ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.220
Asthma Allergy Immunol 2023;21:174-182

RESEARCH ARTICLE

Received: 03.02.2023 • Accepted: 21.07.2023
Online Published: 08.12.2023

Hypersensitivity Reactions to Local Anesthetics: A 5-Year Observational Study in a Turkish Tertiary Referral Center

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ABSTRACT

Objective: Local anesthetics are broadly used in various health care settings with high probability of lifetime exposure. The main aim of this study was to determine the characteristics and risk factors of the patients presenting to our allergy outpatient clinic due to suspected hypersensitivity to local anesthetics.

Materials and Methods: We retrospectively evaluated the clinical data and test results obtained from patients who had presented to our allergy outpatient clinic for allergological work-up of local anesthetics from 2015 to 2020.

Results: A total of 289 subjects were included. The most common referral reason was a history of non-local anesthetic drug hypersensitivity reaction (65.7%, n=190). Twenty-five out of 289 (8.65%) patients had positivity for at least one of the tested drugs in skin prick test/ intradermal test/ subcutaneous drug provocation test. Of these 25 patients, 4 (16%) had a history of DHR to LA and 9 (36%) had a history of multiple drug hypersensitivity (MDH). Allergy to local anesthetics was observed in only 13 (18.6%) of 70 patients with a history of local anesthetic hypersensitivity reaction. Patients with atopy were 5.3 times more likely to have local anesthetic hypersensitivity (odds ratio: 5.254; 95% CI: 1.316-20.974; p=0.019). Cross-reactivity among amide-local anesthetics without a distinct predictive pattern has also been demonstrated in 3 patients.

Conclusion: Most patients who report local anesthetic allergy can tolerate local anesthetics without having a hypersensitivity reaction. Atopic status is associated with increased risk of a hypersensitivity reaction to local anesthetics. Atopic patients are candidates for performing allergy tests to local anesthetics to enable appropriate counseling.

Keywords: Allergy, drug adverse reaction, drug hypersensitivity, drug allergy, local anesthetics

INTRODUCTION

Local anesthetics (LAs) suppress sensory transmission in targeted body areas without resulting in loss of consciousness. While drug hypersensitivity reactions (DHRs) are rare (<1%), adverse drug reactions (ADRs) associated with LAs (2.5-10%), that can be vasovagal, psychosomatic, or toxic, may mimic allergic reactions (1,2). The term "drug allergy" refers to a specific immunologically mediated DHR.

Because of the difficulty in distinguishing among some allergic and non-allergic symptoms associated with LAs, the clinical history is not sufficient for the diagnosis of drug hypersensitivity. Most patients carrying the label "allergic to LAs" are not truly allergic; however, this labeling often leads to unnecessary avoidance of LAs. The current level of knowledge does not enable clinicians to predict which patients will experience a hypersensitivity reaction to LAs. Only previous presentations of adverse reactions following LA administration are considered risk factors for simi-

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lar or more severe reactions for subsequent exposure (3). It is recommended that all cases of suspected DHRs should undergo diagnostic evaluation with the aim of identifying the culprit drug, assessing the patient's risk for subsequent reactions, and advising the patient accordingly on this risk (3). Interestingly, a recent study, which hypothesized that diagnostic allergy testing of LA is unnecessary for many patients, demonstrated that patients with asthma and other allergic diseases who lack a history of drug/LA hypersensitivity did not require LA allergy testing (3,4). Therefore, performing diagnostic allergy testing is not indicated in patients without a history of hypersensitivity reaction following LA administration, nor in patients with asthma, other allergic diseases, or hypersensitivity reaction to drugs to which they would not be exposed to during the procedure (3). However, in our daily practice, many patients including patients with chronic urticaria, allergic rhinitis, and/or asthma but without a history of any DHR, and those with a history of DHRs other than LAs are referred to our allergy outpatient clinic for skin and drug challenge tests even though there is no real test indication, due to both the patients' and physicians' concerns (5). Considering that a comprehensive assessment of the patient's risk of hypersensitivity reaction to LAs is challenging and time-consuming, it is required to define appropriate patient selection criteria.

The main aim of the present study was to determine the characteristics and risk factors of the patients admitted to our outpatient clinic due to suspected LA-induced hypersensitivity over a 5-year period.

