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Local anesthetics allergy: who should be tested?

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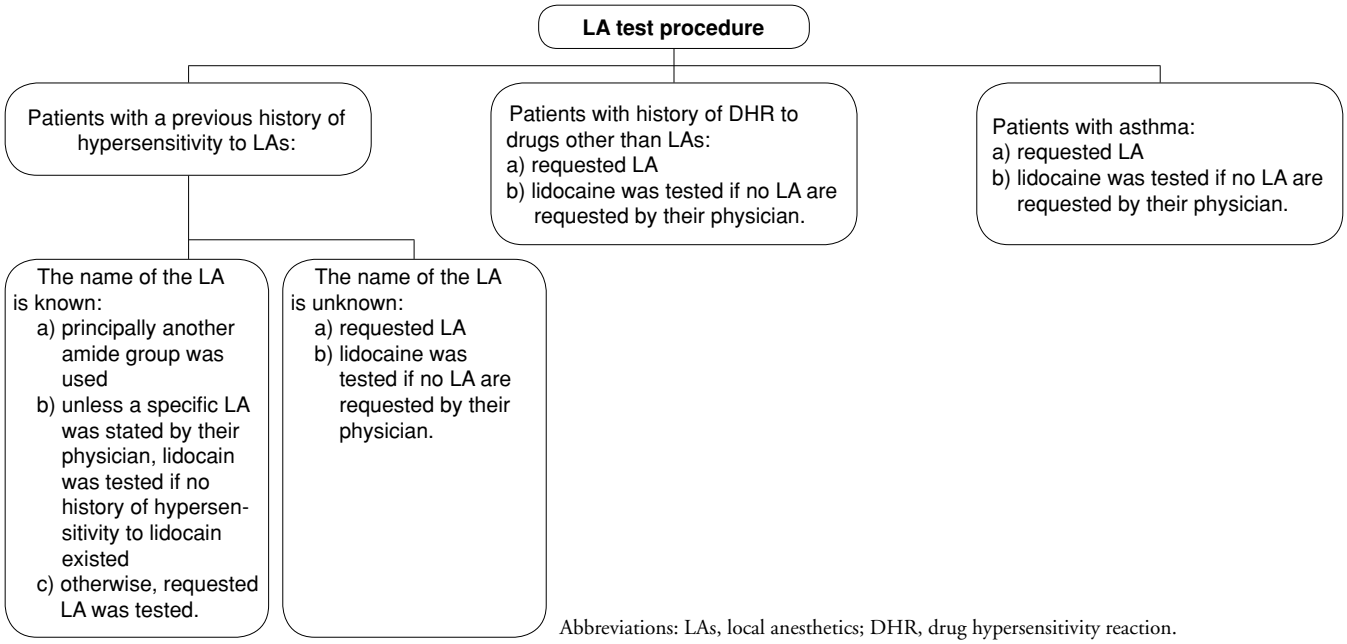
Summary
Objective. *To document the test results of patients referred to our clinic for testing with local anesthetics (LAs) in real life conditions and provide data related to the necessity of these tests.* ***Methods.*** *All consecutive subjects who were referred to be evaluated for LA allergy during a two-year follow up were included in the analysis. All subjects underwent skin prick / intradermal tests followed by a subcutaneous provocation test with the LAs tested.* ***Results.*** *A total of 228 subjects were included. The main referral reason was the presence of a history of drug hypersensitivity reaction (DHR) to drugs other than LAs (n = 128, 56%), whereas a history of LA allergy constituted the second most common referral reason (n = 64, 28.1%). In the majority of cases (n = 39, 60.9%), the culprit LA was not known by the patients. Asthma was the third most common referral reason, presented in 49 cases (21.5%). Ten cases had positivity to the tested LA in skin testing / challenges. Nine out of 10 patients had a history of DHR to drugs other than LA, whereas 5 of them had also a history of DHR to LA. Six of the 10 patients had a history of multiple DHR. None of the asthma patients without any DHR history were positive in the LA tests. Eight out of 10 cases who underwent skin testing / challenge with an alternative LA, tolerated the alternative LA.* **Conclusion.** *The most common referral reason for testing with LA was a history of DHR to drugs other than LAs, whereas asthma was the third most common referral reason. Patients with a history of multiple DHR may be considered for testing with LAs. Asthmatics and those with other allergic diseases without a history of drug / LA allergy do not need to be tested with LA.*

