Delayed-Type Hypersensitivity to Lidocaine

Christine L. Mackley, MD; James G. Marks, Jr, MD; Bryan E. Anderson, MD

Background: Lidocaine hydrochloride is the preferred anesthetic agent used in outpatient surgical procedures. While type I hypersensitivity reactions to lidocaine are uncommon, type IV hypersensitivity is reported even less frequently.

Observations: Between January 1, 2001, and December 31, 2001, 183 patients were patch tested at the Penn State Milton S. Hershey Medical Center (Hershey, Pa) to the North American Contact Dermatitis Group tray. All patients who had a positive patch test reaction to lidocaine were challenged with 0.1 mL of preservative-free 1% lidocaine intradermally. Of the 183 patients patch tested, 4 had positive reactions to lidocaine, 2 of whom had histories of sensitivity to local injections of lidocaine manifested by dermatitis.

Conclusions: Delayed-type hypersensitivity to lidocaine may occur more frequently than previously thought. In cases of suspected lidocaine contact type IV sensitivity, patients should be patch tested to lidocaine. Positive patch test reactions should be confirmed by intradermal challenge with lidocaine. To provide the patient with alternative local anesthetics, patch testing should be performed with other injectable anesthetics. If positive patch test results occur, intradermal testing should follow.

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LIDOCAINE HYDROCHLORIDE IS the favored anesthetic agent used in outpatient surgical procedures. Adverse reactions to lidocaine are uncommon. Most reactions are a type I immediate hypersensitivity.1 There are few published cases of type IV delayed hypersensitivity. It is likely that many cases are not recognized. On January 1, 2001, the North American Contact Dermatitis Group (NACDG) added this antigen to their standard tray to assess the frequency of sensitivity to lidocaine. We report our observations using this antigen in the Penn State Milton S. Hershey Medical Center patch test clinic in Hershey, Pa.

METHODS

Between January 1, 2001, and December 31, 2001, 183 patients referred for potential allergic contact dermatitis were evaluated and patch tested in the Penn State Milton S. Hershey Medical Center Dermatology Department. The patients were patch tested to the NACDG tray using a standardized technique as outlined previously2 with Finn chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster Aksjeselskap, Vennesla, Norway). The current NACDG tray includes several local anesthetics, including 5% benzocaine in petrolatum (pet), 15% lidocaine pet, 1% tetracaine hydrochloride pet, 2.5% dibucaine hydrochloride pet, and 2.5% prilocaine hydrochloride pet. The patches remained in place for 48 hours, and test sites were evaluated twice, initially at 48 hours and again between 72 and 96 hours after initial presentation. A positive patch test result was interpreted to be a 1+, 2+, or 3+ reaction manifested by erythematous papules, vesicles, or a spreading reaction with crust and ulceration.

All patients who had a positive patch test result to lidocaine were tested with an intradermal injection of preservative-free 1% lidocaine. An area of clinically healthy skin on the forearm was cleansed with isopropyl alcohol. One tenth of a milliliter of preservative-free 1% lidocaine was drawn from a glass vial with a tuberculin syringe and injected intradermally. A bandage was placed on the injection site, and the patients were instructed to remove this bandage after 1 hour. The test site was evaluated 48 hours later for erythema, induration, vesicles, and pruritus, and the relevance of lidocaine sensitivity was determined historically. The patients were questioned about potential lidocaine exposure, prior surgical procedures, surgical site complications, and use of medicaments that contain lidocaine. The history, skin examination findings, patch test results, and intradermal injection site reactions were integrated to determine the likelihood of clinical significance.

From the Department of Dermatology, Penn State Milton S. Hershey Medical Center, Hershey, Pa. The authors have no relevant financial interest in this article.
REPORT OF CASES

Case 1

A 65-year-old white woman presented to our clinic for patch testing prior to orthopedic surgery. She had an extensive history of chronic dermatitis. Of note, the patient reported intolerance to dental surgery, having had significant swelling in the area of the injection commencing 2 days after her procedure. She also developed a pruritic red rash in the site of a lidocaine injection after a breast biopsy. Previous patch testing elsewhere using the TRUE Test (Allerderm Laboratories, Petaluma, Calif) revealed a positive response to mercapto mix. Her medical history was notable for arthritis and ileostomy. Our initial skin examination was unremarkable.

