

Adverse reactions to local anesthetics: Analysis of 197 cases

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Background: Adverse drug reactions to local anesthetics are frequently reported. However, little is known about the underlying mechanisms. Therefore we investigated 177 patients with a history of 197 events after application of these drugs.

Methods: The diagnostic approach included prick and intracutaneous tests, provocative challenge tests with causative and unrelated local anesthetics, and in selected cases, radioimmunoassays to detect specific IgE. In addition, tests were performed with preservatives, including sodium metabisulfite and parahydroxybenzoic acid ester.

Results: Results of prick and intracutaneous tests with local anesthetics were all negative. Only three patients reacted after subcutaneous challenge with the causative drug (local anesthetics of the amide type). Although one patient showed a delayed-type response to mepivacaine, two patients had immediate-type reactions to articaine and lidocaine. However, in both cases no specific IgE could be detected. In five patients with positive skin test reactions to preservatives, challenge test results remained negative.

Conclusions: Two immediate-type reactions were not IgE-mediated. In only one of 197 reported adverse reactions were we able to prove delayed-type allergic response. Therefore true allergic reactions caused by local anesthetics are extremely rare. (*J ALLERGY CLIN IMMUNOL* 1996;97:933-7.)

Key words: Local anesthetics, adverse drug reactions, hypersensitivity

Local anesthetics (LAs) are widely used drugs in dentistry and office surgery because they allow a variety of procedures to be performed safely and comfortably. Although generally well-tolerated, patients frequently report adverse reactions to these agents. These responses comprise (1) symptoms not related to the LA, such as psychomotor reactions, (2) dose-related toxic responses in normal individuals, and (3) responses in susceptible persons including both idiosyncratic and true allergic manifestations.¹ In this study we report on our findings obtained from 177 patients who were all referred to the Department of Dermatology (University of Ulm) for allergy workup because of suspected allergic reactions to LAs. They were

Abbreviation used

LAs: Local anesthetics

screened according to a standard protocol. Although a true IgE-mediated immediate-type reaction was never proven, we found evidence of type IV allergy in only one patient and of a pseudoallergic mechanism in two others.

METHODS

Patients

A total of 177 patients (10-year period, 1984 through 1994) with 197 reported episodes of adverse reactions to LAs were included in this study. Age varied from 10 to 74 years (mean age, 36.6 years). Reported symptoms are listed in Table I, and the time course of symptoms is summarized in Table II. In all cases the suspected LA could be identified (Table III) and included predominantly amide-type drugs. Articaine (Ultracaine) was the major anesthetic used in dental procedures. Ultracaine is distributed in 20 European countries and in Canada but is not available on the U.S. market. The chemical structures of the different ester- and amide-type LAs are

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Generic	Chemical structure
Procaine	
Lidocaine	
Butanilicaine	
Prilocaine	
Mepivacaine	
Bupivacaine	
Articaine	

FIG. 1. Chemical structures of the different ester- and amide-type LAs.

shown in Fig. 1. In group I LAs (benzoic acid esters) all substances are considered to be cross-reacting, although it is currently believed that group II LAs (these drugs share an amide structure) may not be substantially cross-reactive with each other or with group I LAs.¹

Standard diagnostic procedures

Standard procedures were performed routinely, beginning with prick testing, followed by intracutaneous testing, and finally by challenge testing after informed consent was obtained (Table IV). In all patients, prick and intracutaneous tests were carried out with the suspected drug and relevant preservatives. Test concentrations for prick and intracutaneous tests with LAs were selected as recommended by Schatz.¹ Both tests were evaluated after 20 minutes and again after 24 hours. Positive histamine controls were done in all cases. To exclude immediate-type reactions to latex as a hidden allergen, which is frequently found in dentists' gloves and dams, we also tested this allergen (low ammonia [0.2%] natural latex from Malaysia, kindly provided by Hartmann, Heidenheim, Germany) in the last 32 cases. Challenge tests with unrelated agents were performed in the first 54 patients, but later on we always challenged

TABLE I. Reported symptoms

Type	Percent
Objective symptoms: urticaria, angioedema, rhinitis, dyspnea, vomiting, chills, speech disorder, tachycardia, arrhythmia, loss of consciousness, cardiac arrest	87.6
Subjective symptoms: fear, sensation of heat, headache, vertigo, paraesthesia, nausea, tenesmus, globus hystericus	12.4

TABLE II. Time course of symptoms

Reported onset	Percent of cases
<30 min	44.1
30-120 min	11.0
>120 min	44.9

TABLE III. Local anesthetics used

LA (generic)	Type	No. of reactions
Articaine	A	82
Mepivacaine	A	43
Lidocaine	A	45
Prilocaine	A	6
Bupivacaine	A	8
Butanilicaine	A	2
Procaine	E	11
Total		197

A, Amide type; E, ester type.

patients with the suspected anesthetics according to the protocol published by Ring.² Briefly, increasing doses of LAs (0.1 ml, 0.2 ml, 0.5 ml, 1.0 ml, and 2.0 ml) were injected subcutaneously on the extensor site of each patient's upper arm at 30-minute intervals. Challenge tests with preservatives were carried out orally in the first 89 patients and subcutaneously in the next 26 patients.

