

Allergic Reactions to Local Anesthetic Formulations

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KEYWORDS

- Allergic reaction • Local anesthesia
- Type I anaphylactic response
- Type IV delayed hypersensitivity response

During the history of local anesthesia administration, a constant effort by chemists and scholars has been made to improve the efficacy and minimize adverse events associated with local anesthesia. Innovative products continue to replace agents that have inferior properties, and practice protocols are constantly being fine tuned to avert problematic practices. Because of this self-assessment within the respective health care fields, the potential for adverse events with currently marketed amide local anesthetics is extremely rare.¹ Dentists need to follow recommended doses, use a stress protocol, take thorough medical histories, aspirate before injections, and slowly disperse anesthetics during injection.² These procedures will help to avert many of the adverse events seen associated with local anesthesia, including allergic reactions.

Although an allergic response to a local anesthetic is remarkably rare, local anesthetics are capable of causing true allergic reactions. Clinicians need to be educated to properly treat and definitively diagnose a true allergic reaction. In the past, most allergic reactions to local anesthetics could be ascribed to procaine. The antigenicity of procaine, and other ester agents, is most often related to the para-aminobenzoic acid (PABA) component of ester anesthetics, a decidedly antigenic compound.³ This finding, as well as procaine's poor efficacy and short duration, led to the development and eventual widespread use of the superior anesthetic lidocaine, an amide compound. The incidence of true allergies to amide local anesthetics is widely accepted to be well less than 1%⁴; unfortunately, poor understanding of adverse reactions to local anesthetic and poor availability of allergy testing, has resulted in unnecessary dental consequences.

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ADVERSE EVENTS: DIFFERENTIATING ALLERGIC REACTIONS

Adverse reactions caused by fear or anxiety, inadvertent intravascular administration of local anesthetic, toxic overdose, intolerance, and idiosyncrasy could be mistaken for a true allergic response.⁵ Toxic adverse reactions associated with local anesthetics are related to systemic exposure or local pharmacologic effect.⁶ Clinicians need to be aware of potential precipitating factors such as needle phobias, chair position, liver or kidney failure, maximum recommended doses, proper safety protocols, and concomitant drug interactions. A thorough medical history is the simplest and most efficient method for the detection of risk factors that can lead to an adverse event.⁷ Patient familiarity is imperative for a provider and will allow for rapid diagnosis and effective treatment when adverse events present.⁸

Anxiety plays a major role in dentistry. Scott and Hirschman⁹ reported that a large portion of the US population becomes increasingly anxious in relation to dentistry. Psychogenic effects are the most numerous and common adverse events seen in a dental office. Because of the similarities, these psychogenic responses are often misdiagnosed as allergic reactions. In addition, needle phobias, panic attacks, and vasovagal syncope are all anxiety-related events with the potential to produce urticaria, edema, bronchospasm and unconsciousness. These reactions can present with a wide array of symptoms, including hyperventilation, nausea, vomiting, and alterations in heart rate or blood pressure.¹⁰ Understanding the differences among allergic reactions from psychogenic reactions is important so that patients receive the appropriate care.^{1,11}

THE ALLERGIC RESPONSE

Initially, the body's immune response system was thought to be purely protective; however, the dangerous potentials of severe allergic responses were eventually discovered. Hypersensitivities or allergies are abnormally vigorous immune responses, in which the immune system causes tissue damage as it fights off a perceived threat, or antigen, that would otherwise be harmless to the body.¹² There are different types of hypersensitivity reactions, which are best classified on the basis of the immunologic mechanism mediating the disease (**Table 1**).

ALLERGY-TESTING PROCEDURES

The history of a reported allergic reaction needs to be thoroughly evaluated and a clear sequence of the events documented. The drugs used, the onset of the reaction, signs and symptoms, and the duration of the event are very helpful in diagnosing a true allergic reaction. Most reported adverse reactions are psychogenic in nature and a smaller proportion of adverse responses can be attributed to avoidable intravascular injection. It is important not to prematurely label the patient as being allergic; the true nature of the problem should be investigated. If the reaction is acute and strongly suggestive of an allergic response, referral to an allergist is considered the standard of care.¹³ As demonstrated in **Fig. 1**, the allergist will use skin prick tests (SPTs), intradermal or subcutaneous placement tests, and/or drug provocative challenge testing (DPT) procedures to aid in the identification of a safe local anesthetic for an individual patient.

