Allergic Response to Metabisulfite in Lidocaine Anesthetic Solution

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True allergies to local anesthetics are rare. It is common for practitioners to misdiagnose a serious adverse event to local anesthetics as an allergic reaction. The most likely causes for an allergic response are the preservative, antioxidant, or metabolites and not the anesthetic itself. This case report illustrates the need for practitioners to understand the many potential allergens in local anesthetics and to correctly diagnose patients that are truly allergic to the local anesthetic.

Key Words: Local anesthetic; Metabisulfite; Allergy.

Frequently, patients present to the dental office labeled as "caine" allergic. While allergic reactions to local anesthetics are rarely reported, less than 1% of the adverse reactions to local anesthetics are true immunologic reactions.[1] If, after a thorough medical history, the possibility of an allergic reaction is likely, then skin testing should be performed. A dental cartridge with vasoconstrictor contains metabisulfite as an antioxidant, while a multidose vial of local anesthetic with vasoconstrictor contains both metabisulfite and methylparaben as a preservative. A multidose vial of local anesthetic without vasoconstrictor contains only methylparaben as a preservative. Therefore, the intradermal testing should include methylparaben, metabisulfite, and local anesthetic solutions. Skin testing allows the clinician to separate autonomic and toxic responses from the true allergic reactions to local anesthetics so those patients are not labeled as caine allergic.

CASE REPORT

A 22-year-old female with a questionable lidocaine allergy presented to her general dentist for a routine four-surface amalgam restoration on tooth 3. She had previously had other restorative work performed by this dentist. The lidocaine reaction first presented in her 6 months prior at a primary physician's office in which she was having several moles removed. The physician told her she was allergic to lidocaine because she apparently had significant swelling all around the surgical site.

The patient claims she told her dentist of her reaction to lidocaine. Regardless, he then proceeded to inject 2% lidocaine with 1 : 100,000 epinephrine and began to prepare the tooth. Apparently the tooth needed root canal therapy and he then proceeded to perform a pulpectomy. The next day, day 2, the patient noticed mild unilateral swelling. The patient thought nothing of it since she was advised to expect mild swelling. The following day, day 3, the swelling intensified and she was told to apply ice until she could be seen later that day. Another dentist in the practice saw her, as an emergency, until the original dentist became available. She stated that she thought she was having an allergic reaction to the lidocaine. The partner then proceeded to perform an infiltration of 2% lidocaine with 1 : 100,000 epinephrine. The canals were cleaned and the tooth temporized and she was started on an antibiotic.

On day 4, the patient complained of intense pain and severe swelling; therefore, she was referred to an oral and maxillofacial surgeon. The surgeon examined her and advised her that she needed to have an incision and drainage (I and D) performed under local anesthesia. According to his records, he presumably performed the

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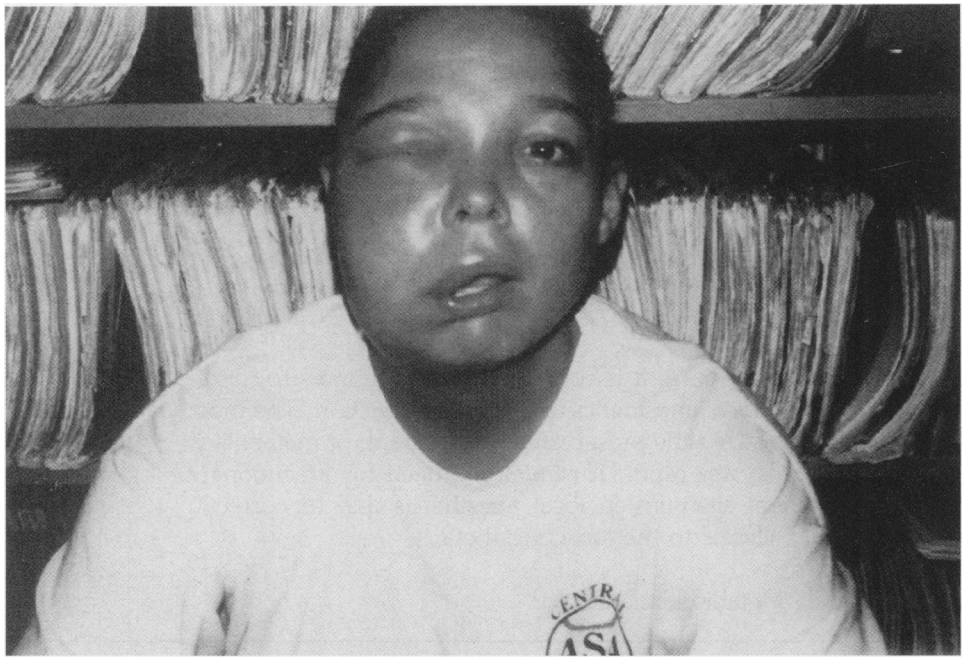


Figure 1. Polaroid photograph taken on the fifth day after the reaction.

