Review

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Local Anesthetic Hypersensitivity Reactions in Pediatric Patients: Recognition and Management

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Local anesthetics (LAs) are commonly used in all medical specialties, particularly in association with surgery, obstetrics, dentistry, and emergency departments. Most individuals, starting from young children, are exposed to LAs during life. LA hardly induces adverse events when used in recommended doses and with proper injection techniques. However, immediate anaphylactic reactions to LA injections may be a rare but life-threatening manifestation. A comprehensive report of the event and performing a specialist examination are crucial to prevent further episodes. The diagnosis should be based on history, medical records, skin and challenge tests.

Keywords: drug adverse reactions; local anesthetic allergy; drug allergy

Introduction

Local anesthetics (LAs) prevent and reduce pain and other sensations in selected body areas without inducing sedation and unconsciousness. They can be used in various settings, such as surgery, obstetrics, dentistry, and emergency departments. In children gels, ointments, and sprays containing LAs are topically applied on skin and mucosa during painful procedures such as venous puncture, arterial puncture, intravenous catheter placement, intravenous or intramuscular injection, simple wound repair, and lumbar puncture. Moreover, LA solutions are used for subcutaneous or tissue infiltration, especially for large wound repair, skin surgery, and dental interventions. Intravenous LAs are used for neuraxial blocks and regional anesthesia [1]. Less than 1% of adverse reactions to LAs are allergic, and there are a few case reports of quick-onset anaphylactic reactions due to LA hypersensitivity [2]. Therefore, this issue is poorly understood by physicians and dentists [3]. Here, we provide a review of developments in the field of hypersensitivity reactions to LAs. This information is helpful for allergists and pediatricians in approaching LA hypersensitivity in clinics, hospitals, and emergency departments.

Pharmacology

LAs act by blocking the entry of sodium through sodium channels in the neuronal membrane. This results in disrupting nerve signal transmission and pain transmission [4].

LA molecules are composed of a lipophilic aromatic ring, a terminal amine hydrophilic group, and an intermediate chain with amides or benzoic acid esters [2] (Fig. 1, produced by Marvin JS (Version 23.14.0, Chemaxon Ltd., Budapest, Hungary)). Ester LAs include procaine, benzocaine, chloroprocaine, and tetracaine. Pseudocholinesterase degrades esters to p-aminobenzoic acid (PABA), which may induce immediate and late hypersensitivity reactions. Amide LAs, including lidocaine, articaine, mepivacaine, and bupivacaine, have an amide linkage at variance from esters. Amides are metabolized in the liver

by microsomal enzymes. Physiochemical properties that determine the activity of LAs are lipid solubility, which allows diffusion through the neural membrane, pKa, molecular weight, and degree of protein binding. Intoxication is more common in children than adults since mucocutaneous absorption is greater and quicker, and the link between LAs and plasma proteins is weak [5]. Amide LAs are chemically more stable and have a longer half-life than the ester LAs. Amide LAs may be short, medium, and long-acting (Fig. 1). Liposomal bupivacaine is an extra long-acting drug (72 hours) that has been approved for children over 6 years of age in Europe [6].

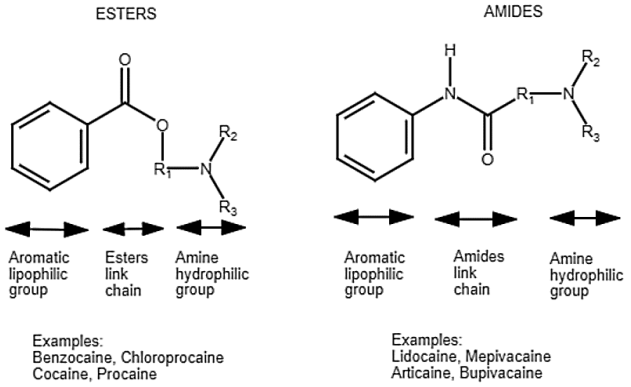

Fig. 1. Types and chemical structure of local anesthetics.