An SPT is usually administered first. The SPT is performed by placing a drop of the test solution on the forearm and puncturing the skin through the liquid. If this test demonstrates a positive result, a wheal and flare should occur within 20 minutes.¹⁴ If a systemic reaction occurs, appropriate treatment protocol for allergic reactions

Table 1
Classification of immunologically mediated hypersensitivity reactions

Type	Response Time	Associated Disorder	Mechanism
Type I – Anaphylactic	5–30 min	Anaphylaxis, bronchial asthma, urticaria	Mediators from IgE-sensitized mast cells cause increased vascular permeability, edema, and smooth muscle contraction
Type II – Cytotoxic	1–3 h	Autoimmune hemolytic anemia, erythroblastosis fetalis, Goodpasture's disease	IgG or IgM antibody reacting with cell surface or cell attached antigens results in cell destruction
Type III – Immune Complex	1–3 h	Arthus reaction, serum sickness, acute glomerulonephritis	Immune complexes (antigen-antibody complexes) activate complement, which attracts leukocytes; mediators released from these cells produce inflammation
Type IV – Cell-Mediated (Delayed)	8–12+ h	Tuberculosis, contact dermatitis, transplant rejection	Sensitized T lymphocytes reacting with antigens release lymphokines that produce cellular inflammation

should be followed. If the test was completed with a significantly diluted agent, and proved negative, then a more concentrated agent should be used.¹⁵ If the SPT proves negative, it would be appropriate to follow with an intracutaneous or intradermal test in which a minute amount of the test solution is injected in the epidermis of the forearm and the site observed for 20 minutes for wheal or flare reactions. A DPT with the suspected drug is performed only if case history, skin test, and laboratory test give equivocal results.¹⁶ Many allergists consider the DPT the gold standard in the diagnosis of

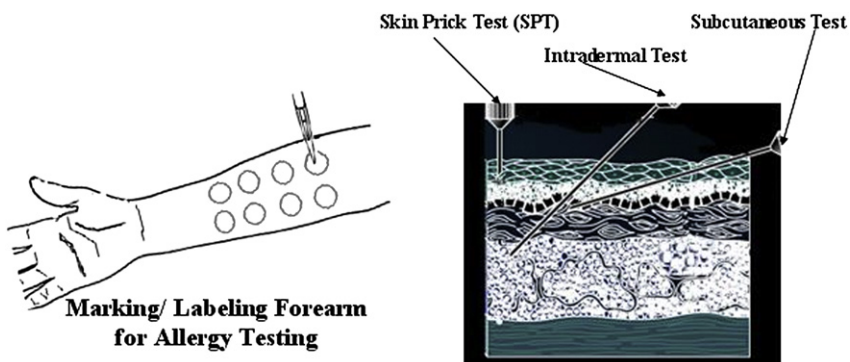


Fig. 1. Allergy testing procedures used for detection of hypersensitivity reactions to local anesthetics.

drug allergy; however, there is concern over the possible adverse consequences of the test.¹⁷ Typically, the DPT uses the commercial preparation of the suspected allergen administered, ideally in the same way as it was given when the reaction occurred. Before performing any DPT, an individual risk-benefit evaluation should be accomplished and strict surveillance is needed with emergency protocols in place. Generally, the clinician should start with a low dose, carefully increasing the dosage with discontinuation of administration at the earliest appearance of any signs or symptoms.¹⁷

The patient should be provided the results of the testing with suggestions to minimize future risks. The success of this protocol is related to the rare instance of true allergic reaction to amide local anesthetics; however, the testing alleviates stress for the patient and doctor and it may permit the diagnosis of the truly rare instance of an amide allergy.¹⁷

ALLERGIC RESPONSE WITH DENTAL LOCAL ANESTHESIA

Allergic Reactions to Local Anesthetics

Although allergic reactions to local anesthetics are exceedingly rare, there are a large number of patients who claim allergy to these agents. This may be attributable to a misunderstanding on the part of the health practitioners, and patient, as to what constitutes allergy. The clinician must be able to differentiate among reactions to local anesthetics that are psychologically initiated, those related to dosage and toxicity, and those that are related to allergy. Skin manifestations of allergy should be used as key indicators of a true response, because an allergy is unlikely in their absence.¹ Corroboration with blood studies is also of value when hypersensitivity to local anesthetics is suspected. These blood studies are administered to differentiate between the 2 responses related to local anesthetics, type I and type IV reactions. Serum IgE (Type 1; Anaphylactic Reaction) levels are decreased within 1 hour after an allergic reaction has commenced. Following this initial decrease, there is a marked increase in the plasma concentration of IgE antibodies that remain elevated for 72 hours after an adverse response.¹ The complement system may also mediate a delayed allergic response with local anesthesia (Type IV; Cell-Mediated Reaction). Plasma samples showing consumption of complement proteins C3 and C4 are suggestive of allergy.¹⁸