I and D with 2% lidocaine with 1 : 100,000 epinephrine. Although there was no pus present to confirm the preliminary diagnosis of an abscess, the surgeon nevertheless placed a drain and prescribed cephradine, clindamycin, demerol, and promethazine.

The next day, day 5, the swelling had become so severe her right eye had swollen shut (Figure 1). She was then admitted to the hospital. She was placed on intravenous clindamycin and pain medications. Her laboratory results were within normal limits except for a slight-

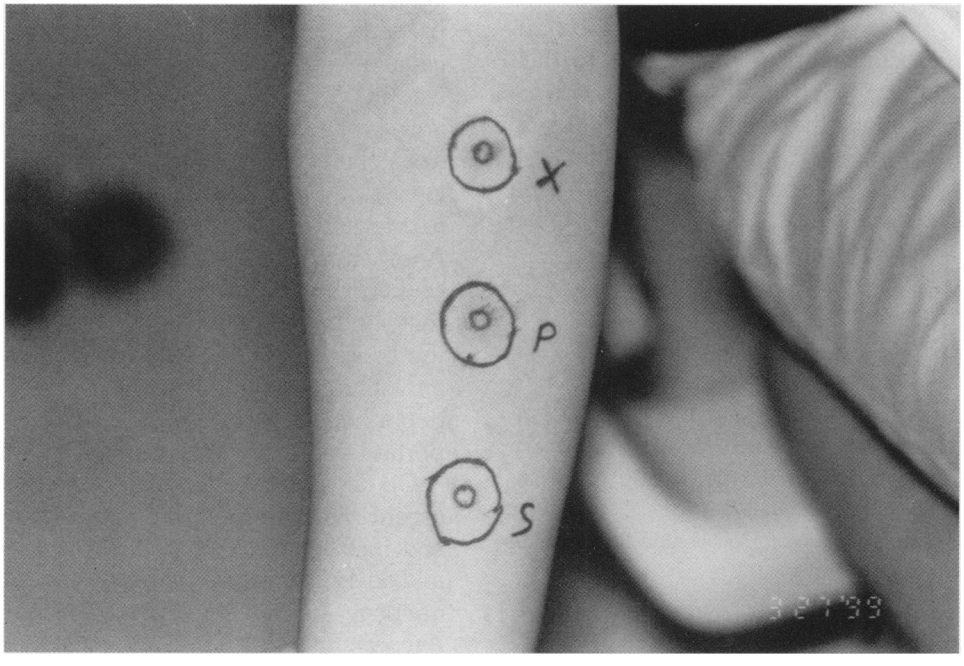


Figure 2. Right forearm at allergy testing: X, lidocaine with epinephrine containing metabisulfite; P, mepivacaine plain with no preservative; S, sterile saline control.

