Is Local Anaesthetic Drug Allergy Really Common? Single Centre Experience

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Abstract

Aim: The main aim of this study is to objectively determine the actual frequency of allergic reactions in patients with a history of allergy to local anaesthetic drugs using skin tests and alternative provocation tests. In addition, it is aimed to evaluate the prevalence of other drug allergies in individuals presenting with local anaesthetic allergy and the effect of this on clinical presentation. The study also aims to shed light on clinical approaches by analysing the test results performed in patients who are administered alternative drugs due to a history of allergy.

Methods: The data of patients who presented to the immunology and allergy outpatient clinic with local anaesthetic agent allergy between 01.01.2019-01.04.2025 were retrospectively reviewed. Other drug reactions, local anaesthetic agent allergy severity and alternative drug test results were recorded.

Results: The mean age of the 99 patients in the study was 45 years (min: 19, max: 77). 79 of the patients were female and 20 were male. 29 of 99 patients (29.3%) had a history of reaction with local anaesthetics. 10 (34,5%) of 29 patients had reactions with other anaesthetics. 9 of 29 patients (31%) had reactions with lidocaine, 7 (24,1%) with articaine and 1 (3,4%) with prilocaine. 91 patients (91.9%) were referred to our clinic by dentists, 6 patients (6.1%) by surgical clinics and 1 patient (1%) by anaesthesia.

Conclusions: It was observed that the majority of the patients described reactions with drugs other than local anaesthetics and therefore consulted a doctor. This situation, in accordance with the literature, showed that the reason for the application of both health professionals and patients was not due to local allergic drug allergy. The fact that only two patients were positive in the tests performed shows that the rate of local anaesthetic allergy is low, although the number of patients is insufficient.

Keywords:*Local anaesthesia; drug hypersensitivity; skin prick test; dentistry*

1. Introduction

Local anaesthetic (LA) agents have been used for various purposes since the late 19th century. Today, it is estimated that 6 million doses of local anaesthetic (LA) are administered daily worldwide.[1] LA chemically consists of three parts. An aromatic ring is linked to a secondary or tertiary amine structure by an ester or amide bond. According to this structure, they are classified as benzoic acid esters (piperocaine, benzocaine, chloroprocaine, procaine, tetracaine, cocaine) or amide derivatives (mepivacaine, lidocaine, bupivacaine, articaine, ropivacaine, prilocaine).[2] Adverse drug reactions (ADRs) to LAs are estimated to occur in 2.5-10% of patients. The vast majority of AERs are non-immunological reactions such as toxicity, intravascular administration of LAAs, LAA overdose, anxiety (needle phobia, panic attacks, vasovagal syncope) and the pharmacological effect of added vasopressors (e.g. adrenaline). Allergic reactions to LAAs may be immediate immunoglobulin E (IgE)-mediated (type I) and/or non- immediate T-cell mediated (type IV). Type I reactions are extremely rare and can cause anaphylaxis, whereas type IV reactions are relatively more common, most commonly present as allergic contact dermatitis and are not life-threatening for the patient.[3] In an open-label prospective study of AIRs due to LAAs in dentistry, 0.5% of 5018 patients experienced mild reactions, but none were considered allergic or hypersensitivity reactions (ADRs). A questionnaire survey of German dentists found that the overall incidence of AIR in 2731 cases was 4.5%, but less than 1% of reactions were allergic.[4] Given both the rarity and risk of allergic reactions to LAAs, there is a need for an appropriate approach to the selection of patients for research, as LA skin tests and challenges to determine allergy are painful, time-consuming and costly procedures. The current level of knowledge does not allow clinicians to predict which patients will have a hypersensitivity reaction to LAAs. Literature information is scarce and data on

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concerns regarding consideration of test indications are controversial.[2] It is recommended that skin testing and subcutaneous provocation tests be performed to determine which alternative LAA drug the patient tolerates. In all case reports of LAA drug reactions, alternative anaesthetics tolerated by patients were identified as such.[5]

