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# A Critical Review of Local Anesthetic Sensitivity

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**Abstract**

With their ability to block pain signals to the brain, local anesthetics (LAs) have made possible many surgical procedures and interventions once thought impossible. LAs are generally safe and well tolerated when used correctly by trained professionals. However, adverse reactions do occur, and may generate a referral to an Allergist for evaluation of LA allergy. LA structure, classification, and metabolism will be briefly reviewed. A critical analysis of the studies and case reports involving LA allergy found via PubMed search for "local anesthetic allergy" and "local anesthetic hypersensitivity" will be discussed. In addition, the clinical evaluation of a patient with concern for a LA allergy will be examined.

## Index Entries

Local anesthetics; hypersensitivity; allergy; anaphylaxis.

## Introduction

Local anesthetic (LA) agents have revolutionized our ability to provide surgical interventions in a pain-free manner. LAs were discovered in 1884, when an ophthalmologist, Carl Koller, used cocaine to provide anesthesia for surgical procedures. Procaine (marketed as Novocaine), an amino-ester, was the first synthetic LA agent and was made by Einhorn in 1904. Mook described the first report of LA allergic-type reaction in 1920 in a dentist who developed eczematous contact dermatitis on his hands after handling apothesin, a congener of procaine. Skin testing was positive, and the dermatitis resolved when apothesin exposure ceased. The amino-ester LA compounds were the only option available until Lofgren discovered the amino-amide LA in 1943 *(1)*. It is important to note that many of the multidose LA

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preparations used in clinical practice contain the LA itself, often a vasoconstricting agent such as epinephrine, and preservative agents such as methylparaben, propylparaben, or sulphites to prolong the shelf-life *(2)*. These additives are thought to play a role in some of the adverse reactions that develop.

## Local Anesthetic Characteristics

### *Structure/Classification*

LA agents have similar molecular configuration with a lipophilic aromatic ring connected to a hydrophilic amine group. The linking bond is used to classify the agents into ester and amide groups (Fig. 1). Ester LAs include cocaine, procaine (Novocaine), tetracaine, benzocaine, and chloroprocaine and are all derivatives of para-aminobenzoic acid (PABA). Amides include lidocaine, mepivacaine, etidocaine, prilocaine, bupivacaine, and dibucaine (two letter "i"s in their name).

### *Mechanism of Action*

In brief, local anesthetics provide an anesthetic effect by blocking nerve conduction, thus blocking afferent signals to the brain. Nerve conduction blockade is obtained by reversible binding of LA to the voltage-gated sodium channels in the nerve-cell membrane, thus preventing action potentials from forming. The LA must rely on its lipophilic component to diffuse across the nerve cell membrane because the site of binding is intracellular. The LA is given in an acidic solution in the ionized form, so it must be converted to the nonionized form for diffusion across the cell membrane *(3)*.

### *Metabolism*

Ester local anesthetics undergo rapid hydrolysis by nonspecific plasma cholinesterases. The exception is cocaine, which undergoes slower metabolism in the liver. PABA is an intermediate metabolite that is inactive for anesthesia induction; however, PABA is a known allergen. In contrast, amide LAs are cleared primarily by hepatic metabolism with renal excretion. As with esters, amide LA preparations may also contain preservatives, such as methylparaben and sulphites, which are both chemically similar to PABA and may be antigenic in sensitized individuals *(3–5)*.

### *LA Reactions*

Schatz reports that true allergic reactions to LAs probably make up no more than 1% of LA reactions *(6)*. This finding is demonstrated in most of the studies reviewed on Table 1, as well as by Finucane (and others), who also state that less than 1% of LA reactions are immune system-mediated *(1)*. LAs are too small to be antigenic by themselves, so they must bind to host proteins as a hapten–carrier complex to be allergenic. This hapten–carrier complex has not been identified. Lu states that various surveys indicate that the number of deaths attributed to the use of local anesthetics ranges from 1 in 1.4 million to 1 in 1.5 million patients *(7)*.

