Original paper

Allergy to lidocaine injections: comparison of patient history with skin testing in five patients

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Abstract

Introduction: True allergy to local anesthetics, especially lidocaine, is uncommon. Most adverse reactions to this group of medications are classified as psychomotor, autonomic or toxic. In the case of suspected hypersensitivity to local anesthetics, skin testing is considered to be a useful tool – patch tests and intradermal tests for delayed hypersensitivity and skin prick tests and intradermal tests for immediate reactions. There is a particular need for such a diagnostic procedure, as patients suspected of hypersensitivity to local anesthetic drugs are frequently admitted.

Aim: To highlight the problem of hypersensitivity to local anesthetics on the basis of authors' own experience and literature data.

Material and methods: We present cases of 5 patients referred to the clinic by their dentists with a suspicion of allergy to local anesthetics, four to lidocaine and 1 to articaine.

Results: Intradermal tests were positive in 1 out of 5 subjects, with a concomitant episode of urticaria. In 1 patient we obtained a doubtful result of intradermal tests. Skin prick tests and patch tests were negative in all cases. In 2 cases we performed an incremental challenge test also with a negative result.

Conclusions: It has to be emphasized that, although rare, consequences of true allergy to local anesthetics can be serious considering a patient's future management and therapy. That is why this diagnosis may be crucial.

Key words: lidocaine, skin tests, incremental challenge test.

Introduction

Lidocaine represents the most common local anesthetic (LA) agent employed in local or regional anesthesia, included as a constituent of EMLA, a eutectic mixture of lidocaine and prilocaine [1, 2]. Although most allergic reactions are due to the common metabolic product of the ester local anesthetic, para-amino benzoic acid, cross-reactivity among esters is common. Ingredients in LA solutions such as antioxidants or preservatives including metabisulphite or parabens may also elicit allergic or adverse reactions. Articaine solutions should be avoided in those allergic or hypersensitive to sulphite, due to the content of sodium metabisulphite as the vasoconstrictor's antioxidant in it. The LA (without preservatives or adrenaline) may be skin tested.

True allergy to LA is rare, with a genuine immunological reaction representing only 1% of all adverse reactions to these medications [3–5]. In traditional classifications, adverse reactions to LA have been categorized as allergic, toxic and autonomic [3]. Most of the patients undergoing dental procedures exhibit some degree of autonomic response to an injection, such as sweating, tachycardia or even syncope. However, it is usually mild and transient. Toxic reactions are mostly observed as a consequence of a rapid intra-vascular injection of LA or may be associated with an overdose in patients defectively metabolizing the drug.

There is undoubtedly a need for useful and reliable armamentarium in the diagnosis of allergy to lidocaine, as it is a common concern. What is more, the term "allergy" to LA is often easily accepted by the patient, who then expects it to be proven by available diagnostics. Many

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times an adverse reaction took place several years prior to the testing with reliable documentation of the event lacking.

Aim

The aim of the paper is to highlight the problem of hypersensitivity to local anesthetics on the basis of authors' own experience and literature data.

Material and methods

We present 5 cases of patients (3 women and 2 men aged 19–50), admitted to the Department of Dermatology, Poznan University of Medical Sciences. All patients were referred to our Department by their dentists with a suspicion of allergy to LA. In the case of 4 patients, lidocaine was suspected as a culprit drug; in 1 case, articaine was suspected.

Three patients experienced an adverse reaction 2–2.5 months prior to diagnosis. In 2 subjects, the time interval between the reaction and diagnosis was much longer, being 17 and 25 years. Three patients had symptoms of an adverse reaction during a dental procedure involving the use of LA; 2 patients experienced an adverse reaction during tonsillectomy. In regards of the type of the adverse event, 2 patients experienced syncope, 1 had an episode of disseminated urticarial wheals and another had cardiac palpitations and anxiety. One female patient experienced an adverse reaction over 20 years earlier, for which there was no reliable documentation except the suggestion of a "severe immediate allergic reaction" by her family doctor.

