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A Guideline to Local Anesthetic Allergy Testing

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Patients with a history of adverse reactions to a local anesthetic may often be incorrectly labeled as "allergic." Determining if a patient is allergic to a local anesthetic is essential in the selection of appropriate pain control techniques. Local anesthetic allergy testing may be performed safely and with reasonable accuracy by a knowledgeable practitioner. This paper presents guidelines for an allergy testing method.

There is no question that pain control is an integral aspect of modern dentistry. From the first inferior alveolar nerve block by Halsted in 1884 to the current pain and anxiety control techniques ranging from behavior modification to general anesthesia, the quest has been to make dentistry as painless as possible.[1,2] Regional analgesia is the most commonly used method of pain control with an estimated one-half million local anesthetic administrations performed daily in the United States.[3] Local anesthetics have proven to be among the safest of drugs in current use, as evidenced by their low incidence of adverse reactions.[4] However, certain patients who have had an adverse reaction to local anesthesia may be improperly labeled as "allergic."[5,6] True allergic reactions to the local anesthetics are actually quite rare, estimated at less than 1% of all adverse reactions.[7] The causes of the allergic reactions may be attributed to either the local anesthetic or additives in the local anesthetic solution.[8–11]

Allergic reactions are classified according to the immune system's response. Type I reactions, which include the anaphylactic reaction, are mediated by antibodies derived from immunoglobulin E (IgE). The anaphylactic reaction is the most feared of all allergic reactions because of its rapid onset and potentially fatal consequences. Anaphylaxis is characterized by circulatory collapse, bronchospasm, upper airway edema, and urticaria, which are associated with the release of histamine, slow-reacting substance of anaphylaxis, serotonin, and bradykinin into the circulatory system.[12–15] These symptoms result from the interaction of IgE antibodies with sensitized cells in the shock organs. Local anesthetics can provoke this type of reaction. Type II responses are mediated by antibodies from IgE, immunoglobulin M (IgM), or both, which interact with complement to create a cytotoxic response such as cell injury and destruction of erythrocytes, leukocytes, and platelets. Local anesthetics could theoretically elicit this type of reaction, although reports of its occurrence are virtually nonexistent. Type III immune responses usually effect vascular or connective tissues resulting in edema and inflammation. These reactions are usually immunoglobulin G (IgG) or IgM mediated. Again, local anesthetics could precipitate this type of response but it has not been reported. Last, type IV immune responses are local and cell mediated, with contact dermatitis being the most common example. The type I and IV responses are involved in the majority of abnormal immune reactions elicited by local anesthetics.[13]

Dental anesthetics are divided into two basic chemical groups, esters or amides, according to the linkage of the intermediate connecting chain. The ester-type anesthetics, represented by procaine, were the dominant agents for almost 50 years. Thus, most sensitization reactions were attributed to the ester anesthetics. One of the breakdown products of procaine is the highly antigenic agent *p*-aminobenzoic acid. As this is a common breakdown product of many ester anesthetics, cross-allergenicity is expected. The breakdown products of the amide local anesthetics do not include a basic amine in the para position as seen with *p*-aminobenzoic acid; therefore, this may account for the rarity of sensitization reactions. Consequently, cross-hypersensitivity among amide anesthetics or between amide and ester anesthetics is not seen.

Other causes of allergy are attributed to additives in local anesthetic preparations: the parabens, which are used as preservatives for the anesthetic solution, and sodium bisulfite, an antioxidant for the vasoconstrictor. A breakdown product of the parabens is *p*-aminobenzoic acid; consequently, a patient allergic to ester anesthetics may also demonstrate an allergic reaction to amide

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anesthetics containing this agent. Fortunately, most single-dose anesthetic solutions no longer contain parabens. Sulfites are used as preservatives in some foods; therefore, one should avoid administering sulfite-containing local anesthetic solutions to patients who have an extensive history of food allergies where sulfites may be involved.[4,5,15–18]

"Allergic" patients are often terrified to receive local anesthesia; consequently, dental treatment is often neglected or rendered without local anesthesia thereby leading to the possible creation of dental "cripples" and phobics.[12] Other methods of pain and anxiety control, such as conscious-sedation or general anesthesia, are not always appropriate or available. Conscious-sedation necessitates local anesthetic administration for pain control; whereas, general anesthesia has additional risks and can be very expensive. Alternatively, some dentists may proceed with a local anesthetic administration without further investigation of the adverse reaction history thereby placing the patient at additional risk. The patient's fear may be alleviated if it can be determined whether or not there is an actual allergy to the anesthetic agent. Patients with suspected allergies can be tested under controlled conditions to determine if an allergy exists, to find what the causative agent or agents may be, or to find a local anesthetic that can be safely administered. Allergy testing can be beneficial psychologically and from a safety perspective for the patient. Certain procedures can enable more accurate and safer testing. The following guideline is a suggested guideline for local anesthetic allergy testing in a suspected allergy patient.