Allergic reactions to LA are rare. When they occur, the mechanism is either an immediate (type I) reaction or a delayed (type IV) reaction. Type IV reactions to LA are thought to occur more commonly than true type I reactions. The type I reactions are immunoglobulin (Ig)E-mediated, immediate, and result in the release of histamine and other inflammatory mediators to cause a reaction. This reaction can range from local or systemic urticaria to bronchospasm, throat edema, and hypotension along the anaphylaxis spectrum, and is a medical emergency. The type IV reaction has a slower onset and involves a non-IgE mediated release of histamine and other inflammatory vasoamines that can result in contact dermatitis to an anaphylactoid response. Incaudo et al. retrospectively reviewed the clinical history of 71 patients with suspected LA allergy. Based on their reaction history, they were grouped into one of four groups: immediate generalized reactions (15%), localized swelling at injection site (25%), nonspecific systemic symptoms (42%), and other (17%). Serial dilutional intra-

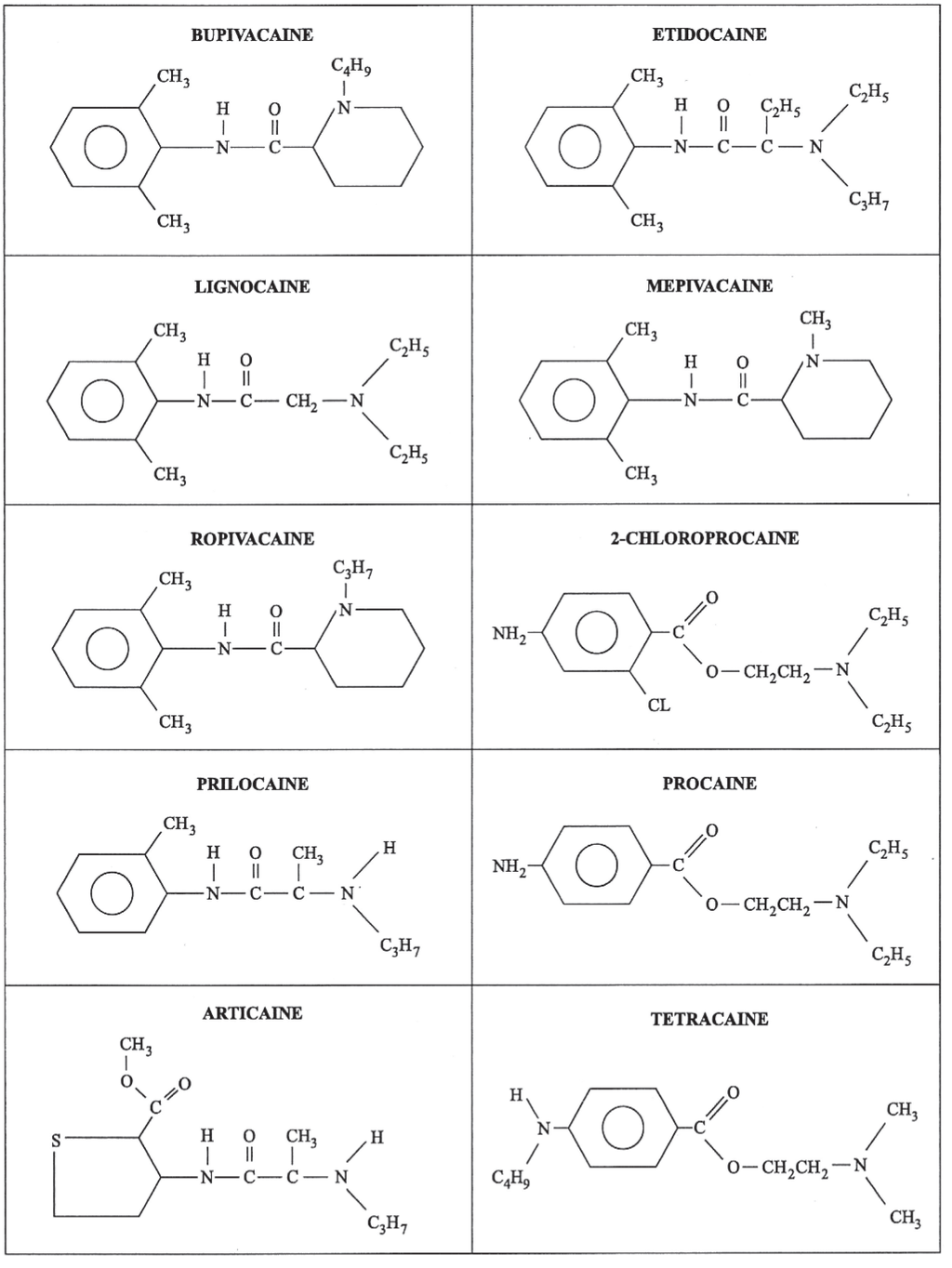


Fig. 1. Examples of local anesthetic chemical structure consisting of a lipophilic aromatic ring connected to a hydrophilic amine group by an ester or amide bond (*3*).

Table 1
Local Anesthetic Reactions Studies