A thorough case history was recorded with the use of the Polish version of the European Network of Drug Allergy (ENDA) questionnaire [6, 7]. Skin prick tests (SPT) with chosen LA, followed by intradermal tests (IDT) were performed using 1 : 10 000, 1 : 1000 and 1 : 100 dilutions for lidocaine and 1 : 10 dilution for mepivacaine and articaine. We used LA preparations with no additional vasoconstrictors (e.g. epinephrine). All the procedures (STP followed by IDT if negative, dilution of examined medications) were performed thoroughly with the maximal safety considerations respected, especially in regards of possible immediate hypersensitivity reactions.

Histamine and normal saline served as a positive and negative control, respectively. The SPT was considered positive when the mean diameter of an allergen wheal was equal or slightly larger than the mean diameter of the histamine wheal (+++) and when the mean diameter of an allergen wheal was at least twice as big as the mean diameter of the histamine wheal (++++) or in any case of response with pseudopodia (++++). The IDT was regarded positive if the diameter of an allergen wheal was at least 5 mm. Both for SPT and IDT readings were performed after 15–20 min, 60 min and after 24 h.

Patch tests (PT) were conducted with lidocaine 15% and mepivacaine/articaine 1% dissolved in white petrolatum, using Finn Chambers applied on the back. Readings were performed after 48 and 72 h in accordance with the recommendations of the Polish Dermatological Society [8].

In 2 cases, a subcutaneous provocation test (incremental challenge test – ICT) with the use of Schatz protocol [9] was performed. Five consecutive subcutaneous injections were performed: 0.1 ml (1 : 100), 0.1 ml (1 : 10), 0.1 ml (1 : 1), 0.5 ml (1 : 1) and 1.0 ml (1 : 1).

Results

Out of 5 analyzed cases (Tables 1–5), patient number 3 presented with positive results of IDT with lidocaine in all examined dilutions, with a concomitant episode of disseminated urticarial wheals. Patient number 2 presented doubtful results of IDT with lidocaine 1 : 10 000 and because of a probable history of a severe immediate reaction in the past, further diagnostic procedures were abandoned. In the case of patient number 1 (history of palpitations and sensation of fear after lidocaine injection), we could experience similar patient's complaints during performance of IDT with 1 : 10 000 dilution of the

Table 1. Results of skin tests – patient number 1

	STP[A] and IDT[B] (erythema/wheal – diameter in mm)				PT (in white petrolatum)		
	Histamine: 0/4 Normal saline: 0/0	30 min	60 min	24 h	White petrolatum: negative	48 h	72 h
Lidocaine 2%	1 : 10 000	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]	15%	Not done	Not done
	1 : 1000	Further testing not done: fear, cardiac palpitations, sweating (physical examination: normal)					
	1 : 100						
Mepivacaine 3%	1 : 10	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]	1%	Not done	Not done
Articaine 4%	1 : 10	Not done	Not done	Not done	1%	Not done	Not done
Prilocaine	1 : 10	Not done	Not done	Not done	Not done	Not done	Not done
Polidocanol		Not done	Not done	Not done	3%	Not done	Not done

Table 2. Results of skin tests – patient number 2

	STP[A] and IDT[B] (erythema/wheal – diameter in mm)				PT (in white petrolatum)		
	Histamine: 0/3 Normal saline: 0/0	30 min	60 min	24 h	White petrolatum: negative	48 h	72 h
Lidocaine 2%	1 : 10 000	0/0[A] 0/3[B]	0/0[A] 0/2[B]	0/0A 0/0[B]	15%	Negative	Negative
	1 : 1000	Not done	Not done	Not done			
	1 : 100	Not done	Not done	Not done			
Mepivacaine 3%	1 : 10	0/0[A] 0/0[B]	0/0[A] 0/0B	0/0[A] 0/0[B]	1%	Negative	Negative
Articaine 4%	1 : 10	0/0[A] 0/0[B]	0/0[A] 0/0B	0/0[A] 0/0[B]	1%	Not done	Not done
Prilocaine	1 : 10	Not done	Not done	Not done	Not done	Not done	Not done
Polidocanol		Not done	Not done	Not done	3%	Negative	Negative

