



Allergic reactions to local anesthetics: should we test those with drug allergies and atopy history?

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Abstract

Aim: Many patients are referred to allergy clinics for allergy tests to local anesthetics. The aim of this study was to evaluate the effect of a history of atopy and drug hypersensitivity on allergy tests made with local anesthetics.

Materials and Methods: A retrospective review was made of the records of patients referred to our clinic within a 5-year period because of a suspicion of allergy to local anesthetics, and who were applied with skin tests and subcutaneous challenge tests.

Results: Evaluation was made of a total of 138 patients, comprising 114 (82.6%) females and 24 (17.4%) males with a mean age of 45.35 ± 14.13 years. A reaction during a dental procedure was reported in 99 (71.7%) patients. Mepivacaine was the most tested local anesthetic ($n = 66$, 40.2%). A positive reaction was determined in the skin tests made with local anesthetics in 6 (4.3%) patients. Lidocaine was the local anesthetic most often showing a positive reaction ($n = 3$, 50%). A history of atopy was present in 30 (21.7%) patients. No correlation was determined between atopy history and the development of a positive reaction to local anesthetics ($p = 0.086$). In the cases determined with a positive reaction to local anesthetics, there was a greater rate of history of hypersensitivity to drugs other than local anesthetics ($p = 0.012$).

Conclusion: Patients with a history of drug hypersensitivity reaction should be tested in respect of local anesthetic allergy prior to a procedure to be made with local anesthetics.



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Introduction

Local anesthetics (LAs) are widely used in surgical, dental, and dermatological interventions as they reduce bleeding, provide pain control and increase patient comfort [1]. Adverse reactions to LAs have often been reported but actual allergic reactions are rare [2]. Non-allergic reactions to LAs are much more common than actual allergic reactions. Sympathetic stimulation, vasovagal syncope, and psychomotor or anxiety-related reactions, and systemic toxic effects associated with the pharmacological properties of LAs are the main reasons for non-allergic reactions [3, 4]. The clinical symptoms of non-allergic reactions may be confused with the clinical symptoms of allergic reactions. Therefore, patients stating that they are allergic to LAs are a familiar situation [5].

Many patients are referred to allergy clinics for tests of allergy to LAs. This study was planned with the assumption

that the majority of LA tests are not necessary. The aim of the study was to evaluate the effect of a history of atopy and drug hypersensitivity on allergy tests made with LAs.

Materials and Methods

Study design

A retrospective review was made of the records of 138 patients referred to our clinic allergy unit within the 5-year period of January 2016-January 2021 because they had experienced an adverse reaction to LAs and were applied with skin tests and subcutaneous challenge tests.

Data collection

Data were retrieved from the medical records, including age, sex, atopy history, history of hypersensitivity to drugs other than LAs, the procedure during which the reaction happened, and from where they were referred.

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Ethics approval

The study protocol was approved by the university Ethics Committee and was conducted in accordance with the Declaration of Helsinki (Decision no: 2020/2406).

Allergic evaluation

Following skin prick tests (SPT) and intradermal tests (IDT) with amide group LAs not containing vasoconstrictors (artivacaine, bupivacaine, lidocaine, mepivacaine, prilocaine), all patients were applied with subcutaneous challenge tests (SCT). Before the skin tests with LAs, any drugs which could cause a false negative were stopped for at least one week. SPT was first made with the undiluted (1/1) LA which was planned to be used for the patient. Sodium chloride 0.9% was used as the negative control and histamine (1 mg/mL) as the positive control. At 20 minutes after the application of the test solution, the diameter of swelling and erythema was measured. If there was a reaction from the negative control of swelling with a mean diameter > 3 mm and if it was surrounded by erythema it was accepted as positive. Subjects with SPT negative results were applied with IDT at 1/100 and 1/10 dilutions. The evaluation of each concentration was made after 20 mins. If there was an increase of at least 3mm in the diameter of the initial swelling, and it was surrounded by erythema, it was accepted as positive.