| Study | Type | Patients/ Reactions | Previous reactions | Techniques |
|---|---|---|---|---|
| Astarita C, et al. | Prospective/Clinic referral | 198 | Yes (1/3) | Skin-prick, patch and intradermal (Intradermal (ID) challenge |
| Berkun, Y, et al. | Prospective/Clinic referral | 236 | Yes | Skin-prick, intradermal, SC challenge unrelated LA |
| Escolano F, et al. | Prospective/Clinic referral | 35 | Yes | Skin-prick, ID, and provocation test |
| Gall H, et al. | Propspective/Clinic referral | 177/197 reaction | Yes | Skin-prick, ID tests, challenge with causative and unrelated LA with preservatives, RAST for IgE |
| Nettis E, et al. | Prospective | 432 | Yes and no | Incremental challenge test (ICT) |
| Ruzicka T, et al. | Prospective | 104/patch postive | Yes | Skin-prick, ID |
| Troise C, et al. | Prospective | 386 | Yes | Skin-prick, ID, and subcutaneous incremental challenge |
| Wasserfallen JB, et al. | Prospective | 28 | Yes | Skin-prick, intradermal skins, challenge |
| Incaudo G, et al. | Retrospective review | 59 | Yes | Serial dilutional ID skin tests |
| Chandler MJ, et al. | Retrospective review of clinic referrals 1964–1985 | 59/70 reactions | Yes | Skin-prick, provocative challenge |
| Klein CE, et al. | Case report | 1 | No | SC injection |
| Noormalin A, et al. | Case report | 1 | No | SC injection |

Table 1
Local Anesthetic Reactions Studies (Continued)

