
Evaluation of adverse reactions to local anesthetics: experience with 236 patients

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Background: Adverse reactions to local anesthetics (LAs) are frequently reported. Although most of these reactions are not immune mediated, many patients are referred to allergy clinics and undergo extensive evaluation.

Objective: To determine the prevalence of true LA allergy among the patients referred for suspected hypersensitivity and to evaluate the usefulness of the currently used evaluation protocol.

Methods: A total of 236 patients referred to our allergy clinic for investigation of LA hypersensitivity were included in this study. The evaluation protocol was composed of skin prick and intradermal tests, followed by subcutaneous challenge with unrelated LA preparations that contained preservatives.

Results: Skin prick and intradermal test results were negative for all subjects. No objective adverse reactions were observed during the challenge in all but 1 patient, who developed local erythema at the site of injection and later underwent an uneventful challenge with a different LA.

Conclusions: Allergic reactions were not reproduced during testing and challenge with LA preparations that contained preservatives or preservatives with adrenaline in our large group of patients with suspected LA allergy. Since both prick and intradermal skin test results were negative in all the patients and did not provide us with useful information, we propose to modify the standard protocol by omitting intradermal tests and shortening the challenge. We also suggest that the whole procedure be performed with LAs that contain preservatives, which are usually the preferred preparations widely used in daily practice.

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INTRODUCTION

Since the first synthetic procaine was produced in 1904, local anesthetics (LAs) have been widely used in surgical procedures, especially in dentistry. These medications are produced in several forms: solution for injection, ophthalmic drops, and dermal creams.

Various adverse reactions to LAs have been described, including vasovagal, anxiety, psychosomatic, and toxic responses.¹ Type 1 immediate hypersensitivity reactions to LAs are rare and have been well documented in only a few cases.^{2–6} Most LA preparations contain adrenaline and preservatives that may also cause adverse reactions.^{1,7,8} Many dental and surgical procedures are still performed under improper anesthesia due to fear of LA allergy. Furthermore, many patients who experienced various adverse reactions in the past are advised by their physicians to avoid LAs.^{1,7}

Because nearly 2 million injections of LAs are given daily in the United States,⁹ many patients with a history of adverse reaction to LAs are frequently referred to allergy clinics and undergo an extensive evaluation. This investi-

gation is complicated due to imprecise history, different types of presentation, local factors, and lack of reliable laboratory tests. Recently, an increase in the referral of patients concerned about LA use was reported. Most of these patients had no history of adverse reaction to LAs.¹⁰ The aims of the present study were to determine the prevalence of true LA allergy among the patients referred for suspected LA hypersensitivity and to evaluate the usefulness of the currently used evaluation protocol.

METHODS

Patients

Between 1987 and 2000, 236 patients were referred to the Allergy Clinic at Hadassah University Hospital in Jerusalem, Israel, for evaluation of LA hypersensitivity. A standard questionnaire, regarding personal and family history of general atopy and specifically food and drug adverse reactions, was filled in for each patient. The clinical presentation of previous reaction to LAs was documented. Adverse reactions were divided into 5 categories according to their description by the patient.¹¹ Group 1 included immediate systemic reactions within 1 hour, including urticaria, angioedema, laryngospasm, wheezing, or hypotension; group 2, appearance of local swelling within 1 hour; group 3, nonspecific complaints that appeared within 1 hour; group 4, delayed reaction after more than 1 hour; and group 5, patients referred due to suspected allergy, without previous adverse reaction to LAs. All antihistamine use was discontinued at least 7 days before evaluation. All patients underwent testing of LAs according

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to an evaluation protocol.⁷ In cases where the implicated agent was known, we used an unrelated amide class LA preferred by the referring physician, usually 2% lidocaine hydrochloride with 0.001% adrenaline, 0.1% methylparaben, and 0.069% sodium metabisulfite (Lidocadren; Teva, Netanya, Israel). When the offending agent was unknown or the patient belonged to group 5 (ie, had no previous adverse reaction), we used 3% mepivacaine with 0.1% methylparaben (Tevacaine; Teva) or 0.5% bupivacaine hydrochloride (Marcaine; AstraZeneca, Sodertalije, Sweden).