MATERIALS and METHODS

Patients admitted to our outpatient clinic of Immunology and Allergic Diseases at Uludag University for allergological workup of suspected LA hypersensitivity between 2015 and 2020 were retrospectively included in the study (n=289). The study was approved by the institutional ethics committee of Uludag University (Approval number: 2020-11/4). Drug hypersensitivity reactions were classified as the immediate (early) type if they occurred within 1 hour after the last drug consumption and the non-immediate (delayed) type if they occurred more than 1 hour after the drug consumption (3). Patients with a history of non-immediate reaction were excluded.

Data were collected from patients' medical files. Atopy was defined as at least one aeroallergen positivity in the skin prick test (SPT). Aeroallergens are any of various airborne substances, such as house dust mites, pollens (tree, grass and weed), or fungal spores, that can cause a type I-IgE mediated allergic response.

For allergological evaluation, the algorithm recommended by the European Network of Drug Allergy/The European Academy of Allergy and Clinical Immunology Drug Allergy Interest Group was used (6,7). Patients with a reliable history of LA hypersensitivity reaction to a known agent were tested with an alternative drug. Patients without a previous history of LA hypersensitivity reaction were tested with the referring physicians' preferred agent. Of the LAs tested, only articaine preparations contained epinephrine. While the mepivacaine, prilocaine, bupivacaine preparations were preservative-free, lidocaine and articaine contained the preservative sodium metabisulfite.

Prior to testing, written informed consent was obtained from all patients. The interval between the index reaction and allergological evaluation was at least 4 weeks. Any use of medications that could interfere with test results (e.g., antihistamines) was discontinued at least 7 days prior to allergological evaluation.

All patients first underwent forearm SPT with an undiluted LA. Histamine hydrochloride (10 mg/ml) and 0.9% saline were applied as positive and negative controls, respectively. The wheal diameter was measured after 20 min and reported in 'mm'. A skin reaction of ≥3 mm than that produced by the negative control with surrounding erythema on the SPT was considered a positive reaction. If the SPT was negative, intradermal tests (IDTs) were performed using ten-fold serial dilutions of the drug (1/1000, 1/100, and 1/10). The IDTs were also examined after 20 minutes. The IDT was considered positive when the size of the initial wheal diameter increased by 3 mm or greater with a flare. If the IDTs were negative, the patients proceeded to the subcutaneous (sc) drug provocation test (DPT). Subcutaneous DPTs were administered at incremental doses of 0.5 ml and 1 ml into the upper arms of the patients at 30-minute intervals. Vital signs, local findings at the injection site, and general symptoms were observed for at least 1 hour. A provocation test was considered positive based on the presence of objective symptoms and signs of type I DHR, which are mucocutaneous (e.g., erythema, urticaria/angioedema) and/or systemic (e.g., respiratory, cardiovascular). Patients were considered as having a systemic reaction when the clinician excluded vasovagal syncope. Patients who experienced anaphylaxis were

treated with adrenaline. Patients were classified as allergic (patients with positive skin or sc drug provocation testing) or non-allergic (patients with no previous history of LA hypersensitivity and negative skin/sc drug provocation testing). Patients with a history of hypersensitivity reactions to local anesthetics (LAs) and negative test results were excluded from the study due to the possibility that they might not have been tested with the specific culprit LA to which they had previously reacted (Figure 1).

Statistical Analysis

Continuous variables were expressed as median (minimum: maximum) and mean ± standard deviation, and categorical variables were expressed as n (%). Chi-square and Fisher's Exact tests were used to compare categorical variables between the groups. The odds ratio and its 95% confidence interval (CI) were calculated. Student's t-test was used for parametric variables, and the Mann-Whitney U test was used for non-parametric variables. Logistic regression analyses were used for multiple analyses. Statistical analysis was performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.), and $p<0.05$ was considered statistically significant. The negative predictive value (NPV) was calculated as follows: number of true negatives / (number of true negatives + number of false negatives).

RESULTS

The mean age of the patients included in the study was 44.1 ± 13.4 years, with the majority being female (81.7%) (Table I).

