

# Contact Allergy to Lidocaine: A Report of Sixteen Cases

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Lidocaine is used widely as an injectable local anesthetic, occasionally as an intravenous drug for cardiac arrhythmias, and increasingly as a topical anesthetic. Reports of allergic contact dermatitis and delayed hypersensitivity reactions to this "amide" anesthetic are limited. We report 16 cases of lidocaine contact allergy seen over 5 years. Concomitant patch-test reactions occurred with neomycin 20% (10 cases), bacitracin 20% (9 cases), fragrance mix 8% (3 cases), balsam of Peru 25% (2 cases), and dibucaine 2.5% and benzocaine 5% (1 case each). Patch tests with lidocaine dilutions (in petrolatum) gave the following results: 10% (3 of 4 positive reactions), 5% (4 of 6 positive reactions), and 1% (3 of 6 positive reactions). Intradermal testing with lidocaine 1%, mepivacaine 2%, and bupivacaine 0.5% was performed on 8 patients, resulting in positive reactions to lidocaine in 3 patients and to mepivacaine in 1 patient. Bupivacaine yielded negative results in each of the 8 patients. Relevance of delayed reactions to injectable lidocaine was definite in 2 cases; past, probable, and unknown in 1 case each; and possible in 11 cases. Delayed hypersensitivity to lidocaine may present as "suture allergy," treatment failure, typical contact allergy, or other local skin or dental reactions. Allergen substitution is based on further patch and intradermal testing, the results of which may be discordant.

THE USE OF CHEMICAL SUBSTANCES for preventing or treating local pain has its origin in South America. For centuries, coca leaves (*Erythroxylon coca*) have been chewed by Andean natives to prevent hunger and to increase endurance. In 1860, cocaine was isolated by Nieman, who noted that it caused a numbing of the tongue. But it was not until 1884 that cocaine was introduced clinically and not until 1905 that procaine was introduced as the first safe local anesthetic. The major breakthrough in the chemistry of local anesthetic agents occurred in 1943, when Lofgren synthesized lidocaine, an amide derivative of diethylamino acid.<sup>1</sup>

Nearly 2 million injections of local anesthetics are given daily in the United States.<sup>2</sup> True immunologic reactions to a local anesthetic are rare and account for less than 1% of all adverse reactions to these preparations.<sup>1</sup> Lidocaine is widely used as an injectable local anesthetic (intravenously for cardiac arrhythmias) and as a topical anesthetic. Reports of allergic contact dermatitis (ACD) and delayed hypersensitivity reactions to this "amide" anesthetic are even more limited. Lidocaine 15% was added to the North American Contact Dermatitis Group (NACDG) Standard Allergen Tray in 2001,<sup>3</sup> after an Australian study reported 29 cases of ACD from lignocaine (lidocaine).<sup>4</sup>

## Materials and Methods

The results of all patients patch-tested with the NACDG Standard Allergen Tray in our department between January 2001 and December 2005 were reviewed; 1,143 patients were patch-tested according to methods described by the NACDG, with Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster Aksjeselskap, Vennesla, Norway). The patches remained in place for 48 hours, and readings were performed on day (D)2 or D3 and again on D6 or D7. Patch-test reactions were interpreted and scored as follows: negative (0); macular erythema (?); erythema, infiltration, and possibly papules (+); erythematous papules and/or vesicles (++); and spreading blisters and/or crusting with ulceration (+++).<sup>3,5</sup> Selected patients were patch-tested with additional lidocaine dilutions (10%, 5%, and 1%).

In selected cases, intradermal tests were performed on the inner aspect of the forearm with 0.1 mL each of preservative-free lidocaine 1%,<sup>6</sup> mepivacaine 2%, and bupivacaine 0.5%. Test sites were evaluated at 48 hours for erythema and induration. Relevance of lidocaine hypersensitivity was determined by the patient's history of prior lidocaine exposure. As per NACDG definitions, relevance was defined as "definite" if the reaction to a use test with the putative item containing the suspected allergen or to a patch test with the object or product containing the allergen was positive; "probable" if the substance identified by patch testing could be verified as present in the known skin contactants of the patient; "possible" if the patient was exposed to circumstances in

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which skin contact with materials known to contain the putative allergen likely occurred;<sup>3</sup> “past” if a positive patch-test reaction could be explained by a previous and unrelated episode of contact dermatitis; and “unknown” if there was no evidence of relevance even after extensive investigations.<sup>7</sup>

## Results

During the study period, 1,143 patients were patch-tested with the NACDG Standard Allergen Tray (Tables 1 and 2; Figs 1 and 2). The two definitely relevant cases are presented here in more detail.