ALLERGY TESTING GUIDELINES

A. Patient Evaluation
   1. A thorough medical history is essential.
      a. The history should include as much detail as possible about allergies and drug reactions. Basic information should include the name of the drug, the amount administered, the presence of any vasoconstrictor or other additive, any medications taken at the time of reaction, details of the reaction, position of the patient in the dental chair, and the treatment given.[16,19] Current medications the patient may be taking cannot be excluded as the cause of the allergic reaction. Thus, one should determine for each drug being taken the duration of use, time of the last administered dose, and the probability of the drug as an allergen. Determining which drug caused the allergic reaction may only be accomplished by a careful process of elimination. This history may be extremely difficult to document with accuracy, even when both the patient and attending doctor are questioned.
      b. Food allergies should be identified, when possible. Food products often contain sulfite preservatives; consequently, their ingestion may elicit an allergic reaction. These individuals are considered high-risk patients.[5,8,13]
      c. The patient's past anesthetic experience(s) including any complications should be evaluated.
      d. Current medications and dosages should be listed and confirmed by consultation.
      e. A review of systems should contain:
         i. A central nervous system evaluation including any history of seizure disorders, cerebral vascular accident, transient ischemic attack, or neuropathies.
         ii. A cardiovascular system review including any history of heart murmurs, rheumatic heart disease, hypertension, incidence of angina, or myocardial infarction.
         iii. A respiratory system evaluation including any history of chronic obstructive or restrictive pulmonary disease, bronchitis, or asthma. Evaluation of the cause and frequency is important.
         iv. An endocrine system evaluation of liver status, any history of thyroid dysfunction or diabetes.
         v. A gastrointestinal and genitourinary systems evaluation including any history of ulcers, hiatal hernia, or renal abnormalities.

B. Patient Preparation and Management
   1. A consent form concerning the procedure and risks should be explained and signed, including the possibility of localized tissue damage, or a systemic response to the anesthetic agent.[20]
   2. Proper measurement of blood pressure, pulse, respiration and electrocardiogram should be employed.
   3. An intravenous infusion using a 16- or 18-gauge catheter is begun to provide a route for drug and fluid administration in the event of a reaction.
   4. A complete emergency kit including oxygen with positive pressure ventilation capabilities must be readily available.
   5. The patient should never be left unattended. Verbal communication and monitoring of vital signs are very important.

C. Preparation of Test Solutions
   1. The local anesthetics to be tested must be free of all additives (preservatives and vasoconstrictor).[21] The recommended agents for a comprehensive test are tetracaine HCl 1%, mepivacaine HCl 3%,