Commercial Local anesthetic (LA) formulations may contain epinephrine, preservatives (i.e., methylparaben), and excipients (i.e., sulfites). Epinephrine is added to LA preparations to lengthen absorption by vasoconstriction to extend the duration of anesthetic action. Notably, epinephrine in LA preparations does not prevent immediate hypersensitivity reactions to LAs [7]. Methylparaben prevents contaminations. The structure of methylparaben is similar to PABA, which has been associated with delayed allergic reactions and with rare immunoglobulin E (IgE)-mediated reactions [8]. The Food and Drug Administration (FDA) banned it from single-dose LA, and only a few LA preparations still contain parabens [9] To prevent oxidation, sodium metabisulphite is required in LAs containing epinephrine [10]. Sulfite sensitivity primarily affects a small subgroup of asthmatics. The role of preservatives in inducing allergic reactions to LAs is probably minimal [11].

Adverse events

Hypersensitivity Reactions

Immediate hypersensitivity reactions to LAs are hardly reported [2]. They are characterized by pruritus, urticaria, angioedema, skin rash, vomiting, oculorhinitis, bronchospasm, laryngospasm, hypotension, and anaphylaxis. Immediate reactions typically develop from a few seconds to one hour after LA administration.

Delayed hypersensitivity reactions to LAs occur in 2.4–4.1% of patients [12]. Late local reactions are characterized by induration, swelling, erythema, and pruritus at the administration site that appears several hours to days after the dose [2]. Allergic contact dermatitis typically occurs at the site of administration within 72 hours. Delayed generalized cutaneous signs, such as maculopapular rash, have been rarely observed. So far, severe cutaneous adverse reactions (SCARs) like Stevens Johnson syndrome (SJS), acute generalised exanthematous pustulosis (AGEP), or DRESS to LAs have not been described [13].

The mechanism of immediate reactions to LAs can be IgE-mediated [14]. LA may act as a hapten that has to be linked to a peptide (e.g., PABA) to activate T cells and the clinical reaction. Other mechanisms that can be involved are the P-I stimulation concept and the pseudo-allergy model [2]. Pseudo-allergic reactions induce symptoms similar to those of IgE-mediated reactions.

Nonallergic Reactions

They are the reactions most frequently reported [2,12].

Psychosomatic reactions are usually related to anxiety and panic. Symptoms such as tremors, tachypnea, difficulty breathing, tachycardia, palpitations, hyperventilation, tingling of the fingers and/or perioral, drowsiness, and sweating can develop.

Vasovagal reactions are characterized by syncope, pallor, asthenia, hypotonia, and bradycardia.

Toxic reactions may be local or systemic. Local toxicity is generally associated with the direct effects of LAs and related to incorrect administration techniques. Symptoms may include pain, bruise, infection, disruption of nerves, and ischemic necrosis [12]. Local Anesthetic Systemic Toxicity (LAST) occurs following systemic absorption of LAs. LAST is rare in children and may be favored by administering higher doses than those recommended for lidocaine, lidocaine + prilocaine, and ropivacaine during surgery [15]. LAST is often severe and includes neurological and cardiovascular symptoms that can be life-threatening. Neurological symptoms include agitation, convulsions, paraesthesia, dysarthria, diplopia, and dizziness and may progress to apnea and delirium. Cardiovascular manifestations are arrhythmias, bradycardia, hypotension, and heart failure [1].

Pharmacological effects are related to the epinephrine contained in some LAs. Epinephrine is added in such low doses that it does not generally provoke side effects. However, in some subjects who respond to low amounts of epinephrine or in the case of systemic absorption, adverse reactions such as tachycardia, anxiety, hypertension, and palpitations may occur.

Idiosyncrasies are associated with the administration of elevated doses of LAs, mainly prilocaine, and consist in the induction of methemoglobinemia [10].