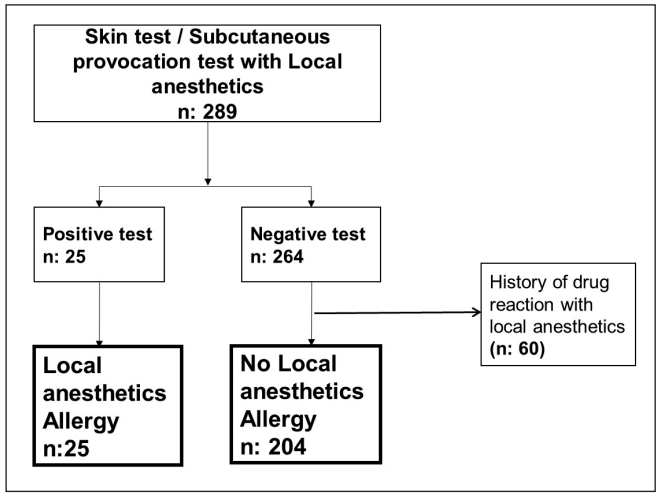

Figure 1. Test and evaluation protocol for local anesthetics

The most common referral reason was a history of non-LA DHRs (65.7%, n=190) (Figure 2). The most common drugs involved in these DHRs were NSAIDs (n=121, 63.7%), followed by antibiotics (n=99, 52.1%), general anesthetics (n=10, 5.3%), radiocontrast agents (n=3, 1.6%), and other drugs (n=21, 11.1%).

Of the patients with a history of hypersensitivity reaction to LAs (n=70), the most common reaction was urticaria/angioedema; however, the culprit LA was unknown in most cases (71.4%) (Table II).

The remaining 29 patients had no history of DHR. However, of these 29, 24.1% (7) had asthma, 37.9% (11) had chronic rhinitis, 10.3% (3) had urticaria, and 3.4% (1) had bee venom allergy.

In total, 313 SPTs, 299 IDTs, and 297 sc DPTs were carried out. There were more tests performed than patients in the study, as some patients were tested with multiple LAs. Articaine was the most frequently tested LA (n=139, 44.4%), followed by prilocaine (n=60, 19.2%), mepivacaine (n=56, 17.9%), lidocaine (n=49, 15.7%), and bupivacaine (n=9, 2.9%), respectively. The majority of SPTs and IDTs returned negative results (94.6%, n=283). Positive results were seen in 11 SPTs and 5 IDTs (at 1/1000 concentration), while 13 originally negative skin tests returned positive results following sc drug provocation (Table IV). The negative predictive value of the skin prick test and intradermal test for immediate-type hypersensitivity reactions was 94% and 96%, respectively. While skin tests (prick/intradermal) were negative in 3.6% of the cases tested with epinephrine articaine, the sc DPTs for these patients were positive (negative predictive value=96%). Twenty-five out of 289 (8.65%) patients had positivity to at least one of the tested drugs in SPT/IDT/sc DPT. Of these 25 patients, 4 (16%) had a history of DHR to LA, 10 (40%) had a history

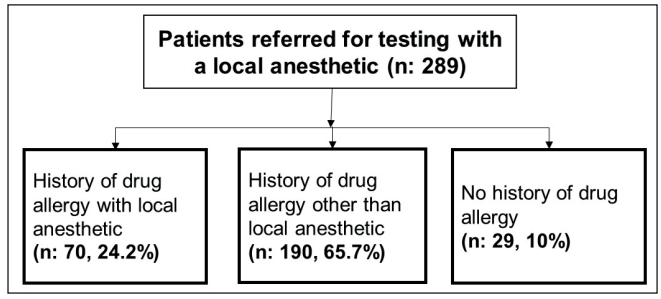

Figure 2. Distribution of drug hypersensitivity reactions of patients

Table I: Demographic, clinical and laboratory characteristics of the study group

	Number of patients
Total patients	289
Mean age, years±SD	44.1 ± 13.4
Female/ Male, n (%)	236 (81.7) /53 (18.3)
Atopic/ Nonatopic, n (%)	89 (58.9) /62 (41.1)
Comorbid allergic diseases, n (%)	
Chronic rhinitis	103 (35.6)
Asthma	81 (28)
Chronic urticaria/angioedema	40 (13.8)
Food allergy	27 (9.3)
Bee venom allergy	5 (1.7)
History of DHRs other than LA, n (%)	
NSAIDs	138 (47.8)
Antibiotics	119 (41.2)
General anesthetics	10 (3.5)
Multiple drug	96 (33.2)
Other drugs	35 (12.1)
History of DHRs to LA	70 (24.2)
Total IgE kIU/L, median (min-max)	69.3 (1.9-1987)
Serum eosinophil cell/µL, median (min-max)	150 (0-5710)
PFT (n:266)	
FEV1/FVC, % ±SD	81.98 ± 7.1
FEV1, % ±SD	100.4 ± 16.5
FEV1, liter ±SD	2.73 ± 0.8
FVC, % ±SD	104.3 ± 14.8
FVC, liter ±SD	3.32 ± 0.9