Radioimmunoassay

In a total of 54 selected cases radioimmunoassay was performed according to standard protocol for detecting specific circulating IgE.

Preparation of allergen disks. The LAs were purchased from Steigerwald (Darmstadt, Germany) or Astra (Wedel, Germany), and the test concentration was 1% in each case. For in vitro testing, one can distinguish between two chemical types of LAs. The ester type (procaine) is coupled to cyanogen bromide-activated disks by free NH₂ groups. In the amide type (articaine, mepivacaine, lidocaine) there are two NH groups, which

TABLE IV. Diagnostic schedule

1. Prick test
 - LA agent (1%)
 - Preservatives (parahydroxybenzoic acid ester 1%, sodium metabisulfite 5%)
 - Natural latex
2. Intracutaneous test
 - LA agent (1%, diluted 1:10 in NaCl, 0.03 ml)
3. Challenge test
 - LA agent (1%, SC cumulative dose to 3.8 ml)
 - Preservatives (parahydroxybenzoic acid ester 20 mg PO, sodium metabisulfite 10 mg PO, methyl-4-hydroxybenzoate 4 mg/ml and 20 mg/ml SC, sodium metabisulfite 2 mg/ml and 10 mg/ml)

SC, Subcutaneous; PO, by mouth.

TABLE V. Number of positive test reactions

LA	Prick test	IC test	Challenge	
			Objective	Subjective
Causative agent	0/197	0/170	3/143	7/143
Unrelated agent	0/682	0/533	0/164	4/164

IC, Intracutaneous.

are in tautomeric balance and can in this way be linked to the activated disk.

Test protocol. Briefly, 50 μ l of the patient's undiluted serum was incubated for 3 hours at room temperature with appropriate antigen-containing disks, which were placed in polystyrene tubes (negative control disks were used in addition). After washing the disks, 50 μ l of iodated anti-IgE with tracer from Amersham (Braunschweig, Germany) were added to each tube and incubated overnight at room temperature. The disks were then again washed three times with 0.9% saline solution. The amount of bound radioactivity was determined with a gamma counter, counting for 2 minutes. Double count—number/per minute, as compared with negative control, indicated a positive result. Procaine was used as positive control for the ester-type LAs, and articaine, for the amide-type LAs. The negative control should have the same total IgE as the tested patients' sera.

RESULTS

Prick and intracutaneous tests

Results of both tests with the causative agent and unrelated substances were negative in early and late readings (Table V). Prick tests performed with preservatives, however, revealed positive reactions with sodium metabisulfite in three of 120 cases and with parahydroxybenzoic acid ester in two of 164 cases (early reading) (Table VI). Results of prick tests with natural latex were negative in all 32 patients studied.

TABLE VI. Positive reactions to preservatives

Preservative	Prick test	Challenge	
		Objective	Subjective
Sodium metabisulfite	3/120	0/109	1/109
Parahydroxybenzoic acid ester	2/164	0/121	4/121

TABLE VII. Radioimmunoassays

LAs	Positive results
Articaine	0/19
Mepivacaine	0/14
Lidocaine	0/14
Bupivacaine	0/3
Prilocaine	0/2
Procaine	0/2

Challenge tests

Tests with unrelated agents showed no objective symptoms in 164 patients. Of these patients, four reported subjective symptoms, including nausea and vertigo. Patients challenged with causative agents had objective symptoms in three of 143 cases, whereas seven additional patients had subjective complaints.

The three patients who were first seen with objective positive reactions included one patient with local itching, erythema, and papules at the test site (upper arm) 1 day after subcutaneous injection of mepivacaine with increasing intensity on the next 2 days. A punch biopsy was taken on day 2, and histologic examination revealed a spongiotic epidermis and a perivascular infiltration of mononuclear cells typical of an eczematous reaction. In this case additional patch tests were performed with all LAs summarized in Table III, with the exception of butanilicaine. Results of patch tests were positive with mepivacaine 1% solution (++ after 48 and 72 hours) and with lidocaine 1% solution (+++ after 48 and 72 hours). The criteria for ++ positive patch test results were erythema, infiltration, and papules; whereas +++ positive results included additional blisters. Results of control tests in 10 volunteers were negative. Two other patients had itchy wheals and erythema at the test sites and also on the trunk shortly after exposure to lidocaine or articaine, respectively, which resolved spontaneously within 2 hours.