In the early use of local anesthesia, most allergic reactions to local anesthetics could be attributed to procaine. The antigenicity of procaine, as well as other ester compounds, relates directly to its structural formula.¹ Because the ester agents are derivatives of PABA, this substance occurs as a metabolite following hydrolysis of the main compound. PABA is responsible for the allergic-type reactions observed.¹⁹ It should be noted that susceptibility to procaine also implies hypersensitivity to structurally similar compounds such as tetracaine or chlorprocaine.²⁰ Therefore, all ester-linked local anesthetics are best avoided in patients with procaine allergy.²¹

Most investigators believe that true allergic reactions to amide local anesthetic agents are extremely rare; however, reports of suspected allergic, hypersensitivity, or anaphylactic responses to these local anesthetic compounds appear in literature.¹⁹ Usually the diagnosis of such reaction is made when no obvious explanation is available for an adverse effect in a patient exposed to a local anesthetic drug; however, true allergic responses have been verified.¹⁹ A true allergy diagnosis requires the formation of an antibody to an antigenic substance. To establish this diagnosis, an intracutaneous or pin-prick challenge with the allergen (amide anesthetic) should be performed by a specialist. Unfortunately, the reported evidence is limited in literature and the techniques used for diagnosis exhibit some variation and lack consistency in reporting.

Aldrete and Johnson²² were among the first investigators to use the technique of intracutaneous testing to study patients with and without a presumptive history of local anesthetic allergy. Positive skin reactions were observed in 25 of 60 patients in the nonallergic group. In all cases, the cutaneous reaction followed injection of an ester-type anesthetic (procaine, tetracaine, chloroprocaine), whereas no reactions were observed after treatment with the amide-type agents (lidocaine, mepivacaine, prilocaine). In a more current evaluation, Gall and colleagues²³ evaluated 197 patients who reported a history of adverse allergic-type events after local anesthetic administration. Procaine was tested along with all of the currently marketed amide local anesthetics. Of the 197 patients, only 3 patients reacted after subcutaneous challenge with the causative drug (local anesthetics of the amide type). Although 1 patient showed a delayed-type response to mepivacaine, 2 patients had immediate-type reactions to articaine and lidocaine; however, in both cases no specific IgE antibody could be detected.

Haugen and Brown²⁴ reported a case of Type I hypersensitivity allergy to lidocaine hydrochloride. Within 15 minutes of the lidocaine injection, the patient complained of lightheadedness, and right periorbital swelling with noted wheezing were documented. Based on the patient's unusual response, an undiagnosed allergy to lidocaine was suspected. The patient was referred to an allergist for skin testing and a positive test to lidocaine was confirmed. An intradermal 1:10,000 dilution of lidocaine 1% produced a 4-mm skin wheal with flare. The saline solution control produced a negative result, and a histamine prick test produced a 7-mm wheal with flare. Although a rechallenge with lidocaine was not performed, a positive immediate hypersensitive reaction to lidocaine was strongly suggested based on the patient's history and positive intradermal skin test.

In an additional case report presented by Noormalin and colleagues,¹⁶ a 7-year-old girl was diagnosed with a type I hypersensitivity to lignocaine (lidocaine) following a dental procedure. The child developed an ipsilateral facial swelling and was immediately administered intravenous antihistamine. The swelling subsided on the same day after the patient returned home with her parents. Because the swelling was at the site where local anesthesia was administered, it was postulated that the patient could have had a hypersensitivity reaction to 2% lignocaine HCL, oral lignocaine dental gel, or latex glove response. To reach a definitive diagnosis of allergy, an SPT was administered. The SPT revealed a positive reaction to pure 2% lignocaine HCL and lignocaine oral dental gel, whereas tests relating to latex were negative. The patient also developed urticaria after 10 minutes of performing the test. The authors did not proceed to intradermal testing because the SPT was positive and the child presented with urticaria. In addition, an immunoblot test demonstrated positive dot-blot reaction (IgE response) to both the 2% lignocaine and lignocaine oral gel.

Although most allergic reports in literature relate to the type I (anaphylactic) response, Fuzier and colleagues²⁵ evaluated 2 database systems to determine the incidence of both the type I and the type IV (delayed) response. The authors studied reports recorded in the French Pharmacovigilance database and the GERAP database over a 12-year period (1995 to 2006). For each report, Fuzier and colleagues²⁵ detailed the clinical features and skin tests used. A total of 16 reports were identified and lidocaine was the local anesthetic most often involved (11 of 16). Cutaneous symptoms were reported as the main features of allergic reactions with local anesthetics. Prick test, intradermal reaction, and challenge tests were used to confirm the diagnosis and type I (immediate) reactions were encountered in approximately 70% of the cases. Type IV delayed reactions were, therefore, noted 30% of the time.