2. Materials and Methods

Between 01.01.2019-01.04.2025, the information of patients admitted to the immunology and allergy outpatient clinic with LAA allergy was scanned through their files in the hospital automation system. 99 patients were included in the study. Demographic data, comorbidities, presence of atopy, and systemic disease medications were noted. The presence of allergy to any other drug group, the type of reaction, the duration and severity of the reaction were recorded. The results of alternative local anaesthetic drug tests and provocation were recorded. Finally, the clinic from which the patient was referred was noted and evaluated. Atopy was determined by skin test and serum total immunoglobulin E (IgE) in appropriate patients. Reactions occurring 60 minutes (min) or more before the onset of reaction with LAA were categorised as early reactions. The severity of the reaction was graded clinically according to the World Allergy Organisations (WAO) grading system , 5 grades.[6] Adult patients who presented with LAA allergy were included in the study. Pregnant women and patients who were not able to perform provocation test and skin prick test were excluded from the study. All patients underwent skin testing including skin prick test (SPT) and intradermal test (IDT), followed by subcutaneous provocation test (SCP) with the tested LAAs. IDT was performed if SPTs were negative. Positive (histamine chloride 1 mg/mL) and negative (0.9% sodium chloride) controls were applied to the forearms of the patients. Skin prick tests were performed with undiluted drug; if negative, intradermal tests were performed using 1/100 and 1/10 dilutions (according to the reaction described). It was considered positive if the mean wheal was at least 3 mm larger than the negative control for SPT and at least 3 mm larger for IDT. In patients with negative skin tests, subcutaneous (0.1 ml and 1 ml) drug provocation tests were performed with increasing doses on the lateral surface of the patients' arms. Local signs around the injection site, general symptoms and vital signs were observed for up to 30 minutes.[7]

3. Results

The mean age of the 99 patients in the study was 45 years (min: 19, max: 77). 79 of the patients were female and 20 were male. 32 patients (32.3%) had chronic diseases and 28 of them were women (Figure 1 and Figure 2). 17 patients (53.1%) had hypertension, 9 (28.1%) had diabetes mellitus, 5 (15.6%) had coronary artery disease, 6 (18.8%) had thyroid pathologies and 2 (6.3%) had malignancy. 39 patients (39.4%) were taking medication for chronic diseases. 38 patients (38.4%) had atopy. Of these patients, 15 (39.5%) had asthma, 27 (71.1%) had rhinitis, and 9 (23.7%) had urticaria-angioedema (Table 1).

In 80 (80.8%) of the patients, there was a previous reaction with other drugs. Of these 80 patients, 49 (61.3%) had a history of reaction with non-steroidal anti-inflammatory drugs (NSAIDs), 41 (51.2%) with antibiotics, 1 (1.3%) with radio contrast material, 1 (1.3%) with chemotherapy agents and 11 (13.8%) with other drugs. There were 18 patients (22.5%) with a history of allergic reaction to both NSAIDs and antibiotics (Table 2).

29 of 99 patients (29.3%) had a history of reaction with local anaesthetics. 10 (34,5%) of 29 patients had reactions with other anaesthetics. 9 of 29 patients (31%) had reactions with lidocaine, 7 (24,1%) with articaine and 1 (3,4%) with prilocaine. In 12 patients (41.4%), the local anaesthetic to which the reaction occurred could not be determined (Table 3). The mean time from drug exposure to reaction onset was 42.9 minutes (min) in grade 1 reactions. The reaction onset time was <60 min in 25 (86%) of 29 patients who experienced a reaction with local anaesthetic.

Table 1

Demographic and Clinical Characteristics of the Study Population

Characteristic	Value (n=99)	
Age (mean, min-max)	45	(19-77)
Sex		
- Female	79	(79.8%)
- Male	20	(20.2%)
Presence of Chronic Disease	32	(32.3%)
- Chronic disease in females	28	(87.5%)
Chronic Diseases		
- Hypertension	17	(53.1%)
- Diabetes Mellitus	9	(28.1%)
- Coronary Artery Disease	5	(15.6%)
- Thyroid Disorders	6	(18.8%)
- Malignancy	2	(6.3%)
Medication Use	39	(39.4%)
History of Atopy	38	(38.4%)
- Asthma	15	(39.5%)
- Allergic Rhinitis	27	(71.1%)
- Urticaria/Angioedema	9	(23.7%)

Table 2

Other Drug Reactions

	n:99	%
- Any Drug Reaction	80	80.8
- NSAID	49	61.3
- Antibiotic	41	51.2
- RCA	1	1.3
- Chemotherapy	1	1.3
- Other Drugs	11	13.8
- Both NSAID and Antibiotic	18	22.5

NSAID: non-steroidal anti-inflammatory drug, RCA: Radiocontrast agent,

The severity of the reactions are summarised in table 4. 64 of 99 patients had serum total IgE results. Total IgE level was >100 in 32 of these 64 patients (50.8%).