None of the patients challenged with preservatives showed any objective symptoms, including

TABLE VIII. Review of the literature

Study	No. of cases	Skin tests	Challenge
deShazo and Nelson ³	90	P, U 0/90 P 1:10 0/90 IC, U 10/90 IC 1:10 0/90	SC (0.6 ml): 0/81*†
Le Sellin et al. ⁴	25	P 0/25	SC (0.5 ml): 1/25‡
Chandler et al. ⁵	59	PU 0/59	SC (3.6 ml): 0/59
Escolano et al. ⁶	35	P 1:100-1:1 0/35 IC 1:100-1/10 1/35	SC (1.8 ml) 0/35
Fisher and Graham ⁷	27	IC 1:1000 1/27	SC (2-4 ml): 0/26§
Incaudo et al. ⁸	59	IC 1:10.000-1:10 5/59*	SC (1.6 ml): 0/50)*

P, Prick; U, undiluted; IC, intracutaneous; SC, subcutaneous.

*Only non-cross-reacting substances.

†Four of 10 patients with positive intracutaneous test (undiluted) results.

‡Only challenged with 1% xylocaine.

§Positive reactor to intracutaneous test, not challenged.

||Three of five patients with positive intracutaneous test results.

those five patients who had positive prick test results. Five patients, however, reported subjective complaints (e.g., vertigo, headache, and nausea). In these patients receiving placebo, the same symptoms were observed.

Serologic tests

None of the patients who were tested for specific IgE revealed a positive result in radioimmunoassay, including the two patients with positive challenge test results (articaine and lidocaine) (Table VII).

DISCUSSION

Skin tests

None of our patients showed a positive prick test reaction to undiluted LA. This is in accordance with the data available from the literature; thus far positive prick test results have not been reported (Table VIII).³⁻⁶ Also, results of intracutaneous tests with diluted LAs (1:10) remained negative in our study. Fisher and Graham⁷ observed a single case, and Incaudo et al.⁸ reported on five additional patients with positive wheal-and-flare reactions after intracutaneous exposure to diluted LAs (up to 1:10,000).

Challenge tests with LAs

In the literature all patients challenged with the causative agents had negative results.⁵⁻⁷ Among the investigators who tested non-cross-reacting substances,^{3,4,8} only Le Sellin et al.⁴ found one positive responder to xylocaine 1% among 25 patients. In this case, they observed edema of one

hand 45 minutes after challenge, which was not indicative of a true immediate-type allergic reaction.

In our 177 patients, who were challenged after negative skin test results were observed, we found three positive events (described above in detail). However, it must be taken into account that all of our challenged patients received only small cumulative amounts of tested LAs (total of 3.8 ml). We therefore cannot rule out pseudoallergic reactions, which might have occurred after exposure to higher doses, such as those used in clinical practice (e.g., regional anesthesia).⁹ The reaction in the patient with eczema and positive patch test results was interpreted as a delayed-type allergy. Contact sensitivity to LAs, predominantly from the ester type, associated with positive patch test results is well documented in the literature.¹⁰⁻¹³

In our two patients with immediate-type reactions to articaine and lidocaine after subcutaneous challenge with causative agents, additional exposure to unrelated substances did not result in local or systemic symptoms. The patient who reacted to articaine subsequently tolerated both lidocaine and mepivacaine. The patient with a positive reaction to lidocaine was challenged only with mepivacaine. Interestingly, specific IgE antibodies recognizing articaine or lidocaine could not be detected in either of the patients. Also, Fulcher and Kataris¹⁴ reported on a patient with anaphylactoid reaction after administration of procaine and lidocaine and positive intracutaneous test responses to both substances, in whom anti-IgE antibodies (procaine) could not be detected by RAST.¹⁴ Therefore it can be presumed that direct histamine

release induced by LAs is most likely to be the major mechanism causing wheal-and-flare reactions in these patients. In this context, it is noteworthy that the patient who reacted to lidocaine also reported anaphylactoid reactions after administration of contrast media and acetaminophen.

Challenge tests with preservatives

Challenges with preservatives did not lead to any objective symptoms. Subjective complaints were equally reported after placebo administration, and hence, were not relevant. With regard to sodium metabisulfite only, one immediate-type and one delayed-type response are well documented in the literature.^{15, 16} Concerning parabens, only three cases with immediate-type reactions are documented.¹⁷

In conclusion, delayed-type allergy to injected LAs is clinically characterized by local swelling, which develops within 2 to 24 hours and generally lasts for several days. This type of reaction is best proven by patch testing. Immediate-type hypersensitivity to LAs or preservatives administered in combination with these products can be considered rare events. This holds especially true for IgE-mediated allergic reactions. Because skin test responses in these patients mostly remain negative, subcutaneous challenge is mandatory. In contrast to the recommendation given by Schatz,¹ we suggest challenges with not only unrelated substances but also with the suspected allergen for future applications. In clinical practice, however, various adverse reactions after the injection of LAs are frequently observed. In most cases, they must therefore be attributed to: (1) dose-related toxic events (both cardiovascular and neurotoxic) of the LA or vasoconstrictor (epinephrine or norepinephrine), also induced by accidental intravascular injections; (2) psychomotor reactions; and (3) reactions caused by hidden allergens, such as latex-containing surgical gloves or dams.¹⁸⁻²⁰

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