### Case 1 (Patient 1)

A 28-year-old woman presented with a history of a postoperative allergic reaction. She had undergone breast augmentation surgery 2 months earlier, during which lidocaine 1% was injected in the periareolar area and the breast pockets were irrigated with bacitracin. Over the next postoperative 2 days, she developed a pruritic vesicobullous generalized rash. On repeated occasions in the past, the patient had developed localized “suture reactions” with vesicles and erythema several millimeters around the sutures each time, occurring 24 to 35 hours after surgical procedures and responding to topical steroids.

Patch-testing with allergens on the NACDG tray, lidocaine dilutions, and suture materials showed positive reactions to lidocaine 15% (++), 10% (+), 5% (+) and 1% (+); also, reactions to neomycin 20%, bacitracin 20%, cobalt 1%, and gold 0.5% were positive. Pertinent negative reactions to the amides dibucaine 2.5% and prilocaine 2.5% and to the esters benzocaine 5% and tetracaine 1% were observed. Intradermal test results with lidocaine 1%, mepivacaine 2%, and bupivacaine 0.5% were positive for lidocaine and mepivacaine. The positive lidocaine intradermal test reaction was not vesicobullous as was noted in the postoperative clinical reaction. The patient had a negative skin-prick test reaction to latex and lidocaine. We recommended the use of bupivacaine for future interventions that require a local anesthetic.

### Case 2 (Patient 10)

A 51-year-old woman presented for patch testing prior to orthopedic surgery. She reported past relevant delayed hypersensitivity reactions to injectable lidocaine administered intraarticularly, with localized and some disseminated rash and swelling. The patient also had a history of metal allergy to gold and cobalt. Patch tests with the NACDG tray and the Cleveland Clinic prosthesis tray revealed positive reactions to lidocaine 15% (+), nickel 2.5%, and palladium 2%. Patch tests with dibucaine 2.5% and benzocaine 5% gave negative results. Intradermal

**Table 1.** Positive Test Results of 16 Lidocaine-Allergic Patients

| <i>Chemical</i>        | <i>Concentration and Vehicle</i> | <i>D2 or D3*</i> | <i>D6 or D7*</i> |
|------------------------|----------------------------------|------------------|------------------|
| Patch test, NACDG tray |                                  |                  |                  |
| Lidocaine              | 15% pet                          | 10/16            | 16/16            |
| Benzocaine             | 5% pet                           | 1/16             | 1/16             |
| Dibucaine              | 2.5% pet                         | 0/16             | 1/16             |
| Prilocaine (2001–2002) | 2.5% pet                         | 0/9              | 0/9              |
| Tetracaine (2001–2004) | 1% pet                           | 0/13             | 0/13             |
| Patch test, dilutions  |                                  |                  |                  |
| Lidocaine              | 1% pet                           | 3/6              | —                |
| Lidocaine              | 5% pet                           | 4/6              | —                |
| Lidocaine              | 10% pet                          | 3/4              | —                |
| Intradermal test       |                                  |                  |                  |
| Lidocaine              | 1%                               | 3/8              | —                |
| Bupivacaine            | 0.5%                             | 0/8              | —                |
| Mepivacaine            | 2%                               | 1/8              | —                |

D= day; NACDG = North American Contact Dermatitis Group; pet = petrolatum.

\*Number of positive test results per number of lidocaine-allergic patients tested.

