunteers have not been seen with 1:100. Studied protocols either consisted of a series of increasing concentrations or a single-dilution IDT. Increasing concentration IDT started from 1:10,000 [36] and increased tenfold to 1:1000 [13], 1:100 [45, 52, 55], and 1:10 [54] until a positive test result or the maximum IDT dilution was reached. The single-dilution IDT was done at 1:1000 [16], 1:100 [7, 18, 22, 33, 50, 56], or 1:10 [17, 19, 47, 57]. A few studies performed single-dilution IDT alone without SPT as either undiluted [37, 58] or at 1:1000 dilution [46]. One protocol screened with a IDT at 1:10 and then performed 1:100 and 1:1000 dilutions if positive to help identify false positive irritant reactions [48].

Challenge. The standard approach is to perform a challenge to the undiluted drug if IDT is negative. The studied protocols either consisted of a series of increasing concentrations (also known as a graded challenge) or a single challenge dose. The protocols for graded challenge increase typically from 0.1 to 0.5 mL to a final dose of 1 mL [7, 13, 16, 29, 36, 55–57] or 2 mL [19, 33, 47, 48, 54, 59, 60]. Challenge testing was typically done with subcutaneous dermal injections, but a few studies did buccal injection challenges. If an ADR is encountered at any step, the challenge should be paused, and the patient should be assessed and treated accordingly. A placebo challenge with normal saline was added in many protocols which could help clarify nonspecific reactions [17, 18, 22, 29, 47, 48, 61]. A few studies performed single challenge dose alone without SPT or IDT; in one protocol, a single challenge dose was performed if low risk but graded challenge was performed if high risk, such as symptoms suggestive of allergy, severe reactions, and/or severe comorbidity [46, 62].

After completion of testing, it is important to communicate which LA drug(s) were tolerated, at what dose, and whether formulations included preservatives or epinephrine to the referring provider and other providers who would be using LA.

Test Characteristics. Predictive values are challenging to calculate since there is variation between testing protocols. The incidence of LA allergy is low, and gold standard challenge testing has not always historically been performed in patients with positive SPT or IDT given the concern for reaction. Two retrospective chart reviews of 178 patients from the Mayo Clinic, USA, and 148 from the Medical University of Gdansk, Poland, both found the negative predictive value of skin tests for LA allergy was 97% [56, 57]. False positive reaction rates are noted in up to 36% of studies with IDT at 1:10 dilution [19, 36, 47, 48, 54, 55] and 2% in studies with IDT at 1:100 dilution [56]. These false positive reactions have been attributed to dermographism or histamine release from cutaneous trauma [7, 22, 45, 53]. False positive reactions may peak rapidly and self-resolve within 20 min [63]. False negatives have also been rarely reported [19, 57]. It has been proposed that this may be due to limitations in the currently recommended testing process where the formulation used for skin testing lacks relevant drug metabolites and identified antigens [7]. Mast cell profiles may also differ between the skin and mucosa, which is a relevant difference since reactions to LA during dental procedures may not be replicated on skin testing [7, 53].

Patch Testing

Delayed reading of provocation skin testing and patch testing has both been used for the evaluation of delayed hypersensitivity reactions to LA. Patients should be screened for delayed hypersensitivity risk factors, including a strong history of contact dermatitis and a report of delayed reaction to prior LA drug use [64]. The T.R.U.E. test is a commercially available patch testing panel that contains 35 antigens and

includes caine mix (a mixture of benzocaine, tetracaine, and dibucaine) [65]. However, patch testing with individual LA drugs may better clarify the culprit LA and alternative LA drugs.

Management of Local Anesthetic Reactions

The goal of testing is to identify safe and effective LA drugs to use in future encounters. If no alternative LA is identified, general anesthesia or conscious sedation may be considered. In the literature, there are case reports of patients tolerating procedures with 1% diphenhydramine [66–68, 68–73], benzyl alcohol [74], ethyl chloride spray [75], and tramadol buccal injections [76]. Rarely, desensitization may be needed for patients when there is no efficacious or safe alternative. One case of successful desensitization with ocular bupivacaine has been reported for a patient receiving intraocular ranibizumab injections every 5 weeks for bilateral central retinal vein occlusion [77]. During her initial desensitization, she required a dose of diphenhydramine after step 5 for brief self-resolving tachycardia but tolerated subsequent desensitization (desensitization protocol in Table 3).