Patch testing using the standard NACDG tray as well as steroid and orthopedic trays revealed positive reactions to neomycin sulfate, bacitracin, methyl methacrylate, tixocortol-21-pivalate, and lidocaine. We then placed a 0.1-mL intradermal wheal of preservative-free 1% lidocaine (this was provided in a glass vial rather than a rubber-capped vial). Two days later there was a red patch at the site of the intradermal injection. The patient was instructed on how to avoid lidocaine. She was told that tetracaine, benzocaine, dibucaine, and procaine were acceptable anesthetic agents, since patch testing results to these agents were negative.

Case 2

A 40-year-old white woman presented to our clinic for confirmation of a positive intradermal challenge to preservative-free 1% lidocaine by an outside allergist. She had a medical history notable for an episode of pruritic, red papules across the dorsum of the foot 2 days after podiatric surgery (with an unknown anesthetic agent). Patch testing to the NACDG tray revealed positive reactions to balsam of Peru (Myroxylon pereirae) and lidocaine. She did not have patch test reactions to dibucaine, benzocaine, prilocaine, or tetracaine. The outside allergist had previously challenged her with an intradermal wheal of procaine, which had a negative result. We instructed the patient to avoid lidocaine, substituting procaine, dibucaine, prilocaine, benzocaine, or tetracaine.

PATCH TEST CLINIC PATIENTS

Of all 183 patients patch tested to the NACDG tray, 4 patients had positive patch test reactions to lidocaine. Of these 4 patients, only the 2 patients discussed previously had positive results to intradermal challenge at 48 hours. The same 2 patients were also the only 2 of the 4 patients to report a relevant history of pruritus and erythema at a surgical site anesthetized with a local anesthetic. All patients denied a history of using a topical medication that contained lidocaine, either prescription or over the counter.

There were other patients with sensitivities to the other local anesthetics on the NACDG tray. Positive anesthetic patch test results are given below.

<table>
<thead>
<tr>
<th>Antigen on NACDG Tray</th>
<th>No. of Positive Patch Test Results (n=183)</th>
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<tbody>
<tr>
<td>Benzocaine (5% pet)</td>
<td>4</td>
</tr>
<tr>
<td>Tetracaine hydrochloride (1% pet)</td>
<td>1</td>
</tr>
<tr>
<td>Lidocaine (15% pet)</td>
<td>4</td>
</tr>
<tr>
<td>Dibucaine hydrochloride (2.5% pet)</td>
<td>4</td>
</tr>
<tr>
<td>Prilocaine hydrochloride (2.5% pet)</td>
<td>0</td>
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COMMENT

Anesthetic agents consist of an aromatic portion and an amine group separated by an intermediate chain, this chain being either an ester or an amide group. Ester compounds such as procaine, benzocaine, and tetracaine are derived from para-aminobenzoic acid. Benzocaine is a common sensitizer in patch test clinic patients as was demonstrated by the 1996-1998 NACDG compilation of over 3400 patch-tested patients, revealing a 2% incidence of type IV sensitivity to benzocaine. Patients sensitive to ester anesthetics are unlikely to demonstrate cross-sensitivity to amide anesthetics. Amide anesthetics include the aminoacylamides lidocaine, mepivacaine, and prilocaine as well as the aminoalkylamides procainamide and dibucaine.

The most commonly used anesthetic agent for dermatologic surgery is lidocaine. It is also known as lignocaine in the European literature. Lidocaine is widely used as an injectable anesthetic agent as well as a topical anesthetic. It is also used intravenously for treatment of cardiac arrhythmias. Despite widespread and frequent use, it is considered uncommon to have a hypersensitivity reaction to lidocaine. In the literature, type I reactions are much more common than delayed-type hypersensitivity reactions.