Epidemiology

Adverse Reactions

Adverse reactions to LAs occur in 0.5%–26% of instances, being more common in dental practice [2]. A French pharmacovigilance database confirmed that neurological and cardiovascular adverse drug reactions (ADRs) were more common. Moreover, it showed that subjective symptoms, including syncope, a transient self-limited loss of consciousness, weakness, feeling faint or unwell, and a vasovagal reaction with anxiety and fear, were the more frequently presenting symptoms of ADRs in adults [16]. At variance, in 73 children with immediate responses to LAs with allergy confirmed in one (1.3%) instance [17]. And objective symptoms such as skin reactions, vomiting, shortness of breath, and eye redness were more common. A Croatian study [18] found only 3 subjects with allergic reactions to LAs in 331 patients (age range 8–88 years) with ADR. ADRs were more frequent in patients with a previous ADR to other drugs, in patients with other allergic diseases, or other illnesses.

Hypersensitivity Reactions

In the general population, the incidence of suspected hypersensitivity reactions to LAs is 0–5%, and less than 10% of hypersensitivity reactions occur in children of pediatric age. The reported incidence of delayed hypersensitivity reactions to LAs ranged from 2.4 to 4.1% and to lidocaine alone from 0.14 to 5%. Unfortunately, studies investigating these reactions with subcutaneous provocation tests are lacking. Above all, delayed hypersensitivity reactions to LAs are associated with ester-LAs. An allergic reaction to preservatives should also be considered [10,14,19].

Allergists rarely confirm suspected, immediate hypersensitivity reactions to LAs. There are few studies on perioperative allergic reactions to LAs.

A study conducted in Denmark investigated the incidence of IgE-mediated reactions to LAs in patients with suspected, immediate hypersensitivity reactions to LAs (162 patients, 9 children with an age range of 2–17 years). None of the patients had a positive subcutaneous provocation test with the suspected LA, but a third of the patients reacted to a different allergen, especially chlorhexidine [20].

A retrospective study over 35 years was conducted in 31 French regional pharmacovigilance centers. The study included 256 patients (49 children) with the aim of focusing on the prevalence of IgE-mediated anaphylactic reactions associated with dental procedures. In 2345 LAs ADR, IgE-mediated anaphylaxis has been found only in 4 cases (0.17%) and without fatal outcome. Lidocaine was the most often involved of LA; mepivacaine, articaine, and procaine were the other LAs listed, but with a much lower frequency [21].

In 2978 patients with suspected LA allergy, a British group found that the frequency of IgE-mediated allergic reactions was 0.97%. Amide LAs were the culprit agents in 75% of cases, probably because amide LAs are used more [22].

A Spanish pediatric study retrospectively analyzed the medical records of 73 patients (43 boys; age range 3–17.8 years) with a history of suspected allergic reactions to LAs who had undergone skin and subcutaneous challenge tests. The most commonly tested drugs were lidocaine (50.6%) and prilocaine (20%). LA allergy was demonstrated in 1/73 patients by the mepivacaine subcutaneous challenge test [17].

A few data on risk factors for hypersensitivity reactions to LAs are available in children. In 17 children, Suleyman A *et al*. [23] found previous responses to more than 2 LAs, having been exposed to LA at least 2 times in the past, and a prior reaction with skin symptoms predisposed to hypersensitivity reactions to LAs. However, Selmanoglu A *et al*. [17] found no risk factor in a pediatric series. In adults, Koca Kalkan I *et al*. [24] found that a positive LA skin/provocation test was significantly related to a previous hypersensitivity reaction to LA and a reaction with generalized skin manifestations and hypotension. Other studies [25,26] were unable to identify any risk factors.

Management

Clinical History

A detailed history of the reaction is the cornerstone of the diagnosis. In 15–37% of suspected patients, history suggests a true allergic reaction to LAs [11]. If history strongly indicates a hypersensitivity reaction to LAs, the patient should be referred to the allergist. An allergy workup in subjects without a clinical history suggestive of an allergic drug reaction to prevent reactions when the patient receives LAs in the future is never recommended. The European Network proposed a questionnaire to Drug Allergy ENDA [27]. The following items should be assessed: type of procedure, the interval between LA administration and the onset of symptoms, type, amount, and concentration of the LA, and personal history, particularly of renal, hepatic, cardiac, and psychological manifestations. It is essential to consider that allergic reactions during a local anesthesia procedure can be caused by allergens different from LAs that were simultaneously administered, such as latex, chlorhexidine, and antibiotics [28]. Allergy workup for LAs is not indicated in atopic patients without a medical history of suspected LAs hypersensitivity since atopy is not a predisposing condition [23], or in case of risk of life-threatening reactions, concomitant severe diseases, including not controlled asthma and mastocytosis.