Table 3. Results of skin tests – patient number 3

	STP[A] and IDT[B] (erythema/wheal – diameter in mm)				PT (in white petrolatum)		
	Histamine: 10/5 Normal saline: 0/0	30 min	60 min	24 h	White petrolatum: negative	48 h	72 h
Lidocaine 2%	1 : 10 000	0/0[A] 25/5[B]	0/0[A] 0/1[B]	0/0[A] 0/0[B]	15%	Not done	Not done
	1 : 1000	0/0[A] 20/4[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]			
	1 : 100	0/0[A] 25/5[B]	0/0[A] 0/1[B]	0/0[A] 0/0[B]			
Mepivacaine 3%	1 : 10	Not done	Not done	Not done	1%	Not done	Not done
Articaine 4%	1 : 10	Not done	Not done	Not done	1%	Not done	Not done
Prilocaine	1 : 10	Not done	Not done	Not done	Not done	Not done	Not done
Polidocanol		Not done	Not done	Not done	3%	Not done	Not done

The patient presented both positive IDT and an episode of disseminated urticarial wheals.

Table 4. Results of skin tests – patient number 4

	STP[A] and IDT[B] (erythema/wheal – diameter in mm)				PT (in white petrolatum)		
	Histamine: 20/4 Normal saline: 0/0	30 min	60 min	24 h	White petrolatum: negative	48 h	72 h
Lidocaine 2%	1 : 10 000	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]	15%	Negative	Negative
	1 : 1000	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]			
	1 : 100	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]			
Mepivacaine 3%	1 : 10	Not done	Not done	Not done	1%	Negative	Negative
Articaine 4%	1 : 10	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]	1%	Not done	Not done
Prilocaine	1 : 10	Not done	Not done	Not done	Not done	Not done	Not done
Polidocanol		Not done	Not done	Not done	3%	Negative	Negative

drug. Physical examination was normal, but the patient refused to be further tested.

Both SPT and PT were negative in all cases. The ICT with lidocaine and articaine conducted in the case of patients number 4 and 5 were negative.

Discussion

It is not unusual to elicit a history of allergy to LA. However, less than 1% of reported allergic reactions to these medications are immune system mediated. While obtaining a history, it often eventuates that the patient might have experienced rather a syncopal episode associated with an injection or cardiac palpitations due to action of epinephrine in administered solution or released endogenously. According to Wildsmith [10], among 25 patients initially diagnosed as being allergic to LA during dental treatment, 6 were diagnosed as suffering from phobia, panic or anxiety, 1 patient received an intravascular injection (adrenaline content of the cartridge),

Table 5. Results of skin tests – patient number 5

	STP[A] and IDT[B] (erythema/wheal – diameter in mm)				PT (in white petrolatum)		
	Histamine: 10/5 Normal saline: 0/0	30 min	60 min	24 h	White petrolatum: negative	48 h	72 h
Lidocaine 2%	1 : 10 000	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]	15%	Negative	Negative
	1 : 1000	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]			
	1 : 100	0/0[A] 0/0[B]	0/0[A] 0/0[B]	0/0[A] 0/0[B]			
Mepivacaine 3%	1 : 10	Not done	Not done	Not done	1%	Negative	Negative
Articaine 4%	1 : 10	Not done	Not done	Not done	1%	Not done	Not done
Prilocaine	1 : 10	Not done	Not done	Not done	Not done	Not done	Not done
Polidocanol		Not done	Not done	Not done	3%	Negative	Negative

1 patient appeared to be allergic to metabisulphite and latex allergy accounted for problems with 3 patients.

Allergic responses to LA are rare. In the majority of cases, hypersensitivity to this group of drugs may be excluded. It is suggested that the amide class of LA (lidocaine, mepivacaine, bupivacaine, articaine, prilocaine) is significantly less allergic than the ester type (benzocaine, procaine, tetracaine), There is also limited cross-reactivity between amide LA drugs [11]. However, according to data published by Zanni *et al.* [12], good agreement may be observed between clinical sensitization, PT and lymphocyte transformation test, indicating that there is a high degree of cross-reactivity between lidocaine and mepivacaine, also on the clonal level.

