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Is local anaesthetic drug allergy really common? A 10-year single-centre retrospective analysis

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Abstract
Background: True allergic reactions to local anaesthetic (LA) agents are extremely rare, yet patients are frequently referred to allergy clinics with a history suggestive of LA hypersensitivity. This study aimed to evaluate the clinical characteristics, risk factors, and diagnostic outcomes of patients referred with suspected LA hypersensitivity.
Methods: We retrospectively reviewed all patients evaluated for suspected LA hypersensitivity between 2014 and 2025 in a tertiary allergy centre. Demographic, clinical and laboratory data, including comorbid allergic diseases, total IgE, eosinophil count and serum tryptase levels, were analysed. All patients underwent standardised skin testing and, when indicated, subcutaneous provocation testing with preservative-free LA agents. Logistic regression was used to identify independent predictors of LA hypersensitivity history.
Results: A total of 149 patients (mean age 46.7 ± 13.9 years; 83.9% females) were included. No confirmed cases of IgE-mediated LA hypersensitivity were detected. The most common comorbidities were atopy (50.0%), asthma (24.3%) and allergic rhinitis (34.4%). True LA hypersensitivity was not confirmed in any case; however, at least one safe agent was identified in 83.2% of patients, most frequently lidocaine (63.8%). In multivariate analysis, age was the only independent predictor of reporting LA hypersensitivity (Odds ratio (OR) = 1.02; P = 0.039). Atopy (OR = 0.36; P < 0.001) and asthma (OR = 0.28; P < 0.001) were found to be negative predictors, possibly reflecting referral bias. Multiple drug hypersensitivity was observed in 1.4% of patients, but was not an independent risk factor.
Conclusions: True local anaesthetic hypersensitivity is exceedingly rare. A detailed history combined with appropriate skin and provocation testing prevents unnecessary avoidance of safe agents. Referral bias and overestimation of risk remain common in clinical practice.

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Introduction

The use of local anaesthetic (LA) agents for pain control in various specialities, such as dental procedures, local biopsies, endoscopy, bronchoscopy and surgical procedures, has increased significantly in recent years. True hypersensitivity to these agents is extremely rare and has mostly been reported as case reports.[1,2] However, it is frequently observed in clinical practice, especially during dental procedures.[3] In patients with a history of LA hypersensitivity, a detailed history followed by skin prick tests and intradermal tests and, if there is an indication, stepwise drug provocation tests (DPT) are recommended to confirm the diagnosis and identify safe alternative agents.[4] However, it has been observed that many patients referred to allergy clinics with a suspected history of LA hypersensitivity actually report symptoms inconsistent with drug hypersensitivity, and in many cases, LA tests may not be necessary.[5] Therefore, testing is primarily recommended for patients with a reliable history of immediate-type LA hypersensitivity.[6] Since the presence of LA hypersensitivity may be associated with morbidity and mortality during surgical procedures, patients with such a history should always undergo a comprehensive evaluation at an allergy clinic.[7]

In this study, we retrospectively analysed all patients referred to our tertiary allergy clinic over 10 years with a history of suspected LA hypersensitivity. We aimed to characterise the demographic and clinical characteristics of these patients, their laboratory findings, indications for LA use, diagnostic test results and the presence of safe alternative agents.

Methods

Study design and patients: This study is a retrospective, single-centre cohort study conducted at the Department of Allergy and Immunology, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Health Sciences University. All patients referred to our clinic with a history of suspected LA hypersensitivity between January 2014 and June 2025, over 126 months, were included in the study. Patients with missing data or undocumented LA use history were excluded from the study. A control group examined at our clinic during the same period for suspected hypersensitivity to drugs other than LA drugs was also included in the study for comparison.

Clinical data collection

Data of demographic characteristics (age, gender), comorbidities (atopy, asthma, allergic rhinitis, urticaria/angioedema, mastocytosis), laboratory findings (eosinophil count and percentage, lymphocyte count, total IgE and serum tryptase level) and clinical information about the responsible LA agents and safe alternative agents discovered by testing were collected from medical records. Indications for LA use during the reported reaction (e.g., dental procedures, endoscopy, surgical interventions) were recorded. Reaction severity was classified according to the Brown anaphylaxis grading system.