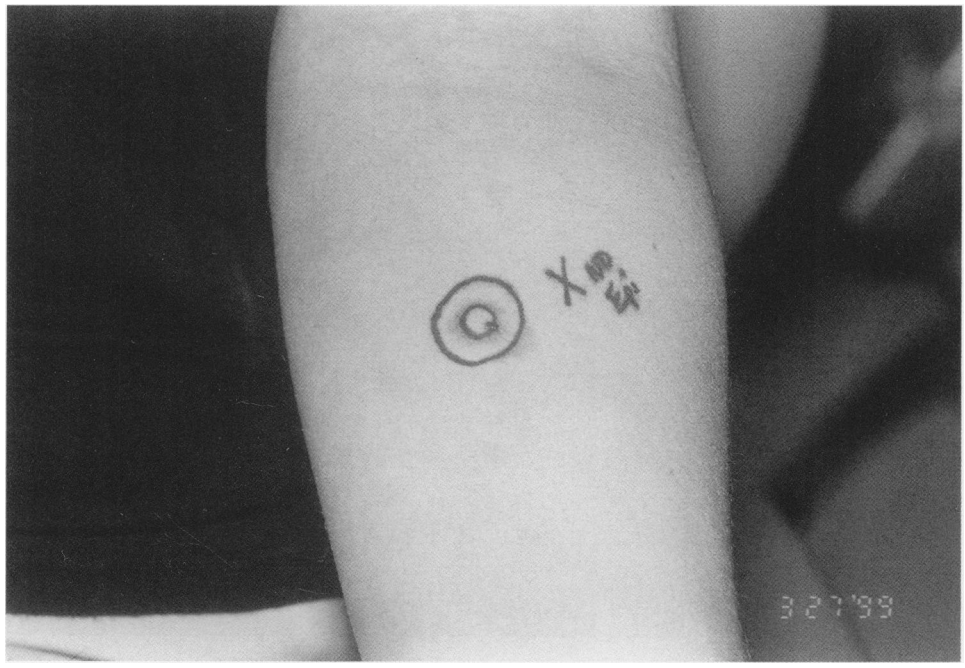


Figure 3. Left forearm at allergy testing: X, no epilidocaine without epinephrine from a multidose vial containing methylparaben.

ly high white blood count (WBC) of 11.2 K (hospital norms were from 4.9 to 10.8 K).

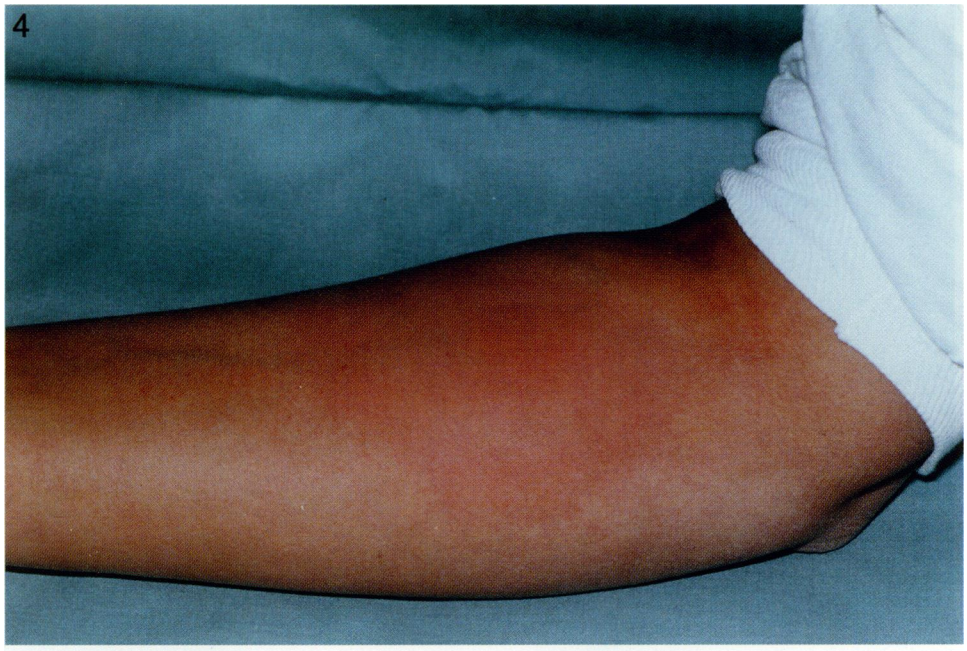
She spent the next day, day 6, in the hospital and was released on day 7 with intravenous clindamycin and home health care nursing. Her WBC had then decreased to 7.2 K. The day after being discharged, she was seen by her primary care physician, who prescribed fexofenadine (Allegra®), then soon changed her to oral clindamycin. Her primary care physician then performed allergy testing on her forearm a few weeks later. He concluded she had an allergic response to the lidocaine solution he used to remove the moles. Allergy testing was performed again by the senior author to clarify whether the patient was allergic to the local anesthetic, the preservatives, or the antioxidant.

