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I. Ertoy Karagol, O. Yilmaz, A. Bakirtas

Challenge-proven immediate type multiple local anesthetic hypersensitivity in a child

Department of Pediatric Allergy and Asthma,
Gazi University School of Medicine,
Ankara, Turkey

Key Words

child; local anesthetic; immediate hypersensitivity; multiple; challenge-proven

Summary

Adverse reactions to local anesthetics (LA) are commonly reported in patients undergoing dental procedures and other minor surgical procedures. Most of these reactions, however, originate from psychosomatic, vasovagal or toxic conditions and are not immune-mediated. True immune-mediated reactions are considered extremely rare and are estimated to account for less than 1% of all adverse reactions to LA. On the other hand, almost all of the immune-mediated LA reactions that have been reported are related to adult patients. Here, however, we will present a pediatric case proven to be hypersensitive to two different amide-derivative LA's.

Corresponding Author
Hacer Ilbilge Ertoy Karagol
Gazi University School of Medicine,
Department of Pediatric Allergy and Asthma
Ankara, Turkey
E-mail: theilbilge@yahoo.com.au

Introduction

Adverse reactions to local anesthetics (LA) are commonly reported in patients undergoing dental procedures and other minor surgical procedures (1). Most of these reactions, however, originate from psychosomatic, vasovagal or toxic conditions and are not immune-mediated. True immune-mediated reactions are considered extremely rare and are estimated to account for less than 1% of all adverse reactions to LA (1).

While the majority of immune-mediated reactions related to LAs are type IV immune responses, immunoglobulin-E-mediated early responses are less common. Usually responsible for both types of immune reaction are the ester-derivative LAs (e.g., procaine, tetracaine). For this reason, amide-type LAs (e.g., articaine, lidocaine) are generally preferred in daily practice (1,2). On the other hand, almost all of the immune-mediated LA reactions that have been reported are related to adult patients (1,3). Here, however, we will present a pediatric case proven to be hypersensitive to two different amide-derivative LAs.

Case report

A twelve year-old male patient presented for consultation on the recommendation of his dentist, who requested an evaluation of the patient's allergy to LAs. It was reported that three months earlier, the boy had broken out in a facial rash immediately after LAs were administered prior to a tooth extraction. It was learned that the patient was first administered an LA containing the active ingredient articaine for the tooth extraction, and that a rash resembling urticaria had broken out. It was reported that the condition had receded by itself in a half-hour without treatment. A week later, again at the same clinic and again for a tooth extraction, an LA with the active ingredient mepivacaine was administered and a similar type of rash appeared; it was stated

Table 1 *- Results of prick, intradermal and provocation tests with local anesthetics.*

Commercial brand	Anesthetic composition	Skin test results		Subcutaneous provocation[1]	Time to reaction[2] (after last dose)
		Prick tests (1/1 undiluted)	Intradermal tests (1/100 dilution)		
Maxicaine fort® solution for injection 2 ml	80 mg Articaine HCL 0.01 mg Epinephrine 1 mg sodium metabisulfite	-	-	+, Urticaria	1 minute
Safecaine %3® solution for injection 2 ml	60 mg Mepivacaine HCL	-	-	+, Urticaria	5 minute
Citanest %2® solution for injection 20 ml	400 mg Prilocaine HCL 20 mg Methyl parahydroxy-benzoate	-	-	-	-

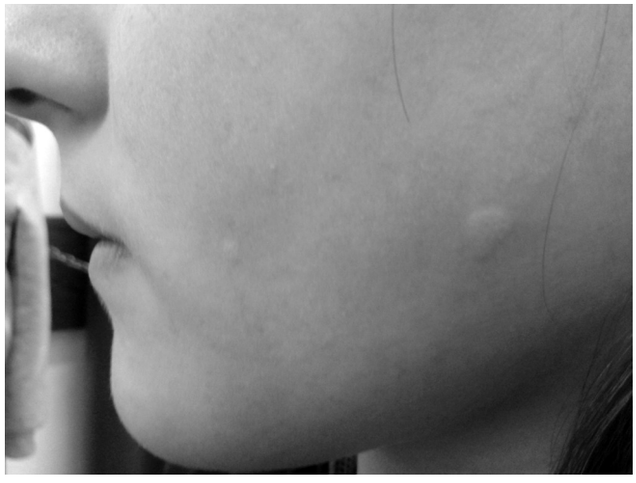
[1] Subcutaneous provocation was performed at 20-minute intervals, at respective doses of 1/10 dilution 0.1 ml, undiluted 0.1 ml and undiluted 1 ml. Before gradual provocation with each 3 local anesthetic, 0.9% saline was used as placebo.
[2] Time elapsed between the application of the subcutaneous undiluted 1 ml local anesthetic and the appearance of the reaction.

that the skin eruption receded within an hour after a single dose of oral antihistamine was administered. In both situations, no other symptom and/or finding that would suggest anaphylaxis was described. The patient had not been taking any antibiotic or analgesic simultaneously in this period. The patient also did not have any concurrent asthma, allergic rhinitis, atopic eczema, food allergy, chronic or stress-related urticaria. The patient and family could not remember whether an LA had been administered for any reason in the past. The patient had no other known illness and his physical examination was normal. The patient's father and sister had been diagnosed with allergic rhinitis. Testing for the two LA agents for which a reaction had been described and latex skin tests were planned, and therefore informed consent was obtained for an allergological workup. Positive (histamine) and negative (normal saline solution) controls were also carried out. The prick test using a commercial latex extract was negative. Additionally, the latex-specific IgE value was negative. Following this, a glove use test was carried out, to which a reaction did not develop. The possibility of a latex allergy was eliminated.