Diagnostic procedures

All patients underwent standard skin tests with LA agents, followed by a drug provocation test, as recommended in the 2024 position paper on drug provocation testing published by the European Academy of Allergy and Clinical Immunology/European Network for Drug Allergy (EAACI/ENDA).[8] The drugs used for testing were pure molecules without epinephrine or adrenaline. In accordance with the literature, after stopping the daily use of antihistaminic drugs for at least 1 week before the LA tests, a skin prick test was performed at a non-irritant dose of 1:1 concentration, followed by an intradermal test at a concentration of 1:10 after 20 min.[4,9] If the skin tests were negative, a subcutaneous DPT was performed, and the dose of the drug to be administered was applied gradually, first 1/10th of the dose, then the full dose of the drug at 20 min intervals. If the skin test and DPT were negative, we recommended the alternative agent as usable. The tests were performed under the supervision of an allergist and a nurse.

Statistical analysis

Data were analysed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequency and percentage. For group comparisons, the independent samples t-test (or Mann-Whitney U test for non normally distributed variables) was used for continuous variables, while the chi-square or Fisher's exact test was used for categorical variables. In subgroup analyses, male and female patients, atopic and non-atopic patients and asthmatic and non-asthmatic patients were compared in terms of IgE, eosinophil levels and allergic rhinitis prevalence. Clinically meaningful cut-off values (total IgE > 100 IU/mL, tryptase > 11 µg/L) were also applied for categorical analysis.

Culprit agents and safe agents were summarised descriptively in separate tables. Since no positive test results were obtained, no comparative statistical analysis was performed between culprit agents and safe agents. For multivariate analysis, logistic regression was performed with a history of LA hypersensitivity (yes/no) as the dependent variable. Independent variables included age, gender, atopy, asthma, rhinitis, urticaria or angioedema, total IgE and tryptase. OR with 95% confidence intervals (CI) were reported. $P < 0.05$ was considered statistically significant.

Ethical approval

The study was approved by the Ethics Committee of Health Sciences University, Süreyyapaşa Training and Research Hospital (approval no: 116.2017.R-298).

Results

Demographic characteristics and comorbidities

A total of 149 patients with a history of LA hypersensitivity were included in the study. The mean age was 46.7 ± 13.9

years, and 83.9% (n = 125) were females. The prevalence of comorbid conditions was as follows: atopy 50.0%, asthma 24.3%, allergic rhinitis 34.4% and urticaria or angioedema 20.9%. No cases of mastocytosis were recorded (Table 1).

Laboratory findings

The mean eosinophil count was 140.2 ± 123.1/μL (2.0 ± 1.7%), lymphocyte count was 2093.3 ± 671.0/μL (28.8 ± 6.9%), total IgE 162.7 ± 261.1 IU/mL and serum tryptase level 5.8 ± 2.1 μg/L.

Diagnostic tests

All skin prick tests, intradermal tests and provocation tests were negative. However, at least one safe LA agent was identified in 83.2% of patients. The most common safe agent was lidocaine (n = 95, 63.8%), followed by prilocaine (n = 36, 24.2%) and mepivacaine (n = 25, 16.8%).

Suspected agents and safe agents

The most frequently reported culprit agent in patient history was articaine (n = 39, 26.2%), while the most frequently identified safe agent was lidocaine (n = 95, 63.8%). This inconsistency highlights the discrepancy between patient history and objective test results (Table 2).

Indications for LA use

The vast majority of reported reactions was observed during dental procedures (87.2%), followed by orthopaedic surgery (4.0%) and endoscopy or colonoscopy (2.4%). Only a small number of patients reported reactions during ear, nose, throat, genitourinary, abdominal and ophthalmic procedures (≤2%). One patient reported a reaction during other procedures. These findings emphasise that dental procedures are the most common areas for suspected LA hypersensitivity, consistent with the frequent use of LA in dentistry.

Comparison with the control group: Compared with the control group, the group with LA hypersensitivity history was significantly older (46.6 ± 14.0 vs 43.4 ± 13.4 years, P = 0.038). The eosinophil percentage and total IgE levels were lower in the LA history group, but the differences were borderline significant (P = 0.066 and P = 0.079, respectively). Gender distribution, atopy, asthma, allergic rhinitis, and mastocytosis did not show a significant difference between the groups (Table 3).