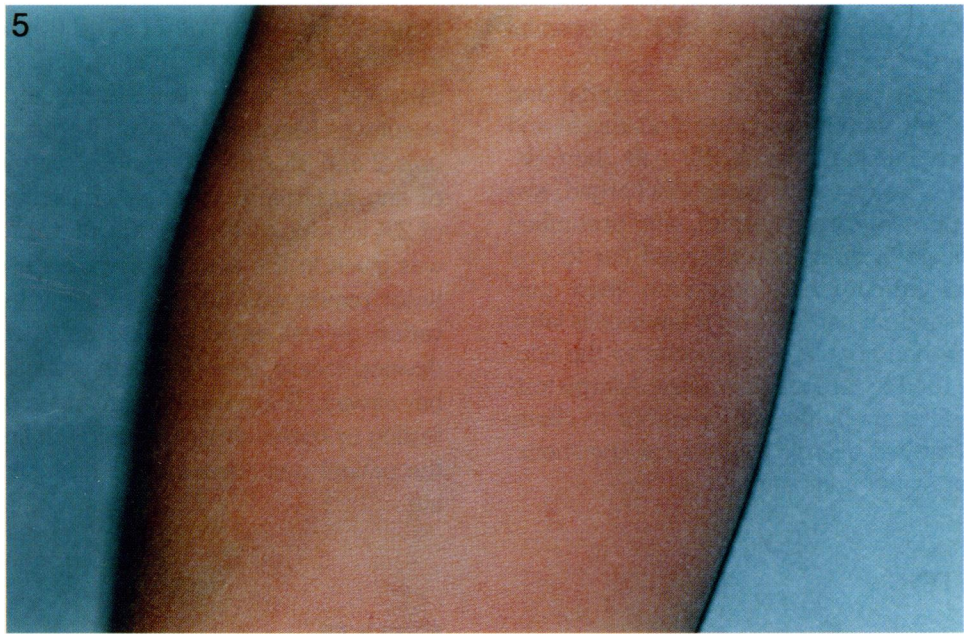
ALLERGY TESTING

The method of testing was a modification of the dermal-nasal-optical technique previously described by Campbell and Giglio.[2] The patient was advised of the complications of allergy testing and knowingly consented to the testing. After the placement of an intravenous access and appropriate monitoring equipment, testing was begun. With the use of a tuberculin syringe and a 25-gauge needle, selected agents were administered to the ventral surface of either forearm. The following agents were injected intradermally to produce a 5-mm diameter wheal approximately 3 inches apart on the right forearm: 2% lidocaine with 1 : 100,000 epinephrine from a dental cartridge, 3% mepivacaine plain from a dental cartridge, and saline plain. In the left forearm, the sole agent was lidocaine 2% plain from a multidose vial (Figures 2 and 3). After 45 minutes without the observation of any systemic reaction, a challenge dose of 1.8 cm^3 of 2% lidocaine with 1 : 100,000 from a dental cartridge was given in the anterior mandibular vestibule. The anterior region was selected to allow for optimum observation as well as to confine any swelling, which may develop locally, to a region that would not compromise her airway. There was no immediate reaction to the skin testing or challenge dose within the first hour; therefore, the patient was released until evaluation the next morning.

RESULTS

The patient returned 24 hours later with a large 10-cm-long, 7-cm-wide raised wheal on the right forearm. It was red and itchy (Figures 4 and 5). The location of the reaction corresponded to the test dose of 2% lidocaine with 1 : 100,000 epinephrine. The anterior vestibule and soft tissue of the chin had mild/moderate edema as well. The other sites, ie, those of saline, mepivacaine, and lidocaine without epinephrine, showed no reaction.





Figures 4 and 5. Reaction in area of lidocaine with epinephrine and metabisulfite 24 hours after administration.

DISCUSSION

This patient had 3 injections of lidocaine with epinephrine solution within 5 days by 3 different dentists. The incision and drainage was performed with the presumptive diagnosis of an abscess. The elevated white blood cell count was minimal and would be considerably more elevated (ie, greater than 20,000) if an abscess were the etiology. The only exception would be an infection in an immunocompromised patient such as someone who has AIDS or is taking steroids.

Local anesthetics are generally classified into either esters or amides. The esters include benzocaine, chloroprocaine, cocaine, procaine, propoxycaine, and tet-

racaine. These local anesthetics are recognized to have a greater incidence of allergic responses than amides. Cholinesterase found in the plasma and liver metabolizes these esters and forms a metabolite called *p*-aminobenzoic acid (PABA).[3] PABA, which is highly antigenic, is the most likely cause of allergic reactions to the ester anesthetics. The amide group includes bupivicaine, dibucaine, etidocaine, lidocaine, mepivacaine, and prilocaine. Preservatives or other substances in these anesthetic solutions or the amide compound itself may cause an allergic reaction. Methylparaben, the preservative agent in a multidose vial with or without epinephrine, is also metabolized to PABA. Therefore, patients who are allergic to PABA theoretically may show cross-reactivity between methylparaben-containing solutions of ester and amide groups.[4] Although uncommon, other substances, such as the antioxidants, may produce an allergic response.[5] These antioxidants, which are found in anesthetic solutions that contain vasoconstrictors, include metabisulfite and sodium bisulfite. Last, in rare cases, an immunologic reaction to an amide anesthetic may be caused by the amide linkage itself.