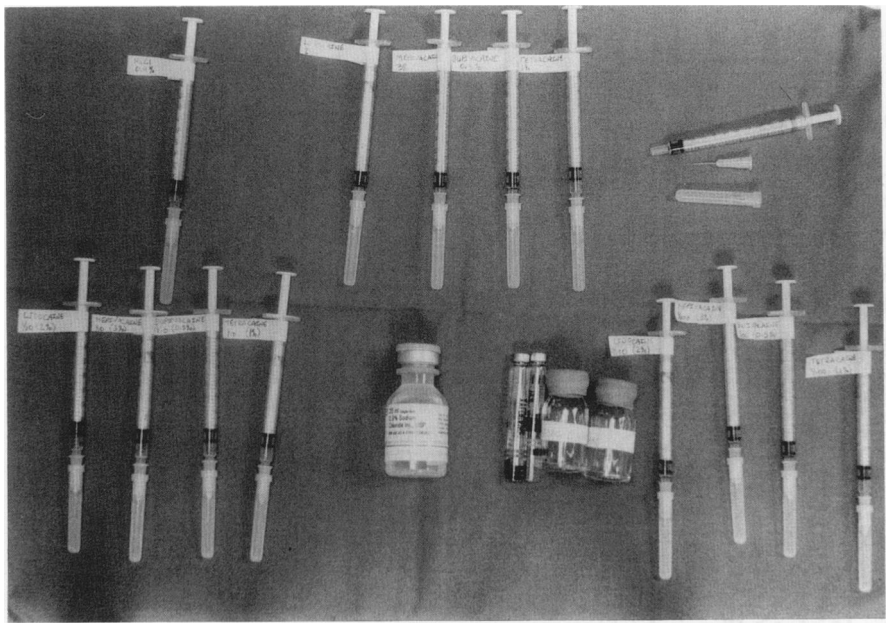


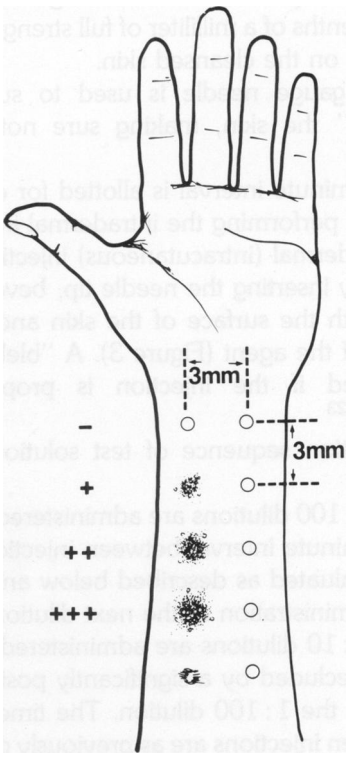
Figure 1. Prepared test dilutions arranged for administration to the patient. Note that each syringe is labeled for identification.

lidocaine HCl 2%, bupivacaine HCl 0.5%, and saline 0.9%. If one desires only to determine a safe local anesthetic for future use, the most common agents currently in use are tested.

2. Local anesthetic test solutions are prepared by diluting the above concentrations to 1:10 and 1:100 dilutions in the following manner using tuberculin syringes:
   a. The 1:10 dilution is prepared by drawing 0.1 mL of the full strength anesthetic solution into a syringe, placing it into a sterile vial, and then diluting with 0.9 mL of sterile saline.
   b. The 1:100 dilution is prepared by drawing 0.1 mL of the 1:10 dilution into a syringe, placing it into a sterile vial, and then diluting with 0.9 mL of sterile saline.
   c. All dilutions must be mixed thoroughly.
3. Sterile 1-mL tuberculin syringes with a 25- or 27-gauge needle are filled with each test dilution (Figure 1). Express any air from the needle so it is filled with the test solution and 0.1 mL of agent remains in the syringe.[22]
4. Prepare additional syringes (one syringe for each agent) containing the anesthetic solutions at full dental cartridge strength and a control solution of 0.9% sodium chloride.

D. Injection Procedure
1. Specific injection areas (usually on the forearms) are marked approximately 3 cm apart and prepared by cleansing with a sterile alcohol swab and allowed to dry.[22] The arm without the intravenous infusion is used (Figure 2).

Figure 2. Injection areas and examples of reactions to test solutions. Scale: − = no visible change; + = 1–2 cm change in diameter (wheal or erythema); ++ = 2–3 cm change in diameter (wheal or erythema); +++ = diameter > 3 cm (wheal with erythema).