**Table 2.** Test Results for 16 Patients with Allergic Contact Dermatitis from Lidocaine between 2001 and 2005

| Patient | Age (yr) | Sex | Distribution of Dermatitis | Allergens Yielding Positive PT Reactions                                                                                                       | L 15% PT (D2/D3) (D6/D7) | L Dilutional PT (1%) (5%) (10%) | ID Test (L 1%) (MV 2%) (B 0.5%) | Relevance |
|---------|----------|-----|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|---------------------------------|---------------------------------|-----------|
| 1       | 28       | F   | Generalized                | Lidocaine, neomycin, bacitracin, gold, cobalt                                                                                                  | (++) (+)                 | (+) (+) (+)                     | (1+) (1+) (0)                   | Definite  |
| 2       | 40       | M   | Groin                      | Lidocaine, neomycin, bacitracin                                                                                                                | (0) (+)                  | NT                              | NT                              | Possible  |
| 3       | 40       | M   | Hands, feet                | Lidocaine, neomycin, bacitracin, shoe piece                                                                                                    | (?) (+)                  | NT                              | (0) (0) (0)                     | Possible  |
| 4       | 40       | M   | Generalized                | Lidocaine                                                                                                                                      | (+) (+)                  | (0) (0) (0)                     | (0) (0) (0)                     | Possible  |
| 5       | 41       | F   | Hands                      | Lidocaine, neomycin, balsam of Peru, fragrance mix, ylang ylang oil, thimerosal, cocamide DEA                                                  | (++) (+)                 | (+) (++) (++)                   | (0) (0) (0)                     | Possible  |
| 6       | 42       | F   | Hands                      | Lidocaine, neomycin, bacitracin, 2-HEMA, PGDMA, HPMA, EGDMA, THFMA                                                                             | (+++)                    | (++) (++) (NT)                  | (1+) (0) (0)                    | Possible  |
| 7       | 44       | M   | Hands, feet                | Lidocaine, dibucaine, neomycin, bacitracin                                                                                                     | (++) (++)                | NT                              | (1+) (0) (0)                    | Probable  |
| 8       | 46       | F   | Hands                      | Lidocaine, carba mix, thiuram mix, p-tert-butylphenol formaldehyde resin, cocamide DEA, glutaral, tea tree oil                                 | (+) (+)                  | NT                              | NT                              | Possible  |
| 9       | 49       | M   | Generalized                | Lidocaine, formaldehyde, quaternium-15, nickel                                                                                                 | (++) (+)                 | NT                              | NT                              | Possible  |
| 10      | 51       | F   | Generalized                | Lidocaine, nickel, palladium                                                                                                                   | (++) (+)                 | NT                              | NT                              | Definite  |
| 11      | 52       | M   | Arms, neck, face           | Lidocaine                                                                                                                                      | (0) (+)                  | NT                              | NT                              | Possible  |
| 12      | 59       | F   | Hands                      | Lidocaine, benzocaine, neomycin, bacitracin, MBT, carba mix, mercapto mix, PPD, potassium dichromate, White Diamonds body lotion,* rubber band | (?) (+)                  | (0) (?) (+)                     | (0) (0) (0)                     | Past      |
| 13      | 60       | M   | Hands, feet                | Lidocaine, neomycin, bacitracin, MBT, mercapto mix, Disperse Blue                                                                              | (0) (++)                 | NT                              | NT                              | Possible  |
| 14      | 64       | F   | Generalized                | Lidocaine, neomycin, bacitracin, gold, Nutraderm lotion <sup>†</sup>                                                                           | (++) (+)                 | NT                              | (0) (0) (0)                     | Possible  |
| 15      | 72       | M   | Hands, arms, legs          | Lidocaine, neomycin, bacitracin, fragrance mix, formaldehyde, diazolidinylurea, imidazolidinylurea, cinnamic aldehyde                          | (0) (++)                 | NT                              | NT                              | Unknown   |
| 16      | 77       | M   | Arms, chest                | Lidocaine, balsam of Peru, fragrance mix                                                                                                       | (+++)                    | (+) (0) (0) (NT)                | NT                              | Possible  |

B = bupivacaine; DEA = diethanolamine; D = day; EGDMA = ethylene glycol dimethacrylate; F = female; 2-HEMA = 2-hydroxyethyl methacrylate; HPMA = 2-hydroxypropyl methacrylate; ID = intradermal test; L = lidocaine; M = male; MBT = mercaptobenzothiazole; MV = mepivacaine; NT = not tested; PGDMA = polyethylene glycol dimethacrylate; PPD = para-phenylenediamine; PT = patch test; THFMA = tetrahydrofurfuryl methacrylate.

\*Cosmair Inc., New York, NY.

<sup>†</sup>Galderma, S.A. Fort Worth, TX.

testing was not performed. The patient was instructed to avoid lidocaine in future procedures.