There are a limited number of reported cases of contact sensitivity to lidocaine. The first case report was by Callan and Stevenson in 1954, describing a chemical process worker involved in the production of lidocaine. The most commonly reported cause of allergic contact dermatitis to lidocaine is through the use of antihemorrhoidal preparations. Kernekamp and Van Ketel reported a patient with an arterial leg ulcer, who, having been treated for the associated pain with gauze soaked in 5% lidocaine, developed “eczema” at the site of the applied gauze. The patch test result to 2% lidocaine was positive. Likewise, sunburn relief agents have also been noted as a source of exposure to lidocaine. Turner reported a patient who developed a widespread rash after use of such an agent. Patch testing revealed strong positive reactions to 2% lidocaine as well as the aerosol itself. Kawada et al presented a patient with a contact dermatitis from a preparation which mixed miconazole, lidocaine, and crotamiton. Patch testing revealed positive reactions to both crotamiton and lidocaine, and the authors speculated that the similar structures of these chemicals may cause cross-sensitization.

There are a few cases reported in the literature in which patients developed a type IV hypersensitivity reaction to a therapeutic injection of lidocaine. Curley et al presented a dental patient who developed swelling of her soft tissues 48 hours after lidocaine injection for a...
dental procedure. She had a similar reaction to prilocaine and, later, mepivacaine injections for further dental procedures. A medical history review revealed that she had been exposed to lidocaine, procaine (injections), and benzocaine (topical) without incident. Patch testing revealed positive reactions to a mixture of benzocaine-tetracaine-dibucaine, as well as to individual aliquots of lidocaine, prilocaine, and mepivacaine. The authors concluded that there was cross-sensitivity to prilocaine and mepivacaine as a result of lidocaine exposure, since the patient had never been exposed to these chemicals until the dates of the reactions. Bircher et al\textsuperscript{24} also reported a patient with localized swelling 24 hours after dental surgery, with patch testing revealing lidocaine sensitivity.

Whalen\textsuperscript{22} reported a patient with a localized, pruritic, vesiculobullous delayed-type hypersensitivity reaction on the dorsum of the hand 12 hours after lidocaine injection. Patch testing confirmed this sensitivity. A recent case report by Breit et al\textsuperscript{20} described a man who developed pruritus, swelling, and erythema at lidocaine injection sites. Results from prick and intradermal testing were negative at 20 minutes, but intradermal test results were positive at 48 hours, thus indicating type IV hypersensitivity. Another patient was described as having had immediate hypersensitivity to lidocaine during an injection for a dental procedure, but patch testing also revealed delayed-type hypersensitivity to the anesthetic.\textsuperscript{23}

Adding more confusion to the scenario is the possibility of cross-sensitization. Klein et al\textsuperscript{24} reported a patient who had a delayed-type reaction to mepivacaine. Patch testing results were positive for lidocaine and mepivacaine sensitivities, but the lidocaine patch revealed a more exuberant reaction. The patient’s medical history was notable for exposure to lidocaine.\textsuperscript{24}

Our first patient reported a medical history positive for a pruritic rash days after an injection of local anesthetic for both dental surgery and breast biopsy. Her patch test result to lidocaine was strongly positive, and intradermal injection also revealed a pink papular eruption consistent with a delayed-type hypersensitivity reaction. The second patient had a similar history of a pruritic rash after podiatric surgery. Both patch and intradermal test results were positive.

Our other 2 patients had positive patch testing results to lidocaine but failed to have a response to the intradermal injection. Interestingly, only the patients with positive clinical histories of sensitivity to anesthetic injection proved positive on intradermal challenge. Thus, we believe that clinical history plays a critical role in evaluating possible sensitivity to anesthetic agents.

The best means in which to evaluate a positive patch test result is through intradermal injection of the anesthetic agent. Many positive patch test results to local anesthetics are not confirmed by intradermal injection. Ruwicka et al\textsuperscript{25} performed patch testing to benzocaine and lidocaine mix. Of 104 patients with positive patch test results, only 14 patients yielded positive intradermal test results to single anesthetic agents. These positive results were divided, with 10 patients having immediate intracutaneous reactions, and 9 patients having delayed hypersensitivity (5 patients overlapped in these groups). None of the 104 patients had an intracutaneous reaction to lidocaine.\textsuperscript{25}

Intradermal challenge should be done with preservative-free anesthetic. It is also advisable to remove the rubber stopper from the bottle prior to drawing up the anesthetic because patients with sensitivities to rubber compounds may have a reaction to these compounds on the needle, yielding a false-positive intradermal test result. Such testing will have increasing importance, since local anesthetics are commonly used for medical purposes and are found in many over-the-counter products.\textsuperscript{26,27} Indeed, sensitization to lidocaine may be due in part to these over-the-counter exposures (Table 1).