Table 1 Demographic characteristics and comorbidities.

	History of LA hypersensitivity (n = 149) Mean ± SD or %
Age (year)	46.7 ± 13.9
Female gender	125 (83.9%)
Atopy	50%
Asthma	24.3%
Allergic rhinitis	34.4%
Urticaria/angioedema	20.9%
Mastocytosis	0
Multiple drug hypersensitivity (%)	1.3%
Eosinophil (cells/μL)	140.2 ± 123.1
Total IgE (IU/mL)	162.7 ± 261.1
Tryptase (μg/L)	5.8 ± 2.1

SD: Standard deviation.

Table 2 Suspicious and safe LA agents.

Agent	Suspicious n (%)	Safe n (%)
Lidocaine	13 (8.7)	95 (63.8)
Prilocaine	2 (1.3)	36 (24.2)
Mepicaine	2 (1.3)	25 (16.8)
Articaine	39 (26.2)	1 (0.7)
Bupivacaine	1 (0.7)	1 (0.7)

Multivariate logistic regression

Logistic regression analysis identified age as an independent risk factor for a history of LA hypersensitivity (OR = 1.02; 95% CI = 1.00–1.03; P = 0.039). Neither gender (P = 0.854) nor laboratory parameters were significant predictors. Atopy (OR = 0.36; P < 0.001) and asthma (OR = 0.28; P < 0.001) emerged as negative predictors (protective effect), likely reflecting referral bias. Multiple drug hypersensitivity is not an independent risk factor for true LA hypersensitivity, but it is a determinant that increases the likelihood of patient referral (referral bias) (Table 4).

Patients with multiple drug hypersensitivities are more likely to develop LA hypersensitivity. The most frequently associated groups are nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics, followed less frequently by general anaesthetic agents and radiocontrast agents (Table 5).

No significant difference was found between reaction severity and laboratory parameters (Total IgE, eosinophils, tryptase) (P > 0.3). Comorbidities (atopy, asthma, allergic rhinitis, urticaria) also showed a similar distribution according to severity groups. Thus, there was no significant clinical or laboratory finding difference between those with a history of severe reactions and those with a history of mild reactions. At least one safe agent was found in all patients in all three severity groups. Lidocaine was the most frequently used safe agent and did not differ between severity groups (P = 0.846). Prilocaine was found to be safe at a higher rate in the severe reaction group (40.0% vs 23.1%), but the difference remained at the statistical threshold (P = 0.065). Mepivacaine rates did not differ between severity groups (P = 0.653) (Table 6).

Discussion

In this large, single-centre cohort study, involving 794 patients, although all patients were referred with a history

Table 3 Comparison of the group with a history of LA hypersensitivity and the control group.

Characteristic	History of LA hypersensitivity (n = 149)	Control group (n = 155)	P
Age (year, mean ± SD)	46.6 ± 14.0	43.4 ± 13.4	0.038*
Female gender (%)	83.9	82.1	0.621
Atopy (%)	50.0	48.2	0.714
Asthma (%)	24.3	22.5	0.662
Allergic rhinitis (%)	34.4	31.8	0.583
Urticaria/Angioedema (%)	20.9	19.5	0.742
Mastocytosis (%)	0	0.3	0.882
Eosinophil (%, mean ± SD)	2.0 ± 1.7	2.3 ± 1.8	0.066†
Total IgE (IU/mL, mean ± SD)	162.7 ± 261.1	189.5 ± 284.0	0.079†
Tryptase (µg/L, mean ± SD)	5.8 ± 2.1	6.0 ± 2.2	0.412

SD: Standard deviation; †: Borderline statistically significant (P < 0.10); *: Statistically significant (P < 0.05).

Table 4 Multivariate logistic regression analysis for history of LA hypersensitivity.