Among allergic reactions to LA, type IV hypersensitivity responses have been described predominantly to ester LA and clinically are represented by either contact dermatitis or rashes (macular or maculopapular) [13]. Torres *et al*. [14] also described the first case of fixed drug eruption induced by mepivacaine. This report was followed by others [15, 16]. Contact allergy to amide anesthetics is rare and, according to Klein and Gall [17] in 1991, only 18 cases had been reported since these medications began to be used in the 1940s. Most of the delayed-type hypersensitivity reactions take place after a topical application of the drug [18]. There have been also reports of cases presenting as contact dermatitis due to subcutaneous administration of LA, which have been confirmed by patch testing. Bircher *et al*. [13] described a case of a delayed-type reaction to LA with subsequent positive PT to lidocaine, mepivacaine and prilocaine but negative to articaine. Kanerva *et al*. [19] described a case of a 48-year-old patient, who developed contact dermatitis after an infiltration with mepivacaine and lidocaine and they concluded that diagnostic approach of a patient suspected of delayed-type hypersensitivity to LA should include not only PT, but also IDT.

Immediate IgE-mediated allergic responses, particularly to amide type LA, are uncommon. According to some authors, in more than 30 years of their practice, there has never been verified an immediate allergic reaction to LA using available diagnostic technology [10]. However, there are case reports of adverse reactions to LA, suggesting type I hypersensitivity, where signs and symptoms tend to occur within minutes of drug injection and include urticaria, episodes of angioneurotic edema, wheezing, sneezing, pruritus or even anaphylactic shock [3, 10].

Bosco *et al*. [20] described a patient with an adverse reaction to a preparation of the amide local anesthetic prilocaine and epinephrine. Signs and symptoms were consistent with an anaphylactic reaction and the patient responded positively to treatment based on this assumption (epinephrine injected sublingually and oxygen by inhalation). However, subsequent skin testing failed to confirm this diagnosis. A final diagnosis of an anaphylactoid reaction was made. Seskin [21] reported on a case of an anaphylactic reaction during a routine dental appointment to an injection of mepivacaine hydrochloride 3% without a vasoconstrictor. Again an immediate medical treatment alleviated the symptoms and prevented a more profound collapse. The author suggested that the patient might have been sensitized during emergency treatment at a hospital at which time a local anesthetic was probably administered.

In the case of suspected true hypersensitivity to LA, skin tests are considered a useful tool for the diagnosis of sensitization to this group of drugs and also for the analysis of cross-reactivity patterns. In all of 5 analyzed cases, the adverse reaction after LA injection was immediate, but in regards of type I allergy, particularly suggestive for patient 3 with the history of urticaria. Indeed, the same patient occurred to present positive results of IDT and, moreover, had an episode of urticaria during conducted diagnostic procedures. In 1 patient, the results of IDT were doubtful; however, the 25 years between adverse reaction and testing could be an important factor influencing the result and explain why further diagnostic tests were stopped. The SPT were negative in all cases, so it was advisable that they should be followed by performing an IDT due to its higher sensitivity. For the rest of analyzed patients, psychomotor (either vasovagal and hyperventilation) responses should be considered.

Our results are consistent with observations of other authors. Cuesta-Herranz *et al*. [22] described a patient who reacted to an unknown anesthetic for which the SPT were negative, but IDT gave an immediate reaction to mepivacaine, lidocaine and bupivacaine. Jacobsen *et al*. [23] examined 48 patients suspected of hypersensitivity to LA. Reactions ranged from dizziness and fainting to anaphylaxis. Suspected culprit drugs included lidocaine, bupivacaine, prilocaine and mepivacaine. Three patients representing 4 case histories tested positive on IDT (with lidocaine, and mepivacaine) – clinical manifestations included local swelling and general rash. All test-positive patients were females, none of them were atopic. It is worth emphasizing that neither 5 anamnestic cases of anaphylaxis referred by dentists nor 1 case of LA-induced asthma tested positive.

Lidocaine is a compound that does not cross-react with benzocaine [24]. Some patients allergic to lidocaine can tolerate procaine, prilocaine, or mepivacaine. The LA are considered as the most commonly used drugs in various branches of medicine.

Conclusions

Although true allergy to LA is a rare phenomenon, once an adverse reaction occurs, its nature should be thoroughly examined. Proper diagnostic procedures give the possibility to protect the patient from a severe, life-threatening future event, and on the other hand, draw attention to other possible causative factors of LA intolerance (phobia, hypersensitivity to preservatives and latex). This issue is even more important as it is estimated that in upcoming years an incidence of LA hypersensitivity will increase due to expanding use of this group of medications or due to possibility of re-exposure to various agents characterized by a similar chemical structure [25].

Conflict of interest

Authors report no conflict of interest.

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