Skin Tests

Skin Prick Tests (SPTs), Intradermal Tests (IDTs), and Patch Tests (PTs) on the culprit LA can be performed. Ana-

Table 1. Different protocols for subcutaneous challenge tests are used to diagnose LA hypersensitivity. The subcutaneous challenge test is considered negative when no immediate allergic reaction occurs within 30 minutes after injection (Adapted from [34]).

Methods	Subcutaneous doses	Timing of administration (minutes)
Single-blind method (patients do not know whether they receive drug or placebo)	1. Saline solution injection 2. Milliliters of undiluted LA: 0.1, 0.2, 0.5, 1, 2	30
Open procedure (no placebo)	1. Saline solution injection 2. Milliliters of undiluted LA: 0.1, 0.5, 1	15
Open procedure (no placebo)	1. 0, 1 mL of diluted 1:10 LA solution. 2. Milliliters of undiluted LA: 0.1, 1, 2	15

LA, Local anesthetic.

phylactic reactions are rare; in these circumstances, a different class of LA may be used [11,29]. If the causative drug is unknown, clinically relevant LA for immediate hypersensitivity reactions, such as tetracaine, mepivacaine, lidocaine, and bupivacaine, should be tested. Skin tests must be performed within 4 weeks up to 6 months after acute symptoms, because skin test sensitivity to drugs declines over time. If timing is over 6 months after the reaction or symptoms during local anesthesia were highly suggestive, but the diagnostic workup was negative, another diagnostic evaluation is recommended after 4–6 weeks. This approach is recommended since the skin test may reactivate hypersensitivity (booster effect) [30]. It is advisable that skin tests are not performed with solutions containing vasoconstrictors as they mask a local wheal and flare reaction. Whether SPTs and IDTs should be performed with preservative-free solutions (sodium metabisulfite, parabens) is controversial. The negative predictive value of skin tests in the diagnosis of LA hypersensitivity is 97% [31], while the positive predictive value is unknown.

SPTs have high specificity but a lower sensitivity. They have a very low risk of anaphylaxis. SPTs are performed with commercially available undiluted LAs. A 10-fold dilution or concentration of 1:1000 or 1:10,000 is used in patients with severe reactions. A negative (saline) and a positive (histamine) control should be done [10].

IDTs may help diagnose both immediate and delayed type immune reactions. IDT false positive reactions are common primarily if the test is performed with undiluted solutions. IDTs are more sensitive and reproducible than SPTs. IDTs have a higher risk of adverse reactions than SPTs. They are performed only when SPT results are negative. It is recommended to perform IDTs with increasing concentrations (1:1000, 1:100–1:10) to reduce the risk of severe adverse reactions [29]. The sensitivity of delayed IDT results (measurement of infiltration diameter after 48 hours) is similar to or even higher than that of patch tests in diagnosing delayed reactions.

PTs are performed with undiluted drugs to confirm a type IV hypersensitivity reaction to topical LAs. They are helpful for diagnosing contact allergy to LAs. The PT panel should include both esters, such as benzocaine and tetracaine, and amides, such as bupivacaine, lidocaine, mepivacaine, prilocaine, articaine, and dibucaine. If relevant, patients with a suspected contact allergy to LAs should also be tested with parabens and metabisulfite [32]. Notably, most patients with contact allergy to a specific LA can safely receive the same compound when it is subcutaneously injected [33].