Of all patients, 28 (28.3%) were tested with lidocaine, 12 (12.1%) with prilocaine, 15 (15.2%) with safecain, 52 (52.5%) with articaine and 1 (1%) with bupivacaine. Provocation with the

offending drug was performed in 2 patients with suspected lidocaine and 1 patient with suspected articaine and resulted negative. DPT, IDT and SCP with all anaesthetics except articaine were negative. One DPT and one provocation test with articaine were positive. In other words, drug tests with local anaesthetics were positive in only 2 of 99 patients.

91 patients (91.9%) were referred to our clinic by dentists, 6 patients (6.1%) by surgical clinics and 1 patient (1%) by anaesthesia. 1 patient was admitted voluntarily. There was no positive correlation between the history of reaction with other drugs and the history of reaction with local anaesthesia and between total IgE level and severity of reaction.

Table 3

Local Anaesthetic Reactions

	n	%
- LA Reaction Present	29	29.3
- With Other Drug Reaction	10	34.5
-Without Other Drug Reaction	19	65.5
- Lidocaine	9	31
- Articaine	7	24.1
- Prilocaine	1	3.4
- Unknown LA	12	41.4

LA: local anaesthetic

Table 4

Local anaesthetic Reaction Severity

Grade of reaction	n	%
Grade 1	22	75.9
Grade 2	3	10.3
Grade 3	2	6.9
Grade 4	2	6.9

4. Discussion

In LA allergies, it can often be difficult to distinguish between allergic and non-allergic AIRs due to the overlap of symptoms related to LAs. Although allergic reactions to LAs are rare, the risk may be greatly exaggerated by health professionals and patients from other disciplines. Even in the absence of a history of AIR to LAs, the use of LAAs in unnecessarily painful procedures is avoided in cases with other allergic comorbidities or a history of drug allergy. As a result, many patients may have to undergo general anaesthesia. This necessitates allergists to test the referred patients.

Multi-drug allergy is considered a risk factor for LA allergy. Patients with a history of allergy to other drugs and a history of reactions to general anaesthetics are considered to be at increased risk of developing LA allergy.[8] However, some studies suggest that the occurrence of unexpected side effects after LA administration is a risk factor for a similar or more severe reaction after further exposure to the same agent. [7,9] In our study, 80 patients had a history of reaction with other drugs. However, only 10 of 29 patients who had a reaction with local anaesthetics had a history of reaction with other drugs. This may indicate that patients with multidrug ADR are not a possible risk factor for LAA allergy. A larger cohort may be needed to say whether having non-LAA drug allergy is a potential risk. This can be considered as one of the limitations of our study.

Similar to the rates in a previous study, 90% of our patients were referred by a dentist.[7] Again, in accordance with this literature information, 80% of our patients had reactions with different drugs and the rate of patients with a history of reaction with LAA was 28%. Only one third of the patients who had a reaction with LAA had a history of reaction with drugs other than LAA.[10] All these data showed that concerns about the safety of LA application in both patients and dentists were the determining reason for consultation and the data of our study were similar.

Saito et al. suggested that the risk of developing allergy with LA is quite high in patients with a general allergic tendency to any drug, food and disease.[11] However, in our study, 38% patients had atopy and/or atopic disease. Only 34% of those who experienced a reaction with LA had a history of allergy to other drugs. This information did not support the literature, whereas Haddi et al. showed that the risk of adverse reactions to drugs was not higher in atopic individuals, which is consistent with our study.[12] According to all our data, we cannot say that having allergic disease or being atopic predicts LA drug allergy, but it may be more accurate to say this with a higher number of patients.

The European Network of Drug Allergy (ENDA) and the Drug Hypersensitivity interest group in the European Academy of Allergy and Clinical Immunology (EAACI) guidelines recommend DPT with undiluted LA and IDT with 1/10 dilution followed by SCP testing.[13] In our study, we first performed DPT and then IDT with 1/10 dilution. However, some researchers advocate the use of 1:100 dilution in intradermal tests to avoid irritant test reactions and even believe that intradermal tests can be skipped because false positive test results may occur against LAAs.[14,15] However, we performed DPT, IDT and SCP in all our patients.