| Agent (LA) | Results | Summary |
|---|---|---|
| Mepivacaine (preservative-free) | 3-yr follow-up: 196 negative skin-prick/patch, 2 patients positive patch testing | Mepivacaine safely give up to 3 yr with patch testing useful predictor of challenge outcome |
| Local anesthetics w/preservatives | Skin-prick and ID tests negative in all but 1 case local erythema | Allergic reactions not reproduced with LA preparations with preservatives and Epi |
| 3 LA: Procaine 2%, lidocaine mepivacaine 1% w/o Epi or parabens | Skin-prick and provocation tests negative; 1 positive to ID test with 1/10 solution of Hostacain (with parabens) | Real allergic reactions to LA are infrequent |
| Causative and unrelated local anesthetics | Skin-prick and ID-negative except 3 reactions with subcutaneous challenge with causative drug reactions (IgE not detected), 1 delayed-type reaction | True allergic reactions to LA are extremely rare |
| LA free of preservative and Epinephrine | 415 Tests completed: 0 clinical events; IgE-mediated reactions to LA are uncommon | IGE-mediated reaction to LA are uncommon and ICT safe to diagnosis adverse reaction |
| 7 LAs | All skin-pricks negative, 14 positive ID tests: 11 with ester Procaine (immed/delayed), 1 with amide butanilicaine (immed) | Risk of anaphylactic reactions to amide LAs low |
| Amide LA without preservatives and Epi | 10 Positive skin tests: all had no reaction to incremental challenge 3 positive ID test with negative incremental challenge different LA | Skin tests and the subcutaneous challenge safe and reliable method to identify LA allergy |
| LA | No patient presented a second reaction after reexposure | The initial adverse reaction not likely allergic |
| Mepivacaine, lidocaine, procaine | 5 Positive ID tests to LA; 3 of 5 tolerated challenge. 50 subsequently given SC challenge with different LA. | Low incidence of IgE-mediated reaction by history; SC challenge safe and useful w/alternative LA |
| 6 LA | No positive skin tests of positive provacative drug challenge | Despite history of prior reactions, no positive skin tests or provocative LA challenges |
| Mepivacaine with methylparaben | Delayed-type reaction with erythema/itching; positive mepivacaine patch test, negative for methyl paraben | Delayed-type reaction to LA can occur |
| 2% Lignocaine | Ipsilateral left facial swelling immediately after injection. Skin-prick test positive to lignocaine, IgE to lignocaine detected | Immediate IgE reaction to Lignocaine |

SC, subcutaneous; ID, intradermal; LA, local anesthetics

dermal skin tests were performed on 59 patients, 5 of which were positive. Fifty underwent subcutaneous challenges with LAs chosen for their chemical nonsimilarity, and no significant reactions were found. This finding reiterates the low incidence of type I/IgE-mediated reactions and the safety of choosing alternative LAs *(8)*.

Ester anesthetic agents are derivatives of PABA and are hydrolyzed to this intermediate form. Parabens are additives in many lotions, cosmetics, and foods; therefore, many people are sensitized and may cross-react to PABA when given the ester anesthetic. This is the proposed reason why allergic reactions are more common with esters than amides. In fact, the rate of allergic reactions to LA decreased in the 1950s with the increasing use of amides. However, both ester and amide preparations may contain methylparaben and/or sulphonamides as preservative agents. Methylparaben is similar to PABA and is thought to be capable of acting as a hapten and being allergenic *(1)*. Sulphonamides are structural analogs to PABA, and are frequently added to food and wine as a preservative, which may also lead to sensitization and an allergic reaction after exposure to a LA preparation. Preservative-free preparations are available from some manufacturers. In general, ester LAs are more likely to cause an allergic reaction when compared with an amide and have more cross-reactivity. Esters typically do not cross-react with amide LAs.

The overwhelming majority of the time the reaction to the LA preparation will not be truly allergic in nature. Symptoms of anxiety and panic can occur before procedures, especially at the dentist office and before ophthalmology procedures *(9)*. Toxic, idiosyncratic, or vasovagal reactions may occur and be confused with allergic reaction. Vasovagal reactions are common and may result in syncope, with the key difference being bradycardia with vasovagal reactions and tachycardia and other symptoms with anaphylaxis. If hives are present, this would be more consistent with true allergy. Another possible etiology of reactions after the use of LA is accidental intravascular injection during the procedure. The LA could suppress action potential generation by the cardiac myocytes, which could lead to arrhythmias and cardiovascular collapse. The vasoconstrictor agent, typically epinephrine, added to the preparation could lead to adrenergic symptoms including tachycardia, diaphoresis, and hypertension that may be interpreted by some as an allergic response. Latex allergy can also cause serious allergic reactions in sensitized individuals and could be confused with LA allergy. Latex allergy should be considered on the differential diagnosis of LA reactions *(1)*. Fortunately, most medical clinics and hospitals are now using non-latex gloves and materials.