Introduction

Following their first application in the late 19th century, local anesthetics (LAs) have been widely used in the areas of dentistry, ophthalmology, obstetrics and gynecology, and for other minor surgical procedures (1). Since then, several cases with undesired side effects have been reported (2-8). However, the problem with the "undesired effects" of LAs is the miscalling of some symptoms as "allergy" because of the indistinct nature of the symptoms. The incidence of true allergic reactions to LAs is lower than 1% (2-5). It's shown that pharmacological, toxic, pseudo-allergic or autonomic reactions are the main reasons of non-allergic reactions (2-8).

Guidelines recommend that LA testings should be performed in patients with a history of LA hypersensitivity (9-11). However, in our clinical experience, we noticed that not only patients with a history of LA allergy, but also those with asthma without a history of any drug allergies, and patients with a history of drug hypersensitivity reactions (DHR) to drugs other than LAs, were referred to be evaluated for a possible allergy to LAs before a minor surgical procedure. In our daily routine, these cases have to undergo skin testing with the requested LAs, in order to relieve the anxiety of both the patients and the referral physicians, despite the fact that no real indication exists. However, we importantly found that the majority of

Figure 1 *- Test and evaluation protocol for LAs.*



Abbreviations: LAs, local anesthetics; DHR, drug hypersensitivity reaction.

these cases had negative skin tests and challenges, which makes performing these tests unnecessary for the evaluation of these groups. Therefore, we designed an observational real life study, aiming to define the groups of patients who referred to our allergy clinic for testing with LAs and the results of these tests, in order to define the characteristics of the patients who should actually be referred for tests with LAs. We hypothesized that it is not necessary to perform many of the LA tests.

Materials and methods

This observational study was designed prospectively, and all consecutive patients who were tested with LAs for any reason were enrolled to the study for a two-year period. The study was approved by Ankara University Ethics Committee. Patients who were unwilling to participate in the study were not included in the analysis. The demographics of the patients were recorded from case files. The following information was also recorded for each case: referral reason, presence of any allergic disorders and other diseases, any history of LA allergy and/or DHR to drugs other than LAs. In the presence of a history of allergy to LAs, the name of the responsible drug(s) and type of reaction(s) were also recorded. Thus, the patients who were tested for LA allergy were categorized under 3 groups:

1. patients with a history of hypersensitivity reactions to LAs
2. patients with a history of DHR to drugs other than LAs without allergy to LAs
3. patients with asthma.

Drug hypersensitivity related reactions were immediate reactions (urticaria / angioedema, bronchospasm, laryngeal edema, rhinitis, and systemic anaphylactoid reactions involving hypotension, laryngeal edema, bronchospasm and/or shock) and non-immediate reactions (maculopapular eruption, fixed drug eruption, photosensitivity, contact dermatitis, and other reactions) to a prescribed drug. Patients with a history of immediate or nonimmediate type reaction to any kind of drug and those tested for DHR, were enrolled in the study.

Allergologic workup

An algorithm recommended by the ENDA/EAACI Drug Allergy Interest Group was applied in our study (11). Antihistamines as well antidepressive therapy were stopped at least one week prior to skin tests with LAs. LAs without vasoconstrictors were used for all tests in order to avoid false negativity. The following protocol was applied in the selection of LAs to be tested:
All patients underwent skin testing including a skin prick test (SPT) and intradermal test (IDT), followed by a subcutaneous provocation test (SCT) with tested LAs. The IDT was performed when SPTs were negative. Positive (histamine chloride 1 mg/mL) and negative (0.9% sodium chloride) controls were applied on the anterior side of the patients' forearms. Tests were firstly performed by undiluted skin prick tests; if negative, they were followed by intradermal tests using 1/100 and 1/10 dilutions. The positivity of the skin test was established when the

mean wheal diameter was at least 3 mm greater than the negative control for SPT, and at least 5 mm greater for IDT. In patients with negative skin testing, drug provocation tests with increasing subcutaneous doses (0.1 ml and 1 ml) at the lateral surface of the patients' arms, were conducted. Local findings around the injection site, general symptoms, and vital signs were observed for up to 30 minutes (11-13).

