

# Allergic manifestations to local anaesthetic agents for dental anaesthesia in children: a review and proposal of a new algorithm



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## Abstract

**Aim** The purpose of this review was to evaluate allergic manifestations to dental local anaesthetic (LA) in children and to propose an algorithm for the diagnosis of LA allergy, in order to minimise the number of children who are wrongly categorised as allergic.

**Materials and methods** A comprehensive literature survey was performed on LA allergy in children before a dental treatment. In proposing a diagnostic algorithm, evidences from literature have been integrated with personal experience.

**Results** Data from literature showed that overall less than 1% of young patients tested for suspected LA have a positive subcutaneous test and have a positive diagnosis. A complete diagnostic procedure should include: clinical history reported by patients, objective medical records, results of skin tests and provocation test with the suspected drug. Patients with negative skin tests should perform a subcutaneous challenge, while patients with a positive skin test should be tested for a different unrelated LA.

**Conclusion** Allergy to LA is a rare condition. A complete diagnostic algorithm will allow to identify paediatric patients correctly.

## Introduction

Local anesthetic (LA) agents block nerve conduction and have been commonly used for local or regional anaesthesia in dentistry, surgical, obstetric and ophthalmic procedures [Yilmaz et al., 2011; Salomon et al., 2012; Cianetti et al., 2017]. The incidence of allergic reactions to LA in children is generally overestimated [Lee and Lee, 2013]. Indeed, in the literature, adverse events are reported in 0.1-1% of procedures in which LA are used and less than 1% of all adverse reactions are due to allergic mechanisms [Gall et al., 1996; Bhole et al., 2012].

### Local anaesthetics classification

LA molecules contain a lipophilic aromatic ring, connected to a hydrophilic amine group by a linking chain, that is used to classify the agents as esters or amides (Table 1). They provide complete but temporary analgesia as a result of their interaction with neural voltage-gated sodium channels. Esters are metabolised by plasma pseudo-cholinesterase and amides by hepatic microsomal enzymes [Campanella et al., 2018; Nastasio et al., 2018].

Esters	Amides
Benzocaine	Short acting
Cocaine	Lidocaine
Procaine	Medium acting
Tetracaine	Mepivacaine
	Prilocaine
	Articaine
	Lidocaine with epinephrine
	Long acting
	Bupivacaine
	Ropivacaine

TABLE 1 Commonly used local anaesthetics.

KEYWORD Allergy; Diagnosis; Local Anesthetic.

### Hypersensitivity and allergy to LA

Hypersensitivity reactions are dose-independent, unpredictable adverse events to a dose well tolerated by the majority of children [Demoly et al., 2014]. Drug allergy can be diagnosed only in situations when an underlying immune mechanism can be identified in the development of hypersensitivity reactions. In all other cases non-allergic hypersensitivity reactions should be considered [Grzanka et al., 2016]. Due to their low molecular weight, LA are weakly antigenic and for this reason allergic reactions should be considered uncommon. However, two types of allergic reactions to LA may occur: IgE-mediated type I reactions or T-cell mediated, type IV, reactions. Immediate allergic reactions (type I reactions) are rare and they generally occur within 6 hours (rarely within 6–12 hours and no longer than 24 hours) after exposure. Clinical manifestations of immediate allergic reactions include: urticaria, angioedema, bronchospasm, rhinitis, conjunctivitis, gastrointestinal symptoms and anaphylaxis, including anaphylactic shock. Amongst allergic reactions to local anaesthetics, type IV delayed cutaneous reactions, such as eczema, are the most frequent. Delayed reactions generally occur within 24 to 72 hours after exposure (rarely already after 6 hours) [Brockow et al., 2015]. Both type I and IV allergic reactions are most common with ester compounds. Para-aminobenzoic acid (PABA)—a metabolite of esters—is responsible for their allergenic potential. Methylparaben and propylparaben are preservatives used in both ester and amide LA, their metabolites are chemically similar in structure to PABA [Enggleston and Lush, 1996]. As a consequence, allergy to methylparaben seems to account for a significant proportion of adverse reactions to LA. Amides have a lower allergenic potential than esters, therefore they are preferred in clinical practice. Cross reactives are common between both the ester and amide group molecules, while cross-reactivity between esters and amides should not occur because their metabolites are different. Nevertheless, some cases of allergic reactions to both esters and amides have been described [Caron, 2007].