Discussion

It is crucial that LA drugs not be misclassified as an “allergy” requiring avoidance in a patient’s chart without further validation of their history and appropriate testing. Incorrect allergy labeling can lead to unnecessary LA avoidance and procedural delays [78].

We suggest the following strategy for evaluating a potential LA drug allergy in a patient (Fig. 3). Patients commonly report symptoms to local anesthetic administration which may be misclassified as an “allergy.” The clinical history is crucial to help classify the type of adverse reaction and guide future use. When the history is strongly suggestive of a non-allergic reaction, reassurance should

Table 3 Desensitization protocol for ocular bupivacaine from McGarry et al. [77]

Step	Dilution	Route	Volume (mL)	Time (min)	Dose/step (mg)	Cumulative dose (mg)
1	1:1000	Topical	0.03	15	0.00015	0.00015
2	1:100	Topical	0.03	15	0.0015	0.00165
3	1:10	Topical	0.03	15	0.015	0.01665
4	1:1	Topical	0.03	15	0.15	0.16665
5	1:1	Topical	0.3	15	1.5	1.66665
6	1:1	Injection	0.03	15	0.15	1.81665
7	1:1	Injection	0.3	15	1.5	3.31665

Pretreatment with cetirizine 10 mg the evening before and day of desensitization

Original concentration bupivacaine 5 mg/1 mL, diluted with 0.9% normal saline

Doses 1–5: 0.03 mL dropped topically to the eye. Doses 6 and 7 injected into the eye by ophthalmology