In Vitro Methods

Serum tryptase is elevated up to 4 hours after an anaphylactic reaction. The basophil activation test (BAT) to LAs could be performed for type 1 allergies, and the lymphocyte transformation test (LLT) to LAs may be useful for delayed hypersensitivity reactions. The predictive values of BAT and LLT are not well established and are currently being investigated [11].

Subcutaneous Challenge

The gold standard for diagnosing LA allergy is the subcutaneous challenge test. Although skin tests may be positive in some patients who can tolerate LA during the challenge, all guidelines indicate that the challenge test should be the last step of the diagnostic procedure only in patients with negative skin test results [29,34]. However, when there is a history of mild reactions, some authors recommend a graded challenge in patients with positive skin test results [20]. Subcutaneous challenge [35] may be performed without a placebo or single-blind method (patients are unaware whether they are given a LA or placebo) to exclude unspecific or psychogenic reactions. It is preferable not to use a placebo in children due to the low frequency of psychological responses compared to adults. Provocation tests must be performed by trained personnel and equipment for treating severe reactions in a hospital setting. The test may start with saline administration and continue with increasing doses of LA every 15 or 30 minutes (Table 1, Ref. [34]). The drug is usually injected subcutaneously into the extensor forearm region. The patient passes the challenge test when no reaction develops within 30 minutes of injection. The patient is observed for one hour following the last injection.

Diagnostic Protocols

The best test procedure for immediate hypersensitivity reactions to LAs remains debatable. SPTs and IDTs are usually performed prior to the provocation test. Some authors argue that all skin tests could be omitted because of low specificity. Others consider that SPTs are inexpensive, quickly performed, and can provide helpful information. At the same time, IDTs may be omitted because they are time-consuming and have more false positive results than SPTs. We believe that subcutaneous challenge without prior skin testing poses an unacceptable risk for a small but significant number of children with suspected immediate immune reactions to LAs. Although different challenge protocols exist, we think children are more suitable for those without a placebo. However, if history does not suggest an IgE-mediated reaction, a challenge test to LAs without skin testing may be performed.

Cross-Reactions

Cross-reactivity among esters should be considered the rule rather than the exception due to the common metabolite para-aminobenzoic acid (PABA). There is generally no cross-reactivity among amide LAs, although there are some case reports of immediate and delayed cross-reactions [36,37]. Cross-reactivity between lidocaine and mepivacaine is the most commonly described [12,16]. This may result from sharing a meta-xylene aromatic ring, which is also present in bupivacaine [38]. In these cases, contrasting data on articaine's safety with a thiophene ring has been provided [18,36]. Between the ester and amide groups, there is no cross-reactivity. The patients and the health personnel should be informed that a negative challenge test to a specific LA does not exclude the onset of non-immunological reactions to a different LA, which may require treatment and can be severe.

Conclusions

True hypersensitivity reactions to LAs are rare but a cumbersome problem in pediatric allergy. A detailed history is of pivotal importance. The type and composition of the used drug, clinical manifestations, timeline of events, and drug treatment should be documented. Differential diagnosis with toxic, psychogenic, and not immunological reactions to LAs or reactions to other agents such as latex, as well as the distinction between immediate and delayed reactions, are of paramount importance.

An algorithm that can cover all aspects of the diagnostic workup for immediate hypersensitivity reactions to LAs is not feasible. An individual approach is always necessary and must be evaluated and established by the allergist, on the basis of the clinical history of every single child.

Availability of Data and Materials

Not applicable.

Author Contributions

FF, CC conceived and designed the study. FF, PB, LL and SC have been involved in acquiring data and drafting the manuscript. FM, AB, GC, SR, FS, RLV have been involved in conception of the study, analysis and interpretation of data. CC, FM, AB, GC, SR, FS, RLV critically revised the manuscript and performed the corrections deemed necessary. The final manuscript was approved by all Authors. All Authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Ozbay S, Ayan M, Karcioglu O. Local Anesthetics, Clinical Uses, and Toxicity: Recognition and Management. Current Pharmaceutical Design. 2023. (online ahead of print)

[2] Jiang S, Tang M. Allergy to Local Anesthetics is a Rarity: Review of Diagnostics and Strategies for Clinical Management. Clinical Reviews in Allergy & Immunology. 2023; 64: 193–205.