### Differential diagnosis of allergy to LA

Most of adverse reactions that may be observed during local anaesthesia procedures are probably not allergic (Table 2). However, using LA, paediatric dentists should know adverse events that may occur in order to identify allergic reactions. The most serious adverse effect of LA is their systemic toxicity, which primarily involves central nervous and cardiovascular systems [Malinovsky et al., 2016]. Local anaesthetic systemic toxicity (LAST) may occur after massive resorption from a large dose of LA or after inadvertent intravascular injection. The first signs of LAST are subjective neurological signs (paresthesia, dizziness, auditory and visual disturbances) followed by severe central nervous system symptoms, such as seizures and coma. These manifestations are precursors of cardiovascular signs which include hypotension, bradycardia and in extreme cases ventricular arrhythmia and asystole [Shapira and Rubinow, 1987]. LA may also cause local toxicity which is generally due to improper technique and includes pain, bruising, infections and haematoma [Boyce et al., 2016]. During minor surgery, children and adolescents may also experience autonomic reactions characterised by symptoms such as vasovagal syncope (pallor, bradycardia), panic attack or spasmophilia crisis with hyperventilation; tachycardia and

1	LA systemic toxicity
2	LA local toxicity
3	Psychomotor response
	a. Vasovagal syncope
	b. Panic attack
	c. Spasmophilia crisis with hyperventilation
4	Responses to procedural trauma
5	Adverse reactions to other agents administered concomitantly
	a. Preservatives and additives
	b. Epinephrine added to LA solution
	c. Latex allergy
	d. Antibiotic allergy

TABLE 2 Differential diagnosis of allergy to LAs.

cardiac arrhythmias, due to epinephrine added to decrease the rate of resorption of LA, may also occur [Malinovsky et al., 2016]. Hypersensitivity or allergic reactions may also be induced by latex gloves or antibiotics given for prophylaxis of post-operative infections; as already seen, preservatives, such as paraben or methylparaben, and additives present in the anaesthetic solution may also cause allergic reactions [Enggleston et al., 1996].

### Incidence of allergy to dental LA in the paediatric population

The reported incidence of allergic reactions to LA in the paediatric population is low, which accounted for less than 1% of all adverse reactions associated with LA [Matsumura et al., 2017].

As for IgE-mediated allergy, in 2012 Bhole et al. [2012] revised the literature from 1975 to 2011 and found 23 case series, involving 2978 patients with suspected allergy to LA. In only 29, out of 2978 patients, an IgE-mediated allergy was proven, meaning a prevalence of 0.97% in patients tested for suspected LA allergy. To define a reaction as IgE-mediated, skin prick tests (SPT), intra-dermal tests (IDT) and subcutaneous challenge were used. 2487 out of 2978 patients (83.5%) were tested with SPT and 30 (1.2%) were positive. 2648 (89%) had IDT and 37 were positive (1.4%). Subcutaneous challenge was performed in 2560 patient (86%) and was positive in 19 (0.74%). In these 23 case series, 2858 amide and 129 ester compounds have been tested. 22 out of the 2858 (0.77%) amides and 7 out of 120 esters (5.8%) tested have been identified as allergic triggers.

Adverse reactions following administration of LA are often reported as 'allergies'. However, of these events, it is estimated that less than 1% are confirmed allergies to the LA in the paediatric population [Allen et al., 2017].

Sulcuk et al. [1996] stated that the safety of LA agents is high but adverse reactions do occur.

It was reported that adverse reactions can be reduced if injections are administered carefully [Rood, 2000]. Most adverse reactions are psychogenic or vasovagal. Physicians and dentists should be aware of these facts in order to minimise the frequent fears and myths concerning the use of LA in the dentist's office [Baluga et al., 2002].