SD: standard deviation, **DHRs:** drug hypersensitivity reactions, **LA:** Local anesthetics, **NSAIDs:** Nonsteroidal anti-inflammatory drugs, **PFT:** pulmonary function test

Table II: Clinical data of suspected hypersensitivity reactions to local anesthetics in 70 cases.

Variables	n (%)
Suspected local anesthetics	
Articaine	9 (12.9)
Lidocaine	6 (8.6)
Prilocaine	3 (4.3)
Bupivacaine	1 (1.4)
Mepivacaine	1 (1.4)
Unknown	50 (71.4)
Clinical manifestations of DHRs	
Urticaria/angioedema	29 (52.7)
Shortness of breath	13 (23.6)
Laryngeal edema	6 (10.9)
Anaphylaxis	5 (9.1)
Other	19 (34.5)
Unknown	14 (25.5)

DHRs: drug hypersensitivity reactions.

of DHR to a single drug other than LA, 9 (36%) had a history of multiple drug hypersensitivity (MDH), and 2 had no history of DHR (Table III). Of the 190 patients with a history of hypersensitivity to any non-LA drug, 10 (5.3%) had hypersensitivity to LA. Allergy to local anesthetics was observed in only 13 (18.6%) of 70 patients with a history of local anesthetic hypersensitivity reaction.

Patients with and without hypersensitivity to LAs were compared on gender and age; the presence of asthma, chronic rhinitis, urticaria, and DHRs (NSAIDs, multidrug, antibiotic, general anesthetic); laboratory tests (eosinophils, total IgE); and respiratory function (Table V).

Multivariate logistic regression analysis revealed that atopic patients were 5.3 times more likely to have LA hypersensitivity (odds ratio: 5.6; 95% CI:1.316-20.974; p=0.019), and patients with NSAIDs hypersensitivity were less likely to have LA hypersensitivity (odds ratio:0.2; 95% CI:0.061-0.671; p=0.009).

In the present study, all tests were carried out with an amide-group LA. Safe alternative LAs were found for 16 of the patients with LA hypersensitivity. However, cross-reactions were observed in 3 cases: 1 reacted to lidocaine and articaine, 1 reacted to mepivacaine and prilocaine, and 1 reacted to prilocaine, lidocaine, and mepivacaine.

DISCUSSION

In the present study, which is one of the largest series reported to date, hypersensitivity to amide-group LAs was detected in 8.7% of the patients. Presence of atopy was found to be independently associated with a higher risk of having LA hypersensitivity. The negative predictive value of the skin prick test and intradermal test for immediate-type hypersensitivity reaction was high. Albeit rare, cross-reactivity among amide-type LAs has also been demonstrated.

In the present study, the probability of having an LA hypersensitivity was increased 5 times in atopic patients. In addition to drug-related factors, various patient-related predisposing factors have been identified regarding DHRs. The role of atopy in DHRs is still controversial; atopy may favour DHRs for a limited number of drugs, particularly for reactions to beta-lactam antibiotics, radiocontrast agents, and NSAIDs. Several studies suggest that only the prior history of ADR with LA is regarded to be a risk factor for subsequent administrations (4). While the risk of experiencing a hypersensitivity reaction increases in indi-

