

Allergy to several local anesthetics from the amide group

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Clinical Implications

- Cross-reactivity within the amide group is rare, but it is important to confirm tolerance to another local anesthetic of the group.
- Testing for eosinophilic cationic protein levels after blood incubation with the suspicious drug might be useful to avoid a challenge test, although further studies are needed.

TO THE EDITOR:

Local anesthetics (LAs) are classified into 2 groups: ester and amide compounds. Adverse reactions are frequent, but most of them are attributed to vasovagal reflexes or hemodynamic changes after the injection of LAs with epinephrine.¹ Allergic reactions to LAs are uncommon. The preponderance of evidence suggests that there is no cross-reactivity between ester and amide LAs.² Contact dermatitis (type IV) has been described, particularly induced by the ester group of anesthetics,² and rarely to lidocaine in the amide group.³ Some isolated cases of immediate allergic reactions with mepivacaine or lidocaine have been previously reported. In most of those cases, tolerance to other amide anesthetics was demonstrated as a safe alternative.^{4,5}

We present the case of a 41-year-old woman, previously diagnosed with endometriosis, who had a back nevus surgically removed. Three hours after the local administration of mepivacaine, she experienced an episode of pruritic maculopapular eruption and hives involving the upper side of the trunk, neck, and arms. She recovered completely 48 hours after the administration of intramuscular 6-methylprednisolone and dexchlorpheniramine maleate as well as oral antihistamines for 2 days. She denied any history of urticarial episodes or an adverse reaction to the ingestion of any food or medication. She reported no adverse reaction with the use of cosmetics or after the intake of foods or beverages containing sulphites.

Skin prick testing results with (1) a standard panel of commercially available (ALK-Abelló, Madrid, Spain) allergen extracts (aeroallergens, foods, profilin, gliadin, latex, *Anisakis simplex*), (2) undiluted lidocaine (1%) (Normon, Madrid, Spain), mepivacaine (2%) (Scandinibsa, Inibsa, Barcelona, Spain), and bupivacaine (0.75%) (Inibsa, Barcelona, Spain), (3) phenolated normal saline solution, and (4) histamine 0.1 mg/mL were all negative with the exception of the histamine control. Total serum IgE level was 11.1 kU/L (normal total serum IgE level range, <100 kU/L) (ImmunoCAP System, Thermo Fisher Scientific, Uppsala, Sweden), and total serum

tryptase level was 3.9 µg/L (normal tryptase level range, <11.4 µg/L) (ImmunoCAP system). Complement factors (C3 and C4) and IgG, IgM, and IgA levels in serum were within the normal range.

A single-blind subcutaneous challenge test with lidocaine was performed. Four hours after the administration of a cumulative dose of 1.5 mL, the patient experienced a similar but milder reaction affecting the same involved body area as occurred in the first reaction. Rather than pursuing further *in vivo* testing such as intradermal skin tests to evaluate hypersensitivity and given the very low rate of cross-reactivity among the amide group of LAs, we elected to proceed with another subcutaneous challenge test with bupivacaine 2 weeks later. Two hours after the administration of a cumulative dose of 0.5 mL, she again experienced pruritic exanthema on the torso and neck. She was treated with 60 mg of intravenous 6-methyl-prednisolone and 5 mg of dexchlorpheniramine maleate, with complete resolution of the reaction in 2 hours.

In an attempt to clarify the underlying mechanism of this hypersensitivity reaction, a basophil activation test with bupivacaine, lidocaine, and mepivacaine (10, 5, and 0.5 µg/mL) was performed. Negative results (<3% activation) were obtained for all the drugs tested. A case report of elevated serum eosinophilic cationic protein (ECP) levels associated with a drug-induced perioperative hypersensitivity has been previously described.⁶ On this basis, we performed a novel *in vitro* test at the Clinical Laboratory of the Department of Immunology. One milliliter of heparinized whole blood was incubated with 5 µg/mL of mepivacaine, lidocaine, and bupivacaine for 16 hours at 37°C, 5% CO₂. ECP was quantified with a Phadia 250 assay (Thermo Fisher Scientific) according to the manufacturer's instructions. The Clinical Laboratory of the Department of Immunology meets ISO 9001:2008, and it is certified by the International Certification Network (IQNet). From baseline ECP levels of 18.4 µg/L, a significant rise in ECP levels was obtained with mepivacaine (38.7 µg/L), lidocaine (58.5 µg/L), and bupivacaine (25.2 µg/L), whereas no significant changes were observed when the sample was incubated without drugs (20.4 µg/L).

We described a patient who experienced a delayed cutaneous hypersensitivity reaction following the administration of mepivacaine during a surgical procedure and following positive subcutaneous challenge tests with bupivacaine and lidocaine. We have demonstrated a significant increase in ECP levels after the incubation of whole blood with these drugs *in vitro*. To our knowledge, this is the first reported case in which this procedure has been used to confirm a positive challenge test with these types of drugs. If further utilization of this novel *in vitro* methodology proves predictive of drug hypersensitivity, it would help avoid subsequent costly and untoward challenge procedures. Furthermore, the elevation in ECP level suggests a possible role of eosinophils in these hypersensitivity reactions, although the underlying mechanism of the reaction is not clear. A classical hypersensitivity mechanism appears unlikely due to the negative skin prick testing and basophil activation test results with the drugs involved. It has been recently suggested that meta-xylene, which is present in some amide and ester LAs as well as parabens, could play a role in certain cases of reactions to LAs.⁷ For this

reason, the tolerance of articaine, which is a thiophene derivative, could have been explored in this patient. Unfortunately, the patient has refused any additional testing.

In conclusion, although cross-reactivity among amide-type LAs is rare, in patients with hypersensitivity to one of them, tolerance to other drugs from this group should always be confirmed by performing a challenge test. Further study is needed to assess whether the measurement of ECP levels after the incubation of whole blood with the suspected drugs *in vitro* could be helpful in drug-allergy diagnosis.

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