[3] Tadin A, Aleric K, Jerkovic D, Gavic L. Knowledge, Practice and Self-Reported Confidence Level of Croatian Dentists in the Use of Local Anesthesia: A Cross-Sectional Study. Healthcare (Basel, Switzerland). 2023; 11: 2006.

[4] Buyan A, Whitfield AA, Corry B. Differences in local anaesthetic and antiepileptic binding in the inactivated state of human sodium channel Nav1.4. Biophysical Journal. 2021; 120: 5553–5563.

[5] Cherobin ACFP, Tavares GT. Safety of local anesthetics. Anais Brasileiros De Dermatologia. 2020; 95: 82–90.

[6] Prabhakar A, Ward CT, Watson M, Sanford J, Fiza B, Moll V, *et al*. Liposomal bupivacaine and novel local anesthetic formulations. Best Practice & Research. Clinical Anaesthesiology. 2019; 33: 425–432.

[7] Mistry N, Kufta K, Mupparapu M, Panchal N. A Patient with Known Allergy to Local Anesthesia Presenting for a Dental Restoration. Dental Clinics of North America. 2023; 67: 527–529.

[8] Macy BE, Shatz M, Zeiger RS. Immediate hypersensitivity to methylparaben causing false-positive results of local anesthetic

skin testing or provocative dose testing. The Permanente Journal. 2002; 6: 17–21.

[9] Burbridge MA, Jaffe RA. Excipients in Anesthesia Medications. Anesthesia and Analgesia. 2019; 128: 891–900.

[10] Lukawska J, Caballero MR, Tsabouri S, Duguè P. Hypersensitivity to local anesthetics 6 facts and 7 myths. Current Allergy & Clinical Immunology. 2009; 22: 117–120.

[11] Thyssen JP, Menné T, Elberling J, Plaschke P, Johansen JD. Hypersensitivity to local anaesthetics–update and proposal of evaluation algorithm. Contact Dermatitis. 2008; 59: 69–78.

[12] Marcelino FC, Rocha Felix MM, Lopex Ferreira MIP, Malaman MF, Aun MV, Queiroz G, *et al*. Update on local anesthetics hypersensitivity reactions. Arquivos de Asthma Alergia e Immunologia. 2022; 6: 63–70.

[13] Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, *et al*. Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: Specific Drugs. The Journal of Allergy and Clinical Immunology. in Practice. 2020; 8: S16–S116.

[14] Gall H, Kaufmann R, Kalveram CM. Adverse reactions to local anesthetics: analysis of 197 cases. The Journal of Allergy and Clinical Immunology. 1996; 97: 933–937.

[15] Schweitzer-Chaput A, Callot D, Bouazza N, Lesage F, Oualha M, Paret N, *et al*. Local anesthetics systemic toxicity in children: analysis of the French pharmacovigilance database. BMC Pediatrics. 2023; 23: 321.

[16] Fuzier R, Lapeyre-Mestre M, Samii K, Montastruc JL, French Association of Regional Pharmacovigilance Centres. Adverse drug reactions to local anaesthetics: a review of the French pharmacovigilance database. Drug Safety. 2009; 32: 345–356.

[17] Selmanoglu A, Güvenir H, Celik IK, Karaatmaca B, Toyran M, Civelek E, *et al*. Immediate local anesthetic reactions and diagnostic test results in pediatric patients. Allergologia et Immunopathologia. 2021; 49: 108–114.

[18] Batinac T, Sotošek Tokmadžić V, Peharda V, Brajac I. Adverse reactions and alleged allergy to local anesthetics: analysis of 331 patients. The Journal of Dermatology. 2013; 40: 522–527.

[19] Ibanez MA, Levoska MA, Zheng DX, Nedorost ST. Sodium Metabisulfite Allergic Contact Dermatitis From Lidocaine Exposure in an Operating Room Nurse. Dermatitis: Contact, Atopic, Occupational, Drug. 2021; 32: e108–e109.