Table III: Characteristics of patients with positive tests to local anesthetics

Age/ Gender	Atopy/ Latex sensitivity	History of drug hypersensitivity reaction other than LA	History of drug hypersensitivity reaction to LA	Tested Drug	Skin prick test	Intradermal test	Subcutaneous drug provocation test
44, F	n/n	No	Yes (not known)	Prilocaine Lidocaine Mepivacaine	Negative Negative Negative	Negative Negative Negative	Positive Positive Positive
27, F	p/n	NSAIDs	No	Lidocaine Prilocaine	Negative Negative	Negative Negative	Positive Negative
63, F	n/n	Antibiotic	No	Mepivacaine Prilocaine	Negative Positive	Positive (1:1000) ND	ND ND
47, F	ND/ND	No	No	Articaine	Negative	Negative	Positive
37, F	ND/ND	No	No	Mepivacaine Articaine	Positive Negative	ND Negative	ND Negative
28, F	p/ND	Yes (not known)	Lidocaine	Lidocaine Prilocaine	Positive Negative	ND Negative	ND Negative
36, F	p/n	NSAIDs	No	Prilocaine Lidocaine	Positive Negative	ND Negative	ND Negative
31, M	p/p	Antibiotic	Articaine	Prilocaine Lidocaine	Negative Negative	Negative Negative	Positive Negative
52, F	p/n	Antibiotic	Yes (not known)	Articaine Lidocaine	Negative Negative	Negative Negative	Positive Negative
34, F	ND/ND	No	Articaine	Articaine Lidocaine	Negative Negative	Negative Negative	Positive Negative
30, F	p/n	No	Articaine	Lidocaine Articaine Mepivacaine	Negative Positive Negative	Positive (1:1000) ND Negative	ND ND Negative
46, F	p/n	Antibiotic	No	Prilocaine	Negative	Negative	Positive
32, F	n/n	Antibiotic, antidiabetic	No	Lidocaine	Negative	Positive (1:1000)	ND
45, F	p/n	Antibiotic	Yes (not known)	Articaine Lidocaine	Positive Negative	ND Negative	ND Negative
39, M	p/n	NSAIDs, Antibiotic	Yes (not known)	Articaine	Negative	Negative	Positive
51, F	ND/ND	NSAIDs, Antibiotic	Lidocaine	Lidocaine Prilocaine	Negative Negative	Negative Negative	Positive Negative
50, F	p/n	NSAIDs	Yes (not known)	Articaine Lidocaine	Positive Negative	ND Negative	ND Negative
34, F	p/n	Antibiotic	No	Articaine	Positive	ND	ND
64, F	ND/ND	NSAIDs, Antibiotic	No	Mepivacaine Articaine	Negative Negative	Negative Negative	Positive Negative
52, F	ND/ND	Antibiotic	No	Articaine Prilocaine	Negative Negative	Positive (1:1000) Negative	ND Negative
50, F	ND/ND	Yes (not known)	Yes (not known)	Lidocaine Articaine	Positive Negative	ND Negative	ND Negative
60, F	p/n	Antibiotic	No	Articaine Mepivacaine	Negative Negative	Negative Negative	Positive Negative
25, F	ND/ND	No	Yes (not known)	Lidocaine Prilocaine	Positive Negative	ND Negative	ND Negative
30, F	ND/ND	NSAIDs	No	Mepivacaine	Positive	ND	ND
43, F	p/n	NSAIDs, radiocontrast	Yes (not known)	Articaine	Negative	Positive (1:1000)	ND

ND: not done; **F:** female; **M:** male; **p:** positive; **n:** negative; **NSAIDs:** Nonsteroidal anti-inflammatory drugs.

viduals who have previously had a reaction to an LA, it is unclear what role atopy plays in this process (8). An association between atopy and LA hypersensitivity has also been suggested by some other investigators but this possible relationship is far from clear in the literature (9,10). To ascertain whether atopy is a definite risk factor for LA hypersensitivity, further research is required in larger representative groups. Referral of the patients with a history of any DHR to LAs for allergic assessment prior to administration may be considered an appropriate approach by physicians, in order to be sure about the safe use of an LA. In our study, the most common referral reason was a history of non-LA DHR (65.7%), and 63.7% of those were NSAIDs. The results of multivariate logistic regression analyses revealed that personal history of DHR and even MDH are not risk factor for LA hypersensitivity. Similar to the results of our study, Kalkan et al. demonstrated that the risk was not higher in these groups (11). In contrast to our findings, Yilmaz et al. have speculated that the presence of MDH could be a possible risk factor for LA hypersensitivity, but additional evidence was needed to confirm the finding (4). Interestingly, subgroup analysis revealed that among patients with a history of DHR to medications other than local anesthetics, those with NSAIDs hypersensitivity showed an associated decreased risk of developing LA hypersensitivity. However, this result should be interpreted in conjunction with patient characteristics of the study. Although an association between atopy and NSAIDs sensitivity has been suggested by some investigators, the influence of atopy on NSAIDs hypersensitivity seems to vary with the type of reaction (12). In a recent study in adults, patients with single NSAID hypersensitivity showed a much higher prevalence of atopic diseases than patients with multiple NSAID hypersensitivity (13). Taken all together, our findings supported that allergologic work-up is not indicated in patients with a history of DHR other than LA, within the group of patients with a potential DHR with LA, and particularly in NSAID-hypersensitive patients.