We chose to test commercial LA compounds that contain adrenaline and preservatives, since these preparations are widely used in dental practice and surgical procedures. The evaluation began with a skin prick test (SPT) with undiluted LA solution, followed by intradermal (ID) injection of 0.02 mL of 1% solution of LA. Histamine (1 mg/mL) served as a positive control and normal saline was the negative control. An SPT result was considered positive when a wheal diameter of at least 3 mm larger than the negative control was measured after 20 minutes.¹² The patients then underwent an incremental subcutaneous challenge, given in 20-minute intervals. The doses were 0.1 mL of 1% and 10% dilution, followed by increasing doses of undiluted LA (0.1, 0.25, 0.5, 1.0 mL), up to a cumulative dose of 1.85 mL as recommended by Schatz.⁷ All tests were performed under the supervision of a physician. During the challenges, patients' blood pressure, pulse rate, and symptoms were closely monitored. Following the challenge, patients were observed for 2 additional hours and were instructed to report any late reaction. A positive reaction led to an immediate termination of the procedure and the tested agent was not used again. To exclude latex allergy, SPTs for latex (latex extract; Stallergens, Fresnes, France) were performed in all the patients evaluated during the last year of the study.

RESULTS

Patient Characteristics

Of the cohort, 188 (79.7%) of 236 were women. The mean $\pm$ SD age at evaluation was 40.6 ± 19.8 years (range, 4–83 years). Eighty patients (33.9%) had a history of adverse reaction to other drugs and 56 to more than 1 drug. Thirteen had a history of an anaphylactic reaction (7 to drugs or food and 6 of unknown origin). Forty-seven patients (19.9%) had a history of food

allergy. Eighty-seven subjects (36.9%) were atopic, including 31 with asthma. In 94 cases (39.8%) familial atopy was reported. One hundred seventy-three patients (73.3%) were referred by dentists, 23 (9.7%) by allergists, 12 (5.1%) by family physicians, and 28 (11.9%) by other specialists.

History of Adverse Reactions

Fifty-one patients (21.6%) reported symptoms compatible with immediate hypersensitivity, including urticaria, angioedema, dyspnea, wheeze, loss of consciousness, or hypotension shortly after LA injection. Twenty-seven (11.4%) described local swelling at the injection site. Sixty-four (27.1%) experienced nonspecific symptoms, such as weakness, dizziness, and nausea, and 36 (15.3%) reported delayed reactions, such as rash, cough, or dyspnea that appeared hours after the injection. The remaining 58 patients (24.6%) were referred by their physicians because they were atopic or had a previous reaction to food or medication, with no history of adverse reaction to LAs.

Evaluation

Two hundred eighteen patients were tested for sensitivity to 1 and 18 to 2 unrelated LAs (Table 1). Both SPT and ID test results to LAs were negative in all subjects. No immediate adverse reactions were observed during the challenge in all but 1 of the 236 cases. In this patient, a local erythema developed at the injection site after challenge with the 1:10 dilution of LA. Subsequently, she had an uneventful challenge with a different LA. During the challenge, 10 subjects complained of nonspecific symptoms, such as weakness, dizziness, and pruritus. No objective signs were found on physical examination. In these cases the challenge was discontinued. All 6 of those who arrived for further evaluation underwent an uneventful challenge with a different LA. Two of 32 tested for latex allergy had positive skin test reactions.

DISCUSSION

We performed 254 SPTs and the same number of ID tests in a group of 236 patients. All yielded negative results. These results are compatible with many other reports^{10,13–17} (Table 2). Skin tests are of limited value in the investigation of adverse reactions to many drugs. This is due to the unavailability of relevant drug metabolites and the lack of reliable identified antigens of most drugs except penicillins.^{1,18} LAs

Table 1. Local Anesthetics Used in the Evaluation

Generic name	Brand name and manufacturer	Adrenaline	Paraben	Sulfite	No.
2% Lidocaine	Lidocadren; Teva, Netanya, Israel	0.001%	0.1% Methylparaben	0.069% Sodium metabisulfite	104
1% Lidocaine	Esracaine; Rafa, Jerusalem, Israel	No	No	No	55
3% Mepivacaine	Tevacaine; Teva, Netanya, Israel	No	0.1% Methylparaben	No	69
0.5% Bupivacaine	Marcaine; AstraZeneca, Sodertalije, Sweden	No	No	No	26

Table 2. Results of Evaluation of Adverse Reactions to Local Anesthetics in the Literature*

Source, y	No. of patients	Positive results		
		Prick test	Intradermal test†	Challenge‡
Macy et al, ⁸ 2002	252	3/252§	1/252§	0/252
Astarita et al, ¹⁰ 2001	72¶	0/72	0/72	0/72
de Shazo and Nelson, ¹³ 1979	90	0/90	1/90	0/89
Wasserfallen and Frei, ¹⁴ 1995	28			0/28
Chandler et al, ¹⁵ 1987	59	0/56	0/59	0/59
Gall et al, ¹⁶ 1996	177	0/177	0/177	0/164
Nettis et al, ¹⁷ 2001	105¶	0/105	0/105	0/105

* With unrelated local anesthetics.