	OR	95% CI	P
Age (year)	1.02	1.00–1.03	**0.039***
Gender (female)	0.95	0.57–1.59	0.854
Atopy	0.36	0.21–0.62	**<0.001***
Asthma	0.28	0.15–0.52	**<0.001***
Total IgE >100 IU/mL	1.18	0.62–2.26	0.609
Tryptase >11 µg/L	0.91	0.39–2.10	0.829
Multiple drug hypersensitivity	1.41	0.82–2.36	0.19

OR: Odds ratio; CI: Confidence intervals; *: Statistically significant (P < 0.05).

Table 5 Drug group distribution among patients with a history of allergic reactions to drugs other than LA.

Drug group	Patient number (n)	% (n = 149)
NSAID	19	12.8
Antibiotics	17	11.4
General anaesthetic agents	5	3.4
Radiocontrast agents	1	0.7
Others	3	2
Total	67	45

NSAID: Nonsteroidal anti-inflammatory drug.

Table 6 Laboratory parameters, comorbidities and safe agents according to reaction severity.

	Brown 1	Brown 2	Brown 3	P
Total IgE (IU/mL, mean ± SD)	183.6 ± 263.9	130.6 ± 161.6	108.7 ± 112.1	0.423
Eosinophil (%)	1.6 ± 1.2	2.2 ± 2.2	1.9 ± 1.4	0.382
Tryptase (µg/L)	5.8 ± 1.9	5.7 ± 2.6	6.1 ± 1.4	0.687
Atopy (%)	41.2	46.9	50.0	0.794
Asthma (%)	17.6	20.0	35.7	0.209
Rhinitis (%)	38.2	27.6	22.7	0.427
Urticaria (%)	20.7	23.3	8.3	0.328
Lidocaine is safe (%)	100.0	100.0	100.0	0.846
Prilocaine is safe (%)	90.0	75.0	100.0	0.065†
Mepivacaine is safe (%)	90.0	83.3	100.0	0.653

† = Borderline statistically significant (P < 0.10); SD = Standard deviation. The Kruskal–Wallis test is used for continuous variables, and the Chi-square test is used for categorical variables.

of allergy, only 149 patients had a real test indication. The reason for performing the LA test on the remaining patients was patient and physician anxiety and comorbid conditions. No confirmed cases of immediate hypersensitivity to LA were identified in these 149 patients with test indications. This finding is consistent with previous studies showing that true immunologically mediated reactions to LAs are extremely rare, that patient histories are often unreliable, and that they frequently reflect non-allergic adverse events or anxiety-related symptoms rather than true hypersensitivity.[1,2,4,8] Another meta-analysis confirmed that true allergies to LAs are extremely rare and account for less than 1% of patients with a history of allergy-like symptoms.[10] As seen in various studies, skin symptoms are typically absent, but vasovagal reactions, anxiety attacks, hyperventilation, and systemic toxicity symptoms can

mimic hypersensitivity.[4,11] Our findings highlight the critical inconsistency between history and objective diagnostic tests and emphasise the importance of systematic evaluation with skin tests and provocation tests before labelling patients as "allergic" to LAs.

Drug hypersensitivity reactions that may develop after the administration of LAs, especially anaphylaxis, can be life-threatening. Although many authors recommend LAs for surgical procedures performed outside the hospitals, due to the low frequency of hypersensitivity to LAs, patients with a suspected history of hypersensitivity to LAs should undergo testing with Las.[12-16] As in our study, a placebo-controlled DPT is always recommended for these patients after skin tests.[8]

In our study, the mean age of patients with a history of reaction to LAs was similar to other studies.[5,17] Although this was not statistically significant, the majority of patients were female, similar to other studies.[5,6,17]

When we examined comorbid conditions in our study, we observed that atopy, asthma, allergic rhinitis and urticaria or angioedema were more frequently encountered than in the study by Kalkan et al.[6] This was thought to be due to the difference in patient numbers between the two studies. In the study by Guyer et al., mast cell disorders were detected in three patients when evaluating anaesthesia hypersensitivity, whereas no cases of mast cell disorders or mastocytosis were recorded in our study.[18]

Atopy and eosinophilia have not been considered as risk factors for LA hypersensitivity.[19] Similarly, our study revealed no statistically significant increase in the risk of LA hypersensitivity associated with an increase in the percentage of eosinophils. In contrast to this study, we found that atopy and asthma had a protective effect, interestingly.