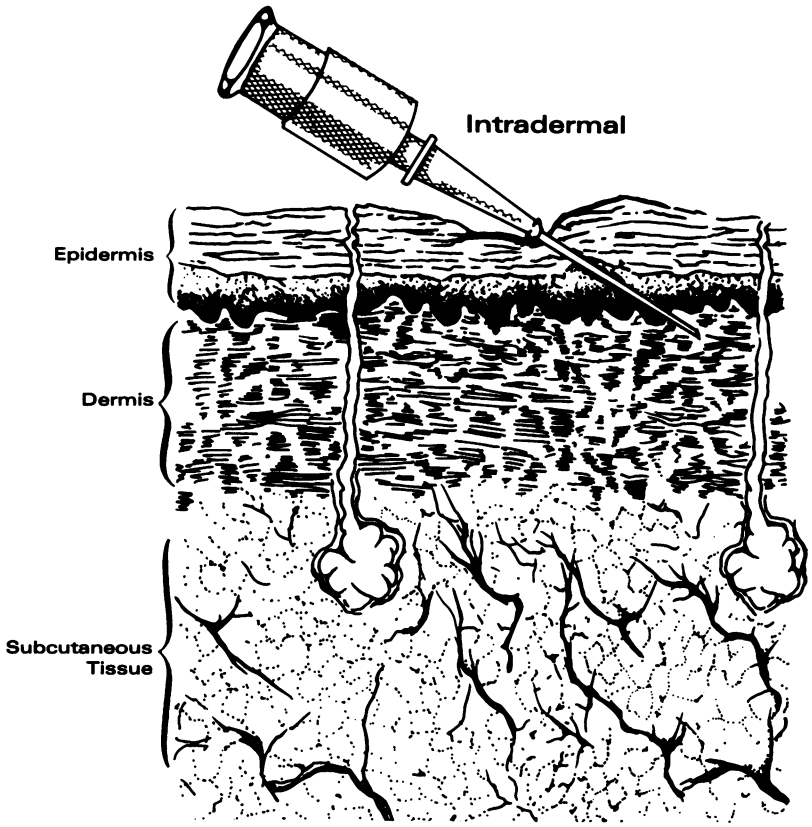


Figure 3. Proper needle placement for intradermal injection. (Modified from Eric W. Martin, *Techniques of Medication,* Philadelphia, J.B. Lippincott, 1969 p 116.)

2. The test agent should be unknown to the patient at the time of injection.
3. A prick test is performed for each agent as follows:
   a. Two-tenths of a milliliter of full strength agent is placed on the cleansed skin.
   b. A 30-gauge needle is used to superficially "prick" the skin, making sure not to draw blood.
   c. A 20-minute interval is allotted for evaluation before performing the intradermal injections.
4. The intradermal (intracutaneous) injection is performed by inserting the needle tip, bevel up, just underneath the surface of the skin and injecting 0.1 mL of the agent (Figure 3). A "bleb" should be formed if the injection is properly performed.[22,23]
5. The injection sequence of test solutions are as follows:
   a. The 1 : 100 dilutions are administered first with a 10-minute interval between injections. They are evaluated as described below and prior to the administration of the next dilutions.
   b. The 1 : 10 dilutions are administered next unless precluded by a significantly positive reaction to the 1 : 100 dilution. The time intervals between injections are as previously described.
   c. The full-strength test solutions are administered next unless precluded by a significantly positive reaction to the 1 : 10 dilution. The time interval between injections are as previously described.
   d. If no response occurs to the prior injections, a 1 mL subcutaneous injection of full strength anesthetic is performed on the arm. If a response occurs to this injection, a tourniquet is placed above the injection site and appropriate treatment rendered.

E. Evaluation of Response
   1. Evaluate each injection site for 15–20 minutes.[24]
   1. The response is measured by the diameter of skin change or wheal, if present. A common guideline is:

–	no visible change at injection site
+	1–2 cm in diameter change, wheal or erythema
++	2–3 cm in diameter change, wheal or erythema
+++	3 cm or greater diameter wheal with erythema[19,25,26]

All observation should be compared with the control (Figure 2).

F. Post-Allergy Test Sequence
   1. If no response to the skin testing occurs, an intraoral injection may be given to confirm the result with the selected local anesthetic.[16,27]
   2. The patient should be observed for 1–1.5 hours after the last injection to determine that no delayed reaction will occur and to insure the patient's safety.
   3. If a reaction occurs, the patient must be monitored and appropriately treated, then referred for additional medical treatment, if necessary.

DISCUSSION

True allergy to local anesthetic agents or their additives are rare, accounting for an estimated less than 1% of all adverse reactions. Reactions often confused by patients or practitioners as hypersensitivity to local anesthetic solutions may include toxicity to the anesthetic agent and/or the vasoconstrictor as well as anxiety reactions. Toxicity due to drug overdose or accidental intravascular injection is manifest as central nervous system excitation including agitation, disorientation, blurred vision, muscle tremors, and/or convulsions. Central nervous system depression may follow or it may occur without other manifestations of toxicity. Vasoconstrictor reactions are predominantly cardiovascular and may be observed as palpitations, tachycardia or hypertension. Other cardiovascular effects including hypotension or bradycardia or psychomotor effects such as hyperventilation or vasovagal syncope may also occur when anxiety is present.[21,22]