Since allergy to LAAs is rare, one study suggested that a negative skin test may exclude an IgE-mediated hypersensitivity reaction[16] . Another study suggested that a single full-dose placebo-controlled SCP with the offending LA could be performed in most patients without prior skin testing.[13] The existence and nature of cross-reactions between LAAs is not yet clear, as many reactions are limited to case reports and there is no consistency between the findings.[2] All patients in our study underwent skin tests and drug provocation tests to find an alternative LA to use. The total number of patients who underwent drug provocation tests was 108. However, only one DPT and one SCP were positive. In other words, only two out of 99 patients showed positivity which may perhaps indicate cross-reaction. However, it would be correct to say this based on a larger number of patients and more criminal drug provocation and skin tests.

In one study, 402 patients with suspected hypersensitivity reactions to LAA were screened over a 20-year period. Only two patients were diagnosed with true LA allergy. However, both had a history of generalised urticaria with arterial hypotension and tachycardia after LA injections.[15] The reaction described in 42% of our patients in the study was of the early type. According to this result, 72% of the patients had grade 1 reaction according to the WAO grading[6] system. Grade 1 reaction included mild skin findings (itching, local urticaria, swelling), mild upper respiratory tract (runny nose and itching, scratching in the throat, etc.) or mild gastrointestinal findings (nausea, mild abdominal pain).[17] All these literature data supported our study. In contrast to our study, another study suggested that in patients with suspected allergy to LA, a history of diffuse skin symptoms and hypotension in LA reaction identifies individuals at risk of LA A allergy to some

extent[18] . In the differential diagnosis of hypotension and acute urticaria, vasovagal reaction should be taken into consideration, because its lifetime incidence is around 20%.[16] The fact that only 29 of 99 patients sent for LA drug testing had a history of LA, and that we found positivity in the tests in only 2 of them, together with the clinical incompatibility described in this LA allergy in the literatures, showed us that mild symptoms may not really be LA drug allergy and may not determine the risk for LA A allergy. It may also indicate that the patient and the intervening physician were afraid of the history of drug allergy and therefore referred to an allergist.

In a study including 430 patients, 216 patients were referred to an allergist because of a history of ADR with non-LA drugs.[2] It was found that 133 of these patients had ADR with more than one drug. Similarly, in our study, the majority of the patients (80%) were referred to us because of ADR with other drugs. Again, 22% of these patients had a history of HSR with more than one drug.

The EAACI/ENDA guideline strongly recommends testing other LAs to determine an alternative in the case of confirmed LA allergy.[13] This is due to the possibility of cross-reaction between LAs, which is often seen in the ester group. The reason for the lower incidence of cross-reaction between amides is not clear. In addition, the aromatic ring (meta-xylene) present in mepivacaine, lidocaine and bupivacaine but absent in articaine has been identified as a possible antigenic determinant. However, there are also studies that do not support this hypothesis.[19] In our study, we provoked 52% of our patients with articaine. In one patient, DPT was found to be positive with articaine and the test was terminated. In the other one, positivity was again seen with articaine provocation. 28% of the patients were tested with lidocaine. We believe that our number of patients is not sufficient to give an opinion about cross reaction.

4.1. Limitations

A larger cohort is needed to determine whether cross-reaction between LA drugs, atopy and other drug allergy predict the risk of LAA allergy.

5. Conclusion

We concluded that LA allergy is not as common as reported in the literature. In addition, alternative drug testing may prevent patients from unnecessary general anaesthesia and we recommend that it be performed. We think that patients and physicians were referred for testing because of high anxiety and fear about LA allergy. The highest referral rate was from the department of dentistry. This may be due to both the frequent use of these drugs in dentistry and perhaps the failure to recognise that it is related to AIR. We believe that studies in larger patient groups are needed for cross-reaction.

Statement of ethics

This study was approved by the Adana City Training and Research Hospital Ethics Committee (Decision No: 2025/554).

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

Author contributions

Both authors contributed equally to the article. Both authors read and approved the final manuscript.