### Management of hypersensitivity to LA

The diagnosis of adverse reactions during local anaesthesia may be difficult. In presence of suggestive

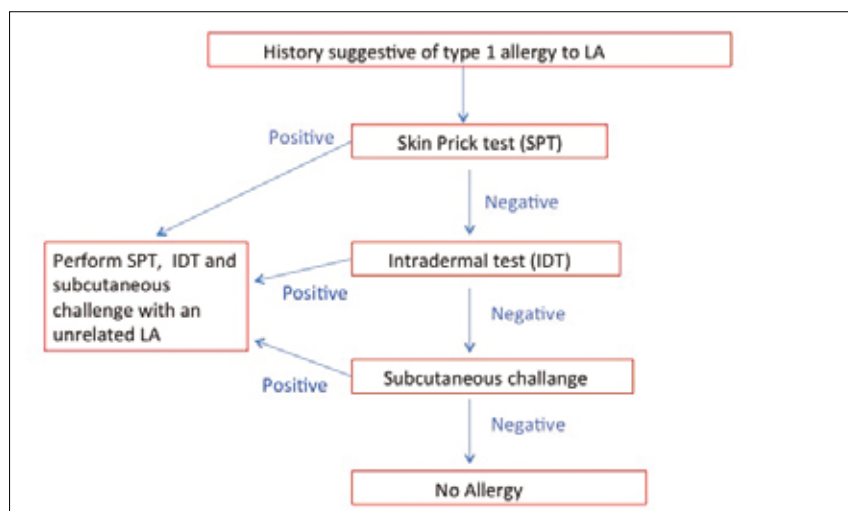


FIG. 1 Algorithm of evaluation of suspected Type 1 allergy to LA in paediatric patients.

symptoms of allergy to LA, it is recommended to use the term “hypersensitivity to LA” until the aetiology is fully understood [Grzanka et al., 2016].

Collaboration between allergologists and dentists or other specialists, who use these drugs in daily practice (dermatologists), is crucial. A precise algorithm has been proposed and should be followed for a correct diagnosis (Fig. 1). Medical history must be accurate [Bücher et al., 2016]. A possible wrong classification based only on the clinical history can have negative consequences on future therapeutic choices. If anamnesis suggests hypersensitivity to LA the patient should be referred to the allergologist, while screening subjects without a prior suggestive history of allergic drug reaction is never recommended [Demoly et al., 2014]. Retrospective evaluation of symptoms based only on patient history may be burdened by a large subjective error due to a sense of fear of patients or patient's parents and the time that has passed since the particular event. To minimise this possible bias, a questionnaire was proposed by the ENDA (European Network for Drug Allergy) [Bousquet et al., 2009].

The anamnestic elements which must refer the paediatric patient to the allergologist are:

- symptoms compatible with an allergic reaction;
- timing of symptoms (relation between drug contact and onset of symptoms).

It is not required allergologic evaluation:

- in absence of a relation between drug intake and reaction;
- in atopic patients without a medical history of suspected LA allergy because just atopy is not a predisposing condition.

An alternative diagnosis must always be taken into account. For example, in paediatric patients infections (especially viral ones) can generate symptoms that can be wrongly attributed to allergic reactions (rash, urticaria, angioedema etc.).

Patient evaluation should also include the tolerance to contact agents concomitantly used during the invasive procedure. In fact, during an invasive procedure, allergic reactions could be caused by other agents: latex (gloves), nickel, drug excipients (parabens, sulfites, adrenaline) [Grzanka et al., 2016].

Clinical tools to make certain diagnosis of allergy to LA are: standardised skin tests (*in vivo*) and drug challenge tests. To preserve test reliability, the specific allergy work-up must be carried out 4-6 weeks after the complete resolution of all clinical symptoms and signs. On the other hand, after a time interval of more than 6-12 months, some drug tests may already have turned negative.

Even though these tests are easy and rapid to perform, it is essential that standardised skin tests are performed according to standardised methodology by trained staff; their negative results have a significantly predictive value of up to 97%; to perform the tests, commercially available drugs are used, they do not contain adrenaline or other additives such as sulfites or parabens [Macy et al., 2002]. It can be used either the specific drug that is suspected to be the cause of the reaction or another one to test its tolerance. In the diagnostic procedure of allergic hypersensitivity to LA skin prick tests (SPTs) and intradermal tests (IDTs) are recommended. SPTs have a higher specificity but a lower sensitivity than IDTs, but they are connected with the lowest risk of anaphylaxis during the procedure. To guarantee the reliability of the test it is necessary to minimise possible confounding factors, such as recent or concurrent infections, recently introduced substances (drugs).