Statistics

The statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Numeric values with normal dispersion were expressed as means ± SD, whereas abnormal dispersed variables were given as median values (min-max). Categorical variables' values were given as n (%). When comparing dichotomous independent variables, chi-square of Fisher's exact test was used. The p value of < 0.05 was considered to be significant.

Results

The patients

The study included a total of 228 patients. The mean age was 42.2 ± 1.3 years, range: 16-74 years. Most of the patients were female (77.6%) (**table I**). The most common referral reason for testing with LA was a history of DHR to drugs other than LAs (n = 128, 56.1%), whereas a history of LA allergy constituted the second most common (n = 64, 28.1%), and asthma was the third most common referral reason (n = 49, 21.5%).
Considering the cases with a history of DHR to LAs, the most common clinical symptoms were urticaria (n = 21, 32.8%) and dyspnea (n = 13, 20.3%) (**table II**). In the majority of cases (n =39, 60.9%), the responsible LA was not known by the patients. Among the identified LAs, articaine was the most commonly (n = 11, 17.2%) reported one.

Test results and characteristics of positive response

Prilocaine was the most commonly (n = 125, 46.8%) tested LA based on referral physicians' requests, which was followed by mepivacaine in 83 cases (31.1%) (**table III**). Ten out of 228 cases (4.3%) had positivity to LA in skin testing / challenges. Considering the subgroups, 9 (90%) out of 10 patients had a history of DHR to drugs other than LAs, whereas 4 of these 9 patients also had a history of DHR to LA. Of the 218 patients without test positivity, 170 (78%) had drug allergy history. Six (60%) of the 10 patients who had positive test results, had a history of multiple drug hypersensitivity. Of the 218 patients without test positivity, 71 (32%) had multiple DHR history.

Table I *- Demographics and disease features of the study population.*

Variable	
study population, n	228
female / male, n (%)	187/41 (82%)
age (years ± SEM) (min-max)	44.22 ± 1.28 (16 - 74)
atopy, n (%)	22/91 (24.1%)
Referral reason n (%)	
asthma	49 (21.5%)
urticaria	20 (8.8%)
history of other allergic diseases	22 (9.6%)
history of any drug allergy, n (%) history of multiple drug allergy, n (%)	179 (78.5%) 77 (35.3%)
history of drug reaction with LA, n (%)	64 (28.1%)
history of drug allergy other than LA, n (%) antibiotics NSAIDs radiocontrast agent general anesthetics other	128 (56.1%) 66 (28.9%) 57 (25%) 4 (1.7%) 7 (3.1%) 16 (7%)

Table II *- Documentation of LA hypersensitivity in 64 cases.*

Variable	**n (%)**
Suspected LA	
articaine (Ultracaine 2%®) lidocaine (Jetocaine simplex®) prilocaine (Citanest 2%®) mepivacaine (Isocaine 3%®, Safecaine 3%®) unknown	11 (17.2%) 6 (9.4%) 3 (4.7%) 1 (1.6%) 39 (60.9%)
Manifestation of drug reactions	
urticaria / angioedema, n (%)	21 (32.8%)
lower airway, n (%)	13 (20.3%)
rhinitis, n (%)	8 (12.5%)
CVC, n (%)	7 (10.9%)
anaphylaxis, n (%)	7 (10.9%)
other, n (%)	7 (10.9%)

Comparison of these groups according to their DHR history and test results showed no statistically significant difference. None of the asthmatic patients without any DHR history had

Table III *- LAs used in the drug tests in the study population.*

		Adjuvants			
Local anesthetics	**Commercial products**	**adrenaline**	**sodium metabisulfite**	**methyl- Paraben**	**Number of the patients tested**
mepivacaine	Isocaine 3%® Safecaine 3%®	-	-	-	83 (31.1%)
prilokaine	Citanest 2%®	-	-	+	125 (46.8%)
lidocaine	Jetocaine simplex®	-	-	-	45 (16.8%)
articaine	Ultracaine 2%®	-	-	+	8 (3%)
bupivacaine	Marcaine 0.5%®	-	-	-	6 (2.2%)

positive LA test result. Apart from other drug allergies, associated allergic conditions such as asthma, chronic urticaria, food allergy, bee venom allergy and other allergic diseases were not found to be common in patients who had positive SPT and/or SC provocation tests results.