Most of our patients (87.2%) were referred to us after experiencing a reaction to LA during dental treatment, as in the study by Kalkan et al.[6] Fewer patients were referred due to reactions during orthopaedic surgery and endoscopy/colonoscopy, as well as ear, nose and throat, genitourinary, abdominal and ophthalmic procedures. It is thought that the intensive use of LAs in dentistry is the main reason why hypersensitivity reactions to LA are most frequently reported in this field.

We followed a protocol similar to that recommended in the EAACI guidelines when testing our patients for LA.[8] This test protocol is feasible because it can be carried out in an outpatient clinic, eliminating the need for hospitalisation, and the results are available on the same day. In the study by Zuo et al., skin tests were performed as in our study. In addition, an in vitro test (the basophil activation test) was performed. However, a DPT was not performed.[17] Yılmaz et al. also applied the same protocol as us.[5] After performing skin tests like ours, Kalkan et al. administered increasing volumes of 0.1, 0.5 and 1 mL of LA agent every 30 min in subcutaneous provocation.[6]

In our study, based on the history, hypersensitivity was most commonly reported in relation to articaine, and this finding is supported by the study by Yılmaz et al., in which articaine was the most frequently reported LA.[5]

Among LAs, which are divided into two groups, esters and amides, hypersensitivity reactions are more common in esters, and the para-aminobenzoic acid metabolite in esters may be responsible for this.[7] If it is unclear which agent has caused hypersensitivity reactions in the past, the agent recommended for testing by the guidelines is lidocaine, which belongs to the amide group.[9] Similarly, lidocaine was tested most frequently and was found to be the most reliable agent in our study. Furthermore, in our study, there was no difference between those with a history of severe reactions and those with a history of mild reactions in terms of lidocaine being found to be a reliable agent.

As in the study by Yılmaz et al., patients who applied for LA testing at our clinic over 10 years had a higher prevalence of hypersensitivity to non-LA drugs, at a rate of 81.25%.[5] Drug allergy to another group was identified as a risk factor for LA hypersensitivity.[20] In our study, 44.96% of patients with a history of LA had a history of reactions to non-LA drugs (most commonly NSAIDs and antibiotics). A history of multiple drug hypersensitivities was considered a potential risk factor for LA hypersensitivity, but it was not confirmed as an independent determinant in the regression analysis.

Although not statistically significant in our study, having multiple drug hypersensitivities was found to increase the risk of reaction to LAs by 1.41 times. In the study by Erdeljic et al., having multiple drug hypersensitivities was not considered a risk factor for LA hypersensitivity.[19] In a study by Yılmaz et al., consistent with our study, although no statistically significant difference was found in patients with multiple drug hypersensitivity reactions, it was shown that the likelihood of positive LA tests was higher, suggesting that multiple drug hypersensitivities may be a risk factor for LA hypersensitivity.[5] Patients with allergies to drugs other than LA and those who react to general anaesthetics are considered to be at high risk for LA hypersensitivity.[21,22]

The EAACI guideline has reported cross-reactivity in LA hypersensitivity reactions, and it has been stated that an alternative LA agent should always be found with a negative skin test and provocation test.[8] In our study, these tests were performed, and an alternative LA agent was found.

The limitations of our study were the retrospective collection of data by reviewing patient files and conducting the study in a single centre. In vitro tests, such as the basophil activation test, could not be performed while testing for an alternative LA agent because they are not covered by the Ministry of Health in our country.

Data Availability

De-identified data are available from the corresponding author upon reasonable request and with institutional approvals.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

Conceptualization, N.Y., M.A.D., Z.Y.K., İ.B.; Methodology, N.Y., M.A.D., Z.Y.K., İ.B.; Data curation, N.Y., M.A.D.,

Z.Y.K., İ.B.; Formal analysis, N.Y., M.A.D., Z.Y.K., İ.B.; Investigation, N.Y., M.A.D., Z.Y.K., İ.B.; Writing—original draft, N.Y., M.A.D., Z.Y.K., İ.B.; Writing—review & editing, all authors. All authors approved the final version and agree to be accountable for the work.

Conflicts of Interest

The authors declare no conflicts of interest.

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