## Discussion

Local anesthetics are classified into two main classes: the ester group includes benzocaine, procaine, tetracaine, oxybuprocaine, chlorprocaine, and butoform; the amide group includes lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, and dibucaine. All local anesthetics share three structural components: a lipophilic

group, an ionizable hydrophilic group, and an intermediate group. Variations in intermediate chains account for the principal differences between ester and amide agents.<sup>8</sup> Esters are associated with a higher incidence of allergic reactions due to a para-aminobenzoic acid (PABA) metabolite. Amide agents do not undergo such metabolism. However, preservative compounds (methylparaben) used in amide anesthetic preparations are metabolized to PABA.<sup>1</sup> Anesthetics in the ester group cross-react with each other but not usually with local anesthetics in the amide group. However, cross-sensitivity between esters

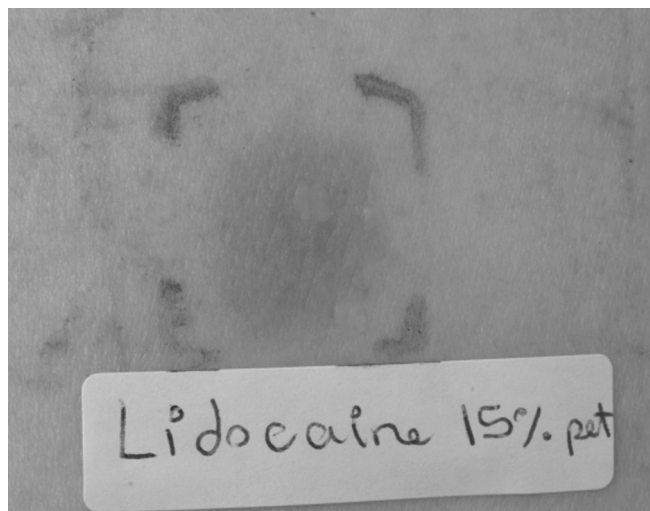


**Figure 1.** Strong patch-test reaction to lidocaine 15% at day 7.

and amides has been reported.<sup>9</sup> Cross-reactivity within the amide group as a whole is much lower.<sup>10</sup>

Despite the frequent use of lidocaine as an anesthetic and its occasional use as a therapeutic agent, reports of ACD from lidocaine and delayed hypersensitivity reactions to it are even more limited. However, such responses appear to have increased because of lidocaine's more frequent use in topical therapies.

We report on 16 patients who had positive patch-test reactions to lidocaine. The patients ranged in age from 28 to 77 years. The dermatitis involved the hands or the hands and feet in 8 patients, the arms in 3 cases, and the face and