True allergic reactions do occur, with anaphylaxis being the greatest concern: its onset is rapid and may be fatal. Management of this life-threatening situation requires prompt and knowledgeable treatment. The management goals are to correct arterial hypoxemia, inhibit further release of endogenous chemical mediators and maintain the vital signs. The patient should be placed in a supine position with the legs elevated to help maintain the blood pressure. Administration of oxygen and epinephrine (0.3–0.5 mg i.v.) is imperative. Oxygen functions to relieve hypoxemia. Epinephrine relaxes bronchial smooth muscle by physiological antagonism of histamine and β-receptor stimulation thereby reducing airway resistance. Also, epinephrine's inotropic and vasoconstrictive effects help maintain blood pressure. Subcutaneous or intramuscular epinephrine (0.3 mg) may be administered as an alternative, but in this allergy testing protocol an intravenous infusion is already in place allowing for the intravenous route of administration. Predetermination of the required epinephrine dose may be made at 3–6 μg/kg of body weight. The rate of intravenous infusion should be increased to help with blood pressure maintenance. Diphenhydramine (0.5 mg/kg body wt i.v.) is administered to reduce the effects of circulating histamine by competing for unoccupied H_1-receptors. An antiinflammatory steroid is often given, although the clinical value is subject to criticism: Steroids do not block interactions of drugs with IgE antibodies or prevent the release of chemical mediators, but they do appear to stabilize lysosomal membranes, decrease capillary permeability, and suppress T cells that may be involved in delayed hypersensitivity reactions. If bronchospasm is still a problem, aminophylline can be administered intravenously.[7,21,28]

The type and sequence of skin tests performed are important. The prick test is valuable because it is accurately reproduced and, even though a full-strength anesthetic is used, it is estimated only 3×10^{-6} mL is injected. There are no known fatalities using the prick test. Intradermal tests have shown value in hypersensitivity testing.[29] The reaction is localized thus presenting less danger to the patient. Intradermal injections can be technically difficult, requiring skill and knowledge to perform properly. The scratch test may be performed, but it is 100 times less sensitive than the intradermal test and not as accurately reproduced as the prick test.[30] Subcutaneous injections are not advised until the prick and intradermal test sequences have been performed because the agent may be rapidly absorbed; therefore, if a response were elicited, the reaction would be systemic. The subcutaneous injection is performed on an extremity so a tourniquet can be placed above the injection site to slow anesthetic absorption in the event of a reaction. Other complications of testing may include erythema, marked induration and local necrosis at the site of administration.

Other areas of difficulty involved in allergy testing involve the interpretation of results. False-positive results can occur due to injection trauma, or localized histamine release from the skin puncture. False-negative reactions can occur if the antigen passed into the circulatory system rather than the skin, or if a drug metabolite was antigenic rather than the drug itself. Interpretation of skin test results is difficult and controversial, but the value of skin testing is that if the patient does have a negative response, he or she can usually be administered the drug safely.[13,15,18,28,30] One must also be able to perform dilutions accurately. Test dilutions are important for patient safety to prevent initial exposure to a full-strength antigen. If a reaction does occur, its severity is diminished if the anesthetic is diluted. The technique of skin cleansing, the volume of anesthetic administered and the depth of injection are additional factors that may affect the result.[23]

The practitioner must be capable of starting an intravenous infusion before testing, then be proficient in treating

any emergency which may arise. The patient should be without food or drink for 6 hours prior to testing to reduce the possibility of aspiration of gastric contents in the event the patient loses consciousness.

Testing gives an indication of the patient's hypersensitivity. Although a negative skin reaction is thought to be conclusive, it is suggested that the best way to determine if a patient can tolerate a given local anesthetic is to actually administer it in a clinical trial because skin tests do not always elicit a reaction. One must always be prepared for adverse reactions.[22,27]

RECOMMENDATIONS

It is important that clinicians be able to evaluate a suspected allergy patient so appropriate management or referral can be made. Allergy testing can be successfully performed, but it should only be attempted by a practitioner familiar with proper testing and interpretation procedures. If a practitioner is unfamiliar with testing, the patient can be referred to individuals such as dental anesthesiologists or oral surgeons who have received appropriate training in local anesthetic allergy testing or allergy specialists. Most importantly, a practitioner must be trained in medical emergencies and be capable of resuscitating a patient.

Patient stress is often elevated, especially during the first treatment period following testing; thus, a stress-reduction protocol should be followed. This may include clinician–patient rapport, hypnosis, biofeedback, relaxation tapes, oral premedication, nitrous oxide/oxygen inhalation, or intravenous sedation.

The ultimate goal is to find a local anesthetic that can be used with the patient to provide safe and comfortable dental treatment.[27]

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