References

1.Kvisselgaard AD, Mosbech HF, Fransson S, Garvey LH. Risk of immediate-type allergy to local anesthetics is overestimated-results from 5 years of provocation testing in a Danish allergy clinic. J Allergy Clin Immunol Pract. 2018;6(4):1217-23. [Crossref]

2.Koca Kalkan I, Koycu Buhari G, Ates H, Basa Akdogan B, Erdem Ozdedeoglu O, Aksu K, et al. Identification of risk factors and cross-reactivity of local anesthetics hypersensitivity: analysis of 14-years' experience. J Asthma Allergy. 2021;14:47-58. [Crossref]

3.Post TW, editor. Allergic reactions to local anesthetics. Waltham, MA: UpToDate; 2020.

4.Jiang S, Tang M. Allergy to local anesthetics is a rarity: review of diagnostics and strategies for clinical management. Clin Rev Allergy Immunol. 2023;64(2):193-205. [Crossref]

5.Domínguez-Ortega J, Phillips-Angles E, González-Muñoz M, Heredia R, Fiandor A, Quirce S. Allergy to several local anesthetics from the amide group. J Allergy Clin Immunol Pract. 2016;4(4):771-2. [Crossref]

6.Turner PJ, Ansotegui IJ, Campbell DE, Cardona V, Carr S, Custovic A, et al. Updated grading system for systemic allergic reactions: joint statement of the World Allergy Organization Anaphylaxis Committee and Allergen Immunotherapy Committee. World Allergy Organ J. 2024;17(3):100876. [Crossref]

7.Yllmaz I, Özdemir SK, Aydin Ö, Çelik GE. Local anesthetics allergy: who should be tested? Eur Ann Allergy Clin Immunol. 2018;50(2):66-71. [Crossref]

8.Mertes PM, Lambert M, Guéant-Rodriguez RM, Aimone-Gastin I, Mouton-Faivre C, Moneret-Vautrin DA, et al. Perioperative anaphylaxis. Immunol Allergy Clin North Am. 2009;29(3):429-51. [Crossref]

9.Grzanka A, Wasilewska I, Śliwczyńska M, Misiołek H. Hypersensitivity to local anesthetics. Anaesthesiol Intensive Ther. 2016;48(2):128-34. [Crossref]

10.Astarita C, Gargano D, Romano C, Cutajar M, Manguso F, Montanaro D, et al. Long-term absence of sensitization to mepivacaine as assessed by a diagnostic protocol including patch testing. Clin Exp Allergy. 2001;31(11):1762-70. [Crossref]

11.Saito M, Abe M, Furukawa T, Yagi M, Koike Y, Wakasugi Y, et al. Study on patients who underwent suspected diagnosis of allergy to amide-type local anesthetic agents by the leukocyte migration test. Allergol Int. 2014;63(2):267-77. [Crossref]

12.Haddi E, Charpin D, Tafforeau M, Kulling G, Lanteaume A, Kleisbauer JP, et al. Atopy and systemic reactions to drugs. Allergy. 1990;45(3):236-9. [Crossref]

13.Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68(6):702-12. [Crossref]

14.Speca SJ, Boynes SG, Cuddy MA. Allergic reactions to local anesthetic formulations. Dent Clin North Am. 2010;54(4):655-64. [Crossref]

15.Trautmann A, Goebeler M, Stoevesandt J. Twenty years' experience with anaphylaxis-like reactions to local anesthetics: genuine allergy is rare. J Allergy Clin Immunol Pract. 2018;6(6):2051-8.e1. [Crossref]

16.Furci F, Martina S, Faccioni P, Faccioni F, Senna G, Caminati M. Adverse reaction to local anaesthetics: is it always allergy? Oral Dis. 2020;26(6):1340-2. [Crossref]

17.Harboe T, Guttormsen AB, Aarebrot S, Dybendal T, Irgens A, Florvaag E. Suspected allergy to local anaesthetics: follow-up in 135 cases. Acta Anaesthesiol Scand. 2010;54(5):536-42. [Crossref]

18.Ing Lorenzini K, Gay-Crosier Chabry F, Piguet C, Desmeules J. Meta-xylene: identification of a new antigenic entity in hypersensitivity reactions to local anesthetics. J Allergy Clin Immunol Pract. 2016;4(1):162-4. [Crossref]

19.De Pasquale TMA, Buonomo A, Pucci S. Delayed-type allergy to articaine with cross-reactivity to other local anesthetics from the amide group. J Allergy Clin Immunol Pract. 2018;6(1):305-6. [Crossref]