## Studies of LA Reactions

Multiple studies and case reports have been published on the topic of LA allergy evaluations. Please *see* Table 1 for a summary of the publications evaluated for this review. Eight of the studies summarized in Table 1 are prospective studies, primarily on patients referred to an allergy clinic with a prior history of a reaction to a LA. Two of the studies are retrospective reviews of patients with prior reactions, and two of the publications are case reports. Publication dates range from 1978 to 2005.

### *Prospective Studies*

The eight prospective studies typically involved skin testing, intradermal testing, provocative challenge or incremental challenges and a few performed patch testing to causative or unrelated LA agents. No reactions were found in four of the prospective studies despite patients typically reporting a previous reaction (except mild erythema in one patient in the study by Berkun et al.) *(10–12)*.

Astarita et al. studied 198 patients with and without LA reactions with skin prick, intradermal, and patch testing over a 3-year period to evaluate for sensitization and reaction to

mepivacaine. Over the 3 years, the results were negative, except in two patients with positive patch testing, indicating a delayed hypersensitivity response. They concluded that mepivacaine was safely given for up to 3 years, with patch testing a useful predictor of challenge outcomes *(13)*.

The study by Escolano et al. found 35 patients with prior LA reactions all negative to skin prick, intradermal, and provocation testing to three LA; however, one intradermal test was positive in a patient given a 1:10 solution of hostacain with parabens. They concluded that real allergic reactions to LA are infrequent *(14)*.

Gall et al. performed skin prick, intradermal, and challenge testing on 177 patients with 197 reactions with causative and unrelated LA, as well as checking a radioallergosorbent test for specific IgE. Three reactions occurred with subcutaneous challenge with the causative agent: two were immediate reactions clinically but with IgE not detected and one was a delayed reaction. They also concluded that true LA allergic reactions are rare *(15)*.

Ruzicka et al. performed skin-prick and intradermal tests on 104 patch-positive patients with 7 local anesthetics. There were 14 positive intradermal tests, 11 patients with an ester LA, 1 with an amide, and 2 patients with positive results to both. They concluded that in patients with a positive patch test and no history of anaphylactoid reactions and negative skin tests, that the risk of anaphylactic reaction to amides is low *(16)*.

Troise et al. performed skin-prick, intradermal, and subcutaneous incremental challenges with an amide in 386 patients with a history of LA reactions. They found 10 patients with a positive skin-prick test who were then negative to incremental challenge. Three that were positive to intradermal testing had a negative incremental challenge with a different LA. They concluded that skin tests and subcutaneous challenge was a safe and reliable method to identify LA allergy *(17)*.

### *Retrospective Studies*

Two retrospective studies on LA allergy were reviewed, as summarized in Table 1. Incaudo et al. was previously discussed with the finding of a low incidence of IgE-mediated reaction by history and the safety of challenge with an alternate LA *(8)*.

Chandler et al. reviewed 20 years of clinic referrals and had 59 patients with 70 reactions who underwent skin-prick and provocative skin challenge to six LAs, and two who received intravenous lidocaine for arrhythmias. None of the patients had positive results *(18)*.

### *Case Reports*

Two case reports were reviewed for this discussion and are also summarized in Table 1. Klein et al. reported the case of a 45-yr-old woman who developed itching and erythema 1 d after mepivacaine exposure, attributed to a delayed-type hypersensitivity reaction. The mepivacaine patch test was also positive, with a negative reaction to the methylparaben preservative *(19)*.

Noormalin et al. report the case of a 7-yr-old girl who developed ipsilateral facial swelling immediately after lignocaine injection. Her skin-prick test was positive to lignocaine. Specific IgE to lignocaine was detected. This case report is the only published study that found specific IgE antibody for the LA after a reaction *(20)*.