Although true allergic reactions to local anesthetics are rare, some have been well documented. In addition, it has been noted that ester-type local anesthetics are more allergenic than amide-type; however, there are a significant number of reports of amide agents causing allergic reactions.²⁵ Cutaneous features, such as urticaria, pruritis, and erythema, are the most common features of local anesthetic hypersensitivity reactions. Furthermore, allergy to local anesthetics may be type I or type IV hypersensitivity reactions with the type I response more commonly reported in dentistry.^{16,25}

Cross Reactivity among Amide Local Anesthetics

Cross reactivity among the amide family of local anesthetics was once thought not to exist; however, recent literature has demonstrated that cross-allergenicity may occur. The French Pharmacovigilance database and GERAP were studied to determine type I immediate and type IV delayed hypersensitivity reactions to local anesthetics, as well as cross reactivity between amide local anesthetics. The report found 11 immediate reactions with 6 having cross reactivity.²⁵ In addition, a case report of a 39-year-old man who attended an allergy unit in Spain presented with an immediate hypersensitivity reaction to mepivacaine and cross reactivity to lidocaine and ropivacaine but could tolerate bupivacaine and levo-bupivacaine. This patient was diagnosed by using prick tests and intradermal tests; challenge tests were not used citing ethical reasons.¹³

Allergic Reactions to Local Anesthetic Preservatives

Methylparaben

Methylparaben, a preservative commonly found in foods and cosmetics, was frequently used in amide anesthetic solutions to prevent contamination of the agent. Methylparaben is bacteriostatic and fungistatic, and has oxidant properties because of its phenol-like action, which acts by denaturation of proteins and by antimetabolite properties of p-hydroxybenzoic acid.¹⁴ The structure of methylparaben is similar to PABA, a metabolite of procaine, which has been associated with a number of documented allergic reactions.^{15,17} In 1984, the Food and Drug Administration (FDA) mandated methylparaben be removed from single-dose local anesthetic cartridges; since then the number of related allergic reactions has been almost nonexistent.¹

Sulfites

Sulfites are commonly used to extend the shelf life of many injectable drugs, such as antibiotics and local anesthetics, as well as foods and wines. Sulfites are antioxidants that release sulfur dioxide, an active component, which may help stabilize epinephrine in local anesthetic solutions.²⁶ Most of the current dental anesthetics with vasoconstrictor contain the preservatives metabisulfite, sodium bisulfate, or potassium bisulfite. Metabisulfites may cause non-IgE-mediated hypersensitivity reactions, characterized by rhinitis, rash, headache, dyspnea, and cramping.²⁷ Koo and Dym²⁸ reported a type III hypersensitivity reaction in a 6-year-old boy anesthetized with lidocaine containing epinephrine. The child developed a delayed skin reaction following the injection that appeared as a leathery pigmented area, which is a similar feature seen in cutaneous necrotizing vasculitis. Metabisulfite was thought to be the primary cause of this reaction; however, because of potential scarring, no biopsy or further skin testing was done.²⁸ For definitive diagnosis, skin biopsy and histopathologic and immunopathologic testing should have been performed. Because of the existence of food allergy to sulfites, local anesthetics containing vasoconstrictor should be used cautiously or withheld in patients reporting food allergies associated with sulfites.²⁹ It

is estimated 500,000 Americans have allergic reactions to sulfite-containing drugs. In 1986, the FDA reported 14 deaths linked to allergic reactions.³⁰ The history of sulfite allergy may be very misleading and skin tests are very inconsistent. Most reactions to sulfites are seen in individuals with asthma; reactions in those who do not have asthma are very rare.³¹ Formulations not containing a vasoconstrictor, such as 3% mepivacaine or 4% prilocaine, do not contain sulfite preservative.

Latex Sensitivity

Dental cartridges contain latex stoppers and diaphragms, which can serve as potential allergens. Latex allergies can lead to type I and type IV hypersensitivity reactions. The type IV reaction is most commonly associated with the area of latex contact and usually presents as contact dermatitis. Estimates of the prevalence of allergy to latex allergens in the general population vary widely, from less than 1% to 6%.³² Health care provider visits for contact dermatitis and other eczemas, which include atopic dermatitis, are approximately 7 million per year.³³

Shojeil and Hass³⁴ conducted an evaluation of relevant publications from 1966 to 2001 to investigate evidence of latex allergies associated with medication vials or dental cartridges for dental local anesthesia. This review found evidence in the literature that latex allergens can be released into pharmaceutical solutions. However, the investigators concluded there were no reports of studies or cases implicating a dental cartridge as the cause of latex allergy. Even though there are no reports to date, it does not rule out the possibility of a future reaction. Fortunately, one of the major local anesthetic manufacturers, in an attempt to reduce latex in health care, has recently developed latex-free dental cartridges.