† Diluted only.

‡ Objective signs only.

§ Local anesthetics with methylparaben.

¶ Patients with previous adverse reaction to local anesthetics only.

are compounds of low molecular weight and must bind a protein carrier to acquire antigenicity. Such molecules, however, have not been identified so far.¹

Since discontinuing the use of ID tests with undiluted LAs due to a high rate of false-positive reactions, positive ID test results are very rare. de Shazo and Nelson¹³ reported only 1 positive ID test result with 1:100 diluted unrelated LA among 90 patients evaluated after adverse reaction to LAs.

Wasserfallen and Frei¹⁴ evaluated 28 patients after adverse reaction to LAs. The SPT results were positive in 4 patients, and the results of ID test with 1:10 dilution were positive in 10. Despite these results, subcutaneous challenge caused no systemic reaction, and all patients were allowed to use LAs. Chandler et al¹⁵ evaluated a group of 59 patients, most of whom had a history consistent with immediate hypersensitivity to LAs. None of them had a reaction during skin tests and challenges with unrelated LAs. Gall et al¹⁶ reported a large series of 177 patients who were tested with both causative and unrelated LAs. All skin test results (SPT and ID) with unrelated LAs were negative. Astarita et al¹⁰ investigated 198 patients who were concerned about LA use. Only 72 of these patients had a previous adverse reaction to LAs. No one showed positive SPT or ID test results. The subsequent challenge with mepivacaine without additives was uneventful in all subjects. Nettis et al¹⁷ evaluated 105 patients with suspected LA allergy. Both SPT and ID test results were negative in the entire group. Provocative subcutaneous challenge with unrelated LAs was uneventful.

Schatz,⁷ reviewing LA hypersensitivity, concluded that except for a few case reports, hundreds of skin tests performed with unrelated LAs all show negative results. These reports, as well as ours, clearly demonstrate that there is no benefit in performing skin tests for adverse reaction to LAs.

Provocative challenge is used as the gold standard in the diagnosis of drug allergy.¹⁸ None of our patients had an objective systemic reaction during challenge with another LA. Our results are similar to those of others (Table 2). In the study by de Shazo and Nelson,¹³ 89 of 90 patients were challenged and all tolerated the procedure well. In the study

by Gall et al,¹⁶ not 1 of the 164 challenged patients reacted to an unrelated agent. In addition, Macy et al⁸ recently reported a large series of 287 patients evaluated for suspected LA allergy, 252 of whom were tested with LA-containing preservatives. All the patients studied had a negative challenge result.

Anaphylactoid, immediate, and delayed-type hypersensitivity reactions to parabens and sulfite preservatives in LA preparations have been reported in several studies.^{19,20} Therefore, preservative-free LAs have been recommended for testing and treatment of patients after adverse reaction to LAs.^{1,7,21} Pure LAs were used in other studies that evaluated suspected LA allergy.^{10,13-15} Gall et al¹⁶ performed tests with preservatives in addition to pure LAs. Although 3 patients had a positive skin test result to sodium metabisulfite and 2 others to parahydroxybenzoic acid ester, challenge with these preservatives did not lead to any objective symptom. Macy et al⁸ used LA preparations containing methylparaben. Skin test results were positive in 3 of 252 tested. In all these 3 cases, subsequent testing with pure LAs was uneventful. The authors concluded that they identified 3 potential (and 1 of them reproducible) reactions to methylparaben. However, in daily practice, LAs containing adrenaline and preservatives are the preparations widely used by dentists, because it is not practical for them in most cases to use pure LAs. In the present report, most of our patients were tested and challenged with LA preparations that contained preservatives or preservatives with adrenaline. Thus, in contrast to general belief, LA preparations with preservatives can be safely used. Indeed, Macy et al⁸ have updated their previous recommendation and suggest that LAs with methylparaben should be used for LA allergy evaluation.

The complete lack of reactivity in any of our 236 patients, concordant with the literature, shows the extreme rarity of LA allergy and supports the safety of incremental challenge in patients with a history of adverse reaction to LAs. This evaluation protocol, suggested almost 2 decades ago, permits the choice of safe LAs and reassures patients and physicians, but it consists of many steps and is time consuming.⁷ Following our results, which are compatible with previous re-

ports, we suggest a modification in the evaluation protocol of patients after adverse reaction to LAs. We propose omitting the ID tests and shortening the challenge procedure.

In cases where no previous reaction occurred or the reaction had no features of immediate hypersensitivity, we recommend the use of unrelated LAs without further testing. In cases where the causing LAs are unknown or the untoward reaction has features of immediate hypersensitivity, a SPT and a shortened challenge with other LAs (with preservatives) should be performed.

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