Table IV: The type of reaction of the patients who experienced a systemic reaction after the drug provocation test

Variables	Number of patients
Reaction time (minute), median (min-max)	10 (5-180)
Clinical manifestations of DHRs, n (%)	
Urticaria/ angioedema	4 (30.8)
Isolated Pruritus	4 (30.8)
Laryngeal edema	2 (15.4)
Shortness of breath	4 (30.8)
Cough	2 (15.4)
Nausea/Vomiting	1 (7.7)
Tachycardia	3 (23.1)
Hypotension	3 (23.1)

Table V: Demographics and disease characteristics of the study population according to LA hypersensitivity

	LA allergy n=25	No LA allergy n=204	p value
Age, years±SD	42 ± 11.4	44.3 ± 13.4	0.421
Female/ Male	24/1	163/41	0.050
Asthma, n (%)	11 (44)	28 (28.4)	0.109
Chronic rhinitis, n (%)	13 (52)	70 (34.3)	0.083
Urticaria, n (%)	6 (24)	33 (16.2)	0.326
Atopy, n (%)	13 (81.3)	55 (53.4)	**0.036**
DHRs other than LA, n (%)	19 (76)	178 (87.3)	0.126
NSAIDs	8 (32)	116 (56.9)	**0.019**
Antibiotics	12 (48)	91 (46.6)	0.748
General anesthetics	0 (0)	10 (4.9)	0.606*
Other drugs	3 (12)	23 (11.3)	0.914
Multiple drug hypersensitivity other than LA, n (%)	10 (40)	59 (28.9)	0.255
Total IgE, median (min-max)	70.7 (2.5-1454)	66.2 (1.9-1987)	0.955
Serum eosinophil, median (min-max)	137.5 (30-540)	140 (0-1310)	0.990

SD: standard deviation, **DHRs:** drug hypersensitivity reactions, **LA:** Local anesthetics, **NSAIDs:** Nonsteroidal anti-inflammatory drugs
*Fisher's exact test

In our study, a remarkable proportion of the patients' referral reason was accompanying atopic diseases, the most common being asthma and chronic rhinitis. However, comorbid diseases such as asthma, chronic rhinitis, or urticaria were not associated with an increased risk of developing a hypersensitivity reaction to LAs. Similar results were reported by Yılmaz et al., who showed that patients with asthma and those with other allergic diseases without LA hypersensitivity do not need to be routinely evaluated for a possible risk of LA hypersensitivity (4).

In daily clinical practice, suspected IgE-mediated hypersensitivity reactions to LAs are evaluated via skin tests (SPTs and IDTs) and DPTs, while the only reliable way to establish a diagnosis of non-allergic immediate reactions is DPTs. The diagnostic accuracy of skin tests in diagnosis of drug allergy is high for only a few drugs, especially for beta-lactams, muscle relaxants, and insulins (14). Skin tests have not been validated for LA hypersensitivity because of the limited and conflicting results of performed studies. Some studies have shown that skin tests were not useful diagnostic tools to predict DHRs to LAs (15-17). However, Furci et al. suggested that returning a negative skin test excludes the possibility of an IgE-mediated hypersensitivity reaction (18). Kalkan et al. calculated diagnostic sensitivity of IDT at 1/100 dilution of 97.56% in their series of 398 patients with a suspected LA hypersensitivity (11). Similarly, we had 13 positive results following sc DPTs in patients who returned negative intradermal tests, and a high negative predictive value (96%) for skin tests was found.

Although performing an IDT with 1/10 dilution of the suspected LA is recommended, lower dilutions (1/100 or 1/1000) may be used depending on the severity of hypersensitivity reaction (6,7). In our clinic, IDT for LA is routinely performed starting with a 1/1000 dilution, if SPT is negative. It has been reported that a false positivity rate of 10-36% can be seen in IDTs using a 1/10 dilution (15). However, none of the current cases showed positivity at this dilution, while 5 returned positive results at a 1/1000 dilution. Therefore, the appropriate starting dilution for IDTs with LAs may be 1/1000; however, this would need to be supported and confirmed by larger cohort studies.