Treatment of an Allergic Reaction

Overall, true allergic responses to local anesthetics may be localized or general, immediate in onset or delayed.³⁵ Most accounts of allergic reactions to amides or to the preservatives added to commercial dental local anesthetic solutions suggest that the type I (anaphylactoid) response is the most likely allergic reaction to produce a generalized effect in patients after intraoral injection.³⁶ Even though the incidence of true allergic reactions is very low, they do occur and anaphylaxis is the major concern and often takes treatment precedence over other situations.^{14,37}

In anaphylaxis, a combination of the anesthetic antigen with antibodies bound to mast cells release specific mediators, such as basophils and neutrophils, which affect various tissues of the body. The common manifestations of anaphylaxis (erythema, pruritis, and urticaria) involve the skin and require a fundamental treatment method. Requiring a more concise treatment methodology, the most concerning manifestation of an anaphylactic reaction relates to smooth muscle contraction. This can lead to bronchial constriction in which death can occur from bronchial spasm or laryngeal edema.

Generally, the signs and symptoms involved with anaphylaxis will follow a progressive pattern that initiates with skin reactions and terminates with respiratory distress and cardiovascular depression.³⁸ In the event of generalized anaphylaxis, the signs will demonstrate a progressive pattern as follows^{38,39}:

- Skin manifestations (erythema, pruritis, and urticaria)
- Gastrointestinal manifestations (muscle cramping, nausea and vomiting, incontinence)
- Respiratory manifestations (coughing, wheezing, dyspnea, laryngeal edema)
- Cardiovascular manifestations (palpitations, tachycardia, hypotension, unconsciousness, cardiac arrest).

Table 2 Management of local anesthesia–related allergic manifestations			
Manifestation	Symptom Occurrence	Signs/Symptoms	Management
Localized Skin Reaction	Usually	Erythema, edema, pruritus	Monitor patient without intervention, or oral antihistamine (Benadryl 25–50 mg)
Generalized Skin Reaction	Often	Pruritus, urticaria, macular rash	Oral antihistamine (Benadryl 25–50 mg), or IM antihistamine (diphenhydramine 25–50 mg)
Respiratory Implication	Occasionally	Bronchoconstriction, laryngeal edema, dyspnea	Epinephrine IM or SC (0.3 mg); oxygen, maintain airway, EMS activation. Supplemental Therapy: IM diphenhydramine (50 mg); IM or IV glucocorticoids
Anaphylactic Shock	Rarely	Skin reactions, bronchoconstriction, edema, dyspnea, marked hypotension, cardiovascular collapse	EMS activation, epinephrine IM or SC (0.3 mg); oxygen, BLS/CPR as indicated. Supplemental Therapy: IM diphenhydramine (50 mg); IM or IV glucocorticoids

Abbreviations: BLS, basic life support; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IM, intramuscular; IV, intravenous; SC, subcutaneous.

Prompt detection and response to emergent allergic reactions will alter the extent of the reaction. It is important to note that, when applicable, the removal of any remaining traces of a possible allergen should always be the initial treatment step. The management of allergic reactions will also follow a progressive pattern of treatment depending on the severity of the patient’s response. **Table 2** outlines the management of allergic responses to local anesthetics.

SUMMARY

True allergic reactions to local anesthetics are rare adverse reactions. At the most, they represent less than 1% of all adverse local anesthetic reactions.^{25,40,41} When true allergic reactions have been confirmed, the reactions are most commonly the type I anaphylactic and type IV delayed hypersensitivity responses. The type I immediate hypersensitivity reactions are the most severe and may be life-threatening.^{24,41}

In the event a potential allergic reaction occurs in a dental office, the dentist needs to properly evaluate the events leading up to the reaction and provide a differential diagnosis. Patients presenting with hives, wheezing, angioedema, bronchospasm, hypotension, unconsciousness, and cardiovascular collapse may have a true allergic reaction. The dentist needs to catalog all drugs and materials that came in contact with the patient to assist in definitive diagnosis. A referral should be given to any patient when an allergic reaction cannot be ruled out as an intravascular injection, toxic overdose, psychogenic reaction, or an idiosyncratic event.

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