

Delayed-type allergy to articaine with cross-reactivity to other local anesthetics from the amide group



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Clinical Implications

- The authors report a case of delayed-type hypersensitivity to articaine with cross-reactivity with bupivacaine and lidocaine and good tolerance to mepivacaine. The exact antigenic epitope is still not known and cross-reactivity among amide local anesthetics is not predictable.

TO THE EDITOR:

Adverse reactions to local anesthetics (LAs) are usually related to vasovagal reflex, anxiety, or toxic effects of epinephrine. Hypersensitivity reactions are rare and account for less than 1% of all adverse reactions. Allergic reactions to LAs can be IgE-mediated (type I) and/or T-cell-mediated (type IV).¹ LAs are classified into benzoic acid esters (piperocaine, benzocaine, chloroprocaine, procaine, tetracaine, cocaine) and amide derivatives (mepivacaine, lidocaine, bupivacaine, articaine, ropivacaine, prilocaine). Ester LAs are metabolized by plasmatic esterases with production of p-aminobenzoic acid, which is highly antigenic. For this reason, allergic reactions, mainly cell-mediated, are more frequent with ester than with amide compounds.² Cross-reactivity between amide compounds is not well defined, but the meta-xylene aromatic ring (which is shared by mepivacaine, lidocaine, and bupivacaine) has been recently identified as a possible antigenic determinant.³

We present the case of a 42-year-old woman who experienced local angioedema followed by an eczematous reaction of the left cheek and of the upper neck, 24 hours after the use of articaine with epinephrine (Figure 1) for a dental procedure (using classic direct inferior alveolar nerve block). The reaction resolved within 15 days. After a subsequent exposure to articaine for another dental procedure, the same symptoms reoccurred within 16 hours, and lasted 30 days despite treatment with oral corticosteroids. The patient denied any previous drug reactions and reported a clinical history of contact dermatitis with some jewelry.

She underwent patch tests with a standard panel of contact allergens (SIDAPA Series, Chemotechnique Diagnostics, Euro-medical srl, Calolziocorte, Italy), a latex extract (ALK-Abelló, Milan, Italy), undiluted articaine 40 mg/mL with epinephrine (Cartidont, Curaden Healthcare, Saronno, Italy), and sodium metabisulphite 1% (AllergEAZE, SmartPractice, Phoenix, Ariz). Patch tests with LAs were performed, putting 2 drops of the undiluted solutions on patch test chambers (AllergEAZE), which were applied on the back and removed after 2 days. Readings were made after 48 and 72 hours and patch test results were evaluated according to international guidelines.^{4,5}

Patch test results with nickel sulfate and articaine were positive (++ and +, respectively) (Figure 2).

Because of the need of an LA to complete dental procedures, the patient underwent patch tests with bupivacaine 5 mg/mL (Bupivacaina Angelini, Angelini Spa, Rome, Italy), lidocaine 20 mg/mL (Lidocaine cloridrato, Bioindustria L.i.m. Spa, Novi Ligure, Italy), and mepivacaine 20 mg/mL (Mepicain 2%, Monico Spa, Venice/Mestre, Italy) to identify a safe alternative LA. Patch tests were positive for lidocaine (+) and bupivacaine (+) but negative for mepivacaine. Patch test results with LAs, also performed in 10 healthy volunteers, were negative, confirming that the concentration used did not yield false-positive results.

Before assessing tolerability we also performed a delayed reading intradermal test with mepivacaine to definitively exclude a delayed hypersensitivity to this drug. Delayed reading intradermal test with a 1/10 dilution of mepivacaine was also negative and so we decided to perform an open subcutaneous challenge test. On the first day, the patient received total 0.3 mL of mepivacaine 2% (0.1 mL of 1:10 solution—0.1–0.2 mL of pure solution administered hourly); on the second day, after a week, she received 1.8 mL of mepivacaine (0.1–0.3–0.4–1 mL of pure solution administered hourly) with no immediate or delayed hypersensitivity reactions. After the test the patient completed dental procedures using local anesthesia with mepivacaine without further reactions.

Despite the wide use of LAs in clinical practice, the rate of true allergic reactions is rare, about 1%.¹ Para-aminobenzoic acid is a common metabolite of ester-type LAs and it explains cross-reactivity among anesthetics belonging to this class. In contrast, a specific pattern of cross-reactivity between amides has not been identified.

Some authors have found a significant cross-reactivity between lidocaine and mepivacaine in type I allergic reactions,⁶ and there is a case report of cross-reactivity between mepivacaine, lidocaine, and ropivacaine with good tolerance to bupivacaine and levo-bupivacaine.⁷ With regard to delayed-type allergy to LAs, the pattern of cross-reactivity seems linked to a meta-xylene ring that is thought to be the common antigenic determinant of lidocaine, bupivacaine, and mepivacaine.³

The pattern of cross-reactivity among amide LAs is still not clear. Although some authors found no cross-reactivity between lidocaine and bupivacaine,¹ which both share the meta-xylene ring, others found cross-reactivity between bupivacaine and mepivacaine and good tolerance to articaine.⁸ There are no previous reports of cross-reactivity between articaine and the other amide LAs. Articaine has a thiophen ring, whereas all other amide LAs have a meta-xylene ring. Although we cannot exclude false-positive patch test results to lidocaine and bupivacaine in our patient, on the basis of our findings, we hypothesize that structures other than the aromatic rings can be recognized by T cells.

For these reasons we think allergy testing, even if time consuming, should always be performed to assess cross-reactivity in individual patients and, in case of positive results, to avoid unnecessary and potentially harmful challenge tests.

Cross-reactivity between the aforementioned LAs was also demonstrated by means of a novel *in vitro* test that showed a



FIGURE 1. Erythema of the neck 24 hours after local anesthesia with articaine.



FIGURE 2. Positive patch test result with articaine.

significant increase in eosinophilic cationic protein after the incubation of whole blood with mepivacaine, bupivacaine, and lidocaine in a patient with delayed reactions.⁹ However,

although detection of eosinophilic cationic protein after incubation of whole blood with a drug is promising, it is more expensive than *in vivo* tests, and larger samples are needed to assess sensitivity and negative predictive value. Patch tests (and delayed reading intradermal tests) are simple and cheap diagnostic tests that can be effective in investigating delayed hypersensitivity reactions to LAs. However, challenge tests remains the criterion standard to definitively assess the tolerability of a certain drug.

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