Later, a prick test with the LA preparation (undiluted) given in **table 1** for articaine and intradermal tests using a 1/100 dilution were administered. When the results were seen to be negative, the same articaine preparation was used in a single-blind placebo-controlled gradual subcutaneous (sc) provocation (**table 1**) (4). One minute after the undiluted 1 ml articaines injection, the patient's face started to itch and this was followed by the appearance of 7-8 urticarial plaques in the face and neck (**figure 1**). No other symptom or finding was observed. The patient recovered with single dose of oral desloratadine within 1 hour.

A week later, another prick test with the LA preparation (undiluted) given in **table 1** for mepivacaine and then intradermal tests were administered; the results were negative. As in the articaine provocation, however, immediately following the 1 ml sc mepivacaine injection, the patient's face and hair roots began to itch. Five minutes after the injection, the urticarial plaques developed. No other symptom or finding was observed. All of the urticarial plaques disappeared in 1 hour with a single dose of oral desloratadine. Thus the patient, who had tested negative on the prick and intradermal tests, showed an immediate type of LA hypersensitivity (LA-H) with provocation with articaine and mepivacaine.

Figure 1 *- Urticarial plaques in the face after articaine provocation.*



A test with the safe alternative prilocaine was planned for the patient. The prick test and the subsequent intradermal test performed with prilocaine yielded negative results. Later, single-blind placebo-controlled sc provocation with procaine was performed. After the last dose, the patient was observed in the clinic for an hour and was seen to show no reaction. The dental procedure was then performed successfully without any adverse reaction with prilocaine.

Discussion

This is the first presentation of a pediatric case of challenge-proven multiple immediate type LA-H. The literature does not reveal any other reports of multiple LA-H such as the present pediatric case. Only one other case of a child with LA allergy besides the present one was reported in the literature, but in that case the hypersensitivity was found to be only to mepivacaine. Another difference in this pediatric case was the appearance of a wheal response with mepivacaine. Multiple LA-H has been reported in a limited number of adult causes (5,6,7). The first case was an adult patient who developed anaphylaxis following the administration of 2 amide LAs, levobupivacaine and ropivacaine, with the patient testing positive in the skin tests for the two LAs. Other adult cases developed reactions with both amide and ester LAs (6,7). These patients too had proven hypersensitivity to LAs in the skin prick tests and/or in vitro tests. The current case did not test positive to either the skin prick test or the intradermal test. Avoiding the use of vasoconstrictor agent-containing LA preparations in skin tests that could mask local wheal-and-flare reaction is a recommended protocol (2). In the current case, however, we do not associate the negative testing in the prick and intradermal tests using articaine and mepivacaine with vasoconstrictor content, since only the preparation we used for articaine contained epinephrine (**table 1**). Moreover, positivity in both skin and intradermal tests for IgE-mediated LA-H is already low, with reported rates being around 1% (8). The diagnosis of IgE-mediated LA-H, therefore, is primarily made by provocation (2,8).

Allergy to LAs may be caused by paraben, methyparaben, or metabisulfite used as preservatives (4). Furthermore, cross-reactivity between various LAs and skin prick test positivity has been associated with parabens (1,8). Methylparaben, a preservative commonly found in foods and cosmetics, is used as a preservative in multiuse LAs (4). We know however that the reactions shown by our patient had no relation to paraben because the articaine and mepivacaine preparations that we used in the test and the medications that the dentist used were paraben-free. It was only the prilocaine preparation that we used as a safe alternative that contained paraben (**table 1**). On the other hand, sulfites are antioxidants used to stabilize epinephrine in LA solutions. Today, however, it is reported that sulfites are responsible for non-IgE-mediated reactions in asthma patients in particular. At the same time, the difficulty of determining the role of sulfites in reactions to LA preparations is known (4). Sulfite allergy, however, may be ruled out in this case, since only the preparation with articaine contained sulfite. The preparation used for mepivacaine did not contain sulfite (**table 1**). At this point, another point that needs to be taken into consideration in terms of differential diagnosis is the possibility of developing hypersensitivity caused by preparations used as antiseptic or disinfectant during surgical processes. As for our patient, chlorhexidine hypersensitivity is especially important. Chlorhexidine hypersensitivity is known to develop from home products, such as mouthwash, toothpaste, dressing, ointments, and over the-counter disinfectant solutions (4,9). However, we did not consider chlorhexidine-induced type 1 hypersensitivity in our patient at this stage. Thus, we did not conduct skin test and/or provocation test for this since we know that the dentist who consulted the patient did not use any product that contains chlorhexidine such as mouthwash before, during or after tooth extraction. In addition, we did not use comorbid chlorhexidine during the provocations we conducted in hospital with each 3 LA. However, while doing tests to make a differential diagnosis of hypersensitivity that develops during minor or major surgical processes, the possibility of hypersensitivity caused by latex, chlorhexidine or other antiseptic solutions should be kept in mind.

Cross-reactivity is common within both the ester and amide groups. It is generally accepted that cross-reactivity between esters and amides does not occur because their breakdown products differ. One case with immune reactions to both esters and amides has been reported however (6). Therefore, the researchers of the current study initially planned to perform testing with ester LA; however, prilocaine was determined as a safe alternative in view of the problems experienced in the supply of ester LAs. Considering that the patient was a pediatric case, the researchers did not consider evaluating cross-reactivity for other amide LAs. Additional prick tests and intradermal tests would be frightening and painful for the patient.

In conclusion, true immediate LA-H is an extremely rare condition in childhood. Immediate type multiple LA-H is even rarer. Skin tests rarely support the diagnosis of LA-H and therefore, challenge tests should be carried out in order to establish a definitive diagnosis. Although the reactions were mild, the documented cross-reactivity implies an even stronger recommendation to test the same type local anesthetics before administration.

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