The NACDG preliminary interim report dated February 2002 (2001-2002 study period) compiled the patch test results from their centers and found that of the 1030 patients patch tested to lidocaine, 12

<table>
<thead>
<tr>
<th>Table 1. Over-the-Counter Medications Containing Lidocaine or Lidocaine Hydrochloride</th>
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<tbody>
<tr>
<td><strong>Bactine Antiseptic-Anesthetic First Aid Liquid</strong> (Bayer Consumer Care Division, Morristown, NJ)</td>
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<tr>
<td><strong>Campho-phenique Triple Antibiotic</strong> (Bayer Consumer Care Division)</td>
</tr>
<tr>
<td><strong>ELA-Max</strong> (Ferndale Laboratories Inc, Ferndale, Mich)</td>
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<tr>
<td><strong>Family Medic Afterburn</strong> (Tender Corporation, Littleton, NH)</td>
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<tr>
<td><strong>Gold Bond Medicated Anti-Itch Cream</strong> (Chattem, Inc, Chattanooga, Tenn)</td>
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<tr>
<td><strong>Mycitracin Plus</strong> (McNeil Consumer, Ft Washington, Pa)</td>
</tr>
<tr>
<td><strong>Norwegian Formula Soothing Relief Anti-Itch Moisturizer</strong> (Neutrogena Corporation, Los Angeles, Calif)</td>
</tr>
<tr>
<td><strong>Palmer’s Medicated Aloe Vera Formula</strong> (E. T. Browne Drug Co, Inc, Englewood Cliffs, NJ)</td>
</tr>
<tr>
<td><strong>Solairen Aloe Extra Burn Relief</strong> (Schering-Plough Healthcare Products, Kenilworth, NJ)</td>
</tr>
<tr>
<td><strong>Triboitic Plus</strong> (Thompson Medical Company, Inc, West Palm Beach, Fla)</td>
</tr>
<tr>
<td><strong>Unguentine Plus</strong> (Mentholatum, Orchard Park, NY)</td>
</tr>
<tr>
<td><strong>Zilacitin-L</strong> (Zila Pharmaceuticals, Phoenix, Ariz)</td>
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</tbody>
</table>

Weightman and Turner\textsuperscript{28} reported 29 cases of type IV hypersensitivity to lidocaine, which were seen in their patch test clinic over a 21-year period. Of these patients, 23 were able to point to an over-the-counter lidocaine exposure as a possible source of sensitization. There are also numerous over-the-counter products that expose patients to other anesthetic agents.

If patients have a positive intradermal reaction to an injectable anesthetic, they should be provided a listing of injectable anesthetic products that may be substituted. This list may be generated from negative patch test results. There are numerous injectable anesthetics\textsuperscript{29-31} (Table 2), which allows for easy therapeutic substitution.

Of note, the NACDG preliminary interim report dated February 2002 (2001-2002 study period) compiled the patch test results from their centers and found that of the 1030 patients patch tested to lidocaine, 12
(0.7%) had positive patch test reactions. This suggests that lidocaine sensitivity may not be rare, at least in patch test clinic patients (unpublished data, NACDG [2001-2002 patch test results], January 27, 2002).

The cases of lidocaine type IV sensitivity discussed here raise important issues. History of exposure to these medicaments and potential reactions is important when evaluating a positive patch test result to lidocaine. Likewise, it is imperative to confirm a positive patch test result to an anesthetic agent with an intradermal test. A true sensitivity may make necessary further patch testing to provide the patient with a list of "safe" anesthetics. Our findings indicate that lidocaine delayed-type hypersensitivity is more common than previously thought, and given its frequent use, may become more widespread.

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Corresponding author and reprints: Christine L. Mackley, MD, Department of Dermatology HU14, PO Box 850, Hershey, PA 17033 (e-mail: cmackley@psu.edu).

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