Additionally, a new local anesthetic was marketed in the United States as of August 2000. This anesthetic, articaine, is classified as an amide, but it has both amide and ester linkages. Articaine also contains the vasoconstrictor epinephrine, metabisulfite, and a sulfur atom in the thiophene ring. Therefore, patients with metabisulfite allergies should not be given articaine. To complicate the situation further, one reference states that a patient with a sulfa allergy is an absolute contraindication to articaine.[6] However, the package insert does not list sulfa allergy as a contraindication. More investigation is needed to see if those patients with adverse responses to esters and true sulfa allergies are at risk when administered articaine.

Allergic reactions are classified into 4 categories based on the immune system antigen–antibody response.[7] Types I, II, and III are immediate-type reactions, and Type IV is a delayed-type reaction. Type I reactions manifest as anaphylaxis. The first exposure to the anesthetic is the sensitizing dose. It causes immunoglobulin E (IgE) antibody production from type B lymphocyte cells and these antibodies bind to basophils and mast cells. On exposure to a second dose of the agent, the antigen binds to the antibodies, causing basophils and mast cells to release inflammatory mediators such as cytokines and histamine.[7]

Type I hypersensitivity reactions may be life threatening. Treatment depends on severity and can include oxygen; intravenous fluids; subcutaneous, intramuscular, or intravenous epinephrine, steroids, and antihistamines; and even endotracheal airway management.[1]

Type II reactions involve primarily IgG or IgM antibodies directed against antigens on an individual's own cells. Hemolysis and agranulocytosis can occur with Type II.[7]

Type III reactions involve antigen–antibody complexes that are not removed by the reticuloendothelial system. The complexes deposit in blood vessel walls, causing vascular and connective tissue damage.[8]

Type IV (delayed-type hypersensitivity) reactions are the most common with local anesthetics. Type T lymphocyte cells are sensitized to the local anesthetic during first exposure (no antibodies are formed). On a secondary exposure, the memory T cells release lymphokines that cause inflammatory reactions and activate macrophages to release mediators of inflammatory reactions.[8] Symptoms of Type IV reactions are similar to those of Type I. These include erythema, swelling, and uticaria. However, these are generally localized to the region of injection.

Most reactions to local anesthetics are not true allergies; rather, they are autonomic or toxic adverse affects. It may be difficult to distinguish between immediate allergic reactions and autonomic adverse effects. Systemic symptoms present as tachycardia, sweating, and hypotension, which may or may not result in a loss of consciousness. In contradistinction, syncope-induced hypotension can occur in patients with fear of receiving injections. However, autonomic affects are short lived and usually require minimal treatment. Toxic reactions occur when excessive amounts of a local anesthetic are given or an inadvertent intravascular injection has occurred. Symptoms of systemic toxicity include dizziness, muscle twitching, diplopia, tremor, bradycardia, decreased cardiac output, and seizures.[8]

If the practitioner cannot discern whether the reaction was autonomic, toxic, or a true allergy, skin testing should be performed. To date, immunoassays have been less than diagnostic. Many medications can modify an allergic response to skin testing. These include antihistamines, cough and cold medications, tricyclic antidepressants, and steroids, all of which should be discontinued for several days prior to testing.

CONCLUSIONS

The 22-year-old female is presumed to be allergic to the preservative sodium metabisulfite, which is present in local anesthetics that have a vasoconstrictor present. While the patient does not suffer specifically from a lidocaine allergy, she does manifest a moderately severe reaction to the antioxidant that would be present in any drug accompanying a vasoconstrictor such as epinephrine or levonordefrin. Under the assumption that, if a patient were to present to any dental office with a strong

history of an allergic reaction, especially verified by a physician who removed moles, as described by this patient, a practitioner should do one of the following: (1) refer the patient for evaluation, which may or may not include allergy testing, or (2) use an agent other than the one the patient stated she was allergic to, including the preservative and antioxidant.

A history of certain food allergies may be an indicator of a metabisulfite allergy. Allergies to sodium bisulfite and metabisulfite are not uncommon.[9] Bisulfites are antioxidants commonly sprayed on fruits and vegetables at salad bars to keep them fresh. Sulfites are also added to bottled wines to prevent oxidation.

The patient tested negative for lidocaine plain with methylparaben present as the preservative. It is important to note that, if the patient had tested positive in this group, a second test involving lidocaine plain from a dental cartridge and lidocaine plain from a multidose vial would have been necessary to rule out a methylparaben allergy. As dental practitioners, we do not generally consider methylparaben allergies because this preservative was eliminated from dental cartridges in 1984. Physicians and many oral and maxillofacial surgeons utilize multidose vials of local anesthetics; therefore, one needs to consider methylparaben as an allergen when a history of allergy to local anesthetics is present.

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