[20] 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. The Journal of Allergy and Clinical Immunology. in Practice. 2018; 6: 1217–1223.

[21] Hascoët E, Mahé J, Meillard H, Théophile H, Cloitre A, Lesclous P. Anaphylactic reactions to local anesthetics in dental practice: a nationwide French retrospective study. Clinical Oral Investigations. 2022; 26: 1667–1676.

[22] Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. British Journal of Anaesthesia. 2012; 108: 903–911.

[23] Suleyman A, Tamay Z, Guler N. Risk Factors for Immediate-Type Local Anesthetic Hypersensitivity Reactions in Pediatric Patients: A Retrospective Case-Control Study. Journal of Asthma and Allergy. 2022; 15: 453–460.

[24] 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. Journal of Asthma and Allergy. 2021; 14: 47–58.

[25] Trautmann A, Goebeler M, Stoevesandt J. Twenty Years' Experience with Anaphylaxis-Like Reactions to Local Anesthetics: Genuine Allergy is Rare. The Journal of Allergy and Clinical Immunology. in Practice. 2018; 6: 2051–2058.e1.

[26] Zuo J, Gong R, Liu X, Zhao J. Risk of True Allergy to Local Anesthetics: 10-Year Experience from an Anesthesia Allergy Clinic in China. Therapeutics and Clinical Risk Management. 2020; 16: 1297–1303.

[27] Bousquet PJ, Demoly P, Romano A, Aberer W, Bircher A, Blanca M, *et al*. Pharmacovigilance of drug allergy and hypersensitivity using the ENDA-DAHD database and the GALEN platform. The Galenda project. Allergy. 2009; 64: 194–203.

[28] Manian DV, Volcheck GW. Perioperative Anaphylaxis: Evaluation and Management. Clinical Reviews in Allergy & Immunology. 2022; 62: 383–399.

[29] Speca SJ, Boynes SG, Cuddy MA. Allergic reactions to local anesthetic formulations. Dental Clinics of North America. 2010; 54: 655–664.

[30] Harboe T, Guttormsen AB, Aarebrot S, Dybendal T, Irgens A, Florvaag E. Suspected allergy to local anaesthetics: follow-up in 135 cases. Acta Anaesthesiologica Scandinavica. 2010; 54: 536–542.

[31] Volcheck GW, Mertes PM. Local and general anesthetics immediate hypersensitivity reactions. Immunology and Allergy Clinics of North America. 2014; 34: 525–546.

[32] Trautmann A, Stoevesandt J. Differential diagnosis of late-type reactions to injected local anaesthetics: Inflammation at the injection site is the only indicator of allergic hypersensitivity. Contact Dermatitis. 2019; 80: 118–124.

[33] Choi C, Vafaei-Nodeh S, Phillips J, de Gannes G. Approach to allergic contact dermatitis caused by topical medicaments. Canadian Family Physician Medecin De Famille Canadien. 2021; 67: 414–419.

[34] Peroni D, Pasini M, Iurato C, Cappelli S, Giuca G, Giuca MR. Allergic manifestations to local anaesthetic agents for dental anaesthesia in children: a review and proposal of a new algorithm. European Journal of Paediatric Dentistry. 2019; 20: 48–52.

[35] Bahar E, Yoon H. Lidocaine: A Local Anesthetic, Its Adverse Effects and Management. Medicina (Kaunas, Lithuania). 2021; 57: 782.

[36] De Pasquale TMA, Buonomo A, Pucci S. Delayed-type allergy to articaine with cross-reactivity to other local anesthetics from the amide group. The Journal of Allergy and Clinical Immunology. in Practice. 2018; 6: 305–306.

[37] González-Delgado P, Antón R, Soriano V, Zapater P, Niveiro E. Cross-reactivity among amide-type local anesthetics in a case of allergy to mepivacaine. Journal of Investigational Allergology & Clinical Immunology. 2006; 16: 311–313.

[38] 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. The Journal of Allergy and Clinical Immunology. in Practice. 2016; 4: 162–164.