## Evaluation for Potential LA Allergy

When evaluating a patient for possible LA allergy, it is crucial to obtain a detailed history including the LA used and a description of the reaction. Review of dental or medical records is advisable. The Joint Council of Allergy, Asthma, and Immunology (JCAAI) recommends that if the LA that caused a reaction is known, consider using a LA for skin testing and incremental challenge from another class. If an ester caused a reaction, than an amide should be used. If an amide caused a reac-

tion, then either an ester or a different amide probably can be used because significant cross-reactivity among amides has not been seen. Ideally, LA preparations used for skin testing and challenges should be preservative and epinephrine-free. Reactions to preservatives such as parabens or sulphites may occur but are rare, and routine testing with these are not recommended. If a preservative is suspected as the underlying cause of a reaction, the additives should be avoided. If the drug causing the reaction is unknown or proof of safety of a LA is needed, incremental/provocative graded dose challenges can be helpful. The great majority of patients, even those with a history of an anaphylactic reaction to LA, do not have similar reactions on provocative dose challenges *(6,8,18,21–23)*. If the patient has multiple comorbidities and the risk of reaction is considered high, procedures can be cautiously performed using nitrous oxide or conscious sedation.

In incremental or provocative graded dose challenges, patients are first given skin-prick testing to an undiluted, preservative and epinephrine-free local anesthetic agent compared with a saline control. If this is negative, then successive subcutaneous or intracutaneous injections are given using dilutions of the LA because of the potential for false-positive results with undiluted local anesthetics. Initially, 0.1 cc of a 1:100 dilution is given, then a 1:10 dilution, and then full strength at 15-min intervals. If no reactions occur, then 0.5–1 cc of the LA is injected subcutaneously. Using this protocol, the JCAAI states that there have been no serious allergic reactions reported with LA administration if the skin tests and test dose are negative *(21–23)*.

Patch testing with LAs can be performed if a patient developed contact dermatitis after exposure to identify LAs less likely to cause a reaction *(21,22)*. In vitro testing of LAs can be performed, but are limited by the lack of proof of a clinically significant reaction. Lymphocyte cell cultures can be exposed to the suspected allergen, and if proliferation occurs, allergy is suspected. If leukocyte histamine release occurs after exposure to the local anesthetic, then a type I allergic reaction is suspected *(1)*. Also, the measurement of specific IgE antibodies against the LA is very useful and is only rarely discovered as discussed previously.

## Conclusion

LA agents have dramatically improved our ability to comfortably undergo procedures. They are classified into esters or amides based on their chemical structure. True allergic reactions occur in fewer than 1% of reactions to LAs. The allergic reactions may be type I reactions with local or systemic urticaria with symptoms along the spectrum of anaphylaxis, or type IV reactions with contact dermatitis or anaphylactoid reactions. Most reactions to LAs are caused by anxiety, vasovagal episodes, or from accidental intravascular injection. Reactions to LA agents can generate referrals to an Allergist. Obtaining a detailed history is crucial, followed by skin testing and incremental dose challenges performed with an alternative or the culprit LA agent. This strategy is recommended by the JCAAI and has shown to be safe and efficacious *(21,22)*.

## Take-Home Messages

- LA agents have made it possible to undergo surgical interventions in a pain-free manner.
- The linking bond is used to classify the agents into ester and amide groups.
- Esters are metabolized by plasma cholinesterases to PABA, which may act as a hapten to cause allergic reactions.
- Amides are metabolized by the liver and are typically less allergenic and not significantly cross-reactive; however, preparations may contain parabens that are metabolized to PABA or other preservatives and vasoconstricting agents that can cause reactions.

- One percent or less of the reactions to LA are truly immune system-mediated.
- Allergic reactions to LA can consist of type I reactions along the spectrum of anaphylaxis or type IV reactions typically with contact dermatitis.
- Adverse reactions are most frequently due to anxiety, panic attacks, intravascular injections, or vasovagal responses and are improperly labeled as an allergic reaction.
- Referral to an Allergist for evaluation of LA reactions consists of obtaining a detailed history, and then skin testing and incremental dosing challenges with a different or the culprit local anesthetic. This has shown to be efficacious and safe in the evaluation of LA allergy.

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