Following negative skin tests, SCT were performed at increasing doses of LA (0.1 ml, 1 ml). The development of skin symptoms (urticaria, angioedema), respiratory symptoms (cough, dyspnea, wheezing) and/or cardiovascular symptoms (hypotension, tachycardia) within 20 mins after provocation was accepted as positive.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS for Windows v. 22.0 software. Continuous variables were stated as mean \pm standard deviation or median (min-max) values, and categorical variables as number (n) and percentage (%). The Chi-square test was used in the comparisons of categorical variables. A value of $p < 0.05$ was accepted as statistically significant.

Results

Clinical characteristics of the patients

A total of 138 patients were evaluated with 164 skin testing /SCT. The patients comprised 114 (82.6%) females and 24 (17.4%) males with a mean age of 45.35 ± 14.13 years (range, 20-80 years). A reaction during a dental procedure was reported in 99 (71.7%) patients. A history of atopy was present in 30 (21.7%) patients, and of these, 21 (61.7%) had a history of drug hypersensitivity reaction (Table 1).

Test results and characteristics of positive response

According to the request of the referring physician, the LA most frequently tested was mepivacaine (n = 66, 40.2%), followed by lidocaine (n = 35, 21.3%) (Table 2).

Positivity in the skin testing/SCT applied with LAs was determined in 6/138 patients (4.3%). All the reactions

Table 1. Clinical characteristics of the study population

	n (%)
Total	138
Age, years, mean \pm SD	45.35 \pm 14.13
Sex	
Female	114 (82.6)
Male	24 (17.4)
Type of procedure	
Dental procedure	99 (71.7)
Minor surgical procedures	15 (10.9)
Procedures in the emergency room	13 (9.4)
Intra-articular procedures	7 (5.1)
Spinal anesthesia	4 (2.9)
Atopy	30 (21.7)
Drug	21 (61.7)
Polen	11 (32.4)
Venom	2 (5.9)

Table 2. Local anesthetics used in the drug tests in the study population

Local anesthetics	Number of the patients tested, n (%)
Mepivacaine	66 (40.2)
Lidocaine	35 (21.3)
Prilocaine	31 (18.9)
Articaine	27 (16.5)
Bupivacaine	5 (3.1)

developed within 1 hour of the application of LA. The LA showing most reactions was lidocaine (n = 3) followed by mepivacaine (n = 2) and prilocaine (n = 1). A history of hypersensitivity to drugs other than LAs was present in 3 of the 6 cases (50%) (Table 3).

Skin test positivity was determined in only 1 patient, and the remaining cases tested positive with SCT (Table 3). To find a safer alternative for positive cases, tests were made with another amide group LA. The result in all the cases was negative (Table 3). In the cases determined with skin testing/SCT positivity, there was a greater rate of history of hypersensitivity to drugs other than LAs ($p = 0.012$) (Table 4).

Discussion

All the patients referred to our clinic allergy unit because of suspected allergy to LAs were tested. The results of this study showed that there was no difference between those with and without a history of atopy in respect of the likelihood of seeing an allergic reaction to LAs. The potential of cases with a history of drug hypersensitivity reaction to experience a reaction to LAs was higher.

Despite the widespread use of LAs, real allergic reactions are rare and constitute < 1% of all reported adverse reactions [2, 6]. Nevertheless, many patients are referred to allergy clinics with suspected allergy to LAs [7]. In this study, a positive reaction was determined in 4.3% of the patients referred to the clinic because of suspected LA allergy. This finding supported the development of non-allergic reactions in the majority of patients following the