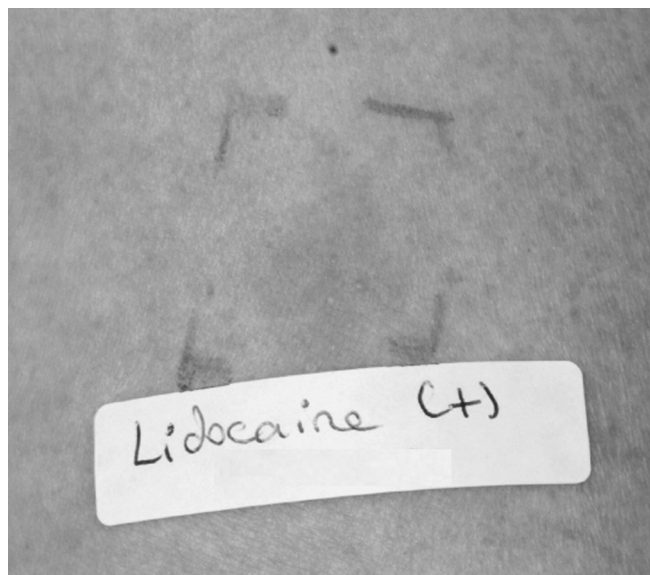


**Figure 2.** Positive response to intradermal test with preservative-free lidocaine 1%.

the groin in one case each; it was disseminated in 5 patients. Concomitant patch-test reactions occurred with neomycin 20% (10 cases), bacitracin 20% (9 cases), fragrance mix 8% (3 cases), balsam of Peru 25% (2 cases), dibucaine 2.5% (1 case), and benzocaine 5% (1 case). Patch tests with lidocaine dilutions (in petrolatum) gave the following results: 3 of 4 patients, 4 of 6 patients, and 3 of 6 patients reacted positively to 10%, 5%, and 1% dilutions, respectively. Of the two patients who had negative reactions to lidocaine dilutions, one (patient 16) had +++ and + reactions to lidocaine 15% at the first and second readings, respectively, and was not tested with lidocaine 10% or intradermally. The other patient (patient 4) had a + reaction to lidocaine 15% at both readings and had negative results with all lidocaine patch-test dilutions as well as on intradermal testing. Intradermal testing with lidocaine 1%, mepivacaine 2%, and bupivacaine 0.5% was performed on 8 patients; 3 had positive reactions to lidocaine, and 1 had a positive reaction to mepivacaine. Results for bupivacaine were negative for each of the 8 patients.

Relevance was definite in 2 cases, probable in 1, possible in 11, and unknown in 1. Past relevance was observed in 1 case. The two patients with definite relevance related overt histories of localized reactions (patient 1) and localized and generalized reactions (patient 10) to injectable lidocaine. Whether initial sensitization occurred by the injectable route rather than the topical route is uncertain in these two cases. Many of the other patients could not recall specific use of lidocaine-containing topical products but likely were exposed to them as well as to injectable lidocaine.

Possible explanations for the discordance between the results of the patch tests and the intradermal tests include false-positive patch-test reactions to lidocaine, allergy to a contaminant or an impurity, and compound allergy, especially since a number of patch-test-positive patients drop off with dilutional patch testing. Repeated open application tests with lidocaine would be an additional method to help confirm the relevance of positive patch-test reactions to topical lidocaine.<sup>7</sup> Recommended or reported patch-test concentrations for lidocaine vary between 5% and 15%.<sup>4,6,8,11</sup> Additional dilutional testing may be helpful in determining an appropriate patch-test concentration.

Over-the-counter lidocaine products purchased for recurrent or chronic medical conditions are a likely source of exposure and sensitization to lidocaine, antihemorrhoidal preparations being the most commonly reported cause of ACD from lidocaine.<sup>6,12</sup> Table 3 lists selected

currently available over-the-counter and prescription topical lidocaine products.

Lidocaine and several other local anesthetics were added to the NACDG tray in 2001 to determine whether the introduction of eutectic anesthetic preparations had resulted in a rise in allergic reactions to their constituents.<sup>3</sup> NACDG patch-test results from 2001 to 2002 revealed that 0.7% of tested patients reacted to lidocaine, 1.7% reacted to benzocaine, 0.6% reacted to tetracaine, and 0.9% reacted to dibucaine.<sup>3</sup> We identified 1.4% of patients who

reacted positively to lidocaine over the 5-year period of our study.

## Conclusion

Delayed hypersensitivity to lidocaine may present as “suture allergy,” as in Case 1. Lidocaine allergy also should be considered in the differential diagnosis of a localized delayed-type hypersensitivity reaction that develops and recurs at sites of surgical procedures.<sup>8</sup> Other