Once the diagnosis of drug hypersensitivity is established, avoidance of the culprit and potentially cross-reactive drugs should be recommended to the patients. The safety of alternative drugs should also be confirmed. Cross-reactivity occurs more frequently among ester LAs due to the antigenic metabolite para-aminobenzoic acid (PABA) (11,19). Although rare, some authors have reported cross-reactivity among several amide LAs: lidocaine, bupivacaine, mepivacaine, and ropivacaine (20,21). In the present study, 3 patients experienced cross-reactions with amide LAs: 1 patient reacted to prilocaine, lidocaine, and mepivacaine; 1 to mepivacaine and prilocaine; and 1 to lidocaine and articaine. A safe alternative LA could be identified for the lidocaine- and articaine-reactive; the aforementioned patient was found to tolerate mepivacaine. Current understanding of cross-reactivity in immediate type hypersensitivity reactions to amide LAs is limited, and therefore it is not possible to establish a distinct predictive pattern (19). Different patterns of cross-reactivity could exist as shown in our study. We therefore recommend that if a patient is hypersensitive to one agent of amide-LA, other drugs from this group should be evaluated to confirm sensitivity/tolerability.

Ideally, LAs that do not contain vasoconstrictors (e.g., adrenaline) are used when performing skin tests, as vasoconstrictors may mask a developing local wheal or flare reaction (6). In the present study, only the articaine preparations contained adrenaline. In our country, a vasoconstrictor-free preparation of articaine is not available. It is well known that the use of LAs combined with vasoconstrictors has several beneficial effects (22). Considering the preference of the referring physician, skin tests were carried out with articaine preparations containing a vasoconstrictor. Skin tests (prick/ intradermal) of the cases tested with epinephrine articaine had a high negative predictive value (96%). Therefore, LAs with epinephrine can be used in skin tests; however, this would need to be supported and confirmed by larger cohort studies.

Study Limitations

The present study has several limitations. Due to the retrospective design of the study, some data, the LA used during the index reaction in particular, were incomplete. In our study, a number of patients with a history of LA hypersensitivity reaction were tested with alternative LAs instead of the culprit LA. If these patients returned negative skin and provocation tests for the alternative LA, they were considered non-hypersensitive and excluded from the assessment. On the other hand, positive skin tests were not confirmed by subsequent sc DPT as performing a sc DPT was unethical due to the risk of causing an excessive

hypersensitivity reaction. Such an approach could have led to under- or over-estimation of the actual prevalence of LA hypersensitivity. Latex and chlorhexidine are used during procedures with LA. Additionally, the antioxidants present in anesthetic solutions containing vasoconstrictors, such as metabisulfite and sodium bisulfite, have been identified as potential triggers for allergic reactions (23). Another limitation is that the role of other potential allergens, such as latex, chlorhexidine, and excipients, were not routinely investigated in all patients.

CONCLUSION

The present study revealed that while history of non-LA DHRs and presence of diseases such as asthma, chronic rhinitis, and urticaria often cause concern for patients and physicians prior to procedures requiring LAs, they are not associated with increased risk of LA hypersensitivity reaction. Therefore, routine LA allergological evaluation is not required in those patients. However, a positive and independent association was observed between atopy and LA hypersensitivity. Although further studies are needed to confirm this finding, atopic patients seem to be more susceptible than non-atopic patients to DHRs to LAs.

Acknowledgments

The authors would like to acknowledge Meral İnal for assistance with data collection.

Conflict of interest

None

Funding

Müge Erbay, Ummühan Seker, Fatma Esra Günaydın, Dane Ediger have no sources of funding to declare for this manuscript.

Authorship Contributions

Concept: **Muge Erbay, Ummuhan Seker, Dane Ediger,** Design: **Muge Erbay, Ummuhan Seker,** Data collection or processing: **Muge Erbay, Fatma Esra Gunaydin,** Analysis or Interpretation: **Muge Erbay, Fatma Esra Gunaydin,** Literature search: **Muge Erbay, Ummuhan Seker,** Writing: **Muge Erbay, Ummuhan Seker, Fatma Esra Günaydin, Dane Ediger,** Approval: **Muge Erbay, Ummuhan Seker, Fatma Esra Günaydin, Dane Ediger.**

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