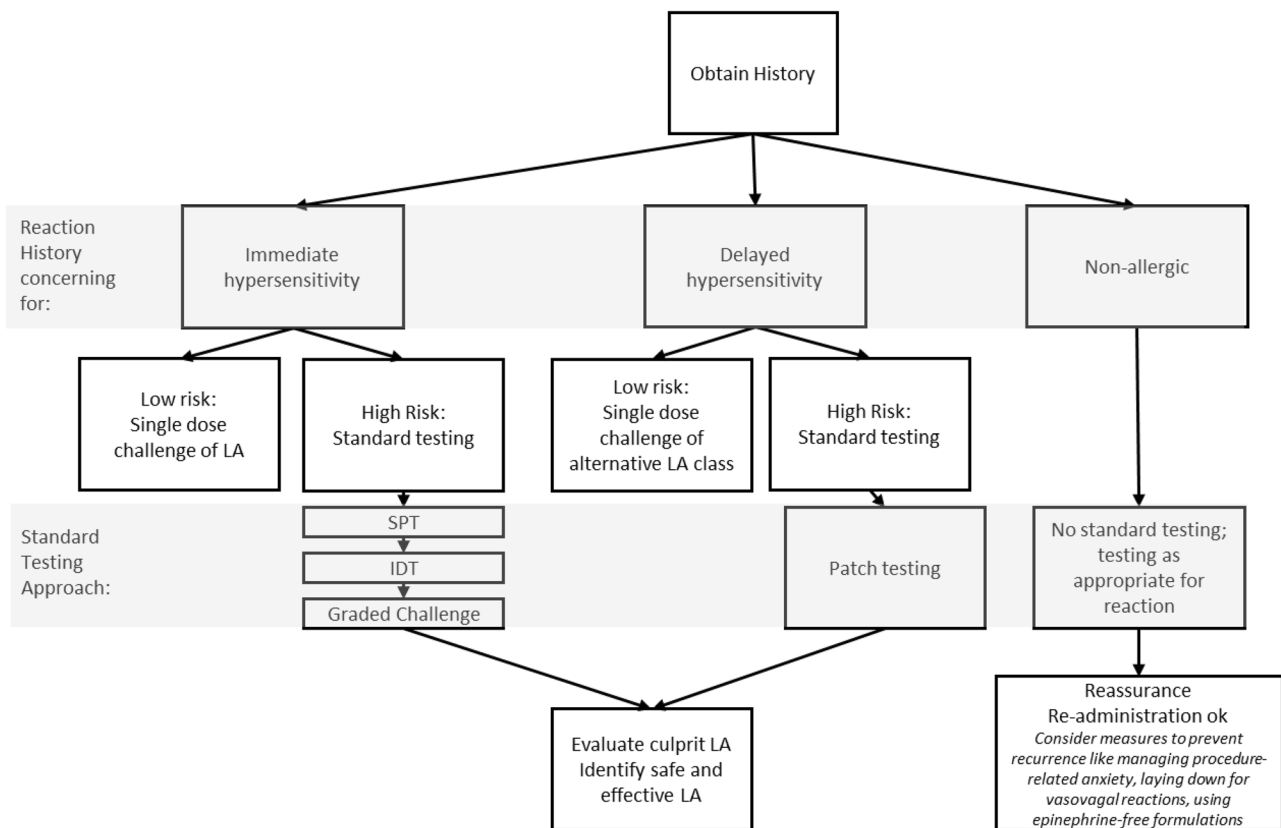


Fig. 3 Algorithm for the evaluation of adverse reactions to local anesthetics. The first step is obtaining a clinical history to help identify if the reaction is concerning for an immediate hypersensitivity, delayed hypersensitivity, or non-allergic reaction. If the history is low risk, a single-dose challenge can be performed. Otherwise, the standard approach for an immediate hypersensitivity reaction is skin prick

testing (SPT), intradermal testing (IDT), and challenge. The standard approach for delayed hypersensitivity reactions is patch testing. There is no standard testing for non-allergic reactions, but depending on the symptoms of the reaction, further workup may be warranted. The goal of this evaluation is to validate the suspected culprit LA and identify safe and effective alternatives

be provided to the patient and often the LA drug may be re-administered. If the history is low risk, a single-dose challenge of LA can be recommended with consideration for switching between ester and amide classes. If the history is high risk, skin testing and challenge can be performed for the evaluation of an immediate hypersensitivity reaction and patch testing can be performed for the evaluation of a delayed hypersensitivity reaction.

There are general recommendations but no current standardization with respect to the use of SPT, IDT, and challenge for evaluation of LA allergy. The negative predictive value of testing is 97%, although the false positive rate of the 1:10 IDT can be as high as 36%. Since the incidence of LA allergy is low, most of the studies were collected over many years, and the evaluation of skin testing and challenge may have been done months or years after the index reaction, which could mean that the circumstances in which the reaction occurred initially may be quite different than the evaluation testing. False negative

testing is possible, so challenge should be completed whenever possible. There are also a significant number of evaluations where patients reacted to placebo, so including a placebo challenge can help distinguish non-allergic reactions.

Summary and Conclusions

LA are common peri-procedural and topical drugs that most of us will encounter in our lives; therefore, ADRs to LA are important to evaluate. Most reactions to LA drugs are non-allergic, not life-threatening, not reproducible on repeat administration, and do not need to be completely avoided. The evaluation of LA allergic reactions often finds delayed hypersensitivity reactions (more commonly known as contact dermatitis) and other culprits (excipients/additives or other perioperative exposures). Classic IgE-mediated type I hypersensitivity allergic reactions are found in <1% of

patients with adverse reactions to LA. Alternative LA can often be tolerated and identified by switching between ester and amide LA classes in delayed hypersensitivity reactions and with skin testing in immediate hypersensitivity reactions. The validity of skin testing is challenging given the lack of standardization. Further investigation is needed to identify the mechanism and antigenic determinant in allergic patients, understand cross-reactivity patterns, and better understand clinical implications of a local anesthetic allergy label.

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Declarations

Ethics Approval and Consent to Participate This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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