**Table 3.** Selected over-the-Counter and Prescription Topical Products Containing Lidocaine

| <i>Brand Name</i>                                                  | <i>Manufacturer (Web Site)</i>                                                               | <i>Lidocaine Strength</i> |
|--------------------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------|
| <b>Over-the-counter products</b>                                   |                                                                                              |                           |
| Aloe Ice Sunburn Relief Jelly                                      | Aloe Up ( <a href="http://www.aloeupflorida.com">www.aloeupflorida.com</a> )                 | 1.9%                      |
| Banana Boat Sooth-A-Caine Pain Relieving Gel                       | Sun Pharma ( <a href="http://www.drugstore.com">www.drugstore.com</a> )                      | 0.7%                      |
| Bactine Antiseptic-Anesthetic First Aid Liquid                     | Bayer Consumer ( <a href="http://www.drugs.com">www.drugs.com</a> )                          | 2.5%                      |
| Band-Aid Hurt-Free Antiseptic Wash                                 | Band Aid ( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> )              | 2%                        |
| Cool Aloe I.C.E. Lidocaine Gel                                     | Hawaiian Tropic ( <a href="http://www.hawaiiantropic.com">www.hawaiiantropic.com</a> )       | 0.8%                      |
| Burn-O-Jel                                                         | S.S.S. Company ( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> )        | 0.5%                      |
| BurnStuff Anti-Bacterial Pain Relieving Cream                      | Activ ( <a href="http://www.walgreens.com">www.walgreens.com</a> )                           | 2%                        |
| DermaFlex Gel                                                      | Zila Pharma ( <a href="http://www.nlm.nih.gov">www.nlm.nih.gov</a> )                         | 2.5%                      |
| Dr. Scholl's Cracked Heel Relief                                   | Schering-Plough ( <a href="http://www.drugs.com">www.drugs.com</a> )                         | 2%                        |
| L-M-X4 (formerly ELA-Max)                                          | Ferndale Lab Inc ( <a href="http://www.drugs.com">www.drugs.com</a> )                        | 4%                        |
| Medi-Quick Spray                                                   | Quantum Pharma ( <a href="http://www.americarx.com">www.americarx.com</a> )                  | 2%                        |
| Neutrogena Norwegian Formula Soothing Relief Anti-Itch Moisturizer | Neutrogena Corp ( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> )       | 2%                        |
| Put It On Ice Pain-Relieving Gel with Lidocaine                    | True Blue Spa ( <a href="http://www.bathandbodyworks.com">www.bathandbodyworks.com</a> )     | NA                        |
| Solarcaine Aloe Extra Burn Relief Gel, Cream, and Spray            | Schering-Plough ( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> )       | 0.5%                      |
| Soothing Repair Ointment                                           | Peter Thomas Roth Labs ( <a href="http://www.shopzilla.com">www.shopzilla.com</a> )          | 2%                        |
| Sunburn Relief Aloe Lotion                                         | South Beach Sun ( <a href="http://www.southbeachsun.com">www.southbeachsun.com</a> )         | NA                        |
| TheraPatch Cold Sore Patch                                         | LecTec ( <a href="http://www.lectec.com">www.lectec.com</a> )                                | 4%                        |
| Topical Analgesic Cream for Bikini Area Irritation                 | Bikini Zone ( <a href="http://www.walgreens.com">www.walgreens.com</a> )                     | 2%                        |
| Xylocaine ointment                                                 | Astra ( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> )                 | 2.5%                      |
| Zilactin-L Liquid                                                  | Zila Pharma ( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> )           | 2.5%                      |
| <b>Prescription products</b>                                       |                                                                                              |                           |
| Anestacon Jelly                                                    | PolyMedica Pharma<br>( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> )  | 2%                        |
| Dentipatch Transmucosal Patch                                      | Noven Pharma ( <a href="http://www.medications.com">www.medications.com</a> )                | 46.1 mg                   |
| EMLA Cream and Disc                                                | AstraZeneca ( <a href="http://www.astrazeneca-us.com">www.astrazeneca-us.com</a> )           | 2.5%                      |
| Lida-Mantle Cream                                                  | Doak Dermatologics<br>( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> ) | 3%                        |
| Lidoderm Patch                                                     | Endo Pharma ( <a href="http://www.uptodateonline.com">www.uptodateonline.com</a> )           | 5%                        |
| Numby Stuff Electrodes                                             | Iomed ( <a href="http://www.iomed.com">www.iomed.com</a> )                                   | 2%                        |
| Xylocaine Oral Spray                                               | AstraZeneca ( <a href="http://www.astrazeneca-us.com">www.astrazeneca-us.com</a> )           | 10%                       |
| Xylocaine Liquid, Ointment                                         | AstraZeneca ( <a href="http://www.astrazeneca-us.com">www.astrazeneca-us.com</a> )           | 5%                        |
| Xylocaine Topical Solution                                         | AstraZeneca ( <a href="http://www.astrazeneca-us.com">www.astrazeneca-us.com</a> )           | 4%                        |
| Xylocaine Jelly                                                    | AstraZeneca ( <a href="http://www.astrazeneca-us.com">www.astrazeneca-us.com</a> )           | 2%                        |

NA = Not available from distributor.

clinical presentations are treatment failure, typical contact allergy, and other local skin or dental reactions.

We concur with Mackley and colleagues<sup>6</sup> that if a patient displays patch-test sensitivity to a local anesthetic, further patch and intradermal testing is recommended although the results may be discordant.<sup>13</sup>

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