Lidocaine (n = 4) was the most common LA exhibiting positivity among 10 patients, which was followed by prilocaine in 3 and mepivacaine in 3 patients (**table IV**). All drug reactions manifested within the first hour following LA application. Only 3 cases showed positivity in skin tests, whereas

Table IV *- Characteristics of patients with positive tests to LA.*

Age and gender	**Atopy**	**Presence of allergic diseases**	**History of drug hypersensitivity other than to LA**	**History of hypersensitivity to LA**	**Tested drug**	**Characteristics of positive test**	**Result of testing to find alternative LA**
36, f	negative	asthma	yes (analgesics)	yes (articaine)	lidocaine	hypotension 1 cc SC challenge	mepivacaine: negative
54, f	negative	chronic urticaria	yes (not known)[1]	yes (not known)	lidocaine	dyspnea 0.1 cc SC challenge	mepivacaine: negative
46, f	nd[2]	no	yes (not known)	yes (not known)	prilocaine	rhinitis and pruritus 1 cc SC challenge	nd
44, m	yes	venom allergy	no	yes (not known)	mepivacaine	skin test positive 1/100 ID	prilocaine: negative
36, f	negative	no	yes (not known)	yes (prilocaine)	mepivacaine	facial flushing and pruritus 0.1 cc SC challenge	lidocaine: negative
52, f	nd	no	yes (not known)	no	prilocaine	skin test positive 1/100, ID	mepivacaine: negative
51, m	positive	asthma	yes (antibiotic and analgesic)	no	prilocaine	skin test positive (1/1 prick)	mepivacaine: negative
55, f	nd	asthma	yes (antibiotic)	no	mepivacaine	laryngeal edema pruritus 1 cc sc challenge	nd
58, f	positive	food allergy	yes (antibiotic)	no	lidocaine	dyspnea 0.1 cc sc challenge	mepivacaine: negative
44, f	nd	no	yes (analgesics)	no	lidocaine	laryngeal edema 0.1 cc sc challenge	marcaine: negative

[1]No specific drug name is available. [2]Not done.
Abbreviations: f, female; m, male.

the remaining cases were positive on subcutaneous challenges (**table IV**).
These positive cases were tested with another amide group LA in order to find a safe alternative and all of these tests were found negative (**table IV**).