Table 3. Characteristics of patients with positive tests to local anesthetics

Age	Sex	Atopy	History of drug hypersensitivity other than to LAs	Tested drug	Characteristics of positive test	Result of testing to find alternative LA
54	M	Yes	Yes (NSAID)	Mepivacaine	0.1 cc SCT, urticaria	Prilocaine: negative
24	F	No	No	Prilocaine	1 cc SCT, uvula edema, cough, dyspnea	Mepivacaine: negative, Lidocaine: negatif
32	F	Yes	Yes (antibiotics)	Mepivacaine	0.1 cc SCT, dyspnea, hypotension	Lidocaine: negative
35	F	Yes	Yes (NSAID)	Lidocaine	0.1 cc SCT, hypotension	Prilocaine: negative
46	F	No	No	Lidocaine	0.1 cc SCT, dyspnea, pruritus	Prilocaine: negative
57	F	No	No	Lidocaine	1/100 IDT, skin test positive	Mepivacaine: negative Prilocaine: negative

Abbreviations: LAs: Local anesthetics, SCT: Subcutaneous challenge test, IDT: Intradermal test, M: Male F: Female

Table 4. Comparisons of the patients showing and not showing a positive reaction to local anaesthetics

	n (%)		p
	Positive reaction	Negative reaction	
Total	6 (4.3)	132 (95.7)	
Atopy	3 (50)	27 (20.5)	0.086
History of drug hypersensitivity other than to LAs	3 (50)	17 (12.9)	0.012

Abbreviations: LAs: Local anesthetics

application of LA. Non-allergic reactions are interpreted as LA allergy by the majority of patients and by healthcare personnel other than allergy specialists [8]. These patients are referred to allergy clinics for the testing of a safe LA to be used before any procedure [9]. To confirm of discount LA allergy, the suspicion of allergy has to be investigated [10]. Not investigating or insufficient investigation of a suspected allergic reaction to LAs causes unnecessary avoidance of LAs. This can cause loss of patient comfort and an increased risk associated with the application of general anesthesia for some procedures.

LAs can be separated into two groups as ester and amide compounds, according to the chemical structure. Amide compounds are being increasingly selected, as the reactions to these agents are less common than to ester compounds [8, 11]. However, patients with an actual allergy to amide compounds and documented cross-reaction within the amide group have been reported [12-14]. One of the aims of the evaluation of suspected LA allergy in the allergy clinic is to identify an agent that can safely be used on the patient in future. Therefore, it is important to take the possibility of cross-reactivity between different agents into account. In the current study, positive cases were tested with other amide group LAs to find a safe alternative. For all the patients determined positive as a result of the tests with LAs, a safe alternative was found. In 4 of the 6 cases in the current series determined with a positive reaction, a negative result was obtained with prilocaine. Two of these cases had a history of hypersensitivity

to NSAIDs. According to these results, prilocaine can be used as a suitable alternative providing safe results.

Previous studies have shown no correlation between a history of atopy and the development of a reaction to LAs [7, 15]. In the current study, there was a history of atopy in approximately 1 in 5 of the patients referred for LA allergy tests. However, no relationship was determined in this series between a history of atopy and the development of a positive reaction to LAs.

In 3 of the 6 cases (50%) determined with a positive reaction as a result of the LA tests there was a history of hypersensitivity reaction to drugs other than LAs. The probability of a positive reaction to LAs was higher in these cases. In the light of the data obtained in this study, it can be recommended that allergy tests to LAs are performed before any procedure to be applied with LA in patients with a history of drug hypersensitivity reaction. However, there is a need for further studies of larger populations to determine the risk factors for LA allergy.

Conclusion

The results obtained in this study confirmed that actual allergic reactions to LAs are rare. Many patients with suspected allergy to LAs are referred to allergy clinics to find a safe alternative. The majority of tests performed for LAs in allergy clinics are unnecessary, leading to loss of time and money. Therefore, there is a need to determine the risk factors for LA allergy and which patients should be tested.

Ethics approval

Ethical approval was obtained for this study by the ethics committee of Necmettin Erbakan University, Meram Faculty of Medicine, drug and non-medical device research (Decision number 2020/2406).

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