Patients with negative SPTs undergo IDTs. IDTs are performed on the volar surface of the forearm, away from the sites of the SPT. IDTs are more sensitive and repeatable, however they have a lower specificity and are related to higher risk of adverse reactions. It is recommended to perform the test with gradually increasing concentrations (1:1000, 1:100, 1:10, undiluted). Patients with negative IDT should undergo provocative challenge test.

Patch tests are performed with undiluted drugs. They allow diagnosis of cell-mediated hypersensitivity and are useful in diagnosis of contact allergies to LA.

The gold standard for establishing a diagnosis of LA allergy is the provocative challenge test [Bernstein et al., 2008]. Provocation tests should be avoided if skin tests are positive, in case of risk of life-threatening reactions, in case of concomitant severe diseases and if the patient is pregnant, unless the drug is necessary for the disease in progress or is required during pregnancy or childbirth.

Protocol	Procedure	Timing
Protocol 1	Single-blind method (patients do not know whether they receive drug or placebo)	Saline subcutaneous injection
	Subcutaneous injection of undiluted LA (without adrenaline) increasing the dose: 0.1, 0.2, 0.5, 1 and 2 ml	<p>Injections are performed with time intervals of 30 minutes</p> <p>If reaction: Stop test</p>
Protocol 2	No placebo	Subcutaneous injection of 0.1 ml of undiluted LA and subcutaneous injection of negative control
	If no reaction, subcutaneous injection of undiluted LA increasing the dose: 0.5 ml and 1 ml	<p>Injections are performed with time intervals of 15 minutes</p> <p>If reaction: Stop test</p>
Protocol 3	No placebo	Subcutaneous injection of 0.1 ml of 1:10 diluted LA solution
	If no reaction, subcutaneous injection of undiluted LA increasing the dose: 0.1, 1 and 2 ml	<p>Injection are performed with time interval of 15 minutes</p> <p>If reaction: Stop test</p>

TABLE 3 Different protocols for drug administration.

Provocation test must be performed in a hospital setting equipped to intervene in case of serious reactions. Paediatric patients' parents should be informed in details about the aim of the test and the risk involved, as well as about the procedure.

There are various protocols for drug administration beginning with very low doses which are progressively increased, in absence of reactions (Table 3). In case of reaction, the test must be interrupted.

The test may be performed with a single-blind method: the test begins with saline subcutaneous injection. Then 0.1, 0.2, 0.5, 1 and 2 ml of undiluted LA (without adrenaline) is given subcutaneously. Injections are performed into the extensor forearm region at the width of a hand over the elbow joint with time intervals of 30 minutes [Ring et al., 2010].

Based on another protocol, the test may be performed by initially injecting 0.1 ml of undiluted LA solution subcutaneously into the upper arm. The injection site is examined after 15 minutes by comparing it with the injection site of negative control. If the 0.1 ml challenge is negative, the test continues with injections of higher quantities of drug into the upper arm at a different location (0.5 ml and, after 15 minutes, 1 ml) [McClimon et al., 2011].

A different test may be performed by injecting 0.1 ml of 1:10 diluted LA solution subcutaneously into the upper arm. The test continues with subcutaneous injections of undiluted anesthetic in increasing doses at 15 minute intervals in absence of reactions (0.1 ml, 1 ml and 2 ml) [Chiriac and Demoly, 2013].

According to all guidelines, provocation test is considered the last step of the diagnostic procedure after negative skin tests. However, according with clinical history, provocative test with an alternative drug without skin tests should also be considered; in this case, a protocol that involves subcutaneous administration of the undiluted LA in doses between 0.5 ml and 1 ml is necessary and a lack of reactions within 30 minutes after injection is considered a negative result [Mertes et al., 2011]. If at the end of the diagnostic procedure, neither immediate nor late reactions have been observed, patient does not have a higher risk of immediate allergic reactions to LA than general population.

## Conclusion

Risk of allergy to LA in paediatric patients is overestimated. A complete diagnostic procedure, comprehensive of clinical history reported by paediatric patients, objective medical records, skin tests and provocations test, is warranted in selected patients in order to confirm or rule out the diagnosis of allergy to LA. In front of a negative skin tests, subcutaneous challenge with the particular LA should be performed. Conversely, patients with positive skin tests, should undergo skin test and challenge with an unrelated LA, in order to find an alternative drug that can be used. This approach will minimise the number of children who are wrongly denied the benefits of LA use in future procedures.

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