Discussion

In this study, we tested all cases that were referred to an allergy clinic for LA testing. The most common referral reason was a history of DHR to drugs other than LAs. Our results showed that unless they had a positive history of allergy to a certain LA, patients with asthma were not suitable candidates for drug tests with LA. We also showed that there was a potential to have positive LA tests in patients with multiple DHR.
We recorded all cases who underwent drug tests (skin tests / SC challenges) with LAs for two years. The patients were mostly referred by their physicians because of DHR to drugs other than LAs. Multi-drug allergy is regarded as a risk factor for LA allergy. Patients with allergy to other drugs, and those who had reactions to general anesthetics, are regarded to be at a high risk for LA allergy (14,15). However, several studies suggest that only the previous appearance of unexpected adverse reactions following the administration of LAs is regarded to be a risk factor of a similar or even more severe reaction after further exposure to the same agent (6,9,16). Among the patients who had positive test results in our study, 60% had multi-drug allergy. Statistical significance was not reached, although the history of multiple drug allergies was more frequent in the patients who had test positivity. Though speculative, a multiple DHR history may be a possible risk factor for LA allergy. A larger cohort might be needed to determine this potential risk.
It is reasonable that patients with a history of any drug allergy are referred for testing with LA before a local procedure is performed, in order to be sure about the safe use of LA. However, in asthma patients with no history of DHR, there is no clear association between the use of LAs and the development of hypersensitivity reactions. Only a few case reports indicated that local anesthetics, particularly in nebulized forms, may induce bronchospasm (17,18). In contrast to the bronchospasm effect of LAs, nebulized lidocaine has also been successfully used in the treatment of persistent cough (19). In our study, asthma patients with no history of DHR did not have any positivity in skin tests and challenges. Three of the patients with positive tests with LA had an asthma history. However, the main characteristic of a positive test in these patients was not pulmonary symptoms. The patients also had a DHR history. Therefore, our results suggest that performing skin tests with LAs as a prescreening tool before minor surgery provides no benefit for the patients. Moreover, these tests are time consuming and costly. Supporting our results, in the study of Berkun 236 patients with histories of either adverse reaction to drugs, anaphylactic reactions, food allergy or atopy, but no history of reactions to local anesthetics, skin prick testing and provocative dose challenges, showed no positivity (6).
A recent meta-analysis confirmed that real allergies to LAs are exceptionally rare, accounting for less than 1% of patients with a history of symptoms which resemble allergy (20). Concomitantly administered agents (preservatives, antiseptic preparations, non-steroidal anti-inflammatory drugs, antibiotics), as well as the materials and equipment with which patients may have been in contact during procedures, should be considered as a possible cause of immediate type reactions (21-23). We lack evaluation and testing of other agents like metabisulfides, parabens and latex, which are commonly used during these minor surgical procedures. Also, epidemiologic studies evaluating the frequency of LA allergic reactions and their causes have been difficult to conduct owing to the fact that the main agent responsible is usually not known in most cases, which was also true in our cases. Therefore, in our study diagnostic workup for LA allergy was not performed in patients with a history of hypersensitivity reactions caused by LAs. However, despite this limitation, the important outcome at the end of the test procedure is that almost all patients found an LA that they can use safely.
Positive cases were challenged with other amide containing LAs, in order to find a safe alternative (**table IV**). The cross-reactivity patterns of LAs are not well reported. The pattern between ester-type LAs is generally well established, whereas that between amide anesthetics is not well known. Cross-reactivity between lidocaine and mepivacaine has been reported (25,26). In our series, patients with positive tests with lidocaine showed a negative response to mepivacaine. In addition, a patient who presented with an allergic reaction to articaine, tested positive on SC provocation test to lidocaine and tolerated mepivacaine favorably (**table IV**). Another case of hypersensitivity to prilocaine with positive tests to mepivacaine on SC provocation tests, showed favorable tolerance to lidocaine (**table IV**). Finally, we were able to find safe alternatives for all cases with a positive test to LA. These findings suggest that cross-reactions may not always occur among amide group LAs, and that allergic reactions may be associated with different antigenic epitopes. This situation shows that another amide chain containing drug can be used as an alternative for LA testing. According to these findings, mepivacaine may be a viable alternative that gives reliable results and could be used for testing in patients with a history of DHR.
In our series, only 3 cases had skin test positivity. Importantly, one previous report yielded a 97% negative predictive value for SPTs and intradermal tests (24). However, in our series, 7 cases who had negative results in skin tests had positivity in the SC challenges. The reactions observed in the SC challenges of our series were more subjective symptoms such as dyspnea and la-

ryngeal edema, which were not confirmed by a spirometry but reported to be positive by the physician who commented on the test. Epinephrine content can not explain these symptoms either, as we avoided its use. Importantly, skin prick test positivity shows an underlying IgE mediated pathophysiology; however, SC challenges do not. Therefore, we cannot say that these reactions are IgE mediated, and there is a possibility that these cases were not really allergic.

In conclusion, high numbers of patients that were suspected to have LA allergy were referred for evaluation to find a safe LA that can be used. However, most of these tests were found to be unnecessary, and to be time and money consuming. Patients with controlled asthma do not need to be tested routinely with a LA. Patients with a history of multiple DHR seem to be suitable candidates for testing with LAs. However, patients with a prior history of LA hypersensitivity should definitely undergo LA testing. Attention should be paid to collaboration between allergologists and the physicians administering local anesthesia. Prior records related to the undesired effects of LAs should also be kept and given to the patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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